

Feasibility of TEE-guided stroke risk assessment in atrial fibrillation—background, aims, design and baseline data of the TIARA pilot study

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Abstract

Background Antithrombotic management in atrial fibrillation (AF) is currently based on clinical characteristics, despite evidence of potential fine-tuning with transoesophageal echocardiography (TEE). This open, randomised, multicentre study addresses the hypothesis that a comprehensive strategy of TEE-based aspirin treatment in AF patients is feasible and safe.

The participants in the TIARA pilot study are listed in the Appendix

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Methods Between 2005 and 2009, ten large hospitals in the Netherlands enrolled AF patients with a moderate risk of stroke. Patients without thrombogenic TEE characteristics were randomised to aspirin or vitamin K antagonists (VKA). The primary objective is to show that TEE-based aspirin treatment is safe compared with VKA therapy. The secondary objective tests feasibility of TEE as a tool to detect echocardiographic features of high stroke risk. This report compares randomised to non-randomised patients and describes the feasibility of a TEE-based approach.

Results In total, 310 patients were included. Sixty-nine patients were not randomised because of non-visualisation ($n=6$) or TEE risk factors ($n=63$). Compared with non-randomised patients, randomised patients ($n=241$) were younger (65 ± 11 vs. 69 ± 9 years, $p=0.004$), had less coronary artery disease (9 vs. 20%, $p=0.018$), previous TIA (1.7 vs. 7.2%, $p=0.029$), AF during TEE (25 vs. 54%, $p<0.001$), mitral incompetence (55 vs. 70%, $p=0.038$), VKA use (69 vs. 82%, $p=0.032$), had a lower mean CHADS₂ score (1.2 ± 0.6 vs. 1.6 ± 1.0 , $p=0.004$), and left ventricular ejection fraction (59 ± 8 vs. $56\pm 8\%$, $p=0.016$).

Conclusions This study shows that a TEE-based approach for fine-tuning stroke risk in AF patients with a moderate risk for stroke is feasible. Follow-up data will address the safety of this TEE-based approach.

Keywords Atrial fibrillation · Stroke risk · Antithrombotic treatment

Introduction

Atrial fibrillation (AF) is an independent risk factor for stroke, and patients with AF have a 5% annual risk for thromboem-

bolic stroke, i.e. five times more than in patients without AF [1, 2]. Therapy with vitamin K antagonists (VKA) reduces the risk of thromboembolism dramatically: ischaemic stroke by 67% and peripheral thromboembolism by 42% [3]. Alternatively, aspirin reduces the risk of ischaemic stroke by 22%, but has a significantly lower risk of bleeding [4].

It is recommended to stratify the risk of ischaemic stroke in patients with AF using straightforward clinical characteristics [5]. However, many AF patients classified as having a high or moderate risk for thromboembolism may actually be at low risk, as was shown in the Stroke Prevention in Atrial Fibrillation (SPAF) III study. In SPAF III, a subset of patients with a very high risk of stroke underwent transoesophageal echocardiography (TEE) [6]. Complex plaques in the aorta and signs of atrial stasis (spontaneous echo contrast, low peak emptying velocities and presence of thrombus in the left atrium or left atrial appendage) appeared strongly associated to a high risk of ischaemic stroke and peripheral thromboembolism [6–8]. Conversely, patients with a normal TEE had an extremely low rate of thromboembolism despite the fact that they had just used aspirin. Up till now no prospective study on the clinical safety and feasibility of a TEE-based risk assessment has been performed.

In the TEE-guided randomized comparison of Aspirin and VKA in patients with AF and an increased risk of stroke (TIARA) pilot study we hypothesise that a comprehensive strategy of TEE-based aspirin treatment is safe and feasible in AF patients who are eligible for vitamin K antagonist therapy on the basis of conventional risk assessment. Our primary objective is to show that—compared with VKA therapy—TEE-based aspirin treatment is safe with respect to a composite endpoint of major cardiovascular and cerebrovascular events, in patients who do not harbour predefined high-risk features on TEE. Our secondary objective is to test the feasibility of TEE as a tool to assess all four echocardiographic features of high stroke risk, i.e. complex atheromatous plaques in the thoracic aorta and signs of atrial stasis including dense spontaneous echo contrast, thrombus or low blood flow velocity.

Here we report the study design and feasibility of TEE-guided stroke risk assessment. In addition we compare the baseline characteristics of randomised patients with those of patients who were not randomised because of thrombogenic TEE abnormalities.

Methods

Patients

Subjects were eligible for participation if they had documented paroxysmal or permanent AF, and a conventional indication for VKA treatment (history of hypertension,

age >60 years with diabetes mellitus or coronary artery disease, age >75 years). Subjects were excluded if they had an indication for VKA treatment other than AF, secondary AF, a contraindication for treatment with VKA or aspirin or a contraindication for TEE [9]. Also patients with a presumed very high risk of stroke and thromboembolism (previous ischaemic stroke, transient ischaemic attack (TIA) or systemic thromboembolism, heart failure or significant left ventricular systolic dysfunction, mitral valve stenosis, hypertrophic cardiomyopathy) were not eligible. The Institutional Review Boards of all participating hospitals approved the study and written informed consent was obtained from all patients. Since the risk of stroke in patients who suffered from TIA but not from stroke is uncertain and its mechanisms vary, the steering committee changed the exclusion criteria of the study accepting also patients with a history of TIA for screening. This protocol amendment was implemented in March 2006.

Design

The TIARA pilot study was an open randomised, multicentre trial in which a risk stratification based on TEE was examined in AF patients with a moderate risk of stroke. The study was performed in ten large hospitals in the Netherlands between 2005 and 2009. All centers are highly experienced in echocardiography. Most patients were enrolled in the outpatient clinic, but also hospitalised patients were included. The trial has been registered under ClinicalTrials.gov # NCT 00224757.

Patients underwent a TEE and were randomly assigned to aspirin or VKA treatment if TEE did not show high-risk abnormalities. Patients assigned to aspirin received a once-daily dose of 100 mg and patients assigned to VKA received adjusted-dose acenocoumarol or phenprocoumon (target INR 2.5 to 3.5). Obviously, patients with one or more abnormalities on TEE were excluded from randomisation and received adjusted-dose VKA and were followed in the high-risk observational group. The Netherlands' regional Thrombosis Service routinely checked the INR. All patients were followed up for at least 1 year. Figure 1 depicts the flow chart of screening, randomisation and follow-up of included patients in the TIARA pilot study.

Echocardiographic procedures

All TEEs were performed and interpreted by certified cardiologists in a standard fashion, as recommended by the American Society of Echocardiography [9]. All echocardiograms were acquired by commercially available equipment: HP Sonos 5500 imaging system (Hewlett-Packard Co., Andover, MA) or Vingmed System V (General Electric Company, Fairfield, Connecticut) equipped with a 5-MHz omniplane probe for TEE. When in doubt, the echocardiograms

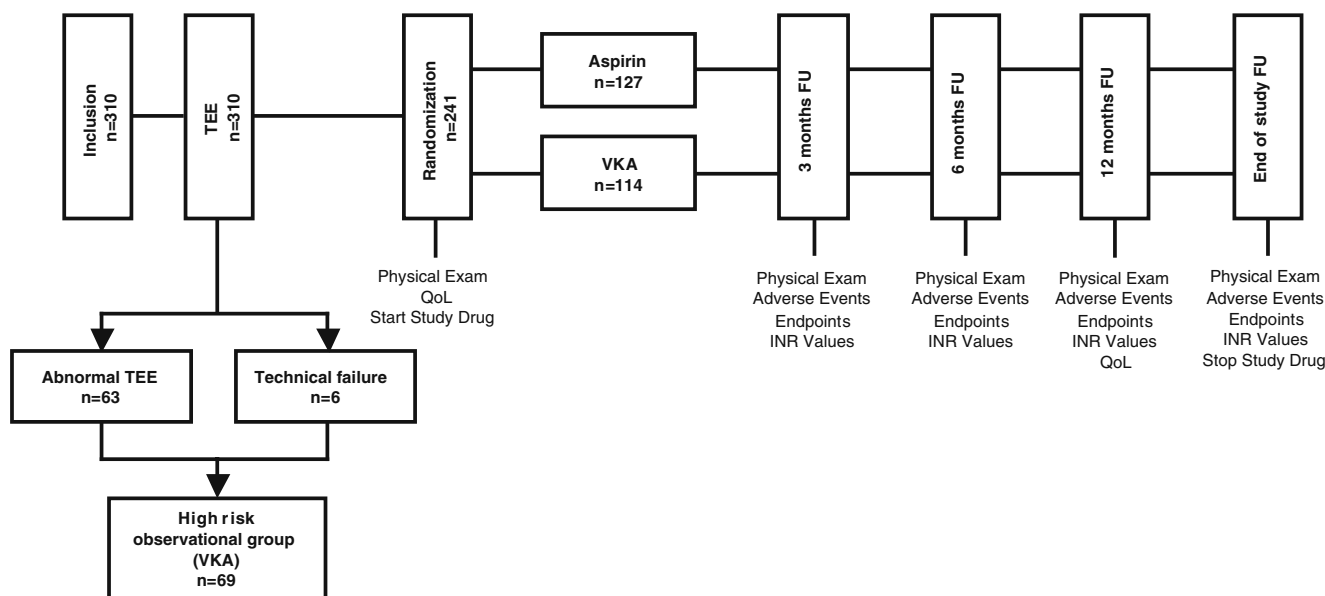


Fig. 1 Overview of the screening, randomisation and follow-up of the TIARA pilot study. Eligible patients were planned for TEE to assess presence or absence of echocardiographic features of high risk of stroke i.e. signs of atrial stasis and complex aortic plaques. *VKA* vitamin K antagonists, *TEE* transoesophageal echocardiography,

Positive TEE presence of at least one of the echocardiographic features of high risk of stroke, *Negative TEE* absence of echocardiographic features of high risk of stroke, *QoL* Quality of life scores using SF-36, EuroQol 5-D, Minnesota and AFSS questionnaires

could be sent to the echo core laboratory (Maastricht University Medical Center) for review.

TEE was performed with a 5-MHz omniplane transducer. The oropharynx was anaesthetised by use of topical lidocaine spray and viscous lidocaine solution prior to insertion of the probe. The left atrial appendage (LAA) was imaged by placing the probe at the level of the mid-oesophagus. The plane of the multiplane probe was adjusted to achieve a short-axis view of the aortic valve (45°); to obtain an optimal view of the left atrial appendage, the shaft of the scope was rotated anticlockwise in 5 to 10° increments from 0 to 180°. Multiple views of the LAA were then obtained; cine loops were acquired [10]. The imaging plane and gain settings were adjusted for optimal visualisation of thrombi and spontaneous echo contrast (SEC) in the left atrium (LA), LAA, right atrium (RA) and right atrial appendage (RAA). For measurement of the blood flow velocities in the LAA, the sample of the pulsed wave Doppler was placed at the orifice of the LAA and the profile of the velocities was recorded over at least five cardiac cycles. A maximum velocity was then calculated by averaging these five cardiac cycles [11]. In order to image complex plaques, the thoracic aorta was carefully visualised by retracting and rotating the probe.

Definition of high-risk echocardiographic features

The following definitions were used for echocardiographic abnormalities. Spontaneous echo contrast was defined as a

persistent pattern of a slow swirling motion of intracavitary echo density throughout the LA and LAA at normal gain [6]. A thrombus was defined as an intracavitary echodense mass with sharp edges, echogenicity different from adjacent structures, some degree of mobility, and present in more than one plane [12]. Low blood flow velocity was defined as peak emptying velocity of less than 25 cm/s on TEE, measured at the orifice of the LAA. Complex atheromatous plaque was defined as a mobile, pedunculated or ulcerated plaque, or plaque thickness ≥ 4 mm in the thoracic aorta [7].

Randomisation

Randomisation was performed by permuted block design with stratification for each participating hospital. Eligible patients were randomised to either treatment with aspirin 100 mg once daily or treatment with adjusted-dose VKA. In patients randomised to VKA, the INR was checked by the regional Thrombosis Service on a routine basis.

Follow-up

Patients visited the outpatient clinic at 3, 6 and 12 months after randomisation and at the end of the study. All patients were followed up for at least 1 year. If needed, patients were seen between regular visits. At every visit, symptoms and signs of the composites of the primary endpoint were checked. Also INR values were collected.

TEE was not repeated on a regular basis in the included patients. Within the study period it was not expected that aortic plaque or left atrial low flow states would develop if not present on the first examination. A TEE was, however, repeated when clinically indicated. If electrical cardioversion was indicated, aspirin patients were temporarily switched to VKA. One month after the shock, irrespective of the rhythm, aspirin was reinstituted.

Quality of life questionnaires

The quality of life was studied using the EuroQol 6-D, the Short Form (SF)-36 Health Survey questionnaire and the Toronto Atrial Fibrillation Severity Scale (AFSS) at inclusion and after 12 months of follow-up. SF-36 contained items to assess physical health and mental health, AFSS secured AF-specific complaints. The quality of life assessment was completed with a multidimensional index that contains five subscales: general, physical, activity, motivation and cognition.

Data collection

Data were collected using an electronic case report form accessed at a secure Internet site. Data were transferred through the Internet to the central database in Maastricht. Data could be either entered online, or offline with frequent data transfer. By using a validation plan, integrated in the data entry software, data were continuously checked for missing or contradictory entries and values out of the normal range. The study-monitoring nurse performed additional edit checks. The data analysis was done at the Maastricht University Medical Center. Patient identification was registered in the participating centres, and was not transferred to the central database. Questionnaires for quality of life were processed by the Center for Data and Information Management (MEMIC), a subdivision of the department of the Faculty of Health, Medicine and Life Sciences (Maastricht University).

Endpoints

The primary endpoint was a composite of (1) stroke including haemorrhagic strokes, (2) systemic embolism, (3) major bleeding, (4) acute coronary syndrome (unstable angina and myocardial infarction) and (5) all-cause mortality.

The Central Independent Adjudication Committee (CIAC) independently adjudicated all events using definitions as mentioned below. In case of doubt the members held a conference for an unanimous adjudication.

Definitions of primary endpoints are described in the [Appendix](#).

Statistical analysis

Sample size calculation was driven by the primary endpoint on safety, i.e. the composite endpoint. The incidence of the composite safety endpoint with aspirin treatment could be estimated from the available literature. In patients with a normal TEE, the estimated yearly incidences of ischaemic stroke and systemic thromboembolism, major bleeding, acute coronary syndrome and death with aspirin treatment were 1.1%, 0.7%, 0.8% and 1.8%, respectively. Therefore, the estimated yearly incidence of the composite primary endpoint was 4.4% with aspirin. With VKA treatment (INR 2.0–3.0) the yearly incidences of ischaemic stroke and systemic thromboembolism, major bleeding, acute coronary syndrome and death were 1.0%, 1.7%, 1.0% and 1.8%, respectively. As a result, the estimated yearly incidence of the composite endpoint with VKA treatment was 5.5%. With an estimated average follow-up duration of 1.5 years, the estimated incidences of the composite safety endpoint were 6.6% for the aspirin group and 8.3% for the VKA group, respectively.

The primary safety objective of this pilot study is to show that applying TEE-based aspirin prophylaxis does not lead to unacceptable high frequency of the safety endpoint. Inclusion of 300 patients (150 per randomisation arm) would rule out an excess of 7% with a power of 80% and a type I error of 5%. The difference in incidence of the safety endpoint in the randomised groups was calculated and described with an exact one-sided 95% confidence interval. A Kaplan-Meier curve will be used to visualise the occurrence of events over time. Hazard ratios will be calculated using Cox regression. Similar analyses will be done for the separate components of the safety endpoint.

The secondary—feasibility—objective will be evaluated by calculating the number of patients eligible for the TEE approach in whom the TEE cannot be performed or does not yield unequivocal information on echocardiographic thromboembolism risk markers.

Data that are not normally distributed will be log-transformed and presented as geometric means. Analyses were done using the *t*-test for independent groups for continuous variables and Fisher's exact test for categorical variables. SPSS was used for all statistical calculations. Analyses will be done using the intention-to-treat principle, that is, patients will be analysed in the group to which they were randomly assigned, regardless of the treatment they actually received. A *P* value less than 0.05 is considered statistically significant. All tests are two-tailed.

Results

Baseline characteristics

The inclusion in the TIARA pilot trial was slower than expected and the follow-up period longer than foreseen. As a consequence inclusion was stopped after 310 patients and a projected mean follow-up duration of 1.6 years. Recruitment was diminished predominantly due to refusal of eligible patients to undergo a TEE examination because of fear for the TEE. Analysis of the patient screening log showed that 35% of patients eligible for participation in the TIARA pilot study refused TEE for this reason.

In the group randomised to aspirin, three patients withdrew their informed consent directly after randomisation. Therefore they will be discarded from further analysis in respect to follow-up. For the secondary (per protocol) analysis, patients not meeting the inclusion ($n=1$ for VKA group, $n=2$ for aspirin group), or exclusion criteria ($n=3$ for VKA group), and patients randomised despite TEE abnormalities ($n=1$ for VKA group), will be discarded from analysis.

We had included 310 patients by July 2008, of which 241 (78%) patients were randomised. In total, 69 patients were not randomised on the basis of an abnormal TEE showing either predefined echocardiographic markers of a high stroke risk or another abnormality considered highly thrombogenic. Summaries of clinical and echocardiographic data are expressed as means or frequencies with 95% confidence intervals (CIs) (Table 1). Non-randomised observational patients had a slightly higher CHADS₂ score due to on average higher age, higher prevalence of diabetes mellitus and previous TIA. The prevalence of hypertension was very high and similar in both groups. On the other hand, the prevalence of TIA was low, while patients with stroke and heart failure were excluded. Non-randomised observational patients were more often in AF at the time of TEE and had mitral incompetence of any grade more frequently. They also more often used a vitamin K antagonist at entry. Distribution of type of AF (paroxysmal or permanent) did not differ among groups.

Feasibility of TEE-guided stroke risk assessment

Of all 310 patients planned for TEE, 69 were not eligible for randomisation because of non-visualisation ($n=5$), technical failure ($n=1$) or abnormal TEE ($n=63$) (Table 2). At least one echocardiographic marker for thromboembolism could not be visualised with certainty in five patients; mostly due to incomplete imaging of the LAA and therefore LAA flow velocities could not be measured ($n=4$). In the remaining patient, the aorta could not be visualised. In one patient, TEE could not be performed because of technical reasons; the patient was not capable of

swallowing the probe and therefore none of the markers for thromboembolism were visualised. Furthermore, 63 patients had abnormalities on TEE, of which 60 patients (19.7%) had at least one predefined risk marker on TEE. Thrombi were detected in ten patients (3.3%), low LAA flow velocities were seen in 33 patients (10.9%), spontaneous echo contrast in 22 patients (7.2%), and complex plaques in 13 patients (4.3%). The majority had only one risk marker ($n=49$, Table 2); LAA flow velocities, SEC, complex plaques and thrombi were seen in 20, 11, 9 and 6 patients, respectively. In 13 patients, two abnormalities were detected with TEE; seven patients had low LAA flow velocities with SEC, three patients had a thrombus with low LAA flow velocities, and three patients had SEC with complex plaques. Only one patient had all four markers of thromboembolism risk on TEE.

Surprisingly, other cardiac abnormalities were observed in three patients who had no other risk markers for stroke; two patients had Lambl's excrescences on the aortic valve and one patient had a myxoma in the left atrium. Lambl's excrescences are not considered to be a primary source of cardioembolism in patients with sinus rhythm, but the importance in atrial fibrillation remains uncertain [13]. These patients were therefore not randomised. The patient with a myxoma refused surgery, and therefore was not randomised because of the need for permanent anticoagulation.

Thus, TEE could provide accurate information on thromboembolic risk in 304 out of 310 patients (98.1%).

Discussion

The TIARA pilot study is a randomised comparison of aspirin and vitamin K antagonists for stroke prevention in patients with a moderate stroke risk who do not harbour predefined high-risk features on TEE. It was constructed as a pilot study to show feasibility and to prepare a larger study later on. Considering the high number of equivocal TEE imaging results (98.1% of patients) and the low number of technical failures of TEE, we feel that a TEE-guided approach is feasible in clinical practice. If our study shows that TEE-based aspirin treatment is also safe, this may form the basis for a large TEE-guided stroke risk assessment trial.

We found that in only six out of the 310 included patients (1.9%) irrefutable information about the thrombogenicity could not be obtained by TEE. In one patient a TEE could not be performed due to technical reasons, and in the remaining five patients the left atrial appendage and aorta could not be visualised accurately. This high technical success rate may relate to the fact that all participating centers in the TIARA pilot study were highly trained in performing TEE. However, TEE is now well incorporated in the daily practice of any cardiology clinic. We hence believe that a TEE-based approach for fine-tuning stroke

Table 1 Characteristics of randomised and non-randomised patients

	Randomised patients	Non-randomised patients (observational group)	<i>p</i> -value
	<i>n</i> =241	<i>n</i> =69	
Clinical characteristics			
Age (years)	65±11	69±9	0.004
Male,%	66	61	0.479
Hypertension,%	90	86	0.388
Coronary artery disease,%	9	20	0.018
Diabetes,%	10	19	0.057
Transient ischaemic attack,%	1.7	7.2	0.029
CHADS ₂ score	1.2±0.6	1.6±1.0	<0.001
- Score 0,%	2.1	4.3	
- Score 1,%	76.3	53.6	
- Score ≥2,%	21.6	42.1	
Time since 1st diagnosis AF (years)	4.9±9.0	4.6±6.1	0.754
Type of AF			0.320
- Paroxysmal,%	85	78	
- Permanent,%	15	22	
Body mass index (g/m ²)	28±5	28±5	0.458
Systolic blood pressure (mmHg)	136±18	137±18	0.615
Diastolic blood pressure (mmHg)	80±9	82±10	0.288
Antithrombotic drug at baseline,%	99	99	0.637
- VKA at baseline,%	69	82	0.032
- Aspirin at baseline,%	32	18	0.023
Echocardiography			
AF during TEE,%	25	54	<0.001
Left atrial diameter (mm)	41±11	42±12	0.389
Left ventricular ejection fraction (%)	59±8	56±8	0.016
Left ventricular mass (g/m ²)	124±83	130±102	0.571
End-diastolic septum width (mm)	9.6±2.6	10.1±3.2	0.204
End-diastolic posterior wall width (mm)	9.1±2.4	9.5±2.6	0.211
Mitral incompetence,%	55	70	0.038

Data are expressed as mean ± SD unless otherwise specified

AF atrial fibrillation, VKA vitamin K antagonists, TEE transoesophageal echocardiography

risk in AF patients with a moderate risk for stroke is feasible, not only in this trial but also in real-life.

In patients using VKA before TEE, VKA was not stopped prior to performing TEE. Of note, VKA does not influence the

presence of SEC and LAA flow velocities, or complex plaques since it does not alter the underlying haemodynamic mechanism [14–16], nor aortic plaque anatomy and complexity [17], respectively. On the other hand, continued VKA therapy may have precluded finding thrombi on TEE. However, we reasoned that the incidence of thrombi after stopping VKA in patients randomised to aspirin would be low, especially since high LAA flow velocities and absence of SEC virtually exclude thrombus [15, 18]. In this respect, of all three echocardiographic atrial thrombosis markers, LAA flow velocity measurement is the most robust concerning sensitivity and specificity for thrombosis risk [8, 19]. Therefore, to prevent unjust randomisation as much as possible we used a higher than usual cut off of LAA flow velocity of 25 cm/s. Notwithstanding the above, temporary discontinuation of stable VKA treatment for e.g. 4 weeks to assess stroke risk markers with TEE off VKA may seem feasible since most patients eligible for the

Table 2 Reasons for non-randomisation

	<i>n</i> =69
Technical reasons/patient refusal	1
At least one TEE risk factor not clearly visible	5
At least one TEE risk factor present	63
- 1 TEE abnormality	49
- 2 TEE abnormalities	13
- 3 TEE abnormalities	0
- 4 TEE abnormalities	1

TEE transoesophageal echocardiography

TIARA approach have a relatively low stroke risk. Although the stroke risk during 4 weeks of interrupted VKA is low, we did not feel justified to do so, especially since the guidelines advise keeping discontinuation of VKA (e.g. to perform elective surgery) as short as possible.

The overall mean CHADS₂ score was fairly low and median CHADS₂ score was only 1, mainly because we did not consider patients with a previous stroke or heart failure. In contrast, patients included in RACE [20] and AFFIRM [21] were older and were presumably in a higher CHADS₂ risk category mostly due to previous stroke and heart failure, although hypertension was less frequent. Obviously, the patients enrolled in the ACTIVE trial [22] and RELY study [23] had higher CHADS₂ scores because patients at higher risk for thromboembolism were included, whereas the TIARA pilot study intended to focus on patients with an intermediate risk, i.e. a lower CHADS₂ score.

Patients who were excluded from randomisation (non-randomised observational group) because of TEE abnormalities had, expectedly, a higher mean CHADS₂ score than randomised patients, mainly due to higher average age and higher prevalence of diabetes. Nevertheless, the median CHADS₂ score is 1 in both randomised and non-randomised groups. We can conclude that the average patient randomised in the TIARA pilot study was the younger patient with well-controlled hypertension and paroxysmal AF without other risk factors of the CHADS₂ risk score (i.e. heart failure, previous stroke or TIA, diabetes, and older age). The relatively high number of women included in the TIARA study is remarkable, considering that women are generally underrepresented in clinical trials.

In the non-randomised observational group, ten thrombi were found (3.3% of patients); eight of these patients were on VKA and two on aspirin. The number of thrombi as well as stroke risk category in our study is comparable with several recent studies showing prevalences of thrombi between 0.6% and 3.6% [24–26]. Remarkably, also three patients (0.97%) with a CHADS₂ score of 0 had at least one TEE stroke risk factor. Scherr et al. also report a prevalence of 0.3% thrombi in patients with a CHADS₂ score of 0 [25]. This underscores our hypothesis that current risk stratification schemes—which are based merely on clinical characteristics (such as the CHADS₂ score)—are unable to detect all patients with a high risk of stroke with certainty. Surprisingly, three patients had no thromboembolic markers but other abnormalities with an indication for treatment with VKA. These patients were asymptomatic beforehand, and they were subsequently treated with VKA and followed in the observational group. To our knowledge, this is the first study to show that routine TEE yields unexpected findings in AF patients, leading to a change of antithrombotic treatment.

Performing TEE in AF patients with a low to average thromboembolism risk (CHADS₂ score of 0 and 1) is useful

since it may enhance aspirin or no antithrombotic treatment in some of these patients which may reduce avoidable bleeding. In addition, in patients considered at low risk, TEE may detect high-risk features warranting VKA therapy, protecting these patients from unexpected strokes. In this respect it is noteworthy that out of 310 patients with an average CHADS₂ risk score of 1, 63 patients had an abnormal TEE (20.3%) necessitating continuation of or switch to VKA therapy. Most noteworthy in this respect were the three patients with a CHADS₂ risk score of 0 who appeared to have thrombogenic features on TEE.

Conclusions

In summary, the TIARA pilot study showed that a TEE-based risk stratification in patients with atrial fibrillation and a moderate risk for stroke is feasible. Decreasing the threats and inconvenience of VKA is a desirable goal. Identifying patients in whom VKA (or other antithrombotic drugs) can be avoided may reduce bleeding and improve quality of life without an increase in stroke complications or costs of care. Application of a new echo-guided antithrombotic strategy may help to reduce bleeding whilst stroke prevention is maintained. If so, this study may significantly change daily clinical practice of antithrombotic management of atrial fibrillation. These results may form the basis for a larger multi-centre study.

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Appendix

Principal Investigator

H.J.G.M. Crijns.

Steering Committee

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Central Independent Adjudication Committee

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Participating centres and persons; number in parentheses indicates numbers of patients enrolled (all the Netherlands)

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CardioResearch Maastricht University Medical Center monitoring activities

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Definitions of primary endpoint events

Stroke was subdivided into ischaemic stroke (including lacunar stroke), haemorrhagic stroke or undefined stroke. Each ischaemic stroke was further subdivided into cardioembolic, large-artery atherosclerotic stroke, lacunar stroke (i.e. small-artery occlusion) or mixed/undefined/other.

Death was divided into cardiovascular death (due to myocardial infarction, heart failure, documented stroke, procedure-related death, due to other cardiovascular causes) or non-cardiovascular death (related to cancer, primary infectious disease, respiratory disease, suicide, accident or other).

Major bleeding was defined as clinically overt and (a) associated with a fall in haemoglobin of 1.25 mmol/l or more, or (b) leading to a transfusion of 2 or more units of packed red blood cells or whole blood, or (c) bleeding in a critical organ, i.e. intracranial, retroperitoneal, pericardial, or (d) contributing to death. All other relevant bleeding was classified as a non-major bleeding.

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