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PLACEBO-CONTROLLED, RANDOMISED TRIAL OF WARFARIN AND ASPIRIN FOR PREVENTION OF THROMBOEMBOLIC COMPLICATIONS IN CHRONIC ATRIAL FIBRILLATION

The Copenhagen AFASAK Study

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Summary From November, 1985, to June, 1988, 1007 outpatients with chronic non-rheumatic atrial fibrillation (AF) entered a randomised trial; 335 received anticoagulation with warfarin openly, and in a double-blind study 336 received aspirin 75 mg once daily and 336 placebo. Each patient was followed up for 2 years or until termination of the trial. The primary endpoint was a thromboembolic complication (stroke, transient cerebral ischaemic attack, or embolic complications to the viscera and extremities). The secondary endpoint was death. The incidence of thromboembolic complications and vascular mortality were significantly lower in the warfarin group than in the aspirin and placebo groups, which did not differ significantly. 5 patients on warfarin had thromboembolic complications compared with 20 patients on aspirin and 21 on placebo. 21 patients on warfarin were withdrawn because of non-fatal bleeding complications compared with 2 on aspirin and none on placebo. Thus, anticoagulation therapy with warfarin can be recommended to prevent thromboembolic complications in patients with chronic non-rheumatic AF.

Introduction

ATRIAL fibrillation (AF) is complicated by a high risk of thromboembolic complications. ¹⁻³ Chronic AF also implies a high risk of clinically silent cerebral infarction. ⁴ Paroxysmal AF, however, is associated with a lower risk of stroke. ⁵⁻⁷ To our knowledge, no randomised study of prophylaxis with anticoagulants or aspirin has been done in patients with chronic non-rheumatic AF, although the question of whether to use such treatment has been debated for decades. ⁸

The aim of this randomised trial was to compare the effects of warfarin anticoagulation, low-dose aspirin therapy, and placebo on the incidence of thromboembolic complications in patients with chronic non-rheumatic AF.

Patients and Methods

The study was carried out between Nov 1, 1985, and June 7, 1988 (the Copenhagen AFASAK study). The patients were recruited from two outpatient electrocardiography (ECG) laboratories to which they had been referred by their general practitioners. Whenever AF was diagnosed, we informed the general practitioner about the study. If he or she agreed, the patient was invited to take part in the study. After giving informed consent, the patient was examined by one of us (P. P.), who measured blood pressure and heart rate and carried out echocardiography to determine left atrial size. The history taken covered previous rheumatic fever, chest pain, symptoms of heart failure, myocardial infarction, and cerebrovascular episodes. Laboratory investigations included a 12-lead ECG, chest X-ray with determination of relative heart volume, and haemoglobin, serum concentrations of sodium and potassium, blood glucose, platelet count, coagulation status, and tests of hepatic, renal, and thyroid function. Diagnostic criteria on the underlying aetiology of AF have been described previously. 9 To be included in the study patients had to be 18 years of age or over and to have ECG-verified chronic AF. The exclusion criteria were: previous anticoagulation therapy for more than 6 months; cerebrovascular events within the past month; contraindications for aspirin warfarin therapy; previous side-effects of aspirin warfarin; current treatment with aspirin warfarin; pregnancy or breast-feeding; persistent blood pressure above 180/100 mm Hg; psychiatric diseases, including chronic alcoholism; heart surgery with valve replacement; sinus rhythm; rheumatic heart disease; and refusal to participate. The trial was carried out according to the principles of the second Declaration of Helsinki. The protocol was approved by the regional ethics committees.

The patients were randomised to receive warfarin, aspirin 75 mg once daily, or placebo. They received consecutive numbers, which corresponded to numbered packages containing the study medication, the order of which was determined by computergenerated randomisation. Warfarin was given openly, but the aspirin and placebo arms were double blind. The warfarin tablets looked different from the aspirin and placebo tablets, which were indistinguishable. Each placebo tablet contained 3.5 mg citric acid to mimic the taste of the aspirin tablets. After a year of treatment the patients on aspirin and placebo were given a new identically numbered package containing their medication for the last year of the study. The patients on warfarin were, when necessary, given new supplies of the drug by the laboratory technicians.

After inclusion of a patient the general practitioner was informed and he or she immediately received the results of the laboratory analyses.

The amounts of warfarin needed were assessed by means of 'Normotest' (NycoMed AS, Oslo, Norway) with a therapeutic range of 4·2–2·8 (international normalised ratio [INR]). 10 All patients were instructed to contact the laboratory immediately in the event of haematuria or other bleeding episodes, starting a new drug prescribed elsewhere, and periods of greater than normal alcohol intake. Initially blood samples were taken every day for 5 days. The maximum interval between blood samples in patients on warfarin was 4 weeks. During each year of treatment a period of 4 weeks without warfarin was allowed (for surgical intervention, evaluation of bleeding complications, or holidays abroad). In case of hospital admission warfarin treatment was continued if no contraindications arose. At the end of the study we calculated for each patient the time within the therapeutic range, the time within and just below it (4·2–2·4), and the time above it.

All patients were followed up at scheduled times. The follow-up time was 2 years for each patient, with clinical check-ups every 3 months for the first 6 months, then every 6 months. They were asked about thromboembolic complications, as well as side-effects of the treatment, chest pain, heart failure, and hospital admissions. Physical examination and echocardiography to determine left atrial size were also carried out. During the second year the presence of AF was confirmed by at least one ECG in all patients. If a patient was withdrawn from the study, the remaining tablets were returned to the laboratory or to the local pharmacy.

Within 2 weeks of a scheduled interim analysis we checked by telephone whether any major events had occurred in all participating and withdrawn patients. If we could not contact a patient, we checked the central data register for hospital admissions and deaths. All recorded thromboembolic episodes were classified by a neurologist (G. B.) according to the criteria below.

The primary endpoint was a thromboembolic complication (transient cerebral ischaemic attack [TIA], minor stroke, nondisabling stroke, disabling stroke, and fatal stroke, embolism to viscera or to the extremities). The criteria for cerebrovascular events were clinical signs or a medically confirmed history of acute onset of a neurological deficit of presumed vascular origin. A TIA was defined as focal symptoms lasting less than 24 h and a minor stroke as symptoms lasting more than 24 h but less than a week. Non-disabling strokes were defined as those not leaving definite functional disability a month after onset-ie, the patient was able to lead an almost normal life. If the patient still had definite functional disability a month after the event, the stroke was classified as disabling. If the patient died within a month of a major event it was recorded as fatal. Thromboemboli to the viscera or extremities were recorded as endpoints when adequate acute symptoms were present followed by relevant diagnostic tests, and, for thromboembolism to the mesenteric arteries, by surgical evidence of ischaemic bowel without severe associated atherosclerotic

TABLE I—CLINICAL DETAILS OF STUDY SUBJECTS

	No (%)		
_	Warfarin (n = 335)	Aspirin (n = 336)	Placebo n = 336)
Male	176 (53)	184 (55)	180 (54)
Female	159 (47)	152 (45)	156 (46)
Previous TIA	4(1)	5(1)	6 (2)
Previous stroke	16 (5)	12 (4)	15 (4)
Previous AMI	27 (8)	23 (7)	27 (8)
Angina pectoris	63 (19)	54 (16)	54 (16)
Diabetes	25 (7)	26 (8)	33 (10)
History of hypertension	108 (32)	112 (33)	103 (31)
Smoking	133 (40)	124 (37)	117 (35)
Heart failure	168 (50)	183 (54)	170 (51)
Thyrotoxicosis	16 (5)	12 (4)	13 (4)

vascular disease. After reaching an endpoint the patient was followed for at least a month or until discharge or death. In the case of a cerebrovascular event a computed tomography (CT) scan was done when possible, and in fatal cases death certificates and necropsy reports were obtained. All cerebrovascular complications, whether haemorrhagic or ischaemic, were considered as endpoints. The secondary endpoint was death.

All bleeding complications were recorded and classified as minor, major (requiring medical intervention), or fatal. When a major complication occurred, the patient was withdrawn immediately from the study or, if justified, the treatment was discontinued for a maximum of 4 weeks for evaluation and treatment of possible underlying disease. If haematuria, gastrointestinal bleeding, or haemoptysis occurred, the patient was referred to general practitioner or to hospital for evaluation of underlying aetiology.

Statistical Analysis

Assuming $2\alpha = 0.05$ and $\beta = 0.10$, the incidence and accrual rates of thromboembolus estimated from pilot studies, we estimated that almost 2000 patients treated for up to 2 years would be required to ensure a significant outcome, provided one (or both) active treatments changed the incidence of thromboembolic complications by 30%. Accordingly, the trial was planned to run until December, 1988, but, because of crucial uncertainties in these estimates (accrual rates, withdrawals, thromboembolus incidence, and treatment effects), we included a group sequential approach. A maximum of five analyses at fixed, irregularly spaced time points were planned. They were carried out by a statistician unaware of the treaments, and the individual probability values were adjusted according to the proposals of O'Brien and Fleming.11 These analyses pertained only to thromboembolic complications. The fourth analysis called for termination of the trial in June, 1988, when 1007 patients had been randomised.

Owing to varying exposure to risk through varying duration of observation, the incidences of thromboembolic complications were estimated by Kaplan-Meier life-table methods. Treatment comparisons of both primary and secondary endpoints were based on log-rank tests (2 df). Pairwise treatment comparisons were inductive analyses using principles for partitioning the degree of freedom in chi-square analyses. Comparability between groups at randomisation was assessed by chi-square (2 df) and Kruskal-Wallis tests.

Results

2546 patients with AF were invited to take part. 1539 were ineligible, of whom 835 refused to take part; 505 had contraindications to one or both treatments; 126 were already receiving one of the treatments; and 73 reverted to sinus rhythm. Of the 1007 subjects included there were 540 men and 467 women; their median age was 74·2 years (range 38–91 years). 335 patients were enrolled in the warfaring group (median age 72·8 years, range 41–88 years), 336 in the aspirin group (75·1 years, range 40–91 years) and 336 in the placebo group (74·6 years, range 38–91 years). The

TABLE II-EMBOLIC COMPLICATIONS

	Warfarin	Aspirin	Placebo
Cerebral emboli			
TIA	0	2	3
Minor stroke	0	1	2
Non-disabling stroke	0	7	3
Disabling stroke	4	4	7
Fatal stroke	1	3	4
l'isceral emboli	0	2	2
Emboli in extremities	0	1	0
Total	5	20	21

differences in age were statistically significant (p < 0.03). The distribution of previous cerebrovascular events and the presence of risk factors such as previous myocardial infarction, angina pectoris, diabetes, hypertension, current smoking habits, heart failure, and thyrotoxicosis are given in table I. There were no statistical differences between the three groups in any of these features.

Patients on warfarin were maintained within the therapeutic range $(4\cdot2-2\cdot8 \text{ INR})$ for 42% of the treatment time and within the $4\cdot2-2\cdot4$ INR range for 73% of the time. The values were above $4\cdot2$ INR (ie, the patients were too strongly anticoagulated) for only $0\cdot6\%$ of the time and below $2\cdot4$ INR for 26% of the time.

Table II gives the number of thromboembolic complications in the three treatment groups. 5 patients on warfarin had strokes (4 patients disabling cerebral infarction and 1 fatal intracerebral haemorrhage [INR = 3.7]). No embolic complications in the viscera or extremities were recorded in this group. Of the 4 infarcts, only 1 occurred during sufficient anticoagulation (INR = 2.9). 2 occurred when treatment had been discontinued (for evaluation of haematuria [INR = 1.3] and before an elective operation [INR = 1.25]). 1 patient had a stroke on the day of randomisation (ie, before treatment started). There were 20 thromboembolic complications in the aspirin group and 21 in the placebo group.

The total 46 thromboembolic complications occurred in 24 men and 22 women, median age 73·7 years (range 38–85 years). There was no significant age difference between patients with and without thromboembolic complications (p>0·90). Also an analysis of age differences between different treatment groups with and without complications showed no correlation between age and thromboembolic complications.

By life-table methods the difference in frequency of events in the three groups was statistically significant (p < 0.05), even after adjustment for our group sequential design and after inclusion of the 3 dubious cases from the warfarin group.

The frequency of thromboembolism rose with the duration of AF, with no evidence of a particularly vulnerable

TABLE III—WITHDRAWALS FROM STUDY

	Warfarin	Aspirin	Placebo
Refusal to continue	63 (19)	19 (5)	20 (6)
Side-effects	23 (7)	8 (2)	6(2)
Treatment with aspirin	2 (1)	0.431	10.4
or anticoagulants	2 (1)	9 (3)	16 (4)
Contraindications to treatment with aspirin			
or anticoagulants	7 (2)	2(1)	0
Non-compliance	23 (7)	3 (1)	3(1)
Sinus rhythm	8 (2)	3 (1)	7 (2)
Total	126 (38)	44 (13)	52 (15)

TABLE IV-SIDE EFFECTS

_	Warfarin $(n = 335)$	Aspirin (n = 336)	Placebo (n = 336)
Bleeding			
Respiratory tract	4	1	0
Gastrointestinal tract	4	1	0
Urogenital	6	0	0
Others	7	0	0
Allergic reactions	0	2	0
Gastrointestinal			
discomfort	0	4	3
Others	2	0	3
Total	23 (7%)	8 (2%)	6 (2%)

period. The yearly incidence of thromboembolic complications was 2.0% (95% confidence limits 0.6%, 4.8%) on warfarin and 5.5% (95% confidence limits 2.9%, 9.4%) on aspirin and placebo.

7 patients on aspirin or placebo had fatal strokes; cerebral infarction was diagnosed at necropsy in 1, on CT scan in 2, and in 4 patients we could not differentiate between infarction and haemorrhage. 28 of 33 patients (85%) with non-fatal cerebrovascular events had CT scans within a short time of the event. None of the patients had haemorrhage on CT.

The numbers of thromboembolic events occurring after cessation of treatment were 6, 1, and 4 in the warfarin, aspirin, and placebo groups, respectively (p > 0.10).

There were only 3 vascular deaths in the warfarin group (both cerebrovascular and cardiovascular), 12 in the aspirin group, and 15 in the placebo group (p < 0.02). 1 patient on aspirin and 1 on placebo died of unknown causes during the study and 1 patient on aspirin died of a presumed vascular cause but there was no further information. 1 patient on aspirin and 1 on placebo died of unknown causes after withdrawal. A total of 71 patients died during the study, including patients on trial medication and those who had withdrawn. An intention-to-treat analysis of all deaths, including those who had withdrawn showed no difference in either vascular or total mortality.

Table III gives the numbers of patients withdrawn from the study and the reasons for withdrawal. Of 23 withdrawn patients with side-effects of warfarin, 21 had non-fatal bleeding complications and 2 discomfort which was attributed to treatment (table IV). 2 patients had malignant and 7 inflammatory diseases discovered after bleeding episodes from the urogenital or gastrointestinal tracts. 1 of them had a normotest result above the therapeutic range and required blood transfusion. A further 3 patients had normotest values above the therapeutic range and 9 patients had bleeding complications without any detectable underlying aetiology.

In the aspirin group only 2 bleeding episodes were noted, 1 requiring blood transfusion. There were no bleeding episodes in the placebo group.

Discussion

The prevalence of AF is 2-4% in populations above 60 years of age. ¹² In the Framingham study ¹ of patients with chronic non-rheumatic AF, the risk of stroke was more than five times higher than normal, corresponding to a yearly incidence of stroke of about $4\cdot2\%$. For several decades there has been debate about whether to use oral anticoagulants for stroke prevention in AF. ^{8.13} Studies of patients with rheumatic AF suggested a beneficial effect of oral anticoagulants on stroke occurrence, ^{14,15} but several

methodological difficulties must be considered, as well as the fact that rheumatic heart disease accounts for only a small proportion of patients with AF. A retrospective study of 134 patients with non-rheumatic AF found that the incidence of thromboembolism was about eight times greater during periods without anticoagulation than during periods on anticoagulants. However, potential selection bias in determining which patients were treated with anticoagulants limits the extrapolation of these observations to patient care. A controlled, randomised study on the effects of anticoagulation and aspirin in patients with AF was therefore needed.

Our protocol stipulated that the general attitude of the trial should be pragmatic rather than explanatory.¹⁷ This eventually turned out to be a crucial issue, because 3 of 5 thromboembolic complications in the warfarin group would certainly have been excluded from a usual explanatory study (per-protocol analysis) thereby presenting very impressive probability values. Even when we included these patients, warfarin had a significant effect in prevention of complications. thromboembolic Since the characteristics were evenly distributed among the groups and since the infrequent differences between groups occurred for features which in our patients had no detectable correlations with thromboembolic episodes or death in any systematic, relevant fashion, we found that a posteriori revision of treatment comparisons (eg, by the Cox regression model) was unwarranted.

This study could be criticised since the warfarin treatment was given openly. However, the endpoints were well-defined thromboembolic complications, most often manifesting themselves by acute, severe deficits and subsequent hospital admission Moreover the risk of missing an endpoint was even lower for the warfarin group than for the aspirin and placebo groups, since that group of patients was followed more intensively. Safety was the primary reason for giving warfarin treatment openly. Also we found it ethically questionable to draw a large number of blood samples in more than 600 patients not on warfarin.

A substantial proportion (38%) of the patients randomised to treatment with warfarin were withdrawn, mostly because of the inconvenience of frequent blood sampling and the side-effects of treatment (table III). Not unexpectedly, some of these patients had thromboembolic events during the rest of follow-up. It is possible that the withdrawn patients had a particularly high risk of thromboembolism, so their withdrawal would favour warfarin treatment. This possibility seems unlikely, however, since only 6 thromboembolic complications occurred in the 126 withdrawn patients. In comparison, aspirin and placebo treatments resulted in fewer withdrawals.

From this study it seems reasonable to recommend anticoagulation with warfarin for stroke prophylaxis in chronic non-rheumatic AF. The proportion of outpatients with chronic AF who would be potential candidates for anticoagulation can be only roughly estimated from our data. Of 2546 eligible patients only 1007 participated. Why did so many patients refuse to take part? One reason could be that the information was decentralised—ie, general practitioners were informed first and patients were invited for further examination and informed consent only if they had no objections. Secondly, the study was done on an outpatient basis, and many patients probably refused when informed of the possibility of frequent blood tests. In the future we expect that more outpatients will accept and

continue treatment with anticoagulants when told of their effectiveness in preventing thromboembolic complications.

Bleeding complications are common during anticoagulant treatment. The frequency and severity depend, among other factors, on the chosen therapeutic range and degree of hypertension. 18,19 In this study 1 fatal intracerebral haemorrhage occurred during adequate anticoagulation. Only 1 serious bleeding episode requiring blood transfusion occurred in a patient who was temporarily too strongly anticoagulated. Since CT or necropsy were not done in all patients on aspirin and placebo who had fatal strokes, no comparison about aetiology can be made. However, severe bleeding complications during this study were few. Moreover, in most of the patients with urogenital and gastrointestinal bleeding, underlying disease was detected, which in 2 cases was malignant. One reason for the low frequency of bleeding complications may be that the treatment was carried out by the same investigator in cooperation with a few laboratory technicians, who themselves took the blood samples, carried out the laboratory analyses, and knew the patients well. Secondly, the retrospective analysis of the degree of anticoagulation showed that the patients were less strongly anticoagulated than intended and thirdly, the largest time accepted between laboratory controls was 4 weeks.

Other studies have dealt with the possible effect of aspirin on cerebrovascular and cardiovascular events,^{20,21} as well as the optimum doses.²² We used aspirin 75 mg once daily, which inhibits platelet aggregation, reduces thromboxane formation to about 3%, and prolongs bleeding time.²² In this study aspirin had no significant effect on the occurrence of thromboembolic complications or vascular death.

One important question that remains is how long should patients be anticoagulated and should any particular period during AF be considered for anticoagulation? The treatment time in this study was 2 years, so we do not know whether anticoagulation for longer periods is desirable. Initial data from the Framingham study¹ showed no vulnerable period for stroke occurrence, whereas a reevaluation of the study showed a clustering of strokes during the first months after the diagnosis of AF.2 However, one explanation for part of the observed clustering of strokes may be that AF has been diagnosed at the same time as the stroke—ie, it is not known how long AF has been present before the event. In our study we detected no clustering of thromboembolic complications, so no particular period of importance for anticoagulation could be identified. However, because of the design of this study it is difficult to rule out clustering of stroke in AF since patients with recent onset of AF and stroke were not included. Studies on the effect of long-term anticoagulation are therefore still needed, but as long as no contraindications are present, we find it reasonable to recommend anticoagulation with warfarin for patients with chronic AF.

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CASE-CONTROL STUDY OF SERUM IMMUNOGLOBULIN-E ANTIBODIES REACTIVE WITH SOYBEAN IN EPIDEMIC ASTHMA

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Since 1981, twenty-six asthma outbreaks Summary have been identified in Barcelona, all coinciding with the unloading of soybean in the harbour. Serum from patients with epidemic asthma and individually matched controls with non-epidemic asthma was assayed for immunoglobulin-E (IgE) antibodies against soybean antigens by means of a radioallergosorbent test. In 64 of 86 cases (74.4%) there was a reaction with commercial soybean antigen extracts, compared with only 4 of the 86 controls (46%) (odds ratio = 61; lower 95% confidence limit = 8·1). The statistical significance was greater for reactions with extracts of soybean dust taken from Barcelona harbour (odds ratio, unquantifiably high; lower 95% confidence limit = 11.7). No other serological covariate (total serum IgE levels or specific IgE levels against the commonest airborne allergens or legumes) confounded the association between serum anti-soybean IgE antibodies and epidemic asthma. These results support a causal relation between the release of dust during unloading of soybean at the harbour and the occurrence of asthma outbreaks, suggesting an underlying allergic mechanism.

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Introduction

SINCE 1981, twenty-six asthma outbreaks have occurred in the city of Barcelona. These outbreaks were characterised by sudden rises in emergency-room admissions for asthma. 1-3 Striking space clustering, hourly time clustering, and simultaneous time-space clustering strongly suggested that the outbreaks were of the point-source type. 3 The asthma cases were clustered near the harbour and near an industrial area. 3 A review of harbour unloading activities showed that all twenty-six outbreaks had coincided with the unloading of soybean, which in turn showed a significant association with epidemic asthma (unpublished).

We studied the relation between epidemic asthma and serum immunoglobulin-E (IgE) antibodies reactive with soybean antigens. We tested the hypothesis that epidemic asthma patients have higher levels of anti-soybean IgE antibodies than individually matched controls with non-epidemic asthma. Positive results would reinforce the evidence that asthma outbreaks had been caused by dust released during unloading of soybean in the harbour.

Patients and Methods

This study had a matched case-control design. 86 patients with epidemic asthma were matched individually to 86 patients with non-epidemic asthma. Cases and controls were selected from the medical records of emergency-room admissions for asthma at four large urban hospitals, which cover 90% of all emergencies in Barcelona. An emergency-room admission for asthma was defined as a visit during which any asthma-related diagnosis was recorded. To take account of differences in terminology, a panel of chest physicians drew up a list of expressions used that would qualify for inclusion as asthma.³ The identification of asthma admissions was made in all the participating hospitals by a specially trained physician from the coordinating centre. All records were reviewed and their completeness checked.

On Sept 4 and 7, 1987, two large asthma epidemics occurred, causing 157 emergency-room admissions for asthma (daily mean asthma emergency-room admissions for 1985–86 = 5.6 [SD = 4.7]). Serum samples were taken from 86 of these patients at the emergency room, who were considered as cases in this study; the concentration of patients—which led to the collapse of some services for several hours—precluded the collection of samples from the remaining 71 patients. Controls were taken from emergency-room admissions for asthma seen in the period October, 1987, to January, 1988, when no epidemic days occurred. Potential controls previously seen for asthma on an epidemic day were excluded. An

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