Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin

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Abstract

Objective To investigate the effectiveness of aspirin and coumarin in preventing thromboembolism in patients with non-rheumatic atrial fibrillation in general practice.
Design Randomised controlled trial.
Participants 729 patients aged ≥60 years with atrial fibrillation, recruited in general practice, who had no established indication for coumarin. Mean age was 75 years and mean follow up 2.7 years.
Setting Primary care in the Netherlands.
Interventions Patients eligible for standard intensity coumarin (international normalised ratio 2.5-3.5) were randomly assigned to standard anticoagulation, very low intensity coumarin (international normalised ratio 1.1-1.6), or aspirin (150 mg/day) (stratum 1). Patients ineligible for standard anticoagulation were randomly assigned to low anticoagulation or aspirin (stratum 2).
Main outcome measures Stroke, systemic embolism, major haemorrhage, and vascular death.
Results 108 primary events occurred (annual event rate 5.5%), including 13 major haemorrhages (0.7% a year). The hazard ratio was 0.91 (0.61 to 1.36) for low anticoagulation versus aspirin and 0.78 (0.34 to 1.81) for standard anticoagulation versus aspirin. Non-vascular death was less common in the low anticoagulation group than in the aspirin group (0.41, 0.20 to 0.82). There was no significant difference between the treatment groups in bleeding incidence. High systolic and low diastolic blood pressure and age were independent prognostic factors.
Conclusion In a general practice population (without established indications for coumarin) neither low nor standard intensity anticoagulation is better than aspirin in preventing primary outcome events. Aspirin may therefore be the first choice in patients with atrial fibrillation in general practice.

Introduction

Coumarin and aspirin have been shown to reduce the risk of thromboembolic events by 68% and 36% respectively in patients with non-rheumatic atrial fibrillation.[1–7] However, it is unclear whether these findings apply to patients with atrial fibrillation in primary care as the patients studied were selected by referral. Referred patients are generally at higher risk of thromboembolic events and the effect of antithrombotic treatment may be greater than that in primary care patients.[8–12]

We assessed the preventive effect of very low intensity and standard intensity anticoagulation among patients in general practice who had no clear indication for coumarin. Some evidence exists that low dose anticoagulation might be as effective as standard dose but with a lower risk of bleeding.[13–17] Since by 1990 placebo was not considered acceptable in trials of atrial fibrillation because of the proved effectiveness of coumarin and aspirin, we compared both anticoagulant doses with aspirin (150 mg/day).[2]

Participants and methods

The study was conducted from January 1990 to December 1996. The 284 participating general practitioners checked the pulse of all visiting patients aged ≥60 years. In addition, patients were identified from general practitioners' and pharmacists' databases. Patients were invited to have their pulse taken if they had not contacted the general practitioner spontaneously.[18]

Eligibility

Patients aged ≥60 years with electrocardiographically confirmed chronic atrial fibrillation or intermittent atrial fibrillation (electrocardiography within past two years) were eligible. Exclusion criteria were treatable causes of atrial fibrillation, previous stroke, rheumatic valvular disease, myocardial infarction or cardiovascular surgery in past year, cardiomyopathy (left ventricular ejection fraction <40%), chronic heart failure, cardiac aneurysm, history of systemic embolism, retinal infarction, coumarin use in the past three months, contraindications for aspirin or coumarin (haemoglobin concentration <7.0 mmol/l, ventricular or duodenal ulcer in the past three years, gastrointestinal or urogenital bleeding in the past year,

aspirin intolerance, coagulation disorder, and severe hepatic or renal disease), pacemaker, and a life expectancy less than two years. Exclusion criteria for standard anticoagulation were age ≥78, retinopathy, ventricular or duodenal ulcer, history of gastrointestinal or genitourinary bleeding, and diastolic blood pressure >105 mm Hg or systolic pressure >185 mm Hg, or both.

Randomisation, data management, and ethical approval

Patients eligible for standard anticoagulation were randomly assigned (centrally, by telephone) to aspirin 150 mg/day, low anticoagulation (international normalised ratio 1.1-1.6), or standard anticoagulation (international normalised ratio 2.5-3.5; randomisation stratum 1). Adaptive biased urn randomisation guaranteed similar group sizes in each practice but kept treatment assignment unpredictable.[19] Patients who were ineligible for standard anticoagulation were randomised between aspirin and low anticoagulation (randomisation stratum 2), giving five subgroups in the two strata. General practitioners followed up participants at four month intervals and checked compliance. Patients gave written informed consent. Patients were single blinded for the two intensities of anticoagulant, but end point ascertainments were blinded for treatment. Events were independently reviewed by two members of the (neurological, cardiological, vascular, ophthalmological, and internal medicine) event committees (or three, in case of disagreement; with deliberation to reach consensus). Either phenprocoumon or acenocoumarol (nicoumalone) was prescribed by the thrombosis centres according to normal prescription practice and monitored at intervals of 2-6 weeks. The medical ethics committee of Maastricht university hospital approved the study.

Outcome measures

The primary outcome events were defined as follows:

Stroke—Classified as not disabling, minor disabling, or major disabling and as ischaemic or haemorrhagic (based on computed tomography).

Systemic arterial embolism—Acute vascular occlusion resulting in recovery, permanent sequelae (major or minor), or death.

Major haemorrhage—Requiring hospital admission and blood transfusion or causing fall in haemoglobin concentration ≥2.0 mmol/l.

Vascular death—Within four weeks after stroke, systemic embolism, myocardial infarction, congestive heart failure, or major bleeding or sudden death (observed within one hour after onset of symptoms or patient found dead).

Secondary outcome events were non-fatal myocardial infarction (electrocardiographically or laboratory confirmed), retinal infarction, transient ischaemic attack, minor bleeding complication, or non-vascular death.

Sample size and statistical analysis

If the treatment results are equivalent, aspirin would be the treatment of choice since anticoagulation is more inconvenient for the patient. Therefore, proof that aspirin is more effective than anticoagulation is not necessary and one sided testing is ethically appropriate as it requires experimental exposure of fewer patients.

Because of constraints on resources and time, we focused the sample size requirements on the comparison of low anticoagulation and aspirin, to be applied in both strata. With a power of 80%, a one sided significance of $\alpha = 0.05$, and an assumed four year cumulative primary event incidence of 24% on aspirin, 310 patients in both intervention groups were needed in order to detect a cumulative reduction in incidence to 16%.[20] We aimed at balanced assignment of patients in both strata, so that 155 patients were required for each intervention in each stratum; 124 primary events were expected in both groups together. Standard anticoagulation was restricted to stratum 1. A reduction in cumulative incidence from 24% to 12% could be detected with 155 patients in each intervention group.

We analysed results using an intention to treat approach with a log rank test and Cox regression analysis. In the regression analysis we adjusted for baseline differences in prognostic factors and analysed potential effect modification[20]; we included age, sex, chronic or intermittent character of atrial fibrillation, recent onset of atrial fibrillation, no cardiovascular comorbidity (lone atrial fibrillation), current smoking, hypercholesterolaemia, history of hypertension (blood pressure ≥160/95 mm Hg), diabetes, raised body mass index, history of ischaemic heart disease, intermittent claudication, left ventricular ejection fraction on echocardiography ≤40%, and exclusion for standard anticoagulation (randomisation in stratum 2 being a covariable).[21]

Interim analyses were planned after 31, 62, and 93 primary events in the low anticoagulation and aspirin groups combined (both strata) with significance levels of 0.001, 0.008, and 0.017 as boundaries for the one sided P value from the stratified log rank test (Snapinn stopping rule).[22] Accordingly, the trial would be stopped when there was at least a 90% probability that the final analysis would result in a significant difference if the trial was continued. Values of 0.71, 0.34, and 0.16 were used as successive boundaries to stop the trial with a P value above the boundary, when there is at least an 80% probability that the final analysis would result in a non-significant difference.

Results

Baseline measurements

Of 1837 identified patients (fig 1), 966 were ineligible; reasons for exclusion were no atrial fibrillation on electrocardiography (309, 32%), current use of anticoagulants (290, 30%), sustained stroke or thromboembolism (193, 20%), aspirin intolerance (17, 2%), and valvular disease (161, 17%), and others (some met more than one criterion). Patients currently using anticoagulants had been previously referred. Nineteen patients who were thought to be eligible were later found to meet exclusion criteria (pacemaker (three), no atrial fibrillation on electrocardiography (three), hyperthyroidism (two), younger than 60 (seven), recent coumarin use (one), previous stroke (one), and too old for standard anticoagulation (two)).

Of the 871 eligible patients, 142 were not randomised; 23 (16%) refused, and in 119 patients reasons were not specified by the general practitioner. These 142 patients differed slightly from the included patients: fewer had new onset atrial fibrillation (16 (11%) *v* 237 (35%)), history of angina (9 (6%) *v* 81

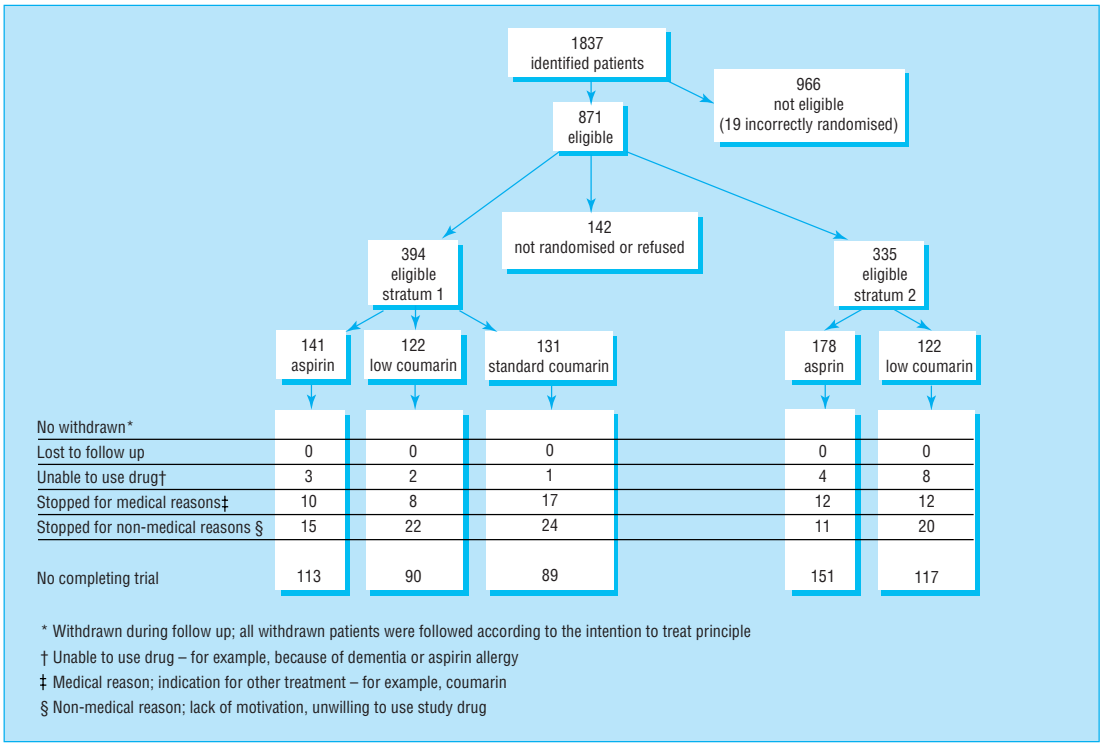

Fig 1 Trial profile

(11%)), and history of diabetes (12 (8%) *v* 121(16%)) and there was a higher proportiona of men (72 (51%) *v* 327 (45%)).

A total of 335 patients met exclusion criteria for standard anticoagulation only (age ⩾78 years (258), history of bleeding or ulcer,[33] severe hypertension,[32] and retinopathy[12]) and were randomised in stratum 2.

Table 1 gives the baseline characteristics. No patient was lost to follow up. There were 77 withdrawals during follow up for medical reasons: intolerance of study drug (five), dementia,[13] cotreatment or contraindication problem,[29] hospital admission,[12] and non-specified medical reasons.[18] Non-medical reasons were given in 92 patients. Before entering the trial, 204 (28%) patients were taking prophylactic aspirin, which was stopped before randomisation.

Compliance with coumarin was checked by thrombosis services. For the 3983 measurements of international normalised ratio, the mean (SD) ratio was 3.1 (1.2) for standard anticoagulation and 1.4 (0.4) for

Table 1 Baseline characteristics of study patients, according to assigned treatment

Characteristics	Total No (%) of patients (n=729)	Stratum 1			Stratum 2	
		Standard anticoagulation (n=131)	Low anticoagulation (n=122)	Aspirin (n=141)	Low anticoagulation (n=157)	Aspirin (n=178)
% of men	327 (44.9)	58 (44)	70 (57)	67 (48)	67 (43)	65 (32)
Mean (SD) age (years)	74.8 (7.5)	70.0	69.4	70.8	80.2	80.5
History:						
Diabetes	121 (16)	25	10	21	25	40
Hypercholesterolemia (>6.5 mmol/l)	173 (24)	39	34	36	25	39
Current smoker	71 (10)	14	13	21	8	15
Body mass index >25	391 (54)	78	73	86	78	76
Heart and vessels:						
Angina pectoris	81 (11)	9*	13	19	17	23
Intermittent atrial fibrillation	127 (17)	35	22	33	19	18
Recent onset atrial fibrillation (⩽1 year)	257 (35)	48	40	51	55	63
Myocardial infarction	63 (9)	9	12	15	15	12
Intermittent claudication	61 (8)	7	9	12	13	20
Left atrial dimension >40 mm	84 (12)	24*	10	18	16	16
Left ventricular ejection fraction <40%	26 (4)	1	5	10	3	7
Lone atrial fibrillation†	292 (40)	59	65	56	48	64
Hypertension	289 (40)	46	35	53	77	78
Mean (SD) blood pressure (mm Hg)						
Diastolic	84 (9)	84 (9)	84 (8)	85 (10)	84 (10)	84 (10)
Systolic	151 (19)	149 (17)	147 (17)	147 (19)	157 (20)	154 (20)

†Atrial fibrillation without cardiac comorbidity (hypertension, claudication, or ischaemic heart disease).
*P<0.05 compared with aspirin group, χ^2 test.

Table 2 Primary outcome events according to treatment groups

Outcome events	Stratum 1*			Stratum 2		Total	Hazard ratio (95% CI)	
	Standard anticoagulation	Low anticoagulation	Aspirin	Low anticoagulation	Aspirin		Standard *v* aspirin	Low *v* aspirin
Follow up:								
No of patients	131	122	141	157	178	729		
No of patient years	400.9	361.1	392.0	373.7	411.2	1938.9		
Mean (SD) follow up (years)	3.1 (1.3)	3.0 (1.3)	2.8 (1.3)	2.4 (1.2)	2.3 (1.2)	2.7 (1.2)		
Range	0.1-5.6	0.3-5.6	0.4-5.6	0.4-5.6	0.1-5.5	0.1-5.6		
Primary outcome event† (No (%/year)):	10 (2)	8 (2)	12 (3)	37 (10)	41 (10)	108 (5.5)	0.78 (0.34 to 1.8)	0.91 (0.61 to 1.4)
Non-fatal stroke:	3	4	4	14	17	42 (2.1)	0.62 (0.10 to 3.7)	0.94 (0.45 to 2.0)
Ischaemic stroke, major	2	1	3	11	10	27 (1.3)	0.67 (0.11 to 4.1)	0.99 (0.45 to 2.2)
Ischaemic stroke, minor	1	2	1	1	3	7 (0.4)		0.81 (0.18 to 3.6)
Cerebral bleeding, major	1	1	1	2	4	8 (0.4)		0.80 (0.18 to 3.6)
Non-fatal systemic embolism	1	2	1	1	5	8 (0.4)	0.97 (0.06 to 15.6)	0.18 (0.02 to 1.5)
Major haemorrhage, extracranial	0	0	0	4	5	13 (0.7)	0.96 (0.06 to 15.4)	1.1 (0.36 to 3.4)
Vascular death:	5 (1)	2 (1)	6 (2)	18 (5)	14 (3)	45 (2.3)	0.76 (0.23 to 2.5)	1.1 (0.58 to 2.0)
Myocardial infarction	1	0	1	0	4	6 (0.3)		
Sudden death, observed	0	1	1	3	1	6 (0.3)		
Sudden death, unobserved	3	1	3	7	5	19 (1.0)		
Congestive heart failure	1	0	1	8	4	14 (0.7)		

*Standard anticoagulation: international normalised ratio 2.5-3.5; low anticoagulation: 1.1-1.6; aspirin=150 mg /day. †Primary outcome events are given according to whichever came first.

low anticoagulation. For standard anticoagulation 48% (328) of the measurements were within the target international normalised ratio (2.5-3.5; 28% were too low and 24 % too high) and for low anticoagulation 75% (2475) were within target (1.1-1.6; 13% too low and 12% too high). A quarter of the anticoagulation patients took phenprocoumon. Pill counts in the 319 patients taking aspirin showed non-compliance in three patients.

The first and second interim analyses gave inconclusive results.

Outcome

In all, 157 major or fatal events occurred, including 108 primary events (analysed on the basis of "whichever came first"): 30 in stratum 1 and 78 in stratum 2 (table 2). Figure 2 shows the Kaplan-Meier curves. After 2.5-3 years of follow up the number of patients decreased. At four years 80 patients in stratum 1 were still at risk (28 low anticoagulation, 29 standard anticoagulation, 23 aspirin) and 34 in stratum 2 (17 each for low anticoagulation and aspirin).

The annual event rate was 5.5%. Mean follow up was 2.7 years with a total of 1939 patient years. Compared with aspirin, the hazard ratio was 0.91 (95% confidence interval 0.61 to 1.4) for low anticoagulation (both strata) and 0.78 (0.34 to 1.8) for standard anticoagulation (stratum 1). The log rank test and the likelihood ratio test gave similar P values. For non-vascular death, the hazard ratio was 0.41 (0.20 to 0.82) comparing low anticoagulation with aspirin (table 3). High systolic and low diastolic blood pressure, and age were independent prognostic factors (table 4). Risk was lower in non-smokers with intermittent atrial fibrillation receiving low anticoagulation.

In the per protocol analysis the risk of primary events was 0.77 (0.49 to 1.2) in the low anticoagulation group compared with aspirin; this fell to 0.66 (0.44 to 0.99) when non-vascular death was included. The hazards ratio for primary events with standard anticoagulation was 0.87 (0.34 to 2.2) and 0.62 (0.26 to 1.5) when non-vascular death was included.

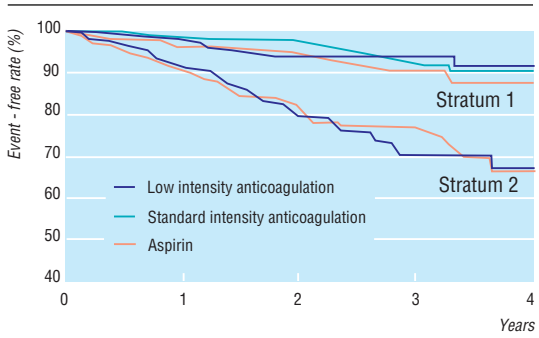

Fig 2 Kaplan-Meier survival analysis for primary outcome events (non-fatal stroke, non-fatal systemic embolism, major haemorrhage, or vascular death) according to treatment group

Adverse effects

The annual bleeding rate was 3.9%, 1.2% for major or fatal bleeding (n=23) and 2.7% for minor bleeding (n=52). Seventeen of the major bleeds occurred in stratum 2, with 10 in the aspirin group. No significant difference in risk of bleeding was found between treatment groups (tables 2 and 5).

Discussion

We found a low overall event rate in this elderly primary care population with non-rheumatic atrial fibrillation. The stroke rate was 1% for patients aged <78 years and 4% for the older patients. Since we could not prove that standard or low anticoagulation was more effective than aspirin, the prophylactic choice in primary care is aspirin if there is no clear indication for full dose anticoagulation.

Other trials have found that standard anticoagulation is better than aspirin. Our results may differ because we included patients with less advanced disease without an established indication for oral anticoagulants. Patients in other trials had annual stroke rates of 3.5-8% with placebo and 2.5-6% with aspirin depending on age and risk factors, which suggests more severe disease.[23 24] Our result was not

Table 3 Number (percentage per year) of outcome events according to treatment

Outcome events	Stratum 1*			Stratum 2		Total (n=729)	Hazard ratio (95% CI)	
	Standard anticoagulation (n=131)	Low anticoagulation (n=122)	Aspirin (n=141)	Low anticoagulation (n=157)	Aspirin (n=178)		Standard *v* aspirin	Low *v* aspirin
All deaths (total)	12 (3)	8 (2)	17 (4)	33 (9)	49 (12)	119 (6.1)	0.52 (0.22 to 1.3)	0.68 (0.44 to 1.1)
Vascular death:	9 (2)	4 (1)	9 (2)	24 (6)	25 (6)	71 (3.6)	0.96 (0.38 to 2.4)	0.93 (0.56 to 1.5)
Myocardial infarction	1	0	1	0	5	7 (0.4)		
Ischaemic stroke	0	1	1	1	5	8 (0.4)		
Stroke, cerebral bleeding	0	1	0	1	2	4 (0.2)		
Sudden death, certain	1	1	1	3	1	7 (0.4)		
Sudden death, uncertain	3	1	3	9	5	21 (1.1)		
Congestive heart failure	2	0	2	8	5	17 (0.8)		
Systemic embolism	0	0	1	1	2	4 (0.2)		
Non-central nervous system bleeding	1	0	0	1	0	2 (0.1)		
Other vascular death	1	0	0	0	0	1 (<0.1)		
Non-vascular death	3 (1)	4 (1)	8 (2)	9 (2)	24 (6)	48 (2.5)	0.35 (0.09 to 1.3)	0.41 (0.20 to 0.82)
Infection	0	2	2	1	7	12 (0.6)		
Malignancy	1	1	5	2	5	14 (0.7)		
Unknown	2	1	1	6	11	21 (1.1)		
Other non-vascular	0	0	0	0	1	1 (<0.1r)		
All strokes (total):	3 (1)	4 (1)	4 (1)	14 (4)	18 (5)	43 (2.2)	0.50 (0.09 to 2.7)	0.94 (0.47 to 1.9)
Ischaemic, major disabling or fatal	2	1	3	11	10	27 (1.3)	0.69 (0.11 to 4.1)	1.06 (0.48 to 2.3)
Ischaemic, minor disabling	0	2	1	1	3	7 (0.4)		0.69 (0.16 to 2.9)
Cerebral bleeding, major or fatal	1	1	0	2	5	9 (0.5)		0.92 (0.25 to 3.4)
All embolisms:	3	3	5	13	18	42 (2.2)	0.61 (0.15 to 2.6)	0.78 (0.41 to 1.5)
Including minor bleeding	37	31	36	72	96	272 (14.0)	0.88 (0.53 to 1.5)	2.2 (0.46 to 1.6)
Excluding minor bleeding	23	23	27	61	86	220 (11.3)	0.73 (0.39 to 1.4)	0.87 (0.63 to 1.2)
Non-fatal myocardial infarction	1	5	2	4	5	17 (0.8)		

*Standard anticoagulation: international normalised ratio 2.5-3.5; low anticoagulation 1.1-1.6; aspirin=150 mg/day.

Table 4 Cox regression analysis determining the effect of prognostic factors and effect modifiers on primary outcome events in all patients

Prognostic factor	No of patients (n=729)	Hazard ratio (95% CI)	
		All prognostic variables without interactions	Reduced model with interactions
Aspirin (reference group)	391	1.0	
Low anticoagulation*	279	0.93 (0.61 to 1.41)	
Standard anticoagulation†	131	0.59 (0.29 to 1.26)	
Randomisation in stratum 2	49	1.6 (0.75 to 2.68)	1.5 (0.74 to 2.56)
Male sex	327	1.3 (0.85 to 1.95)	1.5 (1.01 to 2.30)
Age 70-77 years	318	2.4 (1.24 to 4.53)	2.5 (1.29 to 4.81)
Age ⩾78	216	4.2 (2.15 to 8.30)	5.2 (2.62 to 10.4)
Diabetes	121	0.84 (0.49 to 1.40)	
Hypercholesterolemia (>6.5 mmol/l)	55	1.7 (0.95 to 3.30)	2.1 (1.12 to 3.88)
Current smoking	71	1.6 (0.83 to 3.03)	Treatment dependent
Body mass index >25	391	0.94 (0.63 to 1.40)	
Chronic atrial fibrillation	602	1.4 (0.76 to 2.58)	Treatment dependent
Atrial fibrillation started 0.5-1 year	59	1.4 (0.71 to 2.66)	
Atrial fibrillation started ⩽0.5 year	198	0.87 (0.56 to 1.38)	
Ischaemic heart disease	142	0.83 (0.50 to 1.43)	
Intermittent claudication	55	0.84 (0.40 to 1.77)	
Lone atrial fibrillation	292	0.96 (0.73 to 1.67)	
Left atrial dimension >40 mm	84	1.0 (0.53 to 1.87)	
Left ventricular ejection fraction <40%	26	1.0 (0.31 to 3.21)	
Hypertension	289	0.80 (0.53 to 1.25)	0.80 (0.52 to 1.23)
Diastolic blood pressure (mm Hg):			
<85	383	1.6 (1.02 to 2.67)	1.7 (1.08 to 2.77)
85-94 (reference group)	265	1.0	1.0
⩾95	81	1.9 (0.95 to 3.35)	2.0 (1.04 to 3.67)
Systolic blood pressure (mm Hg)‡		1.02 (1.01 to 1.04)	1.03 (1.01 to 1.04)

*International normalised ratio 2.5-3.5. †International normalised ratio 1.1-1.6.
‡Systolic blood pressure was entered as continuous variable divided in 10 mm Hg steps.

explained by lower age[23] or the number of serious bleeds in the aspirin group.[13] In retrospect, inclusion of a placebo group might have been helpful because of the low risk of events in our study population.

Time and resources forced us to stop follow up around the time that the third interim analysis would have taken place. The number of events in the aspirin and low anticoagulation patient groups slightly exceeded the 93 required for the third interim analysis. The P value (0.37) suggests that a significant difference would not be found with longer follow up, and the stopping rule advised stopping the trial.[22] Our study therefore had sufficient power to compare low anticoagulation and aspirin.

Despite randomisation there were some baseline differences between the groups. They may be partly due to use of computer generated random lists for each practice, since some practices randomised just a few patients. However, the regression analysis adjusted for these covariables, and our results should not be biased.

Recommendations for primary care

Other trials of atrial fibrillation have generally studied younger patients (mean age 69 years *v* 75 in our study). The recommendation to give standard anticoagulation to patients aged >75 years is based on 245 patients taking warfarin,[25] whereas in the general population about 70% of patients with atrial fibrillation are aged 65-85.[12 26] Of our 390 patients aged ⩾75 years, 192 took coumarin (32 standard dose). Our data on low anticoagulation concur with the findings of other studies.[27 28]

The rate of bleeding in patients taking aspirin was higher than in other trials.[1–7] Differences in outcome between the aspirin prevention trials cannot be explained by differences in dose of aspirin.[1 2 29 30] New antiplatelet agents might be an option in future.[31]

The observed difference in numbers of non-vascular deaths between low anticoagulation and aspirin may be related to different drug effects in patients with cancer (30% of the non-vascular deaths), who

Table 5 Major and minor bleedings in patients taking anticoagulants or aspirin. Values in parentheses are bleeding incidences per 100 patient years unless stated otherwise

	No of patients					Hazard ratio (95%CI)	
Adverse effects	Total	Low anticoagulation	Standard anticoagulation	Aspirin	Taking treatment*	Standard anti-coagulation *v* aspirin	Low anti-coagulation *v* aspirin
Major or fatal bleeding:	23 (1.2)	10 (1.4)	2 (0.5)	11 (1.4)	19	1.8 (0.16 to 20.0)	0.99 (0.42 to 2.3)
Cerebral	10	4†	1‡	5	9		
Respiratory	1	1	0	0	1		
Gastrointestinal	7	5	0	2	4		
Subdural haematoma	3	0	0	3	3		
Eye	1	0	0	1	1		
Abdominal aneurysm	1	0	1	0	1		
Minor bleeding:	52 (2.7)	19 (2.6)	14 (3.5)	19 (2.4)	47	1.4 (0.59 to 3.2)	0.99 (0.52 to 1.9)
Cerebral	0	0	0	0	0		
Respiratory	2	1	1	0	1		
Gastrointestinal	14	5	2	7	13		
Urogenital	17	6	5	6	16		
Nasal	12	5	4	3	12		
Skin	6	1	2	3	4		
Eye	1	1	0	0	1		
Total:	75 (3.9)	29 (3.9)	16 (4.0)	30 (3.7)	66	1.3 (0.59 to 3.0)	1.02 (0.58 to 1.8)
Cerebral	10	4	1	5	9		
Respiratory	3	2	1	0	2		
Gastrointestinal	21	10	2	9	17		
Urogenital	17	6	5	6	16		
Nasal	12	5	4	3	12		
Skin	6	1	2	3	4		
Subdural haematoma	3	0	0	3	3		
Eye	2	1	0	1	2		
Abdominal aneurysm	1	0	1	0	1		

*Patients complying with study treatment †International normalised ratios were 1.3, 2.7, and 1.3 (one unknown). ‡International normalised ratios 3.0.

might have a hypercoagulable state.[32 33] However, the finding could also be due to chance, as such an effect was not clear in the (younger) patients taking standard anticoagulation. The observed lower risk in non-smokers with intermittent atrial fibrillation taking low anticoagulation may also be due to chance.

The proportion of measurements of international normalised ratio that were out of range in patients taking coumarin varied from 58% to 20% in other atrial fibrillation trials compared with 25% for low dose and 52% for standard dose in our study.[23] These data underline the difficulties of daily coumarin use. In addition, the effectiveness of anticoagulation in daily practice may be lower than under trial conditions because monitoring of international normalised ratio may be less accurate.[23 34]

Key messages

- Studies have shown that patients with non-rheumatic atrial fibrillation may benefit from anticoagulation
- This study in a general practice population found no benefit of standard or low dose anticoagulation on risk of stroke, systemic embolism, major haemorrhage, or vascular death when compared with aspirin
- Hypertension and age were prognostic factors for event occurrence
- Aspirin is the treatment of choice for preventing thromboembolism in primary care patients at low risk

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Pragmatic randomised controlled trial of local corticosteroid injection and naproxen for treatment of lateral epicondylitis of elbow in primary care

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continued over

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website *extra*

A further table and members of the the Community Musculoskeletal Research Group are given on the BMJ's website

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Abstract

Objective To compare the clinical effectiveness of local corticosteroid injection, standard non-steroidal anti-inflammatory drugs, and simple analgesics for the early treatment of lateral epicondylitis in primary care.
Design Multicentre pragmatic randomised controlled trial.
Setting 23 general practices in North Staffordshire and South Cheshire.
Participants 164 patients aged 18-70 years presenting with a new episode of lateral epicondylitis.
Interventions Local injection of 20 mg methylprednisolone plus lignocaine, naproxen 500 mg twice daily for two weeks, or placebo tablets. All participants received a standard advice sheet and co-codamol as required.
Main outcome measures Participants' global assessment of improvement (five point scale) at four weeks. Pain, function, and "main complaint" measured on 10 point Likert scales at 4 weeks, 6 months, and 12 months.
Results Over 2 years, 53 subjects were randomised to injection, 53 to naproxen, and 58 to placebo. Prognostic variables were similar between groups at baseline. At 4 weeks, 48 patients (92%) in the injection group were completely better or improved compared with 30 (57%) in the naproxen group ($P<0.001$) and 28 (50%) in the placebo group ($P<0.001$). At 12 months, 43 patients (84%) in the injection group had pain scores ≤ 3 compared with 45 (85%) in the naproxen group and 44 (82%) in the placebo group ($P>0.05$).
Conclusions Early local corticosteroid injection is effective for lateral epicondylitis. Outcome at one year was good in all groups, and effective early treatment does not seem to influence this.

Introduction

Lateral epicondylitis (tennis elbow) is a painful condition that affects about 4 adults per 1000 annually.[1] Most cases are managed in primary care, and more than 40 possible treatments have been proposed,[2] reflecting a lack of consensus about optimal management. General practitioners commonly use non-steroidal anti-inflammatory drugs to treat tennis elbow, but there are no trials comparing them with painkillers and one study found no clinically important benefit over placebo.[3] Two reviews of corticosteroid injections concluded that there was insufficient evidence to support their use in treating tennis elbow, but the methodological quality of most trials was poor.[4 5] Only two primary care studies were