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

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Key words: atrial fibrillation; intima-media thickness; epidemiology; population; risk factors

Abbreviations:

AF – Atrial fibrillation
CCA – Common carotid artery
CI – Confidence interval
HF – Heart failure
MI – Myocardial infarction
hs-CRP – high-sensitive C-reactive protein
HDL – High-density lipoprotein
HR – Hazard ratio
IMT – Intima-media thickness
LDL – Low-density lipoprotein
MDC – Malmö Diet and Cancer cohort
SD – Standard deviation

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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.

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.

Materials and methods

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 17 203 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.

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.

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 minutes 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 a 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.

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±6.2% (r=0.85) and the mean inter-observer difference 9.0±7.2% (r=0.77).[16]

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]

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 potential confounding factors, in relation to quartiles of IMT and per 1 standard deviation (SD) increase of log IMT. The proportional hazards assumption was confirmed by plotting the AF incidence rates over time. Three different models were tested. The first model was adjusted for age and sex. The second model was adjusted for cardiovascular risk factors. The third model was in addition adjusted for presence of carotid plaque. Age, waist circumference, systolic blood pressure, LDL, HDL and hs-CRP were fitted as continuous variables. Sex, smoking, carotid plaque, diabetes, education level and physical activity were fitted as dichotomous variables. Possible interactions between IMT and the other risk factors, with respect to incidence of hospitalized AF, were studied by introducing interaction terms in the multivariate model.

The Kaplan-Meier estimator was used to study incidence of first AF hospitalization across quartiles of IMT.
All analyses were performed in Stata/IC 12.1 (StataCorp, College Station, Texas, USA).

Results
Baseline characteristics
Median CCA-IMT (interquartile range) was 0.77 mm in men (0.68 to 0.87 mm) and 0.73 mm (0.66 to 0.82 mm) in women. The relationships between sex-specific quartiles of CCA-IMT and cardiovascular risk factors are presented in table 1. CCA-IMT was positively associated with age, diabetes, carotid plaque, waist

circumference, systolic- and diastolic blood pressure, anti-hypertensive medication, LDL and hs-CRP, and inversely associated with HDL and education level.
IMT in the bifurcation was associated with the same risk factors as CCA-IMT and in addition positively associated with smoking, civil status and total leukocyte count (data not shown).

Risk factors for incidence of hospitalized atrial fibrillation
During a mean follow-up time of 15.3 years, 353 subjects (181 men, 172 women, 4.8 per 1000 person-years) were hospitalized with a diagnosis of AF. The relationships between different cardiovascular risk factors and incidence of AF are presented in Table 2. Age, presence of carotid plaque, use of anti-hypertensive medication, waist circumference and log CCA-IMT were positively associated with incidence of AF, while LDL was inversely associated.

Incidence of AF was significantly associated with quartiles of CCA-IMT (age and sex adjusted hazard ratio (HR): 1.82, 95% confidence interval (CI): 1.30-2.55 for 4th vs. 1st quartile of CCA-IMT). The relationship remained significant after adjustment for potential confounding factors and presence of carotid plaque (HR: 1.52, CI: 1.08-2.16 for 4th vs. 1st quartile of CCA-IMT) (Table 3, figure 1).

Incidence of AF also showed a significant relationship with IMT in the bifurcation (risk factor adjusted HR: 1.66, CI: 1.06-2.61, for 4th vs. 1st quartile of IMT)(Table 4).

Sex-specific multivariate analysis showed that the association between CCA-IMT and incident AF was significant among men (HR: 2.00, CI: 1.24-3.23 for 4th vs. 1st quartile), but not in women (HR: 1.08, 0.65-1.81 for 4th vs. 1st quartile)(Supplemental table 1). A similar relationship was found for IMT in the bifurcation. No significant interaction was observed between IMT (in CCA or bifurcation) and sex with respect to incident AF.

CCA-IMT is a risk predictor for MI and HF in the present cohort. We therefore performed a secondary analysis, in which all cases with MI or HF during the follow-up period were censored at the time of the event. A total of 297 individuals had incident AF without previous or concomitant MI or HF. The age- and sex-adjusted relationship between CCA-IMT and incident AF was essentially unchanged. Comparing the 4th vs. 1st quartile, HR was 1.68 (1.16-2.43), and the risk factor adjusted HR was 1.50 (1.02-2.19).

Discussion
This prospective cohort study found that carotid IMT, a measure of arterial thickening, is associated with incidence of AF hospitalizations among middle-aged subjects, especially among men. The risk estimates remained significant after adjustment for cardiovascular risk factors. In a multivariate analysis including both CCA-IMT and carotid plaque, both were significantly associated with incidence of first AF hospitalization.

Previous studies have shown that carotid IMT can predict future cardiovascular events.[26] Large epidemiological studies have shown strong relationships between IMT and incident MI, coronary heart disease and stroke.[7, 8, 10, 27-29] Few studies have focused on the potential association between carotid IMT and AF, and the results from previous studies are contradictory. The CHS found no association between subclinical atherosclerosis (measured as either carotid IMT, carotid stenosis or ankle-arm index) and incidence of AF.[11, 12] The Rotterdam Study showed a significant association between carotid IMT and incident AF, especially among women.[13] Even though all these studies are population-based, there are important differences

between the studies that might explain the different conclusions. The CHS included self-reported AF while the Rotterdam Study, like the present study, only included patients with a physician's diagnosis of AF. Mean age also differed significantly between studies, being lowest in the present study and highest in the CHS. Since AF is strongly associated with increasing age[4, 30], it is possible that death is a competing risk that reduces the associations between atherosclerosis and AF in older age groups. This could also be a possible explanation why the present study found a stronger association among men, while the Rotterdam Study found the association to be stronger among women. It should however be pointed out that no significant interaction was observed between sex and IMT in the present study or in the Rotterdam study. Thus, it is possible that the observed sex-differences are simply due to chance.

Incidence rates of AF in the present study and the Rotterdam study[13] were comparable with the rates reported in the Framingham Study[31], while the CHS reported twice as high incidence rates. Differences in age distributions as well as case report methods could possibly explain the different results.

Most of the common risk factors for atherosclerosis, such as age, hypertension, diabetes and obesity, have also been reported as risk factors for AF.[1, 32] It has however been debated whether IMT could be used as a marker of atherosclerosis or not. Plaque area or plaque volume has been suggested as more accurate measures of atherosclerosis than IMT.[33-35] In the present study both CCA-IMT and carotid plaque were significantly associated with AF independently from one another, suggesting that CCA-IMT and plaque might affect AF through partly different mechanisms. The results are in concordance with previous studies from the present cohort showing that CCA-IMT was significantly associated with incident stroke even in the absence of carotid plaque.[8] Hence, it is possible that IMT and plaque might reflect different biological aspects of atherogenesis.

Plaque occurrence shows, compared to IMT, stronger associations with hyperlipidemia and smoking and is a stronger predictor of MI, while CCA-IMT shows stronger associations with hypertension and incident ischaemic stroke.[33, 36] IMT likely reflects hypertensive medial hypertrophy and it is possible that IMT could be seen as a marker of the cumulative effect of hypertension or a physiological adaptation to changes in blood flow and wall tension.[23] A substantial portion of the hypertensive population also suffers from left-atrial enlargement, which may predispose to AF.[37] It is notable, though, that carotid IMT remained significantly associated with AF in the present study even after adjustment for blood pressure and anti-hypertensive medication.

Previous studies have shown associations between different markers of systemic inflammation and AF.[25] It has also been shown that the joint exposure to high CCA-IMT and high levels of hs-CRP substantially increases the risk of HF.[9] In the present study, censoring incident cases of HF and MI during follow-up did not have any significant effects on the association between IMT and AF. Leukocyte levels were not associated with IMT, and adjustment for hs-CRP did not influence the observed HR between IMT and AF. Low-graded chronic inflammation seems to be less important for the risk of AF compared to MI or HF.

Some potential limitations need to be considered. History of AF, HF and MI at baseline and incidence of end-points were retrieved using the Swedish Hospital Discharge Register and the Swedish Cause of Death Register. Validation studies of the Swedish Hospital Discharge Register have shown a high validity of AF, MI and HF [24, 38-40] Some cases of AF are only handled in primary health care and are never

treated in hospital. A main limitation is that this group is not included in the present study. Furthermore, no 12-lead electrocardiogram was performed at baseline, suggesting that some cases might have had AF already when entering the study. However, AF is unusual in this age-group and a recent study of AF in the MDC cohort reported estimates of prevalence (about 1%) and incidence (4.3 per 1000 person-years), which are largely comparable with estimates from population-based studies in US, Italy and the Netherlands.[4, 13, 30]

Another shortcoming is that baseline exposures in terms of lifestyle, medical treatment, socio-economic circumstances etc., were obtained from a self-administered questionnaire. The reliability and validity on such data may be questioned. In addition, blood pressure was only measured on a single occasion. Blood pressure is a powerful risk predictor for incident CVD (e.g., coronary events, stroke, HF, etc.) in this cohort[41, 42], which should strengthen its internal validity. But we cannot rule out that multiple measurements at baseline or up-dated information on blood pressure could have weakened the observed relationship between carotid IMT and incident AF. We also lack information on incident HF outside hospital. However, the Swedish HF registry has shown that 90% of HF diagnoses are established following a hospital visit and only 10% following a visit in a primary health care setting.[43] Furthermore, the incidence of HF in the age group 45-68 years (as in the present cohort) is very low.

IMT was measured only in the right carotid artery, whereas many other studies calculated the mean value from both sides.[10, 23] This is another potential limitation. The reproducibility of the IMT measurements and prediction of cardiovascular events in the present study is however comparable with the results from other large population-based cohort studies, which scanned both sides.[10, 23, 44] It is still possible that measuring IMT on both sides could further improve the prognostic value of IMT.

In 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.

Disclosures
None

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Table 1. Baseline characteristics in relation to sex-specific quartiles of intima-media thickness in the common carotid artery (CCA-IMT).

MDC (n=4846)	Sex-specific quartiles of CCA-IMT				
	Q1	Q2	Q3	Q4	*P*, trend
IMT range, men (mm)	0.36-0.67	0.68-0.76	0.77-0.87	0.88-2.06	
IMT range, women (mm)	0.36-0.65	0.66-0.73	0.74-0.82	0.83-1.85	
N (men/women)	497/689	466/812	498/731	483/670	
Carotid plaque (%)	20.8	28.3	33.6	48.7	<0.001
Age (years)	54.8 ± 5.7	56.6 ± 5.8	58.6 ± 5.6	60.1 ± 5.4	<0.001
Smokers (%)	22.2	21.9	20.7	22.9	0.89
Diabetes (%)	5.2	6.2	7.5	10.7	<0.001
Waist circumference (cm)	82.3 ± 12.0	82.2 ± 12.4	83.5 ± 13.0	85.5 ± 13.1	<0.001
Systolic blood pressure (mm Hg)	134 ± 17	139 ± 18	143 ± 19	149 ± 20	<0.001
Diastolic blood pressure (mm Hg)	85 ± 9	86 ± 9	87 ± 9	89 ± 9	<0.001
Anti-hypertensive medication (%)	11.1	12.6	15.6	21.0	0.001
Physical activity (% in top quartile)	24.6	24.8	25.7	25.0	0.71
Married (%)	68.0	67.8	66.9	68.7	0.83
High alcohol consumption (%)	3.4	4.5	3.1	2.9	0.22
High education (%)	32.3	28.0	27.6	24.5	<0.001
Low density lipoproteins (mmol/L)	4.0 ± 1.0	4.1 ± 1.0	4.2 ± 1.0	4.4 ± 1.0	<0.001
High density lipoproteins (mmol/L)	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	<0.001
Total leukocytes (millions/mL)	6.1 ± 2.7	5.9 ± 1.5	6.0 ± 1.6	6.2 ± 1.7	0.17
Hs-CRP[a] (mg/L)	1.1 (0.6-2.3)	1.3 (0.6-2.6)	1.4 (0.7-2.9)	1.5 (0.8-3.0)	<0001[b]

[a]hs-CRP levels are presented as medians (interquartile range in brackets) due to skewed distributions.
[b]*P*-value for log-transformed CRP. All other values are means ± standard deviation unless otherwise stated.

Table 2. Results from Cox proportional hazards regression of incidence of first atrial fibrillation hospitalization.

	Age and sex adjusted	+Risk factors
Age, per year	1.13 (1.11-1.15)	1.11 (1.09-1.14)
Male (vs. female)	1.69 (1.37-2.08)	1.24 (0.94-1.65)
Carotid plaque (yes vs. no)	1.46 (1.17-1.81)	1.37 (1.09-1.71)
Systolic blood pressure, per 10 mm Hg	1.11 (1.06-1.18)	1.04 (0.98-1.11)
Anti-hypertensive medication (yes vs. no)	1.74 (1.37-2.22)	1.40 (1.08-1.81)
Waist, per 1 cm	1.03 (1.02-1.04)	1.02 (1.01-1.03)
Diabetes (yes vs. no)	1.66 (1.21-2.27)	1.19 (0.85-1.65)
Smoking (current vs. never)	1.18 (0.88-1.58)	1.11 (0.82-1.50)
Education (high vs. low)	0.90 (0.70-1.15)	0.95 (0.74-1.22)
Physical activity (highest quartile vs. lowest quartile)	0.78 (0.58-1.06)	0.84 (0.62-1.14)
LDL, per 1 mmol/L	0.88 (0.78-0.98)	0.85 (0.76-0.95)
HDL, per 1 mmol/L	0.85 (0.62-1.17)	1.18 (0.85-1.65)
Log hs-CRP, per 1 SD	1.21 (1.09-1.35)	1.10 (0.98-1.23)
Log CCA-IMT, per 1 SD	1.21 (1.09-1.35)	1.12 (1.00-1.25)

Presented as hazard ratios (95% CI) adjusted for age and sex or in a model including all risk factors in the table.
SD indicates standard deviation.

Table 3. Incidence of first atrial fibrillation hospitalization in relation to sex-specific quartiles of intima-media-thickness in the common carotid artery (CCA-IMT).

MDC (n=4846)	Sex-specific quartiles of IMT				HR per SD[*]
	Q1	Q2	Q3	Q4	
N (men/women)	497/689	466/812	498/731	483/670	
Atrial fibrillation, n (%)	50 (4.2)	89 (7.0)	86 (7.0)	128 (11.1)	
Per 1000 person years	2.7	4.5	4.6	7.6	
Age and sex adjusted HR	1.00	1.46 (1.03-2.07)	1.26 (0.88-1.79)	1.82 (1.30-2.55)	1.21 (1.09-1.35)
+Risk factors[#]	1.00	1.39 (0.98-1.97)	1.17 (0.82-1.66)	1.61 (1.14-2.27)	1.15 (1.03-1.29)
+Carotid plaque[†]	1.00	1.36 (0.96-1.93)	1.12 (0.79-1.61)	1.52 (1.08-2.16)	1.12 (1.00-1.25)

[*]Hazard ratios per 1 standard deviation increase of log-IMT.
[#]Risk factors: Age, sex, smoking, diabetes, waist circumference, systolic blood pressure, anti-hypertensive medication, LDL, HDL, education, physical activity and CRP (log-transformed).
[†]Model adjusted for all risk factors including carotid plaque.

Table 4. Incidence of first atrial fibrillation hospitalization in relation to sex-specific quartiles of intima-media-thickness (IMT) in the bifurcation

MDC (n=3347)	Sex-specific quartiles of IMT in the bifurcation				
	Q1	Q2	Q3	Q4	HR per SD*
N (men/women)	326/422	340/535	361/531	346/486	
Atrial fibrillation, n (%)	33 (4.4)	63 (7.2)	57 (6.4)	80 (9.6)	
Per 1000 person years	2.8	4.7	4.3	6.6	
Age and sex adjusted HR	1.00	1.18 (0.78-1.78)	0.89 (0.58-1.37)	2.00 (1.37-2.91)	1.27 (1.12-1.44)
+Risk factors#	1.00	1.19 (0.79-1.80)	0.87 (0.56-1.34)	1.90 (1.29-2.79)	1.24 (1.09-1.41)
+Carotid plaque†	1.00	1.17 (0.78-1.78)	0.83 (0.53-1.29)	1.66 (1.06-2.61)	1.25 (0.99-1.34)

*Hazard ratios per 1 standard deviation increase of log-IMT in the bifurcation.
#Risk factors: Age, sex, smoking, diabetes, waist circumference, systolic blood pressure, anti-hypertensive medication, LDL, HDL, education, physical activity and hs-CRP (log-transformed).
†Model adjusted for all risk factors including carotid plaque.

Figure 1. Incidence of first atrial fibrillation hospitalization during a mean follow-up of 15.3 years, in relation to quartiles of CCA-IMT.
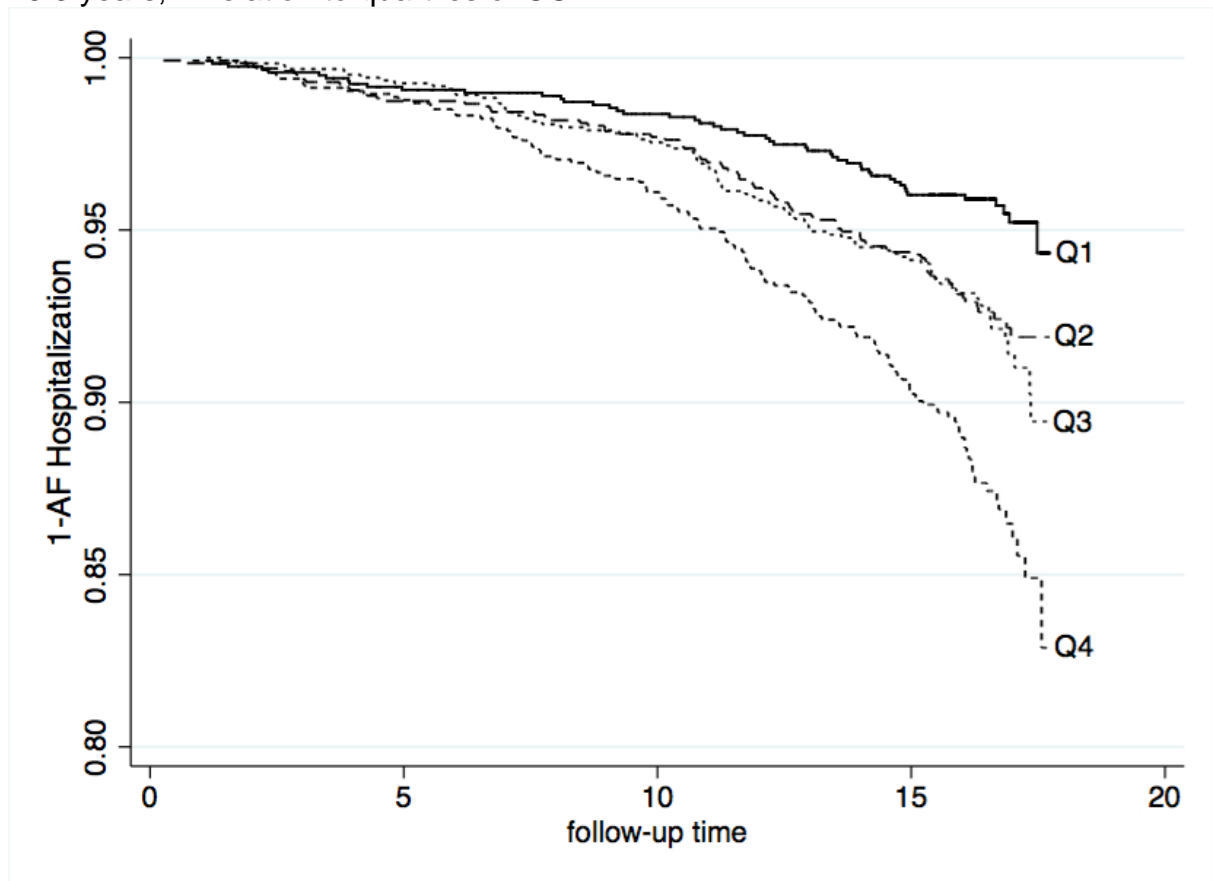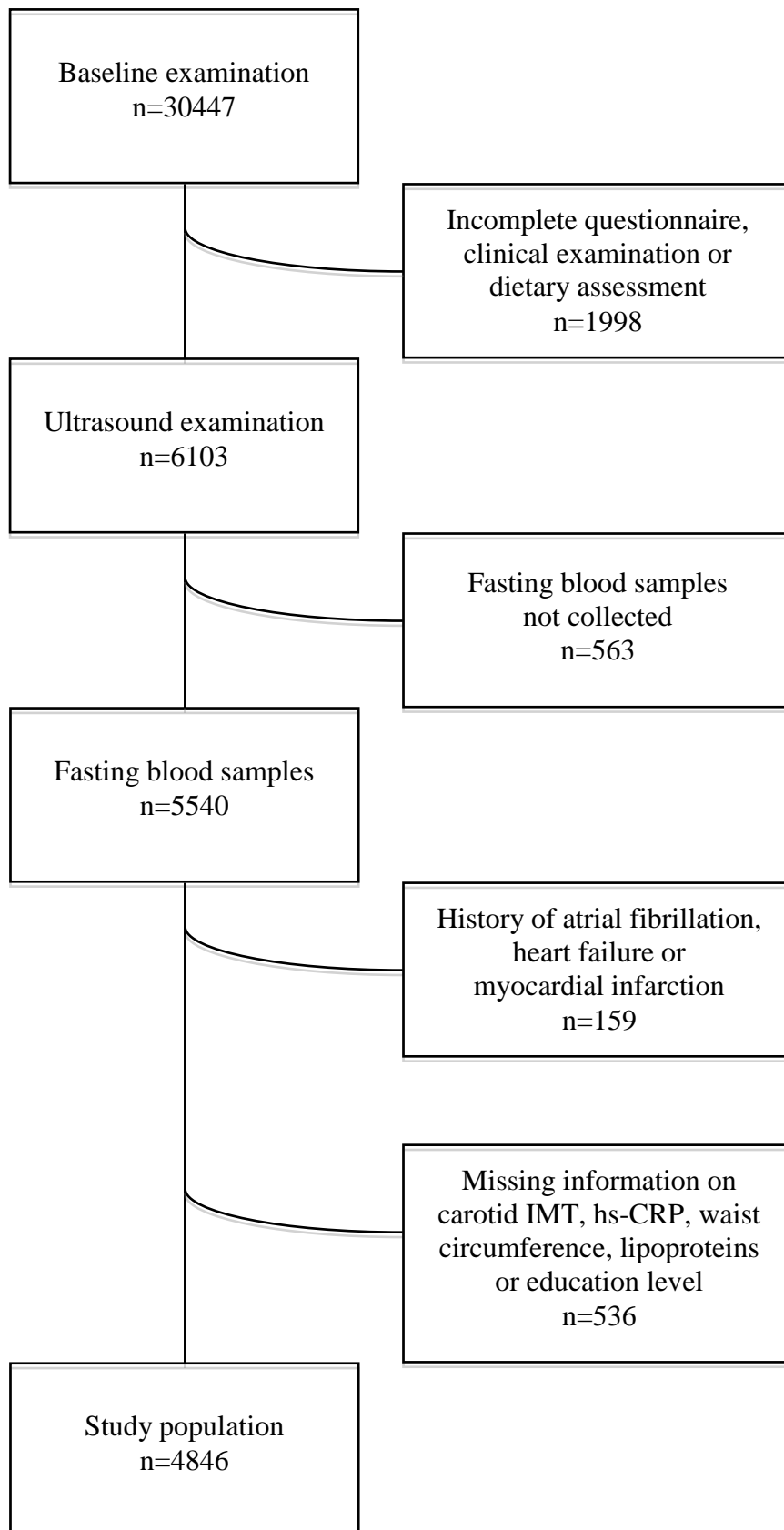
Figure 2. Study population.

Supplemental table 1. Sex-stratified incidence of first atrial fibrillation hospitalization in relation to quartiles of intima-media thickness in the common carotid artery (CCA-IMT).

MDC (n=1944)	Men				HR per SD[*]
	Q1	Q2	Q3	Q4	
N					
Atrial fibrillation, n (%)	26 (5.2)	42 (9.0)	43 (8.6)	70 (14.5)	
Per 1000 person years	3.4	6.0	5.8	10.2	
Age and sex adjusted HR	1.00	1.61 (0.98-2.62)	1.42 (0.87-2.33)	2.35 (1.48-3.74)	1.30 (1.14-1.48)
+Risk factors[#]	1.00	1.52 (0.93-2.49)	1.32 (0.80-2.17)	2.15 (1.34-3.45)	1.24 (1.08-1.42)
+Carotid plaque[†]	1.00	1.45 (0.89-2.38)	1.25 (0.75-2.06)	2.00 (1.25-3.23)	1.21 (1.05-1.39)

MDC (n=2902)	Women				HR per SD[*]
	Q1	Q2	Q3	Q4	
Atrial fibrillation, n (%)	24 (3.5)	47 (5.8)	43 (5.9)	58 (8.7)	
Per 1000 person years	2.2	3.7	3.9	5.8	
Age and sex adjusted HR	1.00	1.28 (0.78-2.10)	1.03 (0.62-1.72)	1.28 (0.78-2.10)	1.08 (0.91-1.27)
+Risk factors[#]	1.00	1.20 (0.73-1.98)	0.99 (0.59-1.65)	1.13 (0.68-1.88)	1.02 (0.85-1.21)
+Carotid plaque[†]	1.00	1.19 (0.72-1.96)	0.97 (0.58-1.62)	1.09 (0.65-1.81)	1.00 (0.83-1.19)

[*]Hazard ratios per 1 standard deviation increase of log-IMT.

[#]Risk factors: Age, sex, smoking, diabetes, BMI, waist circumference, systolic blood pressure, anti-hypertensive medication, LDL, HDL, education, physical activity and hs-CRP (log-transformed).