Prevalence and clinical impact of left atrial thrombus and dense spontaneous echo contrast in patients with atrial fibrillation and low CHADS$_2$ score

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**Aims** To evaluate the prevalence and clinical impact of left atrial (LA) thrombus and dense spontaneous echo contrast (SEC) in patients with atrial fibrillation (AF) and low CHADS$_2$ score undergoing cardioversion.

**Methods and results** A total of 295 consecutive patients with non-valvular AF and a CHADS$_2$ score of 0 or 1 from the prospective single-centre registry ANTIK, who underwent transoesophageal echocardiography before cardioversion, were included in the study. Median follow-up was 5 years. LA thrombus was present in 3% and dense SEC in 8% of patients. Independent predictors for the presence of thrombus or dense SEC were ejection fraction (EF) $\leq 40\%$ and LA diameter $\geq 50$ mm. In anticoagulated patients, thrombus and dense SEC were not independently associated with an increased risk for stroke or death during the 5 year follow-up (OR 1.55, 95% CI 0.50–4.83).

**Conclusions** Despite a low CHADS$_2$ score of 0/1, 3% of patients have LA thrombus and 8% of patients have dense SEC. Independent predictors for the presence of thrombus and dense SEC were EF $\leq 40\%$ and LA dimension $\geq 50$ mm. Thus, echocardiography might be a useful tool for further risk stratification in patients with low CHADS$_2$ score.

**KEYWORDS** Atrial fibrillation; CHADS$_2$; Transoesophageal echocardiography; Thrombus; Spontaneous echo contrast

**Introduction**

The rate of stroke in non-valvular atrial fibrillation (AF) ranges widely and depends on the presence of prior cerebral ischaemia, co-morbid conditions, and the use of antithrombotic therapy.$^{1-4}$ The CHADS$_2$ score is a clinical classification scheme for predicting stroke in non-valvular AF and helps to identify patients eligible for anticoagulation.$^{2,5}$ CHADS$_2$ is an acronym, which combines five stroke risk factors: congestive heart failure, hypertension, age $\geq 75$ years, diabetes, and prior stroke or transient ischaemic attack (TIA).$^2$ Prior stroke or TIA is considered a high risk factor. Consequently, two points are given to these risk factors (hence, the subscript ‘2’), and 1 point is assigned for each of the other factors. Patients having a CHADS$_2$ score of 0 are assigned as being at low risk, patients with a CHADS$_2$ score of 1 or 2 at moderate risk, and patients with a CHADS$_2$ score of 3 or more at high risk for stroke.$^2$ The annual expected stroke in patients with a CHADS$_2$ score of 0 or 1 rate remains still high, ranging from 1.9 to 2.8%.$^2$ Therefore, further risk stratification is warranted in these patients with no or only 1 clinical risk factor according to the CHADS$_2$ score. It is known from both SPAF and AFI that a moderate or severe left ventricular function on echocardiography is an independent predictor of stroke.$^6-8$ In addition, transoesophageal echocardiography (TEE) is a useful method to detect left atrial (LA) thrombus or spontaneous echo contrast (SEC) that are known to be associated with a higher risk of thrombo-embolic events in patients with AF.$^9$ It is also known that TEE risk factors correlates well with clinical factors, and that even a significant number of patients without clinical risk factors have a thrombogenic milieu.$^{10,11}$ However, the CHADS$_2$ score does not implement echocardiographic data into the decision algorithm for antithrombotic therapy.

Thus, the aim of the study was primarily to evaluate the incidence and clinical impact of LA thrombus and dense SEC in patients with AF and low CHADS$_2$ score and, secondly, to analyse the usefulness of echocardiography as a tool for risk stratification in these patients.

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had 3 weeks of effective anticoagulation (INR 2–3) treatment were enrolled in the registry. For the present study, only patients, and cardiothoracic surgery (diagnosis unstable or if they had a recent myocardial infarction) were informed consent was obtained from all patients before participation in the study. Patients were excluded, if they were haemodynamically unstable or if they had a recent myocardial infarction. The ANTIK registry started in 1994 and ended in 2004. Written consent was obtained from all patients before participation in the study. Patients were excluded, if they were haemodynamically unstable or if they had a recent myocardial infarction. Anticoagulation was performed as recommended by the current guidelines of 2001 and 2006. Patients with AF or atrial flutter of prolonged duration (>48 h) had 3 weeks of effective anticoagulation (INR 2–3) treatment before cardioversion, followed by at least 4 weeks of phenprocoumon therapy after cardioversion. Patients with AF or atrial flutter lasting <48 h, oral anticoagulation was not recommended before cardioversion. However, after cardioversion, an overlap of phenprocoumon therapy and intravenous heparin therapy was given to maintain adequate anticoagulation after cardioversion in patients without contraindications for anticoagulation. Patients with atrial flutter were managed with oral anticoagulation at the time of cardioversion in a manner similar to that used for AF. During the first 2 years, cardioversion without TEE was performed. Thereafter, TEE-guided cardioversion was performed in the following consecutive patients. The anticoagulation regime was the same in both time periods. If thrombi or severe SEC were detected, cardioversion was postponed. In patients with moderate SEC, the decision to cardiovert was left to the treating physician.

Anticoagulation was defined as being effective if all INR values measured during the last year of follow-up were between 2 and 3. Coronary artery disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, and hypertensive heart disease were summarized as organic heart disease. Hypertensive heart disease was diagnosed when a history of hypertension and left ventricular hypertrophy was present.

Data collection
Data on patient characteristics on admission were recorded. Data on electrocardiographic and echocardiographic findings, and in-hospital treatment were documented. At discharge, outcome and major cardiovascular and cerebrovascular adverse events were recorded. All patients gave informed consent to process their anonymous data. All data sheets were sent to the central data processing centre (Institut für Herzinfarktforschung Ludwigshafen an der Universität Heidelberg, Germany) for uniform monitoring and registration.

Echocardiography before cardioversion
In the present study, transthoracic echocardiography and TEE was done in all patients before planned cardioversion. During TEE examination, special attention was paid to assess the presence or absence of LA thrombi and SEC. The delay between the echocardiographic investigations and the scheduled cardioversion was <3 h.

Methods
Prospective single-centre registry ANTIK: patient selection
The details of the ANTIKogulation registry have been described previously.12 Patients who were candidates for cardioversion of AF or atrial flutter were eligible for enrolment in the ANTIK registry. The ANTIK registry started in 1994 and ended in 2004. Written informed consent was obtained from all patients before participation in the study. Patients were excluded, if they were haemodynamically unstable or if they had a recent myocardial infarction and cardiothoracic surgery (<30 days). Overall, 1053 patients were enrolled in the registry. For the present study, only patients (n = 295) with non-valvular AF, who had a CHADS2 score of 0 or 1 and underwent TEE before planned cardioversion, were enrolled.

Study design
This prospective single-centre observational study was designed on an intention-to-cardiovert basis, consisting of three subpopulations: patients with pure AF, patients with atrial flutter plus a history of AF, and patients with pure atrial flutter. The diagnosis of AF and atrial flutter was made from a 12-lead electrocardiogram with the use of standard criteria. Anticoagulation was performed as recommended by the current guidelines of 2001 and 2006.13,14 Patients with AF or atrial flutter of prolonged duration (>48 h) had 3 weeks of effective anticoagulation (INR 2–3) treatment before cardioversion, followed by at least 4 weeks of phenprocoumon therapy after cardioversion. In patients with AF or atrial flutter lasting <48 h, oral anticoagulation was not recommended before cardioversion. However, after cardioversion, an overlap of phenprocoumon therapy and intravenous heparin therapy was given to maintain adequate anticoagulation after cardioversion in patients without contraindications for anticoagulation. Patients with atrial flutter were managed with oral anticoagulation at the time of cardioversion in a manner similar to that used for AF. During the first 2 years, cardioversion without TEE was performed. Thereafter, TEE-guided cardioversion was performed in the following consecutive patients. The anticoagulation regime was the same in both time periods. If thrombi or severe SEC were detected, cardioversion was postponed. In patients with moderate SEC, the decision to cardiovert was left to the treating physician.

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A thrombus was considered to be present if a mass detected in the appendage or body of the atrium appeared to be distinct from the underlying endocardium, was not caused by pectinate muscles, and was detected in more than one imaging plane.

Spontaneous echo contrast was defined as dynamic smoke-like echoes within the atrial cavity with the characteristic swirling motion that could not be eliminated by changes in the gain settings. The degree of SEC was characterized independently as absent, mild, moderate, or severe. The definition of mild, moderate, and severe SEC is reported elsewhere. Dense SEC were defined as moderate or severe SEC.

Clinical outcome
The determination of a thrombo-embolic event was based on clinical findings and supported by radiological studies. The clinical safety outcomes were clinically apparent ischaemic strokes, TIsas, systemic embolism, episodes of bleeding, and death. Major bleeding was due to extracranial haemorrhage, defined as a fatal haemorrhage, or one that resulted in the need for transfusion or surgery, and intracranial bleedings. The clinical outcome after discharge was evaluated at 4 weeks and at 5 years after cardioversion. Follow-up information was obtained primarily by telephone contact. The median follow-up was 62 months (upper and lower quartile: 48 and 82 months).

Statistical analysis
Absolute numbers, percentages, means and standard deviation, and median and upper/lower quartiles were computed as appropriate. The Wilcoxon rank-sum test was used for the comparison of continuous variables in the two groups. Categorical variables were compared using the χ² or Fisher’s exact test, as appropriate. Kaplan–Meier curves were used to analyse the differences in the survival rates between the groups. The differences between survival curves then were assessed using a log-rank test. Cox regression analysis was performed to find predictors for thrombus or dense SEC. The following variables were included into the Cox regression analysis: CHADS2 score of 1, gender, organic heart disease, ejection fraction (EF) <40%, and LA ≥50 mm. CHADS2 score of 1 was defined as the presence of one of the following parameters according to the CHADS2 score: age ≥75 years, hypertension, diabetes, or NYHA II plus. To compare the clinical outcome in the different groups, multiple logistic regression analysis was performed adjusting for CHADS2 score of 1, gender, EF, atrial flutter, duration of AF, previous thrombo-embolic complications, concomitant medication including beta blocker, ACE inhibitor, antiarrhythmic therapy, diuretics, and prior use of phenprocoumon. All P-values were two tailed. A P-value of <0.05 was considered statistical significant. The tests were performed using the SAS statistical package (version 8.02, Cary, NC, USA).

Results
Characteristics of the patients
Overall, 295 consecutive patients who underwent TEE before planned cardioversion were included in the present study. A total of 119 (40%) patients had a CHADS2 score of 0, and 176 (60%) patients had a CHADS2 score of 1. In these patients, the prevalence of LA thrombus was 3% and of dense SEC was 8%. Baseline clinical data of the enrolled 295 patients are summarized in Table 1. Patients with thrombus or dense SEC had more often an organic heart disease (P < 0.05), a depressed EF <40% (P < 0.01), an increased LA dimension ≥50 mm (P < 0.001), and more frequently suffered from heart failure symptoms (P < 0.01). There were no differences with regard to age, gender, and AF-characteristics between both groups (Table 1). The duration of the index
AF episode was more often unknown in patients with thrombus or dense SEC. In 14 patients, cardioversion was not performed due to thrombus or dense SEC. Among those patients, four patients underwent a cardioversion during follow-up. In the control group, nearly every patient underwent cardioversion (P = 0.0001). Independent predictors for thrombus or dense SEC in patients with CHADS2 score of 0/1 were EF < 40% and LA dimension ≥ 50 mm (Figure 1). Table 2 outlines the anticoagulation therapy before index admission, at discharge, and after 5 years. Twenty-two (73%) of the patients with thrombus or dense SEC and 161 (61%) patients of the control group received oral anticoagulation before index admission (P = 0.44). All patients in both groups received anticoagulation therapy at discharge. After 5 years, every patient in the group with thrombus or dense SEC and 124 (61%) in the control group received oral anticoagulation (P < 0.001). The quality of oral anticoagulation was high with a median INR of 2.4. All patients with thrombus or dense SEC had an effective INR ≥ 2.

Clinical outcome

Patients with thrombus or dense SEC had a three-fold increased univariate 5 year mortality compared with patients without thrombus or dense SEC (Figure 2). The estimated rate of major cardiovascular and cerebrovascular events after 10 days was 1.4% in patients with thrombus/dense SEC vs. 0.6% in the control group (P = 0.18). In a multivariable analysis adjusted for 11 parameters, thrombus and dense SEC were not an independent predictor for an increased incidence of stroke or death during long-term follow-up in anticoagulated patients (Figure 3). No patient having thrombus or dense SEC identified using TEE developed non-fatal stroke or TIA during the study, whereas seven (3%) patients in the control group suffered from non-fatal stroke or TIA during the long follow-up. The incidence of minor bleedings was observed more than doubled in patients with thrombus or dense SEC compared with the control group (24 vs. 9%, P < 0.05), whereas major bleedings did not occur in both groups. No differences in
clinical outcome were observed between patients with only thrombus, only dense SEC, and a combination of both.

Discussion

Major findings

In patients with non-valvular AF and a low CHADS2 score of 0 or 1, the prevalence of LA thrombus was 3% and that of dense SEC 8%. Independent predictors for the presence of thrombus or dense SEC were EF <40% and LA dimension >50 mm. None of the patients, who had a thrombus or dense SEC, suffered from non-fatal stroke or TIA during the study. The presence of thrombus or dense SEC was not an independent predictor for an increased risk of stroke or death under continued anticoagulation in patients with non-valvular AF and CHADS 0/1.

The value of echocardiography as an additional tool for risk stratification in patients with CHADS 0/1

The CHADS2 score does not implement echocardiographic data into the decision algorithm for antithrombotic therapy. However, a moderate or severe left ventricular function on echocardiography is an independent predictor of stroke. Current guidelines do consider EF 35% or less as an independent moderate risk factor apart from the clinical risk factors. The present study underlines these findings, demonstrating that impaired left ventricular function is an independent predictor for the presence of thrombus or dense SEC. The present study also reveals that an LA dimension of ≥50 mm is an independent predictor for the presence of thrombus or dense SEC. The LA diameter has been less consistently associated with thrombo-embolism. Meta-analysis of three trials found moderate to severe left ventricular dysfunction to be the only independent echocardiographic predictor of stroke in patients with AF after adjustment for clinical features, whereas the LA diameter was less useful. In the SPAF I trial, however, LA diameter was significantly associated with the combined endpoint of ischaemic stroke and systemic emboli.

Estimating the risk of stroke for individual AF patients is crucial for the decision to provide anticoagulation therapy to the individual patient with AF. In the present study, TEE could identify a subgroup of patients who have a thrombo-embolic milieu even in the absence of clinical risk factors. This is in accordance with a study performed by Thambidorai et al., where TEE provided significant incremental value in predicting thrombo-embolism compared with clinical characteristics. Despite the potential for TEE to identify thrombo-embolic conditions, recently published risk stratification schemes have not incorporated...
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the TEE characteristics. This may be because thrombus was the only TEE characteristics used, and other TEE characteristics were not considered in assessing the thrombo-embolic risk. Also, there have been no large-scale clinical trials to assess the TEE risk factors except for the Embolism in Left Atrial Thrombi (ELAT) study, which found no incremental value of TEE compared with clinical factors. Therefore, randomized trials are needed to analyse if TEE-guided long-term anticoagulation strategy can reduce thrombo-embolism in patients with non-valvular AF.

Clinical impact of left atrial thrombus and moderate to severe spontaneous echo contrast under anticoagulation therapy

In the present study, no patient who had a thrombus or dense SEC suffered from non-fatal stroke or TIA during the study. Although characteristics of the thrombus may play a role and some thrombo-embolic events may not have been clinically apparent, the main reasons for the lack of an embolic event in patients who had thrombus or dense SEC might have been therapeutic anticoagulation and the decision for rate control instead of rhythm control therapy, especially in patients with thrombus or severe SEC. Because many thrombi resolve or shrink, anticoagulation prevents embolization of atrial thrombus and prevents new thrombus formation. In addition, large randomized trials like RACE and AFFIRM showed that rate control therapy is associated with a lower incidence of stroke than rhythm control strategy.

The present study shows that patients with CHADS$_2$ score 0 or 1 and thrombus or dense SEC have a three-fold increased univariate 5 year mortality compared with patients without thrombus or dense SEC. This difference is mainly driven by the close association of thrombus and dense SEC to lower EF because after adjusting for EF, thrombus and dense SEC were no more associated with an increased incidence of stroke or death during long-term follow-up. In previous trials, the presence of SEC and the formation of thrombus in the left atrium have been associated with a higher risk of thrombo-embolism and cerebrovascular events in patients with AF. Bernhardt et al. showed that patients with AF and dense SEC had a 22% likelihood of cerebral embolism and/or death during a 12 month follow-up. In patients with AF and atrial thrombi, 50% suffered from cerebral embolism and/or death during a long-term follow-up of 3 years, even despite oral anticoagulation therapy. However, these studies did not stratify their patients according to the CHADS$_2$ score and did not adjust for risk factors like impaired left ventricular function. In addition, 31% of the patients were not effectively anticoagulated during the follow-up period.

Limitations of the study

The study is based on a clinical, observational registry from a single centre and therefore site-specific influences could bias the results. However, the patient population provided a valid representation of patients who presented with sustained clinical features of AF. The sample may have been influenced in favour of patients who had a pre-existing, known, or suspected cardiovascular disorder, which prompted a referral for the initial diagnostic electrocardiogram.

Oral anticoagulation therapy during follow-up was assessed during the fifth year of follow-up in survivors. It is not known whether oral anticoagulation therapy changed during follow-up and how patients were treated, who died during follow-up. When looking at the high rate of anticoagulation after 5 years, according to the current guidelines, the study population seems to be overanticoagulated. However, the study was performed between 1994 and 2004. Patients were treated according to the older guidelines that were more aggressive with regard to anticoagulation therapy than the current guidelines. Secondly, the CHADS$_2$ score could have been increased during the 5 year follow-up and thirdly, all patients received anticoagulation therapy at the beginning of the study due to cardioversion, which might not have been withdrawn later in some patients.

Echocardiographic parameters like LA appendage peak flow velocities or complex aortic plaques which are known to be associated with an increased thrombo-embolic risk were not investigated in the present study. The rate of major bleeding was very low. The reliability of the estimated rate of bleeding might be decreased due to inconsistent follow-up and unknown rate of fatal bleedings. Presumably, the rate of major bleedings has been underestimated.

Conclusions

Despite a low risk for stroke according to the CHADS$_2$ score (CHADS 0/1), 3% of patients have LA thrombus and 8% moderate or severe SEC. Independent predictors for thrombus or dense SEC are EF <40% and LA ≥ 50 mm. Under continued anticoagulation, the presence of thrombus or dense SEC is not an independent predictor for an increased risk of stroke or death in patients with non-valvular AF and CHADS 0/1. These findings underline the need to explore whether echocardiographic risk stratification on top of the CHADS$_2$ score can additionally reduce thrombo-embolism in patients with non-valvular AF.

Conflict of interest: none declared.

References


