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Incidence of stroke is related to carotid IMT  
even in the absence of plaque

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## ABSTRACT

*Background* – The carotid intima-media thickness (IMT) has been associated with incidence of stroke. Whether this association is independent of carotid plaque is controversial.

*Methods and Results* - The associations among B-mode ultrasound determined common carotid IMT, carotid plaque (focal IMT >1.2 mm) and incident stroke, were investigated in 5,163 Swedish middle-aged men and women over a median follow-up of 7 years. Age- and sex-adjusted carotid IMT, and carotid plaque were significantly ( $p < 0.05$ ) related to future stroke. Adjustment for cardiovascular risk factors generally reduced the hazard rate ratios, however more prominently so with regard to the carotid measure of plaque than with IMT. The associations between carotid IMT and stroke remained after adjustment for presence of carotid plaque, and graded associations between carotid IMT and stroke was found both among those with and without carotid plaque.

*Conclusions* - In this population-based study, common carotid IMT was associated with incidence of stroke. This relation was independent of presence of carotid plaque.

## **INTRODUCTION**

Noninvasive-detected increased intima-media thickness (IMT) of the carotid artery is generally accepted as an early indicator of generalized atherosclerosis and cardiovascular complications. IMT has been related to cardiovascular risk factors (1-2Salonen, Bots, Persson, Heiss), and cardiovascular disease including incidence of myocardial infarction (Chambless, Bots, Iglesias, O'Leary) and stroke (2-6Chambless, Bots, O'Leary, Nagai, Cupini, Hollander). However, even though presence of carotid plaque has been shown to be significantly associated with common carotid IMT (7Persson) and also with future cerebrovascular events (8-9Geroloukos, Nagai, Hollander) it is unclear whether the presence of carotid plaque explains the associations between carotid IMT and stroke. Furthermore, the case-fatality after a stroke event has, to the best of our knowledge, not been investigated with respect to the degree of carotid atherosclerosis.

The objective of the present study was to evaluate the role of common carotid IMT, and carotid plaque as predictors of stroke over a median follow-up of 7 years. We also examined whether a potential association between carotid IMT and incidence of stroke persisted after stratification for the presence of carotid plaque. Eventually, in a subanalysis, case fatality rates were examined in relation to the measures of carotid atherosclerosis.

## **MATERIALS AND METHODS**

### **Study population**

The study population constitutes a subcohort of the Malmö Diet and Cancer Study (MDCS) cohort (10Berglund). A random fifty percent of those who entered the MDCS from November 1991 and February 1994 (n=12,445) were invited to take part in a study on the epidemiology of

carotid artery disease (7Persson). Six thousand one hundred and three 6,103 subjects accepted the invitation and were re-scheduled for fasting blood sampling under standardized conditions. Subjects were considered to have cardiovascular disease (CVD) if they had been treated due to myocardial infarction and/or stroke registered in the regional myocardial infarction register or stroke register (11-12Jerntorp). Subjects with known CVD (115 men and 43 women) were excluded from the analyses. Another 556 individuals were excluded due to missing laboratory results, 209 individuals were excluded due to missing data on carotid plaques and 17 individuals were excluded due to missing data on carotid IMT. The remaining 5,163 subjects, 3,074 women and 2,089 men aged 46 - 68 years, constitute the study population.

The Ethics Committee at Lund University approved the study. All participants gave informed consent.

#### *Cardiovascular risk factors*

Participants were categorized into never smokers, former smokers and current smokers. Leisure time physical activity Physical activity at leisure time was a composite measure of 18 different leisure time activities as queried in the health questionnaire. The procedure was adopted from a previous validated questionnaire (13). Overnight fasting blood samples were drawn for determination of cholesterol [high density lipoprotein (HDL), low density lipoprotein (LDL)], triglycerides, HbA<sub>1c</sub> and whole blood glucose according to standard procedures at the Department of Clinical Chemistry, Malmö University Hospital. Serum concentration of LDL-cholesterol was calculated using Friedewald's formula (Friedewald) Systolic and diastolic blood pressure were measured after supine rest for ten minutes. Antihypertensive treatment was self-

assessed by questionnaire. Waist circumference was measured at the umbilicus (14Lean). Subjects were classified as having diabetes mellitus if they reported the diagnosis in the questionnaire, used anti-diabetic medication or had a fasting whole venous blood glucose  $\geq 6.1$  mmol/l.

*Measurement of carotid IMT, carotid plaques and carotid stenosis*

Participants underwent B-mode ultrasonography (Acuson 128 CT system) of the right carotid artery. IMT of the common carotid artery (CCA), and presence of plaques were measured according to a standardized protocol by trained, certified sonographers as previously published (7). In short, the bifurcation area of the right common carotid artery was scanned within a pre-defined “window” comprising three cm of the distal common carotid artery, the bifurcation and one cm of the internal and external carotid artery respectively, for the occurrence of plaques (defined as a focal thickening of IMT  $> 1.2$  mm). **A lumen reduction of 15% or more was required to be counted as stenosis (15).** IMT in the CCA was determined in the far wall according to the leading edge principle, using a specially designed computer assisted analyzing system (15). CCA IMT was then determined off-line as the mean wall thickness one cm proximal to the bifurcation. Each image was analyzed without knowledge of the subject’s identification code to minimize the possibility of observer bias. Methods of quality control have been published previously (7).

Carotid atherosclerosis was assessed by B-mode ultrasound. All ultrasound examinations were performed by trained, certified sonographers (Berglund). The examination procedure has been described in detail elsewhere (Persson). In short, the bifurcation area of the right common carotid artery was scanned within a pre-defined window comprising three cm of the distal common

carotid artery, the bifurcation and one cm of the internal and external carotid artery respectively, for the occurrence of plaques (defined as a focal thickening of IMT > 1.2 mm). The degree of carotid atherosclerosis was further measured by a carotid plaque score, which is a semi-quantitative scale measuring the degree of atherosclerosis in the bifurcation area. The carotid plaque score has 5 units, where 0 = no plaques (defined as focal IMT > 1.2 mm) or wall thickenings; 1 = one small plaque (< 10 mm<sup>2</sup>) or wall thickening (IMT > 1.2 mm); 2 = two or more small plaques (< 10 mm<sup>2</sup>); 3 = one plaque > 10 mm<sup>2</sup>; 4 = one plaque > 10 mm<sup>2</sup> plus one or more small plaques (< 10 mm<sup>2</sup>); 5 = two or more plaques > 10 mm<sup>2</sup>, one circumferent plaque, or one plaque causing more than 50% stenosis. The degree of stenosis was determined by visually judging the plaque on-line and determining to what extent the plaque protruded into the lumen. A lumen reduction of 15% or more was required to be counted as stenosis (Bots). IMT was determined in the far wall of the right distal common carotid artery according to the leading edge principle, using a specially designed computer assisted analyzing system (Wendelhag). IMT was then determined off-line as the mean wall thickness one cm proximal to the bifurcation. Each image was analyzed without knowledge of the subject's identification code to minimize the possibility of observer bias.

At regular intervals during the ultrasound investigation procedure, intra- and interobserver variation analyses with regard to IMT was performed. The mean absolute difference between two measurements in percent with one observer measuring carotid IMT was  $8.7 \pm 6.2$  % ( $r = 0.85$ ) and when using two observers was  $9.0 \pm 7.2$  % ( $r = 0.77$ ) (Persson).

#### *Follow-up Measurement of incident events*

Record linkage with the National Inpatient Register, the Swedish Causes of Death Register and the Stroke Register of Malmö (STROMA) obtained information on morbidity and mortality from Stroke in the MDCS (11, 16). Information on case retrieval, validity and ascertainment of cases in the MCDS has been described in detail previously (12). In short, all cases were followed from the baseline examination until death or December 31<sup>st</sup>, 1999. Stroke was defined as rapidly developing clinical signs of local or global loss of cerebral functioning lasting > 24 hours (or leading to death before then). Classification as subarachnoid (ICD-9 code 430) or intracerebral hemorrhage (ICD-9 code 431) required verification with computed tomography (CT) and/or autopsy. Cerebral infarction (ICD-9 code 434) was diagnosed when CT or autopsy could verify the infarction and/or exclude hemorrhage and nonvascular disease. In subjects with more than one stroke event, only the first event was used for the analyses.

Record linkage with the National Inpatient Register (Swedish Board on Health and Welfare), the Swedish Causes of Death Register (anonymous), and the Stroke Register of Malmö (STROMA) obtained information on morbidity and mortality from Stroke in the MDCS. Stroke was defined as rapidly developing clinical signs of local or global loss of cerebral functioning lasting > 24 hours (or leading to death before then). The stroke subtypes were coded in accordance with the 9<sup>th</sup> version of the International Classification of Diseases (ICD). Incidences of stroke have been updated until 31 December 1999. Classification as subarachnoid (ICD 430) or intracerebral hemorrhage (ICD 431) required verification with CT and/or autopsy. Cerebral infarction (ICD 434) was diagnosed when CT or autopsy could verify the infarction and/or exclude hemorrhage and nonvascular disease. Each individual was followed until 31 December 1999, date of first stroke event or death.



### *Statistical methods*

A Cox proportional hazard model was used to estimate the ratios of hazard rates (HRR) of incident stroke between different levels of common carotid IMT, and carotid plaque under the assumption that the ratios were constant over the period of follow-up. The fit of the proportional hazards model was confirmed by plotting the hazards function in different groups over time.

There was no indication that the proportional-hazards assumption was violated.

Hazard rates were first estimated for each measure of carotid atherosclerosis (IMT and carotid plaque) in relation to incident stroke. The HRRs were presented as age- and sex-adjusted and as risk factor adjusted. Common carotid IMT was divided into tertiles, i.e. first tertile ( $\leq 0.69$  mm), second tertile (0.70 – 0.80 mm) and third tertile ( $\geq 0.81$  mm), and into subintervals of the absolute measure to check for gross deviations from linearity. For carotid IMT, stratified analyses were also made with regard to the presence of carotid plaque in relation to incident stroke. Carotid IMT, and carotid plaque were estimated within subtypes of stroke after adjustment for age, sex and time to event. Case fatality rates were calculated as the proportion of the stroke events that died within 28-days after the event and within 5-years after the event. The rates were adjusted for age, sex, diagnosis and time to event by means of logistic regression analyses.

## **RESULTS**

There were 86 incident cases of stroke (41 for men and 45 for women). Out of these 66 subjects (77%) had an ischemic stroke, 13 subjects (15%) an intracerebral hemorrhage and 7 subjects (8%) a subarachnoid hemorrhage. The unadjusted incidence rate of stroke was 2.4 per 1000

person years for the whole sample. Those with a stroke event had significantly ( $p < 0.05$ ) more unfavourable levels of SBP, DBP, waist circumference, HDL-cholesterol, treatment for hypertension, current smoking, triglycerides, and diabetes mellitus compared to those without a stroke event (data not shown).

#### *Distribution of cardiovascular risk factors at baseline*

Table 1 presents the distribution of cardiovascular risk factors in the study population at baseline....

#### *Baseline carotid ultrasonography characteristics*

Table 2 provides means and prevalences (percentages) for measures of carotid atherosclerosis comparing the levels among those with and those without a stroke event. Stroke cases showed a significantly higher baseline common carotid IMT and a higher proportion with carotid plaque than did noncases.

#### *Incidence of stroke in relation to carotid ultrasound measurements*

Table 3 shows the hazard rate ratios of stroke from Cox proportional hazards model by measures of carotid atherosclerosis. The absolute measure of carotid IMT was divided into subintervals ( $\leq 0.65$  mm, 0.66-0.74 mm, 0.75-0.84 mm, 0.85-0.94 mm, 0.95-1.04 mm,  $\geq 1.05$  mm) to check for gross deviations from linearity (data not shown). The age- and sex-adjusted HRR for stroke (using those with an IMT  $\leq 0.65$  mm as the reference) were 1.92 (95% CI, 0.71 to 5.18), 3.28 (95% CI, 1.26 to 8.53), 3.20 (95% CI, 1.17 to 8.75), 3.84 (95% CI, 1.29 to 11.45), and 2.53 (95% CI, 0.72 to 8.90) respectively. Thus, there was a significantly 3-fold-increased risk of stroke for subjects already in the IMTs interval between 0.75-0.84 mm. Due to small numbers of

stroke in some groups, tertiles of IMT and above and under the mean value, respectively were used in the further analysis. Table 3 shows the hazard rate ratios of stroke from Cox proportional hazards model by measures of carotid atherosclerosis. The risk of stroke gradually increased with increasing carotid IMT (HRR per SD increase, 1.31 [95% CI, 1.12 to 1.53]). Participants in the highest tertile of carotid IMT had a significantly increased risk of stroke compared with those in the lowest tertile. Adjustment for cardiovascular risk factors generally reduced the hazard rate ratios, however more prominently so with regard to the carotid measure of plaque than with IMT.

The absolute measure of carotid IMT was divided into subintervals ( $\leq 0.65$  mm, 0.66-0.74 mm, 0.75-0.84 mm, 0.85-0.94 mm, 0.95-1.04 mm,  $\geq 1.05$  mm) to check for gross deviations from linearity (data not shown). The age- and sex-adjusted HRR for stroke (using those with an IMT  $\leq 0.65$  mm as the reference) were 1.92 (95% CI, 0.71 to 5.18), 3.28 (95% CI, 1.26 to 8.53), 3.20 (95% CI, 1.17 to 8.75), 3.84 (95% CI, 1.29 to 11.45), and 2.53 (95% CI, 0.72 to 8.90) respectively. Thus, there was a significantly 3-fold-increased risk of stroke for subjects already in the IMTs interval between 0.75-0.85 mm. The risk factor adjusted HRRs in the subintervals of the absolute measure of IMT could not be analyzed due to too few subjects in some of the groups.

#### *Incidence of stroke in relation to carotid IMT and plaque*

Figure 1 shows the age- and sex-adjusted association between carotid IMT in tertiles and future stroke stratified by presence of plaque. Subjects with no plaque and with common carotid IMT in the first tertile was used as the reference. The results showed a graded relationship between IMT and risk of stroke, however, more evidently so among those without a carotid plaque (p for

trend=0.005) compared to those with a plaque (p for trend=0.09). Furthermore, the cohort was divided into four groups, i.e. by presence of plaque and by carotid IMT, i.e. above or below the mean carotid IMT (0.765 mm). Table 4 shows the association between carotid IMT and stroke stratified by presence of plaque using these four categories. In the age- and sex-adjusted model, both subjects with and without a plaque and with common carotid IMT above the mean value showed a highly increased HRR (2.61; 95% CI: 1.23-5.54, and 3.44; 1.72-6.89, respectively) compared to the reference group. These risks were reduced, but remained statistically significant after adjustment for cardiovascular risk factors.

#### *Subtypes of stroke*

The risk of cerebral infarction increased with increasing carotid IMT (HRR per SD increase, 1.36 [95% CI, 1.15 to 1.60]). The HRRs was somewhat reduced after adjustment for cardiovascular risk factors (HRR 1.24 [95% CI, 1.03 to 1.50]). Similar analyses were not performed for the other subtypes of stroke due to too few events. When dividing the stroke events into subtypes and adjusting for age, sex and time to event it was also shown that subjects with ischemic stroke tended to have the thickest carotid IMT (0.866 mm) and the highest prevalence of carotid plaque (68.6%), while subjects with subarachnoid hemorrhage showed the thinnest carotid IMT (0.785 mm) and the lowest prevalence of carotid plaque (44.8%). Subjects with intracerebral hemorrhage showed values of carotid IMT and carotid plaque in between the values of the other two groups (0.817 mm and 60.2%, respectively). None of these differences were, however, statistically significant.

### *Case Fatality*

Eleven (12.8%) subjects died within 28 days after their stroke. Five years after the stroke, 17 subjects (19.8%) had died. There were no statistically significant associations between any of the measures of atherosclerosis and short-term mortality (28-days) or long-term mortality (5-years) after a stroke. Thicker carotid IMT tended to be associated with higher case-fatality, while the opposite pattern was seen for case fatality in relation to presence of plaques, especially with regard to the case-fatality based on 28-days mortality. Figure 2 shows the case fatality rates (28-days and 5-year mortality) by carotid plaque after adjustment for age, sex, diagnosis and time to event.

## **DISCUSSION**

The present study shows an association between carotid IMT and carotid plaque and the risk of stroke in subjects with no history of myocardial infarction or stroke. These associations were not firmly dose-dependant. The significant associations between carotid IMT and incident stroke remained after adjustment for presence of carotid plaque, but were reduced after adjustment for established cardiovascular risk factors.

Non-invasive imaging of the carotid arteries has been suggested to be a valid “window” or indicator site for general atherosclerosis in epidemiological studies (17,18Salonen 1993).

According to Grobbee et al (19Grobbee) the use of carotid IMT measurements as an indicator of generalized atherosclerosis is based on three assumptions: that the technique is sufficiently precise and reproducible, that the images reflects the presence of atherosclerosis and that the

degree of carotid atherosclerosis indicate the presence of atherosclerosis in other arteries in which atherosclerosis develops earlier in life. In our study, direct validation of B-mode ultrasound imaging has been established through correlations between wall thickness measured by pathology and B-mode estimates (7Persson). Furthermore, associations between cardiovascular risk factors and carotid IMT and carotid plaques have been established (7Persson, Rosvall), indirectly validating the ultrasound measures. The present study support the view that common carotid IMT reflects the risk of cardiovascular disease, here measured as incident stroke. In accordance with a recent study (20), the relation between IMT and stroke was independent of plaque. Taken together, these data provide supportive evidence for the use of IMT measurements as a marker of generalized atherosclerosis.

In agreement with others (8-9Geroulakos, Hollander) we found strong associations between late atherosclerotic changes, such as carotid plaque, and stroke. It has been suggested that presence or absence of plaque, and not IMT at either the common carotid or bifurcation sites, is the more relevant indicator of early atherosclerosis (21Ebrahim). In our study presence of carotid plaque was strongly associated with future stroke. Furthermore, more than half of those with a stroke event had a carotid plaque. However, this also means that there were many cases of stroke, where a carotid plaque could not be found. Presence of increased common carotid IMT was an important risk indicator for stroke, even when information on carotid plaque or cardiovascular risk factors was taken into account. This finding suggests that there might be different processes linking common carotid IMT and carotid plaques to the development of stroke. The true mechanisms behind these associations are not fully understood. Established cardiovascular risk

factors seemed to be more important mediators of the association between late atherosclerosis and stroke compared to the measure of carotid IMT.

When categorizing the stroke events into subtypes, it was shown that atherosclerotic changes in the carotid artery were common among subjects with ischemic stroke, but also among those with an intracerebral hemorrhage. This is in line with earlier findings suggesting that atherosclerosis is an important precursor also for intracerebral hemorrhage (22).

To the best of our knowledge the relationship with case fatality after a stroke event in relation to carotid atherosclerosis has not been investigated. In our study there were no statistically significant associations between common carotid IMT or carotid plaque and short-term stroke mortality (28-days) or long-term mortality (5-years). Furthermore, there was no general tendency of the group with the most extensive carotid atherosclerosis having the highest mortality rates. This might partly be due to the fact that the short-term and long-term case fatality is to a large extent defined by the size and location of the cerebral area being damaged by the stroke (23Baptista). These factors are probably more important than carotid IMT or plaque in predicting mortality after a stroke. However, due to the small number of events (n=11) and (n=17), respectively, these analyses have to be repeated on larger population samples to be able to draw any major conclusions with regard to case fatality after a stroke event in relation to carotid atherosclerosis. Furthermore, as noted below, change in exposure of cardiovascular risk factor levels and treatment during the follow-up, might affect the results.

Certain methodological issues needs to be addressed. First, misclassification of end-point is a potential cause of bias. However, all cases of stroke were confirmed by either CT and/or autopsy.

Furthermore, vital status at the end of the follow-up was updated on all individuals by data linkage with regional Stroke Register of Malmö (11STROMA, Jerntorp) and national registers (16The National Board of Health and Welfare). The completeness and validity of STROMA has been documented in several other studies from the city (11, 24Merlo; Pessah-Rasmussen Stroke 2003). The proportion of nonhospitalized cases is very small in Sweden, and the proportion in STROMA is similar compared with other Swedish studies (25Engstrom 2001). There is no reason to believe that incomplete retrieval of cases biased the results.

Misclassification of exposure is a potential cause of bias. Although, the bifurcation area is the segment where carotid plaques are most commonly observed (20Grobbee), carotid plaques located at other places in for example the distal part of the internal carotid artery or outside the pre-defined "window" of the carotid artery were not encompassed in this study. However, it has recently been demonstrated that carotid plaques increases the risk of stroke, irrespective of their location (9Hollander Circulation 2002). In addition, assessment of plaque status was performed blinded to clinical information, the reproducibility was good (7Persson 1992), and if misclassification had occurred, it is likely to be non-differential, which would lead to a reduction of the true associations.

Another limitation of the study is that there is no information on whether the cardiovascular risk factors and treatment changed during the follow-up. Subjects with diabetes, hypertension and lipid disorders were referred for further evaluation and treatment. Smokers were advised to quit, but received no further help to achieve that. Because these factors were more common among



subjects with increased carotid IMT and carotid plaques they should benefit most from the interventions.

Several possible confounders were included in the multivariate analyses. Yet it remains to be evaluated to what extent the observations could be accounted for by differences between groups with regard to plaque morphology (26Polak), inflammation (27, 28) or disturbances in the coagulation system.

In conclusion, adjustment for established risk factors generally reduced the association between carotid IMT and stroke, while the association with carotid plaque turned statistically non-significant. The association between carotid IMT and stroke remained after adjustment for presence of carotid plaque, and graded associations between carotid IMT and stroke was found both among those with and without plaque. Carotid IMT is a predictor of future stroke events, independently of carotid plaque.

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**TABLE 1. Distribution of Cardiovascular risk factors at baseline.**

	Study population (n=5,163)
Mean (SD) age (years)	57.5 (5.9)
Mean (SD) HDL (mmol/l)*	1.4 (0.4)
Mean (SD) LDL (mmol/l)*	4.2 (1.0)
Mean (SD) Triglycerides (mmol/l)	1.4 (0.8)
Mean (SD) Waist (cm)	83.4 (12.5)
Mean (SD) SPB (mm Hg)*	141.2 (19.0)
Treatment for hypertension (%)	12.0
Diabetes mellitus (%)	7.9
Former smokers (%)	37.3
Current smokers (%)	22.6
Low physical activity during leisure time (%)	25.1

\*HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure.

**TABLE 2. Age- and sex-adjusted means and prevalences of carotid intima-media thickness, and carotid plaque by stroke event status.**

	Stroke event	No stroke event
	(n = 86)	(n = 5077)
Age, years	61.3	57.4
Male (%)	47.7	40.3
Carotid IMT CCA (mm)†	0.814***	0.760
Carotid plaque (%)	56.6*	42.7

\* P-values are given for the difference in ultrasonographic measures between those with and those without a stroke event; \*  $p < 0.05$ , \*\* $p < 0.01$ , \*\*\*  $p < 0.001$ .  
 † IMT, intima-media thickness; CCA, common carotid artery.

**TABLE 3.** Adjusted Hazard rate ratios (HRR) of Stroke from Cox models with 95% confidence intervals for carotid IMT, and carotid plaque.

	Sample size	Events	Adjusted for age and sex		Adjusted for risk factors§	
			HRR†	95% CI†	HRR†	95% CI†
Carotid IMT CCA (increment=0.15 mm)*			1.31	1.12, 1.53	1.21	1.02, 1.44
1st tertile*	1793	12	1.00		1.00	
2nd tertile	1657	22	1.59	0.78, 3.24	1.77	0.80, 3.92
3rd tertile	1713	52	3.00	1.57, 5.75	2.54	1.20, 5.40
Carotid plaque						
No	2925	30	1.00		1.00	
Yes	213	8	1.93	0.71, 5.15	1.26	0.78, 2.10

\* 0.15 mm increment in the carotid intima-media thickness (IMT). First tertile  $\leq 0.69$  mm, 2nd tertile 0.70-0.80 mm and 3rd tertile  $\geq 0.81$  mm.

† HRR, hazard rate ratios; CI, confidence interval.

‡ IMT, intima-media thickness; CCA, common carotid artery.

§ Adjusted for age, sex, low physical activity, smoking habits, systolic blood pressure, treatment for hypertension, presence of diabetes, LDL-cholesterol, HDL-cholesterol, triglycerides, and waist circumference.



**TABLE 4.** Adjusted hazard rate ratios (HRR) with 95 % confidence intervals for Stroke by common carotid intima-media thickness (IMT) and presence of plaque.

	No plaque		Plaque	
	Low IMT CCA†‡ HRR (95% CI)*	High IMT CCA† HRR (95% CI)	Low IMT CCA HRR (95% CI)	High IMT CCA HRR (95% CI)
<b>Stroke</b>	(cases n=11)	(cases n=19)	(cases n=16)	(cases n=40)
Adjusted for age and sex	1.00‡	2.61 (1.23, 5.54)	2.21 (1.02, 4.78)	3.44 (1.72, 6.89)
Adjusted for age, sex and risk factors§	1.00‡	2.60 (1.14, 5.97)	1.86 (0.78, 4.40)	2.37 (1.08, 5.19)

\* HRR, Hazard rate ratio; CI, confidence interval.

† IMT, intima-media thickness; CCA, common carotid artery; IMT CCA was divided into "low" and "high" at the mean (0.765 mm).

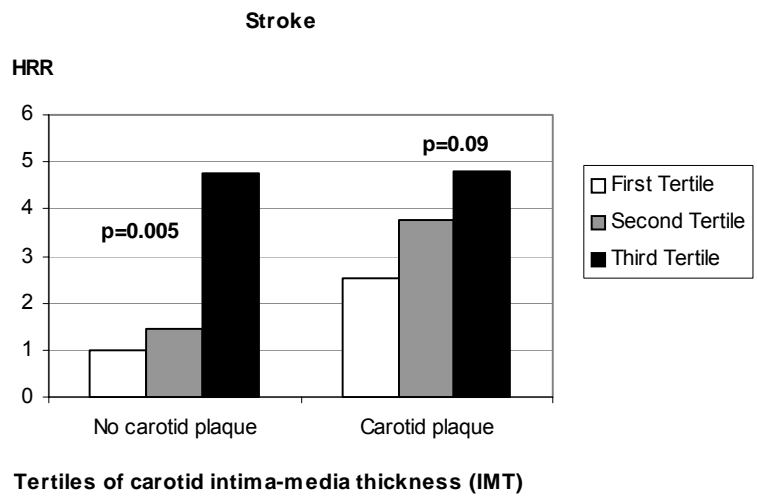
‡ Reference category

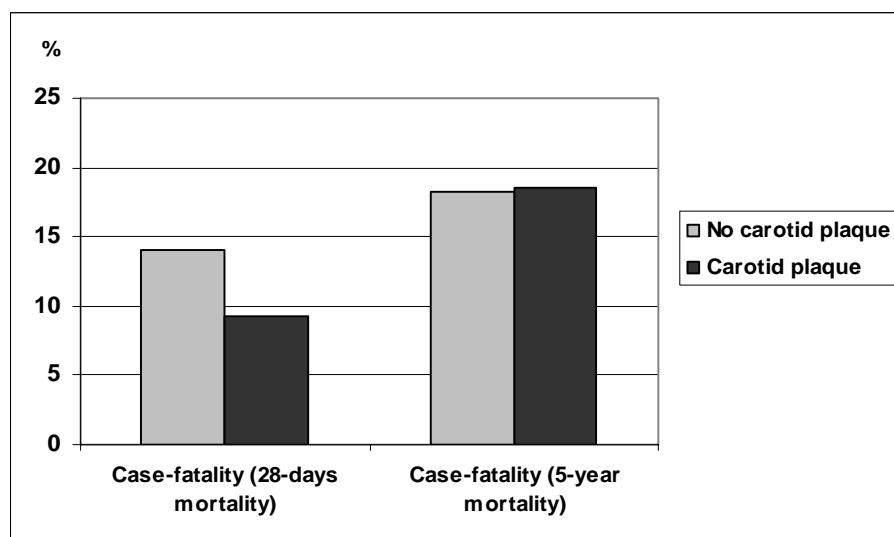
§ Adjusted for age, sex, low physical activity, smoking habits, systolic blood pressure, treatment for hypertension, presence of diabetes, LDL-cholesterol, HDL-cholesterol, triglycerides, and waist circumference.

## Legends

**Figure 1: Age-and sex-adjusted hazard rate ratios of incident stroke by tertiles of common carotid intima-media thickness (IMT) stratified by presence of carotid plaque. Subjects with no plaque and with common carotid IMT in the first tertile is used as the reference. P-values show p for trend among those with and without carotid plaque.**

**Figure 2: Case fatality (28-days and 5-year mortality) by carotid plaque after adjustment for age, sex, diagnosis and time to event.**





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