- 11 Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. *Am J Med* 1989;87:144-52.
- 12 Lundström T, Ryde'n L. Haemorrhagic and thrombotic complications in patients with atrial fibrillation on anticoagulant prophylaxis. *J Int Med* 1989;225:137-42.
- 13 Carlsson A, Gustafsson C. Blödningskomplikationer till antikoagulantabehandling. Abstract vid workshop om förmaksflimmer. *Läkemedelsverket* 1992;1:21-4.
- 14 Wintzen AR, de Jonge H, Loeglinger EA, Bots GTAM. The risk of intracerebral hemorrhage during oral anticoagulant treatment: a population study. *Ann Neurol* 1984;16:553-8.
- 15 UK-TIA Study Group. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry* 1991;54:1044-54.
- 16 Terent A. Kostnader för stroke vård. *Läkartidningen* (in press).
- 17 Persson U, Silverberg R, Lindgren B, Norrving B, Jadback G, Johansson B, et al. Direct costs of stroke for a Swedish population. *Int J Technol Assess Health Care* 1990;6:125-37.
- 18 *Stroke. Towards better management*. London: Royal College of Physicians, 1989.
- 19 Isard PA, Forbes JF. The cost of stroke to the National Health Service in Scotland. *Cerebrovasc Dis* 1992;2:47-50.
- 20 Swedish Bureau of Statistics. *Arbetskraftsundersökningen, Årsmedeltal 1990*. Stockholm: Swedish Bureau of Statistics, 1990.
- 21 Swedish Bureau of Statistics. *Inkomstfördelningsundersökningen 1989*. Stockholm: Swedish Bureau of Statistics, 1989. (BE 21 SM 9101.)
- 22 Swedish Bureau of Statistics. *Färdtjänst 31 December 1990*. Stockholm: Swedish Bureau of Statistics, 1990. (S 20 SM 9101.)
- 23 Lancaster TR, Singer DE, Sheehan MA, Oertel LB, Maravantes SW, Hughes RA, et al. The impact of long-term warfarin therapy on quality of life. *Arch Intern Med* 1991;151:1944-9.
- 24 The Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation. I. Clinical features of patients at risk. *Ann Intern Med* 1992;116:1-5.
- 25 The Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation. II. Echocardiographic features of patients at risk. *Ann Intern Med* 1992;116:6-12.

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Atrial fibrillation and stroke: prevalence in different types of stroke and influence on early and long term prognosis (Oxfordshire community stroke project)

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Abstract

Objective—To determine in patients with first ever stroke whether atrial fibrillation influences clinical features, the need to perform computed tomography, and prognosis.

Design—Observational cohort study with maximum follow up of 6·5 years.

Setting—Primary care, based on 10 general practices in urban and rural Oxfordshire.

Subjects—Consecutive series of 675 patients with first ever stroke registered in the Oxfordshire community stroke project.

Main outcome measures—Prevalence of atrial fibrillation by type of stroke; effect of atrial fibrillation on case fatality rate and risk of recurrent stroke, vascular death, and death from all causes.

Results—Prevalence of atrial fibrillation was 17% (95% confidence interval 14% to 20%) for all stroke types (115/675), 18% (15% to 21%) for cerebral infarction (97/545), 11% (4% to 11%) for primary intracerebral haemorrhage (7/66), and 0% (0 to 11%) for subarachnoid haemorrhage (0/33). For patients with cerebral infarction the 30 day case fatality rate was significantly higher with atrial fibrillation (23%) than with sinus rhythm (8%); the risk of early recurrent stroke (within 30 days) was 1% with atrial fibrillation and 4% with sinus rhythm. In patients who survived at least 30 days the average annual risk of recurrent stroke was 8·2% (5·9% to 10·9%) with sinus rhythm and 11% (6·0% to 17·3%) with atrial fibrillation.

Conclusions—After a first stroke atrial fibrillation was not associated with a definite excess risk of recurrent stroke, either within 30 days or within the first few years. Survivors with and without atrial fibrillation had a clinically important absolute risk of further serious vascular events.

Introduction

People with atrial fibrillation have an increased risk of stroke compared with people with sinus rhythm¹⁻¹⁰; if the arrhythmia is not associated with valvular heart disease the increase in risk may be only slight^{10 11} or even non-existent.⁸ Primary prevention of stroke has been studied in several randomised trials in patients

with atrial fibrillation, the results suggesting that a 3-6% annual risk of stroke can be reduced by at least 20-40% with anticoagulant or antiplatelet treatment.¹²⁻¹⁴ Once a stroke has occurred it is not clear whether the subsequent early and long term risks of death or recurrent stroke are significantly different in patients with and without atrial fibrillation. Some studies have suggested that atrial fibrillation is associated with an increased risk of death in the first four weeks after a stroke^{15 16} whereas another has not.² Similarly, some studies have suggested substantially higher early and long term risk of recurrent stroke in patients with atrial fibrillation compared with sinus rhythm¹⁷⁻¹⁹ whereas others suggested little if any difference.^{2 20} The aim of this study was to determine the contribution of atrial fibrillation to the causation of different types of stroke and to the early and long term risks of death and recurrent stroke after a first stroke, thereby identifying priorities in the early and long term management of patients with stroke and atrial fibrillation. A study of prognosis should satisfy certain methodological criteria.²¹ The Oxfordshire community stroke project satisfies most, if not all, of these criteria.^{22 23}

Patients and methods

The methods used in the Oxfordshire community stroke project and the characteristics of the cohort of patients with stroke have been described elsewhere.^{22 23} Briefly, it was a prospective community based register of all new cases of acute cerebrovascular disease, including cases of stroke and transient ischaemic attack, occurring in a defined population of about 105 000 residents of Oxfordshire. Meticulous case ascertainment methods were used to detect cases whether patients were admitted to hospital, managed at home, or treated elsewhere while temporarily resident outside Oxfordshire. All patients were seen as soon after the event as possible by one of the neurologists on the study (PS, JB, MD, JB, or CW) and basic investigations including electrocardiography, chest radiography, and computed tomography were performed. If computed tomography could not be performed and the patient died every effort was made to obtain a necropsy to determine the pathological type

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of stroke. The classification and definitions of the different pathological types of stroke are detailed elsewhere.^{22 23}

We included only patients with their first ever stroke. Detailed definitions of the subtypes of cerebral infarction are given elsewhere.^{24 25}

Definition of atrial fibrillation—The diagnosis of atrial fibrillation must (a) have been confirmed by an electrocardiogram showing either absent p waves or atrial flutter with an irregular ventricular response and (b) have been documented before the stroke, at the time of assessment by the project team, or within one month after the onset of the first stroke. Patients first found to have atrial fibrillation more than one month after the stroke who did not have atrial fibrillation at the time of the stroke or before were classified as having sinus rhythm. Ambulatory monitoring of electrocardiograms was not routinely performed.

Follow up—Two research nurses followed up the patients at one month, six months, one year, and annually thereafter. Patients who left the area were traced through their general practitioner. The final follow up examination of all survivors irrespective of their area of residence was performed by one of the study neurologists between August 1987 and October 1988.

Recurrent stroke and vascular death—All patients with suspected recurrent stroke were re-examined by one of the study neurologists as soon after the event as possible; the clinical data on all such events were then reviewed at regular consensus meetings of the study team. At the final follow up examination by the neurologist all medical records (including the general practitioners') that related to any suspected recurrent

stroke were reviewed. Events were then classified as a definite recurrence if there was clear clinical evidence of the sudden onset of a new neurological deficit, or an increase in an existing deficit, for which no explanation other than a recurrent stroke could be found. Vascular death included deaths due to either the initial or recurrent stroke as well as sudden and unexplained death, sudden death presumed to have cardiac causes, death associated with cardiac disease, and death due to other vascular causes—for example, a ruptured aortic aneurysm. We planned analyses of survival in patients with cerebral infarction and in patients who survived at least 30 days after the first stroke.

Statistical methods—Confidence intervals for proportions, odds ratios, and differences of proportions were estimated using standard methods^{26 27}; odds ratios were adjusted using log linear modelling. p Values for two by two contingency tables were calculated from the χ^2 statistic, or from Fisher's exact test²⁷ when one or more expected cell frequencies were less than 5. For tables with more cells the Mantel-Haenszel procedure was used to calculate a summary statistic and derive the odds ratio.²⁷

Results

PREVALENCE OF ATRIAL FIBRILLATION IN DIFFERENT TYPES OF STROKE

In all, 115 out of 675 patients (17%) had atrial fibrillation documented by electrocardiography. The prevalence of atrial fibrillation in the different pathological types of stroke and in different subtypes of cerebral infarction and the number known to have atrial fibrillation before stroke is given in table I.

CLINICAL FEATURES IN PATIENTS WITH AND WITHOUT ATRIAL FIBRILLATION

The mean ages of patients with atrial fibrillation and sinus rhythm were 77 (SD 8.8) and 70.6 (13.7) years respectively; the difference was significant ($p < 0.0001$). The prevalence of vascular risk factors, of clinical evidence of large artery disease, and of valvar heart disease associated with atrial fibrillation is given in table II. Thyroid function was not systematically measured in all patients, but review of medical records in a subsample (a consecutive series of the first 323 cases of first stroke registered by the Oxfordshire community stroke project) showed that only one of the 46 patients with atrial fibrillation (2% (95% confidence interval 0 to 6%)) had thyrotoxicosis.

USE OF ANTIPLATELET AND ANTICOAGULANT TREATMENT

Before stroke—Twenty nine of the 675 patients (4.3%) and 11 of the 115 (9.6%) patients with atrial fibrillation were receiving antiplatelet treatment when the stroke occurred. Seven of the 675 (1.0%) patients and four of the 115 (3.5%) patients with atrial fibrillation were taking oral anticoagulants when the stroke occurred.

After stroke—Antiplatelet and anticoagulant treatment were not used systematically after stroke. Of the 97 patients with atrial fibrillation and cerebral infarction, 21 received anticoagulant and 16 antiplatelet treatment at some time after the stroke; few of them were given long term maintenance treatment.

CASE FATALITY RATES AT 30 DAYS

In general, the case fatality rates at 30 days were significantly higher in patients with atrial fibrillation (table III); the twofold or threefold differences were not significant for all subgroups. The differences were significant for all stroke types combined and in patients with cerebral infarction. In patients with cerebral infarction the case fatality rates at 30 days were 23% (14.8% to 32.3%) in those with atrial fibrillation

TABLE I—Prevalence of atrial fibrillation in different types of stroke and subtypes of cerebral infarction. Prevalence in transient ischaemic attacks²⁸ is shown for comparison

	Patients with atrial fibrillation at any time*			Patients with atrial fibrillation before stroke		
	No	%	95% Confidence interval	No	%	95% Confidence interval
Type of stroke:						
Cerebral infarction (n=545)	97	18	15 to 21	61	63	52 to 72
Primary intracerebral haemorrhage (n=66)	7	11	4 to 11	5	71	29 to 96
Subarachnoid haemorrhage (n=33)	0	0	0 to 11	0	0	
Not known (n=31)	11	35	19 to 55	7	64	31 to 89
All (n=675)	115	17	14 to 20	73	63	55 to 72
Transient ischaemic attack (n=184)	26	14	9 to 19	Not known	Not known	
Subtype of cerebral infarction (n=543)†:						
Lacunar (n=137)	18	13	7 to 19	9	50	27 to 73
Partial anterior circulation (n=185)	35	19	13 to 25	24	69	53 to 84
Posterior circulation (n=129)	15	12	6 to 17	10	67	38 to 88
Total anterior circulation (n=92)	28	30	20 to 40	17	61	41 to 78

*Before stroke, at time of stroke, within 1 month after stroke. †Not determined in two cases.

TABLE II—Clinical features in patients with stroke with and without atrial fibrillation. Odds ratios are adjusted for age and type of stroke

	No (%) with atrial fibrillation (n=115)	No (%) with sinus rhythm (n=560)	Adjusted odds ratio (95% confidence interval)	p Value
Hypertension*	68 (59)	307 (55)	1.2 (0.8 to 1.8)	NS
Ischaemic heart disease†	37 (32)	145 (26)	1.4 (0.9 to 2.1)	NS
Cervical bruit‡	6 (5)	66 (12)	0.4 (0.2 to 1.0)	NS
Peripheral vascular disease§	28 (24)	113 (20)	1.3 (0.8 to 2.0)	NS
Diabetes mellitus	17 (15)	46 (8)	1.9 (1.1 to 3.5)	0.04
Any valvar heart disease**	30 (26)	48 (9)	3.4 (2.0 to 5.7)	0.000002
Definite mitral stenosis††	5 (4)	2 (0.4)	12.7 (2.4 to 66.2)	0.002
None of the above	29 (25)	168 (30)	0.8 (0.5 to 1.2)	NS

*Two recordings with systolic blood pressure > 160 mm Hg and diastolic pressure > 90 mm Hg before stroke.
†Confirmed myocardial infarction or angina before stroke or pathological Q waves consistent with previous myocardial infarction on electrocardiogram at time of stroke.
‡Non-transmitted arterial bruit audible over either internal carotid artery high in the neck or over either subclavian artery in supraclavicular fossa.
§History of intermittent claudication or > 2 foot pulses absent.
||Requiring treatment with diet, insulin, or oral hypoglycaemic agents.
**Any one of the following valvar heart lesions clinically diagnosed with or without confirmatory evidence from echocardiography: mitral stenosis, mitral incompetence, mitral leaflet prolapse, mitral annulus calcification, aortic stenosis, aortic sclerosis, or aortic incompetence.
††Diagnosed by characteristic clinical features, supported by chest radiography and electrocardiography and preferably confirmed by cardiologist with or without echocardiography.
NS= $p > 0.05$.

TABLE III—Effect of atrial fibrillation on case fatality rate 30 days after stroke according to type of stroke, subtype of cerebral infarction, and age

	Atrial fibrillation	No of patients:		30 Day case fatality rate (%)	Adjusted odds ratio (95% confidence interval)	p Value
		Dead by 30 days	Alive at 30 days			
Type of stroke*:						
Cerebral infarction	{ +	22	75	23	3.5 (1.9 to 6.2)	0.00003
	{ -	35	413	8		
Primary intracerebral haemorrhage	{ +	4	3	57	1.3 (0.3 to 6.3)	NS
	{ -	30	29	51		
Not known	{ +	10	1	91	5.4 (0.6 to 51.2)	NS
	{ -	13	7	65		
All	{ +	36	79	31	3.1 (1.8 to 5.4)	0.00001
	{ -	78	449	15		
Subtype of cerebral infarction†:						
Lacunar	{ +	2	16	11	14.8 (1.3 to 172)	0.05
	{ -	1	118	1		
Partial anterior circulation	{ +	1	34	3	0.6 (0.1 to 5.1)	NS
	{ -	7	143	5		
Posterior circulation	{ +	2	13	13	2.4 (0.4 to 12.5)	NS
	{ -	7	107	6		
Total anterior circulation	{ +	16	12	57	2.9 (1.2 to 7.3)	0.05
	{ -	20	44	31		
All	{ +	21	75	22	2.5 (1.3 to 4.9)	0.007
	{ -	35	412	8		
Age (years)‡:						
0-49	{ +	0	0	0	2.6 (0.2 to 32.5)	NS
	{ -	4	38	10		
50-59	{ +	1	2	33	1.4 (0.4 to 4.3)	NS
	{ -	8	42	16		
60-69	{ +	4	15	21	2.6 (1.3 to 5.6)	0.02
	{ -	19	103	16		
70-79	{ +	14	35	29	2.0 (1.0 to 4.0)	NS
	{ -	26	172	13		
≥ 80	{ +	17	27	39	2.1 (1.3 to 3.4)	0.001
	{ -	36	112	24		
All ages, all types	{ +	36	79	31		
	{ -	93	467	17		

*All 33 patients with subarachnoid haemorrhage are excluded as none had atrial fibrillation (table I).
†Not determined in two cases, so n=543.
‡All 675 patients are included.

TABLE IV—Unadjusted univariate analysis of effect of atrial fibrillation on outcome in 545 cases of cerebral infarction

Event	Mantel-Cox statistic*	p Value
All cases (n=545):		
Death (all causes)	19.16	<0.00001
Vascular death	15.86	0.0001
Recurrent stroke	0.20	NS
Recurrent stroke/vascular death	7.90	0.005
Survived at least 30 days (n=488):		
Death (all causes)	5.92	0.015
Vascular death	1.43	NS
Recurrent stroke	1.11	NS
Recurrent stroke/vascular death	0.92	NS

*Crude unadjusted log rank analysis of time to first event.²⁹
NS=p>0.05.

and 8% (5.5% to 10.7%) in those with sinus rhythm. This difference in case fatality rate between atrial fibrillation and sinus rhythm persisted after adjustment for differences in age and subtype of cerebral infarction (using log linear modelling); the age adjusted relative odds of death occurring within 30 days for a patient with atrial fibrillation compared with a patient with sinus rhythm was 3.5 (1.9 to 6.2).

RISK OF EARLY RECURRENCE WITHIN 30 DAYS OF ONSET OF FIRST STROKE

In patients with cerebral infarction the risk of recurrent stroke within 30 days of the onset of the first stroke was low: 19 out of 545 (3.5% (1.9 to 5.0)). Recurrences were observed less often in patients with atrial fibrillation (1/97 (1%)) than in patients with sinus rhythm (18/448 (4%)); the relative odds of early recurrence in patients with atrial fibrillation compared with those with sinus rhythm was 0.25 (0.02 to 2.7).

LONG TERM PROGNOSIS

Unadjusted analyses in all cases of first cerebral infarction—Unadjusted univariate analysis of survival free of (a) death from any cause, (b) vascular death, (c) first recurrent stroke, and (d) first recurrent stroke or vascular death, or both, were performed for the 545 cases of first ever cerebral infarction. Using the log

rank statistic to test for the difference in survival between patients with atrial fibrillation and sinus rhythm, we found that atrial fibrillation was associated with a significant increase in the risk of death from all causes, of vascular death, and of recurrent stroke or vascular death, or both (table IV, fig 1). There was no significant excess of recurrent stroke in patients with atrial fibrillation (table IV, fig 2).

Unadjusted analyses in survivors of first cerebral infarction at 30 days—There was a significant excess of deaths from all causes in patients with atrial fibrillation, but no excess risk of vascular death, of recurrent stroke, or of recurrent stroke or vascular death (table IV, fig 3).

Average annual risks—The average annual risks of vascular events are given in table V. The excess observed in patients with atrial fibrillation was not significant and, because of the small number of events, the confidence intervals were wide. Our study had sufficient power to exclude large differences in the long term risk of serious vascular events between patients

FIG 1—Survival free of recurrent stroke or vascular death, or both, in 545 patients with first ever cerebral infarction. Deaths from non-vascular causes are excluded. (Kaplan-Meier survival curve)

FIG 2—Survival free of recurrent stroke in 545 patients with first ever cerebral infarction. Deaths from causes unrelated to stroke are excluded. (Kaplan-Meier survival curve)

FIG 3—Survival free of recurrent stroke or vascular death, or both, in 488 patients surviving at least 30 days after first cerebral infarction. Deaths from causes unrelated to stroke are excluded. (Kaplan-Meier survival curve)

with atrial fibrillation and those with sinus rhythm, but we cannot exclude small differences in absolute risks; the confidence intervals include the possibilities that average annual risks might be 2-3% lower or, equally, that they are 9-12% higher in patients with atrial fibrillation compared with patients with sinus rhythm.

Proportional hazards analysis—Patients with atrial fibrillation had a higher mean age than those with sinus rhythm and were more likely to have large cerebral infarcts (table I). As age and subtype of cerebral infarction were highly significant predictors of long term outcome, we used Cox's proportional hazards model³⁰ to determine the independent effect of atrial fibrillation on survival beyond 30 days (table VI).

TABLE V—Absolute risks: average annual risk over five years (calculated from life tables) in patients who survived at least 30 days after first ever cerebral infarction

	Annual risk (%)	95% Confidence interval
Recurrent stroke:		
Sinus rhythm	8.2	5.9 to 10.9
Atrial fibrillation	11.0	6.0 to 17.3
Difference*	2.8	−2.6 to 8.9
Recurrent stroke or vascular death:		
Sinus rhythm	11.8	9.2 to 14.8
Atrial fibrillation	15.8	9.9 to 24.1
Difference*	4.0	−2.3 to 11.7

*Not significant at $p < 0.05$; adjustment for age and infarct type did not affect significance.

TABLE VI—Relative risks: analysis of effect of atrial fibrillation on long term prognosis, adjusting for age and subtype of infarction in 448 patients with first cerebral infarction who survived at least 30 days

Event	Relative risk*	Relative risk/	
		SE†	p Value
Death (all causes)	1.35	1.99	< 0.05
Vascular death	1.42	1.79	NS
Recurrent stroke	1.08	0.30	NS
Recurrent stroke/vascular death	1.24	1.30	NS

*Or hazard ratio comparing patients with atrial fibrillation with those with sinus rhythm. Ratio=1 implies no difference in risk, >1 implies a greater risk with atrial fibrillation, and <1 implies a reduced risk with atrial fibrillation.

†Test of significance for the difference in hazard ratio for atrial fibrillation and sinus rhythm. If value > 1.96 then $p < 0.05$.

NS= $p > 0.05$.

Allowing for these factors reduced the differences between the atrial fibrillation and sinus rhythm groups, and the only outcome showing a significant difference was death from all causes. Thus, although our data suggest that atrial fibrillation is an independent predictor of death in the early phase of stroke, it is not an independent predictor of early or late recurrence of stroke or of vascular death in the long term; it is a weak predictor of death from all causes in the long term.

EFFECT OF VALVAR HEART DISEASE ON OUTCOME

To see whether the presence or absence of valvar heart disease in patients with atrial fibrillation and sinus rhythm influenced outcome, we performed unadjusted log rank and Cox's regression analyses (adjusting for age and stroke type) on the short and long term risk of stroke, death from stroke or vascular death, vascular death, and death from all causes.

The number of patients with valvar heart disease was small, but the presence or absence of valvar heart disease did not significantly affect the outcomes studied.

Discussion

It is important to determine the role of atrial fibrillation in the pathogenesis and on the prognosis of a first stroke and on the long term risks of recurrent stroke and vascular death. If a major excess risk of vascular occlusive events (as seen in symptom free

people with atrial fibrillation) persists in survivors of stroke such patients require special attention as a high risk group for secondary prevention. If, on the other hand, there is little difference in risk between having atrial fibrillation and sinus rhythm after a stroke then efforts at secondary prevention do not need to be focused on patients with atrial fibrillation.

PROGNOSIS OR UNTREATED NATURAL COURSE?

Many of the patients in this series were known to have had atrial fibrillation before the stroke occurred, though only a few had been taking anticoagulants and very few continued to receive anticoagulant or anti-platelet treatment after their stroke; if they did many did not receive long term maintenance treatment. Our results do not therefore represent a study of the natural course of stroke in a group of untreated patients, rather a study of prognosis in a group not treated aggressively. Any relative differences in prognosis in patients with and without atrial fibrillation are unlikely to be due to the use (or lack of use) of treatment in one group. Though limited use of antithrombotic and other treatments may have reduced the absolute risk of recurrent vascular events to some extent in both patients with atrial fibrillation and those with sinus rhythm, we think that any difference in absolute risk between the patients in our study and a completely untreated group would probably not be large. The Oxfordshire community stroke project therefore provides a representative sample of patients generally not treated with anticoagulants in whom the effect of atrial fibrillation on prognosis after a stroke can be examined.

METHODOLOGICAL STRENGTHS AND WEAKNESSES IN THIS AND PREVIOUS STUDIES

There have been several studies on atrial fibrillation and the risk of ischaemic stroke^{2 13-20 31-51} but none fully meet all the methodological standards suggested by Haynes *et al.*²¹ Several studies used a potentially biased sample by including only patients admitted to hospital.^{15-20 31-33 35-40 44-52} Hospital based series are likely to contain an excess of more severe strokes.⁵³

Our study satisfied (but not perfectly) the criteria for a methodologically sound prognostic study: 675 cases were followed without loss for up to six years, the sample was representative of all strokes in the community and not just those admitted to hospital, patients entered the study at any early stage of the natural course of the disease (with their first ever stroke) soon after its onset, the pathological type of the initial stroke was verified in over 90% of cases, the assessment of outcome events was prospective and as blind to the hypothesis under test as was practicable (since many hypotheses were being examined simultaneously). There were, however, some methodological weaknesses in our study. As this was a community based study we aimed to perform only the essential investigations on every patient. We did not have the resources to undertake detailed cerebral, cardiac, or arterial imaging and function studies as in some hospital based studies^{37 39 40 42 45-47}; we may therefore have underestimated the prevalence of certain cardiac disorders.

FREQUENCY OF ATRIAL FIBRILLATION IN PATIENTS WITH DIFFERENT TYPES OF CEREBROVASCULAR LESIONS

The frequency of atrial fibrillation in our sample of patients with first strokes is similar to that in previous community studies^{37 39 40 42} and some of the large hospital based stroke registers¹⁵⁻¹⁹ but lower than in a hospital case series of hemiplegic strokes⁶ and a hospital registry of stroke in patients aged over 60.⁵¹ Other studies have noted, as we have, that 2-6% of patients with primary intracerebral haemorrhage have atrial fibrillation.^{5 45-48} It is not clear whether the atrial

fibrillation was merely a transient arrhythmia due to the acute stress of the cerebral event because five out of the seven patients with primary intracerebral haemorrhage were known to have atrial fibrillation before the stroke. A maximum of only two of the seven cases could have been due to an arrhythmia as a result of the stress of the acute event; this is a small piece of evidence to support the notion that, in some strokes, the presence of atrial fibrillation is merely coincidental.

These data also highlight the importance of performing computed tomography early to exclude intracerebral haemorrhage in every patient with stroke and atrial fibrillation, before anticoagulants are given.

Of greater importance is the prevalence of atrial fibrillation in different subtypes of cerebral infarction. As anticipated, it is highest in patients with large infarcts presumed to be due to occlusion of the main stem of the middle cerebral artery (total anterior circulation infarction) and lowest in patients with lacunar infarction. In patients with lacunar infarction it is interesting to speculate whether the atrial fibrillation was the cause of the stroke or merely a marker of coincidental atherosclerotic cardiac disease. One other comparable community based stroke register has used a similar classification of cerebral infarction, and the prevalence of atrial fibrillation in the different subgroups was remarkably similar to our results.⁴¹ Other groups have noted the association of atrial fibrillation with clinically large cortical infarcts^{15 39 42 46 48} and angiographically proved occlusion of the middle cerebral artery¹² and that a small proportion of patients with lacunar infarctions have atrial fibrillation.^{39 41 42 46 48 51} In our series patients in atrial fibrillation often had other risk factors for cerebral infarction (table II). Thus, in a particular patient several potential causes for stroke may be present. Therefore, although some strokes in patients with atrial fibrillation are due to large cerebral infarcts presumed to be due to embolism from the heart, many must be caused by other mechanisms: primary intracerebral haemorrhage, atheroembolism from neck arteries, and occlusive small vessel disease of the intracranial perforating arteries. The exact proportion of non-cardioembolic strokes is unclear.

In the Oxfordshire community stroke project the prevalence of atrial fibrillation in patients with transient ischaemic attacks and those with ischaemic stroke was similar (14% and 18% respectively). This contrasts with the results from a tertiary referral centre where the overall prevalence of atrial fibrillation was lower and atrial fibrillation much higher in patients with stroke than in patients with transient ischaemic attacks (5.6% and 10.6% respectively).³⁰ The lower prevalence of atrial fibrillation in the study by Harrison and Marshall can presumably be accounted for by referral bias: elderly patients with an apparent cause (atrial fibrillation) might be less likely to be referred to a specialised centre than those without obvious cause. The reason for the difference in the prevalence of atrial fibrillation between patients with stroke and patients with transient ischaemic attacks within the tertiary centre is not clear.

PRESENCE OF OTHER FACTORS

Compared with patients with sinus rhythm, patients with atrial fibrillation were, on average, older and more likely to have diabetes mellitus, valvar heart disease, and mitral stenosis. On the other hand, cervical bruits (from the carotid or subclavian artery) were less common in patients with atrial fibrillation. The prevalence of hypertension and other markers of vascular disease (ischaemic heart disease and peripheral vascular disease) were similar in patients with atrial fibrillation and sinus rhythm. In our sample most cases of atrial fibrillation were not associated with rheumatic mitral stenosis and 74% were not associated with any

form of valvar heart disease. As a recent review has suggested that the excess risk of stroke in thyrotoxic atrial fibrillation may be small,⁵¹ our inability to determine precisely the proportion of cases associated with thyrotoxicosis is probably unimportant.

EARLY PROGNOSIS: RISK OF DEATH WITHIN 30 DAYS

Atrial fibrillation was clearly associated with an increased risk of death within 30 days of stroke ($p=0.00003$). Most of this excess was explained by the association of atrial fibrillation with large infarcts and by the older age of patients with atrial fibrillation, but a small excess risk persisted after adjustment for these factors. Others have found an increased early case fatality in atrial fibrillation^{15 16 41 49 51} and related it to the size of infarct^{15 41} and to packed cell volume.¹⁶ One plausible explanation for the increased early case fatality might be a high early risk of recurrent stroke in atrial fibrillation which has been reported by some groups^{17 31 33 35 37} but has not been confirmed by others.^{2 15 39 41} We observed a lower risk of early recurrence in patients with atrial fibrillation, so the excess risk of early death associated with atrial fibrillation cannot be accounted for by recurrences in our series. Another possibility for the excess mortality (not accounted for by infarct size and the patients' age) might be diabetes⁴⁹; hyperglycaemia is an adverse prognostic factor in acute stroke. Detailed multiple regression analyses of all possible prognostic factors in acute stroke will be reported separately.

EARLY PROGNOSIS: RISK OF EARLY RECURRENT STROKE

In this series the risk of early recurrence was low in all patients with cerebral infarction and was lower than the risk found in some early studies^{17 31 35 37 50} but comparable to that in some recent studies.^{2 15 39 41 46} This low risk is unlikely to be due to early treatment with antiplatelet or anticoagulant drugs.

The reason for the low early risk in recent studies might be because of differences in methods. Patients in our study were not monitored daily and we may have failed to detect some early recurrences. In addition, differing definitions of recurrent stroke in different studies could account for some of the differences. On the other hand, in our study at least it is unlikely that there was differential ascertainment of recurrences in patients with and without atrial fibrillation; thus our estimate of the relative difference of recurrence between patients with atrial fibrillation and those with sinus rhythm is likely to be unbiased even if we have underestimated the absolute risk of early recurrence. Detailed discussion is not warranted because the number of events was so small.

LONG TERM PROGNOSIS: RISK OF DEATH FROM ALL CAUSES, VASCULAR DEATH, AND RECURRENT STROKE

Several studies have found that after a stroke patients with atrial fibrillation have a substantially greater long term risk of recurrent stroke than have patients with sinus rhythm^{17 19 31 38}; others have not found a greater risk in atrial fibrillation.^{2 40} Many studies have reported life table risk of first stroke for stroke free patients with atrial fibrillation, but only two have reported life table risks for recurrent stroke after a first stroke during long term follow up^{20 46} and one hospital study has reported mortality only.⁵¹ Unadjusted life table analyses of survival in the Oxfordshire community stroke project clearly show a higher risk of death, of vascular death, and of the combined outcome recurrent stroke and vascular death with atrial fibrillation (table IV). However, much of the difference is due to the high early death rate from atrial fibrillation described above. The similarity in the risk of recurrent stroke in the Oxfordshire community stroke project in patients with atrial fibrillation and

sinus rhythm is quite striking. The absolute risk of recurrent strokes in people who survived 30 days expressed as an average annual risk is similar to that reported by Marquardsen (for males in Marquardsen's study, the average annual risk was 14% in patients with atrial fibrillation and 8.5% in those with sinus rhythm).²⁰ The stroke data bank study found two year recurrence risks for patients with first stroke of 12.1% and 9.9% for those with sinus rhythm and atrial fibrillation respectively.⁴⁶ Marquardsen's series may have had a worse prognosis than the other two studies because it consisted of a hospital based cohort of patients with more severe strokes in whom management of risk factors was probably not intensive.²⁰ The Framingham study reported a non-significant trend towards early recurrence in patients with stroke and atrial fibrillation,² but average annual life table risks of recurrence were not reported (crude cumulative totals were not significantly different (atrial fibrillation 25%, sinus rhythm 20%)).

Furthermore, in the Oxfordshire community stroke project, analysis of long term survival among patients who survived at least 30 days showed that although, in unadjusted analysis, death from all causes occurred significantly more often in patients with atrial fibrillation (table IV), multiple regression analyses, adjusting for the older average age and the larger cerebral infarcts among patients with atrial fibrillation, showed that none of these events occurred significantly more frequently with atrial fibrillation than with sinus rhythm. Of course, the lack of any relative difference between atrial fibrillation and sinus rhythm (with respect to long term outcome at least in this community study and in that of the stroke data bank)⁴⁶ emphasises that both atrial fibrillation and sinus rhythm have a relatively high absolute risk of recurrent stroke and vascular death⁴⁶; attention to secondary prevention measures after stroke should not be overemphasised in patients with atrial fibrillation at the expense of those with sinus rhythm.

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- 1 Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 1978;28:973-7.
- 2 Wolf PA, Kannel WB, McGee DL, Meedks SL, Bharucha NE, McNamara PM. Duration of atrial fibrillation and imminence of stroke: the Framingham study. *Stroke* 1983;14:664-7.
- 3 Brand FN, Abbott RD, Kannel WB, Wolf PA. Characteristics and prognosis of lone atrial fibrillation. 30-year follow-up in the Framingham study. *JAMA* 1985;254:3449-53.
- 4 Flegel KM, Shipley MJ, Rose G. Risk of stroke in non-rheumatic atrial fibrillation. *Lancet* 1987;i:526-9 (erratum *Lancet* 1987;i:878).
- 5 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham study. *Arch Intern Med* 1987;147:1561-4.
- 6 Cerebral Embolism Task Force. Cardiogenic brain embolism. The second report of the Cerebral Embolism Task Force. *Arch Neurol* 1989;46:727-43.
- 7 Flegel KM, Hanley J. Risk factors for stroke and other embolic events in patients with nonrheumatic atrial fibrillation. *Stroke* 1989;20:1000-4.
- 8 Davis P, Dambrosia J, Schoenberg B, Schoenberg D, Pritchard D, Lilienfeld A, et al. Risk factors for ischemic stroke: a prospective study in Rochester, Minnesota. *Ann Neurol* 1987;22:319-27.
- 9 Boysen G, Nyboe J, Appleyard M, Srensen PS, Boas J, Somnier F, et al. Stroke incidence and risk factors for stroke in Copenhagen, Denmark. *Stroke* 1988;19:1345-53.
- 10 Cerebral Embolism Task Force. Cardiogenic brain embolism. *Arch Neurol* 1986;43:71-84.
- 11 Kipecky SL, Gersh BJ, McGoon MD, Whisnant JP, Holmes DR Jr, Ilstrup

- DM, et al. The natural history of lone atrial fibrillation. A population-based study over three decades. *N Engl J Med* 1987;317:669-74.
- 12 Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet* 1989;i:175-9.
- 13 Stroke Prevention in Atrial Fibrillation Group. Preliminary report of the stroke prevention in atrial fibrillation study. *N Engl J Med* 1990;322:863-8.
- 14 The Boston Area Anticoagulant Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with non-rheumatic atrial fibrillation. *N Engl J Med* 1990;323:1505-11.
- 15 Britton M, Gustafsson C. Non-rheumatic atrial fibrillation as a risk factor for stroke. *Stroke* 1985;16:182-8.
- 16 Lowe GD, Jaap AJ, Forbes CD. Relation of atrial fibrillation and high haematocrit to mortality in acute stroke. *Lancet* 1983;i:784-6.
- 17 Sage JI, Van Uiter RL. Risk of recurrent stroke in patients with atrial fibrillation and non-valvular heart disease. *Stroke* 1983;14:537-40.
- 18 Sherman DG, Goldman L, Whiting RB, Jurgensen K, Kaste M, Easton JD. Thromboembolism in patients with atrial fibrillation. *Arch Neurol* 1984;41:708-10.
- 19 Fisher C. Reducing risks of cerebral embolism. *Geriatrics* 1979;34:59-66.
- 20 Marquardsen J. The natural history of acute cerebrovascular disease. A retrospective study of 769 patients. Copenhagen: Munksgaard, 1969:138-59.
- 21 Haynes RB, Tugwell P, Sackett D. *Epidemiology: a science for clinical medicine*. Toronto: Little, Brown, 1985.
- 22 Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-6. I. Methodology, demography and incident cases of first-ever stroke. *J Neurol Neurosurg Psychiatry* 1988;51:1373-80.
- 23 Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-6. II. Incidence, case-fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral haemorrhage and subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 1990;53:16-22.
- 24 Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. The classification and natural history of different subtypes of cerebral infarction. *Lancet* 1991;337:1521-6.
- 25 Bamford J. Clinical examination in diagnosis and sub-classification of stroke. *Lancet* 1992;339:400-2.
- 26 Gardner MJ, Altman DG. *Statistics with confidence—confidence intervals and statistical guidelines*. London: British Medical Journal, 1989.
- 27 Armitage P. *Statistical methods in medical research*. Oxford: Blackwell Scientific, 1971:135-8.
- 28 Dennis M, Bamford J, Sandercock P, Warlow C. Incidence of transient ischemic attacks in Oxfordshire, England. *Stroke* 1989;20:333-9.
- 29 Peto R, Pike M, Armitage P, Breslow N, Cox DR, Howard SV. Design and analysis of randomised clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976;34:585-612.
- 30 Dixon WJ. *BMDP statistical software*. Los Angeles: University of California Press, 1985:576-95.
- 31 Darling R, Austen W, Linton R. Arterial embolism. *Surg Gynecol Obstet* 1967;124:106-14.
- 32 Koller R. Recurrent embolic cerebral infarction and anticoagulation. *Neurology* 1982;32:283-5.
- 33 Hart R, Coull B, Hart D. Early recurrent embolism associated with nonvalvular atrial fibrillation: a retrospective study. *Stroke* 1983;14:688-93.
- 34 Sacco R, Wolf P, Kannel W, McNamara P. Survival and recurrence following stroke. *Stroke* 1982;13:290-5.
- 35 Santamaria J. Hemorrhage and anticoagulation after nonseptic embolic brain infarction. *Neurology* 1983;33:1104.
- 36 Harrison MJ, Marshall J. Atrial fibrillation, TIAs and completed strokes. *Stroke* 1984;15:441-2.
- 37 Kelley R, Berger J, Alter M, Kovacs A. Cerebral ischemia and atrial fibrillation: prospective study. *Neurology* 1984;34:1285-91.
- 38 Gustafsson C, Britton M. Prognosis after brain infarction in patients with non-valvular atrial fibrillation compared with sinus rhythm. *Acta Neurol Scand* 1986;73:520.
- 39 Bogousslavsky J, Van Melle G, Regli F, Kappenberger L. Pathogenesis of anterior circulation stroke in patients with nonvalvular atrial fibrillation: the Lausanne Stroke Registry. *Neurology* 1990;40:1046-50.
- 40 Bogousslavsky J, Adnet-Bonte C, Regli F, Van Melle G, Kappenberger L. Lone atrial fibrillation and stroke. *Acta Neurol Scand* 1990;82:143-6.
- 41 Ricci S, Celani MG, Duca E, Scaroni R, Caputo N, Chirullia C, et al. Ischaemic stroke and atrial fibrillation: a community based case-control study. In: Meyer JS, ed. *Salzburg conference on cerebrovascular disease*. Amsterdam: Elsevier, 1991:7-11.
- 42 Olsen T. Atrial fibrillation and stroke. *J Neurol* 1990;237:139.
- 43 Ricci S, Celani M, Guercini G, Rucireta P, Vitali R, La Rosa F, et al. First-year results of a community-based study of stroke incidence in Umbria, Italy. *Stroke* 1989;20:853-7.
- 44 Britton M, de Faire U, Helmers C, Miah K, Ryding C, Wester PO. Arrhythmias in patients with acute cerebrovascular disease. *Acta Med Scand* 1979;205:425-8.
- 45 Mohr JP, Caplan LR, Melski JW. The Harvard cooperative stroke registry: a prospective registry. *Neurology* 1978;28:754-62.
- 46 Hier DB, Foulkes MA, Swintonowski M, Sacco RL, Garelick PB, Mohr JP, et al. Stroke recurrence within two years after ischemic infarction. *Stroke* 1991;22:155-61.
- 47 Bogousslavsky J, Van Melle G, Regli F. Lausanne Stroke Registry: analysis of 1000 consecutive patients with first stroke. *Stroke* 1988;19:1083-92.
- 48 Van Merwijk G, Lodder J, Bamford J, Kester A. How often is non-valvular atrial fibrillation a cause of brain infarction? *J Neurol* 1990;237:205-7.
- 49 Candelise L, Pinardi G, Morabito A. Italian Acute Stroke Study Group. Mortality in acute stroke with atrial fibrillation. *Stroke* 1991;22:169-74.
- 50 Hart R, Easton JD, Sherman DG. Duration of nonvalvular atrial fibrillation and stroke. *Stroke* 1983;14:827.
- 51 Friedman PJ. Atrial fibrillation after stroke in the elderly. *Stroke* 1991;22:209-14.
- 52 Petersen P. Thromboembolic complications in atrial fibrillation. *Stroke* 1990;21:4-13.
- 53 Bamford J, Sandercock P, Warlow C, Gray M. Why are patients with acute stroke admitted to hospital? *BMJ* 1986;292:1369-72.

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