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Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness

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Abstract

Objective To determine whether trial efficacy of prophylaxis with warfarin for patients with atrial fibrillation at high risk of stroke translates into effectiveness in clinical practice.

Design Two year prospective cohort study.

Setting District general hospital.

Participants 167 patients with atrial fibrillation and at high stroke risk who were eligible for anticoagulation.

Interventions Long term anticoagulation with warfarin at adjusted doses to maintain an international normalised ratio of 2.0-3.0.

Main outcome measures Comparison of patient characteristics, comorbidity, anticoagulation control, stroke rate, and haemorrhagic complications with pooled data from five randomised controlled trials.

Results Patients in the study group were seven years older (95% confidence interval 4 to 10) and comprised 33% more women than patients in the pooled trials. The international normalised ratio was in the target range for 61% of the time (range 37%-85%), below for 26% of the time (range 8%-32%), and above for 13% of the time (range 6%-26%). The time that patients in the study group spent in the target range was significantly less than in the pooled analysis. The incidence of stroke in the study group (2.0% per year, 0.7% to 4.4%) was comparable to that of patients receiving warfarin in pooled studies (1.4%, 0.8% to 2.3%). Per year the incidence of major (1.7% v

1.6%) and minor (5.4% v 9.2%) bleeding complications was also similar.

Conclusion Rates of stroke and major haemorrhage after anticoagulation in clinical practice were comparable to those obtained from pooled data from randomised controlled studies for patients with atrial fibrillation at high risk of stroke.

Introduction

Many randomised controlled studies have shown the effectiveness of anticoagulation in preventing stroke in patients with atrial fibrillation.¹⁻⁷ Furthermore, clinical guidelines have been developed to identify patients at high risk who will benefit most from this intervention.⁸⁻¹¹ Recent studies have, however, shown that anticoagulation is underused in clinical practice.¹²⁻¹⁶

Several reasons have been given for the low rate of anticoagulation in eligible patients with atrial fibrillation. Major randomised trials were considered unrepresentative of clinical practice because only a small percentage of screened patients were included, and the proportion of men and younger patients was higher than expected in community settings.¹⁵ A reanalysis of pooled data showed that the benefits of anticoagulation may have been overestimated,¹⁷ and there seemed to be little absolute reduction in stroke rates with anticoagulation in patients with atrial fibrillation unselected for stroke risk.¹⁸ Additionally, a retrospective review of case notes concluded that the extent of anti-

coagulation control, therapeutic efficacy, and low complication rates in randomised trials were not matched in clinical practice.¹⁹ Despite the evidence from randomised trials, there was little proof that anticoagulation in atrial fibrillation would have the desired effect in clinical practice.

We aimed to compare personal characteristics, anticoagulation control, and outcome in patients who were at high risk of stroke and receiving anticoagulation in clinical practice with those of patients in randomised controlled trials.

Participants and methods

Participants

We recruited patients with chronic non-valvular atrial fibrillation under the age of 90 years from general medical clinics in a district general hospital. We excluded those already receiving warfarin for atrial fibrillation or other indications (for example, pulmonary emboli, deep vein thrombosis).

Diagnosis was confirmed by electrocardiography, and patients were assessed for the cause and duration of atrial fibrillation, vascular risk factors, risk of bleeding complications, and comorbidity or other drugs that may influence anticoagulant use.¹⁶ Stroke risk was assessed with clinical and echocardiographic criteria derived from randomised trials, and only patients at high risk were included. Clinical criteria were age over 75 years, history of transient ischaemic attack or a non-disabling stroke at least six months before assessment, and any of previous thromboembolism, hypertension, diabetes mellitus, or congestive heart failure.⁸⁻⁹ Echocardiographic criteria included a left atrium dimension greater than 2.5 cm/m², focal abnormalities in movement of the left ventricular wall, cardiomyopathy (global dyskinesia with left ventricular ejection fraction less than 40%), and intracardiac thrombus.²⁰

Major contraindications to anticoagulation were gastrointestinal or genitourinary bleeding in the past six months, coagulation defects, thrombocytopenia, haemorrhagic stroke, excessive alcohol intake, dementia, recurrent falls, and poor drug or clinic compliance.¹⁻⁵ We included patients already taking aspirin, but it was discontinued during the study.

Anticoagulation practice

Eligible patients were managed by the local anticoagulation services according to local guidelines. The target range for anticoagulation was an international normalised ratio of 2.0-3.0 using adjusted warfarin doses. Blood was taken by phlebotomists in out-patients, and the dose of warfarin was advised by doctors unaware of patients' participation in the study. Monitoring and dose adjustment were at the discretion of the anticoagulation services. The number of blood tests and the results were recorded after induction when the international normalised ratio was stabilised within the target range. The number of days when the international normalised ratio was in the target range was calculated by adding the number of days after the measurement of ratios in the range 2.0-3.0 and a subsequent value out of this range. Patients discontinuing warfarin for more than four weeks were treated as withdrawals.

Follow up

All patients were followed up for two years and reviewed every six months by a doctor unaware of their international normalised ratio values. Patients were assessed for neurological status, episodes of bleeding and intercurrent illness, or changes in drugs that may influence anticoagulation control. Hospital records were consulted to document admissions or events that may not have been recalled by the patient, and further information was obtained from general practice and community sources. Patients who did not attend for appointments were contacted by the research team. This strategy enabled 100% completion of all follow up assessments.

End points and statistical analyses

To maintain consistency with the meta-analysis of pooled data we used ischaemic stroke confirmed by computerised tomography as the primary outcome measure for comparison. We made no distinction between cardioembolic stroke or ischaemic stroke due to other causes. Intracerebral haemorrhages were counted as bleeding complications. The diagnosis of transient ischaemic attacks was based on clinical criteria,²¹ and the number of episodes in the study group was recorded. All deaths were recorded and a cause assigned on the basis of available clinical information. Deaths due to cerebrovascular causes were excluded to prevent double counting. All bleeding events were recorded. Major bleeding was defined as intracranial haemorrhage, fatal bleeding, or bleeding leading to admission to hospital, emergency procedures, or urgent transfusion. All other bleeds were classified as minor.

We used two sample confidence intervals for the difference of means and proportions to compare important prognostic variables between randomised trials and the current sample. Additionally, we assessed the size of the differences in the individual clinical trials using Tukey's correction after analysis of variance. We calculated the event rate per patient year, and the exact Poisson confidence intervals were used for comparisons of clinical outcomes because of the small numbers (due to low incidence) in these groups.

Results

Patient characteristics

Chronic atrial fibrillation was confirmed by electrocardiography in 344 (14%) of the 2457 patients. The median time between the first diagnosis of atrial fibrillation and research assessment was 17.5 months (range 2-34 months). A high risk of stroke on the basis of clinical or echocardiographic criteria was present in 286 of 344 (83%) patients, 38 (13%) of whom had major contraindications to anticoagulation. Of the 248 patients eligible for anticoagulation, warfarin was already being given to 76 (31%), and five refused anticoagulation. We recruited the remaining 167 patients to the study.

The mean age of patients in the study was 76.6 (SD 11.2) years, and 58% were women. Patients in the study group were on average seven years older and comprised 33% more women than those in the pooled analysis (table 1). Although the proportions of patients with hypertension and diabetes mellitus were

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Table 1 Clinical characteristics of patients in clinical study compared with pooled data from five major randomised controlled trials of patients receiving warfarin. Values for pooled data are percentages unless stated otherwise

	Clinical practice	Pooled data [†]	Difference (95% CI)
Mean age (years)	77	69	7 (4 to 10)*
No (%)			
<75 years	87 (52)	80	-28 (-36 to -20)
>75 years	80 (48)	20	28 (20 to 36)
Men	70 (42)	75	-33 (-41 to -25)
Hypertension	72 (43)	45	-2 (-10 to 6)
Diabetes mellitus	25 (15)	13	2 (-4 to 8)
Current smokers	22 (13)	12	1 (-4 to 6)
Previous stroke or transient ischaemic attack (>6/12)	23 (14)	6	8 (3 to 13)
Congestive heart failure	33 (20)	20	0 (-6 to 6)
Ischaemic heart disease	43 (26)	36	-10 (-17 to -3)

comparable between the study group and pooled data, the study group had a significantly higher proportion of patients with previous stroke or transient ischaemic attack and a significantly lower proportion of patients with ischaemic heart disease (table 1).

Quality of anticoagulation

Treatment with warfarin was stopped in 30 (18%) study patients during follow up (table 2). Reasons included death (eight patients), major bleed (four), intracranial haemorrhage (one), disabling stroke (three), patients' choice (eight), poor compliance (four), and interactions with other drugs (two). No correlation was found between age, sex, frequency of blood tests, and duration of anticoagulation and stopping warfarin. The proportion of patients stopping treatment because of bleeding complications (2%; four patients) was no greater than in clinical trials (1.4% to 6%).^{1 3}

Blood tests for monitoring anticoagulation were undertaken less frequently in the study group than in the clinical trials. The interval between tests in the study group varied considerably: 20% were less than 21 days,

47% were between 21 and 28, 23% were between 29 and 42, and 10% were greater than 42. The international normalised ratio for patients in the study group was in the target range for an average of 61% of the time (range 37%-85%), below for 26% of the time (8%-32%), and above for 13% of the time (6%-26%) (table 2). The time spent in the target range in the study group was significantly less than in the pooled trials (difference 4%, 95% confidence interval 2% to 8%).

End points

All surviving patients were monitored for the planned duration, resulting in 313 patient years of follow up, during which they received warfarin for 296 patient years. Six patients in the study group had ischaemic strokes (three cardioembolic, two indeterminate, one small vessel); one died (table 3). Only one of the six cases of infarct occurred during adequate anticoagulation (international normalised ratio 2.6). Two patients who had withdrawn from treatment had strokes (12 and 44 weeks after warfarin was stopped), and three patients had international normalised ratios below the target range. Two of the three patients with transient ischaemic attack had international normalised ratios in the target range; warfarin had been discontinued for three weeks at one patient's request and was restarted after the event. Seven patients died due to non-cerebral causes: two from myocardial infarction, one from sudden death (vascular), and three from unrelated causes.

One patient with an international normalised ratio of 6.9 had an intracranial haemorrhage. Four other patients had major bleeds: two patients required surgery for massive rectal bleeding owing to undiagnosed carcinoma of the colon (international normalised ratio 2.0-3.0), one received a transfusion for haematemesis (2.3), and one received a transfusion for melaena (1.6). Sixteen patients (5.4%) had minor bleeding episodes: epistaxis (five patients), bruising (four), rectal bleeding (three), haematuria (three), and haemarthrosis (one). Warfarin was stopped temporarily (for less than four weeks) in these patients. Seven patients had international normalised ratios greater than 5.0 (range 5.2-10.3) without any bleeding complications, and after adjustment of warfarin dose these were within the target range.

The annual event rate for stroke in patients in the study group (2.0%, 95% confidence interval 0.7% to 4.4%) was higher than that of patients in the pooled analysis who had received anticoagulation (1.4%, 0.8% to 2.3%), but this difference was not statistically significant (table 3). The annual event rate for major bleed (including intracerebral haemorrhage) in patients in the study group (1.7%, 0.5% to 3.9%) was also not significantly different from that of patients in the pooled analysis (1.6%, 0.7% to 2.1%).

Table 2 Anticoagulation practice and quality of control

	Clinical practice	Trial					Pooled data
		Peterson et al ¹	Boston area ²	Stroke prevention ³	Cannolly et al ⁴	Ezekowitz et al ⁵	
Target range (INR equivalent)	2.0-3.0	2.4-4.2	1.5-2.7	2.0-4.5	2.0-3.0	1.4-2.8	Variable
Interval between tests (days)*	31	28	21	30	21	30	21-30
% time spent in range	61	73	83	71	44	56	66
% time below target range	26	26	8	23	40	29	25
% time above range	13	1	9	5	16	15	9
No (%) patients stopping warfarin	30 (18)	126 (38)	21 (10)	40 (19)	49 (26)	81 (29)	316 (26)

*After initial period of stabilisation of international normalised ratio values, during which more frequent sampling was undertaken. Interval between tests includes tests for routine monitoring and more frequent repeat testing when values are outside range.

Table 3 Annual events in patients taking warfarin

	Clinical practice		Pooled data	
	No of events	Annual event rate (95% CI)	No of events	Annual event rate (95% CI)
Ischaemic stroke	6	2.0 (0.7 to 4.4)	26	1.4 (0.8 to 2.3)
Transient ischaemic attack	3	1.0 (0.1 to 4.0)	13	0.7 (0.3 to 1.4)
Death from non-cerebral causes	7	2.4 (0.6 to 6.1)	69	3.6 (2.7 to 4.9)
Intracranial haemorrhage	1	0.3 (0.03 to 2.7)	5	0.3 (0.06 to 0.7)
Major bleeding	4	1.4 (0.2 to 4.6)	24	1.3 (0.7 to 2.1)
Minor bleeding	16	5.4 (2.4 to 10.2)	150	9.2 (3.7 to 12)

Discussion

Patients in the clinical study were older, consisted of more women, and spent significantly less time in the target anticoagulation range than patients in the pooled data from randomised trials. Despite these differences, the rates for stroke and major haemorrhage in the study group were comparable to those in the pooled data. The efficacy of warfarin in preventing

stroke in trial conditions therefore translates into effectiveness in clinical practice for patients at high risk.

To ensure that we chose patients who were comparable to those at high risk of stroke receiving warfarin in randomised studies we made our selection on the basis of criteria derived from randomised trials. We excluded patients who had had a stroke up to six months before the study so that primary and not secondary prevention was being assessed. We conducted our study prospectively to ensure that all withdrawals, anticoagulation deviations, events, and complications were identified. Patients already taking anticoagulants were excluded to ensure that early withdrawals did not bias results in favour of anticoagulation. Recall bias for events, especially transient ischaemic attack or minor bleeds, was prevented by depending not only on patients' memory for events during structured interviews but also by reviewing hospital records and information from general practice sources.

Representativeness was addressed by recruiting patients from general medical clinics and including only those at high risk as these were the patients most likely to receive anticoagulation in clinical practice. In this group there is firm evidence of the superiority of anticoagulation over aspirin¹⁻⁷ compared with those at lower risk, where controversy about best clinical practice exists.¹⁰⁻²² As anticoagulation was undertaken by staff unaware of patients' participation in the study, it is likely that the findings reflect anticoagulation practice in service settings. Blood testing for anticoagulation control was less frequent in clinical practice than in randomised studies, and patients spent significantly less time in the target anticoagulation range. These differences may be clinically relevant as three of the six strokes occurred in patients in whom the international normalised ratio was less than 2.0. Although patients in the study group spent 13% of time above the target range, the frequency of bleeding complications did not exceed that seen in clinical trials.

Long term anticoagulation with adjusted warfarin dose should be considered in all patients eligible for warfarin with atrial fibrillation who are at high risk of thromboembolism, especially as studies have shown that aspirin or fixed low doses of warfarin have limitations.^{6, 23-24} The case for wider but judicious use of anticoagulation is strengthened by this study, which shows that anticoagulation for stroke prevention is feasible, safe, and effective in clinical practice, even in elderly people.

Contributors: LK had the original idea, designed, initiated, and coordinated the study, and was responsible for data analysis, interpretation, and writing the paper. GY discussed core ideas and participated in the protocol design, data collection, and data analysis. IP initiated research and was involved with patient assessments, data collection, and extraction of data from major trials and their analysis. AL discussed core ideas, provided haematology input, initiated research, and participated in data collection, particularly on anticoagulation. ND discussed core ideas, provided statistical guidance, participated in analysis and interpretation of pooled data from randomised studies, undertook comparative analyses, and contributed to the paper. LK, GY, and AL will act as guarantors for the paper.

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What is already known on this topic

Anticoagulation with adjusted warfarin dose in patients with atrial fibrillation consistently reduces the risk of stroke by two thirds at the small risk of major bleeding complications

Despite evidence in the published literature, anticoagulation is underused in clinical practice because it is not known whether trial efficacy translates into clinical practice

What this study adds

Stroke and haemorrhage rates were comparable to those in randomised studies despite significant differences in patient characteristics and anticoagulation control in clinical practice

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