Atrial Fibrillation, Stroke, and Cognition
A Longitudinal Population-Based Study of People Aged 85 and Older

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Background and Purpose—The aim of this study was to investigate the association between atrial fibrillation (AF), stroke, dementia, and their correlation with brain pathology in subjects aged 85 years or older.

Methods—This is a prospective 9-year follow-up population based study in Vantaa, a town in Southern Finland; 553 subjects (92% of the total population) aged 85 years or older were clinically examined by a neurologist. The presence of AF was collected from the medical records or examined by ECG or ambulatory ECG. Neuropathological examination was conducted in more than half of the clinically examined subjects.

Results—AF was significantly associated with stroke at baseline; 32% of patients with AF had clinical evidence of stroke compared with 16.7% of those without such evidence (P<0.001). Dementia at baseline was significantly associated with age, clinical stroke, and the presence of apolipoprotein E ε4 allele, but not with sex, education, or vascular risk factors. Multiple regression analysis including neuropathological results showed that dementia was significantly associated with education (OR, 0.89; 95% CI, 0.80 to 0.98; P=0.019), the β-amyloid load in the brain (OR, 1.26; 95% CI, 1.13 to 1.39; P<0.001) and with the vascular pathology (OR, 2.03; 95% CI, 1.14 to 3.62; P=0.016), but not with sex, age at death, apolipoprotein E ε4 allele, or vascular risk factors.

Conclusions—AF is a significant and preventable risk factor for stroke but not for dementia in the very old. The etiology of dementia syndrome in the very old is multifactorial. Both Alzheimer disease pathology and vascular pathology, particularly multiple small infarcts, contribute to cognitive decline. (Stroke. 2007;38:1454-1460.)

Key Words: atrial fibrillation ▪ autopsy ▪ dementia ▪ elderly ▪ stroke

Atrial fibrillation (AF) is a well-known risk factor for stroke in the elderly.1-2 It has been estimated that AF accounts for approximately one-third of all stroke cases in individuals between 80 and 89 years of age.3 The brain seems to receive a majority (86%) of all symptomatic emboli in patients with AF.4 Also, 13% to 26% of patients with AF have clinically silent cerebral infarcts.5

Several studies have shown that AF predicts the development of poststroke dementia,6-7 whereas others have found no such association.8-9 In one study, the association between poststroke dementia and AF did not remain after controlling for the size and location of brain infarcts.10 Moreover, several studies suggest that AF patients have poor cognitive performance,11-13 and the presence of AF is associated with a decline of cognitive functioning during the follow-up also in the absence of a clinical stroke.14

Thus, the relationship between AF and cognition is complex and may not be explained by the increased frequency of strokes only. In the Rotterdam Study, in which dementia was twice as common in subjects with AF as in those without, AF seemed to exert its effect only partially through stroke. The association was stronger in subjects younger than 75 years and also stronger for Alzheimer disease (AD) rather than for vascular dementia.15 Another study suggested that vascular risk factors could be involved in or even promote the neuropathological changes occurring in AD.16

The aim of this study was to investigate the association between AF and stroke or dementia and their relationship with brain pathology in 553 subjects aged 85 years or older. The subjects were followed-up up to 9 years or until death, with a neuropathological examination performed on 290 clinically examined subjects. The specific objectives were to

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Subjects and Methods

The Vantaa 85+ Study is a prospective, longitudinal, population-based study including all residents aged 85 years or older living in Vantaa (n=601) on April 1, 1991. All subjects, whether living in institutions or at home, were included. The final cohort included 553 (92%) individuals; 11 persons refused to participate, 36 persons died before the clinical examination, and 1 could not be reached. The baseline clinical examinations took place between April 1, 1991 and March 12, 1992, and the follow-up evaluations were conducted in the years 1994, 1996, and 1999. Informed consent was obtained from all participants or from a close relative. The Ethics Committee of the city of Vantaa approved the study.

The evaluation included an interview of a participant and a knowledgeable informant by a trained nurse and a clinical examination by a physician. Information concerning health, health-related behavior, medical history, including all the illnesses and medication, was obtained from an electronic primary health care database that contains all primary care health records.

The diagnosis of dementia according to the DSM-III R criteria was based on data collected during the study: the neurologist’s clinical examination, Mini-Mental State Examination,24 and Short Portable Mental Status Questionnaire25 tests, and the Clinical Dementia Rating,20 Activities of Daily Living,21 and Instrumental Activities of Daily Living scales. Besides the subject, also the relatives, nurses, and other persons taking care of the subject were interviewed. Medical history was also available. The duration of the cognitive symptoms had to be at least 3 months to exclude, eg, delirium. The consensus of 2 neurologists was needed for the dementia diagnosis.

The diagnosis of clinical stroke was based on the history of previous transient ischemic attack or stroke in the medical records and the presence of clinical neurological focal signs indicating previous stroke examined by a neurologist. We also included in the stroke group 27 subjects without a history of cerebrovascular disease who had focal signs indicating stroke. These subjects had spastic hemiparesis with or without dysphasia and no other explanation for the neurological findings.

The diagnosis of AF was made if 12-lead ECG at rest or a short Holter ECG monitoring during the examination showed AF. Because these may fail to detect paroxysmal AF, also individuals with a history of chronic AF in the health records were included in the AF group. The Holter technique with 3 exploring electrodes attached approximately as V1, V2, and V5 was used. The average monitoring time was 1 hour. ECG or Holter recordings were available for 507 participants; ECG was not performed for 46 participants because of technical reasons, severe contractures, limb amputations, or agitation related to dementia. Altogether, 122 participants had AF; ECG or Holter showed AF in 97 participants and 25 additional subjects had a diagnosis of chronic AF in the health records.

A total of 306 deceased individuals from the original study population (n=601) had been autopsied by March 31, 2001. The brains were fixed in buffered 4% formalin for at least 2 weeks before the dissection. The gross and microscopic examinations were performed by one pathologist (T.P.) blinded to all clinical data. After the postmortem examination each brain was coded with a number. Multiple brains were collected during several months’ time periods for each brain dissection session. The clinical information and autopsy report were not available at the brain dissection. The exactly same dissection and examination protocol were used for each brain. Cavitory lesions or solid cerebral infarcts visible to the naked eye were identified by examination of the intact brain and from 1-cm-thick coronal slices of the cerebral hemispheres, from 5-mm-thick transverse slices of the brain stem and sagittal slices of the cerebellum. The size of each infarct was measured with a millimeter scale and their maximal dimension used for size categorization. Infarcts affecting the cerebral cortex were categorized as cortical infarcts. Infarcts in the cerebral white matter and/or subcortical gray matter were included in the subcortical infarct group if they did not extend to the cerebral cortex. The group of other infarcts included macroscopical ischemic lesions within the brain stem or cerebellum. All these lesions were subsequently histologically ascertained to be infarcts.

Samples were obtained from the middle frontal, superior temporal, and middle temporal gyri, and inferior parietal lobule for the estimation of the b-amyloid protein load in the neocortex. The fraction of the cortex covered by methenamine-silver-stained plaques was quantified as described previously21 on 8-μm-thick sections. Tissue blocks recommended for neuropathological staging of the neurofibrillary changes were obtained from the entorhinal cortex at the level of the mammillary bodies, from the hippocampus at the level of the lateral geniculate body, and from the occipital lobe, so that the striate area, parastriate field, and peristriate region were all represented in the same specimen. The tissue blocks were embedded in polyethylene glycol 1000, and then cut at a thickness of 80 μm for free-floating staining with the Gallyas silver method for neurofibrillary pathology.

The apolipoprotein E (APOE) genotyping was performed by the mini-sequence technique of Syvänen et al.26 using the modifications described by Miettinen et al.26

Dichotomous variables were compared with χ² test, and continuous variables were compared with t test or Kruskal-Wallis test. The odds ratios for different factors that might contribute to the baseline stroke or dementia were determined by logistic regression analysis with the backward Wald method. The associations between risk factors and incident stroke or dementia were analyzed with Cox proportional hazards model adjusted for age, sex, and underlying comorbidities (hypertension, myocardial infarction, congestive heart failure, diabetes, AF). Age was used as a categorical variable: 85 to 89 years, 90 to 94 years, and 95 years and older.

Statistical analyses were made by using SPSS for Windows program.

Results

Table 1 gives the baseline data of the study population. Clinical evidence of stroke was found in 20.1% and dementia in 38.7% of the participants at the baseline (Table 1); 79 participants (14.3%) had both stroke and dementia. Data on nonparticipants were collected from the medical records. There were no differences in average age or sex distribution between the participants and the nonparticipants. History of myocardial infarct, hypertension, and cardiac insufficiency was more common in the nonparticipants than in the participating subjects, whereas there was no difference in history of dementia or stroke according to the health records between the groups.

During the follow-up period up to 9 years, 479 participants died. The mean length of follow-up was 3.5 years. 269 participants were examined at the 3-year, 157 at the 5-year, and 62 at the 8-year follow-up. The median time from the last observation to death was 367 (1 to 2201) days.

AF and Clinical Stroke

The frequency of vascular risk factors in the study subjects is shown in Table 2. AF was diagnosed in 122 (22.1%) of the participants. AF was significantly associated with stroke at baseline; stroke was present in 39 (32%) of subjects with AF (n=431), P<0.001. Only 6 subjects (4.9%) with AF were using warfarin, and 25 (20.5%) were using acetylsalicylic acid.

Altogether, 42 subjects who did not have clinical stroke at baseline developed signs of clinical stroke during follow-up.
Information of recurrent stroke was not available. First-ever stroke was as common in participants with baseline AF (9.8%) as in those without (7.0%). In the Cox proportional hazards model adjusted for age, sex, and several vascular risk factors (hypertension, cardiac insufficiency, myocardial infarct, diabetes, and AF), dementia at baseline was a significant predictor for the development of a new stroke, with hazard ratio being 2.38 (95% CI, 1.20 to 4.73; P = 0.013).

**AF and Dementia**

Dementia at baseline was much more common in subjects who had clinical stroke than among the others (71.2% versus 30.5%; P < 0.001; Table 1). The presence of dementia at baseline did not differ between subjects with or without AF (41.0% versus 38.1%). Multivariate analysis showed that age, sex, education, diabetes, hypertension, cardiac insufficiency, myocardial infarct, or AF were not linked to dementia. The corresponding ORs were 1.85 (95% CI, 1.08 to 3.17; P = 0.024) for age 90 to 94 years; 3.52 (95% CI, 1.30 to 9.53; P = 0.013) for age 95 years and older; 2.71 (95% CI, 1.69 to 4.32; P < 0.001) for the presence of APOE e4 allele; and 5.66 (95% CI, 3.34 to 9.58; P < 0.001) for clinical stroke.

**TABLE 1. Demographic Data of the Study Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Dementia at Baseline</th>
<th>Stroke at Baseline</th>
<th>All</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean/SD)</td>
<td>89.0 (3.1)</td>
<td>88.0 (2.6)</td>
<td>88.5 (2.9)</td>
<td>88.4 (2.9)</td>
</tr>
<tr>
<td>Sex</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education (y)</td>
<td>3.9 (3.0)</td>
<td>4.2 (2.9)</td>
<td>3.2 (2.0)</td>
<td>4.3 (3.0)</td>
</tr>
<tr>
<td>MMSE (mean/SD)</td>
<td>8.3 (7.2)</td>
<td>23.2 (4.8)</td>
<td>11.3 (9.3)</td>
<td>19.0 (8.7)</td>
</tr>
<tr>
<td>Dementia (%)</td>
<td>79 (36.9)</td>
<td>32 (9.4)</td>
<td>79 (71.2)</td>
<td>135 (30.5)</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>79 (36.9)</td>
<td>32 (9.4)</td>
<td>79 (71.2)</td>
<td>135 (30.5)</td>
</tr>
</tbody>
</table>

*P < 0.01.

Altogether, 100 new dementia cases were diagnosed during the follow-up. The development of dementia during the follow-up did not differ significantly between subjects with or without AF (16.4% versus 18.6%). A new first-ever stroke during the follow-up was significantly associated with the development of dementia, with 65.5% of those showing evidence of a new stroke developed dementia as compared with 27.3% of those not having a new stroke (P < 0.001). In the Cox model adjusted for age, sex, and vascular risk factors, significant predictors for the development of dementia during the follow-up were APOE e4 allele (hazard ratio, 1.68; 95% CI, 1.05 to 2.70; P = 0.031), and occurrence of a new stroke (hazard ratio, 3.34; 95% CI, 1.91 to 5.83; P < 0.001), but clinical stroke at baseline was not significantly associated with the development of dementia.

**AF, Clinical Stroke, and Vascular Brain Pathology**

Neuropathological examinations were conducted in 290 subjects. Macroscopical brain infarcts were present in 70.4% of subjects with clinical stroke (n = 81) and in 46.4% of subjects without evidence of stroke (n = 209; P = 0.001). Clinical stroke was significantly more common in subjects with macroscopical brain infarcts than in individuals without these changes (Table 3).

A thrombic mass was found more often in the hearts of subjects with AF than in those without (5.6% versus 16.4%; P = 0.019). Although the general vascular pathology was not significantly more severe in subjects with AF than in those without (Table 3), multiple large ischemic lesions (≥2 larger than 15-mm-sized lesions) were more frequently found in patients with AF (14.6%) than in those not exhibiting AF (4.3%; P = 0.005). In the logistic regression analysis including age at death, sex, and the presence of vascular risk factors (diabetes, hypertension, myocardial infarction, cardiac insufficiency, and AF), only cardiac insufficiency was significantly associated with vascular brain pathology (OR, 1.64; 95% CI, 1.02 to 2.64; P = 0.04).

**AF and AD-Associated Pathology in the Brain**

Because AF was associated with probable AD in the Rotterdam study,16 we analyzed the relationship between AF and brain pathology. The amyloid load was not related to AF; the area covered by methenamine-silver–stained plaques was 3.29 (SD ± 3.61) in the AF group (n = 54) and 3.65 (SD ± 3.70) in patients without (n = 224; P = 0.517). Furthermore,
AF was not associated with the neurofibrillary pathology; the Braak stages 4 to 6 were found in 38.2% of subjects with (n=55) and in 45.5% of subjects without AF (n=235; P=0.869).

### Dementia and Brain Pathology

Clinically diagnosed dementia (at baseline or during the follow-up) was significantly associated with education (OR, 0.89; 95% CI, 0.80 to 0.98; P=0.019), β-amyloid load in the brain (OR, 1.26; 95% CI, 1.13 to 1.39; P<0.001), and with vascular pathology (OR, 2.03; 95% CI, 1.14 to 3.62; P=0.016), but not with sex, age at death, or APOE ε4 allele. Univariate analyses showed that dementia was more common in subjects with multiple large infarcts than in those with no or only one large infarct (77.8% versus 63.6%; P=0.020). However, when we included the size and location of the infarcts in the multiple regression analysis, significant predictors of dementia were the β-amyloid load in the brain (OR, 1.25; 95% CI, 1.13 to 1.39; P<0.001) and high number of small infarcts (<15 mm; OR, 1.34; 95% CI, 1.10 to 1.65; P=0.004), whereas education (OR, 0.88; 95% CI, 0.80 to 0.98; P=0.016) and lack of subcortical vascular pathology (OR, 0.39; 95% CI, 0.15 to 1.01; P=0.052) seemed to protect from dementia. Sex, age at death, APOE ε4 allele, or vascular risk factors showed no significant association with dementia. The Braak stage was also included in the final model, but it did not associate significantly with dementia (OR, 1.21; 95% CI, 0.97 to 1.50; P=0.097).

### Discussion

Recent epidemiological data suggest that vascular factors predispose to AD and cerebrovascular disease that are the most common causes of dementia, but there are few studies including the very old subjects. Yet subjects 80 years old or older represent the fastest growing segment of the population. Our population based study including subjects 85 years old or older showed that AF was significantly associated with stroke as well as with macroscopical brain infarcts, particularly with multiple large lesions, but it was not an independent predictor for dementia or AD pathology in the brain. Neuropathological correlates for dementia were amyloid load and multiple small infarcts.

In the present study including very old subjects, dementia at baseline was associated with age, the presence of the APOE ε4 allele, and clinical stroke, whereas sex, education, or vascular risk factors including AF were not linked to dementia. These findings contrast with other studies that have shown a positive association between AF and the development of poststroke dementia6,7,10 or poor cognitive performance,11–13,15 even in the absence of clinical stroke. The Rotterdam Study indicated that AF seems to exert its effect only partly through stroke.15 The other study showed that risk of conversion of mild cognitive impairment to dementia was higher in subjects with AF than in those without.27 In most studies the subjects have been younger than 85 years old. However, the relationship between AF and dementia remains unclear. Some studies suggest that AF is not a predictor for poststroke dementia,8,9 and 2 longitudinal studies that included subjects aged 75 years and older found no association between AF and cognitive decline.14,28 A previous Finnish study showed that AF was associated with cognitive decline after 5 years of follow-up but not at 10 years of follow-up.14

Stroke was a significant predictor of dementia in the present study. According to many studies, AF is associated with stroke, particularly in very old people.3,29,30 In our study, AF, detected in 22.1% of these very elderly people, was the only significant clinical vascular risk factor for stroke at the baseline. The prevalence of stroke at baseline was 32.0% in subjects with AF, whereas only 16.7% of individuals without AF had a history of stroke. However, AF was not associated with the development of a new stroke during the follow-up. This is not an unanticipated finding because previous studies suggest that the majority of strokes occur during the first 3 years after the development of AF.31 AF is related to large-artery cortical infarcts.32 Although the stroke type was not confirmed with brain imaging in the present study, the neuropathological examination revealed a significant association between AF and the presence of macroscopic brain infarcts, particularly multiple large infarcts. We did not find a significant association between AF and subcortical vascular pathology in the neuropathologically examined subpopulation.

Lack of an association between education and dementia was unexpected and may reflect a relative homogeneity of education in this cohort. However, studies in the very old are rare and have shown controversial results. In the Kungsholmen project, there was a significant influence of education on incidence of AD33; the Rotterdam Study suggested an increased risk for AD in women with low education,34 whereas The Cache County Study showed no significant association between education and the prevalence or incidence of AD.35 However, the Religious Olders Study suggested that education modifies the relation between AD pathology and level of cognitive function.36 In our study, education was significantly associated with dementia only in the model that included the neuropathological results.
The contribution of cerebrovascular pathology to the development of dementia seems to increase with age, and previous studies have suggested the role of small vessel disease in development of cognitive decline. In this study, prevalence of dementia in individuals with lifetime stroke was very high (75.7%), higher than found in the previous Swedish study (57%) that included subjects aged 85 years. The difference may be attributable to cohort differences. For example, 25% of the Swedish subjects had high education, whereas only 5% of our subjects had >9 years of education. Moreover, prevalence of dementia for those without stroke was also quite high (49.6%). Our results showed that dementia at baseline was a predictor for new incident strokes. These results agree with the findings in The Kungsholmen project, in which mild dementia at baseline was also associated with the development of a new stroke in the follow-up among subjects aged 75 years or older. Further analyses of the Kungsholmen study showed that APOE e4 allele was not associated with an increased risk of stroke or dementia with stroke, whereas it increased risk of dementia in those without stroke. Because the subjects with mild dementia in whom stroke developed were more likely to have vascular risk factors, the authors proposed that the cognitive impairment at baseline may actually have been a manifestation of a clinically unrecognized cerebrovascular disease.

The mechanisms underlying the relationship between stroke and dementia may be multiple. Stroke may be the main cause of dementia. Although multitude patient-related, stroke-related, and genetic factors influence the development of dementia, many cases of poststroke dementia may be attributable to undiagnosed pre-existing AD that is revealed after stroke. The Nun Study demonstrated neuropathological evidence that brain infarcts may decrease the threshold for the cognitive decline in AD. Our results agree with those reported in the Swedish studies. The development of first-ever stroke was associated with the development of dementia during the follow-up whereas stroke at baseline was not related to incident dementia. The direction of the association remained unclear because we did not have information concerning timing of the cognitive symptoms. Although the etiology of cognitive decline remained unclear in our patients, it is possible that a coexistent AD contributed to the development of dementia in many subjects. At least one-third of subjects with AD have coexistent cerebral infarcts and most have cerebral amyloid angiopathy, microvascular degeneration, or white matter changes related to small vessel disease. Experimental data suggest that cerebrovascular disease may precipitate neurodegenerative changes. Multitude patient-related, stroke-related, and genetic factors influence the development of dementia. Our neuropathological results showed that both AD pathology and vascular pathology, particularly multiple small infarcts and subcortical vascular pathology, were associated with dementia. However, because we do not know the order of the development of clinical symptoms (stroke and dementia) and brain pathology, we cannot exclude the influence of other possible confounders that contribute to these associations.

The strengths of the Vantaa 85+ study include the high participation rate (92%), the long follow-up time, and a high frequency of neuropathological examinations. However, our study has several limitations. For practical reasons, a 24 or 48-hour Holter analysis could not be included in the study protocol (and even these may have missed some cases of paroxysmal AF). The combination of a short Holter examination and the information obtained from the health records was used in stead. Some cases of asymptomatic, paroxysmal AF may have been missed, leading to erroneous classification of these individuals into the “no-AF group.” We believe that the number of these cases is small, but this remains a potential source of bias in our study. The assessment of presence of stroke was based on clinical examination and electronic primary health care database but neuroimaging was lacking in most subjects. Therefore, the subtype of stroke remained unclear. It is possible that we may have missed some stroke cases because we used medical records for collection of medical history. One previous study showed that the prevalence of stroke increased from 13% based on inpatient hospital data to 18.8% when information from 3 different sources were used. Even though hospitalization for stroke may be lower in the very old, it is probable that most subjects visit general practitioner when the acute symptoms develop. We also included 27 subjects without a history of an acute cerebrovascular incident in the stroke group because they had focal signs suggesting stroke. The inter-rater reliability of most items of neurological assessment and the clinical diagnosis of stroke have been shown to be moderate or better. The neuropathological results in this study confirmed that the subjects classified in the clinical stroke group did have significant vascular pathology and there was a significant association between clinical stroke and the presence of macroscopic brain infarcts, particularly multiple large infarcts. Another limitation in our study is lack of comprehensive neuropsychological examination. Mini-Mental State Examination is too crude an instrument to reveal subtle cognitive changes and it is not sensitive for problems in executive functions. Therefore, we focused only on cognitive decline severe enough to be defined as dementia. The median interval between the last observation and death was 367 days, and it is possible that some subjects had dementia develop after the last observation. However, 72.1% of the subjects died in the long-term care institutions, and information of cognitive status until death was available from their medical records. Yet it is possible that we may have missed cases with mild dementia. One shortcoming of the study is lack of etiological diagnosis of dementia. However, many studies have shown that mixed pathology is common in very old patients with dementia. We think that neuropathological examination in more than half of the subjects overcomes this deficiency to a great extent and made it possible to examine neuropathological correlates of dementia. The causality between AF and stroke and stroke and dementia remains unclear because of insufficient information. Although the exact date of cerebrovascular incident was available from medical records, duration of AF was not known in most subjects. Also, reliable information on the first symptoms of cognitive decline was not available in a considerable number of the participants. We did not use any corrections to reduce for the possibility of the type 1 error from multiple compar-
isions, and it is possible that some associations occurred by chance. However, we believe that the associations between AF and stroke, and stroke and cognitive decline, are true relationships because they were consistently found in the analyses, even after controlling for relevant confounders.

Our study confirms that AF is a significant risk factor for stroke in the very old. Because stroke is related to cognitive decline, AF can be considered as being one contributor to dementia, although it is not an independent predictor of dementia. The use of anticoagulation or antiaggregative treatment was extremely low in subjects with AF, and this is one possible reason for the high prevalence of strokes. We do not know how many of our subjects had contraindications for the use of warfarin, but probably, at least partially, the low rate is related to attitudes and concerns of serious adverse events. Previous studies have shown that warfarin is underused, particularly in the oldest old. Prevention of stroke in subjects with AF may be one possible way to help to maintain independent functioning among the very old.

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Disclosures
None.

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