CARDIOLOGICAL EVALUATION OF PATIENTS WITH A CEREBRAL ISCHEMIC EVENT: THE RELATION BETWEEN HEART AND BRAIN

CARDIOLOGICAL EVALUATION OF PATIENTS WITH A CEREBRAL ISCHEMIC EVENT: THE RELATION BETWEEN HEART AND BRAIN

Cardiologisch onderzoek bij patiënten met cerebrovasculaire accidenten:
de samenhang tussen hart en hersenen

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

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A list of investigators and participating centers of the Dutch TIA Trial can be found in the Appendix.

"Le coeur a ses raisons, que la raison ne connaît pas"
(Pensées 277, Blaise Pascal)

to Monica, Stefan and Carmen
to my parents

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CONTENTS

GENERAL INTRODUCTION

There are two major reasons for cardiological evaluation of patients with a cerebral ischemic event. First of all the heart may be the cause of this cerebrovascular event. Cardiac investigations can be directed towards finding a potential embolic source in the heart [1, 2, 3, 4, 5] or detecting causes of cardiogenic circulatory insufficiency leading to prolonged cerebral hypoperfusion [6]. Secondly, there is the fact that atherosclerosis is a generalized vascular disorder, which probably explains the existence of a strong association between cerebral and cardiac ischemic disease, as shown by many previous studies [7, 8, 9, 10, 11, 12]. Patients with a cerebral ischemic event have a high mortality rate (6% per year) and myocardial infarction is the most common cause of death among these patients [8, 13].

Treating a patient with a cerebral ischemic event without looking for possible cardiac causes, or without trying to prevent future cardiac events, can therefore not be justified. Bearing in mind the great number of patients in the Western world affected by cerebrovascular events [14, 15, 16], the social and financial savings for society would be tremendous if a rational, comprehensive and cost-effective plan for investigation and therapy with respect to the cardiological evaluation of these patients could be established. Such a plan is only feasible when neurologists and cardiologists collaborate. The following thesis is the result of such an interdisciplinary cooperation.

Chapter I discusses some basic medical principles and philosophical considerations that one should be aware of when studying the relationship between the brain and the heart. This introductory chapter also provides a survey of the results of cardiological evaluation of patients with cerebral ischemic events to date.

Chapters II and III deal with various cardiac investigations and their possible role in the detection of intracardiac causes of cerebrovascular accidents. In Chapter II transesophageal echocardiography is compared with precordial echocardiography with respect to its accuracy in detecting intracardiac sources of emboli in patients with TIA or minor ischemic stroke. Chapter III describes the value of transmitral flow analysis by pulsed Doppler for the identification of patients at risk of cardioembolic stroke in chronic non-valvular atrial fibrillation. Cardioembolic risk assessment may become quantifiable by means of this non-

invasive and relatively cheap technique and its quantitative results can be compared over a period of follow-up.

Chapter IV compares hemostatic parameters of patients with a cerebral ischemic event with or without atrial fibrillation and patients without previous cerebral ischemia.

In Chapter V the background and the design of the Dutch TIA Trial [17] are described.

In Chapters VI and VII the prevalence and predictive significance of clinical and electrocardiographic signs of ischemic heart disease are described in patients with a transient ischemic attack or minor ischemic stroke; the study population consisted of the patients who participated in the Dutch TIA Trial [17].

Finally a review of the current literature is presented in order to provide some insight into the question whether secondary prevention of major cardiac ischemic events may require a different dose of aspirin from that for secondary prevention of recurrent ischemic stroke (Chapter VIII).

The General Discussion, using the findings discussed in the previous chapters, intends to determine which cardiac investigations should be done in patients with a cerebral ischemic event and we dwell on the need of interdisciplinary cooperation in the diagnosis and treatment of patients with cerebral ischemia.

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CHAPTER I

INTRODUCTION

Atherosclerosis is a generalized vascular disorder, the etiology of which is not yet fully understood. Atherosclerotic cerebrovascular and coronary heart diseases are some of the greatest problems the national health services in the Western world are faced with. The cardiologist is concerned mostly with the aspects of atherosclerosis in the heart, whereas the neurologist deals with its manifestations in the brain. It is not surprising therefore, that a great overlap exists between the work of the neurologist and that of the cardiologist, when both are dealing with patients suffering from atherosclerotic disease. Supraspecialization in each of the two fields does not facilitate communication between these two specialists. Cooperation in the investigation of atherosclerotic manifestations in both specialties would probably disclose similarities as well as differences, which might bring about a better clinical understanding and consequently a more rational treatment of atherosclerotic disease both in the brain and in the heart.

Natural history studies of patients with a transient ischemic attack (TIA) or ischemic stroke have shown a 5% risk of death by ischemic heart disease per year, a rate which exceeds that of patients with angina pectoris [1, 2, 3, 4]. Patients with asymptomatic cervical bruits even have a higher risk of cardiac ischemic events than of stroke [5]. An ischemic event in the brain may also be the first manifestation of an already existing intracardiac embolic source, which in the Western world is mostly caused by ischemic heart disease (non-valvular atrial fibrillation, myocardial infarct, congestive heart failure) [6, 7, 8].

Diagnostic techniques in one field of atherosclerosis have proved their value for detection and prediction of ischemic events in the other field. Early studies of the Framingham group as well as some other more recent studies have shown that the ECG, quite a typical cardiological investigation, has a high predictive power for subsequent stroke in patients with cerebral ischemic events [9, 10]. In reverse, it has also been reported that electrocardiographic changes, arrhythmias, and even myocardial damage result from cerebro-vascular events [11, 12, 13].

Considering these correlations between heart and brain in atherosclerotic disease it is only to be expected that therapies for atherosclerosis both in (extra)cerebral and in coronary vessels have common aspects. An example is the secondary prevention with antiplatelet agents of cerebrovascular as well as coronary thrombotic events [14, 15, 16, 17]. Another example is the recent introduction of thrombolytic therapy in the acute phase of stroke [18, 19], which therapy has already been widely accepted by cardiologists because of its clear benefit in the acute phase of myocardial infarction [20].

Notwithstanding the similarities between atherosclerosis in the heart and in the brain, differences, of course, must exist, because heart and brain are different organs with different histology and physiology. It is not surprising therefore, that different regimens of treatment are used in both fields. However, it is not known whether some of these differences in treatment are based upon fundamental differences between specific properties of the heart vs. the brain or whether they are the consequence of a lack of communication between neurologists and cardiologists. Up till now for example, neurologists have generally used a dosage of 300 mg aspirin a day for the secondary prevention of cerebrovascular events caused by atherosclerosis [21], whereas most cardiologists use only 100-160 mg aspirin a day for the secondary prevention of coronary atherosclerosis [14]. This difference in dosage of aspirin may be caused by the difference in properties between the coronaries and the (extra-)cerebral arteries. Another reason for this, however, may be that these doses were established on the basis of large clinical trials which were designed separately in both fields.

The aim of this thesis is to approach the clinical and epidemiological aspects of patients with cerebral ischemic events, while recognizing the existence of heart-brain interactions in atherosclerotic disease [22]. The general idea is that the organism should be considered as a whole; the philosophical term for this idea is 'holism' [23, 24, 25]. In biology the holistic idea can be confirmed by the existence of generalized diseases such as atherosclerosis [26, 27, 28]. A cerebral ischemic event can be considered as a 'Gestalt'. This 'Gestalt' consists of a figure and a background [21]. In the figure the special or local relationship of atherosclerosis with one part of the organism is expressed: in cerebral ischemia the brain is the affected organ. The figure, however, may never be considered apart from its background. In brain ischemia, the background is formed by atherosclerosis existing in the whole organism; coronary sclerosis is part of this background. The extent to which the specific or local character of an event manifests itself, depends on the influence of the local event on the phenomenon as a whole and vice versa.

The appearance of cerebral or cardiac manifestations of atherosclerotic disease is not only determined by the individual response of an organism to the disease but also by the specialist who is looking at the individual patient. The neurologist and the cardiologist looking at the same symptoms see different things when examining a patient with brain ischemia, even if the cardiac symptomatology may be more serious and prognostically worse [24]. Recognizing the permanent interaction between heart and brain, interdisciplinary study and treatment of patients with brain ischemia may overcome some of the limitations that occur when each discipline examines those patients separately.

Recognizing and investigating heart-brain interactions in atherosclerotic disease will eventually lead to the development of a structural, common plan for diagnostic procedures and therapies for both the neurologist and the cardiologist in their treatment of patients with brain ischemia. The realization of such a common plan is not only mandatory because of the scientific-philosophic premise that the organism is a whole, but also for ethical reasons. Both the neurologist and the cardiologist are not treating an abstract illness but a sick individual, who is of course the same for both specialists. Treating a patient with brain ischemia without recognizing the relation to the heart and without trying to prevent probable future cardiac ischemic events besides recurrent stroke, cannot be justified. Recent studies revealed an increased incidence of stroke in the 1980s after a decline in the 1970s [29, 30] and no difference in survival after transient ischemic attacks during 2 years of follow-up between the 1970s and 1980s [31]. The incidence of stroke as well as the survival after stroke are strongly related to the heart, as stated before. In order to achieve a decline of stroke incidence and prolong survival after stroke in the 1990s; a thorough investigation of the cardiac status in stroke patients is needed; treatment of their coronary artery disease is indicated, maybe even if it is still asymptomatic [3, 22], as well as appropriate prevention of cardioembolism [7].

The heart as a possible cause of cerebral ischemic events

Cardiac causes of cerebral ischemic events are either the presence of an embolic source in the heart or the occurrence of cardiogenic circulatory insufficiency leading to prolonged cerebral hypoperfusion. The presence of an intracardiac embolic source can be suspected from the clinical history (for example, recent myocardial infarction), physical examination (for example, mitral stenosis) or from electrocardiography (for example, atrial fibrillation), but the clinical diagnosis is mostly limited [7] and cannot be made on the basis of neurologic

clinical criteria either [32]. It is thought, that one in six ischemic strokes can be attributed to cardiogenic embolism [6]. Visualization is necessary to confirm the presence of such an intracardiac source of embolism. The most practical and non-invasive tool for its detection is echocardiography [33]. Even after finding a cardiac source of embolism in patients with a cerebral ischemic event, 25% of these cases have coexistent other identifiable causes of stroke [6, 34]. Numerous studies have shown that very little additional information about a cardiac source of embolism is provided by precordial echocardiography if clinical examination and electrocardiography of patients with cerebral ischemic events did not reveal cardiac abnormalities already [6, 7, 8, 35, 36]. The routine use therefore, of precordial echocardiography in patients with a cerebral ischemic event does not seem necessary. Transesophageal echocardiography on the other hand has clear-cut potential advantages compared to precordial echo for the detection of intracardiac sources of embolism [37, 38, 39, 40]. It is, however, an invasive investigation and a strict indication for the cardiac work-up of patients with cerebral ischemic events still has to be established. When cerebral thromboembolism is suspected as coming from the heart or when neurological examination does not reveal extracardiac causes of stroke, transesophageal echo may be more useful than precordial echo and should certainly be considered in young stroke victims [7, 39]. Intracardiac thrombi are located mostly in the left atrium (especially in the left atrial appendage) [41, 42], which can be far better visualized by transesophageal than by precordial echo [37, 38].

The main cardiac causes of prolonged cerebral hypoperfusion are rhythm and conduction disturbances. Several studies have shown that these cardiac causes of cerebral ischemic events are relatively rare [43, 44]. It is not surprising therefore, that 24-hour Holter monitoring does not add much information compared with clinical examination and electrocardiography in the search for a cardiac cause of cerebral ischemic events [8, 35, 45]. Cerebral hypoperfusion from heart pump failure sometimes occurs during cardiac surgery, especially in patients with recent stroke [46], and can be prevented by adequate hemodynamic peroperative monitoring. A recent transesophageal study of Katz et al. [47], however, showed that not hypoperfusion but displacement and detachment of frail, protruding atherosclerotic material in the aortic arch appears to be the most important cause of stroke in patients undergoing cardiac surgery.

The association between cerebral ischemic events and ischemic heart disease

As stated above, the second important reason for cardiological evaluation of patients with cerebral ischemic events is the high prevalence of ischemic heart

disease in these patients, reflecting the fact that atherosclerosis is a generalized vascular disorder. The 6% per annum long-term mortality from heart disease among these patients is three times as high as the 1-2% annual mortality among comparably aged persons without heart disease [1, 3, 4]. It even surpasses the 3-4% per annum cardiac mortality among patients with angina pectoris. A transient ischemic attack or stroke should therefore not only be considered as a harbinger of cerebral infarction but also as a warning signal of death from myocardial infarction.

It is not yet known which patients with cerebral ischemic events are likely to suffer a major cardiac event. Patients with pre-existent cardiac ischemic disease will probably have the highest cardiac risk. The detection of ischemic heart disease depends on the specificity and sensitivity of the cardiac investigations. Thallium scintigraphy has been reported to detect signs of ischemic heart disease in almost 65% of patients with cerebro-vascular events [48]. Even in cerebrovascular patients without angina or previous myocardial infarction dipyridamole-thallium myocardial scintigraphy showed abnormalities in 60% of these patients. These abnormalities were prognostic for short-term perioperative cardiac complications [49]. Considering the high incidence of ischemic stroke in the Western world, the cost of routine thallium scintigraphy in all patients with stroke would be enormous. It is unknown whether the findings of cardiac thallium scintigraphy in stroke patients have more predictive power for cardiac events occurring in the months or years after the stroke, than other, more readily accessible, cardiac investigations [50]. Ideally, one should use the safest, most reproducible, and easiest method to detect associated ischemic heart disease in patients with stroke, and one should know whether patients with the highest cardiac risk can be identified by these screening tests. Also, in this era of cost containment, efforts should be directed towards effective and affordable screening tests.

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CHAPTER II

TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN THE DETECTION OF INTRACARDIAC EMBOLIC SOURCES IN PATIENTS WITH TRANSIENT ISCHEMIC ATTACKS

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Abstract

Using both precordial and transesophageal echocardiography, we studied 72 consecutive patients with a recent unequivocal transient ischemic attack or nondisabling stroke to determine the relative value of the two techniques for detecting potential intracardiac sources of cerebral emboli. Group 1 (n=53) patients had no clinical abnormalities, and group 2 (n=19) patients had abnormal cardiac findings on clinical examination. In group 1, precordial echocardiography detected an abnormality in only one patient (aortic valve thickening) but transesophageal echocardiography defined morphologic abnormalities in five patients (one with a left atrial appendage mass lesion, one with aortic dissection, one with mitral valve prolapse, one with a mitral leaflet mass lesion, and one with aortic valve thickening). In group 2, both precordial and transesophageal echocardiographic studies were normal in 13 patients, while both were abnormal in the remaining six patients. Five of these six patients had pathologic left atrial and/or left ventricular dilatation, but only transesophageal echocardiography defined a left atrial appendage thrombus in two of the six. The sixth patient had mitral chordal rupture, seen on both precordial and transesophageal echocardiography. In addition, in 32 of the 72 patients transesophageal echocardiography identified widespread thoracic aortic atherosclerotic plaques not visualized by precordial echocardiography. We conclude that transesophageal echocardiography significantly increases the yield in visualizing potential intracardiac sources of emboli compared with precordial echocardiography. However, the precise clinical value of the former in the management of such patients requires further study as the number of abnormal transesophageal echocardiographic findings is not high and a causative relation with transient ischemic attacks cannot be proven. (Stroke 1990; 21: 560-565).

Introduction

Cardiologic investigation of patients who have suffered a transient ischemic attack (TIA) or minor stroke is often undertaken because the heart can be the cause of the TIA. Until now, several methods of cardiologic investigation (clinical history, physical examination, electrocardiography, Holter monitoring, and two-dimensional precordial echocardiography) have been used in such patients. Previous studies have shown that the additional information provided by Holter monitoring [1, 2] and precordial echocardiography [2, 3, 4] is limited, and therefore these investigations should be requested only in appropriately selected patients [3, 5]. Two-dimensional precordial echocardiography in particular has

been shown to be of little value in those TIA patients aged > 45 years whose clinical cardiac findings are normal [2, 3, 4].

Compared with precordial echocardiography [6], transesophageal echocardiography has clear-cut potential advantages in the investigation of such patients since both the left atrium and appendage can be visualized [7], pathology of the ascending aorta and aortic arch can be detected [8], and good-quality images may be obtained in patients with problems such as emphysema, obesity, and assisted ventilation. However, this technique has a major disadvantage in that there may be inadequate visualization of the cardiac apex.

Because of the stated advantages, we compared the clinical values of transesophageal and precordial echocardiography in the cardiologic work-up of TIA patients.

Subjects and Methods

Seventy-two consecutive patients with recent TIA or minor stroke were admitted to the hospital for neurologic evaluation and subsequently entered into a prospective study carried out between May 1987 and March 1988. Twenty-four patients were female and the other 48 were men; their age varied between 24 and 73 years (mean 60.2). Two neurologists independently established a definite clinical diagnosis of TIA or non-disabling stroke [9] defined as the sudden onset of a focal neurological deficit in a specific vascular distribution. Patients with possible migrainous events, seizures and vague or non-focal neurologic symptoms were excluded.

All patients underwent computed tomography and laboratory investigations to exclude cerebral ischemia from causes other than artery-to-artery or cardiac embolism as well as disorders mimicking cerebral ischemia. Laboratory investigations included the erythrocyte sedimentation rate (if >30 mm/hr, then also antinuclear factor), hemoglobin, hematocrit, platelet count, fibrinogen, glucose concentrations, hepatic and renal function, and syphilis serology.

Of the 72 patients, 20 had a TIA and 52 a minor stroke. Sixty-three ischemic events were located in the territory of the carotid artery and the other nine in that of the vertebrobasilar artery. Carotid angiography was performed in 27 patients, who were all < 70 years of age and in whom cardiac investigations revealed no abnormality that could have caused the cerebral ischemic event.

The interval from the onset of neurologic symptoms until the cardiologic evaluation varied between 1 day and 3.5 weeks (mean 8 days). The cardiologic evaluation consisted of a clinical history and a physical examination, both carried

out by the same cardiologist, a 12 lead electrocardiogram and a chest roentgenogram.

After this cardiologic evaluation, we divided the patients into two groups. Group 1 patients had no cardiac abnormalities detected, and group 2 patients had cardiac abnormalities. Table 1 shows the criteria used for cardiac abnormalities. Group 1 (n=53) contained 15 patients with TIA and 37 patients with minor stroke; in group 2 (n=19), there were six patients with TIA and 13 patients with stroke.

Table 1. Cardiac abnormalities on clinical examination.

Investigation	Finding
Clinical history	Angina pectoris
	Previous myocardial infarction
	Heart rhythm disturbances requiring medical treatment
Physical examination	Signs of heart insufficiency
	Organic heart murmur
	Ventricular extrasystoles (>10/min.)
	Atrial fibrillation
Electrocardiography	Old myocardial infarction
	Ischemic repolarization disorders
	Atrial fibrillation
	Ventricular extrasystoles (>10/min.)
Chest roentgenography	Cardiac enlargement (cardiothoracic ratio >50%)

All 72 patients underwent precordial and transesophageal echocardiography on the same day, each by a different investigator. After obtaining informed consent, we recorded the precordial echocardiogram with a Toshiba SSH 65 A imaging system (Tokyo, Japan) using 2.5 and 3.75 mHz probes and performed transesophageal echocardiography using a 5.6-mHz phased-array transducer developed at the Thoraxcenter, Rotterdam (type HP-TEE) and interfaced with a Hewlett-Packard 7200 imaging system (Palo Alto, California). Introduction of the esophageal probe was performed after local anesthesia with a 5% lidocain topical spray. No prior sedation was given.

Transesophageal echocardiography was performed systematically and lasted generally for approximately 15 minutes. After introduction, we manipulated the probe until it was located in the stomach, and then we recorded a series of cross-sectional short-axis-of-the-left-ventricle views. The probe was pulled back within the esophagus until a proper four-chamber view was obtained. In this section we focussed attention on the mitral valve and its chordae and visualized the aortic

valve and the aortic root, orienting the probe superiorly. Further withdrawal of the probe superior placement allowed us to record a series of cross-sections through the left atrium just above the mitral valve. This manipulation allowed a complete evaluation of the interatrial septum and left atrial appendage, and with further manipulation good visualization of the main pulmonary artery was obtained. We then rotated the probe through 180 degrees toward the posteriorly located descending aorta. By pulling the probe slightly upwards, we were able to make sequential cross-sections of the descending aorta and ultimately scanned the aortic arch and ascending aorta.

Results

Transesophageal echocardiography was well tolerated in all 72 patients, with no resulting complications. One patient had bulbar palsy, but introduction of the probe in this patient produced no problems. Results are summarized in Table 2.

Table 2. Cardiac abnormalities detected by precordial and transesophageal echocardiography in 72 patients with transient ischemic attack or nondisabling stroke.

	Precordial		Transesophageal	
Group	Abnormality	*n*	Abnormality	*n*
1; No cardiac abnormalities on clinical examination (N=53)	Aortic valve sclerosis without stenosis	1	Aortic valve sclerosis without stenosis	1
			Left atrial appendage mass lesion	1
			Aortic dissection (localized in aortic arch)	1
			Mitral valve prolapse	1
			Mass lesion on mitral leaflet	1
			Ascending, arch and descending aortic plaques	22
2; One or more clinical cardiac abnormalities (N=19)	Left atrial and/or left ventricular dilatation	5	Left atrial and/or left ventricular dilatation	5
	Mitral valve chordal rupture	1	Mitral valve chordal rupture	1
			Left atrial appendage mass lesion	2
			Spontaneous echo contrast effect in left atrium	4
			Ascending, arch and descending aortic plaques	10

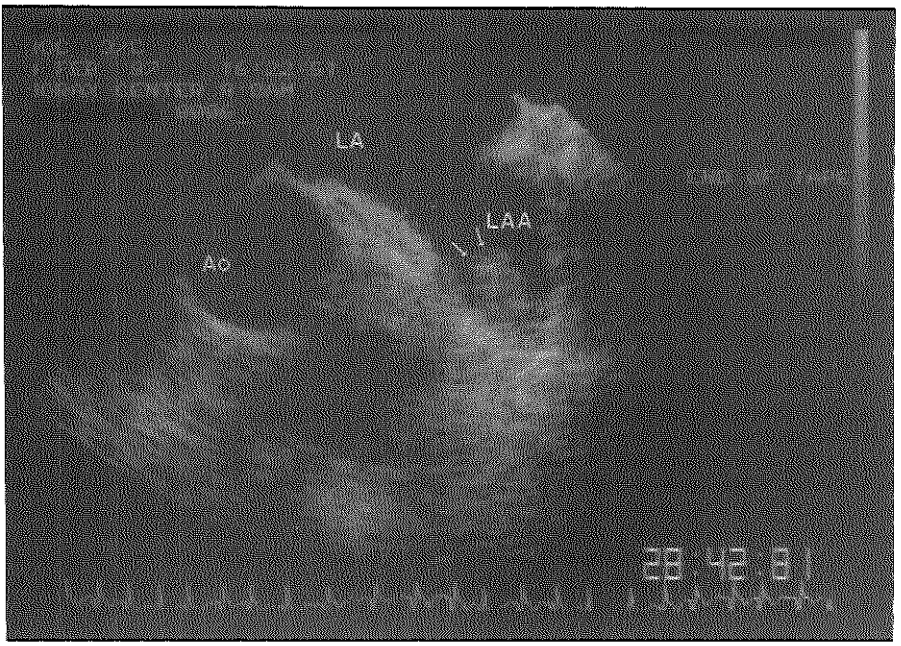

Figure 1. Transesophageal echocardiogram in patient with clinical cardiac abnormality. Mass lesion clearly visible in left atrial appendage, suggesting thrombus (arrows). Ao = aorta; LA = left atrium; LAA = left atrial appendage.

All 53 patients in group 1 had a normal precordial two-dimensional echocardiogram except for one patient who had abnormal thickening of the aortic valve. There was no increase in peak blood flow velocity over the aortic valve on Doppler examination in this patient. Transesophageal echocardiography revealed abnormalities that could predispose to TIA in five patients. These abnormalities consisted of a left atrial appendage mass lesion, a very localized dissection within the aortic arch, a mitral valve prolapse (in a patient < 45 years old), a mass lesion attached to the left atrial side of the posterior mitral leaflet, and thickening of the aortic valve in one patient detected also by precordial echocardiography. The patient with the left atrial appendage mass lesion had no history of atrial fibrillation, and the left atrium was not enlarged.

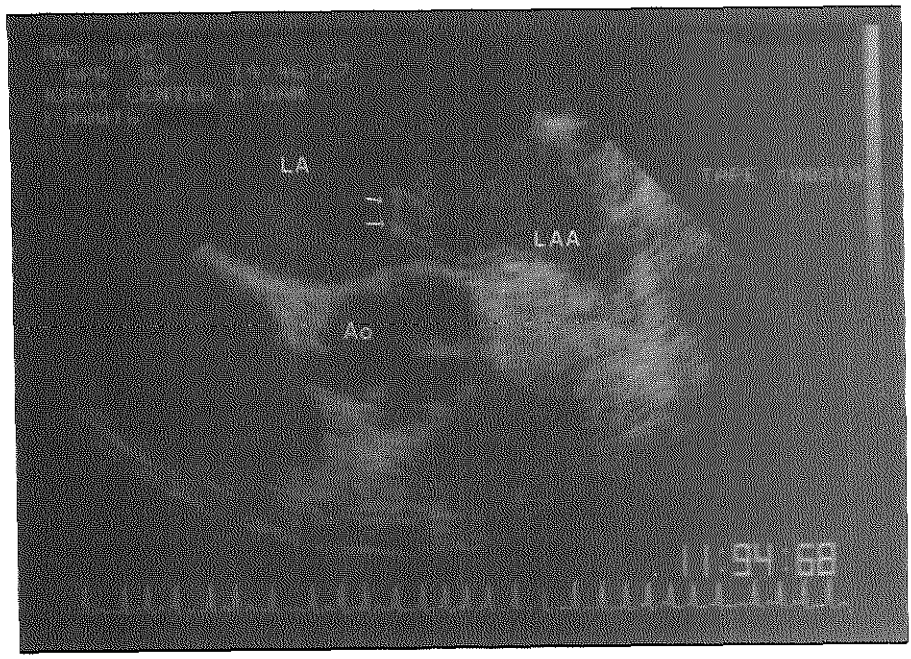

Figure 2. Transesophageal echocardiogram in patient with clinical cardiac abnormality. Spontaneous echo contrast effect indicating slow blood flow is present in left atrium (arrows). Ao = aorta; LA = left atrium; LAA = left atrial appendage.

Of the 19 patients in group 2, both precordial and transesophageal echocardiograms were normal in 13. Of the remaining six patients, five had left atrial and left ventricular dilatation on both precordial and transesophageal echocardiograms and were in atrial fibrillation. Transesophageal echocardiography detected a left atrial appendage mass lesion suggesting thrombus in two of these five patients (Figure 1), and in four of the five a spontaneous echo contrast effect indicating slow blood flow was seen (Figure 2). The sixth patient, known to have an old myocardial infarction, had a mitral chorda tendinea rupture of the anterior leaflet seen on both precordial and transesophageal echocardiography.

In group 1 as well as in group 2, precordial and transesophageal echocardiographic findings did not differ significantly between patients with TIA and those with minor stroke.

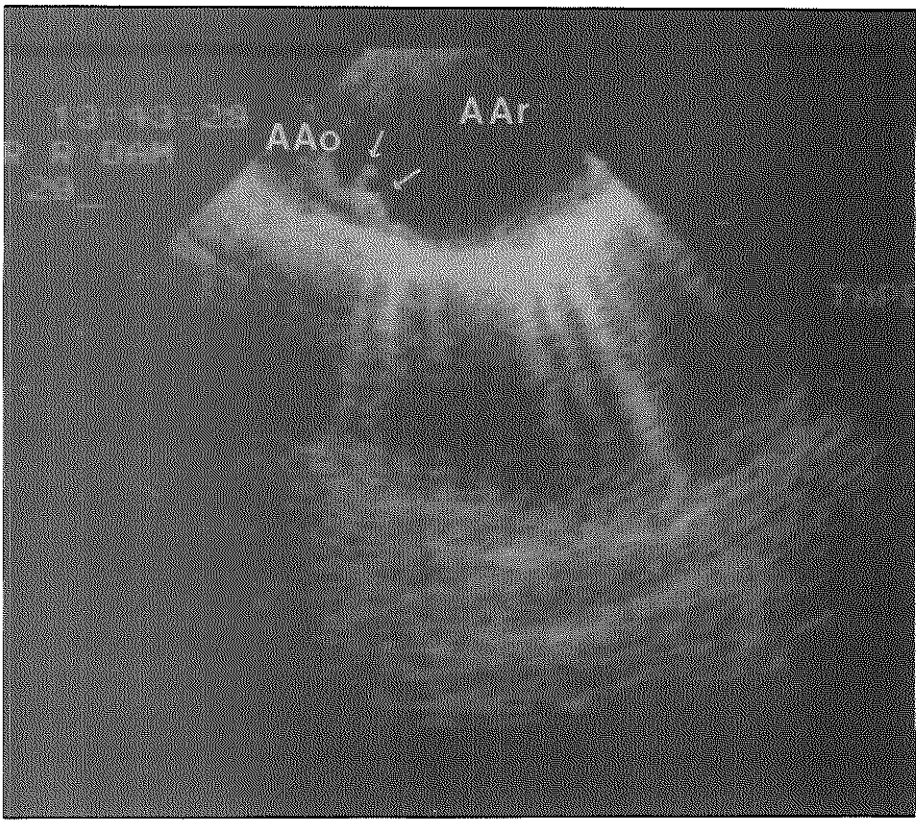

Figure 3. Transesophageal echocardiogram. Aortic wall irregularities (arrows) typical of atherosclerotic plaques. AAo, ascending aorta; AAr. aortic arch.

In 32 of the 72 patients, transesophageal echocardiography identified diffuse aortic wall irregularities typical of atherosclerotic plaques (Figure 3), confirming the frequent presence of associated vascular disease in TIA patients. In group 2, 10 of the 19 patients showed such aortic wall irregularities.

Discussion

Using transesophageal imaging, Daniel et al. [10] recently showed that the heart is a frequent potential source of systemic emboli. However, in patients with TIA or minor stroke, an intracardiac source of embolism is only one of the possible

causes. Atherosclerotic lesions in the intracranial or extracranial territories of the carotid or vertebrobasilar arteries can lead to artery-to-artery cerebral embolism and probably represent the major cause of cerebral ischemia.

It has been demonstrated that in TIA patients aged > 45 years precordial two-dimensional echocardiography does not offer additional information about possible intracardiac sources of emboli beyond that provided by the clinical cardiac examination [2, 3, 4, 5]. Half of all left atrial thrombi are limited to the appendage [11, 12, 13]. Precordial echocardiography rarely visualizes this structure, and the technique is especially insensitive in detecting appendage thrombi. This may explain its low yield of intracardiac thrombi in TIA patients. Transesophageal echo offers advantages for detecting mass lesions in the left atrial appendage [7] and ascending aorta [8] because the improved signal-to-noise ratio and increased frequency of the transducers lead to high-resolution, and high-quality images.

Among group 2 patients, transesophageal echocardiography detected a left atrial appendage mass lesion in two and a left atrial spontaneous echo contrast effect in four. The latter may be an indicator of increased thrombo-embolic risk [14]. These findings did not change our standard therapeutic management policy, which consisted of anticoagulation therapy in patients with significant dilatation of the left ventricle or left atrium. In TIA patients in group 1 (n=53), additional information potentially relevant for their management was found in five patients (10%) by transesophageal echocardiography, while precordial echocardiography was positive in only one patient.

The finding of mitral valve prolapse is of interest because this entity may have a role in cerebral ischemia, at least in patients < 45 years old [15], as in our study patient. Transesophageal echocardiography is especially valuable in distinguishing a benign mitral valve prolapse from a pathologic, complication-prone one. In the latter, subsequent sequential ultrasound studies of the mitral valve seem useful in predicting valve complications [2, 16].

Our results suggest that when echocardiography is considered in TIA patients without clinical cardiac abnormalities, they should undergo transesophageal rather than precordial echocardiography. These results agree with the findings of a recently published comparative study of precordial versus transesophageal echocardiography in young patients with TIA [17]. In TIA patients with some clinical cardiac abnormalities, precordial echocardiography often better evaluates the cardiac abnormality because of improved visualization. Transesophageal echocardiography may provide additional, purely morphologic information, but in every case where this occurred, the new information had no therapeutic consequences and gave no additional information compared with clinical examination and precordial echocardiography.

Our study had some definite limitations. Since it was not performed before the TIA, we may have missed the embolic source. Also, because of the delay between onset of the TIA and transesophageal echocardiography, any intracardiac thrombus could have been dissolved by anticoagulation therapy [18]. Another reason for the low yield of intracardiac thrombi may be that transesophageal echocardiography does not adequately visualize the left ventricle apex, where such thrombi can exist. However, small apical thrombi may be just as easily missed by precordial echocardiography. Recent publications [19] suggest a high prevalence (in some studies up to 20%) of a patent foramen ovale in patients with stroke. We began our study 1 year before these publications, and we did not carry out echo contrast and Doppler investigations of the atrial septum and left atrial appendage [20]. We think that it seems mandatory from now on to include such studies during tansesophageal echocardiogaphy to look for a patent foramen ovale and the possibility of paradoxical embolism.

In our study, transesophageal echocardiography showed 32 (44%) of the 72 TIA patients to have widespread atherosclerotic lesions in the aorta, which confirms the frequent presence of associated atherosclerotic vascular disease in TIA patients reported by other authors [21, 22, 23, 24]. Such atherosclerotic lesions in the ascending aorta and beginning of the aortic arch can cause an embolism, which gives rise to a TIA or minor stroke.

We conclude that in TIA patients without apparent clinical cardiac abnormalities, transesophageal echocardiography significantly increases the yield of potential intracardiac sources of embolism compared with precordial echocardiography. However, the overall yield of potential intracardiac sources of emboli detected by transesophageal echocardiography in these patients remained relatively small (10%), and it is not clear whether the findings were merely an associated abnormality or a direct cause of the TIA. Transesophageal echocardiography detected a higher percentage yield of potential intracardiac sources of emboli in TIA patients with a clinically apparent cardiac abnormality than in those with clinically normal cardiac findings. However, this extra clinical information was of little relevance to clinical decision-making in this series.

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CHAPTER III

PRECORDIAL ECHOCARDIOGRAPHY AND TRANSMITRAL DOPPLER ALLOW IDENTIFICATION OF PATIENTS AT RISK FOR CARDIOEMBOLIC STROKE IN CHRONIC NON-VALVULAR ATRIAL FIBRILLATION

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Introduction

Recent studies have indicated that 6% to 24% of ischemic strokes are associated with atrial fibrillation [1, 2, 3]. Population-based studies indicate a fivefold increased risk in patients with non-valvular atrial fibrillation (NVAF) when compared to their age-matched controls [4, 5, 6, 7]. Autopsy data support a cardiac source of embolism for the majority of these NVAF-related strokes, mostly a thrombus located in the left atrium [8, 9] and confined to the appendage in 50% of patients [10, 11]. Transesophageal echocardiography (TEE) allows excellent visualization of the left atrium and its appendage [12, 13, 14] and is currently considered the method of choice for assessment of cardioembolic risk in patients with NVAF. However, not all patients with NVAF carry the same risk of cardioembolic stroke. An enlarged left atrium carries a higher risk and can be detected by precordial echocardiography [15, 16] while transesophageal echocardiography indicates a higher incidence of cardioembolism in patients with spontaneous echocardiographic contrast in the left atrium (SCLA) [14, 17, 18]. Enlargement of the left atrium and/or SCLA are both reflections of impaired emptying of the left atrium. In the absence of mitral valve disease emptying of the left atrium is directly dependent on the diastolic function of the left ventricle. Transmitral flow analysis by Doppler technique is an excellent, non-invasive, and relatively simple method for assessing the diastolic function of the left ventricle [19, 20]. Abnormal transmitral flow patterns have also been found to be associated with the presence of left ventricular thrombi [21].

The aim of this study is to compare precordial and transesophageal echocardiography and transmitral Doppler velocity patterns in chronic NVAF patients with or without a TIA or ischemic stroke.

Methods

Study patients. Seventeen consecutive patients with chronic NVAF who had suffered a recent unequivocal transient ischemic attack (TIA) or minor ischemic stroke (group A) were compared with seventeen patients with chronic NVAF but without ischemic stroke (group B). Patients were matched by stratified sampling for age and sex. Group A consisted of 8 women and 9 men with a mean age of 72.9 years (sd. 5.9), group B of 8 women and 9 men with a mean age of 70.7 years (sd. 7.7) (table 1). Patients under 50 years of age, and patients with a significant degree of handicap (Rankin score ≥ 3) at the time of study, were excluded. Two neurologists independently established the definitive clinical diagnosis of TIA or non-disabling ischemic stroke, defined as the sudden onset of

a focal neurological deficit in a specific vascular distribution. Patients with possible migrainous events, seizures and vague or non-focal neurological symptoms were excluded.

Non-valvular atrial fibrillation (NVAF). Non-valvular atrial fibrillation (NVAF) was defined as presence of fibrillating atrial waves documented on ECG with absence of p-waves and no evidence of mitral valve disease by precordial echo-cardiography. Pulmonary venous flow patterns on TEE examination were used to exclude blunted systolic flow and/or reversed systolic flow [22]. Patients with a history of paroxysmal atrial fibrillation were also excluded. Chronicity of the atrial fibrillation was assumed on repeat documentation on two occasions with a 3 months interval. Considering the latest results of trials concerning anti-thrombotic treatment in patients with NVAF [23, 24, 25] and in order to match the two groups for factors which probably interfere with cardioembolic risk, patients treated with oral anticoagulants were not included.

Investigations. All patients in both groups underwent a cerebral CT-scan and laboratory investigations to exclude cerebral ischemia from causes other than artery-to-artery or cardiac embolism, and disorders that might look like cerebral ischemia. CT-scan was also performed to exclude patients, with silent brain infarction, which is not uncommon in NVAF patients [26, 27]. Laboratory investigations included the erythrocyte sedimentation rate (if over 30 mm per hour, then also ANF was measured), hemoglobin, hematocrit, platelet count, fibrinogen, glucose, hepatic and renal function, syphilis serology.

All patients underwent precordial two-dimensional (2D) and M-mode echocardiography with pulsed Doppler. With the subject in the left lateral decubitus position the anteroposterior diameter of the left atrium was measured in end-systole with 2D and M-mode by means of a left ventricular longitudinal projection through the left parasternal window. Measurements of the internal diameter and wall thickness of the left ventricle were made at end-diastole. Left ventricular mass was calculated with the following formula: Left ventricular mass (in grams) = $1.04\ ((LVID+VST+PWT)^3 - (LVID)^3 - 13.6$, where LVID denotes the left ventricular internal diameter, VST the ventricular septal thickness, and PWT the posterior wall thickness. To correct for differences in heart size in subjects of different body size, the left ventricular mass (in grams) was divided by the length (in meters). The cut off values for left ventricular hypertrophy were 143 g per meter in men and 102 g per meter in women [28].

Pulsed wave Doppler was performed with a Toshiba SH 165 using a 2.5 MHz transducer.

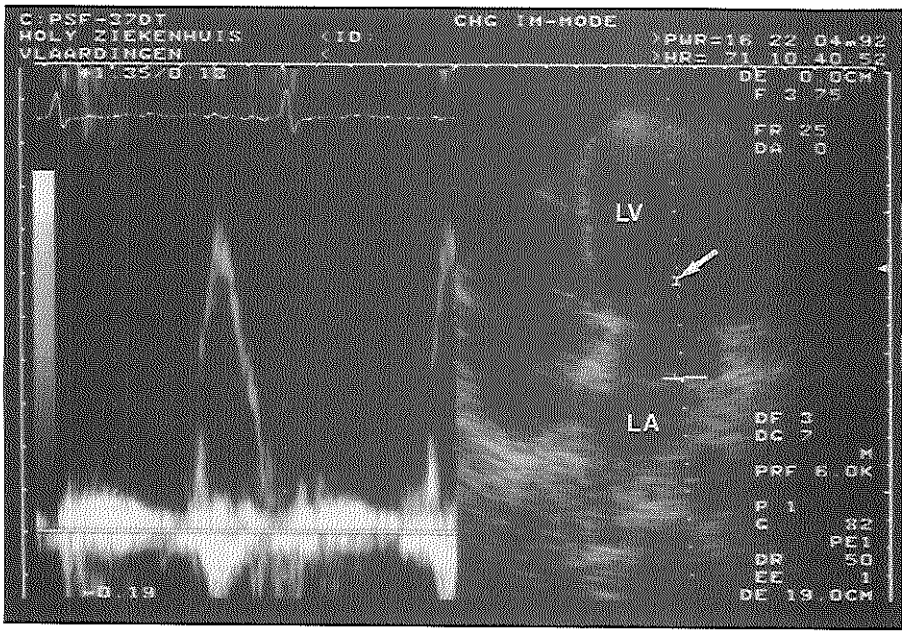

Figure 1. Precordial echocardiographic apical four chamber view and pulsed Doppler recording of transmitral flow with the sample volume placed at the tips of the mitral valve leaflets (arrow). LA= left atrium; LV= left ventricle.

Transmitral flow velocity was recorded with the sample volume placed at the tips of the mitral valve leaflets in the apical four chamber view (Fig 1) [19, 29]. The transducer was angled until flow signals demonstrating the greatest peak flow velocity were recorded. Recordings were made at a paper speed of 50 mm/s for velocity measurements. Flow velocity integrals, or areas in centimeters under the flow velocity curve, were calculated by a computer-aided digitizing system. The time velocity integral (TVI) of transmitral flow in diastole was determined at 10 different RR-intervals within one minute of registration and the results were plotted on a graph showing TVI (in cm) versus heart rate. For all patients TVI at a heart rate of 80/min was extrapolated from the line, which was the best fit of the TVI's at 10 different RR intervals within one minute of registration (fig 2). Patients with left ventricular thrombus on precordial echocardiography were excluded, because further TEE information in these patients generally would not change the therapeutic choice for oral anticoagulation.

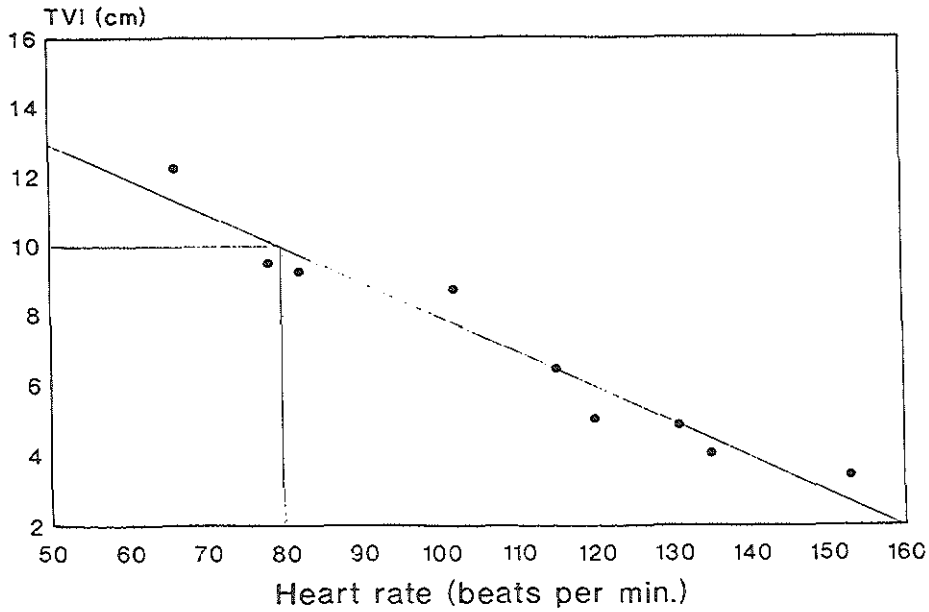

Figure 2. Time velocity integral of mitral inflow at 10 different heart rates, as measured by pulsed Doppler. TVI= time velocity integral.

A transesophageal echocardiographic study (TEE) was performed with a Toshiba SH 165 echocardiography imaging system using a 5-Hz transducer in all patients and this included an echo contrast study and a colour Doppler examination. Echo contrast study was done by peripheral venous injection of 0.9% NaCl solution to exclude a patent foramen ovale [30]. Special attention was given to the blood flow in the left atrial appendage, from which Doppler flow velocity measurements were done. The mean peak velocity in the left atrial appendage was calculated as the mean of peak velocities during 10 consecutive beats (fig 3). Left atrial spontaneous echo contrast was diagnosed when dynamic smoke-like echoes within the atrial cavity, with a characteristic swirling motion distinct from white noise artifact, were present; when spontaneous contrast was suspected, gain settings were decreased to exclude signal-to-noise artifacts [18, 31]. The presence or absence of spontaneous echo contrast was determined independently by two observers without knowledge of the clinical data. In all patients 24-hour ambulatory ECG monitoring was performed [32].

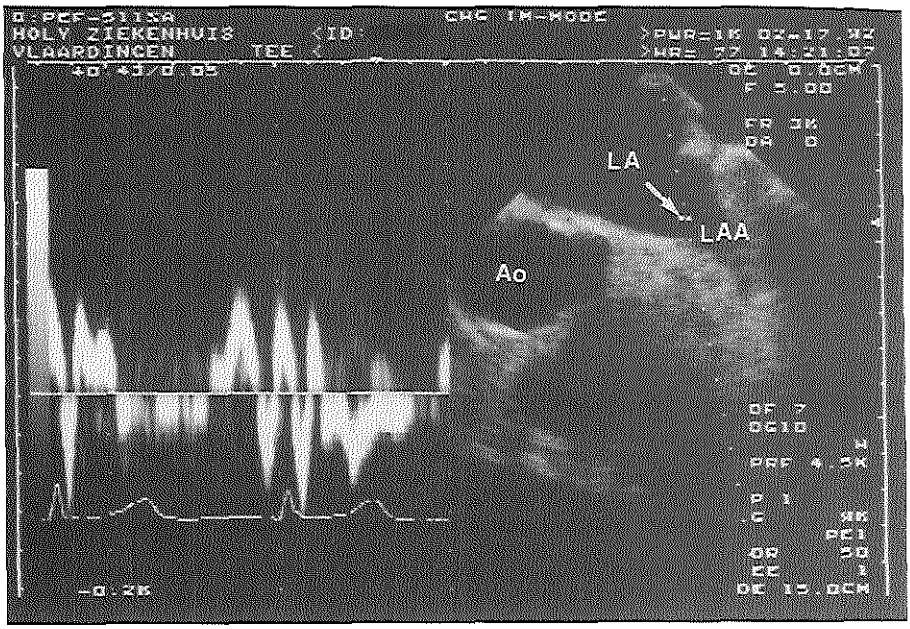

Figure 3. Pulsed Doppler flow measurements in left atrial appendage during transesophageal echocardio-graphy. The sample volume is located at the entrance of the atrial appendage (arrow). Ao= aorta; LA= left atrium. LAA= left atrial appendage.

Statistical methods. The baseline characteristics and echocardiographic findings in both groups were compared by means of the chi-square test for categoric variables and by means of the student T-test for continuous numeric variables. A p-value <0.05 was considered statistically significant.

Results

Clinical history, physical examination, chest X-ray and ECG did not reveal important differences between the two groups; results of 24-hour ambulatory ECG monitoring were also similar in both groups (table 1). The absolute or indexed end-systolic diameter of the left atrium did not differ significantly between the two groups. There were no significant differences with respect to end-diastolic left ventricular volumes or presence of left ventricular hypertrophy (table 2). Presence of spontaneous echo contrast effect in the left atrium (SCLA)

was more often seen by TEE in patients with minor ischemic stroke or TIA, than in patients without (9 pts versus 2 pts; p=0.028; table 2). TEE also identified diffuse aortic wall irregularities typical of atherosclerotic plaques in all the NVAF patients with a cerebral event, and only in 11 NVAF patients without a cerebral event (p=0.024; table 2).

Table 1. Baseline characteristics. Group A: NVAF pts with stroke or TIA and Group B: NVAF pts without stroke or TIA

	(group A) (n=17)	(group B) (n=17)	p
sex	8 women/ 9 men	8 women/ 9 men	
age	72.9 (SD:5.9)	70.7 (SD:7.7)	NS
Clinical History			
previous myocardial infarct	4	9	NS
angina pectoris	3	3	NS
previous heart failure	2	6	NS
history of hypertension	11	7	NS
peripheral vascular disease	1	0	NS
diabetes mellitus	2	3	NS
smoking	1	5	NS
Chest X-ray			
CT-ratio >50%	9	9	NS
Electrocardiogram			
infarct-pattern	1	3	NS
repolarization abnormalities	10	9	NS
LVH (Casale criteria)	7	6	NS
24-hour ECG monitoring			
ventricular pauses >2.5 sec	1	3	NS
short non-sustained ventricular tachycardias	3	4	NS

LVH= left ventricular hypertrophy; SD= Standard Deviation

In patients with SCLA the mean peak velocity in the left atrial appendage was significantly lower than in those without SCLA: 0.12 m/sec (SD=0.02) versus 0.21 m/sec (SD=0.05)(fig 4).

SCLA was not seen in any patient on precordial echocardiogram. However, when the diameter of the left atrium measured by precordial echo was combined with measurement of the mitral time velocity integral (TVI), all patients with SCLA had a corrected base-index LA-diameter of 24 mm or more and a TVI of less than 10 cm when corrected for a heart rate of 80/min (fig 5). SCLA was absent in 6 patients with left atrial size, corrected for base index, > 24 mm and time velocity integral of mitral inflow by pulsed Doppler < 10 cm. So, in our study, the sensitivity for detection of SCLA by precordial echo with pulsed Doppler was 100% and the specificity was 74%.

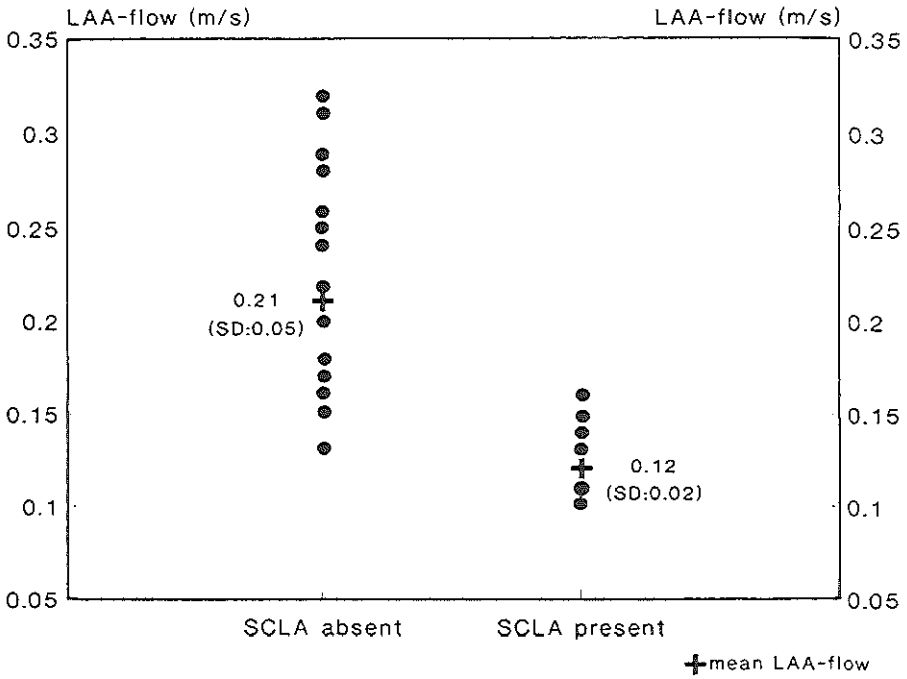

Figure 4: Relation between presence or absence of spontaneous echo contrast in the left atrium and mean peak velocity of flow in left atrial appendage. LAA-flow= mean peak flow velocity in left atrial appendage; SCLA= spontaneous echo contrast in left atrium.

Discussion

In this study, SCLA by TEE was significantly more common in NVAF patients with ischemic stroke than in those without cerebral ischemia (table 2). This finding is in agreement with results of recent TEE studies in NVAF patients with signs of cardioembolic stroke [17, 18]. SCLA reflects diminished blood flow velocity resulting in physical layering of red blood cells [18, 33, 34], both predisposing to thrombosis. In our study SCLA was indeed associated with diminished Doppler flow velocity in the left atrial appendage (fig 4).

Left atrial size is a poor risk marker of occurrence of cardioembolic stroke in NVAF patients [35, 36].

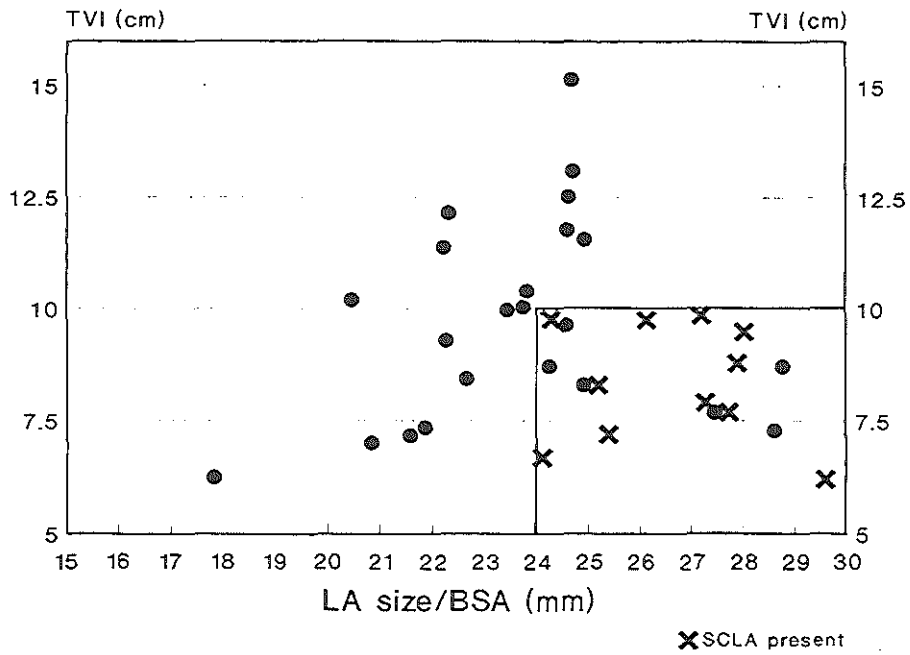

Figure 5: Relation between presence or absence of spontaneous echo contrast in the left atrium and combined measurement of left atrial size, corrected for base index, and time velocity integral of mitral flow at heart rate of 80/min. LA= left atrium; BSA= base indexSCLA= spontaneous echo contrast in left atrium.

Correction of left atrial size for base index or for height of the patient offers a simple yet more accurate means of assessment of normalcy of the left atrial dimension [37]. However, in our study this correction gave only a slightly better differentiation between patients with or without cerebral ischemia (table 2). Enlargement of the left atrium is considered to predict cardioembolism, since left atrial enlargement is an indirect sign of stasis of blood in the left atrium. Correction of the left atrial size for base index might be more appropriate, but besides this indirect structural characterization of stasis of blood in the left atrium, it seems more adequate to use Doppler flow analysis to estimate - on the basis of functional criteria - the presence of stasis in the left atrium. In the absence of stenosis of the mitral valve, stasis of blood in the left atrium is caused mainly by reduced left ventricular diastolic function resulting in elevated diastolic filling pressure causing incomplete emptying of the left atrium. Transmitral pulsed Doppler flow patterns are widely used for determination of left ventricular diastolic function and are indirect markers of elevated left atrial pressure [19, 20]. In a recent in vitro model of mitral filling Flachskampf et al. demonstrated that the stiffer the atrial and ventricular chambers, the more rapid the deceleration of transmitral flow [38]. Our finding of a correlation between reduced TVI and SCLA is in accordance with their results. On the basis of our findings, we propose to use TVI as criterium of flow stasis predisposing for thrombus formation in the left atrium. An earlier pulsed Doppler flow study showed a strong association between decreased ventricular inflow velocities and presence of left ventricular thrombus [21]. Correlation between TVI and left atrial flow does not exist in the presence of mitral valve pathology and in our study these patients were excluded.

Combining the determination of increased base index corrected left atrial size with low transmitral blood flow velocity gives a good correlation with presence of SCLA by TEE with sensitivity of 100% and specificity of 74% (fig 5).

TEE is a semi-invasive relatively expensive investigation and NVAF has a high prevalence in the western world, especially in the elderly. If measurement of left atrial size combined with TVI would allow reliable identification of NVAF patients with increased cardioembolic risk, then precordial echocardiography with pulsed Doppler is a more practical method in NVAF patients and obviates the need for TEE studies. Moreover, absence of an intracardiac thrombus on TEE will not exclude the possibility that a cardiac thrombus has just been embolized or small intracardiac thrombi are missed on TEE [39].

Table 2. Differences in precordial and transesophageal echocardiographic findings and Doppler flow measurements. Group A: NVAF patients with stroke or TIA and Group B: NVAF patients without stroke or TIA

	Group A (n=17)	Group B (n=17)	p
Precordial echocardiography			
endsystolic LA-size (mm)	48.4(SD: 4.6)	45.1(SD: 3.4)	NS
LA-size corrected for base index	2.56(SD:0.23)	2.37(SD:0.27)	NS
enddiastolic LV-size (mm)	55.9(SD: 6.0)	65.0(SD: 7.4)	NS
LVH (gr/m)	166.5(SD:40.0)	143.0(SD:33.2)	NS
mitral TVI (cm)	9.06(SD:2.24)	9.51(SD:1.98)	NS
Transesophageal echocardiography			
spontaneous contrast in LA	9	2	0.028
thrombus in LA	3	0	NS
patent foramen ovale	0	0	NS
aortic wall irregularities	17	11	0.024
mean peak velocity LAA (m/s)	0.17(SD:0.06)	0.20(SD:0.07)	NS

LA= left atrium; LAA= left atrial appendage; LV= left ventricle; LVH= left ventricular hypertrophy; SD= standard deviation; TVI= time velocity integral.

Estimation of mitral TVI corrected for a pre-determined heart rate, and measurement of left atrium size do not only require less sophisticated investigation, but also allow assessment of cardioembolic risk in NVAF patients in a more quantitative and standardized way during follow-up. Detection of SCLA by TEE is a subjective way of describing stasis in the left atrium, and depends on the definitions used and on the gain setting of the echocardiography-machine. This causes considerable inter-observer variability, limiting comparison of repetitive measurements over time.

Measurement of TVI combined with left atrium size by standard precordial echocardiography with pulsed Doppler would be practical in large clinical trials evaluating optimal antithrombotic prophylaxis in NVAF patients. NVAF patients with a combination of low TVI and large LA might profit most from oral

anticoagulant treatment whereas aspirin or other antiplatelet therapy may prove to be insufficient in these patients as the mechanism of cardioembolic risk is blood stasis. Prevention of thrombosis by stasis of blood is probably better achieved with anticoagulants than with antiplatelet-drugs [40]. As altered Doppler diastolic mitral flow profile is suggested to be a primary biologic effect of ageing [41], this may be the explanation why in the SPAF-study patients over 75 years appeared to benefit less from aspirin [42]. However, long-term use of oral anticoagulant therapy, especially in elderly patients, is not without bleeding risk [43]. The net gain or loss in efficacy rate of anticoagulant treatment in patients with NVAF depends not only on the expected risk reduction of stroke, but also on the major bleeding rate [23, 44]. With further use of combined measurements of TVI and LA-size it might be possible to determine cut-off points of cardioembolic risk, where antiplatelet therapy should be replaced or supplemented by anticoagulant therapy. The effect of anticoagulant therapy might even be reflected by changes in TVI, as anticoagulation could diminish blood viscosity thereby increasing blood flow velocity [34, 45].

The significantly higher prevalence of aortic wall irregularities detected by TEE and typical for atherosclerosis, in the NVAF patients with stroke or TIA, suggests that these patients not only have a higher risk for cardioembolic events when compared to the NVAF patients without cerebral event, but they also harbour more extensive atherosclerotic disease. Thus, the chance of artery-to-artery embolism from carotids [46] or the aortic arch [47, 48] may also be higher in NVAF patients with cerebral ischemic events. This suggests that combined treatment of oral anticoagulation with an antiplatelet regimen could be the treatment of choice for the secondary prevention of stroke in NVAF patients after the occurrence of a cerebral ischemic event.

Limitations of the study. A potential critique may be that the use of NVAF patients without previous stroke as control group for cardioembolic risk assessment, does not exclude the possibility that some of these patients may have a stroke in the near future. During a mean follow-up of 12 months, however, no NVAF patient in the control group suffered a cerebral ischemic event.

The other limitation of our study is that not all strokes may have been of cardioembolic origin. Clinical criteria for the diagnosis of stroke by cardiogenic embolism are unreliable [49, 50, 51, 52]. However, autopsy data revealed a cardioembolic cause in 75% of NVAF patients with stroke [8]. Some strokes in our patients could have been caused by artery-to-artery embolism, mainly from the carotid arteries or from the aortic arch [47, 48]. This seems a reasonable assumption when considering the high prevalence of aortic wall irregularities detected by TEE.

Despite the potential critique and limitations mentioned above and the small size of our study population some significant differences were found. Larger prospective studies in NVAF patients will be needed to strengthen our observations.

Clinical relevance. Our study suggests that TEE is the method of choice for detection of spontaneous echo contrast in the left atrium (SCLA), which in our study as well as in that of others was found to be significantly correlated with the occurrence of cardioembolism in patients with NVAF. However, precordial echocardiography with pulsed Doppler including combined measurement of left atrial size, corrected for base index, and time velocity integral of the mitral flow at a normalized heart rate, is sensitive and specific for presence of SCLA. Cardioembolic risk assessment in patients with NVAF may become quantifiable based on functional parameters from precordial echo/Doppler investigation. It has the advantages of being non-invasive, cheaper and more versatile; it can be performed routinely during follow-up and, the quantitative results can therefore be compared on a regular basis.

The higher prevalence of diffuse aortic wall irregularities, typical for atherosclerosis, in patients with NVAF and ischemic stroke or TIA compared with its prevalence in NVAF patients without cerebral ischemic events suggests a more extensive atherosclerosis in the former patients. Thus not only the cardioembolic risk but also the risk of artery-to-artery embolism from carotids or aortic arch seems to be higher in these patients.

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CHAPTER IV

HEMOSTATIC ACTIVITY IN PATIENTS WITH A TRANSIENT ISCHEMIC ATTACK OR MINOR ISCHEMIC STROKE, WITH OR WITHOUT CHRONIC NON-VALVULAR ATRIAL FIBRILLATION

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Introduction

A cerebral infarct in patients with non-valvular atrial fibrillation (NVAF) is considered to be caused by cardiogenic embolism in 50-71% of the cases [1, 2]. Cerebral thrombo-embolic events from artery-to-artery embolism are probably also common; as NVAF is more prevalent in the elderly, carotid lesions are often found in the same patient [3] and NVAF is often a marker of atherosclerosis in general [4].

Not all patients with chronic NVAF have the same risk of stroke. In recent studies, clinical features such as congestive heart failure, previous arterial thromboembolism and history of hypertension were shown to be associated with a high risk of thromboembolism to the brain [5]. Other risk factors for thromboembolism can be identified in these patients with standard precordial echocardiography by measurement of the adjusted left atrial size and the left ventricular function [6]. Hemostatic disorders may also predispose to cardioembolism [7, 8]. A recent study suggested that in patients with acute cardioembolic stroke increased levels of markers of hemostatic activity are useful indicators of recurrent embolization in the near future [9]. Increased plasma levels of thrombin-antithrombin III complexes (TAT) and prothrombin fragment 1+2 (F1+2) have been shown to be sensitive markers for thrombotic activity in humans, and laboratory tests for the measurement of these factors have recently become available [7, 10, 11, 12].

The aim of our study was to determine and compare the prevalence of hemostatic hyperactivity, defined by increased levels of TAT and F1+2, in 4 groups of patients: patients with or without transient cerebral ischemia, both with or without chronic NVAF. Comparison of these 4 groups may result in the identification of a subset of patients with atrial fibrillation and an increased risk of cerebral ischemia.

Subjects and methods

We defined the 4 patient groups as follows. Group A consisted of NVAF patients with recent TIA or minor ischemic stroke. Five patients were female and 9 patients were male and their average age was 73.4 years (SD 4.3). The diagnosis of TIA or minor ischemic stroke was independently established by two neurologists. CT scan and laboratory analysis were performed to exclude non-ischemic causes of the neurological deficit. Patients were included only if they were independent in activities of daily life, because in patients who are (partially) immobile the analysis of hemostasis might be influenced by venous thrombosis. Groups B, C and D were the control groups, which were matched for age and

sex. The first control group (group B) consisted of 14 patients with recent minor stroke or TIA, who were in sinus rhythm; 6 patients were female and 8 were male and their average age was 67.6 years (SD 5.4). Clinical history revealed no attacks of rapid, irregular palpitations, and 24-hour ambulatory electrocardiographic recording in these patients did not show episodes of paroxysmal atrial fibrillation. Rankin scores and CT-scan lesions found in this control group did not differ from those in the NVAF patients with recent cerebral ischemia (group A). Group C consisted of 14 patients with chronic NVAF with neither a clinical history of TIA or minor stroke, nor of peripheral arterial embolism. There were 6 females and 8 males in this group and their average age was 71.4 years (SD 6.4). All patients in group C were examined by a neurologist and a CT-scan was performed to exclude the presence of 'silent' brain infarcts, which is not uncommon in chronic atrial fibrillation [13]. The third control group (group D) was used as reference group to represent normal individuals, matched for age and sex, with neither previous cerebral ischemic event nor atrial fibrillation. This group consisted of 14 elderly volunteers, who visited the dermatology outpatient clinic of our hospital for minor skin lesions. There were 6 females and 8 males in this group and their average age was 70.0 years (SD 5.6). The volunteers had no clinical history of coronary or cerebrovascular events and used no medication. CT-scans were not performed in these patients. None of the patients in group D had signs of previous myocardial infarction or repolarization abnormalities on a standard 12 lead electrocardiogram at rest.

Two blood samples were taken at different times in all patients. In the patients with recent cerebral ischemia (groups A and B) blood samples were taken one and two months after the cerebral ischemic event in order to avoid hematological abnormalities caused by the acute event itself. Venous blood was collected atraumatically from an antecubital vein with minimal stasis by means of a 19-gauge butterfly; blood was drawn in plastic syringes containing 3.8 % sodium citrate (9:1, v/v). Plasma for hemostatic analysis was obtained immediately by centrifugation and stored at -20 °C until the time of measurement. The plasma concentration of prothrombin fragment 1+2 (F1+2) was measured by means of the commercially available immunoassay Enzygnost F1+2 (Behringwerke AG, Germany). Thrombin-antithrombin III complexes (TAT) in plasma were measured with Enzygnost TAT (Behringwerke AG, Germany), an enzyme-linked immunosorbent assay (ELISA). The reference range of TAT concentrations for normal subjects, established in earlier reports [14], is 1.0-4.1 ng/ml; for F1+2 the reference values are 0.44-1.11 nmol/l [15]. Other hematological and hemostatic measurements were also performed: such as hematocrit, hemoglobin, thrombocytes, fibrinogen, bleeding time and APTT. The laboratory personnel was unaware of the patient's group assignment.

All patients in groups A, B and C were already on longterm treatment with aspirin or had been put on it after their cerebral ischemic event (groups A and B); the doses varied between 80 and 300 mg/day. Patients on oral anticoagulants were not included because of the known effect of these drugs on hemostasis [26]. In group D, all patients were asked to take 80 mg of aspirin a day for 5 days, after a loading dose of 160 mg on day 1. Blood samples for hemostatic analysis were taken before and after these 5 days of aspirin ingestion. In all patients of groups A, B and C, precordial echocardiography was performed; patients in whom an intracardiac thrombus was found, were excluded from the study because they were subsequently put on oral anticoagulation.

Informed consent. This study and informed consent procedure were approved by the Committee of Ethics of the Holy Ziekenhuis Vlaardingen.

Statistical methods. We used the paired T-test to see whether the first and second plasma measurement within the groups differed. Student T-test was used in all other comparisons. A two-sided p-value < 0.05 was considered statistically significant.

Results

No statistically significant differences were found between the TAT and F1+2 levels at first and second measurement in the patients with recent TIA or minor ischemic stroke, whether in atrial fibrillation or sinus rhythm (Fig 1 and Fig 2). In group A the mean TAT value at first measurement was 3.01 versus a second mean TAT value of 2.56 ng/ml (p=0.35); the first mean F1+2 value was 1.44 versus a second mean F1+2 value of 1.23 nMol/l (p=0.08). In group B the first mean TAT value was 3.44 versus a second mean TAT value of 2.70 ng/ml (p=0.36); the first mean F1+2 value was 1.67 versus a second mean F1+2 value of 1.43 nMol/l (p=0.19). When the first and second measurements of TAT and F1+2 were combined for both groups with cerebral ischemia, no statistically significant difference was found between patients with or without NVAF: the mean TAT value in group A was 2.79 versus 3.07 ng/ml in group B (p=0.55) and the mean F1+2 value in Group A was 1.33 versus 1.55 nMol/l in group B (p=0.28). In control patients without cerebral ischemia, again no differences in TAT and F1+2 levels could be found between patients with atrial fibrillation or in sinus rhythm: mean TAT in group C was 2.74 versus 2.42 ng/ml in group D (p=0.21), and mean F1+2 in group C was 1.05 versus 0.92 nMol/l in group D (p=0.14).

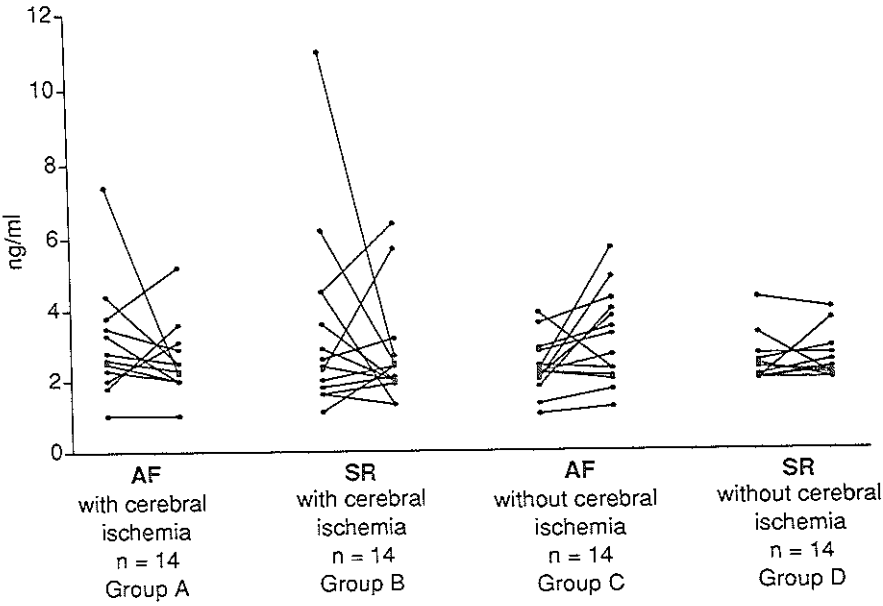

Figure 1 TAT levels at first and second blood sampling in the four different groups. AF=atrial fibrillation; SR=sinus rhythm.

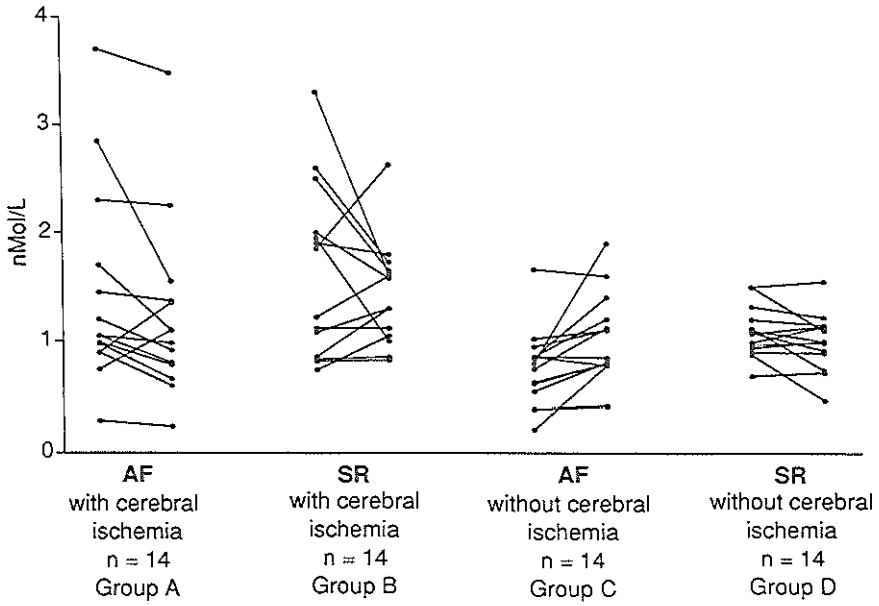

Figure 2 F1+2 levels at first and second blood sampling in the four different groups: AF=atrial fibrillation; SR=sinus rhythm.

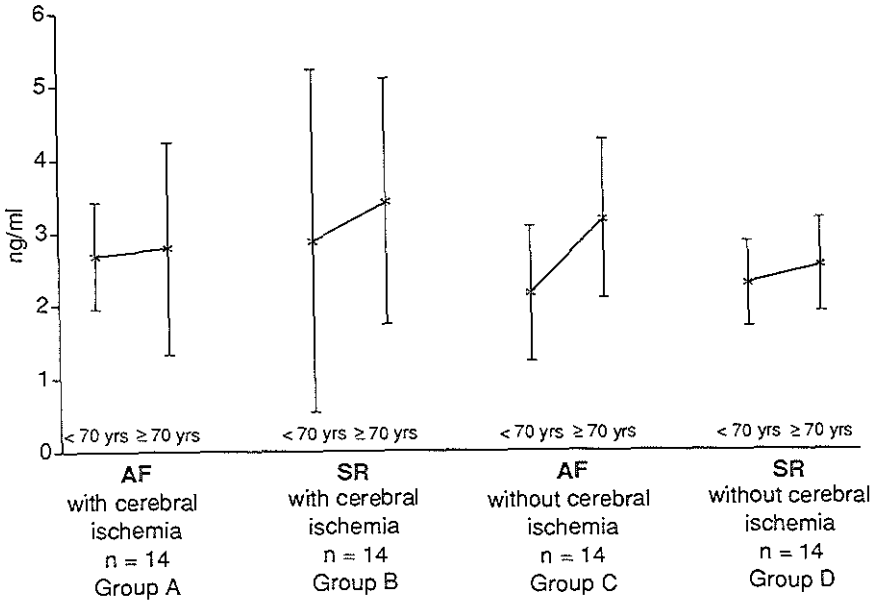

Figure 3 Mean values of TAT in the four different groups according to age (under and over 70 years) AF=atrial fibrillation; SR=sinus rhythm.

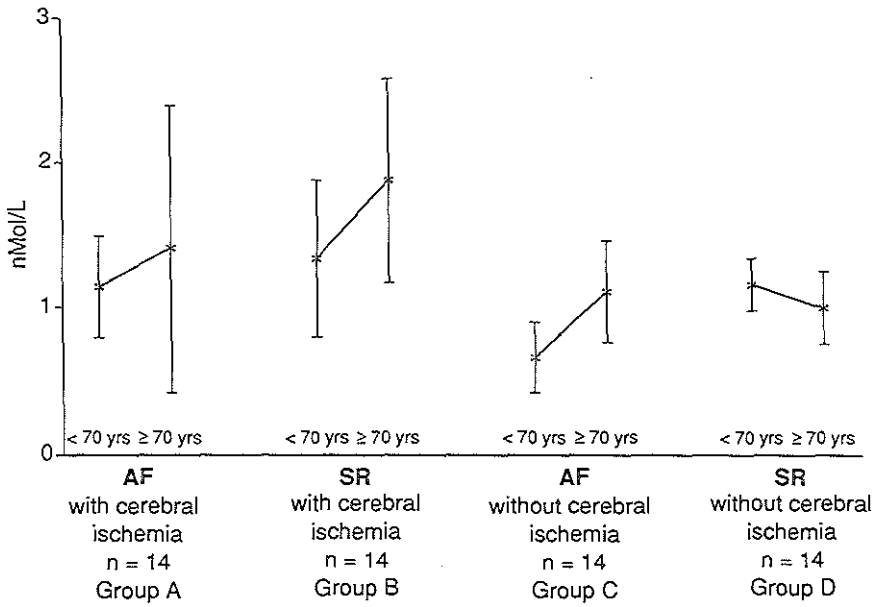

Figure 4 Mean values of F1+2 in the four different groups according to age (under and over 70 years) AF=atrial fibrillation; SR=sinus rhythm.

In control group D, TAT and F1+2 plasma levels did not change significantly before and after ingestion of 80 mg aspirin/day over a period of 5 days. The mean TAT value was 2.35 and 2.49 ng/ml (p=0.43), and the mean F1+2 value was 1.09 and 1.00 nMol/l (p=0.10) resp.

When all patients with recent cerebral ischemia (groups A and B) are compared with all patients without history of previous cerebral ischemia (groups C and D), irrespective of their cardiac rhythm, significantly higher F1+2 values were found in the former group (mean F1+2 1.44 versus 0.98 nMol/l; p<0.001). The TAT values did not differ significantly between patients with or without previous cerebral ischemia (mean TAT 2.93 versus 2.58 ng/ml; p=0.19).

In patients with NVAF taken separately, a significantly higher level of F1+2 was found also if previous cerebral ischemia had occurred; mean F1+2 level in group A was 1.33 versus 0.92 nMol/l in group C (p=0.02). No significant differences were found between the mean TAT values of groups A and C (2.79 versus 2.74 ng/ml; p=0.87).

If patients were divided according to age, those over 70 yrs in all groups had higher mean values of TAT (2.90 ng/ml) than those under 70 yrs (2.57 ng/ml); this difference was not statistically significant (p=0.24) (Fig 3). The mean levels of F1+2 were also higher in patients over 70 yrs (1.32 nMol/l) than in those under 70 yrs (1.07 nMol/l). This difference was statistically significant (p=0.03) (Fig 4), in group D alone however, the values seemed to be similar for both age-groups.

Discussion

We found hemostatic activity that may indicate a prethrombotic state in a proportion of patients one or two months after a transient ischemic attack (TIA) or minor ischemic stroke, irrespective of whether they had chronic non-valvular atrial fibrillation or sinus rhythm [8, 16, 17].

Earlier studies also showed that levels of markers of hemostatic activity were increased in some patients with cardioembolic stroke, especially in those with recurrent embolism [9]. Several other investigators also reported a strong relationship between atherosclerosis and hemostatic activity [17, 18, 19]. This may explain why we found similar hemostatic abnormalities in stroke patients with atrial fibrillation or sinus rhythm, despite a possible difference in the pathogenesis of stroke; in patients with atrial fibrillation cerebral ischemia is mostly attributed to cardioembolism, whereas the cause of stroke in patients with sinus rhythm but without cardiac source of potential embolism is thought to be

mainly artery-to-artery embolism [2, 20]. On the other hand, our findings may also indicate that the cause of a TIA or minor stroke in NVAF patients is not only cardioembolic, but may also result from artery-to-artery embolism as in stroke patients without apparent source of cardioembolism. Our findings suggest a relation between hemostatic activity and the degree of atherosclerosis by the age-related increase of hemostatic markers F1+2 and TAT in the different patient groups (figure 3 and 4), since atherosclerosis is strongly dependent on age. Ono et al. also found an age-related increase in TAT and other hemostatic marker levels [21]. The normal distribution for TAT, F1+2, and probably for other recently developed markers of hemostatic activity should therefore be corrected for age.

In our study patients F1+2 levels were more often increased than TAT levels in patients with recent cerebral ischemia; F1+2 might be a more sensitive marker for hemostatic activity in these patients than TAT. A higher sensitivity of F1+2 compared with TAT as a marker for prethrombotic state has been suggested in earlier reports [22, 23].

The strong relationship between increased levels of markers for hemostatic activity and age might explain to some extent why aspirin compared with anticoagulants did not show any significant benefit for secondary prevention of stroke in two large clinical trials in patients with NVAF over 75 yrs [24, 25]. It is not likely that aspirin will have a significant effect on the cleavage of the prothrombin molecule by activated factor X, which is the process actually measured in the determination of F1+2 levels [15]. The F1+2 and TAT values of the volunteers in our study (group D) did not significantly change after ingestion of 80 mg aspirin for 5 days. The value of this finding, however, is limited by the fact that aspirin was taken for only a few days and by the normal values at onset of hemostatic parameters in this group.

Several large clinical trials in patients with non-valvular atrial fibrillation have demonstrated the efficacy of oral anticoagulants in the prevention of stroke in NVAF patients [24, 25]. Other studies have shown a marked decrease of F1+2 levels in patients who were anticoagulated with warfarin or heparin [11, 26]. If F1+2 is indeed a strong marker for hemostatic activity, and if increased hemostatic activity predicts recurrent stroke [17, 27], then one of the reasons for the greater benefit of anticoagulants, compared with aspirin, for secondary prevention in NVAF patients with previous TIA or minor ischemic stroke could be the presence of increased hemostatic activity in at least a subset of these patients. Our findings also provide a possible rationale for anticoagulant therapy in the prevention of recurrent stroke in patients with recent cerebral ischemia who are in sinus rhythm, since the levels of hemostatic markers in patients with cerebral ischemia were similar, irrespective of the presence of atrial fibrillation.

The value of anticoagulation for these patients has not yet been established in clinical trials.
Our results differ from those of Gustafsson et al. who neither found hemostatic abnormalities in stroke patients with sinus rhythm, nor differences in hemostatic function between NVAF patients with or without previous stroke [28]. The explanation may be that they measured hemostatic parameters other than TAT and F1+2, since especially F1+2 is considered more sensitive for hemostatic activity in these patients. In agreement with our study Boysen et al. did not find a significant difference in TAT complexes between NVAF patients and controls [29]. They did find subtle changes in some other coagulation factors between NVAF patients and controls. In their study, however, no clear distinction could be made between NVAF patients with or without previous stroke, since they did not perform a CT-scan in all patients to exclude silent brain infarction.

Despite the small size of our study groups our results do suggest that the hemostatic parameters TAT and F1+2 have to be measured repeatedly. In the groups of patients with TIA or minor stroke several of them showed significantly increased levels of TAT and/or F1+2 at only one of the two times. Significant dynamic fluctuations of TAT levels were not seen during daytime in healthy subjects in an earlier study [30], but these fluctuations may occur with longer intervals, especially in patients with atherosclerotic disease, in whom periodic exacerbation of atherothrombotic activity is known to occur. Several studies recently discussed the existence of a prethrombotic state [7]; this condition has been evoked in patients with recent stroke, but on the basis of only a single measurement [21, 31].

Our study has some limitations; the higher plasma levels of F1+2 in patients with recent TIA or minor ischemic stroke, whether in atrial fibrillation or in sinus rhythm, compared with patients without previous stroke, may still have been caused by the recent thrombotic event [32]. However, the elevations of F1+2 and TAT levels in the stroke patients in our study did not show a consistent decrease between the second and the third month after the stroke.

Another qualification is that our findings of increased hemostatic function in patients with recent TIA or minor stroke may be valid for older patients only; the mean age of the patients in our groups was 70 years. Ono et al. found that the differences of TAT and D-dimer levels between patients and healthy controls increased with age [21]. In our study, even with a limited number of patients, a relationship of TAT and F1+2 levels with age was also suggested. Larger studies are needed to confirm whether the hemostatic hyperactivity we found also applies to younger patients with recent stroke.

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CHAPTER V

THE DUTCH TIA TRIAL: BACKGROUND AND DESIGN

Transient ischemic attacks (TIAs) are the major precursors of stroke [1] and may be considered warning signals of death from myocardial infarction [2]. The discoveries that most TIAs are caused by thromboembolism [3], and that aspirin is a powerful inhibitor of platelet aggregation [4] has led to the hypothesis that this drug might prevent stroke and other cardiovascular complications in patients with TIAs [5]. This has been confirmed by a number of randomized controlled clinical trials [6, 7, 8, 9]. Most studies have also included patients with prolonged attacks (RINDs) and partial strokes [6, 7, 8]. An overview of all trials has shown that antiplatelet agents - mostly aspirin- decrease the odds of non-fatal stroke by 27% (SD 6%) and of non-fatal myocardial infarction by 32% (SD 5%). The odds of fatal vascular complications are decreased by 15% (SD 4%) [10, 11, 12]. The lowest dose of aspirin that was proven to be effective was 300 mg [8].

During the past years new developments have generated new hypotheses. In the first instance, further clarification of the biochemical effects of aspirin has led to the expectation that lower doses of aspirin might be equally effective or even better. Aspirin mediates its antiplatelet effects by inactivation of the enzyme cyclooxygenase [13]. This enzyme is present in platelets, where it controls the production of thromboxane A2, a powerful promotor of platelet aggregation. It is also found in endothelial cells, where it regulates the production of prostacyclin, which has precisely the opposite effect [14]. Clearly, the latter effect of aspirin - inhibition of an antiaggregant agent - is undesirable. Recent studies have shown that platelet cyclooxygenase is more susceptible to aspirin than vessel wall cyclooxygenase [15, 16]. The production of thromboxane A2, as measured by the serum level of the stable metabolite thromboxane B2, is suppressed by more than 90% by daily doses between 20 and 50 mg of aspirin [17, 18, 19, 20, 21, 22, 23]. Bleeding time is prolonged by doses over 30 mg

[21]. The synthesis of prostacyclin, as measured by its urinary metabolite 6-keto-PGF, shows unchanged excretion with aspirin doses up to 35 mg [20, 21, 24] and is partially suppressed by 50 mg [25]. The extrarenal production of prostacyclin is not spared even with 20 mg aspirin per day [22]. Thus, 20 mg aspirin/day is the minimum dose for inhibition of the synthesis of thromboxane, 30 mg for prolongation of bleeding time, and both these low doses have a slight but transient effect on the production of prostacyclin.

A second development was the most widely recognized importance of ischemic heart disease as the most life threatening complication in patients with cerebrovascular disease [2, 6, 8, 26, 27]. Death from heart disease is estimated at 1.5-5% per year, which is even slightly higher than in patients with angina pectoris [2]. In addition 1-2% of patients suffer a non-fatal myocardial infarct [6, 7, 8]. The discovery that betablockers decrease mortality after myocardial infarction by 20% (95% confidence interval 15-30%) [28] has led to the hypothesis that this benefit might also apply to patients with cerebrovascular disease.

Aims of the study

Two main hypotheses were tested in patients with TIAs or a partial stroke:

1. 30 mg Aspirin/day is more effective than 300 mg in preventing death and disability or, more specifically, the occurrence of vascular death, non-fatal stroke, non-fatal myocardial infarction, or retinal infarction.

2. 50 mg Atenolol is more effective than placebo in preventing these same events.

A subsidiary aim of the study is to investigate the prognostic importance of several variables, including the nature and time course of the ischemic attack, vascular risk factors, age, sex, blood pressure, ECG and various types of ischemic lesions on the CT-scan.

Entry criteria

Transient ischemic attacks.
Time course: the symptoms should develop within a few seconds, should not progress from one part of the body to another in an orderly march, and should last between 1 minute and 24 hours.
Nature: 1) loss of vision (black or grey) in one eye, completely or in the upper or lower half; 2) language disorder; 3) weakness or clumsiness on one side; 4) loss of vision on one side, involving both eyes; 5) bilateral weakness, simultaneously or separately, or symptoms involving the face on one side and the body on the other; 6) combinations of vertigo, diplopia, dysphagia, sensory loss, misdirections of limbs, or drop attacks.
TIAs should not include loss of consciousness, convulsions, incontinence or prominent headache.

Partial strokes.
The mode of onset and nature of symptoms should be as specified above for TIAs, and the degree of disability should not be so severe that preventive treatment is not realistic.

To be included, patients should be independent in most activities of daily living, corresponding to grade 3 or better on the modified Rankin scale [29]:

Grade 0. no symptoms at all.
Grade 1. no significant disability despite symptoms: able to carry out all usual duties and activities.
Grade 2. slight disability: unable to carry out some previous activities but able to look after own affairs without assistance.
Grade 3. moderate disability: requiring some help but able to walk without assistance.
Grade 4. moderately severe disability: unable to walk without assistance or unable to attend to own bodily needs without assistance.
Grade 5. severe disability: bedridden, incontinent and requiring constant nursing care and attention.

Exclusion criteria

I. Last ischemic attack more than 3 months ago.
II. Forms of cerebral ischemia which are unlikely to have been caused by arterial thromboembolism from atherosclerosis:

A. Precipitation of attacks by standing, turning of the head or warming of the face.
B. Migraine, or attacks exactly resembling an aura of migraine previously experienced, or scintillating scotomas not preceded by migraine.
C. Age under 40 years, unless relevant lesions of the carotid artery have been demonstrated.
D. Changes in heart rhythm, directly related to the attack (clinical diagnosis or ECG).
E. A source of embolism in the heart (atrial fibrillation, valve disorders, transmural myocardial infarcts less than 4 weeks old).
F. Hematological disorders: persistent anemia (Hb 6.0 mmol/l or less), polycythemia rubra vera (Ht 0.60 or over), thrombocytosis (500 x 10^9/l or over), thrombocytopenia (100 x 10^9/l or less).
G. Vasculitis (SLE, arteriitis temporalis, polyarteriitis nodosa, lues, herpes zoster ophtalmicus).

III. Disorders that mimick cerebral ischemia:
A. Intracranial hemorrhage, tumor cerebri, subdural hematoma.
B. Hypoglycemia (2 mmol/l or less) during the attack.

IV. Situations likely to confound interpretation of the trial results:
A. Cerebral infarction in the past with disabling residual deficits (Modified Rankin scale grade 4 or worse).
B. Myocardial infarction within the past month.
C. Malignant tumor likely to cause death within a few months.
D. Likelihood of poor patient compliance.
E. Patient does not speak Dutch fluently (an interpreter does not solve this problem).

V. Disorders possibly exacerbated by acetylsalicylic acid:
A. Chronic renal failure (creatinine over 150 mmol/l).
B. Liver failure.
C. Peptic ulceration (proved; within the past three years).
D. Abnormal bleeding tendency (e.g. hemophilia, thrombopathia).
E. Intra-cranial hemorrhage in the past.
F. Asthma bronchiale.
G. Patients already taking antiplatelet drugs for other reasons.
H. Patients already taking acetylsalicylic acid for other reasons.

VI. Disorders possibly exacerbated by betablockers:
   A. Frequency of heartbeat 50/min. or less.
   B. PQ-time on ECG 0.25 second or more.
   C. AV-block of the 2nd or 3rd degree.
   D. Hypotension (diastolic blood pressure less than 80 mm.Hg.).
   E. Decompensatio cordis (heart/thorax ratio on chest X-ray of 0.65 or over).
   F. Asthma bronchiale or chronic bronchitis.
   G. Diabetes mellitus.
   H. Myasthenia gravis.
   I. Raynaud's disease.
   J. Intermittent claudication.
   K. Patient already taking betablockers and having to continue.

Mandatory investigations

Blood tests: hemoglobin, hematocrit, platelet count, erythrocyte sedimentation rate, blood glucose, serum creatinine, hepatic enzymes, syphilis serology.

Chest X-ray.
ECG.
CT-scan of the brain.

Evaluation treatment

1. All events will be analyzed on an "intention to treat" basis. Thus, all randomized patients, including those withdrawn from study medication and those who are non-compliant, will be followed until the end of the study. This includes randomized patients who should have been excluded according to the study protocol (protocol violations). An additional analysis will be undertaken in which these patients as well as those who did not receive the full treatments will have been removed ("explanatory analysis"). In accordance with the intention-to-treat principle, patients should be kept on the study treatment as much as possible.

2. Analysis of events

Primary measures for analysis:
- Death and disability (measured by means of the modified Rankin scale), from all causes.

Secondary outcome events:
- Vascular death.
- Non-fatal stroke.
- Non-fatal myocardial infarction.
- Retinal infarction.

3. The above analyses will also be performed for each of the subgroups defined by the following major prognostic variables:
- sex
- age
- presence of ischemic heart disease
- presence and type of cerebral infarction on CT (cortical, lacunar, borderzone)
- degree of handicap at entry.

Cardiac characteristics of the patients with a transient ischemic attack or minor stroke in the Dutch TIA Trial

Patients with a definite or probable cardiac source of embolism were excluded. A cardiac source of embolism was ruled out by clinical and electrocardiographic (ECG) findings only. Although certainly not all stroke patients with a cardiac source of embolism were excluded, further cardiac investigations such as precordial echocardiography or 24-hours Holter monitoring would not have excluded many more patients, because these investigations do not provide much additional information about the presence of cardiac causes of stroke, as stated in earlier chapters and by others [30, 31, 32].

The exclusion of patients with probable cardiac causes of their cerebral ischemic event resulted in a population of patients in whom, in most cases, the cardiac disease has only a relation of association with the brain ischemia. It must be realized therefore, that the results of our study cannot be extrapolated to all patients with a cerebral ischemic event, because they include those with cardiogenic embolism [33]. About one in six cerebral ischemic events can be attributed to cardiogenic embolism [30].

On the other hand, the patient selection in the Dutch TIA Trial gives the opportunity to discover to what extent atherosclerotic manifestations in one organ, in casu the brain, may reflect, respectively predict, present and future atherosclerotic manifestations in another organ, in casu the heart, and vice versa.

Another consequence of the patient selection in the Dutch TIA Trial is that the future cardiac risk in these patients is expected to be lower than in the whole population of patients with cerebral ischemic events. For example patients with recent myocardial infarction were excluded and it is known that the cardiac risk is higher in the first months after a myocardial infarction [34, 35]. Another exclusion criterion was atrial fibrillation, which can often be regarded as a manifestation of depressed left ventricular function, another important risk factor for future cardiac events [36, 37]. Patients were also excluded, if they were already taking antiplatelet drugs and/or betablockers and had to continue. In the Netherlands many patients with overt ischemic heart disease receive aspirin and/or betablockade for secondary prevention and they could therefore not be included in the trial when suffering a TIA or minor stroke.

These considerations relating to the cardiac characteristics of the patient population of the Dutch TIA Trial are taken into account in the interpretation of the results of the Trial (Chapter VI and VII). They reflect the necessity to be aware of the premisses and methodology upon which a study is inherently based [38, 39].

For participants and committees of The Dutch Trial Study, see Appendix .

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CHAPTER VI

PREVALENCE OF ISCHEMIC HEART DISEASE IN PATIENTS WITH A TRANSIENT ISCHEMIC ATTACK OR MINOR ISCHEMIC STROKE.

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Introduction

A strong association between cerebral ischemic events and co-existent coronary artery disease has been established in various clinical reports, autopsy series and epidemiological surveys [1, 2, 3, 4]. TIA patients have a relatively high mortality rate (up to 6% per year) and myocardial infarction is the most common cause of death. One study reported a 6% per annum long-term mortality from heart disease alone in patients with TIA or minor stroke, which is three times as high as the 1-2% annual mortality among persons of comparable age without evidence of atherosclerotic disease [5], and which is even higher than the 3-4% per annum mortality among patients with angina pectoris [6, 7]. A TIA or minor stroke should therefore be considered not only as a sign of future cerebral infarction but also as a warning signal for major cardiac events [8]. A probable explanation for this high cardiac event rate may be the presence of preexisting but asymptomatic ischemic heart disease in many patients with TIA or minor stroke [9, 10]. On the other hand, a recent study showed a good long-term prognosis in those patients with transient ischemic attacks or minor stroke who had normal cerebral, cardiac and hematological findings [11]. So not all patients with TIA or minor stroke seem to have the same risk. It might be possible to identify a subgroup of patients with high risk for major cardiac and recurrent cerebral events by means of the clinical history and ECG.

Our aim was to study the prevalence of ischemic heart disease as defined by clinical history and standard 12 lead electrocardiography in the 3150 patients with TIA or minor ischemic stroke who participated in the Dutch TIA Trial [12]. In addition we have addressed the question whether specific subgroups of cerebral ischemic events are associated with a relatively high rate of ischemic heart disease.

Patients and methods

Study patients. The original cohort for this study included the 3150 patients admitted to the Dutch TIA Trial, who had a TIA or minor ischemic stroke between March 1986 and March 1989. A detailed description of the design, inclusion criteria, data acquisition, data management and follow-up of the Dutch TIA Trial has been published earlier [12]. The results concerning the dose of aspirin have been separately published [21]. Patients with a definite or probable cardiac source of embolism were excluded by clinical and electrocardiographic (ECG) findings; patients were excluded if they had suffered myocardial infarction within the previous month, presented with atrial fibrillation, or had a valvular

heart defect. Patients in whom disturbances of heart rhythm or intra cardiac conduction occurred in close relation to their neurological symptoms were also excluded. After randomization twenty-three patients were excluded because they were found to have a cerebral hemorrhage, tumor or other non-ischemic cause. Another hundred and six patients were excluded because the randomization electrocardiogram was missing or incomplete. Of the 3021 remaining patients 1050 (35%) were female and 1971 (65%) were male. Their ages ranged from 33 to 92 with a mean of 65.1 years (SD: 9.9).

Neurological definitions and methods. A TIA was defined as an episode of temporary and focal cerebral dysfunction, presumably of vascular (occlusive) origin, rapid in onset (no symptoms to maximal symptoms in less than 5 minutes and usually less than 1 minute) and lasting less than 24 hours. Minor ischemic stroke was defined as symptoms persisting for more than 24 hours, either resolving within 6 weeks (RIND), or persisting deficits though with retained independence in the activities of daily life (non-disabling stroke; Rankin scale 3 or less [11, 13]. Laboratory investigations were performed in order to exclude causes of focal neurological deficit other than atheromatons arterial disease and included the erythrocyte sedimentation rate, hemoglobin, hematocrit, platelet count, fibrinogen, blood glucose, blood tests for liver enzymes and renal function, and syphilis serology. Computed tomography (CT) of the brain was required in all patients except those with transient monocular blindness. All CT-scans were reviewed by at least two neurologists without knowledge of the patient's clinical symptoms and past history. Cerebral infarcts were defined as well-defined radiolucent lesions, and were subdivided into small deep lesions, cortical end zone infarcts, and borderzone infarcts.

Cardiological definitions and methods. Cardiological examination of all patients consisted of clinical history, chest roentgenogram and a standard 12 lead resting electrocardiogram. In the clinical history, information was obtained about previous myocardial infarction, angina pectoris, risk factors and associated diseases such as hypertension, diabetes mellitus or intermittent claudication as well as about any history of vascular surgery (coronary bypass, carotid endarterectomy and peripheral vascular surgery). The blood pressure was measured and the cardiothoracic ratio on the chest X-ray was calculated. The electrocardiograms were interpreted independently by two physicians, without knowledge of the clinical history of the patient. An unrecognized myocardial infarct was considered to be present when electrocardiographic criteria for myocardial infarct were fulfilled (see below), whereas neither the patient nor the

attending physician were aware of the occurrence of a coronary attack in the past [14].

Electrocardiographic criteria [15, 16]. Assessment of the morphology, duration and amplitude of the QRS complex and P and T wave was done by pattern recognition without the use of magnification procedures. The different abnormalities were defined as following. 1) Left intra-atrial conduction delay expressed as increase of left atrial P terminal force in V1 (PTF): if the area of the terminal negative deflection of the P wave in V1 is more than 3 msec.mV [17]. 2) Left ventricular hypertrophy (LVH) according to Sokolow (voltage-criteria only): the sum of the amplitude of the S wave in lead V1 or V2 and the R wave in lead V5 or V6 is more than or equal to 3.5 mV (given that the patient is more than 40 years old) [18, 19]. 3) Intraventricular conduction abnormalities [20]: 3A) complete left or right bundle branch blocks; 3B) nonspecific intraventricular block. 4) Infarction pattern criteria [16]: 4A) anterior: any Q waves in lead V2 or Q waves in V3 and V4 that are more than 0.03 sec; also significant loss of R wave amplitude from V1 to V2 or V3; 4B) lateral: the Q waves in lead I, avL, V5 or V6 must be more than 0.03 sec; a more than 50% loss of R wave amplitude in V5 and/or V6 would also satisfy the criteria for infarction; 4C) inferior-posterior: Q waves more than 0.03 sec in duration in leads III and AVF (a broad Q wave or even a QS pattern in lead III alone is insufficient); a tall R wave, with an R/S ratio of 1 or more and a R duration of more than 0.04 sec in V1. 5) Ischemia [15]: 5A) ST abnormalities: horizontal ST elevation or horizontal or downsloping ST depression equal or more than 0.1 mV deep and 0.08 sec long after completion of the QRS in the absence of hypertrophy or conduction disorders; 5B) T wave abnormalities: symmetric T wave inversions at least 0.1 mV deep, positive symmetric T waves at least more than 50% of R wave-amplitude.

Data analysis. Baseline characteristics in subsets of patients were compared by use of a chi-square or Fisher exact test, whichever was appropriate. A two-sided p-value < 0.05 was considered statistically significant.

Results

The history revealed a previous myocardial infarction in 10% of the patients and 10% angina pectoris; 16% had at least one of these conditions. Smoking, hypertension, diabetes mellitus and intermittent claudication were present in 45%, 42%, 8% and 6%, respectively. Standard 12 lead electrocardiography

showed a pattern of myocardial infarction in as many as 14% , while 19% showed ST-T wave abnormalities suggesting ischemia; left ventricular hypertrophy criteria were present in 12% of the patients.

When the data from the history were combined with the ECG criteria for myocardial infarction, men had suffered myocardial infarction, both clinically recognized and clinically unrecognized, more often than women: 22% (95% CI:20-24) versus 14% (95% CI:12-16), respectively (table 1). The frequency of myocardial infarcts, both recognized and unrecognized, increased with age in both sexes. The proportion of unrecognized myocardial infarcts in relation to all myocardial infarcts was particularly high in women (62%, versus 45% for men; $p<0.001$). The proportion of unrecognized myocardial infarcts did not increase with age, neither in men nor in women (table 1).

Table 1. Frequency of unrecognized and all myocardial infarcts among 3021 patients with TIA or minor stroke according to age and sex.

sex / age	any myocardial infarct n(%; 95% CI)	p#	unrecognized myocardial infarct n(%; 95% CI)	p#
Men				
40-54 (n=338)	42(12; 8.9-15.9)	< 0.001	20(6; 3.7- 9.0)	0.003
55-69 (n=672)	124(19;15.5-21.4)		57(8; 6.5-10.8)	
≥ 70 (n=961)	263(27;24.5-30.2)		114(12; 9.8-13.9)	
Total (n=1971)	429(22;19.9-23.6)*		191(10; 8.4-11.1)*	
Women				
40-54 (n=139)	9(6; 3.0-11.9)	0.016	6(4; 1.6- 9.2)	NS
55-69 (n=259)	36(14; 9.7-18.1)		23(9; 5.7-13.0)	
≥ 70 (n=652)	103(16;13.0-18.6)		63(10; 7.5-12.2)	
Total (n=1050)	148(14;12.0-16.2)*		92(9; 7.1-10.6)*	

CI=confidence interval, #=Chi-square test, *p<0.001, *p=NS.

Table 2. Prevalence of smoking, history of hyperlipidemia, diabetes, hypertension, intermittent claudication and/or peripheral vascular surgery in patients with clinically unrecognized or recognized myocardial infarcts.

risk factors or associated vascular disease	unrecognized myocardial infarct (n=283) n (%)	recognized myocardial infarct (n=294) n (%)	p*
smoking	138(49%)	113(38%)	0.012
history of hyperlipidemia	9(3%)	20(7%)	0.047
diabetes	34(12%)	30(10%)	0.50
hypertension	143(51%)	134(46%)	0.23
intermittent claudication and/or peripheral vascular surgery.	23(8%)	44(15%)	0.010

* Chi-square test.

Table 3. Comparison of clinical and electrocardiographic signs of ischemic heart disease between patients with and without symptoms of peripheral atherosclerosis*.

	symptoms of peripheral atherosclerosis				
	yes (n= 173)		no (n=2848)		
	n	(%)	n	(%)	p*
history of ischemic heart disease					
angina	42	(24)	240	(8)	<0.001
CABG	8	(5)	52	(2)	0.022
myocardial infarct	44	(25)	250	(9)	<0.001
any of these	66	(38)	426	(15)	<0.001
electrocardiogram infarct-pattern or ischemia					
myocardial infarct	43	(25)	383	(13)	<0.001
ST-depression	24	(14)	238	(8)	0.018
negative T wave	30	(17)	275	(10)	0.002
conduction disturbances					
left intra-atrial conduction delay	89	(51)	1292	(45)	0.14
QRS duration> 110 ms	6	(3)	145	(5)	0.44
left ventricular hypertrophy (Sokolow)					
voltage criteria only	23	(13)	350	(12)	0.77

* Symptoms of peripheral atherosclerosis include presence of intermittent claudication and/or history of peripheral vascular surgery; * Chi-square test.

Table 4 Prevalence of characteristics related to ischemic heart disease on the basis of clinical history and ECG in patients with TIA or minor stroke.

	TIA (n= 955)		Minor stroke (n=2066)		
	n	(%)	n	(%)	p*
history of ischemic heart disease					
angina	95	(10)	187	(9)	0.43
CABG	27	(3)	33	(2)	0.02
myocardial infarct	91	(10)	203	(10)	0.80
any of these	158	(17)	334	(16)	0.79
electrocardiogram					
infarct-pattern or ischemia					
myocardial infarct	121	(13)	305	(15)	0.12
ST-depression	73	(8)	189	(9)	0.17
negative T wave	84	(9)	221	(11)	0.11
conduction disturbances					
left intra-atrial conduction delay	381	(40)	1000	(45)	<0.001
QRS duration> 110 ms	9	(1)	25	(1)	0.52
left ventricular hypertrophy (Sokolow)					
voltage criteria only	93	(10)	280	(14)	0.003

* Chi-square test.

Patients with unrecognized myocardial infarcts more often smoked and less often had symptoms of peripheral vascular atherosclerosis than patients with known myocardial infarct; a history of hyperlipidemia, diabetes and hypertension was equally common in the two groups (table 2).

In 61% of the patients who stated to have suffered previous myocardial infarction, an infarct pattern was not (or no longer) present on the ECG.

Patients with peripheral atherosclerosis included those with presence of intermittent claudication and/or history of peripheral vascular surgery. Patients with symptoms of peripheral vascular sclerosis more often had a history of ischemic heart disease and ECG abnormalities suggesting myocardial infarction or ischemia than those without (table 3). A myocardial infarct, either recognized or unrecognized, was diagnosed in 67 (39%) of the patients with peripheral vascular disease.

Patients with minor ischemic stroke or RIND did not have a history of ischemic heart disease more often than patients with TIA. All ECG abnormalities however, were more common (table 4).

Comparison of electrocardiographic signs of ischemic heart disease between patients with and without any infarct on the CT-scan at entry (irrespective of appropriateness to the qualifying event, type or site) showed that most ECG abnormalities were significantly more common in patients with a cerebral infarct (table 5).

Table 5. Comparison of electrocardiographic signs of ischemic heart disease between patients with and without presence of infarcts on CT-scan.

	cerebral infarct on CT-scan				
	yes (n=1202)		no (n=1696)		
	n	(%)	n	(%)	p*
Infarct-pattern or ischemia					
myocardial infarct	189	(16)	223	(13)	0.057
ST-depression	124	(10)	128	(8)	0.011
negative T wave	133	(11)	162	(10)	0.21
conduction disturbances					
left intra-atrial conduction delay	606	(50)	728	(43)	<0.001
QRS duration> 110 ms	59	(5)	87	(5)	0.86
left ventricular hypertrophy (Sokolow)					
voltage criteria only	177	(15)	186	(11)	0.003

* Chi-square test.

Discussion

The high rate of previous myocardial infarction diagnosed on the basis of clinical history and ECG (22% in men and 14% in women) in patients with TIA or minor stroke is remarkable, but in concordance with previous findings [22]. In 150 patients with acute stroke Goldstein also detected an increased frequency (20%) of pathologic Q waves compared with the electrocardiographic records of 150 age- and sex-matched controls. A striking finding in our study was that in about half the patients of our study population the myocardial infarction was previously unrecognized (62% in women and 45% in men). The term 'unrecognized' is used and not 'silent', because some myocardial infarctions may have caused symptoms, though so atypical that neither the patient nor the physician (if consulted) suspected myocardial infarction. In the Framingham Heart study the proportion of previously unrecognized myocardial infarction among all myocardial infarcts was smaller; in patients with a mean age of 65 years about 38% of all infarcts in women and 30% in men [14]. The high rate of unrecognized myocardial infarcts in our study might be a general characteristic of patients with TIA or minor stroke and may contribute to the higher risk for cardiovascular events in these patients as compared with patients of the same age without cerebrovascular disease. The presence of any myocardial infarct is associated with an increased risk of heart disease, especially with sudden death [14, 23, 24]. A recent study by Di Pasquale et al. demonstrated a high prevalence of silent ischemic heart disease even in cerebrovascular patients without angina or previous myocardial infarction as defined by electrocardiogram or echocardiogram [10].

Patients with an unrecognized myocardial infarct showed a similar cardiovascular risk profile as patients with known myocardial infarction, except for smoking (table 2). This similarity in risk profile may explain the finding of others that patients with unrecognized myocardial infarct have the same prognosis with regard to recurrences and mortality as patients with recognized myocardial infarct [14, 23, 24]. The prevalence of peripheral vascular disease was less in patients with unrecognized infarcts; 'painless' cardiac ischemia might be associated with less pain from ischemia in the extremities or complaints of intermittent claudication may have alerted physicians earlier than otherwise to the presence of myocardial ischemia.

The frequency of peripheral arterial sclerosis (5.7%; 95% CI: 4.9-6.6%) in our study population is much higher than that in the general population [25, 26], which again confirms that the episode of cerebral ischemia that qualified the patient for our study often is just another manifestation of a process of generalized atherosclerosis. The patients with symptoms of peripheral

atherosclerotic disease more often had a history of previous myocardial infarction or an infarct on ECG than those without symptoms of peripheral vascular sclerosis (relative risk 2.16; 95% CI: 1.76-2.65) (table 3). This is consistent with previous findings that patients with evidence of cerebral as well as peripheral atherosclerosis are at highest risk for future cardiovascular events [25, 26, 27, 28].

Patients with stroke or RIND more often had electrocardiographic abnormalities than patients with TIA as a qualifying event (table 4). This higher frequency of electrocardiographic abnormalities might explain, at least in part, why some studies have found a higher rate of subsequent cardiovascular events in patients with a minor stroke than in those with a TIA [29, 30, 31, 32, 33]. Patients with infarcts on the CT-scan on entry had more electrocardiographic abnormalities than those without (table 5). The extent of ischemic damage to the brain probably depends on the severity of the same diseases that also affect the heart, as it is associated with a proportional increase of electrocardiographic markers for cardiac ischemic damage. In brain ischemia these two main common diseases are atherosclerosis and arterial hypertension; on the ECG infarct pattern and repolarization abnormalities are typical for coronary sclerosis and left ventricular hypertrophy is a typical consequence of longstanding arterial hypertension in the absence of valvular heart disease. Left intra-atrial conduction delay can be a consequence of both diseases.

The high rate of disappearance of electrocardiographic evidence of an old infarct in our study population is comparable with the findings of Woods et al. [34]. Besides this, in our study group the myocardial infarcts often occurred several years earlier, which is associated with a higher probability of disappearance of Q waves [35, 36]. Furthermore, some of the myocardial infarcts included in the clinical history were certainly non-Q wave infarctions, which generally cannot be recognized on later ECGs. In most studies 15-21% of all myocardial infarctions are non-Q wave infarctions [37, 38]. Finally, the history of myocardial infarction in the Dutch TIA Trial depended on what the patient told the neurologist, and was not necessarily supported by clinical or laboratory evidence of true myocardial infarction in the past.

Patients with a probable source of embolism in the heart were excluded in our study. Inclusion of presumed cardioembolic events might have shown an even higher rate of myocardial ischemia. This would also have affected the frequency and type of TIA or minor stroke at entry, as infarcts caused by embolism from the heart are rarely of the lacunar type [39, 40] and are generally large and of end zone distribution [41].

In conclusion, a high prevalence of ischemic heart disease was found in patients with cerebral ischemia, using the relatively simple and inexpensive methods of clinical history and standard electrocardiography. We had reason to suspect previous myocardial infarct in 22% of men and in 14% of women. Myocardial infarctions had often not been recognized earlier and were detected only on the electrocardiogram. Among patients with transient cerebral ischemia we could identify the following factors associated with an increased rate of myocardial ischemia, clinically or on ECG; neurological deficits lasting for more than 24 hours, evidence of infarction on CT scanning, and a history of peripheral vascular disease. It is these patients in particular, whom might benefit from further cardiologic evaluation and treatment.

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CHAPTER VII

PREDICTIVE VALUE OF CLINICAL HISTORY AND ELECTROCARDIOGRAM IN PATIENTS WITH TRANSIENT ISCHEMIC ATTACK OR MINOR ISCHEMIC STROKE FOR SUBSEQUENT CARDIAC AND CEREBRAL ISCHEMIC EVENTS.

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Introduction

Numerous epidemiological, clinical and autopsy studies have shown a strong association between cerebrovascular atherosclerosis and coronary sclerosis [1, 2, 3, 4]. Therefore, transient ischemic attack (TIA) or minor ischemic stroke are not only a warning sign of recurrent stroke, but also of myocardial infarction and cardiac death [5, 6]. The problem arises how the increased risk of subsequent cardiac complications can be assessed in individual patients who have suffered a TIA or minor ischemic stroke. If a high-risk group can be identified, more aggressive diagnostic or therapeutic measures may be warranted in these patients. In the presence of normal cerebral, cardiac, and hematological findings, the long-term prognosis of patients with transient ischemic attacks was shown to be good [7], but recently we identified several clinical and paraclinical abnormalities as being predictors of subsequent major vascular events [8].

Since most of the major cardiac complications in patients with TIA or minor stroke are ischemic, patients who already suffer from ischemic heart disease probably have the highest risk. Besides clinical history, the resting 12 lead electrocardiogram (ECG) offers a relatively simple, non-invasive and inexpensive tool for the detection of ischemic heart disease. The sensitivity and specificity of these ECG parameters vary with the population under investigation [9, 10, 11] and can be considered as relatively high in patients who are older and have suffered a TIA or minor stroke.

Our present prospective study was designed to evaluate the predictive value of clinical history and electrocardiogram at rest in patients with recent TIA or minor ischemic stroke, with regard to the occurrence of cardiac death or myocardial infarction. In addition we also investigated whether the presence of ischemic heart disease in these patients signified an increased risk of recurrent cerebral ischemic events [1, 8, 12].

Patients and methods

Study patients. The original cohort for this study consisted of the 3150 patients enrolled in the Dutch TIA Trial between March, 1986 and March, 1989 within 3 months of a TIA or minor ischemic stroke. A detailed description of the design, patients, data acquisition and follow-up of the Dutch TIA Trial has been reported previously [13, 14]. According to history, clinical examination or electrocardiographic (ECG) investigation patients with a definite or probable source of embolism in the heart were excluded. A cardiac source of embolism was suspected in patients who suffered a myocardial infarction in the preceding

month, who presented with atrial fibrillation or who had a valvular heart defect. Patients with arrhythmias or conduction disturbances in close relation with their neurological symptoms were also excluded. The follow-up period of the patients ended in June 1990 and lasted from 1 year to 52 months with a mean of 2.7 years. No patient was lost to follow-up.

Outcome events

Cardiac outcome events were defined as nonfatal myocardial infarction and cardiac death; cardiac death included sudden death, fatal myocardial infarction or death from congestive heart failure. Sudden death was defined as unexpected cardiac death occurring within one hour after onset of symptoms, or within 24 hours given circumstantial evidence. 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. Cerebrovascular outcome events included fatal or non-fatal recurrent ischemic stroke. For the diagnosis of non-fatal stroke, relevant clinical features persisting for more than 24 hours had to correspond with a new infarction or a hemorrhage on a repeated CT scan. If sudden and focal neurologic deficits without CT changes (or in the absence of a CT scan) caused an increase in handicap of at least one grade on the modified Rankin Scale, the event was also classified as a stroke. All outcome events were independently classified by at least three members of the Auditing Committee for Outcome Events, without knowledge of the patients' treatment assignments.

Baseline characteristics

Neurological definitions and methods. At entry, transient ischemic attack (TIA) was defined as an episode of temporary and focal cerebral dysfunction, presumably of vascular (occlusive) origin, lasting less than 24 hours whereas the cerebral dysfunction in minor ischemic stroke persisted for more than 24 hours. Patients with stroke had to be independent in most of their activities of daily life (Rankin <3) (non-disabling ischemic stroke) [15]. Laboratory investigations were also performed in order to exclude other causes of focal neurological deficit and included the erythrocyte sedimentation rate, hemoglobin, hematocrit, platelet count, fibrinogen, blood glucose, blood tests for liver enzymes and renal function, and syphilis serology.

Cardiological definitions and methods. Cardiological baseline examination of all patients consisted of clinical history, measurement of blood pressure, chest X-ray and 12 lead electrocardiogram at rest. In the clinical history, information was obtained about presence of previous myocardial infarction, angina pectoris, as well as risk factors or relevant diseases such as hypertension, diabetes mellitus, intermittent claudication, or vascular surgery (coronary bypass, carotid endarterectomy and peripheral vascular surgery). On the chest X-ray the cardiothoracic(CT)-ratio was calculated. The electrocardiograms were interpreted independently by two cardiologists without knowledge of the clinical history of the patient. A myocardial infarct was considered 'unrecognized' if clinical history of the patient did not reveal an infarct but criteria for its presence were found on the standard ECG. The term 'unrecognized' is used and not 'silent', because some myocardial infarctions may very well have caused symptoms, though so atypical that neither the patient nor the physician (if consulted) suspected myocardial infarction.

Electrocardiographic criteria [16, 17, 18] used were as follows: assessment of the morphology, duration and amplitude of the QRS complex and of the P and T wave was done by pattern recognition without recourse to magnification procedures. The different abnormalities were defined as follows: 1) Left intra-atrial conduction delay expressed as increase in left atrial P terminal force in V1 (PTF): if the area of the terminal negative deflection of the P wave in V1 is more than 3 msec.mV [19]. 2) Left ventricular hypertrophy (LVH). 2A): Sokolow (voltage-criteria only): the sum of the amplitude of the S wave in lead V1 or V2 and the R wave in lead V5 or V6 is more than or equal to 3.5 mV (given that the patient is more than 40 years old) [20, 21]. 2B): Casale: For men, at all ages, LVH is suggested by QRS voltage alone when the R wave in lead aVL and the S wave in lead V3 total more than 3.5 mV. LVH is suggested when this voltage exceeds 2.2 mV in men under age 40 years, if the T wave in lead V1 is positive (>0 mV) and in men 40 years or older, if the T wave in lead V1 is at least 0.2 mV. For women at all ages LVH is suggested when the R wave in lead aVL and the S wave in lead V3 total more than 2.5 mV. LVH is suggested when this voltage exceeds 1.2 mV in women under 40, if the T wave is positive in lead V1 (>0 mV) and in women over 40, if the T wave in lead V1 is 0.2 mV or greater [22, 23]. 3) Left ventricular strain: downsloping ST depression with T wave inversion of at least 0.1 mV in the lateral leads V5 or V6 and/or in the standard leads I and aVL with or without the voltage criteria of left ventricular hypertrophy mentioned above [20, 24, 25]. 4) Intraventricular conduction abnormalities [26]. 4A): complete left or right bundle branch blocks; 4B): nonspecific intraventricular block. 5) Infarction pattern criteria [17, 18]. 5A): anterior: any Q waves in lead V2 or Q waves in V3 and V4 that are more than

0.03 sec; also significant loss of R wave amplitude from V1 till V2 or V3. 5B): Lateral: the Q waves in lead 1, aVL, V5 or V6 must be more than 0.03 sec. A more than 50% loss of R wave amplitude in V5 and/or V6 would also satisfy the criteria for infarction. 5C): Inferior-posterior: Q waves at least 0.03 sec in duration in leads III and aVF (a broad Q wave, even a QS pattern in lead III alone, is not diagnostic of infarction). A tall R-wave, with an R/S ratio of 1 or more and an R duration of at least 0.04 sec in V1. 6) Ischemia [16, 18]. 6A): ST abnormalities: horizontal or downsloping ST depression 0.1 mV deep and 0.08 sec long after completion of the QRS in the absence of hypertrophy or conduction disorders. 6B): T wave abnormalities: symmetric T wave inversions at least 0.1 mV deep, positive symmetric T waves at least more than 50% of R wave-amplitude. 7) QT interval prolongation (QT-corrected): QT interval was considered to be prolonged if QT interval measured in standard leads I, II and III was more than 440 ms, corrected for heart rate [27]. 8) Premature ventricular beats (PVC): extrasystoles with wide QRS, unifocal or multifocal, without fixed relation to P waves and not felt to be nodal in origin.

Data analysis

In the univariate analysis we calculated the hazard ratio to define the risk of cardiac and cerebral ischemic events; 95% confidence intervals were used to describe their precision. Hazard ratios were obtained by means of the Cox Proportional Hazard Model (EGRET Statistical Package)[28, 29]. Hazard ratios may be interpreted as relative risks. If the 95% confidence interval did not include the 1.0, the association of the respective variable with the risk of suffering a cardiac or cerebral event was considered statistically significant at a 5% level ($p<0.05$).

The aim of the multivariate analysis was to predict event free survival from a set of independent (risk) factors within the baseline characteristics. Only those characteristics were taken into the multivariate analysis, which were statistically significant at a 5% level in the univariate analysis. Variables selected from univariate analysis were sequentially entered into the model using a stepwise approach until no remaining candidate variable met a significance level of 0.10. Variables were selected following the order in which clinical information became available. Hence, the first model was based on demographic characteristics, clinical history and chest X-ray, whereas in the second model ECG data were included. Independent risk factors from the first multivariate model were included in the second model only if the probability (p) value for inclusion was <0.10.

Results

Of the initial cohort of 3150 patients 3021 were finally included for analysis. 23 Patients had been inappropiately entered in the trial, because the eventual diagnosis was, for instance, a brain tumor or mysasthenia gravis; they were excluded from analysis. In 96 patients no ECG was available or the ECG was incomplete. In 10 patients a permanent pacemakerrhythm was present, which did not permit standard interpretation of the QRS complexes and the repolarization pattern. 1054 Patients were female and 1976 were male. Ages ranged from 33 to 92 years with a mean of 65.1 years (SD 9.9).

In Table 1 the incidence of cardiac and cerebrovascular outcome events is shown. Table 2 shows the presence of a myocardial infarction on ECG to be predictive for subsequent cardiac and cerebral events, whether the infarct has been clinically manifest or not.

Table 1. Distribution of outcome events between March 1986 and June 1990 in 3021 patients with TIA or minor stroke from Dutch TIA Trial of whom complete electrocardiograms were available at entry.

cardiac death or non-fatal myocardial infarction*	189	(6.3%)
sudden death	82	(2.7%)
fatal or non-fatal stroke*	261	(8.6%)

* whichever event occurred first

Table 2. Univariate hazard ratios for cardiac or cerebral vascular events in patients with a recognized myocardial infarct, an unrecognized myocardial infarct or those without myocardial infarct either in clinical history or on ECG.

	CD or non-fatal MI HR# (95%CI)	SD HR# (95%CI)	Stroke HR# (95%CI)
Myocardial infarction recognized (n=294)	3.1 (2.2 - 4.4)	2.8 (1.6 - 4.8)	1.3 (0.9 - 1.9)
unrecognized (on ECG only) (n=283)	2.2 (1.5 - 3.3)	2.7 (1.5 - 4.7)	1.4 (1.0 - 2.0)

CD=cardiac death; SD=sudden death; MI=myocardial infarction; HR=hazard ratio; CI=confidence interval; # Calculated from the ratio of event rates in which the rate in the patients without infarction in clinical history nor on ECG was taken as reference.

Prediction of cardiac and cerebral events by univariate analysis

The occurrence of a cardiac event in our study population was predicted by male gender, age (>65 yrs), diabetes, presence of peripheral vascular disease, past myocardial infarction and current angina (Table 3). An enlarged cardiothoracic ratio on chest X-ray was also predictive for cardiac events. A history of hypertension did not predict a cardiac event. Abnormalities on the electrocardiogram were subdivided according to presence of ischemia or infarct, conduction or rhythm disturbances and the presence or absence of left ventricular hypertrophy. Most of the ECG abnormalities were shown to have predictive power for cardiac events (table 3).

Except for male gender, diabetes and corrected QT intervals on ECG, the relation of all the other above-mentioned characteristics to the risk of sudden death was similar to that of cardiac events in general (Table 4). The ECG characteristics showed slightly higher hazard ratios for sudden death than for cardiac events in general. A higher risk for fatal and non-fatal stroke was found in males and patients over 65 years, patients who smoked and in those who suffered from peripheral vascular disease. Especially diabetes was strongly related with the risk of recurrent fatal or non-fatal stroke. No significant relation was found between occurrence of a cerebral event and history of hypertension or myocardial infarction, or current angina. Several ECG abnormalities had a predictive power for cerebral ischemic events (Table 5).

Table 3. The occurrence of cardiac events (cardiac death or non-fatal myocardial infarction) in relation to selected clinical and electrocardiographic characteristics in univariate analysis.

characteristics	%CDch+	%CDch-	HR*	95%-CI#
male gender	138/1971	51/1050	1.5	1.1 - 2.0
age > 65 yrs	128/1613	61/1408	1.9	1.4 - 2.6
vascular risk factors or disease				
smoking	86/1355	103/1666	1.0	0.8 - 1.3
diabetes	24/ 239	165/2782	1.8	1.2 - 2.8
hypertension	89/1260	100/1761	1.2	0.9 - 1.7
periph.vascular disease	17/ 173	172/2848	1.7	1.0 - 2.8
history of ischemic heart disease				
past myocardial infarction	41/ 294	148/2727	2.8	2.0 - 3.9
angina pectoris	34/ 282	155/2739	2.2	1.6 - 3.3
coronary bypass surgery	5/ 60	184/2961	1.3	0.5 - 3.2
chest X-ray (CT ratio > 50%)	28/ 303	161/2699	1.5	1.0 - 2.3
standard 12 lead electrocardiogram				
infarct-pattern or ischemia				
any infarction	53/ 426	136/2595	2.4	1.7 - 3.3
anterior infarction*	29/ 235	136/2595	1.9	1.3 - 2.8
inferoposterior infarction*	29/ 211	136/2595	2.3	1.5 - 3.4
lateral infarction*	6/ 36	136/2595	2.1	0.9 - 4.8
ST depression	25/ 262	164/2759	1.8	1.2 - 2.7
negative T wave	37/ 305	152/2716	2.4	1.7 - 3.4
conduction and rhythm disturbances				
atrial conduction delay	112/1381	77/1640	1.7	1.3 - 2.2
QRS duration > 110 msec	19/ 151	170/2870	2.1	1.3 - 3.4
QT-corrected	23/ 267	166/2754	1.7	1.1 - 2.6
pvc	19/ 164	170/2857	2.2	1.1 - 2.6
left ventricular hypertrophy				
Sokolow (voltages only)	35/ 373	154/2648	1.7	1.2 - 2.5
Sokolow with LV strain	18/ 117	171/2904	3.0	1.9 - 4.9
Casale criteria	25/ 118	164/2903	3.8	2.5 - 5.8

%CDch+, rate of cardiac events during follow-up in patients with characteristic present; %CDch-, rate of cardiac events during follow-up in patients with characteristic absent; HR, hazard ratio (may be interpreted as relative risk); CI, confidence interval; PVC, premature ventricular beat * versus no myocardial infarction.

Table 4. Univariate analysis of the relative risk for sudden death in relation to selected clinical and electrocardiographic characteristics.

characteristics	%CDch+	%CDch-	HR*	95%-CI#
male gender	55/1971	27/1050	1.1	0.7 - 1.7
age > 65 yrs	63/1613	19/1408	3.1	1.8 - 5.1
vascular risk factors or disease				
smoking	32/1355	50/1666	0.8	0.5 - 1.2
diabetes	8/ 239	74/2782	1.4	0.7 - 2.8
hypertension	38/1260	44/1761	1.2	0.8 - 1.9
periph.vascular disease	9/ 173	73/2848	2.1	1.1 - 4.2
history of ischemic heart disease				
past myocardial infarction	16/ 294	66/2727	2.3	1.4 - 4.0
angina pectoris	14/ 282	68/2739	2.1	1.2 - 3.7
coronary bypass surgery	2/ 60	80/2961	1.2	0.3 - 4.8
chest X-ray (CT ratio > 50%)	16/ 303	66/2699	2.2	1.3 - 3.7
standard 12 lead electrocardiogram				
infarct-pattern or ischemia				
any infarction	29/ 426	53/2595	3.3	2.1 - 5.2
anterior infarction*	16/ 235	53/2595	2.3	1.3 - 4.1
inferoposterior infarction*	19/ 211	53/2595	3.7	2.2 - 6.2
lateral infarction*	3/ 36	53/2595	1.8	0.6 - 6.0
ST depression	14/ 262	68/2759	2.4	1.3 - 4.2
negative T wave	2/ 60	80/2961	1.8	1.0 - 3.3
conduction and rhythm disturbances				
atrial conduction delay	53/1381	29/1640	2.1	1.3 - 3.3
QRS duration > 110 msec	9/ 151	73/2904	2.3	1.2 - 4.6
QT-corrected	8/ 267	74/2754	1.3	0.6 - 2.8
pvc	9/ 164	73/2857	2.4	1.2 - 4.7
left ventricular hypertrophy				
Sokolow (voltages only)	18/ 373	64/2648	2.1	1.3 - 3.6
Sokolow with LV strain	9/ 117	73/2904	3.6	1.8 - 7.1
Casale criteria	12/ 118	70/2903	4.1	2.2 - 7.5

%CDch+, rate of sudden death during follow-up in patients with characteristic present; %CDch-, rate of sudden death during follow-up in patients with characteristic absent; HR, hazard ratio (may be interpreted as relative risk); CI, confidence interval; PVC, premature ventricular beat; * versus no myocardial infarction.

Table 5. Univariate analysis of the relative risk for fatal or non-fatal stroke in relation to selected clinical and electrocardiographic characteristics.

characteristics	%CDch+	%CDch-	HR*	95%-CI#
male gender	187/1971	74/1050	1.4	1.0 - 1.8
age > 65 yrs	172/1613	89/1408	1.8	1.4 - 2.3
vascular risk factors or disease				
smoking	119/1355	142/1666	1.0	0.8 - 1.3
diabetes	45/ 239	216/2782	2.7	1.9 - 3.7
hypertension	120/1260	141/1761	1.2	0.9 - 1.5
periph.vascular disease	22/ 173	239/2848	1.6	1.0 - 2.4
history of ischemic heart disease				
past myocardial infarction	29/ 294	232/2727	1.2	0.8 - 1.8
angina pectoris	27/ 282	234/2739	1.6	0.8 - 1.7
coronary bypass surgery	5/ 60	256/2961	0.9	0.4 - 2.3
chest X-ray (CT ratio > 50%)	32/ 303	229/2699	1.3	0.9 - 1.8
standard 12 lead electrocardiogram				
infarct-pattern or ischemia				
any infarction	51/ 426	210/2595	1.5	1.1 - 2.1
anterior infarction*	34/ 235	210/2595	1.9	1.3 - 2.7
inferoposterior inf.*	22/ 211	210/2595	1.2	0.8 - 1.9
lateral infarction*	3/ 36	210/2595	0.8	0.2 - 2.4
ST depression	35/ 262	226/2759	1.8	1.3 - 2.6
negative T wave	33/ 305	228/2716	1.4	0.9 - 2.0
conduction and rhythm disturbances				
atrial conduction delay	153/1381	108/1640	1.7	1.3 - 2.2
QRS duration > 110 msec	19/ 151	242/2870	1.5	0.9 - 2.4
QT-corrected	33/ 267	228/2754	1.7	1.2 - 2.4
pvc	14/ 164	247/2857	1.1	0.6 - 1.8
left ventricular hypertrophy				
Sokolow (voltages only)	43/ 373	218/2648	1.5	1.1 - 2.1
Sokolow with LV strain	13/ 117	248/2904	1.4	0.8 - 2.5
Casale criteria	17/ 118	244/2903	1.8	1.1 - 2.9

%CDch+, rate of fatal or non-fatal stroke during follow-up in patients with characteristic present; %CDch-, rate of fatal or non-fatal stroke during follow-up in patients with characteristic absent; HR, hazard ratio (may be interpreted as risk); CI, confidence interval; PVC, premature ventricular beat; * versus no myocardial infarction.

Prediction of cardiac and cerebral events by multivariate analysis

For the multivariate analysis a stepwise approach was used, in which the usual order of accumulation of data was followed. Patient characteristics as sex and age are always available and are supplemented with details of the clinical history and information from chest X-ray (Model 1). In model 2 the different ECG abnormalities were added to the multivariate analysis.

Table 6. Multivariate analysis by Cox proportional hazards analysis of risk factors for cardiac events (cardiac death or non-fatal myocardial infarction) resulting from clinical history, chest X-ray and standard 12 lead electrocardiogram.

characteristics	Model 1 HR(95%CI$)	Model 2 HR(95%CI$)
demographics		
male sex	1.5 (1.1 - 2.1)	1.5 (1.1 - 2.1)
age > 65 yrs	1.9 (1.4 - 2.5)	1.6 (1.2 - 2.2)
vascular risk factors or disease		
diabetes	1.7 (1.1 - 2.7)	1.6 (1.1 - 2.5)
history of ischemic heart disease		
past myocardial infarct	2.1 (1.4 - 3.0)	1.5 (1.0 - 2.2)
angina pectoris	1.6 (1.1 - 2.4)	1.5 (1.0 - 2.3)
standard 12 lead electrocardiogram		
infarct-pattern or ischemia		
anterior infarction*		1.7 (1.1 - 2.7)
negative T wave		1.6 (1.1 - 2.4)
conduction and rhythm disturbances		
QRS duration > 110 msec		1.5 (1.0 - 2.5)
pvc		2.0 (1.2 - 3.2)
left ventricular hypertrophy		
Casale criteria		3.2 (2.0 - 4.9)

HR, Hazards ratio; CI, confidence interval; $ Calculated as the 95%-CI for the hazards ratio; * versus no myocardial infarction

For cardiac events age (>65 yrs) and male sex were strong predictive variables, independent of all other characteristics, as was the presence of diabetes, a history of past myocardial infarction and current angina pectoris. ECG characteristics such as anterior myocardial infarction, negative T waves, premature ventricular beats and Casale criteria for left ventricular hypertrophy were shown to be independent predictors of cardiac events (table 6). For sudden death only age (>65 yrs), presence of infarction, premature ventricular beats, or left ventricular hypertrophy on ECG were found to be significant risk factors (table 7). Independent risk factors for recurrent stroke were male gender, age (>65 yrs), diabetes, and on ECG the presence of anterior infarction, ST depression, atrial conduction delay and prolonged QT interval (table 8).

Table 7. Multivariate analysis by Cox proportional hazards analysis of risk factors for sudden death resulting from clinical history, chest X-ray and standard 12 lead electrocardiogram.

characteristics	Model1 HR(95%CI$)	Model2 HR(95%CI$)
demographics		
age> 65 yrs	2.8 (1.7 - 4.7)	2.5 (1.5 - 4.3)
clinical history		
past myocardial infarct	2.1 (1.2 - 3.6)	
chest X-ray (CT ratio > 50%)	1.8 (1.0 - 3.1)	
standard 12 lead electrocardiogram		
infarct-pattern or ischemia		
anterior infarction*		2.9 (1.7 - 5.2)
infero-posterior infarction*		2.4 (1.3 - 4.6)
conduction and rhythm disturbances		
atrial conduction delay		1.5 (0.9 - 2.4)
pvc		2.0 (1.0 - 4.0)
left ventricular hypertrophy		
Sokolow with LV strain pattern		2.1 (0.9 - 4.7)
Casale criteria		2.4 (1.2 - 4.9)

HR, Hazards ratio; CI, confidence interval; $ Calculated as the 95%-CI for the hazards ratio; * versus no myocardial infarction.

Table 8. Multivariate analysis by Cox proportional hazards analysis of risk factors for fatal and non-fatal stroke resulting from clinical history, chest X-ray and standard 12 lead electrocardiogram.

characteristics	Model 1 HR(95%CI$)	Model 2 HR(95%CI$)
demographics		
male sex	1.6 (1.2 - 2.1)	1.6 (1.2 - 2.0)
age > 65 yrs	1.8 (1.4 - 2.3)	1.7 (1.3 - 2.2)
vascular risk factors or disease		
diabetes	2.7 (2.0 - 3.8)	2.6 (1.8 - 3.5)
standard 12 lead electrocardiogram		
infarct-pattern or ischemia		
anterior infarction*		1.5 (1.0 - 2.1)
ST depression		1.5 (1.1 - 2.2)
conduction and rhythm disturbances		
atrial conduction delay		1.5 (1.1 - 1.9)
QT-corrected		1.4 (1.0 - 2.0)

HR, Hazards ratio; CI, confidence interval; $ Calculated as the 95%-CI for the hazards ratio; * versus no myocardial infarction

Discussion

The rate of cardiac and cerebrovascular events in the Dutch TIA study population (5.3 per 100 person-years) is similar to that in the UK-TIA trial (5.0) [30] and lower than in the ESPS[1] study (8.0) [31].

Our hypothesis that major cardiac ischemic events occur mainly in patients with pre-existing ischemic heart disease was confirmed by the predictive power of several clinical and electrocardiographic features reflecting myocardial ischemia which were present at the intake in the study. Clearly more extensive cardiological investigation including tests such as echocardiography or perfusionscintigraphy are more accurate and sensitive in detecting ischemic heart disease adding further prognostic information [32, 33, 34]. However, these investigations are complex and expensive. Futhermore, in an eldery population with TIA or minor ischemic stroke the prevalence of ischemic heart disease is

[1] European Stroke Prevention Study

already high, decreasing the incremental information obtained with these tests above clinical history and ECG [35]. In this regard, it is important to mention that in a recent retrospective study that used a stepwise multivariate model for the determination of predictive variables for cardiac death in patients with stroke, it was found that the clinical history of a previous myocardial infarct and/or Q-waves on the ECG are better indicators than echocardiographic abnormalities of left ventricular wall motion [36].

An interesting finding in our study population was the high prevalence of a previous myocardial infarction and more particularly the high proportion of an unrecognized myocardial infarction (Chapter 6). Goldstein also reported a higher incidence (20%) of pathologic Q waves in a series 150 patients with acute stroke as compared with the ECG findings in age- and sex-matched controls [37]. Our patients with an unrecognized infarct had an increased risk for subsequent cardiovascular events comparable with that of patients with a known infarct. Other ECG variables characteristic for ischemia, i.e. ST depression and T wave abnormalities, with or without symptoms, also had an increased risk of future cardiovascular events. Thus, it appears that silent myocardial ischemia has the same prognostic significance as symptomatic ischemic heart disease [38, 39]. These findings are in accordance with a recent analysis of the Framingham data, in which the presence of ECG abnormalities other than Q waves were potent predictors of long-term prognosis [40].

Signs of left ventricular hypertrophy (LVH) on ECG are recognized prognostic markers for subsequent cardiovascular events [41, 42, 43]. The most likely explanation is that in these patients hypertrophy is an indicator of some cardiac damage as a result of longstanding arterial hypertension. It is remarkable that even in univariate analysis history of hypertension was not an important predictor for either cardiovascular or cerebrovascular events. Hypertension only becomes a predictor if it is associated with left ventricular hypertrophy on the ECG. In multivariate analysis LVH on the ECG did not remain an independent risk indicator for recurrent stroke. We used a simplified Sokolow definition for LVH, in which only voltage criteria of the precordial leads were included. The addition of repolarization abnormalities (LV strain) to the Sokolow voltage criteria increases the predictive power, probably by increasing the specificity for LVH [25]. The Casale criteria include voltage measurements from the standard leads, repolarization abnormalities in V1, and a correction for sex and age. These criteria have an increased specificity for diagnosing the presence of LVH [22, 23]. Our findings confirm the more predictive power of the Casale criteria.

In several studies no correlation between an increased P terminal negative force in V1 (PTF) and the presence of left atrial enlargement as detected by echocardiography was found [44]. The PTF usually results from intra-atrial

conduction abnormalities lengthening the pathway of the impulse. Left atrial enlargement may be another factor. Our study, as well as previous studies [19, 45] show that the presence of PTF is a predictor of subsequent cardiovascular events. In our study population we excluded cardiac sources of emboli. Therefore PTF more likely reflects an intra-atrial conduction delay in the absence of significant left atrial enlargement. Since such a conduction delay may be a marker of atherosclerosis it may explain why it is a predictor of future cardiovascular events, similar to other intra-cardiac conduction abnormalities such as left bundle branch block [45, 46].

Except for age (>65 years), of all the clinical parameters the ECG variables were the best predictors for the occurrence of sudden death. This was also one of the findings in the Framingham Study especially in patients with known coronary heart disease [47]. It is conceivable by means of the ECG a group of patients, in whom signs of cardiac or cerebral ischemia exist, can be identified who might benefit from betablocking treatment to prevent sudden death [49, 50, 51].

Coronary atherosclerosis is one of the manifestations of atherosclerotic vascular disease. It is therefore not surprising, that the ECG, being a sensitive and specific tool for the detection of myocardial ischemia in patients with TIA or minor ischemic stroke, has predictive power for recurrent ischemic stroke, another manifestation of atherosclerosis. Population studies have indicated the prognostic significance of coronary disease for stroke in patients who had not yet suffered a cerebrovascular event [1, 12]. Anterior location of the myocardial infarction had the highest risk for recurrent stroke in our study. The higher incidence of left ventricular thrombi in infarcts located in the anterior wall is a likely explanation [52, 53, 54]. With the unexpected finding of higher recurrence of stroke in patients with repolarization abnormalities such as ST-depression or prolonged QT interval the question arises whether these repolarization abnormalities might be a (temporary) consequence of cerbral ischemia rather than a sign of pre-existent atherosclerotic disease. It is known that electrocardiographic changes can be found in the acute phase of cerebrovascular events, especially when they are hemorrhagic [55]. The ECG changes might reflect the extent of cerebral damage and therefor relate to the risk of recurrent stroke [8].

We excluded patients with potential cardiac sources of embolism and/or receiving antiplatelet therapy. Therefore the results of this study cannot be extrapolated to all patients with TIA or minor ischemic stroke [56].

This study indicates that patients with recent TIA or minor ischemic stroke with signs of ischemic heart disease, revealed by clinical history or standard ECG at rest, have a higher risk for major cardiac events and recurrent cerebral ischemic events. The existence of such a high-risk subgroup could explain the increased cardiac and cerebral risk in the TIA or minor stroke patients as a whole. Screening patients with TIA or ischemic stroke for heart disease is therefore important not only to detect potential cardiac sources of embolism, but also to identify patients with a high risk for future cardiac and cerebral ischemic events. The practical issue is which preventive measures can decrease this risk. A more extensive diagnostic work-up and preventive measures by drug therapy might be warranted in these high-risk patients, but properly controlled prospective studies are needed to resolve the issue.

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CHAPTER VIII

SECONDARY PREVENTION OF CARDIAC AND CEREBRAL ISCHEMIC EVENTS: DIFFERENT DOSES OF ASPIRIN?

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Atherosclerosis is a generalized vascular disorder and it is the most important pathogenetic factor both in ischemic heart disease and in ischemic stroke [1, 2, 3, 4]. It is not surprising therefore, that the occurrence of transient ischemic attacks or stroke may be a harbinger of future ischemic coronary events and vice versa [5, 6].

Several differences, however, between cardiac and cerebral ischemic events can be identified. The incidence of ischemic stroke does not run parallel with the incidence of coronary events; in Japan the incidence of stroke in comparison with that of coronary heart disease is much higher than in Western Countries [7], and over the past few years the incidence of stroke in Western countries showed a much greater decline than that of ischemic heart disease [8, 9]. The same risk factors operate in both clinical entities, although with differing impact; arterial hypertension is by far the most powerful risk factor for stroke [9, 10, 11, 12], whereas hypercholesterolemia and family history play a relatively more important role in the pathogenesis of coronary heart disease [11, 13, 14, 15, 16].

These epidemiological differences between coronary and cerebral vascular events may be explained in various ways [17]. Even though both cerebro- and cardiovascular disease may be predominantly atherosclerotic, differences in structure of the vessel wall between the (extra)cerebral and the coronary vasculature might explain a different reaction to atherosclerosis [4, 25, 18]. Furthermore, the pathogenesis of atherosclerosis may be different; shear stress seems to play an important role in the coronaries, which are continuously subject to the contractions of the heart [19], but in the carotid arteries and brain arteries blood flow may be more laminar. Finally, the classification of cerebrovascular events may be too crude because of the inclusion of events with greatly differing pathogenesis. Studies of both atherosclerotic and non-atherosclerotic origin are included [20, 21, 22] and if atherosclerotic pathogenesis is considered, it might affect different sites of the vascular tree [23, 24].

Blood platelets are an important factor in the process of atherosclerosis [26, 27, 28], and antiplatelet therapy is used in both primary and secondary prevention of myocardial as well as cerebral ischemia. Differences also occur in this respect; the risk reduction of cardiac ischemic events through aspirin is not equal to the risk reduction obtained for cerebral ischemic events. This difference seems to depend on the patient's history of prior cardiac or cerebral events [29, 30, 31]. In the development of acute coronary syndromes, factors that are not directly influenced by aspirin, such as vasoconstriction, might play an important role whereas in acute cerebral ischemia these factors may be less predominant [32, 33, 34, 35].

Not only the preventive effect of aspirin per sé may differ for cardiac or cerebral ischemic events, but also the required dose. In this review we shall present current evidence and opinions about the 'ideal' dose of aspirin for secondary prevention of cerebral or cardiac ischemic events, resulting from different clinical studies and trials in the field of neurology and cardiology in the past decades.

Aspirin dose for secondary prevention of atherosclerosis in neurology and cardiology over the years.

For centuries salicylic acid has been used as an antipyretic agent and the acetylated form, which caused less irritation of the stomach, was developed as early as 1853. In 1968 O'Brien found a specific inhibitory effect of aspirin on the aggregation response of platelets, even in doses as low as 150 mg [36, 37]. In 1971 Vane and his colleagues detected that aspirin was an inhibitor of platelet aggregation by acetylation of cyclo-oxygenase [38].

Very low doses of aspirin (<100 mg daily) still inhibit more than 95% of the production of the aggregating substance thromboxane A2 in platelets by inactivation of the enzyme cyclo-oxygenase, whereas the production of prostacyclin, which takes place in endothelial cells and which has an antiaggregation effect, would be little affected, at least with doses below 40 mg [39, 40]. As early as in 1984 therefore, cardiologists studied doses as low as 80-160 mg/day which were subsequently shown to be equally effective as higher doses in patients with unstable angina [41] and in the prevention of sclerosis in coronary bypass grafts [42, 43]. At that same time, neurologists were treating ischemic manifestations of atherosclerotic disease in the brain with doses as high as 1000 mg/day, on the basis of the first large trials in such patients [44, 45]. After the results of the UK-TIA Trial had been published in 1988 and it was shown that there seemed to be no difference in the preventive effect between doses of 300 and 1200 mg [46], the widely accepted dose of aspirin for secondary prevention in patients after TIA or minor ischemic stroke became 300 mg/day in Europe. This dose was still higher than the dosis of 80-160 mg/day aspirin commonly used in prevention of ischemic heart disease at that time.

In 1985, Weksler et al. published a clinical study concerning low dose aspirin (40 mg) in 23 patients with recent cerebral ischemia. They found no difference in the effect on the platelets of these patients compared with higher doses of aspirin [47]. However, only after publication of the results of two large, prospective, randomized clinical trials, the Dutch TIA Trial and the Swedish Aspirin Low-dose Trial, neurologists gradually seem to be getting convinced of the preventive effects of very low doses of aspirin. The Dutch study showed that

30 mg aspirin/day was indeed at least as effective as 283 mg/day in the prevention of vascular events [48]. The Swedish study showed that a low dose (75 mg/day) of aspirin significantly reduced the risk of stroke or death in patients with cerebrovascular ischemic events compared with placebo treatment [49]. Thus neurologists seem to have overtaken the cardiologists, in that many now recommend the lowest dose of aspirin, between 30 mg (Dutch TIA Trial) and 75 mg (Swedish SALT Trial). Cardiologists as a rule still use between 80 and 160 mg for secondary prevention in ischemic heart disease [29,30, 50]; this latter dose regimen corresponds with the daily aspirin dose of 1-2 mg/kg for prevention of pregnancy-induced hypertension and pre-ecclampsia in the field of obstetrics [51].

The remaining difference in dosage does not seem logical at first sight, because both cerebral and cardiac ischemia are caused mainly by atherosclerosis, with increased platelet aggregation as one of its deleterious consequences. The differences in dosage regimens over the years may result from reluctance of both cardiologists and neurologists to extrapolate beyond their own discipline; in both fields large trials with aspirin were separately conceived, and the results were published at different times. The question arises whether the difference between the current cardiological dose (80-160 mg) and the neurological dose (30-75 mg) is only historically determined or whether there is some true rationale.

Differences between (extra)cerebral and cardiac vascular atherosclerosis?

A rationale for the different dosage regimens in these two fields may be found in a different dose-effect relation of aspirin in the relatively small coronary arteries compared with the considerably larger carotid, vertebral, and basilar arteries. In 85% of the cases of acute myocardial infarction, no hemodynamically important lesions, that is, with a degree of stenosis of less than 75 % of the diameter, are found in the coronary arteries [52, 53]; in contrast, occurrence of ipsilateral stroke in patients with carotid stenosis seems to be related to the severity of the stenosis in both symptomatic and asymptomatic patients [5, 54, 55]. These differences suggest a more important role for syndromes of accelerated atherosclerosis in the coronaries than in the (extra)cerebral arteries [56], and the dosage of aspirin may need to be higher during these episodes. Also, development of collateral circulation in the coronary vasculature when severe stenosis is present, may occur more often than in the large (extra)cerebral arteries.

Alternatively, it might not be the anatomical difference in vasculature but rather a difference in the pathophysiology of atherosclerosis and platelet aggregation that determines the difference between (extra)cerebral arteries and the

coronaries. Shear stress, for example, which is known to be an important stimulus for platelet aggregation, may be higher in coronary arteries. The higher shear stress in the coronaries is caused by their smaller size and the circumferential tensile stress, resulting not only from the intrinsic musculature of the arteries themselves but also from the contraction of the heart [19, 27, 28, 56, 57]. Ratnatunga et al. [58] discovered that aspirin does affect the platelet response to shear forces, but that this requires higher doses than 300 mg/day, suggesting a mode of action probably different from that of interference with thromboxane formation.

Is sparing of prostacyclin synthesis possible, with low doses of aspirin?

In 1985, Patrono et al. showed that in patients with acute myocardial infarction the antiaggregating effect on platelets of aspirin in a dose of 50 mg/day was stable over time and similar to the effects of 324 mg/day [59]. They were therefore among the first investigators to urge the need for large, prospective clinical trials to validate the use of low doses of aspirin [39]. In the same study, after pooling data from each treatment, it was noted, however, that the inhibition of tromboxane production achieved with 324 mg ASA/day was significantly greater ($P<0.05$) than the inhibition obtained with 50 mg/day [59]. In a later study, the same group of investigators examined patients with unstable angina and they observed that very low dose aspirin (20 mg/day iv) profoundly suppressed platelet cyclooxygenase activity, but that the residual enzyme activity (<5%) was sufficient to generate thromboxane B2 levels in excess of control values in appoximately 17 % of all patients [60].

Besides the observation that very low doses of aspirin (<50 mg daily) still inhibit more than 95% of the production of the aggregating substance thromboxane A2 in platelets, the argument for the use of very low dose aspirin was that the production of prostacyclin, which takes place in endothelial cells and which has an antiaggregating effect, would be little affected, at least with doses below 40 mg [39, 40]. Nevertheless, FitzGerald et al. found that even with doses of 20 mg aspirin twice daily bioselectivity for inhibition of thromboxane synthesis is more difficult to achieve in the elderly; higher falls in prostacyclin synthesis by this very low dose of aspirin were seen in elderly patients, both with or without vascular disease, than in young volunteers [63].

Recently, Force and colleagues concluded from their experiments that the aspirin-induced decrease in prostacyclin levels may be unavoidable, because it arises not from cyclooxygenase inhibition in endothelial cells but from a reduction of endoperoxide formation by platelets, which is an inherent feature of

the beneficial action of aspirin [61]. So the rationale for using a low dose of aspirin in order to spare the endothelial production of prostacyclin may be questioned. It may be more important to suppress thromboxane A2 production in platelets completely, by more than 99%, by means of 100-325 mg aspirin daily, rather than to obtain a reduction of 95% with the smaller doses [62].

On the other hand Clarke et al. demonstrated a selective suppression of thromboxane A2 but not of systemic prostacyclin with low-dose aspirin (75 mg) when given in a controlled-release form; they explained these findings by the effects of aspirin being confined within the portal circulation [63, 64].

Differences in platelet aggregation with coronary or cerebral atherosclerosis?

The degree of spontaneous platelet aggregation in vitro has been found by Trip and colleagues to be related to the prognosis in survivors of myocardial infarction [66]. Patients with the highest spontaneous platelet aggregation turned out to have a worse prognosis with respect to coronary events and mortality. Increased spontaneous platelet aggregation, and increased thromboxane biosynthesis have also been demonstrated in patients with stroke [67, 68]. A large inter-individual variation in platelet aggregability and serum thromboxane concentrations was found after very low dose aspirin (40 mg/day) in patients with recent stroke [69]; this study concluded that a dose of 40 mg aspirin/day is ineffective for suppressing platelet function in some individuals. Considering the evidence of a morning increase in platelet aggregability and the concurrent risk of myocardial infarction and sudden cardiac death [70, 71], it might be possible that in spite of approximately 95% inhibition of thromboxane production during 24 hours with very low dose aspirin (<50 mg daily) a moderate peak of thromboxane production will still be present in the morning hours in patients with coronary sclerosis. One might speculate about the existence of a biological association between the activity of atherosclerosis and the degree of spontaneous platelet aggregation, which would explain the need for a higher dosage of aspirin in patients with accelerated ischemic heart disease. In patients with unstable angina Vejar, from Patrono's group, et al. found a 2- to 30-fold higher urinary level of thromboxane-metabolites than in controls [60]. In their study the mere presence of diffuse atherosclerotic lesions, presumably not complicated by plaque fissure, did not seem to be associated with biochemical evidence of episodic platelet activation. Similarly, FitzGerald et al. found a normal thromboxane synthesis only in patients with stable coronary disease [72].

Effects of aspirin independent of acetylation of cyclooxygenase

In the Dutch TIA Trial significantly fewer episodes of minor bleeding were observed in patients taking the lower dose of 30 mg (3.2 % versus 5.3 %, over 2.6 years). Forty patients receiving 30 mg of aspirin had one or more major bleeding complications, as compared with 53 patients receiving the 283-mg dose (hazard ratio, 0,77; 95 percent confidence interval, 0,51 to 1,16). There were 11 episodes of fatal bleeding in the 30-mg group and 18 in the 283-mg group. An equally small number of episodes of minor gastrointestinal bleeding (less than 1%) in both groups [48]. These results were unexpected, inasmuch as one would anticipate a similar incidence of bleeding with doses of the drug that suppress thromboxane-dependent platelet function with equal effectiveness. The explanation may be that higher doses of aspirin enhance bleeding or may have antithrombotic capacity independent of the acetylation of cyclooxygenase; for instance, aspirin was demonstrated to cause a competitive inhibition of acetylcholinesterase, which potentiates the vasodilatory effects of acetylcholine through an endothelial-derived relaxing factor [73, 74].

Another explanation for a possible differential effect between the two doses of aspirin is that aspirin may have effects such as suppression of cell proliferation [75]. Some studies indicated such an effect of aspirin on cell-cell interactions via the arachidonate pathway [76].

The acetylcholine effect as well as cell-cell interactions may play different roles in the vessels of brain or heart during atherosclerotic processes. This might explain why different doses of aspirin are required for secondary prevention of ischemic events in the brain or in the heart. Newman recently stressed the paradoxical narrowing of the coronaries by acetylcholine, if affected by sclerosis [77].

Comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke (Dutch TIA Trial)

The Dutch TIA Trial compared the effects of low dose of aspirin (30 mg a day) versus high dose (283 mg a day) as to the occurrence of death from all vascular causes, non-fatal stroke, or non-fatal myocardial infarction in a double-blinded, randomized controlled clinical trial in patients who had a transient ischemic attack or minor ischemic stroke [48]. A total of 3131 patients participated in the study. A detailed description of the design, patients, data acquisition and follow-up of the Dutch TIA Trial has been previously reported.

The crude hazard ratio for fatal and non-fatal stroke for the group receiving 30 mg daily was 0.82, with a 95 percent confidence interval of 0.64 to 1.04. For cardiac events, which included only cardiac death and non-fatal myocardial infarction, the crude hazard ratio for the group receiving 30 mg daily was 1,14, with a 95 percent confidence interval of 0.86 to 1.51[1]. The crude hazard ratio for the combined event of death from all vascular causes, non-fatal stroke, or non-fatal myocardial infarction was 0.95, with a 95 confidence interval of 0.79 to 1.14. These figures might indicate a trend towards a more favorable effect of the low dose of aspirin for prevention of cerebrovascular events and a more favorable effect of the higher dose for prevention of the other vascular events, which were mainly cardiac in origin.

Conclusions

Data from recent clinical studies in the field of cardiology and neurology demonstrated that for secondary prevention of cardiovascular and cerebrovascular ischemic events low or very low doses of aspirin, between 30 mg and 160 mg, are as effective as higher doses of aspirin [74, 78]. No clinical data, however, are available about the 'ideal' dose of aspirin and whether the 'ideal' dose differs for the secondary prevention of cardiac ischemic events or that of recurrent stroke. Future studies on aspirin should take this into account and, if possible, provide an answer to the suggested hypothesis of different dose-effect relations in the prevention of cerebral or cardiac ischemic events. Notwithstanding the similarities of atherosclerosis in the heart and the brain, differences may exist in pathogenesis and prevention which might have implications not only for therapy with aspirin but also for other drugs used in atherosclerosis.

Finally, more cooperation between cardiologists and neurologists is needed in the battle against atherosclerosis.

1. These data for cardiac events only, have not yet been published. A post-hoc analysis was performed to distinguish a possible differential effect of 30 mg versus 283 mg aspirin a day on cerebral respectivily cardiac outcome events.

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Before discussing the need for a cardiological work-up of patients with cerebral ischemia, I would like to put forward not only the heart of the patient but that of his physician as well. Physicians do not treat diseases that are precisely categorized on the basis of certain manifestations, but they treat sick people. The disease affects the patient in his existence in relation with his material and emotional surroundings. For him recovery does not necessarily imply the complete disappearance of all manifestations of the disease, but signifies a state in which he can again live in equilibrium with the world around him. It is well known that some patients can be quite satisfied with their recovery despite persisting manifestations of their disease. There are several explanations for this, one of which is that because of their persisting complaints they continue to get attention from the people around them and from society as a whole, thereby maintaining the equilibrium of their existence which otherwise might have been endangered, even without their current disease. On the other hand, our competitive society with an emphasis on production, fitness and beauty may condemn a person to illness, although he is for himself and for his relatives in a satisfactory equilibrium with the world around him and has no spontaneous symptoms.

From the above it will be obvious that the doctor, in his relation to the patient, must act not only on the basis of the scientific considerations which he was taught in medical school but also on considerations dictated by his heart if he wants to be receptive to the existential aspects of the patient. Only when the doctor is not merely an expert in a disease but is also dedicated to the patient, can 'the reason of his heart' help him to make the best decision. Augustinus, a philosopher in early christianity, already said: 'someone or something is known only in so far as one is dedicated to him or it' ('Res tantum cognoscitur, quantum diligitur'). And Blaise Pascal, the French philosopher formulated this as follows: 'the heart has his reasons, which the reason does not know' ('Le coeur a ses raisons, que la raison ne connaît pas').

The 'raisons du coeur' go further than emotions. When making a clinical decision for an individual patient, we are free from all kinds of inclusion or exclusion criteria the patient would have to fulfill if he is to be entered into a large randomized double-blind therapeutic trial [1, 2]. This is not saying that we underestimate the information gained by these trials, but in the setting of clinical decision making for an individual patient, extrapolation is needed and other than scientific criteria should be considered as well.

GENERAL DISCUSSION

Cardiological evaluation of patients with cerebral ischemia compared to ophthalmological funduscopy used by clinicians in former days

Stroke is a major cause of disability in the Western world. Of all stroke patients 25% die, 25% recover well and 50% remain more or less handicapped. Annually in the Netherlands, 25.000 people suffer from stroke and at any one time there are some 100.000 people with a previous stroke [3]. In 80% of these cases the stroke is of ischemic origin. Of these, 10-20% are preceded by a transient ischemic attack (TIA) or by a reversible ischemic neurological deficit (RIND). TIA's and minor ischemic strokes are not only precursors of recurrent fatal or non-fatal strokes, but should also be seen as warning signals for major cardiac events. The 6% per annum mortality from heart disease in at least some series of patients with TIA or minor stroke is three times higher than the 1-2% annual mortality among persons of comparable age without evidence of atherosclerotic disease [4] and is even higher than the 3-4% per annum mortality of patients with angina pectoris [5]. The occurrence of TIA or minor stroke should therefore prompt to preventive measures for future major vascular events in the heart as well as in the brain.

The vascular system has the same histiogenesis throughout the organism and basically does not greatly differ in function. It is the transport system for blood, through which the different organs are supplied with oxygen and nutrients and through which carbon oxide and other metabolites are removed. It is not surprising therefore, that the clinicians in earlier days paid so much attention to the vascular aspects of the retinal blood vessels, as soon as these could be observed by means of the ophthalmoscope, as they were thought to reflect the condition of the vascular system in the entire organism. The time of carotid or coronary angiography was still far away. Patients with vascular disorders were categorized in several degrees of severity according to the vascular aspect of the retinal arteries; from this the nature of the vascular disorder was determined. Ophthalmoscopic funduscopy had the advantage of being a non-invasive and relatively simple investigation, which could be repeated periodically.

The cardiological evaluation of patients with cerebral ischemia can be compared to the early use of ophthalmological funduscopy, in that it reflects the

state of the vascular system in general and can be done by means of relatively simple and non-invasive techniques, which also can be repeated periodically. In addition, cardiological evaluation of patients with cerebral ischemia may provide quantitative information on the severity of the vascular disease and may reveal direct causes of brain ischemia (sources of embolism from the heart). It also provides information on the extent to which the heart itself is affected by the atherosclerotic process and allows to detect potentially life-threatening conditions.

Cardiological evaluation of patients with cerebral ischemia should therefore focus not only on the evaluation of possible cardiac sources of emboli but should include an evaluation of both the systemic vasculature and the heart.

Which cardiac investigations in a patient with cerebral ischemia?

The decision which cardiological investigations to use in a patient with cerebral ischemia depends on the following general criteria. The information must be clinically relevant for the individual patient [6], and should provide substantially more insight into the disease. One should also consider whether the results of the investigations will influence management of the patient.

In our study, non-invasive techniques of cardiac evaluation including the clinical history, standard electrocardiography and precordial echocardiography combined with Doppler studies, were found to be highly informative with regard to the state of the vascular system. In patients with cerebral ischemia there was a high prevalence of ischemic heart disease, whether previously recognized or not (Chapter VI). This association was so striking that even the extent of cerebrovascular damage was reflected in the number of electrocardiographic abnormalities that were detected (Chapter VI). Quantitative criteria for the presence of myocardial ischemia, infarction or left ventricular hypertrophy on the ECG have a strong predictive power for the occurrence of vascular events of both the brain and the heart (Chapter VII). Studies of others [7] have revealed a similar or even a higher predictive value of left ventricular hypertrophy for major vascular events, if measured by precordial echocardiography. Echocardiography also allows visualization of intracardiac thrombi [8], measurement of cardiac chamber dimensions and with Doppler studies the characterization of mitral flow is achieved [9; Chapter III). We found that increased atrial size and decreased mitral flow are determinants of cardioembolic risk in patients with non-valvular atrial fibrillation. Transesophageal echocardiography (TEE) permits visualization of the left atrial appendage, which is a site of predilection for thrombus formation [10, 11; Chapter II]. We also emphasized the role of TEE for the visualization

of fragile wall irregularities both in the ascending aorta and aortic arch, which are potential sources of artery-to-artery embolism [12, 13; Chapter II].

The usefulness of cardiological evaluation in patients with brain ischemia has been established beyond doubt. The question is how extensive it should be. Based on our own studies and those of others we would like to make the following remarks.

In all patients with brain ischemia, clinical history and physical examination must be complemented with an 12 lead electrocardiography at rest [14, 15, 16]. With the interpretation of these investigations all aspects of the cardiovascular system should be considered.

If clinical history, physical examination and ECG do not reveal abnormalities and the neurological examination provides no further information regarding the cause of the event, TEE must be considered, especially in younger patients [17, 18, 19, 20]. Colour Doppler study should be part of the TEE investigation in these patients because of the possible existence of a patent foramen ovale, which may cause paradoxical embolism [21]. The additional value of precordial echocardiography in patients with cerebral ischemia who have neither clinical nor ECG abnormalities is very poor [17, 18; Chapter II]. Other cardiac investigations such as thallium scintigraphy are indicated only if major (vascular) surgery is being considered, because of its ability to detect silent cardiac ischemia [22]. This has additional relevance since perioperative ischemia may cause myocardial infarction and mortality.

If standard cardiac evaluation with appropriate clinical history, physical examination and 12 lead electrocardiography does reveal abnormalities, precordial echography may provide useful additional information, especially if combined with Doppler study. Precordial echography allows adequate visualization of the left ventricular function, measurement of the cardiac chambers and detection of left ventricular hypertrophy, which are all indicators for future cardiovascular events [7, 28, 29]. Furthermore, cardioembolic risk assessment in these patients is enhanced by combination with Doppler study, at least in NVAF patients (Chapter III).

Although TEE is a highly sophisticated and sensitive method of detecting intracardiac sources of embolism and even allows to measure the ejection fraction of the left atrial appendage [28], we do not consider it the method of first choice for standard cardiac evaluation of patients with cerebral ischemia if abnormalities are found by clinical examination or ECG. TEE is a semi-invasive investigation. We should use it particularly with younger patients (<45 years) with unexplained stroke after precordial echocardiography with Doppler and with patients in whom

major pathology of the proximal aorta is suspected. In the elderly patients with cerebral ischemia with signs of ischemic heart disease, its use for the evaluation of the left atrium can be replaced satisfactorily by precordial echocardiography combined with Doppler study (Chapter III). Function of both the mitral valve and the left ventricle are important determinants of flow dynamics in the left atrial appendage. Both these indices can be adequately measured by precordial echo/Doppler.

Useful additional information about the heart in patients with cerebral ischemia is provided by considering other parts of the vascular system

Not only the examination of the heart itself is important in patients with cerebral ischemia, but also other indicators of generalized atherosclerosis, of which cerebral ischemia is only one aspect, may be detected in the vascular system and may provide additional information about the state of the heart. The importance of the simple information whether or not a patient with cerebral ischemia has symptoms of intermittent claudication or has an asymptomatic neck bruit on physical examination, should not be underestimated. Several studies have demonstrated a high prevalence of ischemic heart disease in patients with peripheral arterial disease or asymptomatic neck bruits, and an elevated risk for major cardiac events [31, 32, 33]. These findings were confirmed by our study (Chapter VI, VII).

Several studies also showed that analysis of hemostatic factors might contribute to understanding the pathogenesis of (cardioembolic) stroke [34, 35]. We studied the value of several hemostatic factors in stroke patients and could confirm these findings (Chapter IV). The factors TAT and F1+2, however, were elevated not only in stroke patients with a potential cardiac source of embolism but also in patients in sinus rhythm without such a potential source. One patient with an intraventricular thrombus, and no clinical or radiological signs of cerebral ischemia, had significantly elevated hemostatic parameters (TAT and F1+2). After oral anticoagulation TAT and F1+2 levels fell sharply. Until now indications for oral anticoagulation in patients with left ventricular thrombi are based upon echocardiographic indices such as the shape of the thrombus and its mobility [36]. Further refinement of the indications for oral anticoagulation in patients with left ventricular thrombi might be achieved by means of these hemostatic markers. One might speculate that even low doses of anticoagulation can be used and that control of therapeutic levels is possible by measurement of these hemostatic markers in stead of INR values.

The attention should not be focused on trying to find a single possible causative factor for cerebral ischemia. There is always the possibility that other factors coexist and that these may require a different form of treatment. An example of this is the frequent coexistence of carotid lesions and non-valvular atrial fibrillation in elderly patients with cerebral ischemia [25]. Whereas the first would signify an artery-to-artery source of embolism calling for antiplatelet or even surgical treatment [26, 27], the latter is probably most effectively treated with anticoagulants [29, 30].

Plea for more exchange of information about atherosclerosis between different disciplines

I would like to finish this thesis with a plea for more cooperation between neurologists and cardiologists in the area of vascular disease and atherosclerosis. In Chapter VIII the prescription of aspirin treatment by neurologists is compared with the treatment usually prescribed by cardiologists. Different doses of aspirin are still being used in the two disciplines although the aim of preventing vascular events is the same. It is not yet known whether this dose difference is only historically determined or whether there is some rationale for this discrepancy. Had there been more cooperation and communication between the two disciplines we would probably have had an answer to this question and we could have obtained more insight into the complex disease of atherosclerosis.

Although manifestations of atherosclerosis in the brain and in the heart may have much in common, some differences do exist. Extrapolations from one field to the other must therefore be made with caution. In the Dutch TIA Trial, some of the patients were randomised to betablockade because of the recognition that ischemic heart disease is an important life-threatening complication in patients with cerebral ischemia [37]. The known benefit of betablockers for reduction of fatal and non-fatal cardiac events led to the hypothesis that this benefit might also apply to patients with cerebral ischemia [38] . However, no significant reduction of vascular risk was found in patients treated with betablockade (atenolol) compared with patients on placebo in the Dutch TIA Trial [39].

Thrombolytic therapy in the acute phase of ischemic stroke must be differentiated from thrombolytic therapy in the acute phase of myocardial infarction. Whereas occlusion in acute myocardial infarction is almost always caused by a fresh thrombus, occlusion in acute stroke may be caused by atheromatous debris from artery-to-artery embolism and is therefore probably less susceptible to thrombolytic therapy [12, 13].

In a recent study Koudstaal et al. found that an "atypical TIA" may herald cardiac rather than cerebral events [40]. It is possible that the symptoms of an "atypical TIA" might be caused directly by cardiac dysrhythmias or by atypical angina pectoris. Better understanding of and attention for cardiac symptoms of atherosclerosis by neurologists would probably lead to earlier recognition of the cardiac origin of the complaints. Vice versa, cardiologists should also pay more attention to cerebral manifestations of atherosclerosis. There is evidence from animal studies that calcium-antagonists may exert an antiatherogenic effect [41]. In view of these encouraging results a number of studies of calcium-blockers in the treatment of human atherogenesis have recently been performed. It is remarkable that in the two large clinical studies with this design the extensive analysis was focused on coronary events and coronary arteriograms only, whereas cerebrovascular events or Duplex scanning of the carotid arteries were not performed [42, 43]. It seems that neurologists and cardiologists look at the same disease but see different things (Chapter I).

Information from the fields of neurology and cardiology concerning the diagnosis and treatment of atherosclerotic disease must be integrated and further complemented with information from other specialties that deal with atherosclerosis, calling for a discipline 'neurocardiology' or 'cardioneurology' [44].

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SUMMARY

In this study several aspects of the cardiological evaluation of patients with cerebral ischemia are described; its usefulness for diagnosis and treatment is discussed.

In the *General Introduction* it is demonstrated that there are two major reasons for cardiological evaluation of patients with a cerebral ischemic event. First of all the heart may be the cause of the cerebrovascular event. Cardiac investigation can be directed towards finding a potential cardiac source of embolism in the heart or detecting causes of cardiogenic circulatory insufficiency leading to prolonged cerebral hypoperfusion. Secondly, the fact that atherosclerosis is a generalized vascular disorder probably explains the existence of a strong association between cerebral and cardiac ischemic disease. The first part of this thesis deals with the identification of cardiac sources of embolism as potential cause of cerebral ischemia. The second part describes how ischemic heart disease often coexists with cerebral ischemia, both being manifestations of atherosclerosis.

Chapter I consists of a review of the literature, showing clear relations between heart and brain in the presence of atherosclerosis. The aim of this thesis is to approach the clinical and epidemiological aspects of patients with cerebral ischemic events, while recognizing the existence of heart-brain interactions in atherosclerotic disease. With respect to this interaction some philosophical considerations are presented.

In *Chapter II* a comparative study is done in 72 patients with recent TIA or minor stroke to evaluate the usefulness of precordial versus transesophageal echocardiography (TEE) for the detection of intracardiac sources of embolism. It is demonstrated that besides history, physical examination and ECG the additional value of precordial echocardiography without Doppler studies is limited for the detection of intracardiac embolic sources. TEE was demonstrated to increase the yield of potential intracardiac sources of embolism compared with precordial echocardiography. TEE enables the visualization of the left atrial appendage, which is a site of predeliction of intracardiac thrombi. Pathology of the ascending aorta and the aortic arch was frequently detected and we suggested the possibility of artery-to-artery embolism from fragile atheromatous plaques.

The overall yield of potential sources of emboli detected by TEE remained relatively small (10%) and it was not clear whether these findings were merely associated abnormalities or were directly causative of cerebral ischemia. No studies with intravenous contrast injection were performed, nor was Doppler analysis done.

Chapter III demonstrates that if precordial echocardiography is combined with transmitral Doppler analysis, identification of patients at risk for cardioembolic stroke in patients with non-valvular atrial fibrillation (NVAF) is feasible. Presence of spontaneous echocardiographic contrast in the left atrium (SCLA) is known to be a sign of diminished atrial flow and has been shown to be associated with an increased risk of cardioembolism. In our study we found more SCLA in 17 NVAF patients with previous TIA or minor ischemic stroke than in 17 NVAF patients who had had no such event. In addition it was noted that combined measurement of left atrial size, if corrected for base index, and of transmitral flow velocity by precordial echocardiography with Doppler provided highly sensitive and specific markers for SCLA.

Chapter IV describes a study which aimed to determine and compare the prevalence of hemostatic hyperactivity, defined by increased levels of TAT and F1+2. These are highly sensitive markers for thrombotic activity in humans, which have recently become available. Four groups of patients were studied: patients with or without transient cerebral ischemia, both with or without chronic NVAF. We found increased hemostatic activity possibly indicating a prethrombotic state, in the patients with transient cerebral ischemia one or two months after their cerebral ischemic event, irrespective of whether they had NVAF or sinus rhythm. A strong positive relationship was also detected between the levels of hemostatic activity and increasing age.

Chapter V depicts the background and design of the Dutch TIA Trial. The original cohort for this study included 3150 patients, who had a TIA or minor ischemic stroke between March 1986 and March 1989. Two main hypotheses were tested in this study: whether 30 mg aspirin/day is more effective than 300 mg in preventing death and disability from major vascular events and whether 50 mg atenolol is more effective than placebo in preventing these same events. Patients with possible sources of cardiac embolism were excluded as were patients on active treatment with antiplatelet drugs. Follow-up was stopped in June 1990 and the mean follow-up of the patients ranged from 1 year to 52 months with a mean of 2.7 years. No patient was lost to follow-up.

In *Chapter VI* it is shown that a high prevalence of ischemic heart disease could be detected in the patients of the Dutch TIA Trial at entry using the relatively simple and inexpensive methods of clinical history and standard 12 lead electrocardiography. We had reason to suspect previous myocardial infarct in

22% of men and in 14% of women. Often myocardial infarctions had not been recognized earlier and were detected only on the ECG. In patients with transient cerebral ischemia the following factors were found to be associated with an increased rate of myocardial ischemia, clinically or electrocardiographically: neurological deficits exceeding 24 hours, evidence of infarction on CT scanning, and a history of peripheral vascular disease. These findings suggest a correlation between the extent of cerebral ischemic damage and the degree of ischemic heart disease.

Chapter VII demonstrates that the rate of cardiac and cerebrovascular events in the Dutch TIA Study population is similar to that of other large clinical trials with stroke patients (UK-TIA Trial and ESPS Trial). Univariate and stepwise multivariate analysis were used to evaluate the prognostic significance for major vascular events of several clinical and electrocardiographic variables. Major cardiac events mainly occurred in patients with pre-existing ischemic heart disease. Previously unrecognized myocardial infarction on ECG and other ECG variables indicative for ischemia were seen to have the same prognostic significance as symptomatic ischemic heart disease. Some electrocardiographic parameters were also predictive for recurrent stroke. It is argued that screening patients with TIA or minor ischemic stroke for heart disease is important not only to detect potential cardiac sources of embolism, but also to identify patients with a high risk for future cardiac and cerebral ischemic events.

In *Chapter VIII* the authors intend to seek an explanation for the different dosage regimens of aspirin used by neurologists and cardiologists for the prevention of major vascular events in patients with atherosclerosis. A short historical overview on the use of aspirin in both specialties tries to elucidate whether these differences could have originated from a lack of communication between neurologists and cardiologists. Further review of the literature discusses the presence of various factors that might be of different influence on the pathogenesis of atherosclerotic disease and thromboembolism in the brain and heart and which might also explain the difference in required doses of aspirin.

In the *General Discussion* the cardiological evaluation of patients with cerebral ischemia is compared with ophthalmological funduscopy used by clinicians in former days. Both reflect the state of the vascular system in general and can be done by means of non-invasive and relatively simple techniques, which can be repeated from time to time. In addition, cardiological evaluation of patients with cerebral ischemia may provide quantitative information on the severity of the vascular disease and may reveal direct causes of brain ischemia. We have tried to develop a proposal for the choice of cardiological investigations in the evaluation of patients with cerebral ischemia. Apart from clinical history and physical examination, in which all aspects of the cardiovascular system

should be considered, a 12 lead electrocardiogram at rest should certainly be included in the initial investigations. The choice for further investigations depends on whether the initial investigations revealed any abnormalities. It is also important to realize that in some instances more information can be gained from currently accepted investigations by interpreting the results from a different perspective. Precordial echocardiography, for instance, may replace TEE for the assessment of cardioembolic risk in NVAF patients if it is combined with pulsed Doppler analysis. Additional information on other organ systems that are involved in the process of atherosclerosis, might also be helpful. A plea is therefore made for more exchange of information about atherosclerosis between different disciplines.

SAMENVATTING

In dit proefschrift worden verschillende aspecten belicht van de cardiologische evaluatie van patiënten met een doorgemaakt TIA of ischemische beroerte; het belang voor diagnose en behandeling wordt besproken.

De *Algemene Inleiding* laat zien dat er twee belangrijke redenen zijn waarom patiënten met een TIA of ischemische beroerte aan het hart onderzocht moeten worden. Op de eerste plaats kan het hart de oorzaak zijn van de beroerte. Cardiaal onderzoek bekijkt daarom of er mogelijke cardiale emboliebronnnen zijn en zoekt naar oorzaken die leiden tot pompfunctiestoornissen van het hart die leiden kunnen tot cerebrale doorbloedingsstoornissen. Ten tweede is het feit dat atherosclerose een gegeneraliseerde ziekte is van het vaatstelsel waarschijnlijk de verklaring dat er een sterk verband blijkt te bestaan tussen ischemisch lijden van de hersenen enerzijds en het hart anderzijds. Het eerste gedeelte van dit proefschrift gaat over het identificeren van cardiale emboliebronnen, die een mogelijke oorzaak kunnen zijn van een ischemische beroerte. Het tweede gedeelte beschrijft hoe ischemische hartziekte vaak samen voorkomt met cerebrale ischemie, beide zijnde uitingen van atherosclerose.

Hoofdstuk I bevat een literatuuroverzicht, waarin duidelijke relaties worden aangegeven tussen hart en hersenen bij aanwezigheid van atherosclerose. Het doel van dit proefschrift is om in te gaan op de klinische en epidemiologische aspecten betreffende patiënten met een ischemische beroerte, rekening houdend met het bestaan van nauwe verbanden tussen hart en hersenen in atherosclerose.

In *Hoofdstuk II* is een studie gedaan bij 72 patiënten met een recent TIA of ischemische beroerte, waarbij de waarde vergeleken is van precordiale versus transoesphageale echocardiografie (TEE) voor het vinden van intracardiale bronnen van embolie. Op basis van de anamnese, lichamelijk onderzoek en electrocardiografie wordt gevonden dat de toegevoegde waarde van precordiale echocardiografie beperkt is, indien Doppler echocardiografie daarbij niet is inbegrepen. TEE daarentegen vergroot wel de kans op het vinden van potentiële emboliebronnen in het hart vergeleken met precordiale echocardiografie. TEE kan het hartoortje in het linker atrium goed zichtbaar maken, welke een een plaats is met een predelictie voor het optreden van een thrombus. In de studie wordt vaak pathologie gevonden in de wand van de aorta ascendens en in de aortaboog. De

mogelijkheid van het loslaten van embolieën vanuit fragiele atheromateuze plaques wordt geopperd. De uiteindelijke opbrengst van TEE bij het vinden van potentiële cardiale emboliebronnen blijft beperkt (10%) en het is niet duidelijk of de bevindingen uitsluitend een geassocieerd verband vertonen dan wel een direkte causale relatie hebben met de ischemische beroerte. Er worden geen intraveneuze kontrast injekties gegeven, ook wordt geen Doppler echocardiografie gedaan.

Hoofdstuk III laat zien, dat wanneer precordiale echocardiografie wordt gecombineerd met Doppler analyse van de bloedstroom door de mitralisklep, er een identificatie mogelijk lijkt van patiënten met verhoogd risico op een cardiale embolie in patiënten met chronisch niet-valvulair boezemfibrilleren (NVAF). Het is bekend dat de aanwezigheid van spontaan kontrast in het linker atrium bij echocardiografie (SCLA) een teken is van verminderde bloedstroom in het atrium en deze bevinding blijkt geassocieerd met een verhoogd risico op cardiale embolieën. In deze studie wordt bij 17 NVAF patiënten met een eerder doorgemaakt TIA of ischemische beroerte meer SCLA gevonden dan bij 17 NVAF patiënten zonder een TIA of beroerte. Gedemonstreerd wordt dat gecombineerde meting van de grootte van het linker atrium, gecorrigeerd voor lichaamsoppervlakte, en de snelheid van de bloedstroom over de mitralisklep met behulp van precordiale echocardiografie met Doppler zeer sensitieve en specifieke markers blijken te zijn voor het opsporen van SCLA en daarmee van nut kunnen zijn voor het bepalen van het risico op een cardiale embolie bij NVAF patiënten.

Hoofdstuk IV handelt over een studie, welke tot doel heeft om het voorkomen te bepalen van verhoogde stollingsaktiviteit, welke werd uitgedrukt in verhoogde waardes van TAT en F1+2. Deze waardes zijn zeer sensitieve markers gebleken voor het aangeven van stollingsaktiviteit bij de mens en zijn recentelijk commercieel beschikbaar gekomen. Vier groepen patiënten worden onderzocht: patiënten met of zonder ischemische beroerte, beiden met of zonder boezemfibrilleren. We vinden verhoogde stollingsaktiviteit, mogelijk wijzend op een prethrombotische toestand, in de patiënten met een ischemische beroerte welke een of twee maanden daarvoor had plaats gevonden. Of het hartritme van de patiënten sinusritme was of boezemfibrilleren maakte geen verschil. Verder wordt een sterke relatie gevonden tussen de mate van stollingsaktiviteit en toenemende leeftijd.

Hoofdstuk V beschrijft de achtergrond en het ontwerp van de Dutch TIA Trial. Het oorspronkelijke cohort voor deze studie omvatte 3150 patiënten, die een TIA of ischemische beroerte doormaakten tussen maart 1986 en maart 1989. De twee hoofdhypothesen die in deze studie werden onderzocht, waren a: is 30 mg aspirine per dag effektiever dan 300 mg in het voorkomen van dood en invaliditeit door vasculaire complicaties en b: is 50 mg atenolol effektiever dan

placebo in het voorkomen van deze complicaties? Patiënten met een mogelijke bron van cardiale embolie werden uitgesloten alsmede patiënten, die al plaatjesremmende therapie voorgeschreven kregen. Follow-up werd gestopt in juni 1990 en de gemiddelde duur van de follow-up van de patiënten varieerde van 12 tot 52 maanden, met een gemiddelde van 2,7 jaar. Geen enkele patiënt verdween uit de controle tijdens de follow-up.

Hoofdstuk VI laat zien dat ischemische hartziekte vaak voorkomt bij patiënten uit de Dutch TIA Trial aan het begin van het onderzoek, gebruik makend van relatief eenvoudige en goedkope methodes zoals anamnese en standaard 12 afleidingen electrocardiogram. We vinden aanwijzingen om een doorgemaakt infarct te vermoeden in 22% van de mannen en 14% van de vrouwen. Vaak zijn de myocard infarcten van tevoren klinisch niet herkend en worden ze pas vastgesteld op het ECG. In patiënten met voorbijgaande ischemische beroerte wordt gevonden dat de volgende faktoren samengaan met een verhoogde aanwezigheid van ischemisch hartlijden, klinisch dan wel electrocardiografisch: neurologische uitval welke meer dan 24 uur duurt, aanwijzingen voor het bestaan van een infarct op de CT-scan en een voorgeschiedenis van perifeer vaatlijden. Deze bevindingen suggereren de aanwezigheid van een correlatie tussen de ernst van cerebrale ischemische schade en de mate van ischemisch hartlijden.

Hoofdstuk VII toont dat de mate van cardiale en cerebrovasculaire complicaties in de Dutch TIA populatie vergelijkbaar is met die van andere grote klinische trials bij patiënten met een beroerte (UK-TIA Trial en ESPS Trial). Univariate en stapsgewijze multivariate analyse worden gebruikt om de prognostische betekenis te evalueren voor vasculaire complicaties van diverse klinische en electrocardiografische variabelen. Cardiale complicaties treden vooral op bij patiënten met reeds bestaand ischemisch hartlijden. Tevoren niet-herkende myocardinfarcten op het ECG en andere ECG-variabelen, welke wijzen op ischemie, blijken dezelfde prognostische waarde te hebben als ischemisch hartlijden met symptomen die wel als zodanig herkend zijn. Enkele electrocardiografische parameters hebben ook voorspellende waarde voor het heroptreden van een ischemische beroerte. Er wordt daarom aangegeven, dat het screenen van patiënten met een TIA of ischemische beroerte op het voorkomen van hartziekten niet alleen van belang is voor het opsporen van mogelijke cardiale emboliebronnen, maar ook om patiënten te identificeren met een verhoogd risico op het krijgen van cardiale en cerebrale ischemische complicaties.

In *Hoofdstuk VIII* wordt gepoogd een verklaring te vinden voor de vraag waarom neurologen over het algemeen een andere dosering van aspirine voorschrijven dan cardiologen bij de preventie van vasculaire complicaties in patiënten met atherosclerose. Een kort historisch overzicht van het gebruik van aspirine in beide vakgebieden probeert te achterhalen of deze verschillen berusten

op een gebrek aan communicatie tussen neurologen en cardiologen. Verder literatuuronderzoek bespreekt de aanwezigheid van verschillende factoren die van invloed zouden kunnen zijn op de pathogenese van atherosclerose en thrombo-embolie in de hersenen en het hart en welke het verschil in voorgeschreven dosering aspirine zouden kunnen verklaren.

In de *Nabeschouwing* wordt de cardiologische evaluatie van patiënten met een ischemische beroerte vergeleken met het oogspiegelen in de oogheelkunde, zoals dat in het verleden goed gebruik was bij clinici. Beide onderzoeken geven de toestand van het vaatstelsel in het algemeen weer en kunnen gedaan worden middels niet-invasieve en relatief eenvoudige technieken, welke periodiek kunnen worden herhaald. Daarnaast biedt een cardiologische evaluatie van patiënten met een ischemische beroerte kwantitatieve informatie over de ernst van de vaatziekte en kan het direkte oorzaken van hersenischemie aan het licht brengen. Er wordt een voorstel ontwikkeld hoe een keuze gemaakt zou kunnen worden tussen de verschillende vormen van cardiologisch onderzoek bij de evaluatie van patiënten met een ischemische beroerte. Behalve anamnese en lichamelijk onderzoek, in welke alle aspekten van het hart- en vaatstelsel in beschouwing moeten worden genomen, behoort tenminste een 12 afleidingen electrocardiogram in rust te worden vervaardigd. De keuze voor verder cardiaal onderzoek hangt af van de afwijkingen voorzover die bij eerste onderzoek gevonden worden. Het is ook belangrijk om zich ervan bewust te zijn dat in bepaalde gevallen meer informatie kan worden verkregen uit algemeen gangbare onderzoeken door de resultaten van de betreffende onderzoeken vanuit meerdere perspectieven te bekijken. Precordiale echocardiografie bijvoorbeeld zou TEE bevredigend kunnen vervangen voor het bepalen van het risico op cardiale embolieën in patiënten met NVAF, indien het wordt gecombineerd met pulsed Doppler analyse. Additionele informatie over morfologie en functie van andere organen binnen het menselijk lichaam, die meespelen in het proces van atherosclerose, kan ook zinvol zijn. Een pleidooi wordt daarom gehouden voor het intensiever uitwisselen van informatie omtrent atherosclerose tussen de verschillende vakgebieden.

APPENDIX

Participating centers of Dutch TIA Trial (with number of patients randomized, in ranking order)

De Wever Ziekenhuis Heerlen (324; C.L. Franke,* C.J. Hagen, P.J.J. Koehler, J.F. Mirandolle); Academisch Ziekenhuis Dijkzigt Rotterdam (293; W.J.J.F. Hoppenbrouwers, G. de Jong, P.J. Koudstaal,* A. Staal,* M. Vermeulen*); Canisius-Wilhelmina Ziekenhuis Nijmegen (221; H.J.J.A. Bernsen, C.W.G.M. Frenken,* H.J.M.M. Lohmann, E.F.J. Poels, M.J.J. Prick, W.I.M. Verhagen, C.J.W. van de Vlasakker, E.V. van Zuilen); Academisch Ziekenhuis Utrecht (208; J. van Gijn,* J.J. Jansen, L.J. Kappelle,* J.M.J. Krul, W. Weststrate); St. Franciscus Gasthuis Rotterdam (170; P.R. Beneder, C. Bulens,* L.H. Penning de Vries-Bos); St. Geertruiden/St. Jozefziekenhuis Deventer (125; J.A. van Beeck, W.J. Feikema, J.H.M. van Gasteren, N.A.C. Roelvink, A.N. Veltema, C.J.M. Vredeveld); Diaconessenhuis Leiden (107; P.E. Briët, J. van Rossum); Academisch Ziekenhuis Maastricht (103; J. Boiten, J. Lodder, P.J.M. van der Lugt); Academisch Medisch Centrum Amsterdam (100; H. van Crevel,* D.Herderscheê, A. Hijdra*); St. Lucasziekenhuis Amsterdam (100; J.A.L. Vanneste, J. Vos); Ziekenhuis "Ziekenzorg" Enschede (83; E.N.H. Jansen, J. Troost); Twenteborg Ziekenhuis, Almelo (78; J.W.M. ter Berg); Westeinde Ziekenhuis 's-Gravenhage (76; A. Boon, J. Hilbers, J. Nihom, J.T.J. Tans); St. Elisabeth Ziekenhuis Tilburg (74; A.A.W. Op de Coul, A.C.M. Leyten, R.L.A.A. Schellens, C.C. Tijssen); Stichting Oosterscheldeziekenhuizen, Goes (73; A.M. Boon, W.H.G. Lieuwens); Ziekenhuis Gelderse Vallei, Ede (65; M.G. Smits, A.J.M. Vos); St. Maartens Gasthuis Venlo (62; G.D.M. van Hellemondt, B.J. Meems, T.G. Segeren); Merwedeziekenhuis Dordrecht (54; P.A.Th. Carbaat, L.I. Hertzberger, C.S.D. Hoekstein (deceased)); Ziekenhuis Lievensberg Bergen op Zoom (53; P.J.I.M. Berntsen); St. Joseph Ziekenhuis Eindhoven (52; B.J. van Kasteren, L.H.Th.S. Kortbeek, P.M.G.A.W. Mulkens); Diaconessenhuis Eindhoven (48; W. Groeneveld, H.J.Troelstra, A.J. Vermeij); Refajaziekenhuis Dordrecht (44; J.J. Groen, C. Oppelaar); Elisabeth Gasthuis Haarlem (40; J.A.M. Kuster, L. de Vries); Streekziekenhuis Midden Twente Hengelo (39; M.M. Klaver); Hervormd Diaconessenhuis Arnhem (38; H. Becker, F.A. Jongebloed); St. Elisabethziekenhuis Leiderdorp (37; A.J.P. Boesten, F.J.J. Prick, H.G.S. Snijder, M.M. Veering, R.J.W. Witteveen); Medisch Centrum Alkmaar (36; J.W.W.H. Dammers, R. ten Houten, J.A. van Leusden, H.J.S.

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AB, Advisory Board; ACOE, Auditing Committee for Outcome Events; CTC, CT-scan Committee; EC, Executive Committee; ECGC, ECG Committee; SC, Steering Committee.

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CURRICULUM VITAE

The author was born at Sampit in Borneo, Indonesia, on December 15, 1953. In 1971 he completed his high school education at the Gymnasium IC at Venray, The Netherlands, and started his medical training at the RK University at Nijmegen, at the same time starting an academical study at the faculty of philosophy at this university; in 1977 he passed 'cum laude' the doctoral examinations in philosophy under the supervision of Prof. Dr. S. Strasser. In 1978 he received medical training in several general practices during a month spent at the University of Birmingham, Great Britain, and also spent three weeks in Cuba as a member of a studygroup, which resulted in a publication about public health in Cuba. He finished his medical training in 1979 and in the same year went to Rumania for post-graduate training in internal medicine. After three years, in 1982, he received a license in internal medicine at the Medical School of Cluj-Napoca; these three years were granted by a Rumanian fellowship as part of a Cultural Agreement between The Netherlands and Rumania. Between 1982 and 1985 he received training in cardiology as a resident at the 'Instituto Nacional de Cardiologia 'Ignacio Chavez'' in Mexico City. From April 1985 till the end of 1986 he finished his training in cardiology at the Thorax Center of the University Hospital Dijkzigt in Rotterdam under Prof. P.G. Hugenholtz.

From the beginning of 1987 he has been working as a cardiologist at the Holy Ziekenhuis at Vlaardingen. Between 1987 and 1990 he participated in the Dutch TIA Trial as an advisor for cardiology and still has an advisory function for cardiology in the European Atrial Fibrillation Trial. These two trials are chaired by Prof. Dr. J. van Gijn of the University of Utrecht and by Dr. P. Koudstaal of the Erasmus University of Rotterdam respectively. In 1991 he participated in the national workgroup of 'CVA-Consensus'. Between 1988 and 1990 he was actively involved in the organization of "Médicins sans Frontières" in Belgium, for whom he represented contacts with Rumania before the revolution.

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