Left Atrial Thrombus on TransEsophageal Echocardiography: rationale and design of the LATTEE registry - the first multicenter project on the Scientific Platform of the “Club 30” of the Polish Cardiac Society

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Left Atrial Thrombus on TransEsophageal Echocardiography: rationale and design of the LATTEE registry - the first multicenter project on the Scientific Platform of the “Club 30” of the Polish Cardiac Society

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Conflict of interest: none declared

Short title: Design of the LATTEE registry - from the “Club 30” Scientific Platform

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Introduction

Since its establishment 25 years ago, the “Club 30” of the Polish Cardiac Society (PCS) has gathered young Polish scientists with meaningful achievements in cardiology [1]. The “Club 30” Scientific Platform was created to facilitate initiation of and participation in multicenter studies conducted by its Users, and to promote integration of scientific research [2]. Multicenter cooperation, empowered by the Platform, results in increasing the number of enrolled patients and, consequently, enhances research quality and chances for publication in high indexed journals.

In atrial fibrillation (AF) and atrial flutter (AFl), oral anticoagulation (OAC) reduces the risk of both left atrial (LA) thrombus and ischemic stroke [3-5]. Still, some patients develop LA thrombus and experience thromboembolic events despite OAC [6-9]. The CHA2DS2-VASc-RAF score was recently proposed to improve LA thrombus prediction in AF [9].

The aim of this study is to assess the prevalence of LA thrombus in real-world patients with AF or AFl referred for transesophageal echocardiography (TEE), to identify predictors of LA thrombus in these patients, and to validate the CHA2DS2-VASc-RAF score.

Methods

The LATTEE (Left Atrial Thrombus on TEE; NCT03591627) registry is an on-going, multicenter, prospective, observational study, conducted in 13 Polish cardiology centers. The registry includes all consecutive AF/AFl patients hospitalized in a participating center during the study period, who were scheduled for catheter ablation or cardioversion for AF or AFl, and had TEE performed prior to the procedure (irrespective of whether the procedure was finally carried out). There are no specific exclusion criteria, except for age below 18 years and inconclusive TEE result regarding the presence of LA thrombus. Patients are enrolled in the study irrespective of the presence or type of OAC. Each of the 13 participating centers will include at least 200 patients, and thus, the total number of patients in the registry is estimated
to exceed 2600. In each participating center, recruitment will last 12 months, starting from the date of enrollment of the first patient in this center, or longer if the required number of 200 patients is not reached by the participating center in 12 months.

In all patients, data on clinical characteristics, pharmacotherapy, routine blood tests and TEE results are collected. All other tests are performed at the discretion of the attending physician within the standards of care in a given center. However, if available, data from transthoracic echocardiography and Holter monitoring are gathered (Table 1). If a patient undergoes repeated TEE during the study period (e.g. before another procedure or a control TEE for LA thrombus), this is also reported in the registry (separately for a given patient), together with data on the current antithrombotic treatment.

The study was approved by the Ethics Committee of the Medical University of Warsaw (AKBE/113/2018). The Ethics Committee waived the requirement of obtaining informed consent from the patients.

**Study endpoint**

The primary endpoint is the presence of LA thrombus on TEE.

**Statistical analysis**

Depending on the profile of a participating center, the proportion of “ablation” to “cardioversion” patients, as well as their clinical characteristics and thromboembolic risk may vary from center to center. Still, it may be anticipated that approximately 85-90% of enrolled patients will receive OAC. In OAC-treated populations, the prevalence of LA thrombus ranges from 1 to 10% [8-12]. Should the registry include a total of 2600 patients, over 100 cases of LA thrombus are to be anticipated, providing an adequate number of study endpoints for logistic regression analysis of predictors of LA thrombus. Receiver operating characteristic (ROC) curves will be constructed and area under the curve (AUC) calculated to assess the prognostic accuracy of the CHA2DS2-VASc-RAF score (in comparison to other models) in identification
of patients with LA thrombus. Analyses will be performed using the SAS software, version 9.2 (SAS Institute, Cary, North Carolina, United States).

**Discussion**

The CHA\textsubscript{2}DS\textsubscript{2}-VASc score is a recommended tool for thromboembolic risk stratification in AF and AFib [3]. Still, it may not encompass all clinically relevant predictors of LA thrombus formation [6,7,13-15]. AF type has long been perceived as irrelevant for thromboembolic risk assessment. However, recently, non-paroxysmal AF has been shown to be independently associated with a higher risk of thromboembolic events than paroxysmal AF [6,7,9]. Moreover, in paroxysmal AF, evaluation of AF burden might improve thromboembolic risk stratification [14]. Renal dysfunction is another variable, not included in the CHA\textsubscript{2}DS\textsubscript{2}-VASc score, found to be a strong predictor of stroke and systemic embolism [15]. Recently, a new, CHA\textsubscript{2}DS\textsubscript{2}-VASc-based model - the CHA\textsubscript{2}DS\textsubscript{2}-VASc-RAF score (R for renal dysfunction, AF for AF type) - proved superior to both the CHADS\textsubscript{2} and the CHA\textsubscript{2}DS\textsubscript{2}-VASc score in identifying patients with LA thrombus [9]. The primary goal of the LATT\textsubscript{EE} registry is to validate, and possibly recalibrate, the CHA\textsubscript{2}DS\textsubscript{2}-VASc-RAF score. Secondary analyses will include evaluation of LA thrombus risk in patients on different OAC regiments, depending on LA appendage morphology, as well as in various, predefined subgroups, including patients with heart failure, aortic stenosis, mitral regurgitation, diabetes, chronic kidney disease, men vs women, and the elderly.

The main limitation of the LATTEE registry is the use of a surrogate endpoint of LA thrombus and not ischemic stroke. However, LA thromboembolism represents the primary mechanism involved in the etiopathology of ischemic stroke in AF. Thus, we feel that the presence of LA thrombus on TEE may be considered an adequate surrogate endpoint. Another limitation, arising from the study methodology (inclusion of patients referred for TEE) is that its participants - scheduled for ablation or cardioversion - can be expected to have lower thromboembolic risk than AF population as a whole. However, identifying novel, additional
risk factors for LAA thrombus formation seems of special value particularly in patients with presumed low or intermediate thromboembolic risk (who will be adequately represented in the LATTEE registry) rather than in patients who are already known to be at high thromboembolic risk. Finally, ideally, all TEE studies would be recorded and the presence of LA thrombus verified centrally in a core laboratory - this was not undertaken in our registry.

In conclusion, the LATTEE registry is the largest study of AF/AFl patients undergoing TEE in Poland and will investigate the prognostic accuracy of the CHA\textsubscript{2}DS\textsubscript{2}-VASc-RAF score. It will also provide information on residual LA thrombus risk in patients treated with OAC, and in different AF subpopulations. A significant number of centers participating in the LATTEE registry proves the utility of the “Club 30” Scientific Platform as well as the will for integration of the young Polish scientific community.

Acknowledgments

The LATTEE registry was initiated on the Scientific Platform of the “Club 30” of the PCS [3].

Investigators (other than those listed as Authors):
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References


Table 1. Laboratory data collected in the LATTEE registry

<table>
<thead>
<tr>
<th>Test</th>
<th>Collected data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In all patients</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Blood tests</strong></td>
<td>• complete blood count</td>
</tr>
<tr>
<td></td>
<td>• creatinine, GFR</td>
</tr>
<tr>
<td></td>
<td>• alanine and aspartate aminotransferases</td>
</tr>
<tr>
<td></td>
<td>• INR, APTT</td>
</tr>
<tr>
<td><strong>TEE</strong></td>
<td>• presence of LA thrombus</td>
</tr>
<tr>
<td></td>
<td>• location of LA thrombus (LAA vs LA cavity)</td>
</tr>
<tr>
<td></td>
<td>• presence of SEC, including dense SEC</td>
</tr>
<tr>
<td></td>
<td>• LAA emptying velocity (in relation to rhythm during TEE)</td>
</tr>
<tr>
<td><strong>If available</strong></td>
<td></td>
</tr>
<tr>
<td><strong>TEE</strong></td>
<td>• LAA morphology (windsock, chicken wing, cactus or cauliflower)</td>
</tr>
<tr>
<td><strong>Transthoracic echocardiography</strong></td>
<td>• left ventricular ejection fraction (Ap4Ch/Ap2Ch)</td>
</tr>
<tr>
<td></td>
<td>• LA dimension (PLAX)</td>
</tr>
<tr>
<td></td>
<td>• LA area (Ap4Ch)</td>
</tr>
<tr>
<td></td>
<td>• LAVI (Ap4Ch/Ap2Ch)</td>
</tr>
<tr>
<td><strong>Holter monitoring</strong></td>
<td>• presence of AF or AFl</td>
</tr>
<tr>
<td></td>
<td>• AF/AFl burden</td>
</tr>
</tbody>
</table>