Non-Rheumatic Atrial Fibrillation as a Risk Factor for Stroke

Mona Britton, M.D., and Claes Gustafsson, M.D.

SUMMARY The association between non-rheumatic atrial fibrillation (AF) and stroke has been studied in 402 patients consecutively admitted to a stroke unit. Brain infarction patients with sinus rhythm (n = 196) and non-rheumatic AF (n = 92) were further compared. Some findings supported an embolic origin of the stroke: half of the deceased AF patients (n = 24) at autopsy either had left atrial thrombosis or arterial embolism compared to none of the ten with sinus rhythm. Patients with AF also had a higher mortality and more severe brain lesions, findings compatible with a sudden occlusion of blood flow. However, these differences might also be explained by an atherothrombotic occlusion with impaired autoregulation in the ischaemic region in conjunction with heart failure, which was more common in the AF patients. Other findings supporting an atherothrombotic mechanism were: the prevalence of AF was higher (19–29%) in all kinds of stroke, including haemorrhage, than in age-matched controls (3–9%). Also patients with previous AF and no present embolic source resembled the whole AF group and differed from patients with sinus rhythm. Thus embolism is a plausible cause of stroke in many AF patients, whereas an atherothrombotic origin is more likely in others. Characteristics identifying the mechanism in an individual case were not found.

Patients and Methods

Between October 1976 and December 1979, 402 patients with cerebrovascular diseases were treated in the Stroke Unit at the Medical Department of Serafimerlasarettet, Stockholm. Criteria for admission, organization of the unit and diagnostic definitions have been described elsewhere. The material comprised 200 men and 202 women of mean age 73 years (men 71, women 75 years). As a basis for diagnosis, the results of the following investigations were used: ordinary clinical procedure, routine laboratory tests, ECG and chest X-ray. Lumbar puncture with CSF analysis including spectrophotometry was performed in 95% of the cases and brain scan in 82%. From May 1978 computerized axial tomography (CT) was also included and 45% of the patients were examined by this method as well. Autopsy was performed in 90% of deceased patients. Totally, CT or autopsy were performed in 55% of the material. In the remainder 180 cases CSF and brain scan constituted the basis. Hereby haemorrhages might be missed in 2–3 out of 100 stroke patients and overdiagnosed in as many. Possible diagnostic errors in the study material were therefore few and similar in the AF and SR groups.

Patients with brain infarction (n = 318) were further studied (fig. 1). Seven patients were excluded due to missing ECG and 23 because of possible rheumatic heart disease. Such was earlier diagnosed in 4 subjects and compatible with the history and physical findings in another 19. RHD was verified in two of these patients who came to autopsy. No clinically defined non-rheumatic AF were disproved post mortem. The remaining 288 patients were divided into three groups according to the occurrence of ECG-verified AF: chronic AF (n = 61) — constant AF during hospital stay, with or without earlier known AF, paroxysmal AF (n = 31) — inconstant occurrence of AF during hospital stay or earlier diagnosed episodes of AF, sinus rhythm (SR) — no known episodes of AF during hospital stay or earlier. The mean ages in the two AF groups were 77 and 76 years respectively and signifi-
ATRIAL FIBRILLATION IN STROKE/Britton and Gustafsson

STROKE PATIENTS

TIA 45
CEREBRAL HAEMORRHAGE 32
ECG MISSING 5
UNSPECIFIED 7

FIGURE 1. Diagnostic distribution in 402 consecutive stroke patients. Brain infarction patients are divided into three groups according to their heart rhythm. For each group sex distributions and mean age are given. RHD = rheumatic heart disease.

The prevalence of AF increased with increasing age of patients. It was higher in all the cerebrovascular groups than in the surgical but was especially high among patients with cerebral infarction. Risk Factors and Arteriosclerotic Manifestations in Brain Infarction Patients With and Without AF

As shown in table 1, there were more smokers in the SR group. Most previous circulatory diseases were equally distributed. However, a history of heart failure was more than twice as common among AF patients. This was confirmed by more frequent X-ray findings of heart enlargement and pulmonary congestion. The AF patients also had lower toe blood pressure more often and slightly lower blood pressure at admission and on day 1 but not later on. No other differences in arteriosclerotic or hypertensive manifestations were noted.
### Table 1  
**Risk Factors, Arteriosclerotic and Hypertensive Manifestations in Brain Infarction Patients with AF and SR**

<table>
<thead>
<tr>
<th>Patient history data, %</th>
<th>AF n = 92</th>
<th>SR n = 196</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>37</td>
<td>49</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>63</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>27</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption (n = 154)* ≥ 667 g/year</td>
<td>28</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>None of the above mentioned factors</td>
<td>17</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>34</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>16</td>
<td>33</td>
<td>*p &lt; 0.01</td>
</tr>
</tbody>
</table>

**Hospital findings**

- Mean blood pressure, mm Hg:
  - On admission: 173/94 vs 180/95, *p < 0.05/NS*
  - Day 1: 161/85 vs 171/90, *p < 0.01/p < 0.01*
- Toe blood pressure (n = 82)*: 78 vs 55, *p < 0.05*
- Carotic bruits, %: 8 vs 10
- ECG, %:
  - Normal (except rhythm): 7 vs 16, *p < 0.05*
  - Signs of earlier infarction: 23 vs 19
  - Left ventricular hypertrophy: 3 vs 4
  - Bundle branch block: 19 vs 19
- Chest X-ray: %
  - Heart enlargement: 53 vs 17, *p < 0.001*
  - Pulmonary congestion: 49 vs 18, *p < 0.001*

**Laboratory data, mean values**

<table>
<thead>
<tr>
<th></th>
<th>AF</th>
<th>SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin, g/l</td>
<td>146</td>
<td>142</td>
</tr>
<tr>
<td>Haematocrit, %</td>
<td>44</td>
<td>43</td>
</tr>
</tbody>
</table>
| Blood glucose, mmol/l| 6.8      | 6.0      | *p < 0.01*
| Triglycerides, mmol/l| 1.4      | 1.7      | *p < 0.05*
| Cholesterol, mmol/l  | 5.9      | 6.5      | *p < 0.05*
| Prothrombin, %       | 76.4     | 84.1     | *p < 0.001*
| Platelets, x 10^9/l  | 221      | 219      |
| Leucocytes, x 10^9/l | 8.8      | 7.5      | *p < 0.01*

*No. of patients participating in investigations limited to parts of the material.

Concentrations, prothrombin values and leucocyte counts also differed between the groups.

No difference in causes of death could be seen between those with AF or SR. Autopsies were performed in 34 of the deceased. The AF group had left auricular thrombi in 21% of cases (5/24) and peripheral emboli (spleen, kidney, femoral or mesenterial artery) in one third (9/24). In the ten autopsied SR patients neither atrial thrombosis nor peripheral embolism was found. Occlusion of the relevant cerebral artery was found in 40% of cases, a similar proportion in both groups. It could be classified as embolic in three of the AF cases. In the remaining seven the pathogenesis of the occlusion could not be determined, nor in the four patients with occlusion in the SR group.

### Brain Lesion Characteristics in Brain Infarction Patients With and Without AF

The symptoms were known to have occurred suddenly in 50–60% of cases in both groups. Paresis was the dominating symptom. Seizure at debut or in the first hours occurred in 7% of the AF group compared to 2% of the SR group (*p > 0.05*). No difference was seen between the groups as regards the location of the lesions.

At admission to hospital the AF group had several signs of more serious brain damage than the SR group (table 3). The condition of AF patients was worse as evaluated by level of consciousness, ability to walk and total neurological score. Mortality was higher (in...
Haemorrhagic components were looked for. Nor were differences between the groups as regards mean protein concentration or degree of xanthochromia as measured spectrophotometrically.

Haemorrhagic infarctions at CT or autopsy were found in about the same frequency in both groups. Nor was there any difference when only CSF findings of haemorrhagic components were looked for.

### Table 3

<table>
<thead>
<tr>
<th>Brain Lesion Characteristics in 288 Patients with AF and SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>&lt;59</td>
</tr>
<tr>
<td>60-69</td>
</tr>
<tr>
<td>70-79</td>
</tr>
<tr>
<td>80+</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition on admission</th>
<th>AF</th>
<th>SR</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological score, mean points</td>
<td>53</td>
<td>67</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Impaired consciousness, %</td>
<td>33</td>
<td>10</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Cannot walk independently, %</td>
<td>77</td>
<td>64</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>26</td>
<td>5</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>&lt; 70 years</td>
<td>26</td>
<td>8</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>70-77 years</td>
<td>26</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>&gt; 77 years</td>
<td>26</td>
<td>7</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Brain scan and CT findings, %
- Brain scan (n = 233)*: Positive, % | 63 | 37 | p < 0.001 |
- CT (n = 127)*: infarction visible, % | 56 | 35 | p < 0.05 |
- Brain scan or CT (n = 247)*: Positive findings, % | 68 | 42 | p < 0.001 |
- Haemorrhagic infarction, % | 11 | 2 |
- Revealed at autopsy (n = 34)* | 42 | 50 |
- CSF: Haemorrhagic component in cerebral infarction verified at CT or autopsy (n = 156) | 6 | 12 |

*Differences Between Patients with Chronic and Paroxysmal AF*

The paroxysmal AF group was rather heterogenous. In one third of the patients AF had been recorded earlier but never during the present hospital stay. In spite of this, the blood pressure tended to be lower, as did the frequency of heart enlargement. The higher blood glucose level in AF than SR patients was mainly confined to the paroxysmal group. Thus the two AF groups turned out to be similar in most respects and with common differences when compared to the SR patients (table 4).

### Analysis of the Present Material According to Suggestions by Hart et al.15

When our study was finished this journal published a paper by Hart et al15 who were also questioning embolism as the sole pathogenetic mechanism of stroke in patients with nonvalvular AF. Fifty-six cases were classified as probably embolic, nonembolic and indeterminate on the basis of clinical characteristics. Abrupt onset while awake, no further progress, history of embolic episodes, young age, absence of carotid artery stenosis, bilateral CT infarcts ie, were considered signs of embolism. We divided our material accordingly (table 4). The proportion of embolic strokes was 19% in our material compared to 63% in that of Hart. Possible reasons for the discrepancy were: Our patients were six years older, frequent regular controls were done to detect progression of symptoms. As a patient could have characteristics fitting into more than one group the classification was open for varying interpretations. Also, we did not alter the primary group division according to autopsy results. Instead we used them to evaluate correctness of the clinically based classification. Thus it was evident that embolism was revealed in a high extent of deceased patients even when clinically classified as nonembolic. Except as regards factors included in the definition the three Hart groups turned out similar to our original groups of chronic and paroxysmal AF with common differences as compared to the brain infarction patients with sinus rhythm (table 4).

### Discussion

The most striking findings in this study were that AF was more common in patients with stroke than among controls. The AF patients were older and had more serious brain damage than those with SR. Some factors

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*No. of patients investigated.*

Neurological score as modified after Mathew, 100 points = normal function. CSF findings of a haemorrhagic component = protein conc. > 1 g/l and/or spectrophotometric absorbance ≥ 0.040 at 415 nm.14
have to be dealt with before discussing whether these and other differences between the groups favour an athero-thrombotic or embolic origin of stroke in AF patients.

We chose to compare all patients with AF with those with SR. It has been claimed that a sudden onset of maximum symptoms in a patient with an embolic source, like AF, is typical of embolism.\textsuperscript{16,17} On the other hand a stepwise or gradual debut has been shown to occur in some patients.\textsuperscript{16,18} We found progression of symptoms after arrival at hospital to be as common among AF patients as among others.\textsuperscript{16,18} Therefore it was not possible to define a subsample within the non-rheumatic AF group in which embolism would be more likely. Furthermore, we divided our AF patients in the same way as Hart et al have presented.\textsuperscript{15} Still, the same main differences appeared as in the whole material in comparison to the SR group.

Then what do the present findings suggest as regards the pathogenetic mechanism underlying the increased incidence of stroke in AF? We found considerable evidence arguing against embolism. The prevalence of AF in stroke patients was much higher than in the matched surgical controls and also as compared to the 3–7% found in a Swedish population study of 75-year-old persons.\textsuperscript{20} However, AF was also common among patients with haemorrhage which is difficult to explain by the embolism theory.

The AF patients were moreover older, reflecting the increasing prevalence of AF with increasing age. More extensive arteriosclerosis was also noted through the finding of a higher proportion of pathologically lowered toe blood pressure and fewer, normal ECGs in AF patients. Arteriosclerotic macro- and microangiopathy progressing with age, might instead be the cause of the stroke as well as the heart disease. The latter can either reveal itself by AF leading to heart failure, or as heart failure which in turn provokes AF.

Further evidence against the embolic theory was the findings in the paroxysmal AF group. Even patients with previous AF and no present embolic source were similar to the whole AF group in all main aspects and differed from patients with SR.

High haematocrit values are associated with a risk of thrombotic disease.\textsuperscript{21,22} No difference in mean values, or in the proportion of pathologically raised ones, were seen between the two groups. Haemorrhagic infarctions, claimed to be more common after embolism,\textsuperscript{18,23} were found in half of the deceased whether AF or not. Only a few haemorrhagic infarctions were revealed by CT in both groups.

The AF group had higher blood glucose levels known to be associated with a worsened prognosis.\textsuperscript{24} Patients with normal blood glucose (<6.0 mmol/l) though, still differed from the control group. Both the raised concentrations of blood glucose and leucocytes
might also be connected with the more serious brain lesions in this group.25,26

There was, however, also evidence favouring an embolic cause of stroke in AF patients. In 50% of those who died, atrial thrombosis or signs of arterial embolism were revealed at autopsy whereas such findings were absent in the autopsied SR patients. This is in accordance with results from previous autopsy studies.6,7 Atrial thrombosis has also been confirmed in vivo in 27% of stroke patients with AF by pulmonary cine-angiography, whereas such findings were much more uncommon in the absence of arrhythmia.8 Jorgensen and Torvik have shown that in cases in which cerebral embolism was revealed at autopsy, 82% had suffered from AF compared to 32% of those with cerebral thrombosis.27 In a surgical material, in which peripheral embolism had been proven at surgery, 72% of the patients had AF.28

The findings in this study of more severe brain damage in AF patients may also argue in favour of embolism. A sudden interruption of blood flow caused by an embolus might give rise to larger infarctions than a gradual occlusion with opportunity for development of the collateral circulation. More severe lesions in embolic strokes have also been found at autopsy by Jorgensen and Torvik.28 In some clinical materials where this problem was analyzed, AF was noted to be associated with a worse prognosis25,29 but this was not so in the Framingham study.30

There might be other explanations than embolism for the poor outcome of stroke in AF patients. Their blood pressure was somewhat lower. A decreased cardiac output due to the higher incidence of heart failure might also contribute to a reduced cerebral blood flow when autoregulatory mechanisms are impaired as in an ischaemic region.31

We would like to conclude that embolism is a plausible cause of stroke in many AF patients. In a large group though, an atherothrombotic origin may be more likely. We have not been able to find any characteristics helpful in defining which mechanism is involved in an individual case. Nor have we found convincing evidence in the literature for assured recognition of embolism. The most promising, but not practicable, methods so far presented might be an immediate carotid angiography or pulmonary cine-angiography.8

Anyhow, brain infarction in non-rheumatic AF patients, taken as a group, constitutes a special problem. The patients are worse struck than others and therefore make up a "high risk" group for which acute treatment trials would be especially indicated. Also available data point to a favourable effect of secondary prophylaxis with anticoagulants in these patients.32,33

Another possibility would be to attack the AF problem primarily. Not only do these patients have increased incidence of stroke but also their strokes are more serious. Primary prophylaxis with anticoagulants might therefore be considered. However, this treatment is difficult, many patients are old and contraindications often exist. Due to the likely atherothrombotic pathogenesis in a considerable number of patients, there is also a rationale for a much easier prophylactic treatment with, for example, aspirin.

Acknowledgments

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23. Fisher CM, Adams RD: Observations on brain embolism with
The Incidence of Stroke in the Kuopio Area of East Finland

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SUMMARY During a 20-month study period there were 373 strokes in a geographically defined population (235/100,000/year). When age and sex were adjusted to the mean population of Finland in 1979, the annual incidence of stroke was 270/100,000 persons. The distribution of incident cases by diagnostic category was as follows: cerebral infarction 80%, ICH 9%, SAH 8% and NOS 3%. Case fatality of stroke within one year was 37%. The recurrence rate was 6% during the first year after any stroke.

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IN THE COLLABORATIVE STUDY coordinated by WHO from 1971 to 1974 the incidence of stroke was investigated in 17 populations.1 The annual age and sex adjusted incidence rates for first stroke varied from 0.24 to 2.87/1000 persons. The lowest rate was observed in Sri Lanka and the highest rate in Japan. Two Finnish populations were included in this study. The population of North Karelia county had an annual incidence rate of 1.71/1000 persons and it was fourth highest; the population of Espoo and Kauniainen towns in Southern Finland had an incidence rate of 1.17/1000 persons, which was seventh highest among the WHO study populations.

The purpose of the present study was to determine the incidence and prognosis of stroke in four communities of the Kuopio county in East Finland.

Study Population and Methods

The Department of Neurology at the University Hospital of Kuopio started a Stroke Register for the Kuopio area on October 1st, 1978. The register functioned for twenty months, up to May 31, 1980. The study area consisted of one town, Kuopio, and three rural communities (fig. 1). The study was based on the population of this area. The distribution of the total population was: Kuopio 73,733 and the rural communities 21,687. Thus the majority of the study population consisted of urban inhabitants.

All new cases of stroke in the study population were registered during the study period. The clinical examination was scheduled to take place as soon as possible after the onset of symptoms. Most of the patients included in the register were examined by one of the authors (JS) (74%), some examinations were performed by a consulting neurologist or by the neurologist on duty (17%). The remaining 9% of the patients were cases, who died in the very early phase of the stroke, so that neurologist’s examination was not possible. In such occurrences the patients’ hospital files and possible autopsy documents were decisive in taking the patient to the study.

Prior to the study all general practitioners (25) in the area were personally asked to send all new cases of stroke either to the emergency unit or to the outpatient department of Kuopio University Hospital. During the study physicians repeatedly stated, when contacted, that only mild cases of stroke were treated at home in extremely exceptional circumstances.

All death certificates of the study population were

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