EUROPEAN ATRIAL FIBRILLATION TRIAL

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Secondary prevention in non-rheumatic atrial fibrillation

(Secundaire preventie bij niet-reumatisch atriumfibrilleren)

PROEFSCHRIFT

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Jeanette Christine van Latum
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PROMOTIECOMMISSIE

Promotores	:	Professor dr FGA van der Meché
		Professor dr J van Gijn
Co-promoter	:	Dr PJ Koudstaal
Overige leden	:	Professor dr DE Grobbee
		Professor dr FWA Verheugt

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"To this variety of apoplexy those are most liable who lead an idle life,
who are obese, whose face and hands are constantly livid
and whose pulse constantly unequal"

Wepfer, 1658

CONTENTS

LIST OF ABBREVIATIONS

AC	Oral anticoagulants
AF	Atrial Fibrillation
ASA	Acetylsalicylic Acid
Asp	Aspirin
CI	Confidence Interval
CT(-scan)	Computed Tomography (-scan)
DASYs	Disability-adjusted survival-years
EAFT	European Atrial Fibrillation Trial
ECG	Electrocardiogram
HR	Hazard Ratio
INR	International Normalised Ratio
ISI	International Sensitivity Index
MI	Myocardial Infarction
NRAF	Non-rheumatic atrial fibrillation
OR	Odds Ratio
Plac	Placebo
PT(ratio)	Prothrombin time (ratio)
Pyr(s)	Patient-year(s)
QASYs	Quality-adjusted survival-years
SD	Standard Deviation
SE	Systemic Embolism
TIA	Transient Ischaemic Attack
Yr(s)	Year(s)

GENERAL INTRODUCTION

It was in 1847 that Virchow first reported occlusion of arteries in the brain by thrombi that seemed to have originated in the heart; he called this phenomenon embolism (from the Greek word 'embolus' which means plug), a term that would later be used to describe, in general, the occlusion of some part of the cardiovascular system by impaction of a foreign mass transported through the bloodstream to the site of occlusion. Over the following decades, in their attempt to understand the underlying pathogenesis of cerebral infarction, the medical profession focused primarily on the concept of local "thrombosis cerebri" as a consequence of atheromatous degeneration of the vessel walls with adherent thrombus formation. It was not until the seventies that embolism from the heart was again recognised as an important cause of ischaemic stroke. With the introduction of improved echocardiographic techniques, more and more cardiac disorders were identified and linked to the occurrence of cerebral ischaemia and today, as much as 10-20% of patients with acute cerebral ischaemia are found to have a cardiac abnormality that may potentially have caused their stroke. The commonest source of cardiac embolism is non-rheumatic atrial fibrillation, a dysrhythmia that affects 2-5% of the general population over the age of 60. This thesis aims to provide a better insight into the relationship between non-rheumatic atrial fibrillation and ischaemic stroke, and of the value of antithrombotic treatment in the prevention of thromboembolic events in patients with non-rheumatic atrial fibrillation.

Chapter 1 reviews the available information on the epidemiology of atrial fibrillation and the associated risk of stroke. It continues with an evaluation of clinical studies that assessed the merits of antithrombotic treatment in the primary and secondary prevention of embolic events in patients with atrial fibrillation and concludes that adequate clinical trials are necessary to establish the effect of long-term anticoagulant treatment or aspirin in the secondary prevention of morbidity and mortality in patients with non-rheumatic atrial fibrillation and a recent transient ischaemic attack or minor ischaemic stroke.

A protocol for such a study was first submitted to the funding agencies (the Dutch Heart Foundation and Bayer Wuppertal) in 1987 and resulted in the start of the European Atrial Fibrillation Trial (study acronym EAFT) in October 1988. Design and conduct of this study are described in Chapter 2. This chapter also addresses specific problems related to the international and multicentre nature of the trial and offers detailed information on issues of data-handling and trial organisation.

The main results of the EAFT are presented in Chapter 3. Treatment effects of oral anticoagulation and aspirin were assessed primarily with conventional outcome event analyses (Chapter 3A). In addition, a more holistic approach was attempted through analysis of the obtained quality of life in the different treatment groups (Chapter 3B).

To ensure correct interpretation and generalisation of the main treatment effects reported in Chapter 3, further subgroup analyses were performed for the identification of clinically relevant predictors of recurrent vascular events in general and of stroke alone (Chapter 4) and for the determination of the optimal therapeutic intensity of long-term anticoagulation (Chapter 5).

Chapters 6 and 7 focus specifically on the CT-scan characteristics of cerebral infarcts in patients with non-rheumatic atrial fibrillation. In order to determine which CT-scan characteristics are typically associated with cardioembolic stroke, the CT-scan features of stroke patients in sinus rhythm (a cohort of 3,150 patients with transient or minor cerebral ischaemia who were enroled in the Dutch TIA trial) are compared with those of stroke patients with atrial fibrillation (the EAFT cohort) in Chapter 6. The finding of multiple, sometimes asymptomatic (= 'silent'), infarcts is often associated with atrial fibrillation, and this subject is addressed in Chapter 7.

Finally, Chapter 8 (general discussion) provides a critical review of the studies presented in this thesis, with recommendations for further research.

CHAPTER 1:
ATRIAL FIBRILLATION AND STROKE

"It is disgraceful in every art, and more especially in medicine, after much trouble, much display, and much talk, to do no good after all."
Hippocrates, Articulations, 44

Atrial fibrillation is the archetype of cardiac arrhythmias. Known in the 19th century as "arrhythmia perpetua", it was defined clinically by MacKenzie and electrocardiographically by Lewis at the beginning of this century.[171] Over the past decades, therapeutic management of atrial fibrillation has attracted relatively little interest among electrophysiologists and still depends largely on the use of two of the oldest drugs for heart disease: digitalis and quinidine. Yet atrial fibrillation remains a vexing problem for many clinicians. It is by far the most common arrhythmia, with serious clinical implications. Not only is atrial fibrillation often associated with concomitant cardiovascular disease, it is also recognised as an important indicator for future cardio- and cerebrovascular disease.

Prevalence, incidence and etiology

Estimates on the prevalence and incidence of atrial fibrillation differ widely between study cohorts, depending on the age and the general health of the studied population (Table 1.1). Amongst older patients it is, however, a relatively common dysrhythmia, affecting 2-5% of the general population over the age of 60, with an incidence that sharply increases with age. Atrial fibrillation is found in 6% to 19% of all stroke patients[21,27,38,79,107,143,165,208] and in 2 to 8% of patients with transient ischaemic attacks.[18,91,114] In most patients with atrial fibrillation, the arrhythmia can be attributed to organic heart disease or metabolic disorders. In western countries, hypertensive and ischaemic heart disease[104,105,116,145] (especially in association with heart failure) are more frequent as underlying conditions than the classical causes of atrial fibrillation -rheumatic heart disease and thyrotoxicosis- which are declining in incidence.[137] In a proportion of patients, atrial fibrillation is not related to any other heart disease (so-called "lone" atrial fibrillation). Depending on the exact definition used and the age of the studied popula-

Table 1.1 Prevalence of atrial fibrillation

Study	Study population	cohort assembly	patients (n)	Age (yrs)	Prevalence (%)
US Air Force[98]	US Air Force cadets and personnel	1957-1962	122,043	16-50	0.004
Tecumseh[146]	Community survey	1959-1960	5,129	≥ 16	0.4
Whitehall[76]	Screening of male civil servants	1967-1969	19,018	40-69	0.4
Reykjavik[145]	Population sample	1967-1970	9,067	32-64	0.28
CASS[34]	Multicentre registry: patients with angiographically proven coronary artery disease	...	18,343		0.6
				18-39	0.2
				40-59	0.4
				≥ 60	1.4
Hill[95]	asymptomatic patients form UK general practice	1983-1985	819	> 65	3.7
Edinburgh[111]	Random sample from city population	1972-1977	487	62-90	5.0
Australia[117]	Triennial population survey	1966-1981	1,770	60-64	1.7
				65-69	3.0
				70-74	7.0
				≥ 75	11.6
British Regional Heart Study[172]	Patient sample from town and group practices	1979-1980	7,727	40-59	0.7
Rose[160]	Screening of male civil servants	1971-1976	18,403	40-49	0.16
				50-59	0.37
				60-64	1.13
Shibata[188]	Population sample	1977-1983	1,339	> 40	1.2
Rochester[58]	Patients attending the Mayo clinic	1960	1,804	55-64	3.2
				65-74	4.5
				75-84	7.9
				≥ 85	25.0
Framingham[204]	Population sample	1948*	5,070	50-59	0.5
				60-69	1.8
				70-79	4.8
				80-89	8.8
Copenhagen[24]	Random population sample	1976-1978	13,088	> 35	0.6

* Evaluation after 34 years of follow-up

tion, lone atrial fibrillation constitutes 3% to 33% of all cases of chronic atrial fibrillation.[25,50,104,105,113,145] Paroxysmal atrial fibrillation is often a precursor of sustained atrial fibrillation in patients with structural heart disease, but this transition is uncommon in younger patients, most of whom have lone atrial fibrillation. The true incidence of paroxysmal atrial fibrillation is unknown, because patients may experience self-limiting episodes of paroxysmal atrial fibrillation in association with an acute illness (myocardial infarction, acute respiratory illness, cardiothoracic surgery and thyrotoxicosis).[137]

Risk of stroke

Several cohort studies have reported mortality rates in patients with atrial fibrillation of approximately twice that of those without atrial fibrillation.[34,76,105,111,117] In part, this reduced survival with atrial fibrillation is likely to be related to associated heart disease present in the majority of patients, but most studies found an independent relationship between atrial fibrillation and outcome, through an excess risk for systemic embolism. Although the term "systemic" embolism encompasses emboli to limb-, mesenteric- and renal vasculature in addition to the brain, the majority of all reports focus specifically on the relationship between atrial fibrillation and risk of ischaemic stroke. This is probably because 70% of the clinically recognised cardiogenic emboli involve the brain.[96,163]

The incidence of ischaemic stroke in fibrillating patients without rheumatic heart disease, so called non-rheumatic (non-valvulopathic) atrial fibrillation (NRAF), varies widely in different reports and depends on the characteristics of the studied patient population (Table 1.2). In general it is estimated to lie between 2% and 5% per year. In patients with "lone atrial fibrillation" the risk of embolism is substantially lower, ranging between 0.2 and 2.4% per year. Following initial embolism patients are at increased risk of suffering a recurrent embolic event. The stroke recurrence rate varies in different studies, but is generally estimated to lie between 10 and 20% yearly depending on the type of underlying cardiac abnormality.[16,47,70,125,164,165,174,175,208] The risk for early recurrence is reported to be even as high as 0.1% to 1.3% per day in the first 14 days after the initial event.[92,107,164,175] The consequences of these embolic strokes are often devastating, with either death or persisting severe neurological deficits in

Table 1.2 Stroke incidence in non-rheumatic atrial fibrillation (first strokes only)

Study	Age (yrs)	Mean follow-up (yrs)	Patient-years of observation	Stroke incidence (per 100 patient-years)
Population based				
Framingham[205]	50-59	6	218	2.8
	60-69	6	612	2.1
	70-79	6	654	4.9
	80-89	6	238	7.1
Reykjavik[145]	52	14	238	2.1
Whitehall[76]	...	10	673	1.8
British Regional Heart[76]	...	> 5	248	0.3
Shibata[188]	...	5.7	± 143	5.0
Rochester[58]	63	4.6	± 589	2.0
Copenhagen[24]	...	5	± 390	3.1 (all strokes)
Hospital based (in- and/or outpatients				
Roy et al[163]	± 54	2.5	302	4.0
Fisher[73]	± 70	± 4	192	8.8
Davis et al[58]	63	4.6	783	1.7
AFASAK Study[148]	74	1.2	403	4.7
SPAF Study[181]	67	1.3	731	5.7
CAFA Study[52]	67	1.3	248	4.4
SPINAF[70]	67	1.7	450	4.3
Flegel et al[75]	71	3.9	355	6.8
"Lone" atrial fibrillation				
Kopecky et al[113]	44	14.8	1440	0.5
Framingham[25]	±70	10.9	327	2.4
Close et al[50]	54	7.5	540	0.2
Paroxysmal atrial fibrillation				
Fortin et al[78]	62	6	200	2
Petersen et al[150]	66	2.9	± 830	2

40 to 70% of the affected patients.[35,107,148,165,174,181,209,210] Still, atrial fibrillation is also found in patients with transient ischaemic attacks and has been related to the occurrence of silent (subclinical) ischaemic strokes.[108,152] Despite the relatively benign outcome of such non-disabling events, they might herald future major cerebrovascular events or take a cumulative toll on the elderly patient's cognition.[157] It is clear that adequate strategies for primary and secondary prevention of vascular events are necessary.

Pathogenesis of AF related stroke

Both atrial fibrillation and ischaemic strokes are relatively common disorders among the elderly. When confronted with a stroke patient who happens to have atrial fibrillation, the relationship between the two therefore need not always be a causal one. A number of factors supposed to cause NRAF, e.g; age, atherosclerosis and hypertension, are equally well known risk factors for ischaemic stroke. It is estimated that in 20-50% of NRAF patients with stroke, the presence of AF is just coincidental, the dysrhythmia merely reflecting a state of advanced atherosclerosis.[17,26,42,102,-133,173,200] In some instances, the relationship might even be the other way around, that is, AF may have occurred because of the stroke.[197] Still, as indicated in the previous paragraph, there is ample evidence, both direct and indirect, for a more causal relationship between NRAF and cerebral ischaemic episodes even after correction for concomitant cardiovascular disease.[24,204] The distinct clustering of ischaemic episodes around the time of onset of atrial fibrillation,[47,150] the high embolism rate in patients with thyrotoxic atrial fibrillation,[47] data from epidemiological studies suggesting that patients with NRAF have a four- to tenfold increased risk of stroke but no increased risk of developing ischaemic heart disease in comparison to non-NRAF patients with similar risk profiles[24,25] and autopsy studies[42,102] all support this hypothesis. The underlying factor is generally thought to be left atrial enlargement with stasis and formation of intra-atrial thrombi which embolise to the systemic and cerebral vasculature. Why embolisation of these thrombi should have such an intermittent pattern (sometimes following each other in quick succession, only several minutes apart, in other cases several years apart) might theoretically be explained by subtle changes in blood viscosity and coagulability,[187,211] or by intermittent changes in blood flow patterns related to periodical changes in rhythm.[86]

Although largely overlooked in the literature, haemodynamic dysfunction related to atrial fibrillation might also play an important role in the pathogenesis of stroke in many patients with non-rheumatic atrial fibrillation, with or without embolism. Episodes of low cardiac output related to high or excessively low ventricular response rates might directly cause typical border zone cerebral infarctions related to hypotensive crises. Bogousslavsky reported that 18% of the patients with non-rheumatic atrial fibrillation and stroke had bradycardia below 50 beats per minute or decreased blood pressure (compared with their usual blood pressure) at the time of admission.[22] As no clinical or diagnostic measures have yet been developed that reliably distinguish between cardioembolic and arteriogenic strokes, choices for preventive measures have at best been ambiguous, sometimes depending only on whether the neurologist or the cardiologist was the first to see the patient.

Secondary prevention and other treatment strategies

Treatment strategies in stroke patients with non-rheumatic atrial fibrillation should not be focused solely on reducing the risk of recurrent stroke and systemic embolism, but should also take account of the underlying heart disease, with prevention of recurrent cardiac events and the treatment of the arrhythmia itself.

Antiarrhythmic treatment

With a rapid and uncontrolled ventricular rate, atrial fibrillation can become symptomatic in a patient because of a variety of complications such as hypotension, myocardial infarction, heart failure, reduced cerebral blood flow and diminished exercise capacity. In these cases, treatment is aimed at abolishing the pulse deficit, controlling the ventricular rate, and, if possible, eliminating the arrhythmia.[212] If acute atrial fibrillation is precipitated by myocardial infarction, respiratory illness, or thyrotoxicosis, it usually resolves with successful treatment of the underlying condition. Recurrent episodes of atrial fibrillation (paroxysmal atrial fibrillation) are more difficult to abolish completely so here the options are to reduce the severity, duration and frequency of these episodes. The most commonly used drugs are digoxin and quinidine, but it is advised to adapt the therapy according to patients' individual characteristics.[137] Although it has never been proven

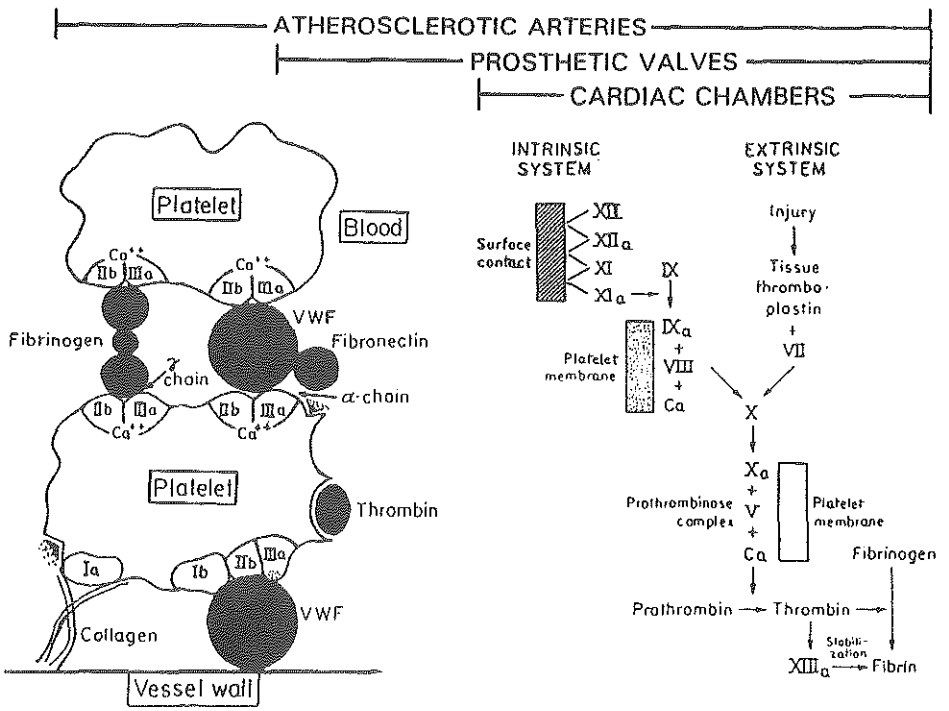
that electrical or pharmacological cardioversion actually reduces the risk of embolism, cardioversion is often undertaken in the expectation that in addition to a resolution of symptoms, the risk of embolisation might also be reduced.[61] In patients with sustained (e.g. chronic) atrial fibrillation, the likelihood that sinus rhythm can be restored depends on the duration of AF (the shorter the better), age of the patient, absence of underlying disease and heart failure, and a non-enlarged left atrium.[57] The rate of maintenance of sinus rhythm, even with the use of antiarrhythmic drugs, is low however, and the safety of some of these drugs has been debated.[33,71,74,137,158] In chronic AF careful control of ventricular response rate and cardiac output should at least prevent some of the haemodynamically induced cerebrovascular events.

Antithrombotic therapy

Thrombosis within the circulatory system has long been recognised as the principal mechanism responsible for cardiovascular morbidity and mortality, and various antithrombotic drugs have been used for purposes of prevention and therapy. The pathogenesis of thrombosis has been outlined more than a century ago by the pathologist Rudolf Virchow, who defined a triad of precipitating factors: endothelial injury, a zone of circulatory stasis, and a hypercoagulable state. In ischaemic stroke patients with non-rheumatic atrial fibrillation, two important factors in the formation of thrombi can be distinguished. The first is related specifically to thrombus formation in the cardiac (atrial) chambers through blood stasis. In atrial fibrillation effective mechanical activity is impaired, causing stasis of blood flow which is tantamount to conditions of low shear rate, in which activation of the coagulation system rather than of platelets leads to fibrin formation and constitutes the predominant factor in the development of intracavitary thrombi.[180] However, studies on spontaneous echo contrast in atrial fibrillation have suggested that low shear rate conditions not only lead to erythrocyte aggregation but also directly cause platelet deposition and aggregation.[15]

The second element in the formation of thrombi is related to general vascular injury through atherosclerosis, with thrombus formation in coronary, carotid or intracerebral arteries.[81,180] With the injury of the endothelial cells lining the intimal layer of the cardiovascular system, for

Figure 1.1



instance through rupture of an atherosclerotic plaque or after ischaemic injury, marked platelet activation occurs, with release from intracytoplasmic granules of substances as adenosine diphosphate, thromboxane A_2, and serotonin, all of which further potentiate platelet aggregation and thrombus formation. Vascular damage also stimulates thrombin formation through both the intrinsic (surface-activated) and extrinsic (tissue factor dependent) coagulation pathways, in which the platelet membrane facilitates interactions between clotting factors (Figure 1.1). Thrombin then promotes the formation and polymerisation of fibrin, but it is also a powerful activator of platelet aggregation. Whatever the exact sequence of events, it is obvious that both platelets and the coagulation system are interrelated in the genesis of arterial or intra-cardiac thrombosis. Treatment options would therefore involve the use of oral anticoagulation, antiplatelet drugs or even a combination of the two.

Figure 1.1 (legend)
Left: Schematic representation of biochemical interactions between platelet membrane receptors, vessel wall, and adhesive macromolecules during platelet adhesion and aggregation. Right: Intrinsic and extrinsic systems of the coagulation cascade, and association of clotting factors with platelet membrane. Arteriogenic disease is associated with both platelet and coagulation processes. Prosthetic valves stimulate mainly the coagulation cascade, although platelet activation occurs. Thromboembolism from cardiac chambers mainly results from activation of the coagulation system. Ca, calcium; Ia, glycoprotein Ia; Ib, glycoprotein Ib; IIb/IIIa, glycoprotein IIb-IIIa;VWF, von Willebrand factor. (From: Stein, Fuster et al: Antithrombotic therapy in cardiac disease, an emerging approach based on pathogenesis and risk.[180])

Anticoagulant therapy - Coumarin blocks vitamin K-dependent gamma-carboxylation of glutamate residues. This action results in production of modified factors VII, IX, X and prothrombin molecules, which are inactive in promoting coagulation. The rationale behind the use of anticoagulation is generally accepted because its beneficial effect in the management of venous thrombosis and pulmonary embolism had already been extensively demonstrated[99] and because the structure of stasis-related thrombi in atrial fibrillation is probably comparable to those formed in venous thrombosis. By 1992, the value of anticoagulants for the primary prevention of vascular events in non-rheumatic atrial fibrillation had been convincingly established by 5 controlled clinical trials[23,52,70,148,181] (Tables 1.3 and 1.4) which reported risk reductions ranging from 37% to 86% in intention-to-treat analyses. This effect of anticoagulant therapy was not offset by an increased risk of haemorrhage. The incidence of major bleeding complications was low, ranging between 0.4 and 1.7 per 100 patient-years. The risk of intracranial bleeding ranged between 0.2 and 0.4 per 100 patient-years. It remained uncertain, however, whether extrapolation of these findings to secondary prevention was justified. Studies on long-term anticoagulant therapy in post-myocardial patients had shown significant reductions in the rate of recurrent myocardial infarction and cerebrovascular events and a beneficial trend towards all-cause mortality with relatively low incidence rates of major haemorrhagic complications.[4,178,179] Yet, similar controlled trials involving post-stroke patients had never been performed, despite the continuing recommendations voiced by authors of 'meta-analysis' and

'review reports' on the potential value of acute or long-term anticoagulant therapy in cerebrovascular disease.[68,101,201] Common problems with respect to the available reports on anticoagulation in stroke patients in general, have been lack of randomised and blinded control design, small number of patients entered, variability of clinical definitions for the diagnosis of transient ischaemic attack or ischaemic stroke, scarcity of information on past history of cerebrovascular disease, inclusion of patients both with and without potential sources of cardiac embolism, lack of information on bleeding complications, and overlap in treatment with heparin.[68] With respect to the use of anticoagulants specifically for the prevention of vascular (embolic) events in patients with non-rheumatic atrial fibrillation and a recent stroke, even fewer clinical data are available. Again, most studies on the prevention of recurrent embolic stroke were non-randomised and uncontrolled, included a mixture of underlying causes for cardiogenic embolism, or included only small numbers of patients.[1,9,12,41,54,70,125,147,186]

Table 1.3 Randomised primary prevention trials of antithrombotic therapy in non-rheumatic atrial fibrillation

	AFASAK	SPAF	CAFA	BAATAF	SPINAF
1°/2° prevention	1°	1°	1°	1°	1°+2°
Target INR	2.8-4.2	2.0-3.5	2.0-3.0	1.5-2.7	1.5-2.5
Control group	aspirin and placebo	aspirin and placebo	placebo	usual care	placebo
Aspirin (mg/day)	75	325			
Anticoagulants blinded	no	no	yes	no	yes
1° outcome events	S,SE,TIA,ICB	S,SE	S,SE,ICB,FB	S	S
patient recruitment	1007	1330	383	420	525
mean follow-up (yrs)	1.2	1.3	1.3	2.2	1.8

AFASAK: Atrial Fibrillation, Aspirin, Anticoagulation Study from Copenhagen, Denmark. BAATAF: Boston Area Anticoagulation Trial for Atrial Fibrillation. CAFA: Canadian Atrial Fibrillation Anticoagulation study. SPAF: Stroke Prevention in Atrial Fibrillation study. SPINAF: Veterans Administration Stroke Prevention in Nonrheumatic Atrial Fibrillation study.
1°/2°: primary and secondary; FB: fatal bleed; ICB: intracerebral bleed; INR: international normalised ratio; MI: myocardial infarction; S: stroke; SE: systemic embolism; TIA: transient ischaemic attack; V: vascular death (including fatal non-cerebral bleed).

Table 1.4 Main results of primary prevention trials in patients with non-rheumatic atrial fibrillation

STUDY	Primary outcome events° Annual rate/100 pyrs			RR Reduction	Major bleeds Annual rate/100 pyrs		
	AC	ASA	Plac	95% CI	AC	ASA	Plac
AFASAK	2.7		6.2	56% ($p < 0.05$)*	1	0.2	0
		5.2	6.2	18% (- 60% to 58%)			
SPAF‡	2.3		7.4	67% (27% to 85%)	2	1.4	1.6
		3.6	6.3	42% (9% to 63%)			
CAFA	3.5		5.2	37% (- 63% to 76%)	3		1.5
BAATAF	0.4		3	86% (51% to 96%)	1		0.4
SPINAF	0.9		4.3	79% (52% to 90%)	2		0.9

AC: Anticoagulation; ASA: aspirin; Plac: Placebo or control treatment;
pyrs: patient-years; RR: relative risk; CI: confidence interval.

° Definitions of the primary events differ between studies (see Table 1.3).

AFASAK data are derived form the intention to treat analysis that were published at a later date.

* No confidence interval available.

‡ Data for anticoagulant/placebo comparison were derived from group 1 patients, data for aspirin/placebo comparison from group 1 and 2.

Furthermore, most of the recent studies focused primarily on treatment in the acute phase after stroke, with a view to reducing the high risk of early recurrence.[44,112,162]

Antiplatelet therapy - Although theoretically sound, the pharmacological rationale for the use of antiplatelet drugs is generally less accepted. These drugs may inhibit platelet function by a variety of actions but it has been questioned whether they are at all effective in the prevention of intra-atrial thrombus formation. Their value in the prevention of arteriogenic emboli however, has been unequivocally demonstrated by the data from the Antiplatelet Trialists' Collaboration.[5] In 11 trials of antiplatelet therapy (mainly aspirin) among about 20,000 patients with transient or non-disabling cerebral ischaemia during a weighted mean follow-up of 27 months, there was an absolute reduction in recurrent vascular events of about 1.6 per 100 patient-years and an absolute reduction in all-cause mortality of 0.53 per 100 patient-years. Therefore a certain degree of efficacy is to be expected for those patients in whom the AF-related stroke results from concomitant atherosclerotic disease rather than from cardiac embolism itself. Subsequent analyses of the Antiplatelet Trialists' Collaboration have also demonstrated a beneficial effect of antiplatelet therapy in venous thromboembolism,[6] and low embolic event rates were found in an uncontrolled study in which patients with prosthetic valves were treated with aspirin.[141] Two of the primary prevention studies in patients with non-rheumatic atrial fibrillation (AFASAK and SPAF)[148,181] included an aspirin arm in their study designs in order to address the efficacy of antiplatelet treatment. No benefit of aspirin was found in the AFASAK study (which used 75 mg aspirin/day) but the SPAF study found a 42 percent relative risk reduction with 325 mg aspirin/day, which was most marked in patients under 75 years of age.

Why the European Atrial Fibrillation Trial?

A drawback of oral anticoagulant therapy is the complexity of administration which requires regular monitoring of prothrombin time prolongation and, more importantly, the risk of haemorrhage. Not only major bleeds but also recurrent minor bleeds can oblige patients to alter their lifestyle; the overall burden of anticoagulation for the individual

patients should therefore not be underestimated.[139] For NRAF patients who already suffered a recent ischaemic stroke that did not leave them severely disabled, prevention of worse events remains an important issue. However, an aggressive approach to the treatment of these patients is often tempered by their advanced age and by the fear for major haemorrhagic complications. The probably more advanced stage of cerebral atherosclerosis together with the presence of a fresh ischaemic brain lesion[43,45] and often concomitant hypertension might lead to unacceptably high risks of intracerebral bleeding.[77,80,119,120,122,123,177,202] Since in elderly and increasingly less mobile patients a high standard of anticoagulant control is not easily maintained on a long-term basis, also because of concomitant medication and poor drug compliance, clinicians have remained hesitant to extrapolate the results from primary prevention studies to secondary prevention. In this specific patient population, the cheaper, safer and less burdensome preventive therapies in the form of antiplatelet drugs might well be as adequate as oral anticoagulant treatment and certainly more widely applicable.[166]

In order to address this problem, 108 hospital departments (mostly of neurology) all over Europe decided to collaborate in a randomised controlled trial with open oral anticoagulant treatment (INR 2.5-4.0), or double-blind treatment with either aspirin (300 mg/day) or placebo in NRAF patients with recent minor ischaemic stroke or transient ischaemic attack.

CHAPTER 2:
DESIGN AND CONDUCT

"Come now, and let us reason together, saith the Lord."
Isaiah 1:18

EUROPEAN ATRIAL FIBRILLATION TRIAL: Design and Conduct

Background

By the late 1970's it had become clear that atrial fibrillation in the absence of rheumatic valvular disease is associated with an increased risk of ischaemic stroke.[73,96,207] Furthermore, it was also evident that once the patient had suffered such an initial event, the risk of a recurrent vascular event was even higher. The need for preventive treatment was apparent but unfortunately no consensus existed on the subject especially with respect to the secondary prevention with antithrombotic therapy. Whereas some physicians opted for oral anticoagulants, others would prescribe acetylsalicylic acid, and some physicians would choose not to treat. Part of the confusion was caused by the uncertain pathogenesis of the strokes in patients with non-rheumatic atrial fibrillation. Although a substantial proportion are probably a direct result of cardiogenic embolism, other events are almost certainly caused by associated disease of arteries supplying the brain. Another important factor was the fear surrounding anticoagulant treatment. The physicians treating these stroke patients were also the ones most likely to be confronted with the intracranial haematomas related to anticoagulant use, in contrast to most of the cardiologists involved in primary prevention. Understandably, these physicians were more reluctant to use anticoagulation as treatment for secondary prevention where most of their patients were of advanced age, hypertensive and almost certain to have a high risk of intracranial bleeding associated with ischaemic cerebrovascular disease.

In 1986, a group of Dutch neurologists from several institutions joined together in order to discuss the possibilities for a large clinical trial which

would determine the efficacy and safety of anticoagulation and aspirin for the secondary prevention of vascular events in patients with non-rheumatic atrial fibrillation and a transient ischaemic attack or minor ischaemic stroke. It soon became clear that Dutch neurologists alone would not be able to randomise enough patients within a reasonable period of time. When several other European colleagues expressed their interest to collaborate, the idea for the European Atrial Fibrillation Trial (acronym: EAFT) was born. A first protocol was submitted to the Dutch Heart Foundation and to the Bayer Company in 1987. Together they agreed to guarantee the substantial financial backing and so it was possible by October 1988 to enter the first patient into the EAFT.

Objectives

The main objective of the EAFT was to investigate whether oral anticoagulants or acetylsalicylic acid (ASA), when given separately, would be effective in the prevention of death and disability, and more specifically of vascular death, non-fatal stroke, non-fatal myocardial infarction, and systemic embolism in patients with non-rheumatic atrial fibrillation and a transient ischaemic attack or minor ischaemic stroke. These possible treatment effects were compared with the risk of fatal or disabling haemorrhagic complications in patients treated with anticoagulants or ASA. A subsidiary question was whether the risk of recurrent embolism was related to atrial fibrillation being recent, chronic or intermittent, to age, or to the presence of an enlarged left atrium or congestive heart failure.

Study design

The EAFT was a randomised, controlled, multicentre, clinical trial in patients with non-rheumatic atrial fibrillation who had suffered a recent transient ischaemic attack or minor ischaemic stroke. Patients were classified as eligible for treatment with oral anticoagulants (group 1) or not eligible (group 2). Patients in group 1 were randomised for open anticoagulant treatment or double-blind treatment with acetylsalicylic acid (aspirin) or placebo. Patients in group 2 were randomised only for double-blind treatment with aspirin or placebo. Placebo groups were included in the study design in order to evaluate the absolute effect of both studied treatment regimens (anticoagulants and aspirin).

Randomisation

Eligible patients were to be randomised as soon as possible after their qualifying event. Therapeutic measures aimed at limiting the extent of ischaemic brain damage, e.g. haemodilution, glycerol, calcium antagonists and subcutaneous heparin as prophylaxis for thrombophlebitis were allowed as far as they did not delay early randomisation. If anticoagulants or aspirin had been prescribed after the qualifying event by a physician not involved in the trial (e.g. the emergency department or by a general practitioner), this did not exclude the patient from randomisation as long as the treatment was stopped at study entry. If the patient was already on some form of antithrombotic treatment at the time of the qualifying event, this treatment was to be stopped at the time of randomisation. Patients were randomised centrally by means of a telephone call to an independent randomisation office in Amsterdam. At randomisation each patient received a unique identification number. These numbers were in serial order for each participating centre, preceded by the centre code. The randomising physician was asked to identify whether or not the patient was eligible for treatment with anticoagulants. Treatment would then be assigned by means of pre-prepared randomly generated coded lists (see Appendix A). Two separate lists were available for each centre, one for group 1 patients and one for group 2 patients. Codes indicated either open anticoagulant treatment (code = AC; not included in the randomisation list for group 2 patients) or double-blind aspirin-placebo treatment (codes 01 to 10). Randomisation in both group 1 and 2 was balanced in blocks of 10 to ensure equal sizes of the treatment groups per centre. Centres were not aware of the size of these blocks.

Blinding

Treatment with oral anticoagulants was not blinded for a number of reasons. Although other trials had shown that it was technically possible to 'fake' anticoagulant control in placebo-treated patients by using series of sequential sham prothrombin time results and adjusting the study medication dose accordingly,[4,52,70] a lot of effort is required for the training and monitoring of all involved laboratory personnel. It was expected that each centre would randomise only a few patients for anticoagulants and also that each of these patients would probably have to be monitored by

different institutions (specialised anticoagulant clinics, hospital laboratories, general practitioners or otherwise). It therefore seemed highly unlikely that any attempt to regulate anticoagulant control centrally, nationally or even on a regional level would turn out to be feasible. Further reasons included the ethical issues involved when two-thirds of the patients in group 1 would undergo unnecessary monthly blood tests, and the risk that, because of the complicated organisation, codes for anticoagulant treatment might not be broken as quickly as deemed necessary in case of emergencies. An additional methodological advantage of the open design was that there would be no logistic contamination between the simple prescription of aspirin (or placebo) and the more complicated control of anticoagulation. In other words, we compared strategies (pragmatic design) rather than drugs (explanatory design).[170]

Aspirin and placebo treatment were double-blind. Only the central trial pharmacist and the manufacturer of the trial tablets were aware of the codes (01 to 10) assigned to either aspirin or placebo medication. These codes could be broken only by the central trial pharmacist, after a specific request to do so. Requests would be honoured only if unblinding actually influenced the further treatment of the patient, or in case of specific request by the patient. If at all possible results of the unblinding would not be communicated directly to the randomising physician but only to the other physicians involved in the management of the patient at that particular time.

All data that had to be audited centrally (e.g. outcome events and side-effects but also CT-scan auditing and ECG-reading) were first blinded before being submitted to the various committees.

Number of centres involved

Although the question posed in this study is of great clinical importance, only few patients with a transient ischaemic attack or minor ischaemic stroke have atrial fibrillation. Even hospitals with a large referral population did not expect to be able to randomise more than 5 - 10 patients per year. It was therefore clear that as many centres as possible needed to be involved in this study if any meaningful sample size was to be obtained

within a reasonable period of time. (A list of all participating centres is included in Appendix A).

Selection of patients

Source

Patients were identified through the outpatients' and inpatients' clinics of 108 participating centres, both teaching and non-teaching hospitals in 12 European countries and Israel. Depending on the local organisation of each hospital, different medical disciplines would be involved, ranging from emergency wards through wards of general medicine and/or geriatrics to highly specialised stroke units.

Definition of disease state under investigation

Eligible patients had non-rheumatic atrial fibrillation in combination with a recent transient ischaemic attack or minor ischaemic stroke. Non-rheumatic *atrial fibrillation* was defined as fibrillating atrial waves documented on ECG or Holter monitor with absent p-waves. There was to be no evidence or suspicion (both by history, clinically and on echocardiography) of rheumatic valvular disease. Patients with transient self-limited atrial fibrillation due to other causes (thyrotoxic atrial fibrillation) or with atrial flutter were not to be randomised. Patients with intermittent atrial fibrillation and sinus rhythm on the ECG at the time of the qualifying event were eligible if atrial fibrillation had been documented by ECG or Holter monitoring in the past 2 years and no successful cardioversion had been obtained in the mean time.

For the diagnosis *transient ischaemic attack* we required neurological symptoms consisting of:

1. unilateral weakness, language disorders, partial or complete blindness of one eye;
2. a minimum of two of the following: bilateral, alternating weakness or ditto sensory symptoms, vertigo, double vision, disturbance of swallowing, uncoordinated movements and sudden weakness of both legs;
3. blindness of one half of the visual field or disorders of articulation.

Symptoms should last at least 1 minute and not longer than 24 hours. They should develop within a few seconds, and should not progress from one part of the body to another in an orderly march. Syncope, loss of consciousness or confusion, convulsions, incontinence of urine and faeces, dizziness, scintillating scotoma and focal symptoms associated with migrainous headache were not considered acceptable for the diagnosis.

Minor ischaemic stroke was defined by means of the same clinical criteria as for transient ischaemic attacks but symptoms had to last longer than 24 hours and the residual degree of disability (measured up to 3 months after onset) should not exceed grade 3 of the modified Rankin scale (Figure 2.1).[14,194] No attempt was made to distinguish cardioembolic strokes from other forms of ischaemic stroke as it was considered questionable whether specific neurological features allowed one to do so reliably.

Figure 2.1 Rankin handicap score

RANKIN HANDICAP SCORE (total handicap)

0	No symptoms
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out some previous activities but able to look after own affairs without assistance
3	Moderate disability: symptoms which significantly restrict lifestyle and/or prevent totally independent existence (e.g. requiring some help)
4	Moderately severe handicap: symptoms which clearly prevent independent existence though not needing constant attention (e.g. unable to attend to own bodily needs without assistance)
5	Severe handicap: totally dependent, requiring constant attention day and night
6	Deceased

Exclusion criteria

Exclusion criteria are listed in Figure 2.2. Patients were excluded if 1. Their last cerebral ischaemic event had taken place more than 3 months before

Figure 2.2 Exclusion criteria

EXCLUSION CRITERIA

Ia. **GENERAL**
- last cerebral ischaemic event > 3 months ago
- intercurrent illness with life expectancy < 12 months
- total handicap (including both neurological and non-neurological symptoms) > Rankin scale 3
- inability to return for follow-up appointments
- age < 25 years
- unwillingness to participate
- poor medication compliance expected
- history taking is unreliable because the patient speaks only a foreign language
- scheduled for carotid endarterectomy

Ib. **CARDIAC**
- rheumatic mitral valve disease
- eligibility for cardioversion, both electrical and pharmaceutical. If cardioversion fails to produce permanent sinus rhythm the patient can still be randomised.
- myocardial infarction less than 1 month previously
- endocarditis
- cardiac aneurysm
- atrial myxoma
- prosthetic heart valve of any type
- dilated cardiomyopathy (cardiothoracic ratio > 0.65, or heart/thorax volume > 800ml/m^2 BSA)
- scheduled for coronary bypass surgery or PTCA within the next three months

Ic. **BLOOD ANALYSIS**
- anaemia (haemoglobin < 6.0 mmol/l)
- thrombocytopenia (platelet count < 100 x 10^9/l)
- hyperthyroidism (T4 > 150 nmol/l)
- hypoglycaemia (blood glucose < 2.0 mmol/l)

Id. **CT-SCAN**
- intracranial haematoma
- cerebral tumour
- subdural haematoma
- subarachnoid haemorrhage
- randomisation should be postponed in case of haemorrhagic infarction

Ie. **CONTRAINDICATIONS TO BOTH ACETYLSALICYLIC ACID AND ANTICOAGULANTS**
- liver failure
- active peptic ulcer in past 3 years
- bleeding disorder
- prior intracerebral haemorrhage
- bronchial asthma and known hypersensitivity for acetylsalicylic acid
- continuing need for the use of NSAIDs or other platelet-antiaggregating agents
- renal failure exacerbated by aspirin
- active source of bleeding in the gastrointestinal or urinary tract within the past 6 months
- pregnancy

IIa. **CONTRAINDICATIONS FOR ANTICOAGULANT TREATMENT (exclusion from group I)**
- chronic alcohol abuse
- age (decisions on age limits however are left to the discretion of the randomising physician)
- chronic, poorly controlled hypertension (diastolic > 100 mmHg or systolic > 180 mmHg on at least two successive days, while receiving antihypertensive treatment)
- haemorrhagic retinopathy

randomisation. 2. They were found to have disorders mimicking cerebral ischaemia. 3. Other sources of cardiac embolism were present. 4. Haematological disorders were present that might have precipitated cerebral ischaemia. 5. Contraindications existed for both acetylsalicylic acid and anticoagulants or acetylsalicylic acid alone. 6. Factors were present that would hamper follow-up or interfere with continued compliance to study medication.

Patients with specific contraindications for the use of oral anticoagulation could be entered in group 2 and were randomised only for aspirin or placebo. No exhaustive list of contraindications to oral anticoagulants was defined: the decision was left to the discretion of the treating physician.

Informed consent

All patients were to be informed about the background and the objectives of the study by the local investigators. This included information about possible side-effects of the study treatments, the inclusion of a placebo group, and the implications of anticoagulant control. Patients were reassured that the trial results were monitored at regular intervals by an independent committee and that requests to withdraw from the study would be honoured at any time. Patients were explicitly informed that they could refuse to participate in the study and that in that case they would receive normal standard care. Information sheets were provided to supplement the oral explanation, in all relevant languages (Appendix A). These information sheets could be adapted according to the rules and regulations of local, regional or national ethical committees. In principle informed consent was required from each individual patient.

Treatment schedules

Anticoagulants

Each investigator was free in the choice of anticoagulant congener to be used in the patients randomised to anticoagulation and whether or not oral anticoagulant treatment was initially combined with heparin. These choices depended mostly on personal experience with and availability of the different trade marks and treatment regimens. The dose of anticoagulant

treatment was controlled by measurement of the prothrombin time (PT). To accommodate variations in compositions and responsiveness of the thromboplastins and methods necessary for PT measurement, all centres were asked to use calibrated commercial preparations only. This would allow reporting of PT values in International Normalised Ratio (INR) equivalents, which are independent of the reagents and methods used.[30,110,126] The INRs had to be maintained at 3.0 with a range of 2.5 to 4.0.[127,155] PT had to be monitored at least once a month (Appendix A).

Aspirin/placebo

The hospital pharmacy of each participating hospital had supplies of overboxes with trial medication, each overbox containing 40 patient packs of tablets. The packs were coded 01 to 10 (four of each). Five of these codes had been randomly assigned to aspirin tablets, the other five to placebo. Patients randomised to aspirin/placebo were allocated a treatment number between 01 and 10. This treatment number would then be transferred to a trial prescription form (Appendix B) and sent to the local hospital pharmacy (in some instances trial medication would be supplied directly through the randomising physician). There the patient would receive a pack which carried the corresponding code. Each pack contained 150 tablets, sufficient for 4 months of treatment, plus a safety margin for missed appointments. Patients were advised to take one tablet daily, with water in the morning at/or after breakfast. Aspirin tablets contained 300mg acetylsalicylic acid, placebo tablets were identical in taste and appearance. The labels on the patient packages were detachable so that part of the label including the medication code could be sticked on the prescription sheet and sent to the trial office. This made it possible to check whether patients were actually receiving the treatment they were randomised for. Compliance was further monitored by pill counts at each follow-up visit. Prescription labels describing the method of use in the appropriate language and displaying the telephone number of the national coordinators were issued with each patient package; they were further labelled with a Bayer logo which stated clearly that the packages contained trial tablets to be used for trial purposes only and which also displayed batch/charge numbers.

Duration of therapy

Patients were asked to continue with their study medication for the duration of the trial. Treatment withdrawal was to be discouraged if at all possible. The occurrence of outcome events or transient side-effects were not by definition considered reasons for discontinuation. If treatment was discontinued, follow-up was still required.

Evaluation of patient response

Baseline data

The patient's personal characteristics, clinical condition and history were recorded by means of a simple and concise baseline data form (Appendix B). The requested data included information on the patient's age and sex; nature and duration of the qualifying event and number of previous cerebrovascular events; the degree of handicap by means of the modified Rankin scale; cardiac status involving information on congestive heart failure, angina pectoris, duration of atrial fibrillation; history of prior cardiovascular surgery and/or cardiovascular events; the presence of cardiovascular risk factors as diabetes, hypertension, smoking status and the existence of other vascular symptoms such as intermittent claudication. Common definitions and criteria that were to be applied were formulated in a User's Manual but apart from random checks no formal data monitoring was planned.

Ancillary investigations included blood analysis, twelve lead ECG and Holter when applicable, chest X-ray, a pre-randomisation brain CT-scan and echocardiography. Non-invasive investigation of the carotid arteries was optional but the results were recorded if they had been performed. CT-scans and ECG's were audited and coded centrally (Appendix B). Echocardiography reports were transcribed to a common format in order to summarise the most relevant information.

Follow-up data

Follow-up visits were planned at four-monthly intervals, independent of the patients' continued use of the allocated study treatment. If patients were unable or unwilling to visit the outpatient clinic, follow-up information was obtained through the general practitioner or in any other

feasible way. At follow-up visits, the occurrence of TIA's, outcome events (see below), hospital admissions, and possible adverse effects were recorded, as well as blood pressure, pulse rate, current handicap (by means of the modified Rankin scale) and changes in medication (Appendix B). All reported adverse effects (including bleeding complications) were reviewed centrally, without knowledge of patient's treatment assignment. Bleeding complications were further classified according to severity. Fatal bleeding complications had to be documented by convincing clinical evidence or autopsy. Non-fatal bleeding complications were considered major if hospital admission and blood transfusion or surgery were necessary or when these caused a permanent increase in disability. Compliance was assessed by interviews with the patients, pill counts and prothrombin-time monitoring (by means of INR).
All patients had to be followed for the duration of the study, with an additional year of follow-up after termination of the randomisation period.

Criteria of response
(1) The primary and pre-determined measure of outcome was a composite event of vascular death, non-fatal stroke (including intracranial haemorrhage), non-fatal myocardial infarction or systemic embolism, whichever occurred first. Secondary outcome events were death from all causes, and all strokes, fatal or non-fatal. Interim analyses considered only major thromboembolic events (vascular death, major stroke, major systemic embolism and myocardial infarction) and major strokes (fatal or major disabling). *Vascular death* included sudden death (death seen by an eyewitness, with a reliable observation of the interval between onset of symptoms and death; or the patient being found dead), or death from stroke, myocardial infarction, congestive heart failure, systemic embolism, extra-cranial bleed, and other vascular causes (including pulmonary embolism and peripheral vascular disease). The diagnosis of *non-fatal stroke* required a focal neurological deficit persisting for more than 24 hours. Equivocal symptoms, in particular those not assessed by a neurologist, were classified as possible or no stroke, and were not included in the analysis. CT-scans made at the time of the outcome event were centrally audited by physicians who were unaware of the allocated treatment. On the basis of these scans the distinction between ischaemic stroke, ischaemic

stroke with haemorrhagic transformation, and primary intracerebral haemorrhage was made. All non-fatal strokes were further classified as non-disabling (leaving no functional disability, Rankin grade 0 or 1), moderately disabling (increase of Rankin score to grade 2 or 3) and major disabling (Rankin grade 4 or 5); this assessment of functional disability took place 3-6 months after onset of symptoms. The diagnosis of *systemic embolism* was clinically defined as abrupt vascular insufficiency of limbs or internal organs associated with clinical or radiological evidence of arterial occlusion, in the absence of previous obstructive disease; it did not include pulmonary embolism. Systemic embolism was classified as major if the event required surgery or caused permanent increase of disability. *Myocardial infarction* had to be documented by at least two of the following characteristics: a history of chest discomfort, specific cardiac enzyme levels more than twice the upper limit of normal, or the development of Q waves on the standard 12-lead electrocardiogram.

All outcome events were independently classified by at least three members of the Clinical Audit Committee, after the medical records had been summarised and edited to ensure that the reviewers remained unaware of the allocated treatment (Appendix B). Differences of opinion were discussed within the Executive Committee, which was also blinded, and then decided by majority vote.

(2) It was thought that restricting analysis to the outcome events stipulated above would have several disadvantages. First, such analysis would allow only for known benefits and side-effects of the studied treatment and not for the unexpected ones. Furthermore, such analyses would not take into account that different outcome events may have differing impacts on patients' lives. For instance, the degree of disability after a small myocardial infarction may be minor compared to the effects of a severely disabling stroke, yet both events would have equal weight in the proposed analyses. From the patient's perspective, it is the prevention of death and disability that counts, regardless of its cause. Disability was therefore measured with the modified Rankin scale. This scale not only measures the overall independence of patients and allows comparison between patients with different kinds of neurological and non-neurological deficits, but it also adds one further dimension by referring to previous activities. This is

important because patients may be independent but still dissatisfied by restriction of their former life style.
Attempts were made to try and analyse the effect of the different treatments on the time spent in each class of the Rankin scale.

Planned statistical analyses
The principal comparisons of treatment efficacy for both primary and secondary events would be oral anticoagulation versus control in group 1 and aspirin versus placebo for group 1 and 2, both separately and combined, the latter with the provision that no differences in treatment effect existed between the two groups. Subgroup analyses were planned to compare the rates of primary outcome events and treatment efficacy according to the level of anticoagulation, prior history of congestive heart failure, type of atrial fibrillation, sex, and age category.

The occurrence of primary outcome events in the treatment groups would be compared in terms of hazard ratios that were obtained by means of the Cox proportional-hazards model and adjusted for baseline differences (Egret statistical package) where applicable. The precision of the hazard ratio estimates would be described with the 95% confidence intervals obtained from the Cox model.[103]

All analyses were to be based on an intention-to-treat premise in which all patients, also those withdrawn from study medication, remain in the treatment groups they were initially randomised for. Additional on-treatment analyses were planned that would include only outcome events that had occurred whilst study medication was being taken or within 28 days after treatment discontinuation.

Quality control

Sample size estimation
Assuming α = 0.05 (two-sided testing) and β = 0.20, an incidence of recurrent non-fatal stroke and vascular death of 20% in the first year and 10% yearly thereafter in untreated patients, a mean follow-up of 24 months and treatment efficacy estimations of 30% risk reduction with anticoagulation and 25% risk eduction with aspirin, it was estimated that 1500 patients would be required to obtain adequate sample sizes.[131] Later

this estimate could be recalculated to 1000 patients as randomisation was slow and the estimated mean follow-up would be longer than anticipated.

Interim analyses

During the trial the study results were monitored by a Data Monitoring Committee. These interim analyses were initially planned on a yearly basis, but the results of the primary prevention trials that were published over the course of the trial and which showed a substantial therapeutic effect of oral anticoagulation prompted a different scheme. Unblinded, aggregated data were submitted to the Data Monitoring Committee 6, 18, 27, 36 and 44 months after the start of the trial. The Data Monitoring Committee were to advise the Steering Committee if, in their view, the comparison in the EAFT provided both (a) 'proof beyond reasonable doubt' (i.e. at least 3 standard deviations) that for all, or for some types of patients one particular treatment was clearly indicated or clearly contraindicated in terms of a net difference in seriously life-threatening events, and (b) evidence that might reasonably be expected to influence materially the patient management of many clinicians who were already aware of other trial results.[7]

Data handling

One of the major, albeit easily neglected, aspects of clinical trial is the collection, checking and organising of data, as erroneous or incomplete data may seriously compromise the subsequent analyses.[132,154] All forms were completed by an on-site data-handler which could be either the physicians themselves or specially appointed research nurses. Copies of the forms were retained at the local centres (carbonless multi-copy sheets were used) and the originals were sent to the coordinating centre. As each form arrived a series of checks was carried out:

(a) General checks: Was the form sent at the right time, had all previously required forms for that patient been received, did the identification number and assigned treatment correspond to that on the randomisation form?

(b) Missing data: Were there any specific items or even whole sections of the forms that had not been completed? If outcome events or side-effects were reported, had additional clinical information, CT-scans, ECG's etc. been enclosed?

(c) Range checks: Were there any items that did not fall within the appropriate range of replies? An example is that of errors such as length being reported at an exceptionally low value of 54 cm.
(d) Logical checks: Were there any inconsistencies in replies to different but related questions? For instance: unexplained deterioration in Rankin score or date of CT-scan being before the date of the qualifying event.

Usually these checks were carried out as the data were transferred to a computer data-base. Similar checks also controlled the data-entry process. Range checks for instance were incorporated in the data-base program so that inappropriate codes could not be entered. Because our data-entry system did not support double data entry, all forms were visually cross-referenced with the data-base entries in the final phase of the study. At that time also computer analyses were performed to detect any persisting data inconsistencies.

Investigators were notified that their forms had been received by the trial office and edit queries were enclosed in case of missing data or data errors that could not be solved at the trial office. Copies of outstanding edit queries and requests for overdue forms were enclosed with each monthly newsletter.

Each centre was visited at least once and random checks were made to ensure agreement between the information in patients' hospital files and the data on the study forms. Discrepancies were discussed with the local investigators and corrected in cases of evident error. The primary intention of these checks however was to identify any existing ambiguity or confusion with respect to the entries on the data forms so that these could be taken into account when anything was inferred from the data in future analyses.

Organisation

Research group

The EAFT study group was formed by the following organisational units: The Steering Committee, the Executive Committee, the Data Monitoring Committee, the Clinical Audit Committee and Advisory Board, 108 participating centres and the trial office, including the clinical coordinator (Appendix A).

Local investigators from the participating centres entered eligible patients into the trial and were responsible for continued follow-up and compliance to the study medication. The other committees were formed in order to guarantee correct trial conduct and to safeguard the quality of data collection and analyses. The Steering Committee was composed of one or more representatives from each participating country. They were usually senior clinicians already involved in other European trials (e.g. the European Carotid Surgery Trial[69]) who were well known and acknowledged for their scientific merits by their compatriot colleagues. The Steering Committee held the following responsibilities: 1. Responsibility for the general design and conduct of the trial, including preparation of essential study documents, such as manual of operation, data forms, treatment protocol etc. 2. Considering and adopting changes in study procedures as necessary and desirable during the course of the trial. 3. Making decisions on resource allocation and on priorities for dealing with competing demands in the trial. 4. Reviewing the progress of the study in achieving its main goal and taking steps required to enhance the likelihood of success in achieving them. 5. Reviewing and reacting to recommendations and/or general advice of the Data Monitoring Committee and the Advisory Board. For these purposes the Steering Committee met approximately once a year with a slightly higher frequency in the first stages and a lower frequency once the trial was well underway. Most committee members had an additional responsibility as National Coordinator. Any problems related specifically to national laws and/or customs were dealt with by the national coordinators. They acted as liaison officers for both the coordinating centre as well as the participating centres in their country in cases where language problems or differences in clinical practice might have caused confusion with respect to protocol and data form issues. The enlistment of suitable new centres to partake in the study was primarily the responsibility of these national coordinators, as was the finding of any additional sponsoring on a national or regional level. The Chairman of the Steering Committee served as principal investigator for the duration of the trial. In this function he was spokesman for the study and responsible for maintaining communications within the study and with the sponsor.

An Executive Committee was appointed for the handling of day-to-day issues on behalf of the Steering Committee. This included 1. Scheduling and

preparation of meetings and progress reports for the various committees and collaborators. 2. Obtaining funding for the main study and budget management. The Executive Committee met on a (two-)weekly basis.

An independent Data Monitoring Committee, consisting of a neurologist, an epidemiologist and a statistician, had an advisory function towards the Steering Committee. Their task was the monitoring of accumulating data for early evidence of treatment effects between the study treatments and the placebo group. In addition, the Data Monitoring Committee reviewed the quality of data-collection and adherence to protocol by the participating centres. The Data Monitoring Committee was entitled to recommend early termination of the trial to the Steering Committee and to advise the Steering Committee on operational procedures affecting the quality of the trial.

The Advisory Board consisted of cardiologists, epidemiologists, specialists in internal medicine and vascular surgery, an ophthalmologist, a haematologist, a computer consultant and representatives of the sponsoring agencies. They were invited to Steering Committee meetings, usually as non-voting members, to clarify and give their opinions about specific study details that lay in their field of speciality.

Subcommittees included 1. The Clinical Audit Committee that was responsible for the classification of blinded outcome event reports. Each outcome event was audited by at least three representatives of the committee on a rotating basis. The Clinical Audit Committee encompassed all Steering Committee and Advisory Board members. 2. The CT-scan Audit Committee consisted of neurologically trained members of the Executive Committee. 3. The ECG Audit Committee was formed by the cardiologists in our Advisory Board.

Trial Office

The trial office was first located at the University Hospital of Utrecht (May 1988 to July 1990) and thereafter at the University Hospital of Rotterdam (August 1990 to July 1993). Its staff consisted of a trial coordinator and a data-manager. Its primary responsibilities were: 1. Maintaining communiations between the collaborating centres and ensuring adherence to the prooocol. 2. Data collection and entry, quality control and analysis. 3. Providing study progress reports and patient reports to the various committees and

participating centres. 4. Administration and control of trial medication distribution. 5. Organisation of annual collaborators' meetings. 6. Budget management.

Time schedule

Original plans envisaged a randomisation period from May 1988 to May 1991, an additional follow-up period till May 1992, with study results to be published by the end of 1992.

Some delay was experienced in the actual recruitment of patients so that randomisation took place between October 1988 and May 1992, follow-up continued to May 1993 and the final results were published in November 1993.

Financial aspects

The European Atrial Fibrillation Trial was sponsored by the Dutch Heart Foundation from May 1988 to May 1992. This support covered personnel costs, mailing, printing, data-handling facilities and most of the travel expenses. Medication production, labelling and distribution were sponsored and executed by the German Bayer Company and their subsidiaries in all involved countries. Bayer also financed personnel costs in the last year of the study. Additional sponsoring was obtained from the UK Chest Heart and Stroke foundation, regional funding projects and other pharmaceutical firms involved in the organisation of the various collaborators meetings. The University Hospitals of Utrecht and Rotterdam supplied office facilities.

Discussion

Patient recruitment

At the start of the EAFT it was thought feasible to enter 1,500 patients within 3 years of randomisation and funding proposals were based on these calculations. This, however, turned out to be too optimistic. The first difficulty was the inability to start randomisation procedures quite as soon as planned due to delays in obtaining the permissions of local Ethical Committees in the various centres and unforeseen problems relating to the distribution of trial medication. These delays and the fact that data-forms,

operating manuals and data-base systems had yet to be set up at the formal start of the sponsoring period, caused a delay of almost half a year before patient recruitment could be started in the first few centres to almost 1 year before the last countries could actually join. It was clear almost from the start that the study period (originally with randomisation from May 1988 to May 1991, and 1 year of follow-up to May 1992) would have to be prolonged with at least one year. Even then, as time went by, it became more and more obvious that patient recruitment was much slower than anticipated. When it was decided to close the randomisation in May 1992, 1007 patients had been entered. The number of outcome events, however, exceeded expectations and it was thought that with the actual sample size the ß-error would be acceptably small for the expected treatment effects we were hoping to discern. Either way, by that time a considerable "study fatigue" had set in among the randomising physicians and any further prolongation of randomisation did not seem advisable.

Several factors have played an important role in lowering the expected accrual rate:

1. The nature of the disease being studied

As explained in Chapter 1, cardioembolic strokes are usually thought to be severely disabling. When estimating the number of patients eligible for the study, physicians might have underestimated their patients' actual disability which is in fact quite a common experience in many clinical trials. Confronted with patients in whom one had to assess the eligibility for study entry, disabilities that might in retrospect have seemed insignificant now played a much more important role. Another factor was that patients were often seen relatively late by the randomising investigators. By that time, some had already experienced a recurrent stroke which left them seriously disabled and ineligible for study entry.

In the first phase of the study, a number of patients were not randomised because they had already been treated with either aspirin or oral anticoagulation at the time of their qualifying event, altogether not an unlikely occurrence given the underlying cardiac disorder. It was therefore decided at the first collaborators' meeting to allow randomisation of these patients as well.

2. Interaction with other physicians

In a typical setting the principal investigator of a participating centre would be either a neurologist or a general physician. Because all patients had to be evaluated cardiologically (ECG and echocardiography) narrow collaboration with the local cardiology department was mandatory. In many instances however, cardiology departments did not support study participation. A common occurrence was the initiation of either anticoagulant or aspirin treatment without prior consultation with the local investigator. In these cases it would usually be considered unethical to discontinue this treatment and to randomise the patient. Even when the cardiologist merely advised a certain treatment, it could be difficult for the randomising physician to ignore this advice. Centres with a high accrual rates usually had a close working relationship with their cardiology department, from which cardiologists were also represented in the study team.

3. Ethical issues of the placebo group and obtaining informed consent

Although all participants and the ethical committees of their centres had agreed to the inclusion of a placebo group in the study design, the theoretical justification for such a decision was easier than its practical application. As Hill(1963) put it quite pointedly:

> *The situation implicit in the controlled trial is that one has two (or more) possible treatments and that one is wholly, or to a very large extent, ignorant of their relative values (and dangers). Can you describe that situation to a patient so that he does not lose confidence in you - the essence of a doctor/patient relationship - and in such a way that he fully understands and can therefore give an 'understanding' consent to his inclusion in the trial?*

Hill illustrates clearly most of the important issues involved when trying to enter a patient in a controlled trial. First of all, the essence of randomisation is that as a physician you have no clear idea about the best treatment to give, in which circumstance it is quite ethical to let "fate" determine the decision. As more and more primary prevention studies published their results showing a clear benefit for anticoagulation, and because of continuing peer pressure from colleague physicians (see point 2), quite a few physicians were confronted with the ethical problem of having to

randomise for a placebo group. Even if some of them could still "live" with this decision from a theoretical point of few, their ingrained apprehension towards the placebo treatment might possibly have influenced their selection of patients for randomisation and might also have been reflected on the patients they were trying to convince to participate in the study. This brings up the second important point of obtaining informed consent. It is well known that different countries have adopted widely divergent attitudes to informed consent and in contrast to the situation in the United States, obtaining written informed consent for every patient in a clinical trial is not a legal requirement in most European countries. Although National Health Committees might strongly recommend that consent should be obtained for individual patients, in practice the final decision on how to go about it is left to the discretion of local or regional ethical committees. Informed consent procedures were usually considered sufficient if they included informing the patient about the essentials of the trial and the treatment options involved. An important argument for this attitude is that the final responsibility of deciding whether or not it is proper to prescribe, or withhold, a treatment always lies with the doctor who cannot divest himself of it simply by means of an illusory consent.[154] To what extent detailed information was given on the implications of placebo treatment might well have differed between centres and from patient to patient and will probably have influenced the individual accrual rates of the centres. Centres in which informed consent procedures were stringently adhered to (e.g. obtaining written consent) certainly had more trouble recruiting patients. The pragmatic attitude towards clinical research prevalent in European countries can be considered one of the main factors that this trial could be done and completed in a satisfactory manner.[2,51,198]

4. Other factors

Quite possibly recruitment would have been better if more time and effort had been invested in the actual visiting of centres. Annual meetings nor monthly newsletters can take the place of person-to-person contact and a number of participants have actually voiced their discomfort of being only one of so many and not feeling 'personally' involved in the trial. In this context having randomisation done by an external service, for the mere reason of 24 hour availability (which in retrospect was hardly ever an

important issue) might not have been such a good choice. Randomisation calls were often the only contact with the collaborators and could be very helpful in establishing a comfortable 'working' relationship. Luckily, copies of the randomisation lists were available at the trial office and because of a close collaboration with the randomisation service we were able to randomise at both sites simultaneously.

The strength of a clinical trial is to establish a working routine in which all eligible patients are seen and randomised as part of the day-to-day clinical practice. If only a few patients are found to be eligible per year, such an ingrained routine will not be reached and randomising a patient will never become 'a matter-of-course'. Having to randomise over-the-border and in a foreign language at that, will not have simplified matters as reflected by the fact that of the 146 centres interested to join the EAFT, only 108 actually randomised patients.

Multicentre trials and quality control

Current trends in research are in favour of multicentre clinical trials, not only because they are a means to ensure enrolment of an adequate number of patients within a feasible period of time. The fact that a trial involves patients and clinicians from several centres implies that a more heterogeneous population is included in the study population which provides a broader basis for generalisation of the study results. Furthermore, because different clinics and clinicians are involved the need for continuing discussion to resolve the differences in treatment, data collection policies and the formal organisational structure required for the monitoring of protocol adherence should all lead to a high standard in design, conduct and interpretation of the study.

There are, however, also a number of disadvantages to consider, apart form purely organisational and financial ones. The same heterogeneity allowing for broader generalisation might also make it more difficult to detect treatment differences. Unbridled forms of heterogeneity are therefore not to be welcomed and careful control is required to safeguard strict protocol adherence. Consistency with respect to measurements, clinical observations and data recording must be maintained by continuous training, and explanation, and by the use of definition lists. It is this last point that has given rise to most of the discussion surrounding multicentre

clinical trials.[129] Big is not always beautiful, nor simple always wise. In an attempt to detect even small treatment differences or to study relatively uncommon conditions, trials have been mounted that not only surpass the borders of the investigator's clinic but also that of his country. Rather than bogging down the collaborators (often working pro deo) with complex study designs, cumbersome forms and bulky manuscripts containing definitions of every possible clinical parameter that might be measured, investigators are starting to choose simple study designs with one page forms often leaving the interpretation of clinical features to the discretion of each participating clinician. The truth, as always, most probably lies somewhere in the middle.

Certainly, studying a heterogeneous population supplies one with the opportunity for subgroup analysis, for instance, evaluating whether treatment effects differ between patient groups with varying baseline characteristics. In order to benefit from this opportunity sufficient data should be collected to be able to identify these varying baseline characteristics which again implies that entry forms should not be too concise. Similar considerations apply for the issue of quality control. From a pragmatic point of view only clear-cut definitions for eligibility, in- and exclusion criteria as well as definitions for the measure of outcome need to be defined, requiring no such control for other clinical variables. Considering that all investigators involved have successfully completed their medical training implies that all of them are aware of the meaning of general clinical expressions, e.g. the distinction between dysphasia and dysarthria. The interpretation of these clinical definitions might differ because of differences in training and local, regional or national notions, but are nevertheless to be respected as it is unlikely that any degree of teaching, explanation or training in conjunction with the trial (and therefore short and temporary) is going to change these attitudes. Furthermore, when the results are published often no opportunity is given to elaborate on these definitions so that the results are going to be interpreted according local customs anyway. Not specifying clinical definitions, however, leads to interpretational reporting rather than the reporting of facts. This not only influences the degree to which, in the final phase of the study, conclusions can be drawn from the gathered data, but it also makes it difficult to perform additional forms of quality control such as on-site data audits

during the course of the study. If, on the other hand, one does decide to guarantee consistent use of measurements, clinical definitions and data recording, the financial implications and the additional workload for data-management personnel should certainly be weighed against the added value.

The EAFT was not only a multicentre, but also a multinational trial and had the additional problem that only a small number of patients were expected to be recruited by each centre. It was therefore judged of paramount importance to make the data-forms as simple and as concise as possible. Although pilot forms were tested by volunteering physicians from the coordinating clinics, in retrospect it would have been better to include volunteers from other centres and other nationalities in order to identify existing ambiguities with respect to language, terminology and the way in which certain questions were formulated. Some evident errors in the forms could have been prevented that way. Given the fact that at the start of the study it was already clear that underlying cause of stroke might influence the expected benefit of the different study treatments, it may perhaps seem odd that so few of the questions at study entry were focused on the elucidation of this suspected etiology. With respect to the extent of quality control it is evident that the investigators of the EAFT were inclined to have a more pragmatic point of view. Collaborators meetings and site-visits were planned in order to clarify and check adherence to the most basic principles of the study protocol (definition of in- and exclusion criteria, use of study medication, reporting of outcome events) but apart from offering guidelines on these matters no interventional measures were taken. Some inconsistencies in this policy can be detected; for instance CT-scans were centrally audited with great care, whereas baseline characteristics (including clinical symptoms of the qualifying event) were not checked at all apart from occasional verifications at site-visits.

Organisation

In order to ensure a sound execution of a trial it is essential not only to have a good protocol, adequate financial backing, properly defined criteria for quality control and an appropriate administrative support system, but also to ensure clear delineation and separation of responsibilities within the whole organisational structure.

Important separations are said to include separation of personnel responsible for patient care from those responsible for safety monitoring; separation of the investigative and advisory roles; separation of sponsor and investigative roles and separation of the data collection and data processing functions.[132] About the organisational structure of the EAFT one might argue that, even though these requirements were generally met, the concentration of nearly all central tasks and most of the decision-making largely within the coordinating centre, involving only a very small group of people, may have restricted the range of ideas presented to the steering committee and investigative group, and have made it more difficult to establish the checks and balances needed for a robust structure.

Conclusion

In all sincerity, it can be said that with the design and conduct of the European Atrial Fibrillation Trial, every effort was made to ensure adherence to the guidelines of Good Clinical Practice as formulated by the European Community in 1991,[51] in so far as they were applicable given the fact that no innovative drugs were being studied. With standards and regulations for clinical research evolving as rapidly as they have done over the past years, studies of better quality are being performed but, unfortunately, are also getting more expensive to conduct. In the EAFT, some issues of quality control and the use of standard operating procedures might have been neglected, but in that case lack of financial and personnel support almost certainly played an important role. Due to the same low-budget character of the trial, however, it can be safely said that issues of financial reimbursement and other secondary benefits cannot have instigated possible fraudulent practices. All investigators were involved because of professional motivations and it was therefore in everyone's interests to maintain a high standard of performance. The end of the EAFT possibly also signals the end of an era in which large multicentre trials could be conducted on this basis. More and more requests for financial reimbursement are being voiced not only by the investigators, and by other involved departments within their institutions, but also by health insurance companies and other third parties. With the increased costs of clinical research, it is becoming harder to obtain sufficient sponsoring, and more and more trials will necessarily have to be initiated by the drug companies

as only these still have the resources and the motivation from a commercial point of view to do so. How this affects the research projects that still need to be mounted in order to evaluate current clinical practice is a question to be seriously considered by Government agencies, charities and other funding institutions. It would be a questionable development if in the long run the generally accepted standards and regulations for clinical research would, and could, apply only to for-profit contract research firms working by order of the larger pharmaceutical companies, leaving the non-profit oriented research to define their own standards.

CHAPTER 3A:
MAIN RESULTS

"I have fought a good fight, I have finished my course, I have kept the faith."
II, Timothy 4:7

EUROPEAN ATRIAL FIBRILLATION TRIAL: Main results

Introduction

Non-rheumatic atrial fibrillation (NRAF) can be found in about 15%[175,207] of all stroke patients, and is by far the most common source of cardiogenic embolism to the brain. In different studies the stroke recurrence rate varies between 2% and 15% in the first year, and 5% yearly thereafter, with a mortality rate of 5% per year.[47,175] It is still uncertain which medical treatment is the most effective in the secondary prevention of these thromboembolic complications. In the primary prevention of cerebral embolism in patients with NRAF, five clinical trials[23,52,70,148,149,181] have shown unequivocal evidence of the value of anticoagulants. In addition, one study found a significant benefit for aspirin, in particular in patients under 75 years.[181] However, extrapolation of these findings to NRAF patients with a recent transient ischaemic attack (TIA) or minor ischaemic stroke may not be justified.[166,199] Firstly, these patients are likely to have more advanced atherosclerosis of intracerebral blood vessels,[143,200] which with a fresh ischaemic brain lesion and higher mean age may lead to a much higher risk of intracerebral bleeding.[122,130,177] Secondly, in at least a third of the patients with NRAF and recent cerebral ischaemia the stroke is related to an arterial lesion rather than to embolism from the heart[17,47] and aspirin may be the most effective drug in those patients.[5,134] One randomised trial has addressed the value of anticoagulation in the secondary prevention of stroke in patients with NRAF,[70] but with only forty-six patients entered in the study no conclusions could be drawn.

We have investigated the value of anticoagulants and aspirin by entering 1007 patients with NRAF and a recent TIA or minor ischaemic stroke in a randomised, placebo-controlled multicentre clinical trial, the European Atrial Fibrillation Trial (EAFT).

Patients and methods

Details on the methods of the European Atrial Fibrillation Trial are described in detail in Chapter 2. In summary, eligible patients were those over 25 years of age who had suffered a TIA or minor ischaemic stroke (grade 3 or less on the modified Rankin scale)[14,194] in the previous 3 months and in whom atrial fibrillation had been documented by electrocardiography at the time of the qualifying event or, in case of paroxysmal atrial fibrillation, in the preceding 24 months, and if echocardiography showed no evidence of rheumatic valvular disease. Patients eligible for anticoagulant treatment (group 1) were randomly assigned to receive either open-label oral anticoagulants, or double-blind treatment with aspirin or matched placebo. Criteria of ineligibility for assignment to oral anticoagulant treatment included the unwillingness of patients or their physicians to accept this form of therapy, for instance because of circumstances associated with excessive risk of haemorrhage. Age limits were not defined but left to the discretion of each randomising physician. Patients not eligible for treatment with anticoagulants were entered in group 2 and randomised to double-blind treatment with either aspirin or placebo. Oral anticoagulant treatment was adjusted to obtain International Normalised Ratios (INR) between 2.5 and 4.0, with a target value of 3.0.[62,127]

All patients were followed at four monthly intervals for the duration of the study, with an additional year of follow-up after termination of the randomisation period.

The primary and pre-determined measure of outcome was a composite event of vascular death, non-fatal stroke (including intracranial haemorrhage), non-fatal myocardial infarction or systemic embolism, whichever occurred first. Secondary outcome events were death from all causes, and all strokes, fatal or non-fatal. All outcome events were independently classified by at least three members of the Auditing Committee for Outcome events, after the medical records had been

summarised and edited to ensure that the reviewers remained unaware of the allocated treatment. Differences of opinion were discussed within the Executive Committee, which was also blinded, and then decided by majority vote. The occurrence of adverse events was recorded at each follow-up visit for all patients. All possible side-effects (including bleeding complications) were reviewed by the Executive Committee, without knowledge of patient's treatment assignment. Bleeding complications were further classified according to severity. Fatal bleeding complications had to be documented by convincing clinical evidence or autopsy. Non-fatal bleeding complications were considered major if hospital admission and blood transfusion or surgery were necessary or when these caused a permanent increase in disability.

Statistical analysis

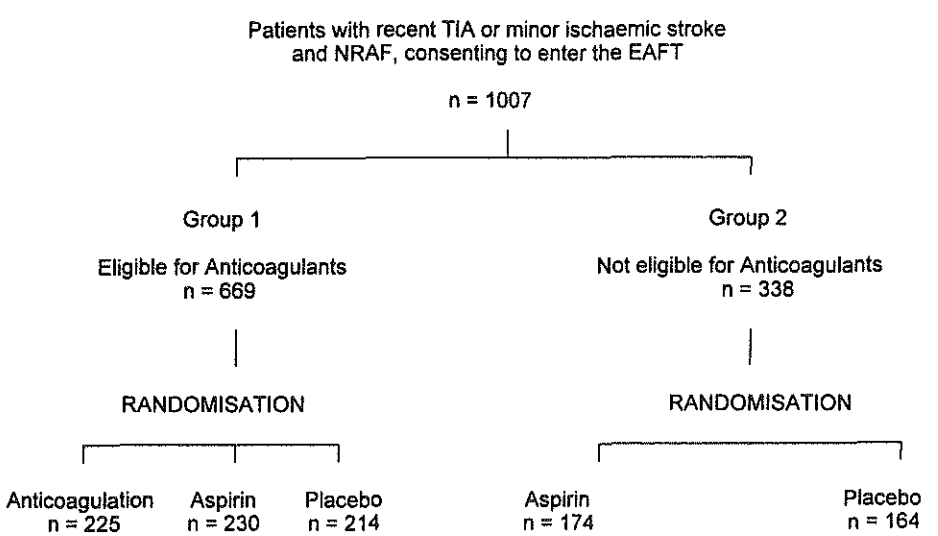
The principal comparisons of treatment efficacy for both primary and secondary events were oral anticoagulation versus control in group 1 and aspirin versus placebo for group 1 and 2 both separately and combined, the latter provided that no differences in treatment effect existed between the two groups. Baseline comparisons between group 1 and group 2 were performed by means of chi-square test for categorial data and a t-test for continuous data. The occurrence of primary outcome events in the two treatment groups was compared in terms of the hazard ratio (HR), which may be interpreted as a relative risk. The hazard ratios were obtained by means of the Cox proportional-hazards model and adjusted for baseline differences (Egret statistical package[67]) where applicable. The precision of the hazard ratio estimates was described with the 95% confidence intervals obtained from the Cox model. Risk reductions can be calculated as (1-HR); for instance a hazard ratio of 0.80 is equivalent to a risk reduction of 20%. All analyses were based on an intention-to-treat premise except when reported otherwise. Additional on-treatment analyses were performed by including only outcome events that had occurred whilst study medication was being taken or within 28 days after treatment discontinuation.

Results

Patient characteristics

Over a period of 43 months, 1007 patients were recruited; 669 patients in group 1 (eligible for anticoagulants), the remaining 338 in group 2 (not eligible for anticoagulation) (Figure 3.1). Age was the main reason for ineligibility for anticoagulant treatment (55%); other reasons were chronic poorly controlled hypertension (13%), a history of haemorrhagic episodes such as haemorrhagic retinopathy or haemorrhagic infarction (16%), chronic alcoholism (5%), refusal to use anticoagulants either by patient or by a physician outside the trial (4%) and questionable compliance (6%). The reasons for ineligibility remained unclear in 1% of the patients. Five patients had been inappropriately enroled in the study; 3 had had no atrial fibrillation ever, 1 had a cerebral tumour at study entry and one had a primary intracerebral haematoma on entry CT-scan; these five patients were included in the intention-to-treat analyses but not in the on-treatment analyses.

Figure 3.1 Flowchart of randomisation



Clinical and demographic characteristics of the patients in group 1 and 2, according to treatment assignment, have been summarised in Table 3.1. Some of the more important significant differences were the older age in group 2 compared with group 1 (mean age 77 yrs vs 71 yrs, $p < 0.001$) and the higher prevalence of a history of hypertension in group 2 (52% vs 44%; $p = 0.02$).

Follow-up

All patients had their last follow-up visit between April 1 and April 30, 1993. The mean duration of follow-up was 2.3 years with a minimum of 12 and a maximum of 55 months. Two patients were lost to follow-up.

Medication compliance

The most common reason for the withdrawal of study medication was the occurrence of an outcome event. Other important reasons for discontinuation, shown in Table 3.2, occurred at an average rate of 10/100 pyr in AC assigned patients and 20/100 pyr in both aspirin and placebo patients. Because the aspirin/placebo blind was not broken routinely on withdrawal, treatment was unblinded for only 3 patients in the course of the trial.

Treatment outcomes: Anticoagulation versus Control

The rate of vascular death, non-fatal stroke, myocardial infarction and systemic embolism was substantially reduced in those assigned to oral anticoagulant treatment (8/100 pyrs) compared with those on control (17/100 pyrs) (hazard ratio 0.53; 95% confidence interval (CI): 0.36 - 0.79; Table 3.3. Figure 3.2). With respect to the reduction in risk of stroke alone the effect of oral anticoagulant treatment was even more impressive (hazard ratio 0.34; 95% CI 0.20 - 0.57). Anticoagulants reduced the risk of subsequent major disabling or fatal stroke by 62% (hazard ratio 0.38; 95% CI 0.18 - 0.81; $p = 0.012$). No significant benefit of oral anticoagulants was found with regard to mortality (vascular and non-vascular; hazard ratio 0.82, 95% CI 0.54 - 1.26), vascular death alone (hazard ratio 0.76; 95% CI 0.47 - 1.24; $p = 0.27$) or major thromboembolic events (hazard ratio 0.70; 95% CI 0.44 - 1.13; $p = 0.14$).

Table 3.1 Demographic and Clinical Characteristics of the Study Groups

Baseline characteristics	Group 1 AC	Group 1 Control	Group 1 + 2 aspirin	Group 1 + 2 Plac	Group 1	Group 2	
No. of patients[1]	225	214	404	378	669	338	
Men (%)	55	58	59	53	59	49	*
Mean Age ± SD yrs	71 ± 7	70 ± 8	73 ± 8	73 ± 8	71 ± 7	77 ± 8	*
< 70 yrs (%)	37	43	33	31	41	18	*
Qualifying event (%)							
Transient ischaemic attack	28	22	23	20	24	20	
Minor ischaemic stroke	72	78	77	80	76	80	
Time between qualifying event and randomisation (%)							
≤ 14 days	46	38	44	41	44	43	
History (%)							
Multiple strokes in the year prior to randomisation	19	25	22	24	22	22	
Minor stroke > 1 yr ago	8	7	8	6	8	6	
Hypertension	43	41	49	47	44	52	*
Diabetes	12	14	13	13	13	13	
Hypercholesterolaemia	12	7	10	7	10	9	
Regular smoking	19	22	20	18	21	14	*
Angina pectoris	11	12	11	11	11	11	
Myocardial infarction	7	10	7	9	8	7	
Cardiac status (%)							
Chronic atrial fibrillation	78	72	75	76	75	78	
Onset AF > 1 year earlier	54	55	52	57	53	57	
Congestive heart failure	8	10	11	12	9	13	
Cardiothoracic ratio > 50%	25	23	22	24	23	25	
Echocardiography (%)							
Cardiac thrombus	5	2	1	2	3	1	
Left atrial diameter > 40 mm	44	44	41	42	43	39	
CT-scan of the brain (%)							
Appropriate infarct	43	42	38	42	41	40	
Other infarct	19	22	17	23	20	20	
Multiple infarcts	12	13	10	13	11	11	
White matter hypodensity	14	13	18	17	14	23	
Mean BP ± SD (mmHg)							
Systolic	145 ± 20	147 ± 21	149 ± 21	148 ± 21	146 ± 21	151 ± 21	*
Diastolic	84 ± 11	85 ± 11	86 ± 11	86 ± 12	85 ± 11	87 ± 13	*

[1] 1007 observations, 1006 notification forms, 987 observations for CT-scan characteristics, 994 observations for echocardiography characteristics

* denotes a significant difference ($p < 0.05$) in baseline characteristics between groups 1 and 2.

AC: Anticoagulants; Plac: Placebo; SD: Standard Deviation; AF: Atrial Fibrillation; BP: Blood pressure

Table 3.2 Reasons for discontinuation of trial medication

Variable	Group 1		Group 1 + 2	
	AC	Control	aspirin	Placebo
Time - no. taking medication/ no. at risk (%)*				
Start	225/225 (100)	214/214 (100)	404/404 (100)	378/378 (100)
6 months	196/211 (93)	158/184 (86)	306/359 (86)	279/324 (86)
1 year	171/195 (88)	138/166 (83)	259/324 (80)	229/283 (81)
2 years	118/134 (88)	66/95 (69)	147/208 (71)	117/171 (68)
3 years	62/68 (90)	31/45 (69)	67/102 (66)	55/79 (70)
Reason for discontinuation - no. of patients				
Inappropriate inclusion	1	1	1	2
Wrong medication prescribed at randomisation	0	4	2	4
Non-fatal stroke	0	23	30	41
Other non-fatal outcome event	1	5	8	11
Bleeding events	18	3	13	9
Other adverse effects	4	6	19	13
New indication for AC	0	10	11	14
New indication for aspirin	0	2	10	5
Poor compliance	6	2	11	5
Patient's request	7	15	29	26
Physician outside trial advised against trial participation	3	14	17	22
Other reasons	8	11	18	19
TOTAL	48	96	169	171
Treatment of choice after stop - no. of patients (%)				
None	17 (35)	14 (15)	41 (24)	35 (21)
Aspirin	27 (56)	36 (38)	56 (33)	54 (32)
Anticoagulants		39 (41)	42 (25)	58 (34)
Other	3 (6)	5 (5)	15 (9)	13 (8)
Unknown	1 (2)	2 (2)	15 (9)	11 (6)

* At risk for the primary outcome event - vascular death, non-fatal stroke, non-fatal myocardial infarction or non-fatal systemic embolism

AC: Anticoagulants

Table 3.3 Primary and secondary events: Anticoagulation versus Control

	Anticoagulants n = 225	Control n = 214	HR (95% CI)
follow-up years*	507 yrs	405 yrs	
PRIMARY OUTCOME EVENT‡	43 (8/100 pyr)#	67 (17/100 pyr)	0.53 (0.36 - 0.79; p = 0.001)
Non-fatal strokes	18	47†	
Non-fatal myocardial inf.	2	5	
Non-fatal systemic embolism	1	4	
Vascular death	22	11	
Cerebral	2	1†	
Cardiac	14	7	
Non-cerebral bleed	3	1	
Other°	3	2	
ALL STROKES‡	20 (4/100 pyr)	50† (12/100 pyr)	0.34 (0.20 - 0.57; p < 0.001)
Ischaemic strokes, CT	16	39	
Major/fatal	5	15	
Moderately disabling	3	10	
Non-disabling	8	14	
Cerebral bleeding	0	0	
Undefined, no CT	4	11	
Major/fatal	3	4	
Moderately disabling	1	4	
Non-disabling	0	3	
ALL DEATHS	41 (8/100 pyr)	44 (9/100 pyr)	0.82 (0.54 - 1.26; p = 0.37)
Vascular death	30	35	
Cerebral	8	18	
Cardiac	15	12	
Non-cerebral bleed	3	1	
Other°	4	4	
Non-vascular death	11	9	

* Follow-up years are given for the composite primary outcome event. Patient-years of exposure for other outcome events varied slightly

‡ First events only

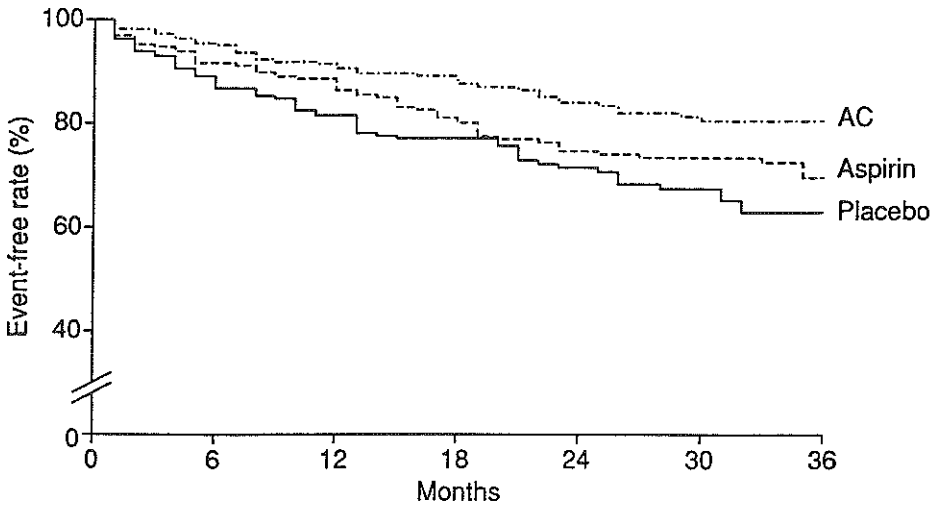
Event rates (per 100 patient-years)

† The difference in number of strokes between the 'primary outcome event' analysis and the 'all stroke' analysis can be explained by the fact that only first events are presented and that two patients first suffered a myocardial infarction or systemic embolism prior to their recurrent stroke.

° Including vascular death due to systemic or pulmonary embolism, peripheral vascular disease and other undefined causes

HR: Hazard ratio; CI: Confidence interval

Figure 3.2 Survival analysis for the primary outcome event (vascular death, non-fatal stroke, non-fatal myocardial infarction or non-fatal systemic embolism, whichever came first); Anticoagulants, Aspirin and Placebo; Group 1



The results of on-treatment analyses differed slightly from intention-to-treat analyses: for primary outcome events the hazard ratio was 0.43 (95% CI 0.28 - 0.66; $p < 0.001$); for the occurrence of all strokes 0.23 (95% CI 0.12 - 0.42; $p < 0.001$) and for the effect on all mortality it was 0.80 (95% CI 0.46 - 1.39; $p = 0.43$). Hazard ratios adjusted for differences in baseline characteristics (sex, age, congestive heart failure, hypertension and stroke severity) were approximately similar to the crude hazard ratio estimates.

In order to assess a possible time-dependent effect of anticoagulant treatment, separate hazard ratios were calculated for the first 150 days after randomisation (0.40; 95% CI 0.19 - 0.84) and the period thereafter (0.59; 95% CI 0.38 - 0.93), but these effects were not significantly different.

Treatment outcomes: Aspirin versus Placebo

Because treatment effects of aspirin versus placebo did not differ between group 1 and group 2, the results in the two groups were combined. Patients assigned to aspirin had a lower risk of a primary outcome event (hazard ratio 0.83; 95% CI 0.65 - 1.05; Table 3.4. Figure 3.3) and of stroke alone (hazard ratio 0.86; 95% CI 0.64 - 1.15) but neither effect was statistically significant. For all deaths the hazard ratio for patients on aspirin compared

Table 3.4 Primary and secondary outcome events: Aspirin versus placebo; Group 1 and 2 combined

	Aspirin n = 404	Placebo n = 378	HR (95% CI)
follow-up years*	838 yrs	715 yrs	
PRIMARY OUTCOME EVENT†	130 (15/100 pyr)#	136 (19/100 pyr)	0.83 (0.65 - 1.05; p = 0.12)
Non-fatal strokes	87	85‡	
Non-fatal myocardial inf.	8	8	
Non-fatal systemic embolism	6	9	
Vascular death	29	34	
Cerebral	1	2‡	
Cardiac	23	24	
Non-cerebral bleed	1	1	
Other°	4	7	
ALL STROKES†	88 (10/100 pyr)	90‡ (12/100 pyr)	0.86 (0.64 - 1.15; p = 0.31)
Ischaemic strokes	64	73	
Major/fatal	29	33	
Moderately disabling	17	18	
Non-disabling	18	22	
Cerebral bleeding	1	0	
Undefined, no CT	23	17	
Major/fatal	12	7	
Moderately disabling	4	5	
Non-disabling	7	5	
ALL DEATH	102 (11/100 pyr)	99 (12/100 pyr)	0.91 (0.69 - 1.20; p = 0.48)
Vascular death	78	78	
Cerebral	37	33	
Cardiac	32	33	
Non-cerebral bleed	1	1	
Other°	8	10	
Non-vascular death	24	21	

* Follow-up years are given for the composite primary outcome event. Patient-years of exposure for other outcome events varied slightly

† First events only

\# Event rates (per 100 patient-years)

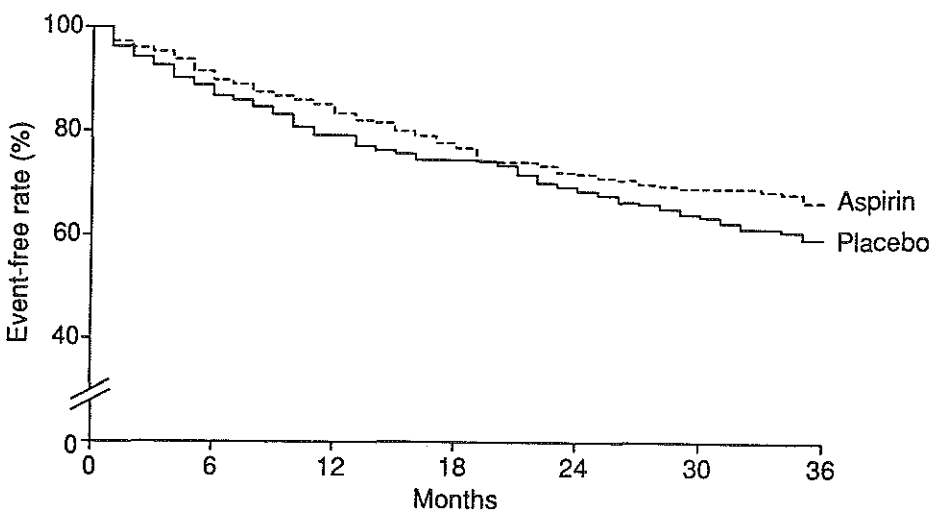
‡ The difference in number of strokes between the 'primary outcome event' analysis and the 'all stroke' analysis can be explained by the fact that only first events are presented and that two patients first suffered a myocardial infarction or systemic embolism prior to their recurrent stroke.

° Including vascular death due to systemic or pulmonary embolism, peripheral vascular disease and other undefined causes

HR: Hazard ratio; CI: Confidence interval

with those on placebo was 0.91 (95% CI 0.69 - 1.20), for vascular death only it was 0.88 (95% CI 0.65 - 1.21; p = 0.45). No treatment benefit was found with respect to the composite outcome events used in interim analyses; hazard ratio for major thromboembolic events 0.92 (95% CI 0.69 - 1.24; p = 0.59) and for major cerebrovascular events 1.01 (95% CI 0.68 - 1.52; p = 0.93).

Figure 3.3 Survival analysis for the primary outcome event (vascular death, non-fatal stroke, non-fatal myocardial infarction or non-fatal systemic embolism, whichever came first); Aspirin and Placebo; Group 1 and 2



The results of the on-treatment analyses were slightly different from the intention-to-treat analyses. For the analysis of primary outcome events the hazard ratio was 0.76 (95% CI 0.58 - 0.99; p = 0.049); for the occurrence of all strokes 0.81 (95% CI 0.59 - 1.12; p = 0.20) and for the effect on all mortality the hazard ratio was 0.94 (95% CI 0.66 - 1.35; p = 0.75). Hazard ratios adjusted for differences in baseline characteristics (sex, age, congestive heart failure, hypertension and stroke severity) hardly differed from the crude estimates.

No relationship between treatment effect of aspirin and time after randomisation was found.

Table 3.5 Adverse effects (worst symptoms only); numbers represent patients

Adverse effects	Group 1 AC n = 225	Group 1 Control n = 214	Group 1 HR (95% CI)	Group 1+2 Asp n = 404	Group 1+2 Plac n = 378	Group 1+2 HR (95% CI)
Major and fatal bleeding complications[#]	13	3	3.20 (0.91 - 11.3)	6	4	1.29 (0.36 - 4.56)
Respiratory	2					
Gastrointestinal	4			2	1	
Urogenital	1					
Cerebral		1		2	1	
Anaemia	1			1		
Other	5	2		1	2	
Minor bleeding complications	47	11	3.33 (1.72 - 6.43)	29	21	1.25 (0.71 - 2.18)
Respiratory	15	3		6	5	
Gastrointestinal	7	2		8	5	
Urogenital	12	2		4	3	
Cerebral						
Anaemia	1	3		4	5	
Other	12	1		7	3	
Gastrointestinal symptoms	13	25	0.39 (0.20 - 0.76)	70	47	1.41 (0.97 - 2.04)
Other symptoms	3	4	0.59 (0.13 - 2.66)	6	7	0.79 (0.26 - 2.34)

[#] All bleeding events requiring hospital admission with blood transfusion and/or surgery, or those events that caused a permanent increase in disability or death.

HR: Hazard ratio; CI: Confidence interval; AC: Anticoagulants; Plac: Placebo

Treatment outcomes: Anticoagulation versus Aspirin

In group 1, oral anticoagulants were more effective than aspirin in preventing the occurrence of a primary outcome event (hazard ratio 0.60; 95% CI 0.41 - 0.87; p = 0.008), largely because of the more effective prevention of all strokes, fatal or non-fatal (hazard ratio 0.38; 95% CI 0.23 - 0.64; p < 0.001; Figure 3.2).

Adverse effects

Patients on oral anticoagulant treatment significantly more often suffered bleeding events (both major and minor) than patients on aspirin (hazard ratio 2.8; 95% CI 1.7 - 4.8; p < 0.001) or placebo (hazard ratio 3.4; 95% CI 1.9 - 6.0; p < 0.001). Patients on aspirin suffered bleeding complications slightly more often than patients on placebo (hazard ratio 1.3; 95% CI 0.8 - 2.15; p = 0.39). Separate hazard ratios for the major and minor bleeding complications are listed in Table 3.5. The on-treatment incidence of major bleeding complications was low in this study; 2.8 per 100 patient-years in the group of patients randomised for anticoagulation, 0.9 per 100 patient-years in the aspirin group and 0.7 per 100 patient-years in the placebo group. The absolute excess of major bleeds with oral AC was therefore 21 per 1000 treated patients per year. Of the patients assigned to anticoagulants who had a subsequent stroke and underwent CT-scanning (16 of 20), none proved to have an intracranial haemorrhage (Table 3.3). One fatal cerebral bleed occurred in the placebo group, and two in the aspirin group. Two of these three patients had already suffered an earlier recurrent ischaemic cerebral event; for this reason they do not appear separately in Tables 3.3 and 3.4. Gastrointestinal symptoms were more often reported by patients on aspirin than by those on placebo (Table 3.5) but this difference did not reach statistical significance.

Discussion

This study shows that in patients with non-rheumatic atrial fibrillation and a recent TIA or minor stroke, oral anticoagulant treatment almost halves the risk of vascular complications. The risk of recurrent stroke, disabling as well as non-disabling, is even decreased by two-thirds. This benefit is not negated by an increased risk of serious bleeding complications. Despite a mean age of 71 years in patients on AC the absolute annual excess of major

bleeding events was acceptable at 21 per 1000 treated patients, and there was no documented intracerebral bleeding. A proportion of the unspecified strokes and deaths might well be related to acute bleeding events, but these still occurred more often in the placebo group. Our findings are strikingly similar to those of five recently completed primary prevention studies of NRAF patients, i.e. patients who had not had a recent thromboembolic event.[23,52,70,148,149,181] The most important difference between the primary and secondary prevention studies is the much higher absolute risk of recurrent stroke. In our study we observed an annual incidence of 12 per 100 patient-years in the placebo-treated group (groups 1 and 2 combined), which is almost three times as much as in the placebo-treated groups of the primary prevention studies (4.5 per 100 patient-years). This makes the value of anticoagulation for secondary prevention even more impressive in absolute terms: 90 vascular events (mainly strokes) are prevented if 1000 patients are treated for one year.

Our study also suggests that aspirin reduces the risk of vascular events in NRAF patients, although the effect is significantly smaller than that of anticoagulation. Until now, the efficacy of aspirin in patients with atrial fibrillation was unclear. Of the two primary prevention studies which addressed the value of aspirin, one showed a relatively small benefit of 16%,[148,149] whereas the other showed a significant 42% risk reduction.[181] The findings of the recently completed prolongation of the latter study showed no substantial difference in the absolute rate of stroke in patients given anticoagulation versus aspirin. These results probably reflect the low absolute risk of embolic events in primary prevention studies, especially in patients under 75 years.[185] Our results show also that in NRAF patients with recent cerebral ischaemia, aspirin is a safe and probably effective alternative when anticoagulants are contraindicated. Aspirin prevents 40 vascular events (of all types) per 1000 patients treated for one year. This benefit is of similar magnitude as that found in an overview of studies in patients with a variety of arterial diseases, including patients with a recent TIA or minor stroke without atrial fibrillation.[5]

A theoretical disadvantage of our study, but an inevitable consequence of the complicated study design, is that anticoagulant treatment was not blinded, especially since the results of the five primary prevention trials, which were published whilst the EAFT was still ongoing, could have biased

both the Auditing Committee and the individual investigators. However, all members of the Clinical Audit Committee were absolutely blinded for the assigned study treatment. Furthermore, the majority of recurrent vascular events in this study were major, and often fatal events, which left little room for interobserver variation.

Our findings do not definitively answer the question *when* antithrombotic treatment should be started after a cerebral ischaemic event in a patient with atrial fibrillation. Only 43% of the patients were randomised within two weeks after onset of neurological symptoms. Given the high efficacy of anticoagulation it may be that treatment should be started as soon as possible. However, several studies have recommended withholding anticoagulants during the first few days after suspected cardiogenic emboli to the brain, especially in patients with large infarcts.[33,43,45] A large, ongoing trial (the International Stroke Trial) will determine, in 20,000 patients randomised within 48 hours of onset, which is the safest and most effective antithrombotic policy in patients with acute cerebral infarction. About 18% of the 2,000 patients randomised in the trial to date were in AF, so, when the trial is complete, data on the balance of risk and benefit of immediate anticoagulant therapy in the acute phase of stroke in patients with AF will be available for about 3,500 patients.[100,167]

Neither do the results presented here answer the question for *how long* antithrombotic treatment should be continued in the studied patient group. Survival curves (Figures 3.2 and 3.3) dispel the common notion that the risk of recurrent events is confined to the early period after the initial event. Both risk and benefit of treatment remained fairly constant during the relatively short period of follow-up (mean follow-up 2.3 years). In the primary prevention studies a previous thromboembolic event was identified as an important risk factor for thromboembolic complications even if it had occurred years before. Thus, the available data suggest that both anticoagulant and aspirin treatment should be given for as long as possible, that is, until a contraindication or a serious bleeding complication occurs.[40]

In conclusion, our study shows that NRAF patients with a recent TIA or minor ischaemic stroke should be treated with anticoagulants if at all possible. In case of a contraindication, aspirin is a safe, though significantly less effective alternative.

CHAPTER 3B:
QUALITY OF LIFE ANALYSIS

"The excellence of the body is health; that is, a condition which allows us, while keeping free from disease, to have the use of our bodies"
Aristotle, Rhetoric, 1361^{b}3

EUROPEAN ATRIAL FIBRILLATION TRIAL: Quality of life analysis

Introduction

The results of the European Atrial Fibrillation Trial, as presented in Chapter 3A, have shown oral anticoagulant treatment to be effective in the secondary prevention of vascular events in general, and of strokes alone (fatal and non-fatal) in patients with non-rheumatic atrial fibrillation who had a recent transient ischaemic attack or minor ischaemic stroke. A possible beneficial effect of aspirin was also found (Chapter 3A). The conventional outcome event analyses that were used in this study, however, did not account for the actual impact of the events on the patients' lives in terms of disability. The occurrence of minor side-effects, other diseases often present in elderly patients, and vague vascular symptoms that were not classified as events because of the use of strict event definitions, might well have had an equally important impact on disability and life-expectancy. The failure of both treatment regimens to significantly reduce the overall mortality in this patient cohort confirms the need for treatment comparisons that not only consider the duration, but also the quality of survival, especially since in cohorts of elderly patients death should to some degree be viewed as a more or less natural and inevitable phenomenon.

In this study the concepts of disability adjustment of life expectancy were applied to data from the European Atrial Fibrillation Trial, in order to assess the treatment effect of oral anticoagulants and aspirin on mortality and morbidity, after acute minor cerebral infarction in patients with non-rheumatic atrial fibrillation. In addition, some attention was paid to the

uses of this approach to decide the choice of treatment in the individual patient.[60]

Patients and methods

A detailed description of the methods of the European Atrial Fibrillation Trial can be found in Chapter 2. Eligible patients were those over 25 years of age with documented non-rheumatic atrial fibrillation who had suffered a TIA or minor ischaemic stroke (grade 3 or less on the modified Rankin scale)[14,194] in the previous 3 months. Patients eligible for anticoagulant treatment (group 1) were randomly assigned to receive either open-label oral anticoagulants, or double-blind treatment with aspirin or matched placebo. Patients not eligible for treatment with anticoagulants were entered in group 2 and randomised to double-blind treatment with either aspirin or placebo.

All patients were followed at four-monthly intervals for the duration of the study, with a close-out visit in April 1993. At each follow-up visit patients were ranked according to the seven categories of disability of the modified Rankin scale (0: No symptoms; 1: No significant disability despite symptoms: able to carry out all usual duties and activities; 2: Slight disability, unable to carry out some previous activities but able to look after own affairs without assistance; 3: Moderate disability, symptoms which significantly restrict lifestyle and/or prevent totally independent existence (e.g. requiring some help); 4: Moderately severe handicap, symptoms which clearly prevent independent existence though not needing constant attention (e.g. unable to attend to own bodily needs without assistance); 5: Severe handicap, totally dependent, requiring constant attention day and night; 6: Deceased). The modified Rankin scale measures not only the overall independence of patients, thereby allowing for comparison between patients with different kinds of neurological deficits ánd non-neurological deficits, but it also adds one further dimension by referring to previous activities. This is important, because patients may be independent but still dissatisfied by restriction of their former lifestyle. Strictly speaking, the Rankin scale does not measure 'quality of life' but a subjective, physician's interpretation of the disability as perceived by the patient. Therefore we will be using the term 'disability-adjusted survival-years' (DASYs) instead of the better known 'quality-adjusted survival-years' (QASYs). In the first

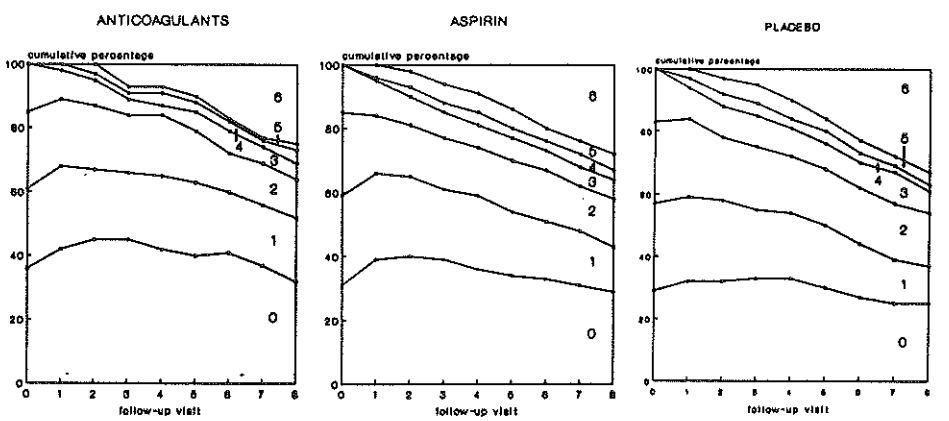
year of the study, investigators were trained in the use of the Rankin scale by regularly circulating case-reports of patients together with recommendations for the appropriate Rankin score.

The term 'survival-years' as opposed to 'life-years' is used to indicate that the presented analyses are necessarily restricted to the time spent in the study (maximum follow-up 55 months). Estimates of this (restricted) survival time for each patient were calculated as the mean time elapsed between study entry and death (of all causes) or until end of follow-up (censoring in April 1993), on an intention-to-treat basis. The restricted mean survival time was further subdivided into the mean time spent in each category of the Rankin scale, 0 to 5. This was based on the exact date of transition in cases where increase of disability was related to the occurrence of a specific non-fatal event (mostly conventional outcome events like recurrent stroke, myocardial infarction or systemic embolism). If no underlying acute event was reported, transition between two categories of disability was assumed to have occurred halfway between two subsequent follow-up visits. For patients who suffered a fatal outcome event prior to the end of the study, an approximation of the maximal attainable restricted survival time was calculated as the time between randomisation and the censoring date of 15 April 1993.

The treatment effect on morbidity and mortality was evaluated for oral anticoagulation versus control in group 1 and for aspirin versus placebo in group 1 and 2 combined. For this purpose, the average time spent in the different categories of disability were compared, after adjusting for differences in maximum attainable days of follow-up. By assigning predetermined utilities to each of the Rankin categories, an overall estimate of attained disability-adjusted survival-years was calculated, allowing an overall comparison of the treatment effects. In deciding on the weighting scheme we took account of the possibility that minor disability is viewed differently by older patients,[29] as they might expect and therefore more easily accept some form of health restriction with increasing age. Rankin categories 0 and 1 were assigned a utility of 1, categories 2 and 3 a utility of 0.75, category 4 a utility of 0.50, category 5 a utility of 0.25 and death a utility of 0. In order to adjust for differences in disability status at baseline, additional comparisons included average time spent at disability levels higher or lower than at baseline. No formal statistical tests were planned.

A threshold analysis was planned in order to determine the critical values of the utilities for the clinician's and patient's treatment choice. We computed which combination of utilities for the disability categories would yield equal disability-adjusted survival-years for treatment with aspirin and treatment with anticoagulation. As some patients might perceive a certain inconvenience related to the use of anticoagulation (change in life-style and minor bleeding complications) these calculations were repeated for a range of disutilties assigned to anticoagulant treatment. In order to simplify the necessary calculations, a parameter (u) was defined, such that $U_{0,1} = 1$ for Rankin score 0 and 1, $U_{2,3} = (1-u)$ for Rankin score 2 and 3, $U_4 = (1-2u)$ for Rankin score 4, $U_5 = (1-3u)$ for Rankin score 5 and $U_6 = 0$ for Rankin score 6, where $0 < u < 0.33$.

Figure 3.4 Proportion of patients in each Rankin category at first 8 follow-up visits according to treatment group.



Results

Of the 1,007 patients entered in the study, five were inappropriately included and no information on disability was available for one. The remaining 1,001 were included in this analysis. Figure 3.4 compares the change in Rankin categories over the first 8 follow-up visits, between patients assigned to treatment with anticoagulants (n = 225), aspirin (n = 401) and placebo (n = 375). Patients assigned to anticoagulant treatment had a slightly more favourable disposition at the start of the study (36% had

no symptoms, versus 31% of the aspirin-treated patients and 29% of the placebo-treated patients). This should be kept in mind when interpreting the data. Approximately 24% of all patients reported intercurrent illnesses other than outcome events that had affected an increase in disability. This included both newly developed complaints and illnesses that were already present at study entry but were causing more complaints during follow-up. In patients randomised to anticoagulant treatment, musculoskeletal afflictions (arthrosis, arthritis, sprains and fractures), cardiac problems (mostly angina and congestive heart failure), malignancies and bleeding events were the most important competing causes of disability (Table 3.6). Patients randomised for aspirin or placebo treatment, however, more often reported disability due to cognitive deterioration in addition to cardiac and musculoskeletal problems. This same trend was seen for aspirin and placebo-treated patients in group 1 alone, thereby dispelling the notion that the higher proportion of reported cognitive deterioration was due to the higher mean age of patients in group 2 (77 years), because in group 1 the mean age of patients assigned to anticoagulants was comparable to that of aspirin and placebo-treated patients (71 years).

Table 3.7 shows the mean time spent in each category of disability for the comparison between anticoagulants and control (group 1), and aspirin and placebo (groups 1 and 2). The presented results have been standardised to adjust for differences in the maximum attainable follow-up between the treatment groups (on average 911 days for placebo-treated patients in group 1 versus 962 days for patients assigned to oral anticoagulants; on average 998 and 953 days for aspirin and placebo-treated patients respectively, in groups 1 and 2 combined) which originated from slight imbalances in the randomisation scheme. Compared with control patients, patients treated with anticoagulants gained an average of 22 days of life in 2.7 years of treatment, if unadjusted for disability. In terms of disability-adjusted survival-years this gain was roughly 38 days. In groups 1 and 2 combined, for every 2.7 years of treatment, patients treated with aspirin on average lived 15 days longer (a gain of 0.08 DASYs) than patients who were assigned to placebo. Table 3.8 illustrates the average time spent at levels of disability that were higher (or lower) than patients' overall disability at study entry. In group 1, placebo-treated patients spent more time at levels of increased disability (160 days) than patients assigned to aspirin or

Table 3.6 Reported intercurrent illnesses other than outcome events, that influenced patients' disability. Figures in parentheses are percentage of total number of illnesses reported.

Intercurrent illness	Anticoagulation	Aspirin	Placebo
Cardiac	8 (15)	21 (22)	18 (20)
Other vascular insufficiencies[#]	0 (-)	7 (7)	5 (5)
Cognitive decline	4 (8)	18 (19)	11 (12)
Other neurological complaints	4 (8)	6 (6)	4 (4)
Depression/fatigue	2 (4)	7 (7)	4 (4)
Musculoskeletal complaints	11 (22)	12 (13)	18 (20)
Pulmonary complaints	1 (2)	7 (7)	8 (9)
Neoplasms	6 (12)	3 (3)	6 (7)
Bleeds, treatment side-effects	6 (12)	0 (-)	1 (1)
Other	9 (17)	14 (15)	16 (17)
TOTAL reported	51	95	91

[#] Including for instance intermittent claudication, arterial occlusions from local thrombosis and hypertensive retinopathy

anticoagulant treatment (139 and 117 days, respectively). For group 1 and 2 combined this difference between aspirin and placebo-treated patients was more pronounced (32 days).

Threshold analyses showed that (for group 1 and 2 combined) aspirin would be the preferred treatment over placebo irrespective of the utility values assigned to each disability category providing that $U_{0,1} > U_{2,3} > U_4 > U_5 > U_6$. The same dominance was seen for the comparison between oral anticoagulants and placebo under the same conditions. For the comparison between oral anticoagulants and aspirin the threshold was reached for

parameter u = 0.03 ($Utility_{0,1}$ = 1, $Utility_{2,3}$ = 0.97, $Utility_4$ = 0.94, $Utility_5$ = 0.91 and $Utility_6$ = 0), implying that any patients giving higher values to their life at these stages of disability would be satisfactorily treated with aspirin. When also taking the disutility of using oral anticoagulants into account (e.g. disutility factor 0.01) this threshold would be reached at u = 0.17 ($Utility_{0,1}$ = 1, $Utility_{2,3}$ = 0.83, $Utility_4$ = 0.66, $Utility_5$ = 0.49 and $Utility_6$ = 0). The threshold values for other levels of disutilty are shown in Figure 3.5.

Table 3.7 Standardised mean number of days spent in different categories of disability. Figures in parentheses are percentages of time alive.

Rankin Score	GROUP 1 Maximum follow-up 1000 days			GROUP 1 + 2 Maximum follow-up 1000 days	
	Anti-coagulants	Aspirin	Control	Aspirin	Placebo
6 (Deceased)	105	103	127	151	166
5	4 (< 1)	22 (2)	8 (< 1)	18 (2)	15 (2)
4	17 (2)	21 (2)	22 (2)	21 (2)	22 (3)
3	57 (6)	65 (7)	84 (10)	73 (9)	93 (11)
2	171 (19)	163 (18)	189 (22)	160 (19)	197 (24)
1	232 (26)	207 (23)	236 (27)	225 (26)	205 (24)
0	414 (46)	419 (47)	334 (38)	352 (41)	302 (36)
Survival time (days)	895 (100)	897 (100)	873 (100)	849 (100)	834 (100)
Disability-adjusted survival years	2.26	2.23	2.16	2.10	2.02

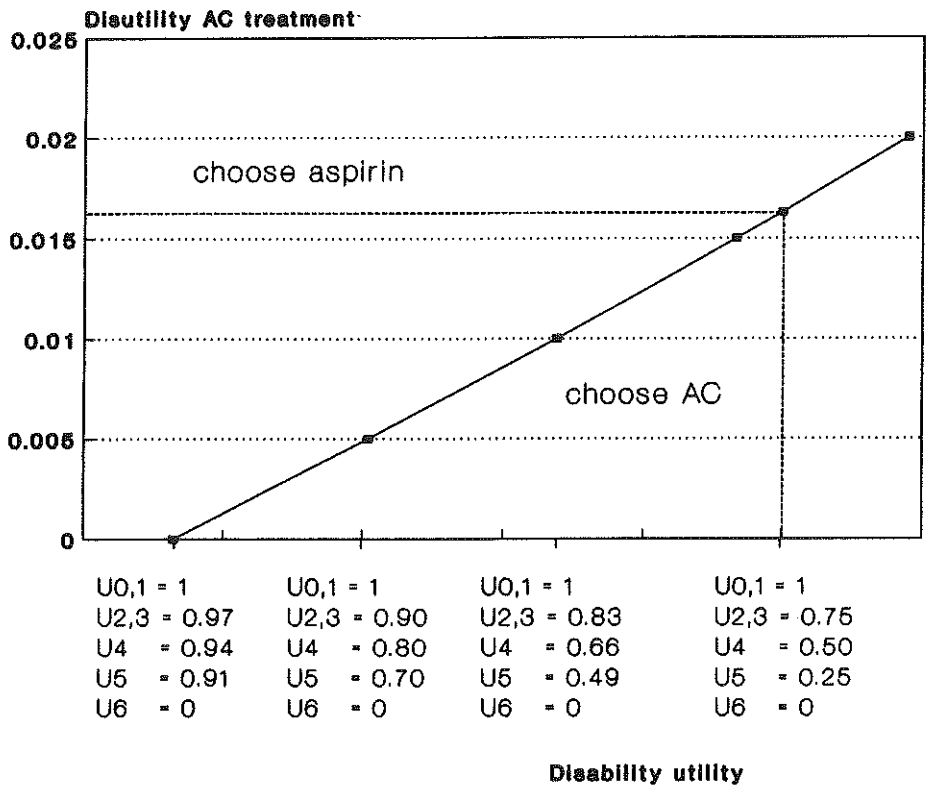
Table 3.8 Standardised mean number of days spent with a degree of disability lower or higher than the disability present at study entry. Figures in parentheses are percentages of time alive.

Disability	GROUP 1 Maximum follow-up 1000 days			GROUP 1 + 2 Maximum follow-up 1000 days	
	Anticoagulants	Aspirin	Control	Aspirin	Placebo
Deceased	105	103	127	151	166
Worsened	117 (13)	139 (15)	160 (18)	137 (16)	169 (20)
No change	509 (57)	483 (54)	470 (54)	458 (54)	439 (53)
Improved	269 (30)	275 (31)	243 (28)	254 (30)	226 (27)
Survival time (days)	895 (100)	897 (100)	873 (100)	849 (100)	834 (100)

Discussion

In clinical trials of elderly patients one might argue that improvement of 'quality of life' rather than increase of life-expectancy alone, should be the primary aim of any interventional strategy, for the simple reason that the life-expectancy is limited by the older age of the patients. Nevertheless, results of clinical trials are usually reported as relative frequencies of various non-fatal and fatal events, with inclusion of only those events that occurred first, making it difficult to infer the exact effect of treatments on patients' health state over time. In this re-analysis of the European Atrial Fibrillation Trial data, an attempt is made to present a more pragmatic picture of what effect was actually achieved, in terms of preventing disability, with anticoagulant and aspirin treatment in comparison with placebo treatment. By means of an approach suggested by Olsson et al,[144] and based on concepts that were derived from clinical decision analysis, the estimated average time spent in each predefined category of disability

Figure 3.5 Break-even line for the decision to prescribe aspirin in stead of anticoagulation in patients with NRAF and a recent minor ischaemic stroke who are eligible to be treated with both. X-axis: different sets of utility values for the categories of disability according to the rankin scale (0-6). Y-axis: disutility value for anticoagulant treatment.



(Rankin scale) was calculated for all treatment groups. Patients on anticoagulant treatment spent less time at increased levels of disability (in reference to their disability at study entry) than control patients, which, together with a longer restricted mean survival time, resulted in a gain of 0.10 disability-adjusted survival-years. In group 1 and 2 combined, a similar though slightly smaller effect was seen with aspirin treatment (a gain of 0.08 DASYs in comparison with placebo). These results are completely in line with the results from conventional outcome event analyses, with possibly more evidence to support a beneficial effect of aspirin over placebo. Seen from the perspective of overall morbidity and mortality, the

treatment effect of oral anticoagulant therapy seemed less impressive (only 1.2 months are gained on average with a treatment period of 2.7 years) than what would be expected from the formidable risk reductions of vascular events in general (47%) and strokes alone (66%) (Chapter 3A). The comparison between the treatment effect achieved with anticoagulants and that obtained by aspirin (in group 1), showed an even less impressive difference (0.03 DASYs). These analyses confirm that, although oral anticoagulant treatment greatly reduces the risk of recurrent vascular events, its overall effect on morbidity and mortality is limited. It is however possible that the improvement of quality-of-life might increase over longer treatment periods.

It would be presumptuous to draw any definite conclusions from the presented analyses as many unsolved methodological issues might have clouded the results. The scale that was used for the measure of disability (the Rankin scale) might not have been sufficiently standardised to allow for adequate comparisons in this multicentre trial. Although it is a relatively uncomplicated scale, factors that distinguish the transition between the subcategories are mostly of a subjective nature. Determining whether or not elderly patients are independent in their daily living can be influenced by cultural, social and economic factors. Furthermore, the extent to which illnesses other than neurological afflictions were actually taken into account in the assessment of overall disability, may have differed depending on the background of the rating physician. Physicians specialised in geriatrics were probably more used to evaluating the functional status of a patient as a whole, whereas neurologists from highly specialised stroke units might have focused more on the extent of neurological damage alone. Attempts to decrease these differences by training and evaluation were probably only partly successful as, contrary to baseline and outcome event forms, follow-up forms were often completed by different (junior) physicians, who would not always be informed about the study. Nevertheless, comorbidity must have played a part, and it is only natural that biological effects of treatment are diluted by other factors as the measure of outcome shifts across the spectrum from disease process to impairments, from impairments to disability, and from disability to handicap.[192]

Rather than assigning more or less arbitrary weights to 'disability' states after the occurrence of an outcome event as done in most of the cost-effectiveness studies in this field (utility of 0.50 for years after a major stroke[139,140]), the next challenge in this analysis was that of attributing appropriate utilities to the different categories of disability that were actually reached. Several methods have been proposed for this purpose, the two most important ones being: 1) the time-trade-off method[153] (a utility value of 0.50 for a given level of disability implies that the patient would be willing to trade 2 years of life at that level for 1 year of absolute (100% quality) health). And 2) The standard gamble approach[169] (a utility value of 0.75 for a given level of disability implies that the patients would be willing to take any gamble with a risk of death versus normal life to prevent living with such a disability, if the risk of death is < 0.25). As the first method is less appropriate because it requires that patients value each life year equally, even when it is (far) away in the future, our choices for the weighting scheme were based on the standard gamble approach using our own subjective opinion as a reference point. Ideally these utilities would have been validated in the study population at the onset of the study. To assume that these values are similar for all patients, irrespective of differences in age, nationality, and personal preferences would however be wholly inadequate, irrespective of the validation. This problem can be circumvented by assessing the effect on the analyses using different utilities. In this way it is possible to determine whether for instance treatment choices are sensitive to the patient's individual set of utilities (for both changes in Rankin and treatment).[94,138,176] In the presented analysis the choice of treatment seemingly was not dependent of the quality co-efficients, with the exception of the choice of anticoagulants over aspirin in patients eligible to be treated with either one of these medications. In this latter instance the calculated 'threshold' utilities if no disutility of treatment was taken into account, were probably too extreme to be considered plausible implying that most patients and physicians would choose for treatment with anticoagulants. If however, a disutility of 0.01[66,139] was assigned to oral anticoagulant treatment, the threshold utilities were in range with valuations of approximately similar disability states reported earlier by Kind et al.[109] Hypothetically these results suggest that some patients might reasonably choose to be treated with aspirin rather than with

oral anticoagulation, depending largely on the extent to which they perceive anticoagulant treatment to be burdensome.[118]

Last but not least, the usefulness of the above described approach is restricted by the fact that theoretically optimal statistical approaches are not readily available for the comparison of treatment effects on this level. Methods that have been proposed[83] require a progression of discrete states, which was not the case in our study group where disability states fluctuated over time. Furthermore there are no sophisticated methods to control for the effects of covariates (in this study, for instance, the difference in baseline health status between the treatment groups might have influenced the results). Unfortunately, despite sometimes vehement protests against the continuing, almost 'obsessive', use of significance testing in epidemiological research,[142] physicians today still tend to rely primarily on the statistical rather than intuitive interpretation of study data.

In conclusion, when clinical trials involve cohorts of elderly patients, presentation of data on the actually achieved status of health in addition to more conventional outcome event analyses might supply new and helpful insights in the assessment of treatment effects. For this purpose, more attention should be given to the development of adequate rating systems that focus not only on the disease under investigation but on the individual as a whole.

CHAPTER 4:

PREDICTORS OF MAJOR VASCULAR EVENTS

"The highest probability amounts not to certainty, without which there can be no true knowledge"

Locke, Concerning Human Understanding, Bk IV,III,14

PREDICTORS OF MAJOR VASCULAR EVENTS IN PATIENTS WITH A TRANSIENT ISCHAEMIC ATTACK OR MINOR ISCHAEMIC STROKE AND WITH NON-RHEUMATIC ATRIAL FIBRILLATION

Introduction

In different studies the reported risk for recurrent arterial embolism and other major vascular events following an initial episode of embolism in patients with non-rheumatic atrial fibrillation (NRAF) varies between 2 to 15% in the first year, and is approximately 5% yearly thereafter,[47,175] depending on the type of underlying cardiac abnormality. The value of anticoagulant therapy for the secondary prevention of these events in patients with non-rheumatic atrial fibrillation has been well established by the results of the European Atrial Fibrillation Trial (Chapter 3A). However, an ingrained reluctance of physicians to prescribe oral anticoagulant therapy over any extended period of time,[28,48] especially in older and less mobile patients, has prompted the question whether specific risk factors for recurrent stroke and other vascular events can be used to identify high risk subgroups within this patient population. Very few studies have addressed this specific question. Predictors for thromboembolism have been identified both in prospective cohorts of patients with non-rheumatic atrial fibrillation, derived from the five primary prevention studies in this field,[10,23,151,182,184] and in retrospective studies,[53,75,136] but the most important determinant was that of previous thromboembolism, and therefore of little value in secondary prevention. Other studies have identified risk factors for recurrent vascular events in patients with a TIA or minor ischaemic stroke,[36,59,64,89] but most of these studies included patients with and without

atrial fibrillation[36,59,89] and little attention was given to predictors according to the presumed source of thromboembolism.

We analysed clinical features of 375 patients assigned to placebo treatment in the European Atrial Fibrillation Trial in order to determine clinical predictors for recurrent stroke and other major vascular events in patients with NRAF and recent transient ischaemic attacks or a minor ischaemic stroke. Consequently, the identified risk factors were used to stratify all study patients in high and low risk subgroups and to assess the value of antithrombotic therapy for these different subgroups.

Patients and methods

Background, design, and results of the EAFT have been described in chapters 1 to 3. In summary, patients with one or more non-disabling episodes of cerebral ischaemia and concomitant non-rheumatic atrial fibrillation were randomised between treatment with oral anticoagulants (INR 2.5 - 4.0), aspirin (300 mg/day), or placebo. Patients with other cardiac sources of embolism, and patients with specific causes for cerebral ischaemia, such as haematological disorders or vasculitis, were excluded, as were patients with contraindications for aspirin. Patients ineligible for anticoagulant treatment were randomised between aspirin or placebo only. After randomisation, patients were followed every 4 months in order to assess treatment compliance and the occurrence of outcome events or bleeding complications.

Clinical predictors for recurrent vascular events

Risk factors for vascular death, recurrent stroke, and other vascular events were identified in a subgroup of 378 patients randomised to placebo treatment. Two of these patients were excluded from further analyses as they had been inappropriately entered in the study (no atrial fibrillation ever); one other patient was excluded because no adequate baseline information was available (these three patients suffered no outcome events during follow-up). The remaining 375 patients were followed for a total of 818 patient-years. Of them, 135 had a recurrent vascular event (vascular death, non-fatal myocardial infarction, stroke or systemic embolism). During the study period 133 (35%) of the patients were taken off their placebo medication and prescribed other regimens of antiplatelet or

anticoagulant therapy. In most instances such a change of therapy was instigated by the occurrence of an outcome event but in 10 patients the first thromboembolic event occurred after discontinuation of placebo treatment. Another 35 patients stopped taking placebo tablets but were not prescribed any other form of treatment; 9 of them had their first recurrent vascular event after discontinuation. The following analyses include only the follow-up period whilst on placebo treatment.

A baseline data form was completed for each patient at study entry, on which nature, duration and severity of patient's qualifying event were recorded, along with demographic data, vascular risk factors, vascular and cardiac history, duration and pattern of atrial fibrillation. Uniform working definitions for most of the requested data had been supplied in a User's Manual. Hypertension was defined as a history of hypertension or current treatment for hypertension. Diabetes was defined as glucose intolerance controlled either by diet alone or by medication. Congestive heart failure was judged present if the patient had clinically evident congestive heart failure at the time of study entry. Prior myocardial infarction (MI) was defined on the basis of history and medical records. Previously unrecognised MI in cases where only the baseline ECG showed MI were not included. Previous thromboembolism comprised patients with clinically evident ischaemic stroke, transient ischaemic attacks or systemic embolism other than pulmonary embolism, preceding the qualifying event; it did not include evidence of silent cerebral infarction on baseline CT-scan. Patients were required to have a CT-scan before randomisation; these scans were reviewed by an independent committee of at least two neurologists who were not aware of the clinical data, which assessment took place as soon as possible after study entry (Chapter 6 and 7 provide a more extensive report on the classification of CT-scan abnormalities). M-mode, and if possible 2D, echocardiography was mandatory in all patients in order to exclude the presence of rheumatic valve disease and to assess left atrial size. Echocardiography results were not audited centrally and no specific criteria were defined for the mode of measurement. Left atrial size, defined as $>$ or $\leq$ than 40 mm on M-mode, was registered on the baseline data form as was the presence of a cardiac thrombus. In addition, 70% of all centres were able to supply copies of the complete echocardiography reports for more than 75% of their patients (Table 4.1). The results of carotid

investigations (Duplex or angiography), which were not mandatory, were recorded on the baseline form if available. Only 40% of all centres performed routine carotid investigations in more than 75% of the patients they entered in the trial (Table 4.2).

Table 4.1 Echocardiographic features of placebo-assigned patients

Variable	Placebo assigned patients n = 375	Percent of Data Available
M-Mode measurements (cm)		
Mean left atrium ± SD	4.4 ± 0.8	56
Left atrium ≤4 cm (%)	54%	99
Mean interventricular septum ± SD	1.2 ± 0.3	38
Mean left ventricular posterior wall ± SD	1.1 ± 0.2	38
Mean left ventricular end diastolic ± SD	5.1 ± 0.8	46
Mean left ventricular end systolic ± SD	3.4 ± 0.8	40
Mean left ventricular mass ± SD (g)	260 ± 102	35
Mean fractional shortening ± SD (%)	32 ± 10	39
Interpretational indices (%)		
Regional left ventricular dysfunction	10	71
Global left ventricular dysfunction	20	71
Moderate-severe LV dysfunction	8	71
Intracardiac thrombus	1	99
Mitral valve prolapse	3	77
Mitral annular calcification	13	77

SD: Standard deviation
LV: Left ventricular

Table 4.2 Results of carotid investigations in placebo-treated patients

Variable	Placebo assigned patients, n = 365 Results of carotid investigations available in 197
No atherosclerotic lesions	116 (59%)
Symptomatic carotid disease[†]	
Plaques	32 (16%)
0 - 29% stenosis	6 (3%)
30 - 69% stenosis	9 (6%)
70 - 99% stenosis	3 (2%)
Occlusion	4 (2%)
Only asymptomatic carotid disease	
Plaques	9 (6%)
0 - 29% stenosis	2 (1%)
30 - 69% stenosis	10 (5%)
70 - 99% stenosis	-
Occlusion	-
Other lesions	6 (3%)

[†] Symptomatic with respect to current and past neurological symptoms. In patients where both carotid arteries were symptomatic: Only the patent, and/or most severely stenosed, carotid artery would be considered symptomatic. Else, the left carotid artery would arbitrarily be classified as symptomatic.

Our analyses were primarily aimed at the identification of clinical predictors for the occurrence of any important arterial occlusion, represented by the composite outcome event of stroke, myocardial infarction, systemic embolism or vascular death, whichever occurred first. Additional aims were to evaluate the relation between these variables and the occurrence of stroke alone (both fatal and non-fatal). Suitable factors for analysis were identified in advance both on grounds of biological plausibility and on the basis of earlier reports on risk factors for vascular events in patients with non-rheumatic atrial fibrillation and patients with

transient ischaemic attacks or minor ischaemic strokes.[8,10,23,32,36,37,53,59,-64,75,85,89,136,151,182,184,196] Univariate hazard ratio's and 95% confidence intervals for each characteristic were calculated by means of the Cox proportional hazards model (EGRET statistical software). Variables selected from univariate analyses were sequentially entered in a multivariate model until no remaining candidate variable met a significance level of 0.10. Variables were removed from the model when the probability value for removal exceeded 0.15. Three multivariate models were assessed. The first included only those variables that are usually recorded during the first patient contact by means of clinical history taking. A second model further included variables obtained by standard ancillary investigations such as chest X-ray and cerebral CT-scan. The last, exploratory, model included information for subsets of patients for whom extensive echocardiography reports or carotid investigations were available.

Antithrombotic therapy for high and low risk subgroups
The identified clinical predictors were used to define high, moderate, and low risk subgroups. Within each treatment group of the EAFT study cohort (oral anticoagulation and aspirin, in addition to the placebo group from which these predictors were derived), event rates, confidence intervals and rate ratio's were calculated for all risk subgroups assuming a Poisson distribution and on an intention-to-treat basis.

Results

Univariate analyses
Table 4.3.a summarizes the results of the univariate analyses of the baseline characteristics. Of all evaluated potential risk factors, evidence of ischaemic heart disease (angina pectoris, prior myocardial infarction), and prior vascular surgery were associated with a significantly increased risk for recurrent vascular events. This association was less pronounced for the risk of recurrent stroke. Other probable risk factors were female gender, a history of previous thromboembolic events, longstanding chronic atrial fibrillation and a systolic blood pressure > 160 mmHg at study entry. Tables 4.3.b and 4.3.c summarize the univariate analyses of risk factors obtained

Table 4.3.a Results of Univariate Analysis of Risk Factors for the Combined Event of Vascular Death, Stroke, Systemic Embolism or Myocardial Infarction and for Stroke Alone (Fatal or Non-fatal)

BASELINE CHARACTERISTICS	No. of patients	Vascular death, stroke, systemic embolism or myocardial infarction†		Fatal or non-fatal stroke	
		No of events	HR (95% CI)	No of events	HR (95% CI)
Demographic factors					
Female sex	177	63	1.4 (1.0-2.0)	45	1.6 (1.0-2.5)
Age < 60 years	26	6	-	6	-
60 ≤ x < 70 years	89	29	1.6 (0.7 3.8)	21	1.2 (0.5-2.9)
70 ≤ x < 80 years	181	53	1.6 (0.7-3.8)	38	1.2 (0.5-2.8)
x ≥ 80 years	79	28	1.9 (0.8-4.7)	13	0.9 (0.3-2.3)
Neurological symptoms persisting > 6 weeks	212	66	1.1 (0.7-1.5)	39	0.8 (0.5-1.3)
Chronic atrial fibrillation	285	93	1.4 (0.9-2.2)	61	1.2 (0.7-2.1)
Duration of atrial fibrillation > 1 year	213	77	1.7 (1.2-2.5)	57	2.3 (1.4-3.8)
Vascular risk factors					
History of hypertension	176	66	1.5 (1.0-2.2)	42	1.3 (0.9-2.1)
History of diabetes	49	19	1.4 (0.9-2.3)	13	1.5 (0.8-2.7)
Hypercholesterolaemia	27	6	0.7 (0.3-1.6)	4	0.7 (0.3-1.9)
Congestive heart failure	44	17	1.3 (0.8-2.1)	12	1.4 (0.7-2.5)
Angina pectoris	41	18	1.7 (1.0-2.7)	8	1.0 (0.5-2.1)
Past myocardial infarction	35	19	2.4 (1.5-3.9)	11	2.0 (1.1-3.8)
Intermittent claudication	14	6	1.9 (0.8-4.3)	3	1.4 (0.4-4.5)
Current regular smoking	67	17	0.8 (0.5-1.3)	14	1.0 (0.6-1.8)
Previous thromboembolism	104	40	1.4 (1.0-2.1)	30	1.7 (1.1-2.7)
Previous vascular surgery	11	6	3.4 (1.1-5.6)	4	2.5 (0.9-6.8)
Physical examination and laboratory					
Systolic BP > 160 mmHg	76	32	1.6 (1.1-2.4)	20	1.5 (0.9-2.5)
Diastolic BP > 90 mmHg	24	7	0.8 (0.4-1.7)	5	0.8 (0.3-2.1)
Haematocrit > 0.45 l/l	110	39	1.1 (0.7-1.7)	26	1.2 (0.7-1.9)
Glucose > 7 mmol/l	66	20	1.2 (0.8-1.7)	10	0.8 (0.4-1.5)

† Whichever came first
BP: blood pressure

Table 4.3b Results of Univariate Analysis of Risk Factors for the Combined Event of Vascular Death, Stroke, Systemic Embolism or Myocardial Infarction and for Stroke Alone (Fatal or Non-fatal)

		Vascular death, stroke, systemic embolism or myocardial infarction[†]		Fatal or non-fatal stroke	
ANCILLARY INVESTIGATIONS ,	No. of patients	No of events	HR (95% CI)	No of events	HR (95% CI)
Chest X-ray					
Cardiothoracic ratio > 0.50	91	40	1.6 (1.1-2.4)	27	1.7 (1.0-2.6)
CT-scan of the brain					
Any infarct*	211	76	1.7 (1.1-2.5)	51	1.7 (1.0-2.7)
Only small deep infarcts*	34	13	2.0 (1.1-3.7)	9	2.1 (1.0-4.4)
Only large vessel disease*	154	54	1.6 (1.1-2.5)	36	1.6 (1.0-2.7)
Multiple ischaemic lesions*	49	22	2.1 (1.2-3.5)	15	2.3 (1.2-4.4)
Any silent infarct(s)*	64	28	2.1 (1.3-3.3)	19	2.3 (1.2-4.1)
End zone infarct*	117	45	1.8 (1.1-2.7)	28	1.6 (0.9-2.8)
Border zone infarct*	26	8	1.3 (0.6-2.8)	7	1.7 (0.7-3.9)
Cerebellar infarct*	18	8	3.4 (1.6-7.4)	7	4.5 (1.9- 11)
White matter hypodensity	61	22	1.3 (0.8-2.1)	15	1.4 (0.8-2.4)
Echocardiography					
Left atrial diameter > 40 mm	200	67	1.2 (0.8-1.7)	45	1.2 (0.8-1.9)
Left atrium M-mode, cm/m^2					
< 2.3	76	15	reference[‡]	11	reference[‡]
2.3 to 2.6	55	16	1.5 (0.7-3.1)	13	1.7 (0.7-3.7)
≥ 2.6	76	31	2.4 (1.3-4.5)	18	1.8 (0.9-3.8)
Left ventricular end diastolic, cm/m^2					
< 2.7	64	19	reference[‡]	10	reference[‡]
2.7 to 3.0	50	17	1.1 (0.6-2.1)	13	1.5 (0.7-3.5)
≥ 3.0	53	16	1.1 (0.6-2.1)	11	1.4 (0.6-3.4)
Left ventricular end systolic, cm/m^2					
< 1.7	47	15	reference[‡]	8	reference[‡]
1.7 to 2.1	60	15	0.7 (0.4-1.5)	11	0.9 (0.4-2.4)
≥ 2.1	39	13	1.2 (0.6-2.5)	8	1.3 (0.5-3.6)
Left ventricular mass, g/m^2					
< 121	45	10	reference[‡]	8	reference[‡]
121 to 159	48	18	1.9 (0.9-4.2)	10	1.4 (0.6-3.6)
≥ 159	35	9	1.3 (0.5-3.2)	7	1.3 (0.5-3.7)
Fractional shortening < 25%	35	10	0.9 (0.4-1.8)	5	0.7 (0.3-1.9)
Regional left ventricular dysfunction	51	16	1.0 (0.6-1.7)	11	1.0 (0.5-2.0)
Focal left ventricular dysfunction	27	12	1.5 (0.8-2.7)	7	1.3 (0.6-3.2)
Moderate to severe ventricular dysfunction	22	9	1.4 (0.7-2.8)	6	1.4 (0.6-3.2)
Mitral annular calcification	37	13	1.3 (0.7-2.4)	8	1.2 (0.6-2.5)
Intracardiac thrombus	5	4	4.4 (1.6-12)	1	1.6 (0.2-12)

CI: confidence interval; * Compared to no ischaemic lesions; ⊦ Whichever came first
P-value for continuous variables; left atrial diameter p = 0.04; left ventricular end diastolic p = 0.70; left ventricular end systolic p = 0.86; left ventricular mass p = 0.77
⊦ P-value for continuous variables; left atrial diameter p = 0.22; left ventricular end diastolic p = 0.76; left ventricular end systolic p = 0.92; left ventricular mass p = 0.89

Table 4.3.c Results of Univariate Analysis of Risk Factors for the Combined Event of Vascular Death, Stroke, Systemic Embolism or Myocardial Infarction and for Stroke Alone (Fatal or Non-fatal).

		Vascular death, stroke, systemic embolism or myo-cardial infarction⊦		Fatal or non-fatal stroke	
CAROTID INVESTIGATIONS	No. of patients	No of events	HR (95% CI)	No of events	HR (95% CI)
No atherosclerosis of carotid arteries	123	40	reference group	30	reference group
Plaques and/or 0 - 29% stenosis	49	16	0.9 (0.5-1.7)	10	0.8 (0.4-1.6)
30 - 69% stenosis	19	7	1.1 (0.5-2.4)	4	0.8 (0.3-2.3)
70 - 99% stenosis	3	1	2.6 (0.4- 19)	1	1.9 (0.3- 14)
occlusion	4	1	0.7 (0.1-5.3)	1	1.0 (0.1-7.3)

⊦ Whichever came first
CI: confidence interval

through ancillary investigations. An enlarged cardiothoracic ratio on chest X-ray was found to be associated with both a higher risk of recurrent vascular, and a higher risk for recurrent stroke. Presence of any ischaemic lesion on CT-scan also indicated a higher risk for recurrent strokes as well as for recurrent vascular events in general. This association was more marked if (one of) the ischaemic lesions involved the posterior fossa, or if lesions were found in more than one vascular territory. Crude categorial echo-cardiography data on left atrial diameter as obtained routinely in all patients, offered little extra information. A cardiac thrombus was visualised in 5 patients only, 4 of whom suffered a new vascular event during follow-up (2 sudden deaths, 1 myocardial infarct and one minor ischaemic stroke).

In exploratory univariate analyses of echocardiography data that were collected in a subgroup of patients, left atrial diameter, corrected for body surface area and entered as a continuous variable, was identified as the strongest risk factor in relation to recurrent vascular events ($p = 0.04$). No features from echocardiographical investigations were associated with the risk of recurrent stroke alone.

Non-invasive investigations of the carotid arteries were performed in 198 of the placebo-treated patients. Atherosclerotic lesions of the carotid and or vertebrobasilar arteries were found in 81 of them (41%), and were on the side of the qualifying event (or earlier stroke) in 54 patients. No association could be found between the presence of such lesions and the risk of stroke alone or of recurrent vascular events in general.

Multivariate analyses

Nine clinical variables were selected for multivariate analyses; gender, ischaemic heart disease (previous MI, angina or coronary bypass surgery), peripheral vascular disease (intermittent claudication and/or previous vascular surgery), history of thromboembolism, history of hypertension, diabetes, congestive heart failure, duration of atrial fibrillation > 1 year, systolic blood pressure > 160 mmHg at entry; age was forced into the model as an association between age and recurrent vascular events seemed highly probable even though not statistically proven. Only ischaemic heart disease, history of thromboembolism, duration of atrial fibrillation and systolic blood pressure remained independent factors (Table 4.4). In the second multivariate model, radiological indices (chest X-ray and CT-scan) were added. The same baseline characteristics (ischaemic heart disease, prior thromboembolism, duration of AF > 1 year, and systolic blood pressure > 160 mmHg) from model 1 remained in model 2, but the presence of one or more ischaemic lesions on CT-scan as well as an enlarged cardiothoracic ratio on chest X-ray were additionally identified as independent risk factors for recurrent vascular events. Presence of ischaemic heart disease and cardiomegaly on chest X-ray did not contribute to the risk of stroke alone (Table 4.4). Model 3 was to include detailed echocardiography data (cardiac thrombus and left atrial diameter corrected for body surface area), available for 204 patients. However, left atrial diameter was not selected into the model with the stepwise procedure.

Adding information on the presence of an intracardiac thrombus formation (available for 365 patients) to model 2 showed a significant association with recurrent vascular events (hazard ratio 4.6; 95% confidence interval 1.6-13), without altering the estimated coefficients for the variables already in the model. The presence of an intracardiac thrombus on echocardiography was not related to the risk of recurrent stroke alone.

Table 4.4 Results of multivariate analysis of risk factors for the combined event of Vascular Death, Stroke, Systemic Embolism or Myocardial Infarction and for Stroke Alone (Fatal and Non-fatal).

	Vascular death, stroke, systemic embolism or myocardial infarction				Fatal or non-fatal stroke			
	Model 1		Model 2		Model 1		Model 2	
Variable	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Demographic factors								
Age < 60 years[#]	-		-		-		-	
60 ≤ Age < 70 years	1.2	0.5-3.0	1.0	0.4-2.4	0.8	0.3-1.9	0.7	0.3-1.8
70 ≤ Age < 80 years	1.3	0.6-3.1	1.3	0.5-3.0	0.9	0.4-2.1	0.9	0.4-2.2
Age ≥ 80 years	1.5	0.6-3.8	1.5	0.6-3.6	0.6	0.2-1.6	0.6	0.2-1.6
Female gender	...	...	...	...	1.5	1.0-2.4	...	...
Vascular risk factors								
Ischaemic heart disease	1.8	1.2-2.8	1.5	1.0-2.3	...	...	...	...
Previous thromboembolism	1.4	1.0-2.1	1.5	1.0-2.2	1.6	1.0-2.6	1.7	1.0-2.7
Systolic BP > 160 mmHg	1.7	1.1-2.6	1.8	1.2-2.7	1.7	1.0-2.9	1.7	1.0-2.9
Duration AF > 1 year	1.6	1.1-2.4	1.5	1.0-2.3	2.3	1.4-3.9	2.3	1.4-3.9
Ancillary investigations								
Number of infarcts on CT 0[#]	...	...	-		...	...	-	
1	...	...	1.7	1.1-2.6	...	...	1.5	0.9-2.6
≥2	...	...	2.3	1.3-4.0	...	...	2.1	1.1-4.9
Cardiothoracic ratio > 50% on chest X-ray	...	...	1.6	1.0-2.3	...	...	1.9	1.2-3.0
Thrombus on echocardiography	...	...	4.6	1.6-13	...	...	...	...

[#] Reference group
BP: blood pressure

Effect of antithrombotic therapy in high and low risk patients

Of the independent clinical predictors identified in the placebo group, history of previous thromboembolism, ischaemic heart disease, enlarged cardiothoracic ratio on chest X-ray, systolic blood pressure > 160 mmHg at study entry, presence of any form of atrial fibrillation for more than 1 year, and a visible ischaemic lesion on CT-scan were thought to be the most readily available indicators for risk stratification. Nine percent of the complete EAFT study cohort (n = 1,001) had no risk factors at all, 61% had 1 or two risk factors and 30% had three or more risk factors. Multivariate analyses showed that the proposed risk stratification adequately identified high, moderate and low risk subgroups for recurrent vascular events in general and for recurrent stroke alone, independent of allocated treatment and age differences (Table 4.5). Contrary to the previous findings in placebo-treated patients only, age was now shown to be a significant risk factor for the occurrence of recurrent vascular events. Incidence rates of recurrent vascular events were calculated for differing risk strata within each treatment group (Table 4.6), showing that the largest therapeutic effect of oral anticoagulation was obtained in patients under 75 years of age with 1 or two risk factors. Strikingly, the event rate on oral anticoagulation in patients over 75 years of age with 3 or more risk factors was 30 per 100 patient-years as compared to 30 per 100 patient-years on aspirin and 37 per 100 patient-years on placebo. When only on-treatment events were considered, the difference in event rates between the treatment groups for this subset of patients were somewhat larger (24 per 100 patient-years on AC, 31 per 100 patient-years on aspirin and 37 per 100 patient-years on placebo) indicating that, in part, the reduced efficacy of AC in high risk older patients was related to decreased compliance, with more patients stopping treatment due to either side-effects, comorbid diseases or difficulty in maintaining proper anticoagulant control. Still, a significant interaction between anticoagulant therapy and age (under or over 75 years) was found in multivariate analyses ($p = 0.001$ for all vascular events and $p = 0.017$ for recurrent stroke only), not only on an intention-to-treat basis but also for on-treatment data, which implies that factors other than compliance also played a role in reducing the overall benefit of anticoagulants in older patients. The treatment effect of aspirin for the prevention of vascular events in general, though not significant, was most pronounced in high risk

Table 4.5 Adjusted treatment and risk-set specific rate ratios for recurrent vascular events and recurrent strokes

	Recurrent vascular events (vascular death, stroke, systemic embolism and myocardial infarction; whichever came first)		Recurrent stroke (fatal and non-fatal)	
Treatment				
Placebo	1.0	-	1.0	-
Aspirin	0.8	(0.6 - 1.1)	0.9	(0.6 - 1.1)
Oral anticoagulation	0.5	(0.3 - 0.7)	0.3	(0.2 - 0.5)
Risk				
No risk factors*	1.0	-	1.0	-
One or two risk factors	1.9	(1.1 - 3.3)	1.9	(0.9 - 3.9)
Three or more risk factors	3.6	(2.0 - 6.3)	3.9	(1.9 - 8.0)
Age				
≤ 75 years	1.0	-	1.0	-
> 75 years	1.4	(1.1 - 1.8)	1.1	(0.9 - 1.5)

* Risk factors are: history of previous thromboembolism, ischaemic heart disease, enlarged cardiothoracic ratio on chest X-ray, systolic blood pressure > 160 mmHg at study entry, presence of any form of atrial fibrillation for more than 1 year, and a visible ischaemic lesion on CT-scan.

patients (event rate 23 per 100 patient-years on aspirin and 33 per 100 patient-years on placebo), both in patients over 75 years of age and under. Here too, aspirin seemed slightly less effective in patients older than 75 years in preventing recurrent vascular events, but no significant interaction term with age was found in multivariate analyses.

Table 4.6 Annual event rates (and 95% confidence limits) per treatment group according to age and number of risk factors. Events include vascular death, non-fatal stroke, non-fatal myocardial infarction and systemic embolism

	Placebo (n = 375)		Aspirin (n = 401)		Oral AC (n = 225)	
	%*	# Events; event rate†	%*	# Events; event rate†	%*	# Events; event rate†
Age ≤ 75 No risk factors	4%	2; 6.3 (0.8-23)	6%	4; 6.5 (1.8-17)	7%	1; 2.6 (0.1-14)
Age > 75 No risk factors	2%	0; 0.0 (0.0-15)	4%	5; 15 (4.9-35)	3%	1; 8.9 (0.2-50)
Age ≤ 75 1-2 risk factors	35%	41; 15 (11-20)	36%	40; 13 (9.2-17)	41%	10; 4.4 (2.1-8.1)
Age > 75 1-2 risk factors	27%	30; 16 (11-23)	25%	28; 15 (10-21)	17%	11; 14 (6.9-25)
Age ≤ 75 3 or more risk factors	16%	32; 30 (21-42)	14%	24; 18 (12-27)	20%	9; 8.0 (3.6-15)
Age > 75 3 or more risk factors	15%	30; 37 (26-53)	15%	28; 30 (21-43)	12%	11; 30 (15-53)

* Percentage of patients in stratum
† Absolute number of events and event rate in events per 100 patients-years

Discussion

In this study, 6 independent predictors for recurrent vascular events were identified in 375 patients with non-rheumatic atrial fibrillation who had recently suffered a transient ischaemic attack or minor ischaemic stroke and who were receiving placebo treatment in the context of a randomised clinical trial involving a total of 1,001 patients. These variables were a history of previous thromboembolism, ischaemic heart disease, enlarged cardiothoracic ratio on chest X-ray, a systolic blood pressure over 160 mmHg at study entry, atrial fibrillation existing for more than 1 year and evidence of an ischaemic lesion on CT-scan. Thirty-one percent of the placebo-treated patients had 3 or more risk factors and their event rate for recurrent vascular complications (vascular death, myocardial infarction, strokes, and systemic embolism) was 33 per 100 patient-years, almost 10 times the rate in placebo-treated patients with no risk factors (4 per 100

patient-years). This method of risk stratification also adequately distinguished high and low-risk patients in the two treatment groups of aspirin and oral anticoagulation.

The practical application of this profile of risk factors for the clinical decision making process in the initiation and choice of antithrombotic prophylaxis is however not so straightforward. No significant treatment effect of either aspirin or oral anticoagulants was found in low-risk patients but the number of events were probably too small to allow any definitive conclusions. In moderate- and high-risk subgroups, event rates on oral anticoagulation were lowest. However, compared with placebo treatment, quite good results were also obtained with aspirin, especially in high-risk patients. Being able to identify patients at moderate or high risk of recurrent vascular events may support clinicians in their choice of a more aggressive approach with anticoagulant treatment in patients whom they would otherwise have preferred to prescribe aspirin. On the other hand, our data also suggested that older patients benefited relatively less from oral anticoagulant treatment, to the extent that in elderly patients with three or more known risk factors the event rate on aspirin was comparable to that on oral anticoagulation.

Criticisms of the scientific and clinical merits of these exploratory analyses of predictive factors in studies that were originally designed to assess treatment effects relate to issues of (internal) validity, generalisability and clinical relevance. Secondary analyses often involve multiple comparisons which, on mathematical grounds alone, are bound to yield significant findings in 5% of all comparisons (in case of a 5% significance level). It is therefore important that all of the performed comparisons are based on a biologically plausible hypothesis. In addition, both negative (non-significant) findings and significant findings should be reported, allowing the reader to evaluate each conclusion in the light of all available data. The issue of validity is not restricted to statistical inferences. For instance, the validity of data that are used to test hypotheses for which they were not primarily collected can be seriously questioned. In this study, data on echocardiographic features were not collected routinely because the main reason to perform echocardiographic investigations was to exclude patients with concomitant rheumatic valvular disease. Although some echocardiography data could be collected in retrospect and were even

found to be of some prognostic significance (increased left atrial diameter and the presence of an intracardiac thrombus were both related to a higher risk of recurrent vascular events), these results need to be interpreted with appropriate caution as they refer to only a small subset of patients from an already strongly selected study population.

An indispensable method of evaluating the external validity (generalisability) of study results is the comparison with similar studies in other patient groups. Meta-analysis of the pooled data of all primary prevention trials in patients with non-rheumatic atrial fibrillation showed increasing age, previous stroke or TIA, history of hypertension and diabetes to be independent risk factors for stroke.[10] Our results do not directly conflict with these findings. It is conceivable that, because of the higher average age of our placebo-treated patients, age was no longer found to be an independent risk factor within this subgroup. Age was indeed identified as an independent risk factor for recurrent vascular events when the analysis involved the entire EAFT study population, including patients randomised to aspirin or to oral anticoagulation. As for hypertension, the distinction 'history of hypertension' was not identified as an independent risk factor in our secondary prevention study group, but the closely related variable of high systolic blood pressure at study entry was. In other studies of risk factors for recurrent strokes in patients with TIA or minor ischaemic stroke, as well as in studies assessing risk profiles for first-ever stroke, evidence of ischaemic heart disease (angina pectoris, prior myocardial infarction), peripheral vascular disease (intermittent claudication, prior vascular surgery), history of previous thromboembolic events, diabetes, an enlarged cardiothoracic ratio on chest X-ray, systolic blood pressure >160 mmHg at study entry and presence of any ischaemic lesion on CT-scan have all been reported on one or more occasions to be associated with a higher risk for recurrent strokes as well as for recurrent vascular events in general.[24,27,36,58,59,64,88,206] The predictive value of left atrial size is also in agreement with previous studies.[8,32,37,182] Probably one of the most striking findings was that any ischaemic lesion on CT-scan, and multiple ischaemic lesions in particular, were predictive for both cardiac events and recurrent stroke. Despite marked differences between CT-scan findings after one or more episodes of transient or non-disabling cerebral ischaemia in patients with atrial fibrillation and patients with sinus rhythm (chapter 6), the

presence of typically 'embolic' infarcts (large end zone infarctions) was no stronger predictor of recurrent events than that of typically 'non-embolic' lesions (small deep infarcts). Whereas border zone infarcts were found to be strongly associated with recurrent vascular events in sinus rhythm patients,[64] an association that could be explained by assuming severe carotid stenosis in these patients, no such relationship was found in patients with atrial fibrillation, possibly because of the differences in underlying pathogenesis. We did find an unexpectedly high recurrence rate of ischaemic strokes in patients with lesions in the cerebellum or brainstem at study entry, but this might well have been a chance effect.

Risk factors associated with recurrence of vascular events (including strokes) have in common that they are either manifestations of atherosclerosis or contribute to the certainty with which the initial diagnosis of cerebral events (in case of CT-scan indices) or atrial fibrillation (long-standing history of arrhythmia, enlarged left atrial diameter) could be made. The individual merits of each separate risk factor should be viewed in this context and the fact that different studies report slightly different predictors should therefore not be considered as evidence of poor validity of the conclusions. Because of the multicentre (108 centres) and multinational (13 different countries) character of the EAFT study group, the results of our secondary analyses can be applied to a broad spectrum of patients with NRAF who have experienced a recent TIA or minor ischaemic stroke. The clinical definitions of the various predictors used in this evaluation may well have been interpreted differently in the many collaborating centres. This will have caused an underestimation of most of the reported associations, but on the other hand biologically plausible associations that were found are therefore more likely to hold up in the general clinical situation. With the availability of easily accessible high powered computing facilities, multivariate analysis for the development of predictive models has become very popular. The clinical relevance of such models is not always clear. In a clinical situation individual characteristics are considered when deciding on a course of treatment, rather than the sum of a set of broadly classified risk factors. The clinical consequences of diabetes, for instance, can vary widely between patients and the mere classification as 'present' or 'not present', fails to take account of the extent of the underlying disease. Furthermore, the most often used method of

predictive modelling until now considers only the risk factor status at study entry, whereas risk factors that develop over the course of follow-up are not entered into the equation. In a clinical setting however, risk factor evaluation will always consider the most up-to-date situation. Last but not least, predictions derived from hospital-referred patients might well overestimate the actual risk in the general population.[87] Despite these misgivings about the clinical relevance of prognostic modelling, knowledge of risk factors and their association with future vascular events will always be of some help in treatment decisions and patient counselling. Finally such knowledge enables the physician to recognise, treat and possibly prevent the development of new risk factors thereby hopefully bettering patients' chances for a healthy, event-free future.

CHAPTER 5:
OPTIMAL INTENSITY OF ANTICOAGULANT THERAPY

"As Ed Murrow once said about Vietnam, anyone who isn't confused doesn't really understand the situation"

Walter Bryan, The improbable Irish (1969), ch.1

OPTIMAL INTENSITY OF ANTICOAGULANT THERAPY IN PATIENTS WITH NON-RHEUMATIC ATRIAL FIBRILLATION AND A RECENT, NON-DISABLING EPISODE OF CEREBRAL ISCHAEMIA

Introduction

The efficacy of oral anticoagulant treatment in reducing the risk of stroke and systemic embolism has been unequivocally demonstrated for both primary and secondary prevention in patients with non-rheumatic atrial fibrillation, with risk reductions of thromboembolic events (usually defined as ischaemic stroke and systemic embolism) ranging from 37% to 86% and major bleeding complications occurring at rates of 5 per 1000 patient-years to 28 per 1000 patient-years.[23,52,70,148,181,183]

A logical next step would be to determine which intensity of oral anticoagulant treatment in non-rheumatic atrial fibrillation offers the optimal balance between prevention of thromboembolism and the occurrence of bleeding complications. Addressing this question has proved difficult, not only because the studied therapeutic ranges of anticoagulant control differ widely between the studies, but also because most of these studies failed to report their achieved anticoagulant control in terms of International Normalised Ratios (INR), and instead used prothrombin time ratios (PTR). PTR measurements differ markedly depending on the responsiveness of thromboplastin preparations, and INR values were therefore developed as a measure of anticoagulant control that was independent of the properties of the thromboplastin used. The INR is calculated by raising the PTR to the power of the international sensitivity index (ISI) of the preparation of thromboplastin ($INR = PTR^{ISI}$).[110,126] Because

especially thromboplastins used in the United States show a large variation in sensitivity, the continuing use of PTR's in reporting anticoagulant intensity should be considered inappropriate.[30] With respect to the primary prevention studies in non-rheumatic atrial fibrillation, the study with the highest therapeutic intensity, the AFASAK study, reported a 56% reduction of thromboembolic events with oral anticoagulant therapy aimed at a therapeutic range between 2.8 and 4.8 INR.[148] INR values were reported to be under 2.4 twenty-six percent of the treatment time. Of the 4 presumably embolic brain infarcts, 3 occurred at inadequate therapeutic intensities (below 1.5 INR) (Table 5.1). The SPAF study reported a 67% reduction of thromboembolic events with warfarin dose-adjusted to prolong prothrombin time to 1.3-fold to 1.8-fold that of control.[181] This therapeutic range was initially stated to lie between 2.0 to 3.5 INR,[183] but the thromboplastin reagents used in this multicentre study were not standardised and the confusion becomes apparent when a range of 2.0 to 4.5 is reported in the final results.[181] Seventy-two of all reported prothrombin times were within the therapeutic range; no information was available on the INR's at the time of thromboembolic events. The CAFA study, with a comparable therapeutic range of anticoagulant intensity between 2.0 and 3.0 INR, reported a non-significant risk reduction (37%) of thromboembolic complications, but this study was terminated early (without interim analysis) after the publication of the other primary prevention studies.[52] The achieved INR's were within target range 43% of the study days. Of the six thromboembolic events, only one occurred in a patient whose INR was within the target range. The other events occurred at INR values below 1.5 (n = 4) or 17 months after discontinuation of AC treatment (n = 1). The lowest target intensity of anticoagulation (prothrombin time ratio 1.2 to 1.5) was used in the BAATAF study[23] and in the VA study.[70] In both studies, prothrombin times were obtained by means of non-standardised thromboplastins and were originally not reported as INR. The INR values of the target range were estimated to be approximately 1.5-2.7 and 1.4-2.8, respectively.[23,70] Of the thromboplastins used in the VA study, ISI's (if available) ranged between 1.5 and 2.6, so that in fact therapeutic ranges differed between centres from INR 1.3-1.8 to INR 1.6-2.8. The BAATAF study reported a reduction of thromboembolic strokes of 86%. Prothrombin time ratios were within the desired range 83%

of the time and the two warfarin treated patients who suffered a stroke had (approximate) INR values below 2 at the time of their event. In the VA study the risk reduction with anticoagulant treatment was 79%; on average patients were within therapeutic range 56% of the time, and three of the 4 patients who suffered cerebral ischaemic events on warfarin treatment had approximate INR values below 2 (assuming an ISI value of 2.3).

Table 5.1 Overview of oral anticoagulant control obtained by primary prevention studies in patients with non-rheumatic atrial fibrillation

STUDY	RR[†]	target intensity (INR)[‖]	Measure of obtained AC control (INR)[‖]	Reported outcome events[*]
AFASAK	56%	2.8 - 4.2	< 2.4 26% of the time > 4.2 0.6% of the time	3 out of 4 events occurred at INR < 1.5
SPAF	67%	2.0 - 3.5[‡] (PT 1.3 - 1.8)	< 2.0 23% of the time > 3.5 5% of the time	not available
CAFA	37%	2.0 - 3.0	< 2.0 40% of the time > 3.0 17% of the time	4 out of 5 events occurred at INR < 1.5
BAATAF	86%	1.5 - 2.7 (PT 1.2 - 1.5)	< 1.5 8% of the time > 2.7 9% of the time	2 events, INR 1.7 and 1.5 (assuming ISI 2.4)
SPINAF	79%	1.4 - 2.8 (PT 1.2 - 1.5)	< 1.4 29% of the time > 2.8 15% of the time	4 events, INR 1.6, 1.7, 1.9 and 2.4 (assuming ISI 2.1)

RR: Risk reduction; AC: Oral anticoagulant therapy; ISI: International Sensitivity Index; AFASAK: Atrial Fibrillation, Aspirin, Anticoagulation Study from Copenhagen, Denmark. BAATAF: Boston Area Anticoagulation Trial for Atrial Fibrillation. CAFA: Canadian Atrial Fibrillation Anticoagulation study. EAFT; the European Atrial Fibrillation Trial. SPAF: Stroke Prevention in Atrial Fibrillation study. SPINAF: Veterans Administration Stroke Prevention in Nonrheumatic Atrial Fibrillation study.

[*] Only events occurring on-treatment, or within 28 days after discontinuation of AC treatment. Events include the primary outcome event definitions of the individual studies (usually cerebral ischaemia and systemic embolism)

[†] Risk reduction of primary outcome events with anticoagulation compared with the control group (mostly placebo)

[‖] Approximate INR (International Normalised Ratio) in cases where only PT ratio's were reported.

[‡] Range mentioned in the preliminary report of the SPAF[183]

It is obvious that since none of the above studies have used the actually achieved anticoagulant intensity for additional efficacy analyses, lack of adequate data impedes the establishment of reliable guidelines for the optimal intensity of anticoagulant treatment in patients with non-rheumatic atrial fibrillation. Following a recently proposed method to determine the optimal intensity of oral anticoagulant therapy,[161] we calculated INR-specific incidence rates for both vascular and major haemorrhagic events occurring in the study cohort of the European Atrial Fibrillation Trial, a secondary prevention trial in patients with non-rheumatic atrial fibrillation and a recent minor episode of cerebral ischaemia.[65]

Patients and methods

Patients

The study group consisted of all patients of the European Atrial Fibrillation Trial who had been randomised to oral anticoagulant therapy. The study design is described in more detail in Chapter 2. In short, the EAFT was a randomised, multicentre clinical trial which aimed to assess the therapeutic efficacy and safety of both oral anticoagulants and aspirin for the prevention of vascular events in patients with non-rheumatic atrial fibrillation and a recent minor cerebral ischaemic event. When eligible for treatment with oral anticoagulants, patients were randomised between either open anticoagulant treatment (INR 2.5-4.0) or double-blind treatment with either aspirin (300 mg/day) or placebo.

Anticoagulant control

Choice of anticoagulant congener was left to the discretion of the randomising physician and depended largely on personal experience with and availability of the different trade marks. The dose of anticoagulant treatment was controlled by the prothrombin time (PT). To accommodate variations in composition and responsiveness of the thromboplastins and methods necessary for PT measurement, all centres were asked to use calibrated commercial preparations only. This would allow reporting of PT values in International Normalised Ratio (INR) equivalents. The INRs had to be maintained at a target value of 3.0, with a range of 2.5 to 4.0.[127,155] PT

had to be monitored at least once a month and these values were reported every four months at the follow-up visit of the patient. In cases where achieved anticoagulant intensity consistently fell below the proposed range, centres would be notified by the trial office.

Assessment of anticoagulant control

Different approaches have been proposed for the assessment of therapeutic anticoagulant control:

I Indices without time dimension
   a. Cumulative INR's: The number of INR measurements within the target range expressed as a percentage of the total number of values obtained.[90]
   b. Cross-section-of-the-files: Same as above but considering only the most recent (within 56 days) INR obtained in each patient at pre-defined intervals.[190]

II Time each patient's INR was at pre-defined levels of therapeutic intensity (e.g. INR < 2.5, INR 2.5-4.0 and INR > 4.0) as a percentage of the total time on treatment. Two algorhythms can be used to allocate the time between two INR measurements.
   a. The full time preceding an INR measurement is counted as belonging to this INR.
   b. Half of the time preceding and half of the time following an INR measurement until the previous and next measurements, respectively, are counted as belonging to the current INR.[191]

Approach II has the added benefit that it allows for the calculation of INR specific incidence rates of thromboembolic as well as haemorrhagic events. A further sophistication of this method is to assume a linear change of INR values between visits, and to use small increments of time (days) and INR values (0.1 INR) to allocate time between two INR determinations.[161] Because it seemed likely that not all available INR values were actually reported in this study, such a refinement was thought to be inappropriate for the analysis of our data. In the present study, methods Ia and IIb were used.

Efficacy analysis for subgroups of therapeutic intensity (indices without time dimension)

In the original study protocol, subgroup analyses for the treatment effect of oral anticoagulants were planned by means of predefined measures for the

achieved level of anticoagulant control that were obtained with the method of cumulative INR's described above (Ia). Three methods of dichotomisation were proposed: 1. Per-protocol treatment if 70% or more of the patient's INR values were within the range of 2.5-4.0 as opposed to less than 70%. 2. High intensity level of anticoagulant treatment, defined as 50% or more of the obtained INR values exceeding INR 3.0, versus 50% or more equal to 3.0 or lower. 3. Low intensity treatment was defined as 50% or more of the INR values lying below 3.0, versus 50% or more equal to or higher than 3.0.

Calculation of INR-specific event rates
Data required for these analyses included not only the results but also the dates of all prothrombin time assessments for the observation period of each individual patient, and also the date of all events and the prothrombin times at the time of these events.

Definition of events (numerator) - In order to assess the optimal anticoagulant intensity, both major bleeding complications and vascular outcome events were considered. The primary measure of outcome was the composite event of vascular death, non-fatal stroke (including intracranial haemorrhage), non-fatal myocardial infarction or systemic embolism, whichever occurred first. A secondary analysis included only strokes, fatal or non-fatal. Vascular death included sudden death (death seen by an eyewitness, with a reliable observation of the time between onset of symptoms and death; or the patient being found dead), or death from stroke, myocardial infarction, congestive heart failure, systemic embolism, non-cerebral bleed, and other vascular causes (including pulmonary embolism and peripheral vascular disease). The diagnosis of non-fatal stroke required a focal neurological deficit persisting for more than 24 hours. CT-scans made at the time of the outcome event were centrally audited by physicians who were unaware of the allocated treatment. Based on these scans the distinction between ischaemic stroke, ischaemic stroke with haemorrhagic transformation, and primary intracerebral haemorrhage was made. The diagnosis of systemic embolism was clinically defined as abrupt vascular insufficiency of limbs or internal organs associated with clinical or radiological evidence of arterial occlusion, in the absence of

previous obstructive disease; it did not include pulmonary embolism. Myocardial infarction had to be documented by at least two of the following characteristics: a history of chest discomfort, specific cardiac enzyme levels more than twice the upper limit of normal, or the development of Q waves on the standard 12-lead electrocardiogram.

The occurrence of bleeding complications was recorded at each follow-up visit for all patients. Haemorrhagic episodes were classified according to severity. Fatal bleeding complications had to be documented by convincing clinical evidence or autopsy. Non-fatal bleeding complications were considered major if hospital admission and blood transfusion or surgery were necessary or when such a complication caused a permanent increase in disability. Nose bleeds, bruising, haematemesis, haematuria and the like, were considered minor if no blood transfusion or operative intervention were required.

All events were independently classified by at least three members of the Auditing Committee for Outcome events, after the medical records had been summarised and edited to ensure that the reviewers remained unaware of the allocated treatment. Differences of opinion were discussed within the Executive Committee, which was also blinded, and then decided by majority vote. The instantaneous INR measurement at the time of an event was recorded on the same form on which the event was reported. If no INR measurement was available at the date of the event, the last INR measurement obtained within 28 days before the event was considered.

Calculation of observation time for different INR-levels (denominator) - The total observation time for each patient was counted from entry in the study until either the close-out visit in April 1993, the time of an event, or 28 days after discontinuation of anticoagulant treatment, whichever occurred first. This observation time was stratified according to INR level by means of method IIb (described above). In cases where the time between 2 INR measurements for a given patient exceeded 56 days, the maximal period that the two INR levels could contribute to the analysis of this period was set at 28 days; the intermediate period of undefined anticoagulant intensity was allocated to a separate stratum of "unknown INR".

Statistical analysis

Event rates, 95% confidence intervals and event rate ratios were derived through standard calculations based on the assumption of a Poisson distribution of the number of events. A multivariate Poisson regression model was used to control for confounding through possible differences in age, systolic blood pressure, history of ischaemic heart disease and the presence of an enlarged cardiothoracic ratio (> 50%) on chest X-ray. These variables had been identified as the most important predictors for recurrent vascular events in patients treated with oral anticoagulants (Chapter 4). In addition, other studies have identified age and systolic blood pressure as predictors for the occurrence of bleeding complications.[123]

Results

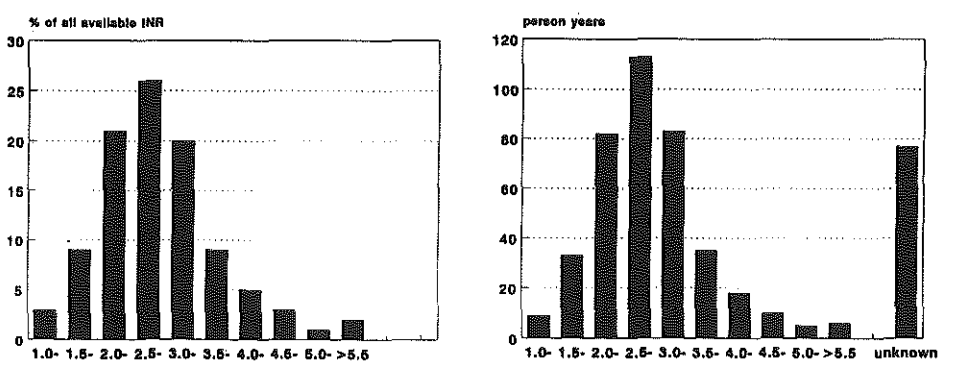
Between October 1988 and May 1992, 1007 patients were entered in the European Atrial Fibrillation Trial. Of the patients eligible for anticoagulant treatment (n = 669), 225 were randomised to treatment with oral anticoagulants. They contributed 532 years to the total patient observation time of the study, 475 years of which were actually on treatment. Baseline characteristics of this treatment group were described in Chapter 3. In summary, 55% of the patients were male, their mean age was 71 years, and 43% had a history of hypertension. Two patients refused to start treatment with anticoagulants, and in one patient treatment was stopped within 7 days because of erratic compliance. In another 8 patients no INR values were obtained because, before their first follow-up visit, they either suffered a major outcome event (n = 4) or stopped using anticoagulant treatment (n = 4) (INR's were reported by means of the follow-up forms). These eleven patients were excluded from further analyses.

Anticoagulant control

In total 4,883 INR values were reported to the trial office, with a median of 21 determinations per patients (range from 1 to 63). Given an average on-treatment follow-up of 2.1 years, INR determinations were reported approximately every 5 weeks. In 47 patients INR values were unavailable for periods exceeding 3 months at some point in time, indicating that in them only assumptions can be made about the overall level of anticoagulant control. Figure 5.1 visualizes the level of anticoagulant

control that was obtained. Fifty-six percent of all available INR measurements were within the target range of 2.5-4.0 INR. Thirty-five percent were under this range and 9% were above. These percentages were similar in all age groups (under 65, between 65 and 75 years, and above 75 years). According to our pre-defined definitions for anticoagulant control, 26% of all patients were treated per-protocol (70% or more of all INR measurements within the target range), 36% received low-intensity treatment (50% or more of all INR measurements below 3.0), and 24% were treated with a high-intensity regimen (50% or more of all INR values above 3.0). Again, these percentages were similar for the different age groups.

Figure 5.1 Anticoagulant control. The left graph depicts % of all reported INR's at given INR increments. The right graph shows person time in years spent at each INR intercept. If time between two consecutive INR measurements surpassed 56 days, the INR's in the middle of this period were classified as unknown.



Efficacy analyses for subgroups of therapeutic intensity

Table 5.2 shows stratification of anticoagulant control by means of the proposed crude dichotomisations 'per-protocol treatment vs inadequate treatment', 'low intensity treatment vs normal and/or high intensity treatment' and 'high intensity treatment vs normal and/or low intensity treatment ' in relation to vascular events in general, strokes (fatal and non-fatal), and major bleeding complications, after correction for possible differences at baseline in age, systolic blood pressure, history of heart disease, and the presence of cardiomegaly on chest X-ray. Although lower

rates of recurrent vascular events, strokes, and bleeding complications were obtained with 'per-protocol' treatment than with inadequate AC treatment (more than 30% of all INR values under or over the target range), these differences were not statistically significant. Patients on low-intensity regimens suffered more vascular events than other patients (rate ratio 1.2), but apparently low-intensity treatment was not detrimental for the prevention of strokes alone (rate ratio 0.8), and strikingly, low-intensity treatment was not associated with a lower rate of major bleeding complications (rate ratio 1.0).

Table 5.2 Incidence rate ratios for thromboembolic and haemorrhagic events for different measures of anticoagulant control (three methods of dichotomisation), corrected for baseline imbalances with respect to age, systolic blood pressure at study entry, presence of ischaemic heart disease and a cardiothoracic ratio exceeding 50%.

Event	Subgroup	RR	95% CI
All vascular events	'Per-protocol' AC control	0.7	(0.3-1.8)
	Low intensity control	1.3	(0.6-2.7)
	High intensity control	1.9	(0.9-4.1)
Strokes (fatal or non-fatal)	'Per-protocol' AC control	0.2	(0.03-1.9)
	Low intensity control	0.9	(0.3-3.1)
	High intensity control	1.0	(0.3-4.0)
Major haemorrhagic events	'Per-protocol' AC control	0.6	(0.1-2.6)
	Low intensity control	1.0	(0.3-3.2)
	High intensity control	1.6	(0.5-5.5)

RR: Rate ratio; CI: Confidence interval; AC: Anticoagulants

High-intensity anticoagulant control was less effective in preventing recurrent vascular events and was associated with higher rate of bleeding complications. All confidence intervals were wide in these analyses, and probably the best conclusion is that these results are inconclusive and that better classification methods are called for.

INR-specific event rates

An overview of all events with corresponding INR's is given in Table 5.3. The incidence of vascular events increases at higher INR levels reflecting the fact that these events included vascular deaths from non-cerebral haemorrhages. It is also possible that some of the sudden deaths were actually undiagnosed fatal haemorrhages. Because of the relatively small number of events, further analyses were restricted to the combined outcome event of all ischaemic vascular complications or major haemorrhagic episodes, whichever came first.

Table 5.3a Overview of thromboembolic and haemorrhagic complications, first events only

Outcome event	Nature of events	Number of events
Vascular events (all)	Sudden Death	5
	Fatal CHF	3
	Fatal Non-CNS Bleed	2
	Vascular death other	1
	Fatal+non-fatal strokes	14
	Fatal+non-fatal MI	3
	Fatal+non-fatal SE	2
	Total	30
Strokes (fatal and non-fatal)	Non-haemorrhagic stroke	10
	Haemorrhagic ischaemic stroke	1
	Stroke, no CT available	3
	Intracranial bleed	0
	Total	14
Major bleeding	Respiratory	2
	Gastrointestinal	4
	Urogenital	1
	Cerebral	0
	Anaemia	1
	Other	5
	Total	13

CHF: Congestive heart failure; CNS: central nervous system; MI: Myocardial Infarction; SE: Systemic embolism

Table 5.3b Overview of thromboembolic and haemorrhagic complications (absolute numbers and event rates) for first events only, in relation to INR at the time of the event

INR at time of event	Vascular events (all)		Strokes (fatal+non-fatal)		Major bleeding	
	#	Rate	#	Rate	#	Rate
unknown	5	7/100 py	2	3/100 py	2	3/100 py
< 2.0	7	17/100 py	5	12/100 py	2	1/100 py
2.0 - 3.0	4	2/100 py	2	1/100 py	2	1/100 py
3.0 - 4.0	5	4/100 py	2	1/100 py	3	3/100 py
4.0 - 5.0	7	26/100 py	3	11/100 py	1	4/100 py
≥ 5.0	2	20/100 py	-	-	5	46/100 py
ALL	30	7/100 py	14	3/100 py	13	3/100 py

INR: International Normalised Ratio; py: patient-years

The total number of patient-years spent within INR-specific intervals for the combined events were: 40 years for INR < 2.0, 186 years for INR 2-3, 114 years for INR 3-4, 27 years for INR 4-5, and 10 years for INR ≥ 5. Seventy-two patient-years were unaccounted for because of insufficient information on INR measurements. In 31 of the 39 events, INR measurements were available at the time of the event. INR-specific incidence rates with corresponding 95% confidence intervals are illustrated in Figure 5.2. The highest event rates were seen at INR values below 2.0 (predominantly thromboembolic events; rate 18 per 100 patient-years) and above INR 5.0 (predominantly haemorrhagic events; rate 60 per 100 patient-years). The lowest incidence rate for the combined event of thromboembolic and haemorrhagic events was found in the interval between INR 2.0-3.0. Multivariate Poisson regression analyses were performed to assess the independent risk of events (vascular and major haemorrhages) for INR-specific intervals, after controlling for age, systolic blood pressure at study entry, history of ischaemic cardiac disease and cardiomegaly; the results are presented in Table 5.4. Relative to INR intensities below 2.0, anticoagulant therapy with intensities between INR 2.0 and 3.0 reduced the incidence of vascular events with 80% (rate ratio 0.2; 95% confidence interval 0.1-0.6). This effect was slightly less with intensities between 3.0 and 4.0 (rate ratio

0.4; 95% confidence interval 0.1-1.1). At higher intensities the event rate was increased, because the beneficial effect was offset by an increased risk of haemorrhagic complications (Figure 5.2). With INR levels between 4.0 and 5.0 the rate ratio for vascular events and major haemorrhages was 1.6 (95% confidence interval 0.6-4.6), at levels above INR 5.0 this rate ratio increased even further (3.6; 95% confidence interval 1.2-11). In these analyses both age and the presence of cardiomegaly remained important risk factors for recurrent vascular events (thromboembolic or haemorrhagic), confirming the prognostic value found in the entire group of randomised patients (Chapter 4). Additional analyses showed that age over 75 years was also associated with a higher risk of major bleeding alone (rate ratio 3.6; 95% confidence interval 1.0-13), independent of the therapeutic intensity of anticoagulants. Systolic blood pressure over 160 mmHg at study entry was not associated with a higher rate of major bleeding complications.

Figure 5.2 INR specific incidence rates for major vascular events and bleeding complications, with 95% confidence intervals

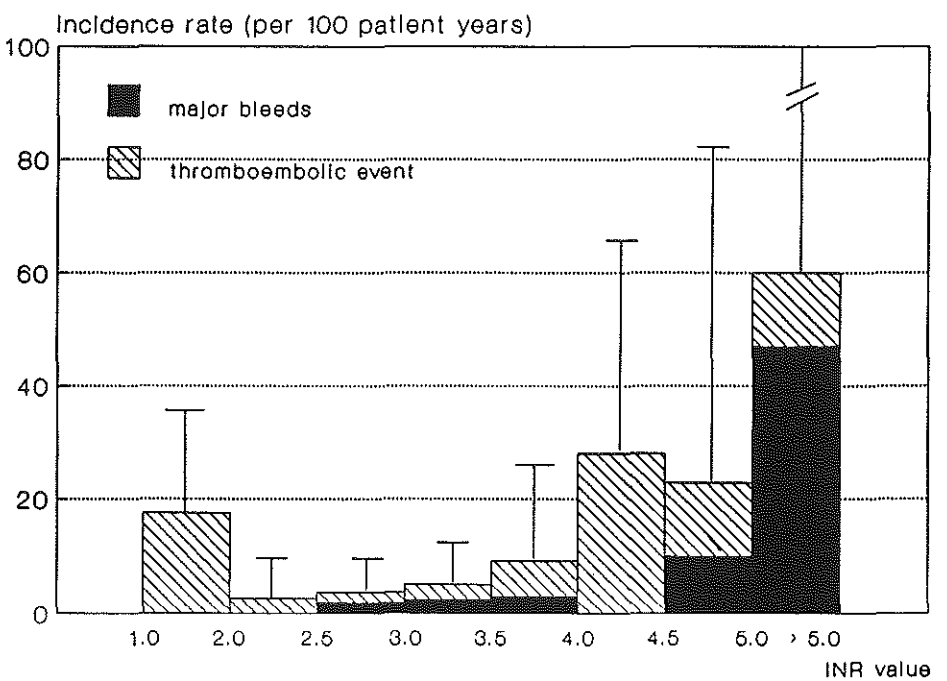


Table 5.4 Multivariate analysis for the combined event of vascular death, stroke, MI, systemic embolism and haemorrhagic complications, whichever occurred first, including level of anticoagulation, age, systolic blood pressure at study entry, history of ischaemic heart disease and cardiomegaly.

	RR	(95% confidence interval)	p-value
INR			
< 2.0	1.0	reference	
2.0 - 3.0	0.2	(0.1-0.6)	0.003
3.0 - 4.0	0.4	(0.1-1.1)	0.075
4.0 - 5.0	1.6	(0.6-4.6)	0.378
≥ 5.0	3.6	(1.2- 11)	0.022
Age			
≤ 75 years	1.0	reference	
> 75 years	3.1	(1.5-6.4)	0.002
Systolic blood pressure			
≤ 160 mmHg	1.0	reference	
> 160 mmHg	1.6	(0.6-3.9)	0.325
Rx of ischaemic heart disease			
no	1.0	reference	
yes	1.4	(0.6-3.4)	0.431
Cardiothoracic ratio > 50%			
no	1.0	reference	
yes	2.9	(1.4-5.9)	0.003

RR: Rate ratio

Discussion

In this study of 225 patients with non-rheumatic atrial fibrillation and a recent transient ischaemic attack or minor ischaemic stroke who were randomised to treatment with oral anticoagulation, the optimal intensity of therapy was evaluated by calculating INR-specific incidence rates both for important vascular events in general (vascular death, stroke, myocardial infarction and systemic embolism) and for major bleeding complications. Treatment at an anticoagulant intensity of INR 2.0-3.0 offered the best balance between reducing the risk of recurrent thromboembolic events and

taking an unacceptably high risk of major bleeding complications. The incidence of adverse events was slightly higher, but still acceptable, in the range from INR 3.0 to 4.0. Although according to the original study protocol the target intensity for anticoagulant treatment had to be aimed at INR 3.0 (range 2.5-4.0), 46% of all INR measurements fell below 3.0 (between 2.0-3.0) and 29% were in the range of INR 3.0-4.0. It therefore seems that aiming at a target intensity of 3.0 INR will safeguard an optimal therapeutic effect. Aiming at lower target intensities will probably entail an unacceptable proportion of treatment-years falling within INR levels below 2.0, at which intensity the incidence rate of vascular events was as high as in the placebo-treated cohort of the same study population (17 per 100 patient-years). These findings are in agreement with guidelines that were formulated in recent overviews and in guidelines from the American College of Chest Physicians (ACCP),[97,121] but suggest a slightly lower intensity of anticoagulation than recommended by Dutch guidelines for high-risk patients (target INR 3.5; range 3.0-4.5).[128] The optimal range of anticoagulation in our study is also slightly lower than what was found in a similar analysis for post-myocardial infarction patients (target INR 3.5; range 3.0-4.0).[11] Because of the limited number of observations, this study provides insufficient evidence to refute either the ACCP or Dutch guidelines. Physicians should probably adhere to the guidelines they are most familiar with, as long as INR levels below 2.0 or above 4.0 are avoided.

Following the publication of the EAFT study results, Bussey remarked on the need for explanatory analyses in anticoagulation research.[31] He argues that intention-to-treat analyses may provide incomplete or misleading conclusions since in most studies the actually obtained levels of anticoagulation differ widely from the intended target ranges. The present, more detailed, report on anticoagulant efficacy in the EAFT proves that even with relatively few data, the method of reporting event rates at different INR intervals, originally proposed by Rosendaal and others,[161] can supply clinicians with helpful additional insights. Nevertheless these analyses should not replace intention-to-treat analyses. The effect of erratic anticoagulant compliance can be assessed by this method, but the impact of withdrawals from anticoagulant treatment for reasons other than major bleeding complications (e.g. recurrent minor bleeds, patient's reluctance to

adhere to stringent PT control regimens) are lost in such an analysis, even if person-years after treatment withdrawal are allocated to a stratum with INR levels of 1.0. Intention-to-treat analyses allow for more general conclusions with regard to the strategy of prescribing anticoagulants, irrespective of attained levels of therapeutic intensity which, even with intensive laboratory control, are largely dependent on patient characteristics that are not always easily defined or recognised, let alone controlled.[170]

Our study can be criticised concerning the measurements used for the determination of anticoagulant control. Although all participating centres in our study used calibrated commercial preparations, obtaining INR measurements instead of locally used measures (seconds, ratio, index or percentage activity) proved to be difficult for some participants, no country excepted. In these cases approximate INR's would be deduced from conversion tables supplied by the manufacturer of the thromboplastin used. However, these tables were not always updated when a new batch of thromboplastin was taken into use, and in some cases laboratories switched to other thromboplastin substrates without notifying the physician. Added to the fact that not all available INR measurements were actually reported to the trial office, and that for 77 of the in total 470 patient-years we had no reliable INR measurements, all these qualifications indicate that the results should be considered with appropriate caution. Nevertheless, incidence rates in treatment-years with unknown anticoagulant intensity are similar to those reported for the entire treatment group, implying that no serious bias has occurred.

The incidence rate of major bleeding complications related to oral anticoagulant use amounted to 2.8 per 100 patient-years in our study, which was slightly higher than in the primary prevention studies of patients with non-rheumatic atrial fibrillation, but within the ranges reported by other studies that considered a wider range of indications.[122,123,130,191] Differences in the intensity of anticoagulation may in part explain this difference (overall, the obtained INR levels in the EAFT were possibly slightly higher than in the primary prevention studies) but the higher mean age of our patients (71 years) may also have influenced the findings. The relationship between higher age and an increased risk for major haemorrhagic events is still controversial,[84,119,120] but it seems

plausible to expect a higher risk of complications because of increasing comorbidity (hypertension, diabetes, atherosclerosis, malignant disease, concomitant medication and erratic compliance). In our study population no association was found between high systolic blood pressure or history of hypertension on the one hand and risk of bleeding on the other.[120,122,202] Possible explanations might be that only patients with adequately controlled hypertension were entered in the study, and that the blood pressure measurements at study entry which were used for this analysis probably were not representative for systolic blood pressures during the rest of the study period.

In conclusion, the optimal therapeutic range for anticoagulant treatment in the secondary prevention of vascular events in relatively old patients (mean age 71 years) with non-rheumatic atrial fibrillation who have recently suffered a minor ischaemic event, lies within the INR range of 2.0-3.0, with a target INR of 3.0. At INR levels above 5.0, the risk of serious bleeding complications becomes unacceptable, whereas no apparent reduction in thromboembolic events is obtained with intensities below INR 2.0.

CHAPTER 6:
COMPARISON OF CT-SCAN FINDINGS

"If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties."

Bacon, Advancement of Learning, Bk.I,V,8

COMPARISON OF CT-SCAN FINDINGS IN TIA AND MINOR STROKE PATIENTS, WITH OR WITHOUT NON-RHEUMATIC ATRIAL FIBRILLATION

Introduction

Although the role of non-rheumatic atrial fibrillation (NRAF) as a risk factor for stroke has been well established by several epidemiological studies,[205,207] the pathogenesis of NRAF related strokes continues to be uncertain. The presence of NRAF in itself is insufficient evidence of cardiogenic embolism to the brain, as NRAF might also be a mere marker of coexistent atherosclerotic (cerebro)vascular disease, present in a large percentage of the elderly population. Both direct and indirect arguments however, support a more causal relation between atrial fibrillation and cerebral ischaemic episodes. A distinct clustering of ischaemic episodes is seen around the time of onset of atrial fibrillation,[46,150] the rate of embolism in patients with thyrotoxic atrial fibrillation can be as high as 30%,[47] and epidemiological studies indicate a four- to tenfold increased risk of stroke in patients with non-rheumatic atrial fibrillation, without a concomitant increase in risk of ischaemic heart disease.[24,25]

Because prognosis and choice of secondary preventive treatment possibly differ according to whether the suspected cause of the stroke is of arterial or cardiac origin, the distinction is important in individual cases. Numerous classification schemes have been proposed that are based on a combination of clinical, laboratory, and sometimes, pathology data, and are mostly derived from literature reviews.[79,156] These classification schemes usually include 'typical' CT-scan characteristics (e.g. large ischaemic lesions with cortical involvement, multiple lesions in different vascular territories,

isolated posterior infarcts) that might help to distinguish between cardioembolic en thromboembolic ischaemic strokes in patients with NRAF. These criteria are based on relatively few studies that have actually assessed CT-scan differences between cardioembolic and thromboembolic stroke. Most of these studies included patients with other sources of cardiac embolism than NRAF, for instance patients with rheumatic heart disease, prosthetic valves, or recent myocardial infarction.[17,21,38,143] Studies focusing specifically on CT-scan characteristics of stroke patients with non-rheumatic atrial fibrillation were usually small[22,55,91,134] and did not always supply a comparison with CT-scan findings in stroke patients without atrial fibrillation.[22,55,134]

We have compared the CT-scan characteristics in two prospectively studied cohorts of patients with transient ischaemic attack (TIA) or minor ischaemic stroke, with (n = 985) or without (n = 2987) non-rheumatic atrial fibrillation.

Patients and methods

CT-scans were analysed in 985 of the 1007 patients with NRAF presenting with symptoms of TIA or minor ischaemic stroke (Rankin ≤ 3) who had been entered in the EAFT. Background and design of this study are described in Chapter 1 and 2. Five patients were excluded from the analysis because their scan showed evidence of a cerebral tumour (1 patient), a primary intracerebral haemorrhage (1 patient), or because they had no evidence of atrial fibrillation ever (3 patients). No CT-scan was available in 17 patients. The control group in which we also analysed CT-scans consisted of 2987 patients in sinus rhythm (SR) who had no known potential source of cardiac embolism and who had also presented transient ischaemic attacks or non-disabling ischaemic strokes (Rankin ≤ 3). These control patients were part of a study cohort of 3150 patients randomised in the Dutch TIA Study, a study which aimed to investigate the protective effects of low-dose aspirin and atenolol in TIA and minor ischaemic stroke patients.[63] Twenty-three patients of this cohort had been incorrectly entered and another 9 were known to have atrial fibrillation. Of the remaining 3118 patients, no CT-scan was available in 131.

For both study populations, CT-scan investigations were mandatory at study entry and patients had to be randomised within 3 months of their

(last) cerebrovascular event. The CT-scans of both patient groups were independently reviewed by at least two neurologists from a group of 4 investigators who used the same protocol for both studies. Visible infarcts were classified according to gross location (left or right hemisphere or posterior fossa), vascular territory,[56] and to whether or not the cortex was involved. Subcortical infarctions were further classified as being small (≤15 mm) or large (> 15mm). Small subcortical ('lacunar') infarctions were considered indicative of small vessel disease; all other ischaemic lesions (large subcortical, end zone and border zone infarctions) were presumed to be associated with large vessel disease. White matter hypodensity with ill-defined borders was interpreted and recorded as periventricular leukoencephalopathy.[195] CT-scans with multiple infarcts that could not be explained by occlusion of a single intracerebral artery or its branches, were classified as showing involvement of multiple territories. CT-scans on which multiple border zone infarcts were present, or on which border zone infarcts were seen in combination with cortical infarcts in vascular territories not involved in the border zone area, were also regarded as involvement of multiple territories. During the auditing procedure clinical details were not given until the relevancy of the recorded CT-scan abnormalities had to be assessed. Focal hypodensities of presumably vascular origin that were not related to the qualifying event were classified as non-related ischaemic lesions. No attempt was made to blind reviewers for the study allocation of the patients (SR or NRAF). Baseline information on both groups of patients had been prospectively obtained at study entry, on standardised forms. Although different forms were used for the two studies, the information concerning the presence of major vascular risk factors as hypertension, diabetes mellitus, hypercholesterolaemia, previous cardiovascular events or surgery, angina pectoris, intermittent claudication, and current smoking was recorded according to the same criteria. Information on clinical symptoms, functional disability, duration of neurological deficits and ancillary investigations (cardiothoracic ratio, glucose levels and haematocrit) also satisfied the same criteria. In the sinus rhythm group no consistent information was obtained on the presence of carotid artery disease nor was echocardiography routinely performed.

Data were analysed with the Statistical Package for Social Sciences (SPSS), Epistat and EGRET statistical software. Differences in CT-scan and

baseline characteristics between the two study groups were evaluated by Chi-square test for categorial data and a t-test for continuous data. Comparisons were expressed as odds ratios with the corresponding 95% confidence intervals. Multivariate logistic regression analyses were performed to assess whether differences in CT-scan characteristics could be attributed to differences in baseline characteristics.

Results

The total group of studied patients included 1524 (37%) women and 2596 (63%) men. The mean age was 66.9 years (standard deviation 10 yrs) with a minimum age of 29 and a maximum age of 96 years.

Frequency of ischaemic lesions

Table 6.1 lists the CT-scan characteristics in NRAF and SR patients. Of the CT-scans available for analysis (n = 3972), 2201 (55%) showed no evidence of ischaemic infarction. The percentage of 'normal' CT-scans was smaller in the NRAF group (46%) than in the SR group (59%), despite as much as 18% of the scans in the NRAF group having been made within 24 hours of the onset of neurological symptoms, versus only 8% in the SR group. Patients with NRAF more often had multiple ischaemic lesions on their scans (12%) than patients in sinus rhythm (9%) (odds ratio 1.42; 95% confidence interval 1.13-1.80). Of the patients with multiple ischaemic lesions, more than one vascular territory was involved in 84% (79% for SR patients). In keeping with this finding NRAF patients more often had infarcts on their CT-scan that could not be ascribed to their current neurological symptoms (20% vs 15%; odds ratio 1.47; 95% confidence interval 1.22 -1.77). Compared with SR patients, NRAF patients more often had only large vessel infarcts on CT than only small vessel lesions (odds ratio 5.08; 95% confidence interval 3.90-6.58). White matter hypodensity was found in 17% of all patients with only small vessel infarcts on their scans versus 10% of the patients with only large vessel infarcts (odds ratio 1.82; 95% confidence interval 1.37-2.42), but this association was stronger in SR patients (odds ratio 2.70; 95% confidence interval 1.81-4.04) than in patients with NRAF (odds ratio 1.12; 95% confidence interval 0.56-2.20). Isolated infarcts in the territory of the posterior cerebral artery were more often seen in NRAF patients (odds ratio 1.81; 95% confidence interval 1.29-2.54).

Table 6.1 Comparison of CT-scan findings in patients with a recent transient ischaemic attack minor ischaemic stroke, with sinus rhythm (SR) or with non-rheumatic atrial fibrillation (NRAF)

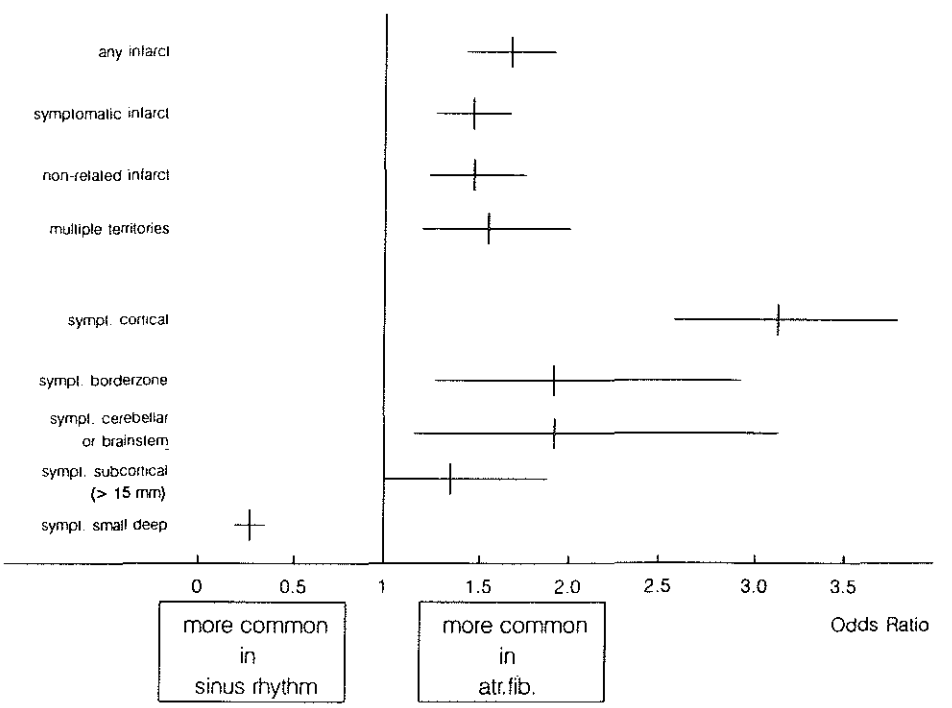
CT-SCAN CHARACTERISTICS	SR n = 2987	AF n = 985
White matter hypodensity	*333 (11%)*	*165 (17%)*
moderate	238 (8%)	133 (14%)
severe	95 (3%)	32 (3%)
No ischaemic lesions on CT	*1748 (59%)*	*453 (46%)*
Single ischaemic lesion	*985 (33%)*	*417 (42%)*
not related to qualifying event	219 (7%)	91 (9%)
uncertain relevancy	24 (1%)	10 (2%)
symptomatic	742 (25%)	316 (32%)
cortical end zone	227 (8%)	182 (18%)
cortical border zone	49 (1%)	28 (3%)
cerebellar or brain stem	33 (1%)	17 (2%)
large subcortical	112 (4%)	53 (5%)
small subcortical	321 (11%)	36 (4%)
Multiple ischaemic lesions	*254 (9%)*	*115 (12%)*
all non-related	31 (1%)	24 (2%)
uncertain relevancy	3 (< 1%)	4 (< 1%)
one symptomatic lesion	220 (7%)	87 (9%)
cortical end zone	42 (1%)	50 (5%)
cortical border zone	17 (<1%)	13 (1%)
cerebellar or brain stem	9 (<1%)	9 (1%)
large subcortical	25 (1%)	8 (1%)
small subcortical	127 (4%)	7 (1%)
infarcts in multiple territories	198 (7%)	97 (10%)
only small vessel disease	115 (4%)	13 (1%)
only large vessel disease	66 (2%)	60 (6%)
both small and large vessel	73 (2%)	42 (4%)
no prior cerebrovascular events in the past year	170 (6%)	81 (8%)

Percentages are column percentages.
SR: Sinus Rhythm; AF: Atrial Fibrillation; CT: Computed Tomography of the brain

Type of symptomatic infarction (Figure 6.1)

NRAF patients more often had symptomatic cortical end zone infarcts (24% vs 9%; odds ratio 3.11; 95% confidence interval 2.57-3.78) and symptomatic cortical border zone infarcts (4% vs 2%; odds ratio 1.92; 95% confidence interval 1.27-2.91) than patients with sinus rhythm. Symptomatic cerebellar or brainstem lesions also more frequently occurred in patients with NRAF (4% vs 1%; odds ratio 1.90; 95% confidence interval 1.16-3.12). With respect to symptomatic subcortical infarcts, small deep ('lacunar') lesions were more often found in SR patients (15% vs 4%; odds ratio 3.87; 95% confidence interval 2.77 - 5.41), whereas in NRAF patients large subcortical infarcts (> 15mm) were more common (6% vs 5%; odds ratio 1.37; 95% confidence interval 1.00-1.87).

Figure 6.1 Comparison of CT-scan characteristics between ischaemic stroke patients with non-rheumatic atrial fibrillation or sinus rhythm. Horizontal lines represent 95% confidence intervals.



Non-related infarcts

NRAF patients more often had infarcts on their CT-scan that could not be ascribed to the qualifying symptoms (odds ratio 1.47; 95% confidence interval 1.22-1.78). In the SR patients, 434 had evidence of previous stroke (14%). These patients had a total of 500 currently asymptomatic infarcts on their scans, 67% of which were small deep (lacunar), 16% cortical, 7% large subcortical, 7% border zone and 3% in the cerebellum or brain stem. In the NRAF group, 197 patients had evidence of previous stroke on their CT-scans (20%). Thirty-six percent of the in total 240 currently asymptomatic ischaemic lesions were of the small deep (lacunar) type, 37% were cortical, 10% border zone, 9% large subcortical and 8% involved either the cerebellar cortex or the brain stem. Thirty-three percent of the NRAF patients and 31% of the SR patients with non-related infarct(s) on their CT-scan had reported cerebrovascular symptoms in the year before study entry. Another two percent of the NRAF patients had had symptomatic cerebrovascular events before that time; this information was not available for patients in the sinus rhythm group.

Baseline characteristics

As shown in Table 6.2, there were some differences in baseline characteristics between patients with NRAF and those with sinus rhythm, most of which were statistically significant because of the large numbers of patients studied. NRAF patients were older and more often female. With the exception of smoking habits, well known vascular risk factors such as a history of hypertension or diabetes were reported more often in NRAF patients. Measured blood pressures at study entry however were significantly lower in the NRAF group (mean systolic blood pressure 158 mmHg in SR patients and 148 mmHg in NRAF patients; t-test $p < 0.0001$) (mean diastolic blood pressure 91 mmHg and 86 mmHg resp.; t-test $p < 0.0001$). A remarkable difference between the two groups was the relatively high rate of hypercholesterolaemia in NRAF patients (9.6% vs. 3.7%). This probably reflects the difference between a multinational European patient cohort (the NRAF patients) and a Dutch cohort of patients (SR group), which explanation is confirmed by the finding that of the Dutch NRAF patients (n = 187) only 3.7% (similar to SR patients) had hypercholesterolaemia. When only Dutch NRAF patients were compared with

Table 6.2 Comparison of baseline characteristics in patients with a recent transient ischaemic attack or minor ischaemic stroke, with and without non-rheumatic atrial fibrillation.

BASELINE CHARACTERISTICS	SR n = 3118	NRAF n = 1002
Demographics		
Male	65.3	55.8
Age in years (SD)	65.1 (10)	72.7 (8)
Neurological status		
Symptoms lasted < 24 hours	31.9	22.9
Rankin grade > 1 at study entry[194]	21.5	41.3
CT-scan available	95.8	98.3
CT-scan made within 24 hrs	7.8	17.8
History of vascular events		
Prior myocardial infarction	9.8	8.1*
Vascular surgery	1.5	2.4*
Cerebrovascular events in the past year	31.5	22.0
Vascular risk factors		
History of hypertension	41.9	47.0
Hypercholesterolaemia	3.7	9.6
Diabetes	7.9	12.9
Current regular smoking	44.8	18.8
Angina pectoris	9.3	10.9
Intermittent claudication	5.0	4.2*
Additional investigations		
Systolic BP > 160 mmHg	35.5	19.7
Diastolic BP > 100 mmHg	14.5	5.0
Haematocrit > 0.45 l/l	39.6	29.1
Glucose levels > 7.0 mmol/l	15.7	16.9*
Cardiothoracic ratio on chest X-ray > 0.50	10.2	23.5

Numbers in columns are column percentages.
SR: Sinus Rhythm; AF: Atrial Fibrillation; SD: standard deviation; BP: blood pressure
* Non-significant difference. All other baseline characteristics differ significantly ($p < 0.001$)

their SR counterparts all other reported differences in baseline characteristics were confirmed but the absolute differences were slightly smaller in all instances and did not always reach statistical significance. Cardiomegaly (defined as a cardiothoracic ratio > 0.50 on chest X-ray) was more often found in NRAF patients (odds ratio 2.71; 95% confidence interval 2.25-3.27). All reported differences in CT-scan characteristics between patients with sinus rhythm and those with non-rheumatic atrial fibrillation were independent of differences in baseline characteristics. In both study groups, 50% of all patients with only small vessel disease had a history of hypertension, versus 43% of the patients with only large vessel involvement (odds ratio 1.35; 95% confidence interval 1.10-1.65), and 40% of the patients without infarcts on CT (odds ratio 1.50; 95% confidence interval 1.26-1.78).

NRAF patients less often showed complete recovery within 24 hours than patients in SR (22.9% vs 31.9%; odds ratio 0.63; 95% confidence interval 0.54-0.75). Accordingly, the Rankin grade for handicap at study entry was 2 or over in 41% of the NRAF patients versus 21% of the SR patients (odds ratio 2.57; 95% confidence interval 2.21-2.99).

Specificity of CT-scan characteristics

On the premise that the mere presence of NRAF alone is not sufficient for the diagnosis of cardioembolic stroke, we assessed whether certain CT-scan characteristics were specifically associated with NRAF related infarcts as opposed to SR. For patients with visible infarcts on their CT, the presence of multiple large vessel infarcts in different vascular territories and isolated posterior artery infarcts had the highest specificity (96% and 92% respectively), but these characteristics occurred in only a small minority of patients with NRAF with infarcts on their scan (9% and 11% respectively, overall 19%). The presence of only small deep infarcts was fairly specific for SR related stroke (83%) but was found in only 51% of SR patients with ischaemic lesions on their CT.

Discussion

This study shows that patients with a transient ischaemic attack or minor ischaemic stroke in combination with non-rheumatic atrial fibrillation relatively often have 1. Large infarcts (> 15 mm), either cortical or

subcortical. 2. Infarcts in different vascular territories. 3. Currently asymptomatic infarcts. 4. Isolated infarcts in the territory of the posterior cerebral artery. These differences are in accordance with the most commonly used criteria for cardioembolic stroke.[17,21,22,38,55,91,108,134,143,152] Despite these statistically significant differences in CT-scan features between NRAF patients and SR patients, the characteristics, alone or in combination, do not in individual cases allow a reliable distinction whether the presence of NRAF is causal or incidental. In part this modest discriminatory value of CT-scanning may be explained by the selection of patients that suffered only minor or transient neurological symptoms. Possibly, because of this selection, the source of embolism in NRAF patients was relatively often in the arterial system and not in the heart, other than in the entire population of stroke patients with non-rheumatic atrial fibrillation. The most specific CT features associated with NRAF were the occurrence of large infarcts in different arterial territories, or of isolated infarcts in the territory of the posterior cerebral artery. These features are also found in a minority of stroke patients in sinus rhythm (4% and 8% in our series, respectively), but in the context of atrial fibrillation they strongly argue in favour of the heart being the source of embolism.

Another CT-scan feature which was potentially useful, but this time in decreasing the probability of a cardiac source of embolism, was the presence of only small deep lacunar infarction. Our study shows that infarcts in the territory of the penetrating arteries occasionally occur in cardioembolic strokes, as reported by previous studies,[82,168] but then usually involve more than one penetrating artery. Typical lacunes, which are thought to be caused by (local) obstruction of a single penetrating artery and which are often associated with arterial hypertension, were significantly more often seen in the SR population, although symptomatic lacunes were also found in the NRAF group (4%). In 36% of the NRAF patients and 29% of SR patients with multiple ischaemic lesions, small deep infarcts were seen together with the larger infarcts. Furthermore, although hypertension was significantly more often known to exist in patients with only small ischaemic lesions on their CT-scan than patients with only large ischaemic lesions in both patients with NRAF and those with SR, the absolute difference (50% vs 43%) was not impressive, as found earlier.[193] All these findings confirm the impression that 1. 'Lacunar' infarcts are not

exclusively caused by small vessel disease[135] but may also be associated with cardiogenic emboli. 2. Emboli from the heart are often larger than artery-to-artery emboli and therefore less likely to cause small deep infarcts.[124,133]

In as much as 63% of patients with NRAF the pattern of infarction on CT does not allow to postulate a high probability of either cardiogenic embolism (9% with large infarcts in multiple territories, 11% with isolated infarction in the territory of the posterior cerebral artery), or small vessel disease (17%). It is probably incorrect to assume that artery-to-artery embolism is the cause in all these remaining patients. In an unknown proportion an embolus from the heart must have resulted in a first and single infarct in the territory of a major branch of the internal carotid artery. Emboli from the heart tend to produce relatively large infarcts,[143] but on the other hand atherosclerotic plaques in the aortic arch may be associated with multiple, small infarcts.[3] Therefore there is a great overlap in size between infarcts from cardiogenic emboli and those caused by arterial disease.[133]

With respect to baseline characteristics, one of the most striking findings was that of lower systolic and diastolic blood pressure measurements at study entry in the NRAF patient group compared with SR patients, despite the fact that NRAF patients more often had a history of hypertension. Because NRAF patients could be randomised to anticoagulant treatment, poorly controlled patients were mostly excluded and extra care might have been taken to achieve proper control of blood pressure. On the other hand, the lower diastolic blood pressure in NRAF patients could reflect a more progressive state of atherosclerotic disease with stiffening of the vessel wall.[203] A more banal explanation would be the difficulty of obtaining consistent blood pressure measurements in patients with NRAF. The other differences in baseline characteristics between NRAF and SR patients can mostly be attributed to the higher mean age of the patients with non-rheumatic atrial fibrillation (more often female, more often diabetes, less often current smoking). The higher prevalence of cardiomegaly in NRAF patients probably reflects a long standing history of hypertension, chronic atrial fibrillation, or both. Neurological deficits tended to last longer and be more severe in NRAF patients than in SR patients, which is in agreement with the higher rate of cerebral infarcts in general, and of large infarcts in particular.

The results of CT-scan comparisons reported in this study may have been biased because the reviewers were aware whether patients had SR or NRAF. On the other hand, these reviews were intended to establish a baseline register for each of the two trials, and not to compare the two groups. Another potential source of bias might have been the fact that CT-scans in the Dutch TIA-study were made earlier, between 1986 and 1989, and therefore may have been of lesser quality than the scans in the EAFT (1988-1992). If this had indeed been a problem fewer small deep infarcts (sometimes difficult to distinguish on 2nd generation CT-scans) would have been found in the SR group, which was not the case. Finally, with the interpretation of all 'statistically significant' differences between NRAF and SR patients, both of CT-scan and baseline characteristics, one should keep in mind that because of the large study size even small differences become statistically significant but that the clinical significance of many of these reported differences is not always clear.

We conclude that, although there are striking differences between the CT-scan features of stroke patients with and without non-rheumatic atrial fibrillation, which cannot be explained by differences in baseline characteristics, within the group of patients with NRAF these differences are of little help in distinguishing between strokes of presumed cardioembolic origin and strokes caused by arterial disease. A possible exception is the presence of only small deep infarction on CT-scan, a finding that is less likely to be associated with cardiogenic embolism.

CHAPTER 7:
SILENT CEREBRAL INFARCTION

"Next to entertaining or impressive talk, a thoroughgoing silence manages to intrigue most people"
Florence Hurst Harriman, From pinafores to politics (1924), ch 4.

SILENT CEREBRAL INFARCTION IN NON-RHEUMATIC ATRIAL FIBRILLATION

Introduction

Atrial fibrillation is associated with a high risk of cerebral infarction. Cardiogenic embolism to the brain most commonly causes permanent neurological disability, but several studies have also reported a large proportion with silent brain infarcts on CT-scan in this same patient group.[72,108,152] These studies, however, were small and the rate of silent cerebral infarcts differed widely (13% to 48%). Some published examples of 'silent infarcts' made it clear that the criteria for this diagnosis are not always water-tight.[152] It therefore remained unclear whether silent brain infarcts are indeed more often seen in patients with non-rheumatic atrial fibrillation than in other patients with transient ischaemic attacks or strokes. The purpose of this study was to assess more exactly the prevalence of silent brain infarcts in 985 patients with non-rheumatic atrial fibrillation who recently suffered a symptomatic transient ischaemic attack or non-disabling ischaemic stroke, and to evaluate the predictive value of asymptomatic infarcts for the future development of recurrent vascular events.

Patients and methods

Study Design

The study considers patients enroled in the European Atrial Fibrillation Trial. These were patients with non-rheumatic atrial fibrillation who had

suffered a transient ischaemic attack (TIA) or non-disabling ischaemic stroke not more than 3 months before study entry. In total, 1007 patients were randomised to open oral anticoagulant treatment, or to double-blind treatment with aspirin 300 mg/day or placebo. Five patients did not satisfy the entry criteria and for another 17 patients no CT-scan was available, leaving 985 patients for the present analysis.

CT-scan

Computed tomography of the brain was mandatory before study entry. All CT-scans were audited centrally by an independent committee of at least two neurologists. Infarcts were defined as hypodense lesions of presumably vascular origin and they were classified as either end zone (with cortical involvement), border zone (hypodensities between arterial territories), large subcortical (no cortical involvement, diameter > 15 mm), lacunar (small deep lesions with a diameter ≤ 15 mm), or lesions in the posterior fossa, including both cerebellar and brain stem infarcts. Focally dilated sulci were not classified as infarction. During the auditing procedure clinical details were not given until the relevancy of the recorded CT-scan abnormalities had to be assessed. Infarcts were categorised as relevant if their location corresponded with the symptoms of the qualifying event. Focal hypodensities of presumably vascular origin that were not related to the qualifying event were classified as (currently) asymptomatic ischaemic lesions. The randomisation form that was completed for each patient at study entry contained information not only on the symptoms and localisation of the qualifying event, but also on the occurrence of previous, symptomatic cerebrovascular events and their presumed localisation (left or right hemisphere, posterior fossa, left or right eye). Ischaemic brain lesions on CT that were in keeping with reported cerebrovascular events in the past were further classified as past symptomatic infarcts. If no localising information was available about previous strokes (n = 8), the currently asymptomatic lesion was classified as probably being a previously symptomatic infarct. Silent brain infarcts were defined as ischaemic lesions on CT-scanning that were not only currently asymptomatic, but that also did not correspond with known past events.

Follow-up CT-scans

Twelve participating centres managed to have a close-out CT-scan made for all patients that they had entered in the EAFT (n = 76). Additionally, new CT-scans were made in 159 patients who were reported to have suffered a recurrent symptomatic stroke (including one intracerebral haemorrhage) during the course of the study. These scans were audited by the same committee of neurologists that had audited the study entry CT-scans. Separate analyses of these CT-scans were performed in order to assess the occurrence of asymptomatic infarction during follow-up.

Data-analysis

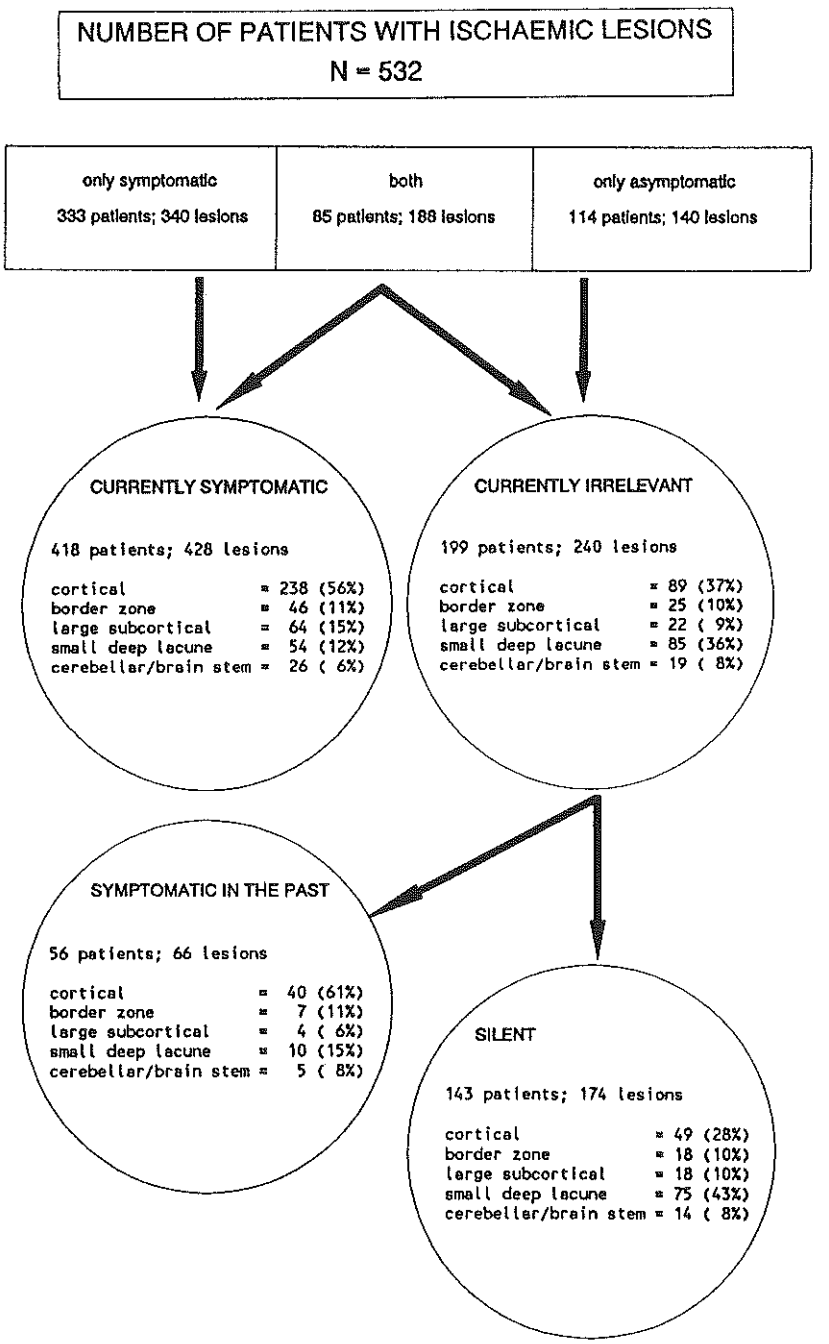
Univariate analysis of differences between study subgroups were performed with a t-test for continuous variables and Chi-square statistic for categorical data. Differences were described by means of an odds ratio with 95% confidence interval. To determine the independent influence of risk factors for asymptomatic cerebral infarctions that had been identified by univariate analysis, multivariate analyses were performed with the logistic regression module supplied by the EGRET statistical package. To determine the association between the presence of asymptomatic cerebral ischaemia and the occurrence of recurrent vascular events during follow-up, multivariate analyses by means of the Cox proportional hazards model were used.

Results

Baseline CT-scans

Of the 985 patients that were studied 199 (20%) were shown to have asymptomatic infarcts on their CT-scan. Eleven percent had only asymptomatic lesions, 9% had both symptomatic infarcts and asymptomatic infarcts. In addition, 333 patients (34%) had only symptomatic infarcts, and 453 patients (46%) had no ischaemic lesions on CT-scan (Figure 7.1). In total 668 ischaemic lesions were classified as either symptomatic (n = 428; 64%) or asymptomatic (n = 240; 36%). Of the currently asymptomatic lesions, 73% (n = 174) could not be explained by previously reported cerebral ischaemic events; these ischaemic lesions were categorised as silent. Of all patients, 14% had evidence of silent infarctions on their scan. For the remainder of

Figure 7.1 Frequency and nature of symptomatic and silent ischaemic lesions



this paper, the term 'symptomatic ischaemic lesions' will encompass both the lesions that were currently symptomatic and those that were symptomatic in the past. Of all silent infarcts, small deep lacunes represented 43%, large subcortical lesions 10%, cortical border zone lesions 10%, cortical end zone lesions 28% and lesions in the posterior fossa 8% (Figure 7.1). Silent ischaemic lesions were found in 23% of the patients with relevant cerebellar or brain stem infarcts, in 15% of the patients with relevant border zone infarcts, in 13% of the patients with relevant end zone infarcts and in 9% with relevant subcortical infarcts (both small and large). These differences were not significant, nor was the type of relevant infarct related to the type of silent lesion (end zone, border zone, large subcortical or lacunar).

Small deep infarcts were significantly more often silent than other infarcts (odds ratio 5.09; 95% confidence interval 3.35-7.74). End zone infarcts were significantly more often symptomatic than other infarcts (odds ratio 3.28; 95% confidence interval 2.22-4.86). The anatomical distribution of the 75 silent lacunes in the anterior circulation was as follows: anterior limb of the internal capsule 9%; genu 1.5%; posterior limb 11%; corona radiata 13%; basal ganglia 36%, thalamus 16%; others 5.5%; involving more than one anatomic structure 8%. In comparison with their silent counterparts, symptomatic lacunes were more often situated in the corona radiata (28% vs 13%) and less often in the posterior limb of the internal capsule (3% vs. 9%) or in the basal ganglia (22% vs. 36%); they also more often involved more than one anatomic structure (20% vs. 8%). Large subcortical lesions usually were in the territory of the middle cerebral artery; there were no differences in the distribution of sites between asymptomatic and symptomatic infarcts. Symptomatic cortical border zone infarcts more often involved the left hemisphere (66% vs. 39% of the silent border zone infarcts). A more or less similar distribution was found for cortical end zone infarcts (57% vs. 39%). Both symptomatic and silent border zone infarcts were usually situated between the territories of the middle and posterior cerebral arteries (85%). A higher percentage of the silent end zone infarcts (45%) involved the territory of the posterior cerebral artery than the symptomatic end zone lesions (28%).

Rankin Scale Grade

Seventy-one percent of patients with no ischaemic lesions at all on baseline CT had a Rankin scale grade 0 or 1 (no symptoms, or only signs not interfering with the patient's life style). This proportion did not change when only those patients in whom the CT-scan was made more than 24 hours after the qualifying event were taken into account. Fifty-seven percent of the patients with only silent cerebral infarcts on their baseline CT had a Rankin grade of 0 or 1, vs. 47% of the patients with only symptomatic strokes and 45% of the patients with both silent and symptomatic strokes.

Vascular risk factors and silent cerebral infarction

Baseline characteristics of the patients in this study group have been summarised in Table 7.1. In comparison to all other patients, the finding of silent ischaemic lesions on CT was significantly related to male gender (odds ratio 1.68; 95% confidence interval 1.16-2.44) and a history of cardiovascular disease (previous myocardial infarction, intermittent claudication, or angina pectoris) (odds ratio 1.61; 95% confidence interval 1.06-2.44). If the comparison was restricted to patients with symptomatic disease (with or without additional silent infarcts) or to patients with only silent infarcts on the one hand and only symptomatic infarcts on the other hand, the findings were similar. In a multivariate analysis both gender and history of cardiovascular disease proved to be independent of other risk factors. Duration or type of atrial fibrillation (chronic vs. paroxysmal) were not related to the presence of a silent infarct on CT-scanning.

Asymptomatic lesions on CT and risk for recurrent vascular events

Table 7.1 also gives an overview of stroke rates (fatal and non-fatal) and vascular event rates in general (vascular death, myocardial infarction, systemic embolism, or stroke, whichever came first). Both event rates increased with the number of ischaemic lesions on CT. In accordance with this, both event rates were higher in patients with silent brain infarcts on their CT-scan. This trend remained the same after correction for differences in treatment allocation (anticoagulants, aspirin or placebo) and for baseline characteristics in multivariate analyses. Compared with patients in whom the CT-scan was normal, patients with a single ischaemic lesion had a higher risk for recurrent vascular events in general (hazard ratio 1.52; 95%

confidence interval 1.18-1.94) and for recurrent stroke in particular (hazard ratio 1.66; 95% confidence interval 1.21-2.28), similar to patients with 2 or more ischaemic lesions on their scan (hazard ratios 1.63; 95% confidence interval 1.13-2.34 and 2.16; 95% confidence interval 1.41-3.33, respectively).

Table 7.1 The presence of asymptomatic or multiple infarcts on CT, in relation to baseline characteristics and outcome events

CHARACTERISTICS	No ischaemic lesions	1 ischaemic lesion	2 or more ischaemic lesions	only symptomatic lesions	any 'silent' lesions
No. of patients	453	417	115	389	143
BASELINE CHARACTERISTICS					
Mean age ± SD	73 ± 8	72 ± 8	73 ± 8	72 ± 8	73 ± 7
Age > 65 years	385 (85%)	344 (83%)	97 (84%)	320 (82%)	121 (85%)
Male	243 (54%)	237 (57%)	70 (61%)	212 (55%)	95 (66%)
Known vascular disease	74 (16%)	83 (20%)	30 (26%)	76 (20%)	37 (26%)
History of hypertension	207 (46%)	196 (47%)	60 (52%)	185 (48%)	71 (50%)
Diabetes	56 (12%)	60 (14%)	12 (10%)	56 (14%)	16 (11%)
Hypercholesterolaemia	41 (9%)	39 (9%)	14 (12%)	40 (10%)	13 (9%)
Current regular smoking	87 (19%)	75 (18%)	24 (21%)	70 (18%)	29 (20%)
Haematocrit > 0.45 l/l	124 (27%)	130 (31%)	34 (30%)	122 (31%)	42 (29%)
Chronic atrial fibrillation	345 (76%)	317 (76%)	91 (79%)	297 (76%)	111 (78%)
Duration atrial fibrillation > 1 yr	248 (55%)	228 (55%)	57 (50%)	210 (54%)	75 (52%)
Cardiothoracic ratio > 50%	97 (22%)	109 (26%)	25 (22%)	95 (24%)	39 (27%)
White matter hypodensity on CT	84 (19%)	54 (13%)	27 (24%)	54 (14%)	27 (19%)
OUTCOME EVENTS					
Vascular events, all	114 (12%/yr)	145 (17%/yr)	41 (20%/yr)	131 (16%/yr)	55 (22%/yr)
Strokes, fatal and non-fatal	68 (7%/yr)	93 (11%/yr)	31 (14%/yr)	88 (11%/yr)	36 (14%/yr)

Compared with patients who had only symptomatic lesions on their scan, patients with silent infarcts (only, or in combination with symptomatic infarcts) had a slightly higher risk for recurrent vascular events in general (hazard ratio 1.17; 95% confidence interval 0.85-1.62) and for recurrent strokes (hazard ratio 1.18; 95% confidence interval 0.79-1.77), but these estimates were lower after correction for differences in number of ischaemic lesions on CT (hazard ratio 1.12; 95% confidence interval 0.77-1.64 and 0.98; 95% confidence interval 0.60-1.58 respectively), suggesting that the risk of recurrent events depends on the extent of ischaemic brain damage rather than on whether or not these lesions were symptomatic. To illustrate this, in Table 7.2 we have listed the event rates according to the presence of silent lesions and the total number of ischaemic lesions on CT in placebo patients only.

Table 7.2 Event rates (per 100 patient-years) stratified for number of ischaemic lesions on CT-scan and presence of silent ischaemic lesions, in patients randomised to placebo treatment

No. of lesions	No. of patients	All vascular events* (vascular death, stroke, MI, SE)		All strokes (fatal and non-fatal)	
		No. of events	Event rate	No. of events	Event rate
No lesions	155	41	13/100 pyr	25	8/100 pyr
Only sympt					
1	135	56	22/100 pyr	39	15/100 pyr
≥2	12	5	20/100 pyr	3	12/100 pyr
Any silent					
1	27	11	22/100 pyr	7	14/100 pyr
2	31	12	25/100 pyr	7	14/100 pyr
≥3	6	5	100/100 pyr	5	100/100 pyr

* Whichever came first
Only sympt: patients with only symptomatic infarcts on their scans.

Follow-up CT-scans

Of the 76 scans made at the end of the EAFT trial (mean interval 2.19 years), 9 showed evidence of only symptomatic new ischaemic lesions (recognised in the course of the study and classified as outcome events), 9 of new ischaemic lesions with no known symptoms (other than, in some cases, general deterioration of cognition); 2 patients showed both new symptomatic and new silent lesions, and 1 showed a new lesion that was clearly associated with the event at study entry at which time the CT-scan had been made within 24 hours. In total 14% of all close-out scans showed evidence of silent infarction (event rate 7 per 100 patient-years). Five of these events occurred in patients that were randomised to placebo (n = 30), 4 events occurred in patients in the aspirin group (n = 30), and 2 in patients on anticoagulants (n = 16).

We also evaluated scans made at the time of a possible recurrent symptomatic cerebrovascular event, which included information on 159 patients. Apart from some ischaemic lesions related to the qualifying event that had not yet been seen on the baseline CT-scan, 48 scans showed no new ischaemic lesions, 88 showed only new symptomatic infarcts, 9 showed only new silent infarcts, and 14 showed both new symptomatic and new silent infarcts. In conclusion, 14% (23 out of 159) of all CT's made at the time of a symptomatic recurrent stroke (mean time between outcome event scan and baseline scan 1.29 yrs) showed evidence of silent infarction (event rate 11 per 100 patient-years). Nine out of 73 placebo-treated patients, 12 out of 70 aspirin-treated patients and 2 out of 16 anticoagulant-treated patients were found to have new asymptomatic ischaemic lesions on their outcome event CT-scan. The higher rate of silent infarcts in this subgroup is probably directly related to the fact that they already suffered symptomatic recurrent strokes.

Discussion

In our study cohort of 985 patients with non-rheumatic atrial fibrillation who underwent neurological evaluation because of a recent (less than 3 months ago) TIA or minor ischaemic stroke, 20% had evidence of unrelated ischaemic lesions on their CT-scan. In 14% of all patients the unrelated ischaemic lesions could not be explained by symptomatic episodes of cerebral ischaemia in the more distant past. Kempster et al[108] reported

finding asymptomatic infarcts in 13% of NRAF patients who had also presented with recent symptoms of cerebral ischaemia. In NRAF patients with no known history of previous or current cerebral ischaemia, Petersen and colleagues[152] reported a markedly higher rate of asymptomatic infarcts (48%) as did the group of Feinberg et al[72] (26%); in the former study the criteria for diagnosing infarction may have been too lenient. The results of Kempster and the current study are in line with the proportion of silent infarcts found in other patients with recent symptomatic cerebral ischaemia (10%-13%)[49,93,106] the only exception being the community-based study of Ricci et al,[159] which reported a frequency of silent ischaemic brain lesions of 38% in first-ever stroke patients. The results presented here contradict the notion that non-rheumatic atrial fibrillation is associated with an unduly high risk of *'silent'* cerebral infarction. Non-rheumatic atrial fibrillation *is* however associated with a higher rate of (multiple) ischaemic lesions on CT; in total 668 ischaemic lesions were seen on the scans of the NRAF patients (0.7 lesion/patient), compared with only 969 lesions on the scans of the 2329 patients in the comparable patient cohort of the Dutch TIA Study (0.4 lesion/patient),[93] which study included patients in sinus rhythm who had suffered a recent minor ischaemic stroke or TIA.

Comparisons between the studies are difficult because there seem to be no uniform criteria for the diagnosis of silent or asymptomatic cerebral infarction. CT-scan evaluations can easily be biased by differences in the quality of the scans, and there is considerable interobserver variation. Correct interpretation of suspected lesions can be impeded by the inability to relate the lesion to abnormalities found at neurological examination. Moreover, the extent to which information on previous cerebrovascular events (including transient ischaemic attacks and non-disabling strokes[19,20,115]) contributes to the radiological diagnosis differs widely between studies; this factor may lead to considerable error especially if interpreted in retrospect. Symptoms related to cerebrovascular events need not have been recognised as such by patients or their physicians, certainly if they were brief or occurred during the night. Minor symptoms of limb numbness, clumsiness, rotational vertigo, and dysarthria can easily be given other and more banal explanations than brain ischaemia. Other sources of error include an inadequate history or insufficient recording of the precise nature of neurological symptoms. Therefore the distinction

between silent and symptomatic cerebral infarction may to some extent be an artificial (and arbitrary) one, and more attention should perhaps be given to the broader concept in which silent infarction signifies nothing more or less than evidence of previous cerebrovascular events. Moreover, multiple silent infarcts can take a cumulative toll on a patient's cognition and therefore become 'symptomatic' in the long run.[157] That a distinction between symptomatic and silent ischaemic lesions is probably of limited clinical importance is further supported by the fact that no study has reported the same risk factors for silent cerebral infarct, whether these involved sinus rhythm patients,[93] NRAF patients[108,152] or general populations.[49,106] Finally, this study shows that the association between asymptomatic lesions on CT and a relatively high rate of recurrent vascular events or strokes can be explained by the presence of multiple ischaemic lesions rather than by whether or not these lesions were symptomatic.

The event rate for new asymptomatic cerebral ischaemia (7 per 100 patient-years) found in this study seems high, and is even higher when considering new asymptomatic lesions on CT-scans that were made at the time of recurrent symptomatic events (11 per 100 patient-years). This latter estimate however is probably biased by the fact that these patients were at high risk of stroke in general. Whether or not the incidence rate of new asymptomatic cerebral ischaemia is higher in NRAF patients than in other stroke patients remains uncertain as no other studies have addressed this question. However, the recurrence rate for symptomatic stroke (10 per 100 patient-years in aspirin-treated patients)[65] in this same study population is considerably higher than that reported by studies of hospital-referred non-NRAF patients (3-4 per 100 patient-years),[36,63,189] but comparable to the recurrence rate of asymptomatic infarcts in NRAF patients. This supports our belief that the pathogenesis and prognostic importance of asymptomatic or silent infarcts is no different from that of symptomatic strokes. Any differences that are found should probably be ascribed to specific properties of the underlying lesions. For instance, in this and other studies, small deep infarcts were more often found to be asymptomatic than large infarcts with cortical involvement and it is possible that their natural history differs from that in other stroke subtypes.[13]

The duration of atrial fibrillation was not related to the presence of asymptomatic lesions in this study, nor to the number of ischaemic lesions

on CT or to the rate of recurrent vascular events (Chapter 4). These findings might imply that the presumed causal relation between atrial fibrillation and (embolic) stroke is not very strong, but this lack of association can also be explained by inadequate ascertainment of the exact date of onset of atrial fibrillation in the individual patients. Atrial fibrillation is often asymptomatic, and also a brief episode of paroxysmal atrial fibrillation may precede the onset of permanent atrial fibrillation.[150]

In conclusion, patients with non-rheumatic atrial fibrillation are at high risk of stroke. Some of these cerebral ischaemic events will be symptomatic, others, because of site or size, can leave the patient apparently unaffected. Either way, as patients suffer more ischaemic episodes, symptomatic or not, their risk for recurrent stroke or other vascular events increases. Less attention should be focused on the presence of 'silent' ischaemic brain lesions alone, particularly as the term 'silent' is confusing in patients who did actually suffer related, albeit transient, cerebrovascular events[39] and is furthermore often incorrectly used.

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GENERAL DISCUSSION

"Science is nothing but developed perception, interpreted intent, commonsense rounded out and minutely articulated"

Santayana, Life of Reason, V, II

Despite initial enthusiasm for anticoagulant therapy, its widespread application in various clinical fields was brought into jeopardy when concomitant side-effects of the therapy (complicated logistics surrounding therapeutic control and the occurrence of bleeding complications, intracerebral or otherwise major) became apparent. This, in combination with an increasing popularity of antiplatelet therapy probably explains why, especially within the field of neurology, anticoagulant treatment was never given a fair 'trial' in these early years. Several new developments over the past decade have however led to an increasing interest in the use of oral anticoagulants not only as a direct therapeutic short-term measure, but also as a potentially useful drug in long-term primary and secondary prevention of thromboembolic complications. With the introduction of improved cardiac imaging techniques, the importance of heart disease as source of emboli to the brain became more apparent and required adequate preventive strategies. At the same time, international recommendations for the control of anticoagulant therapy were formulated, including the use of standardised thromboplastin preparations and a uniform method of reporting prothrombin time by means of the International Normalised Ratio (INR). It was hoped that this method of standardisation would in part simplify the logistics of adequate anticoagulant control.

The European Atrial Fibrillation Trial was one of the first randomised clinical trials to assess the benefit of long-term anticoagulant therapy in patients who had suffered a recent transient ischaemic attack or minor ischaemic stroke. It included only patients with non-rheumatic atrial fibrillation, on the assumption that the presence of this dysrhythmia formed a potential source of cardiogenic emboli. Oral anticoagulants were found to almost halve the risk of vascular complications in general, and to reduce the risk of recurrent stroke by two-thirds. Importantly, this benefit was not

negated by an increased risk of serious bleeding complications (Chapter 3A). The results of this study showed a striking similarity to the results of earlier primary prevention studies in patients with non-rheumatic atrial fibrillation. Due to the much higher absolute risk for recurrent vascular events and stroke in patients who had already experienced an ischaemic stroke, the net benefit of anticoagulants for secondary prevention was, however, even more impressive. For patients with non-rheumatic atrial fibrillation and a recent minor ischaemic event, who cannot be treated with oral anticoagulation, aspirin therapy is still thought to be the adequate choice of treatment even if, so far, studies assessing the exact value of aspirin in patients with non-rheumatic atrial fibrillation have been inconclusive. An approximate 20% risk reduction of vascular events is, however, supported by all and would be in line with what is reported for a wider population of patients. Meta-analysis of the data of all primary and secondary prevention trials assessing the value of aspirin in patients with non-rheumatic atrial fibrillation are planned in the near future and will hopefully supply some conclusive results.

In an attempt to elucidate which clinical variables are contributory to the high risk of recurrent vascular events in minor ischaemic stroke patients with NRAF mentioned above, we identified a risk set of 6 independent predictors including a history of previous thromboembolism, ischaemic heart disease, an enlarged cardiothoracic ratio on chest X-ray, a high systolic blood pressure and evidence of cerebral ischaemia on CT (Chapter 4). These features, together with age, were thought to be helpful in the assessment of an individual patient's risk for recurrent vascular events thereby supplying the clinician with additional grounds on which to base his choice of preventive treatment. It was not the intention of these subgroup analyses to supply conclusive recommendations on this point, because the analyses of treatment effect for the different risk groups was compromised by the relatively small number of patients and events in each subgroup. Still, from exploratory analyses it was apparent that the expected absolute benefit of both oral anticoagulant treatment and aspirin was less impressive in patients with very high risk of recurrent events due to their age and underlying vascular comorbidity. This somewhat paradoxical finding possibly reflects a methodological issue that is of added importance when studying cohorts of elderly patients. Not only will the actual

treatment effect be diluted by the presence of co-existent (fatal) diseases that are 'resistant' to the studied therapy, the overall expected number of years of life 'left' in this patient group is per definition lower than compared with younger patient groups, implying that quality rather than quantity of life should form the focus of treatment assessment. An attempt to such a holistic approach to clinical research was made in Chapter 3B where we tried to combine the outcome measurement of both quality of life and survival. With this analysis some of the pitfalls in quality of life assessment immediately became apparent. Although a multitude of measurement instruments are available, for clinical trials ultimately the choice is dictated by a trade-off between requiring an easily available, quick to perform rating system and a valid outcome measure that encompasses all physical, social and emotional domains of life. Then, if an adequate measure should be available, the next problems to surmount would be those emanating from a need for formal (statistical) testing of the study results. Although more and more research groups are recognizing the need for quality of life assessment in clinical trials, the methods to do so adequately still require further development.

Persisting issues surrounding the use of oral anticoagulation

Whereas the treatment effect of oral anticoagulation on the prevention of recurrent vascular events, and possibly also the improvement of quality of life, in patients with non-rheumatic atrial fibrillation has now been established successfully, there are still a number of issues that have remained unanswered. For instance, we have no definite answer to the question *when* antithrombotic treatment should be started after a cerebral ischaemic event in a patient with atrial fibrillation. Given the high efficacy of anticoagulation it may be that treatment should be started as soon as possible. However, several studies have recommended withholding anticoagulants during the first few days after suspected cardiogenic emboli to the brain, especially in patients with large infarcts. A large, ongoing trial (the International Stroke Trial) will have to determine which is the safest and most effective antithrombotic treatment in patients with acute cerebral infarction. We also do not know for *how long* antithrombotic treatment should be continued in these patients. The available data, however, suggest that both anticoagulant and aspirin treatment should be given for as long as

possible, that is, until a contraindication or a serious bleeding complication occurs. Because there was no exhaustive list of contraindications to oral anticoagulant treatment for patients entered in the EAFT, it is difficult to adequately describe the study population actually entered in the study. On the one hand, generalisation of the trial results to a much wider population than originally entered in the study might well cause an increase in the number of (major) bleeding complications seen on oral anticoagulation. The issue about *which* patients can 'safely' be treated with oral anticoagulants therefore remains unsolved. On the other hand, there is continuing uncertainty about the issue which 'strokes' can effectively be treated with anticoagulation. Originally, the scientific justification for use of oral anticoagulants was the assumption that ischaemic events in association with atrial fibrillation are caused by clot formation in the left atrium due to stasis of the blood flow. Part of the cerebral ischaemic events in these patients however are caused by concomitant atherosclerotic changes in the cerebral vasculature. In some cases, for instance when only small deep 'lacunar' infarcts are seen on the CT-scan, a cardioembolic pathogenesis seems improbable (Chapter 6) and a physician might be uncomfortable prescribing oral anticoagulants if aspirin treatment might do just as well. Whether or not such a differential effect exists for both anticoagulation and aspirin, remains to be evaluated through further analyses of the European Atrial Fibrillation Trial data, but also by assessing the value of oral anticoagulation (in comparison to aspirin treatment) in patients with a minor ischaemic stroke and no cardiac source of embolism (currently being evaluated in the SPIRIT trial).

What is the optimal therapeutic intensity of oral anticoagulation?

Despite the introduction of international standardisation of thromboplastins almost 20 years ago (1976), many anticoagulant clinics and laboratories have still not adopted the uniform method of reporting prothrombin times in INR's. Confusion therefore still persists concerning both the level of control in individual patients and the reported intensity of anticoagulant therapy studied in the different clinical trials with oral anticoagulants. In view of the increasing use of long-term anticoagulant treatment, this is probably somewhat worrisome as oral anticoagulant treatment presents a delicate balance between over-coagulation (risk of

bleeding) and under-coagulation (decreased treatment efficacy with higher risk of thromboemboli). Clinical trials have reported low frequencies of major bleeding complications, but this does not necessarily imply a comparatively low rate of major bleeding complications if anticoagulation is prescribed on a larger scale. This is not only because treatment in the context of a clinical trial is probably subject to more rigorous control, but also because failure to report the intensity of anticoagulant therapy in a standardised fashion will lead to differing intensities of anticoagulation being employed, possibly resulting in a higher rate of side-effects or a decreased treatment efficacy. Furthermore, it is important to realize that what would be described as minor bleeding in protocols of trials seeking to find a positive treatment effect of anticoagulation, might well be considered major from the perspective of a general practice (e.g. nose bleeds that require cauterisation). Future research should direct more attention to unambiguous definitions for bleeding complications, make proper use of the available standardisation methods for measuring anticoagulant control and will consequently report on INR specific treatment effects so that more information will become available about optimal anticoagulant intensities for different clinical indications (Chapter 5).

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SUMMARY

Atrial fibrillation is by far the most common form of cardiac dysrhythmia, and although most patients experience no direct symptoms from the disorder itself, atrial fibrillation is associated with a high risk of cardio- and cerebrovascular disease and for this reason remains a vexing problem for many clinicians.

Chapter 1 presents a review of the literature. The prevalence and etiology of atrial fibrillation in general, and of non-rheumatic atrial fibrillation in particular, are discussed, as are the direct and indirect association with the occurrence of ischaemic stroke. Atrial fibrillation is found in 6% to 19% of all stroke patients, and in 2 to 8% of patients with transient ischaemic attacks. Following initial embolism, patients are at high risk of recurrent stroke with risk estimates ranging from 10 to 20% yearly, depending on the type of underlying cardiac abnormality. In western countries, hypertensive and ischaemic heart disease are probably the most important precursors of atrial fibrillation. The concomitant direct causal relation between these diseases and ischaemic stroke, however, clouds the issue of establishing the exact pathogenesis of ischaemic stroke in the individual patient with atrial fibrillation. This is reflected, in part, by the persisting uncertainty surrounding the choice of preventive treatment strategies. By 1992, the value of anticoagulants for the *primary* prevention of vascular events in non-rheumatic atrial fibrillation had been convincingly established by 5 controlled clinical trials (risk reductions between 37 and 86%). One of these studies also found a significant risk reduction of 42% with aspirin treatment. It remained uncertain, however, whether extrapolation of these findings to *secondary* prevention was justified. In conclusion, it is recommended that a randomised, controlled trial should be conducted in order to finally settle this important issue.

Chapter 2 describes in detail the study design and conduct of 'the European Atrial Fibrillation Trial (EAFT)', a multicentre clinical trial which aimed to establish the preventive value of both oral anticoagulation and aspirin in patients with non-rheumatic atrial fibrillation and a transient

ischaemic attack or minor ischaemic stroke. From 108 participating centres in western Europe and Israel, patients were enroled in the study and randomised for treatment with oral anticoagulation (INR 2.5-4.0), acetylsalicylic acid 300 mg/day or placebo. In cases of contra-indications for anticoagulation, patients were randomised between aspirin or placebo only. Anticoagulant treatment was not blinded, aspirin and placebo treatment were double-blinded. Randomisation took place between October 1988 and May 1992, and follow-up was continued by an additional year till the beginning of May 1993. Treatment effects of anticoagulation and aspirin, compared with placebo, were evaluated by conventional outcome event analyses (including vascular death, stroke, systemic embolism and myocardial infarction, whichever occurred first) and by a more pragmatic analysis including death and handicap. All analyses were on an intention-to-treat basis.

Chapter 3A reports on the main results of the EAFT. In total 1,007 patients were enroled in the study, 669 were considered eligible for oral anticoagulant treatment (group 1) and 338 were randomised to only aspirin or placebo (group 2). The event rate for primary outcome events was 8 per 100 patient-years in patients assigned to anticoagulants (n = 225) versus 17 per 100 patient-years in placebo-treated patients in group 1 (n = 214) (hazard ratio 0.53; 95% confidence interval 0.36-0.79). The event rate of stroke alone was reduced from 12 per 100 patient-years to 4 per 100 patient-years (hazard ratio 0.34; 95% confidence interval 0.20-0.57). Among all patients assigned to aspirin (group 1 and 2; n = 404), the event rate of outcome events was 15 per 100 patient-years, against 19 per 100 patient-years in those on placebo (n = 378) (hazard ratio 0.83; 95% confidence interval 0.65-1.05). Anticoagulation was significantly more effective than aspirin (hazard ratio 0.60; 95% confidence interval 0.41-0.87). The event rate of major bleeding complications was low, both on anticoagulation (2.8 per 100 patient-years) and on aspirin (0.9 per 100 patient-years). No intracranial bleeds were identified in patients assigned to anticoagulation.

Chapter 3B takes a more pragmatic view of the results presented in the previous chapter. Over the course of the trial not only the occurrence of outcome events were registered, but stock was also taken of the individual

patient's dependency status. At each four-monthly follow-up visit, physicians were asked to classify their patients' disability by means of the modified Rankin Scale. In this study, the estimated average time spent in each category of dependency was calculated for all treatment groups. By assigning utility values to each of the Rankin categories, an estimate was then obtained of gained disability-adjusted survival-years (DASYs) on anticoagulant and aspirin treatment in comparison with placebo treatment. Given the impressive risk reduction of recurrent vascular events in general and stroke in particular with oral anticoagulant treatment, the average gain in DASYs (0.10 years) was somewhat disappointing and not much higher than what was achieved with aspirin treatment (0.07 DASYs) in group 1. In group 1 and 2 combined, patients assigned to aspirin gained 0.08 DASYs in comparison with placebo-treated patients. These results were to be expected to some extent as conventional outcome analyses had already shown that there was no apparent treatment effect of either anticoagulation or aspirin with respect to reducing overall mortality (vascular and non-vascular), and confirm the important dilution of overall treatment effect by co-existing diseases.

Chapter 4 in part addresses the problem of distinguishing high risk subgroups of patients with non-rheumatic atrial fibrillation who had a minor ischaemic stroke. The study presented in this chapter assesses the predictive value for recurrent vascular events in general and stroke in particular, of several baseline characteristics in the group of placebo-treated patients. By means of univariate analyses and multivariate modelling, six independent variables were identified: a history of previous thromboembolism, ischaemic heart disease, enlarged cardiothoracic ratio on chest X-ray, a systolic blood pressure over 160 mmHg at study entry, atrial fibrillation for more than 1 year and presence of an ischaemic lesion on CT-scan. These variables could be used to effectively stratify patients in low, medium, and high risk subgroups for all treatment categories. Older patients with a large number of risk factors seemingly benefited less from both aspirin and anticoagulant treatment.

Chapter 5 goes on to establish the optimal therapeutic intensity of oral anticoagulation. INR specific incidence rates were calculated for important

vascular events in general (vascular death, stroke, myocardial infarction and systemic embolism) and for major bleeding complications by means of the available INR (International Normalised Ratio) data of 225 patients that had been randomised to oral anticoagulant treatment in the European Atrial Fibrillation Trial. Relative to INR intensities below 2.0, anticoagulant therapy at intensities between 2.0 and 3.0 reduced the incidence of vascular events with 80% (rate ratio 0.2; 95% confidence interval 0.1-0.6). This effect was slightly less with intensities between 3.0 and 4.0. At higher intensities, the beneficial effect was offset by an increased risk of haemorrhagic complications. With INR levels over 5.0 the rate ratio for vascular events and major bleeding complications was as high as 3.6 (95% confidence interval 1.2-11). Age over 75 years was also found to be an independent risk factor for major bleeding complications. When prescribing oral anticoagulation for the secondary prevention of vascular events in patients with non-rheumatic atrial fibrillation who already suffered a minor ischaemic stroke, one should probably aim at a target intensity of INR 3.0 and avoid intensities below INR 2.0 or above INR 5.0.

Chapter 6 attempts to unravel some of the confusion surrounding the diagnosis of cardioembolic stroke. The CT-scan features of 985 patients with non-rheumatic atrial fibrillation who had suffered a minor ischaemic stroke were compared with those of 2987 patients with minor ischaemic stroke who were in sinus rhythm. The first group of patients were from the EAFT cohort; ischaemic lesion(s) were seen on 54% of their scans. The second group of patients were derived from the Dutch TIA-study, and 41% of their scans showed one or more ischaemic lesions. Compared with sinus rhythm patients, NRAF patients more often had multiple ischaemic lesions on their scans (odds ratio 1.42; 95% confidence interval 1.13-1.80). Comparison of the features of symptomatic lesions alone, showed that NRAF patients more often had cortical end zone infarcts (odds ratio 3.11; 95% confidence interval 2.57-3.78) and cortical border zone infarcts (odds ratio 1.92; 95% confidence interval 1.27-2.91). Sinus rhythm patients on the other hand more often had small deep infarcts (odds ratio 3.87; 95% confidence interval 2.77-5.41). Despite these striking differences, none of the evaluated CT-scan characteristics were specific enough to help predict,

within individual patients, whether a stroke was of presumed cardioembolic origin or caused by arterial disease.

Chapter 7 directs attention to one specific CT-scan characteristic of patients with non-rheumatic atrial fibrillation; that of multiple infarcts in general and more specifically that of 'silent' infarcts. Of the 985 stroke patients that were studied by CT-scanning, 20% had evidence of ischaemic lesions that were unrelated to the current event and could not be explained by previous symptomatic episodes of cerebral ischaemia in 14%. In comparison to symptomatic lesions, these so-called 'silent' infarcts more often were of the small deep lacunar type (odds ratio 5.09; 95% confidence interval 3.35-7.74). Silent end zone infarcts more often involved the territory of the posterior cerebral artery (45%) or the right hemisphere (61%) than symptomatic end zone infarcts (28% and 43% respectively). Close-out CT-scans, not prompted by outcome events, were available for 76 patients. In total 14% of these scans showed evidence of new asymptomatic infarcts (event rate 7 per 100 patient-years). In addition, 14% of all scans made at the time of a recurrent symptomatic stroke (n = 159) also showed new asymptomatic infarcts. The significance of silent infarcts lies in the fact that their presence reflects widespread arterial disease which is in turn associated with a high risk for recurrent vascular events and stroke.

SAMENVATTING

Atriumfibrillatie is de meest voorkomende vorm van hartritmestoornis. Ondanks het feit dat de meeste patiënten weinig klachten hebben van hun atriumfibrillatie, brengt de aandoening zelf een hoog risico met zich mee voor cardiale en cerebrovasculaire complicaties. Om die reden is het adequaat behandelen van deze aandoening een belangrijke uitdaging voor veel clinici.

Hoofdstuk 1 geeft allereerst een literatuur overzicht. Het vóórkomen en de etiologie van atriumfibrillatie in het algemeen, en van niet-reumatisch atriumfibrillatie in het bijzonder, worden besproken en er wordt tevens ingegaan op het directe en indirecte verband tussen atriumfibrillatie en cerebrale ischemie. Bij 6 tot 19% van alle patiënten die een beroerte hebben doorgemaakt wordt atriumfibrillatie gevonden. Bij patiënten die een lichte voorbijgaande beroerte hadden (TIA = Transient ischaemic attack) ligt dit percentage tussen de 2 en 8%. Afhankelijk van de onderliggende hartaandoening, krijgen per jaar 10 tot 20% van deze patiënten na hun eerste beroerte opnieuw een herseninfarct. In westerse landen is atriumfibrillatie over het algemeen gebonden aan lang bestaande hypertensie of een ischemische hartziekte. Omdat deze aandoeningen zelf ook voorbestemmen tot een hoger risico op beroerten is het vaak moeilijk na te gaan in hoeverre een episode van cerebrale ischemie bij een patiënt met atriumfibrillatie werd veroorzaakt door een embolie uit het hart of door trombo-embolieën uit door atherosclerose aangetaste vaten. Deels vanwege deze onzekerheid, was er ook lang geen consensus over de therapie-keuze bij primaire en secundaire preventie. Rond 1992 hadden de resultaten van 5 gerandomiseerde klinische onderzoeken onweerlegbaar aangetoond dat orale anticoagulantia effectief waren bij de primaire preventie van vasculaire complicaties bij patiënten met niet-reumatisch atriumfibrilleren (risico-reducties tussen 37 en 86%). Eén van deze studies vond ook een significant behandelingseffect met aspirine (risico-reductie van 42%). Of deze resultaten ook geëxtrapoleerd konden worden naar secundaire preventie bij patiënten met atriumfibrillatie die al een beroerte

hadden doorgemaakt, was echter onbekend; daarmee werd de noodzaak tot het opzetten van een gerandomiseerd klinisch onderzoek ter secundaire preventie duidelijk.

Hoofdstuk 2 beschrijft in detail de studie opzet en uitvoering van het Europese Atriumfibrillatie onderzoek (EAFT). In dit onderzoek wordt het therapeutisch effect van zowel aspirine als orale anticoagulantia nagegaan ter secundaire preventie van vasculaire complicaties bij patiënten met atriumfibrilleren en een recent doorgemaakte, niet-invaliderende beroerte. In de 108 aan het onderzoek deelnemende klinieken werden patiënten gerandomiseerd voor orale antistolling (INR 2.5-4.0), acetylsalicylzuur 300mg/dag of placebo. In die gevallen waar contraindicaties bestonden voor het gebruik van antistolling, werden patiënten alleen gerandomiseerd voor aspirine of placebo. Behandeling met antistolling werd niet geblindeerd, aspirine en placebo tabletten daarentegen waren dubbel-blind verpakt. Randomisatie vond plaats van oktober 1988 tot mei 1992; alle patiënten werden daarna nog één jaar lang vervolgd zodat het onderzoek begin mei 1993 definitief afgesloten kon worden. Het behandelingseffect van antistolling en aspirine in vergelijking tot placebo, werd geevalueerd door middel van een conventionele eindpunten-analyse (eindpunten waren vasculair overlijden, recidief beroerte, systemische embolie of myocard-infarct, afhankelijk van wat het eerst optrad) en tevens door een meer pragmatische analyse van overlijden en handicap. Alle analyses zouden in eerste instantie volgens het "intention-to-treat" principe gedaan worden.

Hoofdstuk 3A rapporteert over de hoofdbevindingen van de EAFT. Van de 1007 gerandomiseerde patiënten waren 669 geschikt om met orale anticoagulantia behandeld te worden (groep 1), 338 patiënten werden alleen voor aspirine of placebo gerandomiseerd (groep 2). De incidentie van het hoofdeindpunt was 8 per 100 patiënt-jaren op antistolling (225 patiënten), tegen 17 per 100 patiënt-jaren voor patiënten die placebo hadden geloot in groep 1 (n = 214) (hazard ratio 0.53; 95% betrouwbaarheidsinterval 0.36-0.79). De incidentie van recidief beroerten alléén werd van 12 beroerten per 100 patiënt-jaren gereduceerd tot 4 per 100 patiënt-jaren (hazard ratio 0.34; 95% betrouwbaarheidsinterval 0.20-0.57). Voor patiënten die gerandomiseerd waren voor aspirine (groep 1 en 2

samen; n = 404) was het risico op het krijgen van een eindpunt 15 per 100 patiënt-jaren, tegen 19 per 100 patiënt-jaren indien zij gerandomiseerd waren voor placebo behandeling (n = 378) (hazard ratio 0.83; 95% betrouwbaarheidsinterval 0.65-1.05). Antistolling was significant beter in het voorkómen van eindpunten dan aspirine (hazard ratio 0.60; 95% betrouwbaarheidsinterval 0.41-0.87). In de loop van het onderzoek kwamen ernstige bloedingscomplicaties relatief weinig voor; tijdens behandeling met antistolling was de incidentie 2.8 per 100 patiënt-jaren, bij gebruik van aspirine 0.9 per 100 patiënt-jaren. Er werden geen primaire intracraniële bloedingen gezien bij patiënten die met antistolling werden behandeld.

Hoofdstuk 3B beschouwt de resultaten van het voorgaande hoofdstuk vanuit een meer pragmatisch oogpunt. Bij de controle bezoeken van de patiënten werd niet alleen gevraagd naar het optreden van eindpunten, maar werd ook een inschatting gevraagd van zijn handicap, door middel van een Rankin score. Voor iedere behandelingsgroep werd vervolgens berekend hoeveel tijd gemiddeld in iedere categorie van handicap werd doorgebracht. Door aan iedere categorie een utiliteits-waarde toe te kennen kon een schating gemaakt worden van de winst in 'disability-adjusted survival-years' (DASYs) die bereikt werd met antistolling of aspirine, in vergelijking tot behandeling met placebo. Het indrukwekkende behandelings resultaat van antistolling op het voorkomen van vasculaire complicaties in beschouwing nemend, was de gevonden gemiddelde toename van DASYs (0.10 jaar) wat teleurstellend en bovendien niet veel meer dan de toename die in groep 1 verkregen werd met aspirine (0.07 DASYs). Voor de vergelijking aspirine-placebo bij groep 1 én 2 patiënten was de winst tijdens aspirine-gebruik 0.08 DASYs. Overigens waren deze resultaten tot op zekere hoogte te verwachten gezien het feit dat conventionele eindpunt analyses al hadden laten zien dat noch antistolling noch aspirine duidelijk effectief waren in het voorkómen van overlijden in het algemeen (vasculair en niet-vasculair), en ook omdat de handicap mede bepaald werd door andere aandoeningen, waarop de behandeling geen invloed had.

Hoofdstuk 4 gaat deels in op het vraagstuk welke atriumfibrillatie patiënten met een recent doorgemaakte cerebrale ischemie waarschijnlijk

het meeste voordeel hebben van een behandeling met orale antistolling of aspirine. In de met placebo behandelde patiëntengroep werd de voorspellende waarde voor het optreden van vasculaire complicaties in het algemeen en beroerten in het bijzonder nagegaan voor een aantal klinische variabelen. Middels univariate en multivariate analyses werden uiteindelijk 6 onafhankelijke variabelen geselecteerd: een voorgeschiedenis van trombo-embolische complicaties, klachten van ischemisch hartlijden, aanwijzingen voor hartvergroting op de thorax foto, een systolische bloeddruk van hoger dan 160 mmHg, het langer dan een jaar bestaan van atriumfibrillatie en een infarct op de CT-scan van de hersenen. Met behulp van deze variabelen konden in de 3 behandelingsgroepen patiënten gestratificeerd worden naar hoog, middelmatig en laag risico. De incidentie van vasculaire complicaties was in alle drie risicogroepen beduidend lager bij patiënten die voor antistolling werden gerandomiseerd dan bij patiënten die met placebo werden behandeld. Echter, ook onder antistolling was het risico op vasculaire complicaties hoog bij oudere patiënten met meerdere risicofactoren. In deze kleine subgroep was het risico op vasculaire complicaties bijna hetzelfde in beide behandelingsgroepen (antistolling of aspirine). Aspirine leek het grootste effect te hebben in jongere patiënten met meerdere risicofactoren.

Hoofdstuk 5 is gewijd aan het bepalen van de optimale intensiteit van de behandeling met orale anticoagulantia. In de groep van patiënten die in het kader van de EAFT voor antistollings behandeling gerandomiseerd waren (n = 225) werden INR-specifieke incidentie cijfers berekend voor belangrijke algemene vasculaire complicaties (vasculair overlijden, beroerten, systemische embolieën en myocard infarcten), en voor ernstige bloedings-complicaties. In vergelijking tot intensiteiten lager dan INR 2.0, verminderde een antistollings behandeling met intensiteiten tussen INR 2.0 en 3.0 het aantal vasculaire complicaties met 80% (rate ratio 0.2; 95% betrouwbaarheidsinterval 0.1-0.6). Dit behandelings effect was iets minder sterk bij intensiteiten tussen INR 3.0 en 4.0. Bij hogere intensiteiten werd het gunstige therapie effect te niet gedaan door de toegenomen frequentie van ernstige bloedingscomplicaties. Verder was leeftijd (boven 75 jaar) ook een onafhankelijke risico factor voor het optreden van bloedingscomplicaties. Bij het voorschrijven van orale anticoagulantia aan patiënten met niet-

reumatisch atriumfibrilleren en een recente episode van cerebral ischemie moet waarschijnlijk gemikt worden op een intensiteit van INR 3.0, waarbij waarden onder INR 2.0 en boven 5.0 zoveel mogelijk moeten worden voorkomen.

Hoofdstuk 6 tracht iets meer inzicht te geven in de verwarring rond de diagnose 'embolieën uit het hart'. CT-scans van 985 patiënten met niet-reumatisch atriumfibrilleren (NRAF) en een recente episode van cerebrale ischemie werden vergeleken met 2987 scans van patiënten met soortgelijke episoden van cerebrale ischemie maar zonder atriumfibrilleren. De eerste groep patiënten was afkomstig uit de EAFT; op 54% van hun CT-scans waren ischemische lesies zichtbaar. De tweede groep patiënten kwam uit het Nederlands TIA-Onderzoek, en van deze scans toonde 41% één of meerdere ischemische lesies. In vergelijking tot patiënten met sinus-ritme hadden NRAF patiënten vaker multipele ischemische lesies op hun CT-scan (odds ratio 1.42; 95% betrouwbaarheidsinterval 1.13-1.80). Alleen de symptomatische infarcten in ogenschouw nemend, hadden NRAF patiënten vaker corticale (odds ratio 3.11; 95% betrouwbaarheidsinterval 2.57-3.78) of waterscheidings infarcten (odds ratio 1.92; 95% betrouwbaarheidsinterval 1.27-2.91). Sinus-ritme patiënten daarentegen hadden vaker kleine diepe 'lacunaire' infarcten op hun scan (odds ratio 3.87; 95% betrouwbaarheidsinterval 2.77-5.41). Ondanks deze opvallende verschillen konden er geen karakteristieke CT-scan aspecten worden onderscheiden met behulp waarvan in afzonderlijke patiënten, met meer zekerheid gesteld kan worden of het ging om een infarct van cardioembolische oorsprong of een infarct op basis van atherosclerotische vaatafwijkingen.

Hoofdstuk 7 richt zich specifiek op één van de bij patiënten met NRAF veel voorkomende CT-scan kenmerken, namelijk dat van multipele infarcten in het algemeen, en zogenaamde 'stille' infarcten in het bijzonder. Van de 985 onderzochte patiënten hadden 532 tekenen van focale ischemie op hun scan. In het totaal werden 688 infarcten uitgeboekt, 240 (36%) van deze infarcten konden niet in verband gebracht worden met de actuele neurologische uitval van de patiënt. Van deze asymptomatische infarcten konden 73% ook niet verklaard worden door eerder doorgemaakte beroerten. In vergelijking tot symptomatische infarcten waren deze

zogenaamde "stille" infarcten vaker lacunair (kleine diepe subcorticale infarcten) (odds ratio 5.09; 95% betrouwbaarheidsinterval 3.35-7.74). Stille corticale infarcten bevonden zich vaker in het stroomgebied van de a. cerebri posterior (45%) of in de rechter hemisfeer (61%) dan de symptomatische corticale infarcten (respectievelijk 28% en 43%). Van 76 patiënten waren ook vervolg scans aanwezig die, zonder bijzondere aanleiding, gemaakt waren aan het einde van de studie. Op 14% van deze scans waren nieuwe asymptomatische infarcten te zien (7%/jaar). Van de herhalings-scans die gemaakt werden in het kader van verschijnselen van cerebrale ischemie (n = 159) vertoonden ook 14% tekenen van bijkomende, asymptomatische infarcten. De klinische relevantie van stille infarcten ligt niet zo zeer in het feit dat ze geen aanleiding geven tot duidelijke neurologische uitval, maar meer in het gegeven dat hun aanwezigheid duidt op multipele vaat-afwijkingen in de hersencirculatie hetgeen weer leidt tot een toegenomen risico op recidief vasculaire complicaties en beroerten.

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Thanks also to the other (un)official members of the EAFT executive committee. Jaap Kappelle, you were one of the first to make me realise I had probably more to offer than only administrative support. The icecreams we ate together and the articles in which you had me actively involved, have meant more to me than you will ever know. Memories of working together with John van Swieten are a confused mingling of too much champagne and hundreds of scans. By allowing me to participate in some of your leucoaraiosis projects specifically, and by just being there in general, you made good company in the slow periods of the EAFT. Without the never ending optimism and willingness to help solve each minor and major problem involving the preparation, distribution and coding of trial medication of Fred Schobben and Giselle Latta (Bayer Germany), we might never have been able to start the EAFT. A study that would not have led to results without the support of the actual trial office personnel. Ariane den Ouden and Patricia Vermeulen ought to be decorated for their perseverance in coping with all my little quirks and continued meddling

with their affairs and I am happy to have been able to work with them. Francine van Vliet and Anita te Nijenhuis have been wonderful colleagues in the old times when the trial office was still situated in Utrecht and it has been a pleasure to maintain contact with Francine and her new room-mate Paut Greebe, even if from a distance. Yolanda de Graaf and Ale Algra both contributed to my epidemiological training, the first by introducing me to the department of epidemiology in Utrecht, the latter by pointing out the possibility of attending a summer school programme in Boston thereby setting me off in the right direction.

I would like to express my sincere appreciation of the way in which my colleagues from the department of neuropsychology in Rotterdam (Hanneke, Evy, Mieke, Inge, Sandra, Nel, Huug, and Frans) uncomplainingly accepted the strange phenomenon of the EAFT into their midst. Your warm friendship has made working in the 'ivory' tower more than just enjoyable. The new CPON+ department, with in contrast a predominantly male population, formed an interesting change of environment. Fop and Henk, thank you for all the support on the job and outside of it. It is an honour for me that the two of you agreed to be my para-nymphs and I will miss the evening-hours we used to spend together (sometimes just to make up for time lost during the day). Kris, Lourens, and Dirk, your help and sense of collegiality added fun and diversity to a job that was sometimes more tedious than challenging. Last, but certainly not least, I owe a lot to Betty Mast and Djo Hasan. The first for her initial work as formal secretary of the EAFT, but more importantly for her continuing support after this position had come to an end. Djo and Betty gave me a crash course on the does and don'ts of the neurology department in Rotterdam, and despite the fact that we were unable to keep close contact I have always much appreciated this initial support.

It would be beyond the scope of this chapter to address a personal note of gratitude to all other friends and colleagues. Still I would like to close by mentioning the following groups:
The people from the mail-room both in Utrecht and Rotterdam whom without grumbling, would send off hundreds of newsletters each month. Mr. Malais and Mrs. Takke whom both had a hard time keeping the financial books in order. Friends and colleagues of the Daniel den Hoed

Kliniek with whom I spent an instructive half year whilst trying to summon enough courage for the final stages of this thesis. Prof. E.A. Loeliger and Diederik Dippel, who, as experts in their fields, were kind enough to take my amateurish first attempts in anticoagulant and quality of life research seriously and supplied helpful comments for the respective chapters. Fellow 'actors' and 'musicians' who provided exactly the right environment for creative thoughts, and finally, my family for putting up with a disgraceful form of neglect over these past years.

CURRICULUM VITAE

Schrijver dezes werd op 4 mei 1963 geboren te Eindhoven. Na wat rondzwervingen door Venezuela en Engeland, behaalde zij in 1981 het VWO-B diploma aan het Laurenscollege te Rotterdam. Datzelfde jaar kon zij met behulp van een Shell studiebeurs aan de Erasmus Universiteit met de opleiding Geneeskunde beginnen. Als student was zij actief binnen de universitaire politiek en in het verenigingsleven van het Rotterdamse Studenten Gezelschap (bestuursfunctie 1982-1983). Na in 1986 als lid en coördinator van de Rotterdamse Bouwbrigade in Nicaragua werkzaam te zijn geweest, werd zij uiteindelijk in april 1988 tot arts bevorderd. Van 1988 tot 1994 was zij werkzaam als projectleider van het Europese Atriumfibrillatie Onderzoek, met in de laatste helft van 1993 een deeltijd aanstelling aan het trial bureau van de Dr Daniel den Hoed Kliniek. In die tijd behaalde zij het diploma van statistisch analist VVS-A (1990) en B (1992), werd geregistreerd als epidemioloog A en was als vrijwilliger actief bij het Nederlandse Rode Kruis, afdeling Rotterdam (1989-1994). Eind 1994 reist zij af naar de noordelijke gebieden van Pakistan om daar werkzaam te zijn in het primary health care programma van de AKHSP.

LIST OF PUBLICATIONS

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14. Kappelle LJ, van Latum JC, van Swieten JC, Algra A, Koudstaal PJ, van Gijn J. Cerebral infarcts preceded by a TIA or minor ischaemic stroke: Does the distinction between small- and large vessel disease remain true to type? (submitted).

15. The European Atrial Fibrillation Trial Study Group. Predictors of major vascular events in patients with a transient ischaemic attack or minor ischaemic stroke and with non-rheumatic atrial fibrillation (in preparation).

16. The European Atrial Fibrillation Trial Study Group. Optimal intensity of anticoagulant therapy in patients with non-rheumatic atrial fibrillation and a recent non-disabling cerebral ischaemic event (in preparation).

17. Van Latum JC, Koudstaal PJ, Kappelle LJ, van Kooten F, Algra A, van Gijn J, for the European Atrial Fibrillation Trial and Dutch TIA Trial Study Groups. Comparison of CT-scan findings in TIA and minor stroke patients, with or without non-rheumatic atrial fibrillation (in preparation).

18. Van Latum JC, van Kooten F, van Gijn J, Kappelle LJ, Algra A, Koudstaal PJ, for the European Atrial Fibrillation Trial Study Group. Silent cerebral infarction in non-rheumatic atrial fibrillation (in preparation).

19. Van Latum JC, Dippel DWJ, Koudstaal PJ, Kappelle LJ, for the European Atrial Fibrillation Trial Study Group. Quality of life after minor ischaemic stroke in patients with non-rheumatic atrial fibrillation: effect of antithrombotic treatment (in preparation).

APPENDIX A

1. Active centres in the EAFT
2. Committees
3. Randomisation/Code lists
4. Patient information letter
5. Family doctor information letter
6. Information letter for anticoagulant control
7. Patient identification card and AC control card

COLLABORATORS IN THE EUROPEAN ATRIAL FIBRILLATION TRIAL
( ) Denotes number of randomised patients

BELGIUM
Brugge; Algemeen Ziekenhuis Sint Jan - I Dehaene, M D'Hooghe, M Marchau, M van Zandijcke (3)
Brussels; Clinique Universitaire Saint Luc - C Delwaide, A Depré, EC Laterre (3)
Dendermonde; Algemeen Ziekenhuis Onze Lieve Vrouwe van Troost - E van Buggenhout (5)
Geel; Algemeen Ziekenhuis Sint Dimpna - J Schurmans, E de Smet, L Swerts (4)
Gent; Kliniek Heilige Familie - G van den Abeele (4)
Leuven; Universiteits Ziekenhuis Gasthuisberg - H Carton, PMA Verdru (8)
Mons; Sint Joseph Ziekenhuis - PhA Indekeu, D Lam, Tanghe (13)
Turnhout; Elisabeth Ziekenhuis - V van den Bergh, L Mol (1)
Wilrijk; Medisch Instituut Sint Augustinus - W van Landegem, T Strauven (2)

DENMARK
Copenhagen; Rigshospitalet - G Boysen, J Gyring, P Petersen, P Würtzen-Nielsen (11)

FRANCE
Besancon; Centre Hospitalier Regional de Besancon- T Crepin-Leblond, T Moulin (12)
Bordeaux; Hôpital Pellegrin - S Auriacombe, JM Orgogozo (2)
Bourg-en-Bresse; Centre Hospitalier de Bourg-en-Bresse - J Boulliat (36)
Brest; Hôpital Augustin Morvan - J-Y Goas, Y Mocquard (5)
Grenoble; Centre Hospitalier Regional Universitaire de Grenoble - G Besson, M Hommel (5)
Lille; Centre Hospitalier, Hôpital B - C Adnet-Bonte, E Josien, Petit (2)
Meaux; Centre Hospitalier de Meaux- F Chedru (5)
Paris; Hôpital de la Salpêtrière - S Evrard, M Levasseur (2)
Paris; Centre Hospitalier Raymond Garcin/Saint Anne - JL Mas, O Meyniard, M Zuber (7)
Paris; Hôpital Saint Antoine - P Amarenco, MG Bousser, E Roullet (2)
Rennes; Centre Hospitalier Pontchaillou - JF Pinel (5)
Rouen; Hôpital Charles Nicolle - E Massardier, B Mihout (2)
Toulouse; Centre Hospitalier Universitaire Purpan - F Chollet, A Rascol (1)
Tours; Centre Hospitalier Universitaire Bretonneau - A Autret, D Saudeau (5)

GERMANY
Bochum; Neurologische Universitätsklinik Sint Josef - Th Büttner, W Niemczyk (1)
Gießen; Klinik der Justus-Liebig-Universität - KD Böhm, C Hornig (3)
Heidelberg; Klinikum der Ruprecht-Karls-Universität - W Hacke, C Heiss, R Reuther (1)
Homburg/Saar; Universitäts Nervenklinik - A Haaß, M Stoll (2)
Mainz; Klinik der Johannes Gutenberg-Universität - G Krämer, G Rothacher (10)

Minden; Klinikum Minden - M Bauer, O Busse, S Koch-Rose, B Mueffelmann (13)
Tübingen; Eberhard-Karls-Universität - J Dichgans, C Thomas (2)
Wuppertal;Klinikum Barmen - OAD Hennen, J Jörg, H Schwan, R Siepen (3)

ISRAEL
Tel-Aviv; Ichilov Hospital - NM Bornstein (15)

ITALY
Ancona; Ospedale di Torrette - B Censori, M Ceravolo, L Provinciali (7)
Aosta; Ospedale Regionale di Aosta - G D'Alessandro, E Bottacchi, L Carenini, E Duc (8)
Bari; Ospedale Policlinico Universitario - F Federico, A Fiore, P Lamberti, P Lattanzi (11)
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Amsterdam; Academisch Medisch Centrum - D Herderschêe, A Hijdra, M Vermeulen (3)
Amsterdam; Academisch Ziekenhuis der Vrije Universiteit - FW Bertelsmann, GJ Hazen-berg, JC Koetsier (10)
Bergen op Zoom; Ziekenhuis Lievensberg - PJIM Berntsen, ThB Gebbink, FM Sleegers (6)
Deventer; Stichting Deventer Ziekenhuizen - JA van Beeck, WJ Feikema, JHM van Gasteren, AN Veltema, CJM Vredeveld (1)
Dordrecht; Merwede Ziekenhuis - PATh Carbaat, LI Hertzberger, RP Kleyweg (12)
Goes; Stichting Oosterscheldeziekenhuizen - AM Boon, WHG Lieuwens, F Visscher (13)

's-Gravenhage; Westeinde Ziekenhuis - WFM Arts, A Boon, LCM Moll, WVM Perquin, JThJ Tans, R Tonk, AW de Weerd (10)
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Nieuwegein; Sint Antonius Ziekenhuis - HW Mauser (2)
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Rotterdam; Academisch Ziekenhuis Dijkzigt - WJJF Hoppenbrouwers, PJ Koudstaal, A Staal (27)
Rotterdam; Sint Fransiscus Gasthuis - PR Beneder, C Bulens, LH Penning de Vries-Bos (5)
Tilburg; Sint Elisabeth Ziekenhuis - AAW Op de Coul, ACM Leyten, CC Tijssen, RLLA Schellens (9)
Utrecht; Academisch Ziekenhuis - JPM Cillessen, J van Gijn, LJ Kappelle (14)
Vlaardingen; Holy Ziekenhuis - JJM Driesen, WF van Oudenaarden, JCB Verhey (6)

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Arendal; Aust-Agder Sentralsjukehus - B Aslaksen, F Gallefoss, KO Laake (5)
Bodo; Nordland Sentralsykehuset - LK Berg (1)
Drammen; Sentralsykehuset i Buskerud - S Balsliemke, S Ritland (8)
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Skien; Sentralsykehuset i Telemark - Welund (1)

PORTUGAL
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Coimbra; Hospital Universitario - R Amaral, C Machado, A Mestre, F Ribeiro, L Sousa (3)
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Trial Office, University Hospital Utrecht ('88-'90) Erasmus University Rotterdam ('90-'93):

PJ Koudstaal, principal investigator: October '87 - July '93
JC van Latum, clinical co-ordinator: May '88 - July '93
A den Ouden, data-manager: May '88 - January '90
PC Vermeulen, data-manager: October '90 - October '92
B Mast, secretary: May '88 - May '89

Rotterdam: Acad. Ziekenhuis Dijkzigt	08-16

YES, eligible for AC

Nr	CODE	Patiëntnr	Datum	Par
1	5	08 - 16 - 002	21 / 10 / 1988	
2	10	08 - 16 - 004	10 / 11 / 1988	
3	AC	08 - 16 - 005	07 / 12 / 1988	
4	AC	08 - 16 - 006	27 / 13 / 1989	
5	7	08 - 16 - 007	09 / 02 / 1989	
6	3	08 - 16 - 008	06 / 03 / 1989	
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8	AC	08 - 16 - 011	15 / 06 / 1989	
9	2	08 - 16 - 013	19 / 10 / 1989	
10	6	08 - 16 - 014	10 / 11 / 1988	
11	AC	08 - 16 - 015	5 / 12 / 1989	
12	AC	08 - 16 - 016	8 / 12 / 1989	
13	7	08 - 16 - 018	23 / 03 / 1990	
14	3	08 - 16 - 019	12 / 04 / 1990	
15	9	08 - 16 - 020	26 / 09 / 1990	PN
16	8	08 - 16 - 021	15 / 02 / 1991	
17	4	08 - 16 - 022	04 / 05 / 1991	
18	1	08 - 16 - 023	12 / 03 / 1991	
19	AC	08 - 16 - 024	14 / 06 / 1991	
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29	AC	..... - ..... -	..... / ..... / 19.....	.....
30	AC	..... - ..... -	..... / ..... / 19.....	.....
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32	5	..... - ..... -	..... / ..... / 19.....	.....
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NO, not eligible for AC

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1	1	08 - 16 - 001	13 / 10 / 1988	
2	9	08 - 16 - 003	10 / 11 / 1988	
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4	6	08 - 16 - 012	29 / 09 / 1989	
5	5	08 - 16 - 017	15 / 05 / 1990	—
6	2	08 - 16 - 025	19 / 06 / 1991	—
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31	5	..... - ..... -	..... / ..... / 19.....	.....
32	10	..... - ..... -	..... / ..... / 19.....	.....
33	9	..... - ..... -	..... / ..... / 19.....	.....
34	8	..... - ..... -	..... / ..... / 19.....	.....
35	10	..... - ..... -	..... / ..... / 19.....	.....
36	6	..... - ..... -	..... / ..... / 19.....	.....
37	3	..... - ..... -	..... / ..... / 19.....	.....
38	7	..... - ..... -	..... / ..... / 19.....	.....
39	2	..... - ..... -	..... / ..... / 19.....	.....
40	1	..... - ..... -	..... / ..... / 19.....	.....
41	4	..... - ..... -	..... / ..... / 19.....	.....
42	5	..... - ..... -	..... / ..... / 19.....	.....

COUNTRY: NEDERLAND

CENTRE : ROTTERDAM - DIJKZIGT ZIEKENHUIS
INVESTIGATORS : de Jong, Vermeulen, Koudstaal, Staal

ID-NUMBER	DATE OF RANDOM.	SURNAME	INT.	DATE OF BIRTH	SEX	NEUROLOGIST	ELIG.AC Y/N	ALLOCATED TREATMENT	SIGN.
08-16-001									
08-16-002									
08-16-003									
08-16-003									
08-16-004									
08-16-005									
08-16-006									
08-16-007									
08-16-008									
08-16-009									
08-16-010									
08-16-011									
08-16-012									
08-16-013									
08-16-014									
08-16-015									
08-16-016									
08-16-017									

INFORMATION FOR THE PATIENT

Dear Sir, Madam,

You have been admitted to our hospital after experiencing a light form of stroke. The medical term is TIA; which stands for Transient Ischaemic Attack, or minor stroke. TIA's and minor strokes should be seen as so called 'warnings' for impending, more serious, strokes.
In your case the TIA was most probably caused by an irregularity in the heartrhythm which caused a small blood clot to form in the heart, from where it was transported to the brains where it temporarily blocked a blood vessel.
We have asked the cardiologist for advice in the treatment of your irregular heartrhythm, but even when the heartrhythm has returned to normal there still seems to be a possibility that blood clots from the heart enter the bloodstream. Of course we are interested to minimize this possibility as much as possible.

Up till now three treatment forms were used:
- Some physicians prescribe oral anticoagulation, a medication form that is controlled once a month by the local thrombosis-service or the hospital.
- Other physicians use aspirin to make the blood thinner.
- Yet another group of physicians believe that the positive effects of above named treatment forms do not outweigh negative effects that could occur in a small percentage of patients, namely bleeding complications.

Because physicians still disagree on the best form of treatment, we have decided to do the following study in collaboration with other hospitals in Europe. We are going to treat three groups of patients with the treatments as described above. Each patient will be monitored carefully to check if any differences arise between the groups.
To make sure that no subjective differences arise, patients in the last group (receiving no medication to make the blood thinner) will receive an inactive tablet that is not to be distinguished from an aspirin tablet. In emergencies it is always possible to trace the real form of medication when necessary. Patients receiving oral anticoagulation will know their treatment form because of the necessity for monthly control.
If, for any reason, you are not allowed to use oral anticoagulation, but may use aspirin, you will be treated with either aspirin or inactive tablets.

We would really appreciate it if you permitted us to classify you in to one of these treatment groups. But if you are not willing to join this study you will be treated according to the hospital's normal policy (a policy that has, as yet, not been proven to be the best one). If you do join the study you are justified to refuse further co-operation at any time if you find this necessary. In that case you can still count on our full attention.

Your general practitioner will be informed about this study.

For any remaining questions you can always call upon your treating neurologist or general physician.

Finally some important instructions:
If you decide to join the study you will receive sufficient medication to last you through to the next check-up visit. These check-up visits wil take place every four months. It is very important for you to return the box with left-over medication every time you come for a check-up visit.
If you ever need to take any 'painkillers' please use only Paracetamol.
Aspirin or placebo tablets should be taken one a day, please dissolve the tablet in water before taking it in.
If you are allocated to oral anticoagulant treatment there are some other instructions which you will receive from the controlling thrombosis-service or your physician.

INFORMED CONSENT

Based on the information supplied by the patient information letter and discussed by the randomising physician, undersigned agrees to voluntary participate in the European Atrial Fibrillation Trial. Subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Signature: _____

Full name patient: _____

City: _____ Date: _____/_____/19____

INFORMATION FOR THE GENERAL PRACTITIONER
sent by the Trial Office or the randomising physician

Dear Colleague,

With this letter we wuld like to inform you that patient

name of patient.....

address of patient.....

postal code.....**city**.....

date of birth ...../...../**19**.....

has been randomised for the European Atrial Fibrillation Trial on ..... 19..... by colleague

....., the treating physician.

This trial aims at estanlishing the preventive value of both anticoagulation and aspirin in patients with non-rheumatic (non-valvular) atrial fibrillation and TIA or minor stroke.
The study is double blind for the treatment aspirin/placebo, meaning that neither the patient not the treating physician knwo which treatment thepatient is receiving. In emergencies it is always possible to get this information from the Trial Office Pharmacist:

++ - 31 - 30 - 50.72.17 (Dr. Schobben)

Anticoagulant treatment is not blinded because of the necessity for regular adjustment of the anticoagulant dosage.

The patient has been fully informed about the trial by the treating physician and has given his/her consent for study-treatment.

The patient was randomised for:
O Anticoagulant treatment
O Aspirin/placebo treatment

We would like to stress that you should avoid prescribing the following medication:
O No acetylsalicylic acid (Aspirin, Ascal, etc.)
O No anti-inflammatory medication that might influence platelet-aggregation (Indocid, etc.)
Please prescribe only Paracetamol as painkiller.

Finally we request you to contact the treating physician, Dr. ....., as soon as possible if any unexpected complaints or illnesses arise, or when the patient has passed away.

Thank you very much for your co-operation.

With kind regards,

On behalf of .....

Trial co-ordinator European Atrial Fibrillation Trial

Appendix A 5.GP

TREATING PHYSICIAN

Dear Colleague,

October 1988 a large European clinical trial was started to establish the preventive value of both anticoagulant treatment and aspirin (300 mg/day) in patients with non-rheumatic atrial fibrillation and a TIA or minor ischaemic stroke. In 12 countries and 130 centres, patients are being randomised for three treatment groups: Acetylsalicylic Acid (double-blind), placebo (double-blind) and oral anticoagulants (not blinded).

Mr./Mrs. :

Date of Birth :

Randomising physician :

Hospital :

has recently joined the European Atrial Fibrillation Trial (EAFT) and has been randomised for anticoagulant treatment. In this respect we wouldlike to ask you the following:

1) The patient mentioned above has also brought a registration card for PT-times.
Would you be so kind as to to fill in these PT-values and their corresponding INR-values at each follow-up visit. INR-values can be found in the conversion table that is included with each new batch of thromboplastin used in your laboratory. Please note that each new batch of thromboplastin has another conversion table.

2) According to our protocol, patients should be anticoagulated between **2.5 and 4.0 INR**. Our aim is **3.0 INR**. Could you take special notice of this?

We would sincerely appreciate you co-operation in this matter.

With best regards,

For further information : .....

Or : European Atrial Fibrillation Trial Office
Institute of Neurology Ee 2287
Erasmus University Rotterdam
PO Box 1738, 3000 DR Rotterdam, The Netherlands

Tel: ++ - 31 - 10 - 408 78 18

Appendix A 6.AC

EUROPEAN ATRIAL FIBRILLATION TRIAL
KONTROLLKARTE ANTICOAGULANTIA

Bitte nehmen Sie diese Karte zu jedem Besuch bei Thrombosestation und/oder Facharzt mit und lassen Sie sie ausfüllen.

Herr/Frau : Geburtsdatum :
Patientennummer : Behandelnder Arzt :
Anfangsdatum :

	Datum	PT in Sek.oder %	INR		Datum	PT in Sek.oder %	INR
1				9			
2				10			
3				11			
4				12			
5				13			
6				14			
7				15			
8				16			

Erläuterung: Patient nimmt teil am European Atrial Fibrillation Trial und wird mit oralen Anticoagulantia behandelt. Für Forschungszwecke muß die Prothrombine Zeit (PT), die oft in Sekunden oder als Prozentsatz angegeben wird, auch im sogenannten INR-Wert (International Normalized Ratio) aufgeführt werden. Darum bitte auf jeden Fall immer den INR-Wert eintragen.

TEILNEHMERKARTE EUROPEAN ATRIAL FIBRILLATION TRIAL

Patient nimmt Teil am European Atrial Fibrillation Trial und bekommt:

- O orale Anticoagulantia
- O Aspirin (300 mg) pro Tag, oder Placebo

Für weitere Informationen können Sie sich an den behandelnden Facharzt wenden:

Dr.
Abteilung
Krankenhaus
Ort
Telefon

APPENDIX B

CASE REPORT FORMS E.A.F.T.

1. Notification form
2. Medication form
3. Follow-up form
4. Outcome event form
5. Non-randomised patient form
6. CT-scan auditing form
7. Outcome event auditing forms:
   - Death
   - Stroke
   - Cardiac
   - Systemic embolism

EUROPEAN ATRIAL FIBRILLATION TRIAL : NOTIFICATION FORM

1. PATIENT

1.1 surname _____ initials _.._.._

1.2 date of birth DAY [ ][ ] - MONTH [ ][ ] - YEAR [ ][ ][ ][ ]

1.3 sex male ☐ female ☐

1.4 randomising physician

- name _____
- hospital _____
- city _____

1.5 general practitioner

- name _____
- address _____
- city _____

2. RANDOMISATION

2.1 Any use of trial medication (anticoagulation or aspirin) prior to randomisation

	before and/or at the time of the qual. event	after the qualifying event (by someone not involved in the trial)
☐ no		
☐ anticoagulation	☐	☐
☐ aspirin	☐	☐

If any, by whom _____

for which indication _____

treatment form and dosage _____

for how long : _____ hrs _____ days _____ weeks _____ months.

Do not randomise this patient if you yourself have prescribed anticoagulation or aspirin (2.1) after the qualifying event, causing an unnecessary delay in randomisation (see 2nd edition user's manual).

2.2 Subcutaneous heparin treatment - for thrombosis prophylaxis - in the initial phase after the qualifying event (this is allowed if this is standard policy in your centre)

☐ no

☐ yes, by whom _____

dosage _____

for how long : _____ hours _____ days.

2.3 AC eligibility

☐ a. eligible for AC

☐ b. NOT eligible for AC because of: _____

!! please fill in the rest of this form after the randomisation telephone call (++31 20 83 92 61) !!

2.4 date of randomisation DAY [ ][ ] - MONTH [ ][ ] - YEAR [ ][ ][ ][ ]

2.5 ID-number country [ ][ ] - centre [ ][ ] - patient [ ][ ][ ]

2.6 AC [ ]

ASA/placebo: treatment-number [ ][ ] (fill in 01 to 10)

2.7 If the patient has been randomised for AC treatment, will the initial medication form be heparin combined with oral anticoagulants?

☐ Yes

☐ No

3. TIA/MINOR STROKE

3.1 Date of event qualifying for randomisation — DAY ☐☐ - MONTH ☐☐ - YEAR ☐☐☐☐

3.2 Symptoms of the qualifying event:

	no	yes
a. amaurosis fugax	☐	☐
b. hemianopia	☐	☐
c. muscle weakness	☐	☐
d. loss of sensation	☐	☐
e. dysphasia	☐	☐
f. dysarthria	☐	☐
g. other vertebrobasilar sympt.	☐	☐
h. other, specify _____		

3.3 Which localisation?

☐ a. hemisphere ☐ left ☐ right
☐ b. vertebrobasilar
☐ c. eye ☐ left ☐ right
☐ d. uncertain localisation

3.4 Duration of symptoms of qualifying event

days ☐☐ . hours ☐☐ minutes ☐☐ seconds ☐☐

a.
b. ☐ still persisting

3.5 Residual signs no ☐ yes ☐ if yes, which: _____

3.6 Number of attacks (both TIAs and minor stroke) in past year, including qualifying event ? ☐☐☐

3.7 If events prior to randomisable event, which localisation(s)?

☐ a. no other events than qualifying event
☐ b. hemisphere ☐ left ☐ right
☐ c. vertebrobasilar
☐ d. eye ☐ left ☐ right
☐ e. uncertain distribution

4. CARDIAC STATUS AT TIME OF RANDOMISATION

	no	yes
4.1 Atrial fibrillation		
a. chronic AF	☐	☐
b. paroxysmal AF	☐	☐
4.2 Congestive heart failure	☐	☐
4.3 Recent cardioversion	☐	☐

c. how long has the patient been known to have AF? YEARS ☐☐ MONTHS ☐☐ DAYS ☐☐

5. CARDIOVASCULAR RISK INDICATORS

	no	yes, treated	yes, not treated
5.a hypertension	☐	☐	☐
5.b diabetes	☐	☐	☐
5.c hypercholesterolemia	☐	☐	☐

	no	yes
5.d angina pectoris	☐	☐
5.e intermittent claudication	☐	☐
5.f current regular smoking	☐	☐

6. PAST CARDIOVASCULAR EVENTS

	no	yes
a. myocardial infarction	☐	☐
b. non-disabling stroke	☐	☐
c. systemic embolism	☐	☐

7. PAST CARDIOVASCULAR SURGERY

	no	yes
a. coronary bypass	☐	☐
b. carotid endarterectomy	☐	☐
c. aorta bifurcation prosthesis	☐	☐
d. femoral-popliteal bypass	☐	☐

e. other _____

8. CURRENT DRUGS

- ☐ a. none
- ☐ b. beta-blocker
- ☐ c. diuretic
- ☐ d. digoxine/digitoxine
- ☐ e. other anti-arrhythmic
- ☐ f. calcium-antagonist
- ☐ g. other drugs

9. PHYSICAL EXAMINATION

		systolic	diastolic
9.1	Blood pressure	☐☐☐	☐☐☐
			regular ☐ irregular ☐
9.2	Apex rate, beats/min	☐☐☐	
9.3	Height, cm	☐☐☐	
9.4	Weight, kg	☐☐☐	

10. RANKIN HANDICAP SCORE (scored at the time of randomisation)

10.1
- ☐ 0 No symptoms
- ☐ 1 No significant disability despite symptoms: able to carry out all usual duties and activities.
- ☐ 2 Slight disability: unable to carry out some previous activities but able to look after own affairs without assistance.
- ☐ 3 Moderate disability: symptoms which significantly restrict lifestyle and/or prevent totally independent existence (e.g. requiring some help)
- ☐ 4 Moderately severe handicap: symptoms which clearly prevent independent existence though not needing constant attention (e.g. unable to attend to own bodily needs without assistance).
- ☐ 5 Severe handicap: totally dependent, requiring constant attention day and night

10.2 Does the patient suffer any intercurrent illnesses that may influence the Rankin score? no ☐ yes ☐

if yes, which illness(es): _____

10.3 What was the worst Rankin score caused by the qualifying event?

☐ Fill in 1 to 5.

11. ANCILLARY INVESTIGATIONS

11.1 Blood tests, measured at least one week after the qualifying event

a. Ht ☐.☐☐ l/l

b. glucose ☐☐.☐ mmol/l fasting ? no ☐ yes ☐ conversion factor: 5,6 x gr/l

c. cholesterol ☐☐.☐ mmol/l no ☐ yes ☐ conversion factor: 0,026 x mg%

11.2 Chest X-ray, AP, heart ratio >1/2 (or > 500 ml/m^2 BSA) no ☐ yes ☐

(patient is not eligible if heart ratio >65%, or > 800 ml/m^2 BSA !)

11.3 Echocardiography
- atrial thrombus ☐ ☐
- enlarged (>40 mm) left atrium ☐ ☐

11.4 Non-invasive investigation of the carotid arteries performed? If yes, please complete: ☐ ☐

INTERNAL CAROTID ARTERIES		COMMON CAROTID ARTERIES	
☐ normal		☐ normal	
☐ stenosis	☐☐☐ % left ☐☐☐ % right	☐ stenosis	☐☐☐ % left ☐☐☐ % right
☐ plaques	☐ left ☐ right	☐ plaques	☐ left ☐ right

☐ other: _____

12. ADDRESS OF A RELATIVE (to help find back the patient if lost to follow-up)

_____

_____

EUROPEAN ATRIAL FIBRILLATION TRIAL MEDICATION FORM

To be completed by treating neurologist

* Date : .....

* Name of patient : .....

* Identification-number : .....

* Treatment-number[1] : .....

* First medication/ follow-up visit

no. follow-up _____

Name neurologist :

Signature :

To be completed by the supplier of the trial medication (pharmacist or neurologist)

* Old medication

no. of left over tablets[3] : .....

* New medication

Please affix flag-label[2] of new medication box.

Date of delivery : .....

Paraph :

Explanatory notes:

1. During the randomisation telephone-call, the patients assigned to randomisation for ASA/placebo will receive a treatment-number.

2. The patient will receive a box with medication containing enough tablets for the following 4 months, till the next follow-up visit. The number on the flag-label of this box must correspond with the treatment-number of the patient. By attaching the loose part of this flag-label to this form it is possible for the trial-office to check the received treatment.

3. The patient must be instructed to return all medication at the next follow-up visit. Counting the remaining tablets allows us to assess compliance.

4. After completion, please return this form as soon as possible to the trial-office. Keep the copy for your own administration.

5. For further information we would like to refer to the protocol, if any questions still remain please do not hesitate to contact the trial-office.

EUROPEAN ATRIAL FIBRILLATION TRIAL: FOLLOW-UP FORM

1. PATIENT

1.1 ID-number ☐☐ - ☐☐ - ☐☐☐ 1.2 AC ☐ ASA/placebo: treatment-number ☐☐ (fill in 01 to 10)

1.3 surname _____ initials _.__.__

1.4 randomizing physician

- name _____

2. FOLLOW-UP

2.1 Date of follow-up DAY ☐☐ - MONTH ☐☐ - YEAR ☐☐☐☐ 2.2 Number of follow-up ☐

2.3 Has the patient suffered from any of the following events since the last report ?
If yes, please fill in an outcome events form.

- ☐ a. none
- ☐ b. ischaemic stroke
- ☐ c. intracranial haemorrhage
- ☐ d. myocardial infarction
- ☐ e. retinal infarction
- ☐ f. systemic embolism

2.4 Did the patient have TIAs since the last report, if yes which localisation?

- ☐ a. no other TIAs
- ☐ b. hemisphere ☐ left ☐ right
- ☐ c. vertebrobasilar
- ☐ d. eye ☐ left eye ☐ right eye
- ☐ e. uncertain localisation

	no	yes
2.5 Has the patient been admitted to a hospital since the last report?	☐	☐

reason: _____

_____

3. SIDE-EFFECTS

3.1 Has the patient experienced any side-effects of the study medication?

- ☐ a. none
- ☐ b. stomach discomfort/dyspepsie
- ☐ c. peptic ulcers
- ☐ d. diarrhoea
- ☐ e. constipation
- ☐ f. allergic reactions
- ☐ g. skin necrosis
- ☐ h. bruising
- ☐ i. occult bleeding, anaemia
- ☐ j. nose bleed
- ☐ k. haematuria
- ☐ l. severe gastrointestinal bleeding
- ☐ m. severe urogenital bleeding
- ☐ n. severe bleeding from tumour
- ☐ o. severe bleeding from pulmonary cavity
- ☐ p. severe bleeding from aneurysm (GI or intracranial)
- ☐ q. severe bleeding in vitreous body in the eye
- ☐ r. other: _____

		no	yes
3.2 Did occurrence of side-effects necessitate:	a. blood transfusion	☐	☐
	b. operative treatment	☐	☐
	c. changes in trial medication	☐	☐

4. COMPLIANCE

4.1 All options refer to the most recent follow-up period. Only tick one box.

☐ The patient has used his trial medication without interruption.

☐ The trial medication has been discontinued temporarily for approximately ☐☐☐ days.

☐ The trial medication was discontinued permanently at DAY ☐☐ - MONTH ☐☐ - YEAR ☐☐☐☐

Please state reasons : _____

_____

4.2 Were there other changes in the patient's medication? no ☐ yes ☐

If yes, please fill in

drug	S=stop/B=Begin	indication

5. Does the patient (still) smoke? no ☐ yes ☐

6.1 Blood pressure systolic ☐☐☐ diastolic ☐☐☐ 6.2 Apex rate, beats/min ☐☐☐ regular ☐ AF ☐ other ☐

7. RANKIN HANDICAP SCORE (total handicap)

7.1
- ☐ 0 No symptoms
- ☐ 1 No significant disability despite symptoms: able to carry out all usual duties and activities
- ☐ 2 Slight disability: unable to carry out some previous activities but able to look after own affairs without assistance
- ☐ 3 Moderate disability: symtoms which significantly restrict lifestyle and/or prevent totally independent existence (e.g. requiring some help)
- ☐ 4 Moderately severe handicap: symptoms which clearly prevent independent existence though not needing constant attention (e.g. unable to attend to own bodily needs without assistance)
- ☐ 5 Severe handicap: totally dependent, requiring constant attention day and night

7.2 Has the patient suffered any intercurrent illnesses during the last follow-up period, that may have caused changes in the Rankin-score? no ☐ yes ☐

If yes, which illness: _____

_____

8. If the patient is on anticoagulants, please fill in the mean (monthly) prothrombin times (expressed in INR values)

DAY	MONTH	YEAR	INR-value
☐☐	☐☐	☐☐☐☐	☐.☐
☐☐	☐☐	☐☐☐☐	☐.☐
☐☐	☐☐	☐☐☐☐	☐.☐
☐☐	☐☐	☐☐☐☐	☐.☐
☐☐	☐☐	☐☐☐☐	☐.☐

EUROPEAN ATRIAL FIBRILLATION TRIAL: OUTCOME EVENTS FORM

1. **PATIENT**

1.1 ID-number [ ][ ] - [ ][ ] - [ ][ ][ ] 1.2 [ ] AC ASA/placebo: treatment-number [ ][ ] (fill in 01 to 10)

1.3 surname [ ] initials [ ].[ ].[ ]

1.4 randomising physician

- name [ ]

1.5 Date of last follow-up DAY [ ][ ] - MONTH [ ][ ] - YEAR [ ][ ][ ][ ]

2. **NON-FATAL OUTCOME EVENTS**

2.1. INTRACRANIAL EVENTS

Did any intracranial events occur?

☐ a. no intracranial events

☐ b. yes, ischemic stroke (symptoms persisting >24 hrs) Date of event: DAY [ ][ ] - MONTH [ ][ ] - YEAR [ ][ ][ ][ ]

☐ c. yes, intracranial haemorrhage Date of event: DAY [ ][ ] - MONTH [ ][ ] - YEAR [ ][ ][ ][ ]

PLEASE ENCLOSE CT-SCAN NOW ! COMPLETE AN EC-IC SCALE FORM !

2.2. OTHER NON-FATAL EVENTS

Did any other non-fatal events occur?

☐ a. no other non-fatal events

☐ b. non-fatal myocardial infarction Date of event: DAY [ ][ ] - MONTH [ ][ ] - YEAR [ ][ ][ ][ ]

☐ c. retinal infarction or optic nerve infarction Date of event: DAY [ ][ ] - MONTH [ ][ ] - YEAR [ ][ ][ ][ ]

☐ d. systemic embolism Date of event: DAY [ ][ ] - MONTH [ ][ ] - YEAR [ ][ ][ ][ ]

ENCLOSE ECG, OPHTHALMOLOGIST REPORT, PRESSURE RECORDINGS, ANGIOGRAPHY!

3. **RANKIN HANDICAP SCORE** (total handicap)

3.1 What was the worst RANKIN-score immediately after the event

☐ 0 No symptoms

☐ 1 No significant disability despite symptoms: able to carry out all usual duties and activities

☐ 2 Slight disability: unable to carry out some previous activities but able to look after own affairs without assistance

☐ 3 Moderate disability: symptoms which significantly restrict lifestyle and/or prevent totally independent existence (e.g. requiring some help)

☐ 4 Moderately severe handicap: symptoms which clearly prevent independent existence though not needing constant attention (e.g. unable to attend to own bodily needs without assistance)

☐ 5 Severe handicap: totally dependent, requiring constant attention day and night

3.2 What was the RANKIN-score, one week after the event? [ ] (0 to 5, see above)

3.3 Has the patient suffered any intercurrent illnesses during the last follow-up period, that may have caused changes in the Rankin-score? no ☐ yes ☐

If yes, which illness: _____

4. **FATAL OUTCOME EVENTS**

4.1 Did the patient die ? no ☐ yes ☐ Date of death: DAY [ ][ ] - MONTH [ ][ ] - YEAR [ ][ ][ ][ ]

4.2 If YES, what was the place of death?

☐ a. at home ☐ b. in hospital name hospital: [ ]

city : [ ]

PLEASE ENCLOSE AUTOPSY REPORT IF AVAILABLE !

5. FURTHER CLINICAL INFORMATION

5.1 Describe all relevant clinical details below (including if applicable the cause of death), in english, and enclose all relevant documents including letters of discharge.

5.2 If no details are available, who can be contacted for further information ?

Name : _____ function _____

Address: _____

City : _____ Tel: _____

5.3 Is it possible for you to contact this person? no ☐ yes ☐
If yes, please do so as soon as possible.
Send all the relevant obtained information to the trial-office.

6. COMPLIANCE

6.1 All options refer to the most recent follow-up period. Only tick one box.

☐ The patient has used his trial medication without interruption.

☐ The trial medication has been discontinued temporarily for approximately ☐☐☐ days.

☐ The trial medication was discontinued permanently at DAY ☐☐ - MONTH ☐☐ - YEAR ☐☐☐☐

Please state reasons: _____

_____

6.2 If patient is treated with AC, what was the approximate INR at the time of the event? INR-value ☐.☐

6.3 Were there other changes in the patient's medication? no ☐ yes ☐

If yes, please fill in

drug	stop/start	indication

USE THE OUTCOME EVENT CHECK-LIST TO SUPPLY THE TRIAL OFFICE WITH ALL NECESSARY INFORMATION!

EUROPEAN ATRIAL FIBRILLATION TRIAL: NON-RANDOMISED ELIGIBLE PATIENTS

1. PATIENT

1.1 Surname _____ initials _.__.__

1.2 date of birth DAY - MONTH - YEAR

1.3 sex ☐ male ☐ female

1.4 randomizing physician

- name _____
- hospital _____
- city _____

2. CARDIAC STATUS

		no	yes
2.1	Atrial fibrillation		
	a. chronic AF	☐	☐
	b. paroxysmal AF	☐	☐
2.2	congestive heart failure	☐	☐
2.3	recent cardioversion	☐	☐

3. CARDIAC RISK FACTORS

- ☐ a. hypertension
- ☐ b. diabetes
- ☐ c. hypercholesterolemia
- ☐ d. angina pectoris
- ☐ e. intermittent claudication
- ☐ f. current regular smoking
- ☐ g. myocardial infarction

4. ANCILLARY INVESTIGATIONS

		no	yes
4.1	Chest X-ray, AP, heart ratio >1/2 (or > 500 ml/m^2 BSA)	☐	☐
4.2	Echocardiography, M-Mode - thrombus	☐	☐
	- enlarged (>40 mm) left atrium	☐	☐
4.3	Non-invasive investigation of the carotid arteries performed ?	☐	☐

If yes, please describe the results: _____

_____

_____

5. RANKIN HANDICAP SCALE (scored at the time that patient would have been randomized)

5.1
- ☐ 0 No symptoms
- ☐ 1 No significant disability despite symptoms: able to carry out all usual duties
- ☐ 2 Slight disability: unable to carry out some previous activities but able to look after own affairs without assistance
- ☐ 3 Moderate disability: symptoms which significantly restrict lifestyle and/or prevent totally independent existence (e.g. reuiring some help)

5.2 Has the patient suffered any intercurrent illnesses during the last follow-up period, that may have caused changes in the Rankin-score? ☐ no ☐ yes

If yes, which illness: _____

_____

6. REASONS FOR NOT RANDOMISING THE PATIENT

Please state clearly why this patient, although fully eligible, will not be randomized.

CT-scan form

Patient ID-number ☐☐-☐☐-☐☐☐

1.1 surname ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ initials ☐.☐.☐

1.2 date of birth DAY ☐☐ - MONTH ☐☐ - YEAR ☐☐☐☐

1.3 sex male ☐ female ☐

1.4 CT-scan no: ☐

1.5 Date of CT-scan DAY ☐☐ MONTH ☐☐ YEAR ☐☐☐☐

1.6 Scantype ☐

2. CONTRAST

O 1. made only without contrast
O 2. made with contrast
O 3. made with and without contrast

O a. with leakage of contrast
O b. no leakage
O c. dubious leakage

4. LESIONS

O 0. none
O 1. recent ischaemic lesions
O 2. old ischaemic lesions
O 3. ischaemic lesions of unknown date
O 4. haematoma
O 5. AVM
O 6. tumor
O 7. abces
O 8. hypodensity of the white matter
O 9. other,.....

3. QUALITY

O 1. no motion artefacts
O 2. light motion artefacts, assessment possible
O 3. light motion artefacts, no assessment possible

5. LOCALISATION I

O L. left hemisphere
O R. right hemisphere
O P. posterior fossa

6. LOCALISATION II

O a. vasc.territory a. basilaris
O b. vasc.territory a. cer. ant.
O c. vasc.territory a. cer. media
O d. vasc.territory a. cer. post.
O e. watershed inf. ant-med
O f. watershed inf. med-post
O g. watershed inf. deep-superf.
O h. uncertain

7. LOCALISATION III

O 1. complete vasc.territory 1 art.
O 2. partial vasc.territory 1 art.
O 3. vasc.territory > 1 art.
O 4. lac inf. ant. part capsula int.
O 5. id genu
O 6. id posterior part capsula int.
O 7. id corona radiata
O 8. id thalamus
O 9. id basal ganglia
O 10. id brainstem
O 11. id other (subcortical)
O 12. cerebellair infarction

8. HAEMORRAGHIC INFARCTION

O yes
O no
O uncertain

10. INTERVAL SYMPTOMS -> CT-scan

O 1. within 24 hours
O 2. 24-48 hours
O 3. 3 days
O 4. 4 - 7 days
O 5. 8 - 10 days
O 6. 11 - 14 days
O 7. 15 - 28 days
O 8. > 28 days

9. RELEVANCY

O 1. symptomatic lesions:
O 2. asymptomatic lesions:
O 3. lesions with uncertain relevancy:
O 4. not applicable, no lesions

EUROPEAN ATRIAL FIBRILLATION TRIAL

OUTCOME EVENT FORM DEATH

Patient's ID number :
Name :
Date of birth :
Date of outcome event :

VASCULAR DEATH

0 fatal M.I. : documented myocardial infarction followed by death. Death took place more than 1 hour after the onset of complaints.

0 fatal stroke : stroke causing an increase in handicap to Rankin scale 4 or 5, followed by death. It must be within reason to assume that the patient wouldn't have died if there had not been a history of stroke.

0 definite non-hemorrhagic ischemic stroke, CT-scan < 2 wks
0 probable non-hemorrhagic ischemic stroke, CT-scan > 2 wks
0 hemorrhagic ischemic stroke
0 CNS bleeding, other
0 no CT-scan made

0 definite sudden death: Sudden death in attendance of an eyewitness, with reliable observation of the time in relation to the onset of the complaints.

0 probable sudden death: Witness was present at death but there was no reliable observation of the time lapse between onset of complaints and death, or patient was found dead.

0 fatal congestive heart failure: death resulting from terminal left and/or right sided heart failure, in the absence of any other apparent cardiac cause of death.
0 fatal systemic embolism.
0 fatal non-CNS bleeding (GI-bleeding, hemopericardium etc.).
0 other (rupture of aortic aneurysm, pulmonary embolus, gangreneous extremities due to peripheral vascular insufficiency)

NON VASCULAR DEATH

0 infection : death caused by a primary manifest infection (unrelated to eg. stroke).
0 malignancy : death correlated to terminal malignancy
0 unnatural death : death through accident, criminal offence, suicide etc.
0 unknown cause : no information about confirmed death.

reviewed by:

date:

REASONS FOR CLASSIFICATION:

EUROPEAN ATRIAL FIBRILLATION TRIAL

OUTCOME EVENT FORM STROKE

Patient's ID number :
Name :
Date of birth :
Date of outcome event : Date of CT-scan:

The reported stroke should be classified as follows:

CLASSIFICATION

0 Definite stroke : characteristic symptoms and/or signs, with an increase of handicap at the time of the event.
- 0 definite non-hemorrhagic inf., CT-scan < 2wks, normal or showing infarct.
- 0 definite hemorrhagic inf. on CT-scan.
- 0 probable non-hemorrhagic inf., CT-scan > 2wks, no signs of resolving hemorrhage.
- 0 definite CNS bleeding other than hemorrhagic infarction.
- 0 no CT-scan made.

0 Possible stroke

0 No stroke

CLINICAL MANIFESTATION, 3 to 6 months after the event

0 Non-disabling : Rankin scale 0 or 1
0 Minor disabling : Increase of Rankin to scale 2 or 3
0 Major disabling : Increase of Rankin to scale 4 or 5.
0 Categorisation not possible due to other events influencing Rankin, within 3 months after stroke.
0 Not applicable, no stroke.
(Fatal strokes are audited on the "death outcome event" form)

reviewed by:

date:

REASONS FOR CLASSIFICATION:

EUROPEAN ATRIAL FIBRILLATION TRIAL

OUTCOME EVENT FORM CARDIAC EVENTS

Patient's ID number :
Name :
Date of birth :
Date of outcome event :

NEW MYOCARDIAL INFARCTION

0 DEFINITE : new Q wave / changed R wave on E.C.G and/or documented history of enzyme elevation (2 to 10 x normal value of SGOT, LDH and CPK(-MB)).

0 PROBABLE : typical pain, sustained elevation of ST segment on E.C.G., no documented enzyme elevation.

not included in analysis

0 POSSIBLE : sustained ST elevation on E.C.G., without pain or documented enzyme elevation.

0 ANGINA PECTORIS

0 NO myocardial infarction.

reviewed by:

date:

REASONS FOR CLASSIFICATION:

E.C.G.;

HISTORY OF ENZYME ELEVATION;

PATIENT'S HISTORY;

REMARKS;

EUROPEAN ATRIAL FIBRILLATION TRIAL

OUTCOME EVENT FORM — SYSTEMIC EMBOLISM

Patient's ID number :
Name :
Date of birth :
Date of outcome event :

CLASSIFICATION OF SYSTEMIC EMBOLISM

0 EXTREMITY EMBOLISM

0	DEFINITE:	Sudden onset of severe pain, pallor and absence of pulse in an extremity. Verified with peripheral pressure recordings, angiography and/or operation.
0	PROBABLE:	Typical clinical symptoms and verification by adequate physical examination. No angiography and/or peripheral pressure recordings. Examination was performed by a medical doctor.
0	POSSIBLE:	Clinical symptoms, no verification by physical examination, or no conclusive history recording.

0 MESENTERIC ARTERY EMBOLISM

0	DEFINITE:	Acute abdominal pain, located peri-umbilical or in right upper quadrant. Pain out of proportion to physical findings. Followed by vomiting and/or bowel evacuation. Confirmed by angiography or operation.
0	POSSIBLE:	Clinical symptoms but history recording not conclusive.

0 RENAL ARTERY EMBOLISM

0	DEFINITE:	Acute, non-radiating flank pain and any combination of the following symptoms: nausea, vomiting, sustained or transient hypertension, fever, non-specific leucocytosis, haematuria, proteinures, elevation of serum LDH and creatinin. Angiography, scintigram show arterial occlusion and/or ischaemic segment.
0	POSSIBLE:	Clinical symptoms, angiography not done. No possibility to exclude other pathogenesis.

0 OTHER SYSTEMIC EMBOLISM

Describe _____

_____

_____

0 PULMONARY EMBOLISM

0 NO EMBOLISM

SEVERITY OF EMBOLISM

0	TRANSIENT	symptoms disappeared over time without treatment or after treatment with anticoagulants.
0	MINOR	embolism removed by operative or interventional radiological procedure. No permanent organ damage.
0	MAJOR	embolism leading to permanent organ damage (e.g., limb loss)

Date: reviewed by:

REASONS FOR CLASSIFICATION: