Is transesophageal echocardiography necessary before electrical cardioversion in patients treated with non-vitamin K antagonist oral anticoagulants? Current evidence and practical approach

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Abstract

According to current guidelines, non-vitamin K antagonist oral anticoagulants (NOACs) should be used at least 3 weeks before planned electrical cardioversion. In accordance with international atrial fibrillation (AF) guidelines, transesophageal echocardiography (TEE) is a pre-procedural examination recommended as an alternative to adequate oral anticoagulation. The strategy related to qualifying patients treated with NOACs for pre-procedural TEE differs in individual centers. Therefore, it is necessary to create an algorithm that will standardize estimation of left atrial appendage thrombus (LAAT) prevalence risk and thereby qualify NOAC-treated patients to TEE in the most effective way. We assessed the available studies on LAAT predictors. Risk factors for LAAT formation are not necessarily the same as the risk factors for thromboembolic events in patients with AF. The main risk factor for LAAT are as follows: previous intracardiac thrombus, irregular use of NOAC, inappropriate dose reduction of NOAC, previous stroke, CHA₂DS₂-VASc score ≥ 3 points, glomerular filtration rate < 60 mL/min/1.73 m², reduced left ventricular ejection fraction, or left atrial enlargement. Based on available evidence, we proposed algorithm guarantees more systematic approach to performing TEE in patients undergoing electrical cardioversion. (Cardiol J)

Key words: electrical cardioversion, non-vitamin K antagonist oral anticoagulant, transesophageal echocardiography

Introduction

Electrical cardioversion (ECV) is a procedure commonly used in atrial fibrillation (AF) patients for whom a strategy of restoring sinus rhythm was adopted. The EAST (Early treatment of Atrial fibrillation for Stroke prevention Trial) study found that early rhythm-control therapy was associated with

lower risk of cardiovascular outcomes than usual care among patients with early AF and cardiovascular diseases [1]. ECV is a safe practice provided a patient is appropriately prepared and procedures minimizing risk of thromboembolic complications are introduced. In patients with AF undergoing ECV, secondary analyses from the landmark non-vitamin K antagonist oral anticoagulant (NOAC)

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trials, as well as prospective randomized trials, showed that NOACs are of similar efficacy and safety to warfarin [2–6].

Thromboembolic risk in the peri-cardioversion period

Occurrence mechanisms of thromboembolic complications in patients after ECV can be different. Thromboemboli after ECV are thought to be caused by embolization of already existing thrombi present in the left atrial appendage (LAA) at the time of ECV. In the first weeks after ECV atrial function is depressed, impairing the left atrium's ability to empty sufficiently.

This impairment could lead to formation of thrombi even if their presence had not been diagnosed before ECV [7, 8]. Therefore, performing transesophageal echocardiography (TEE) before ECV and excluding thrombus in the left atrium does not guarantee that after ECV emboli will not be formed. In the analysis of the data from 32 studies and a total number of 4621 patients, 92 patients had a thromboembolic event after ECV. Thromboembolic complications appeared from 1 to 18 days after ECV. It was shown that the vast majority of events occurred within 72 hours of ECV, 82% of thromboembolic complications appeared in 3 days, 96% in 1 week, and 98% within 10 days of ECV [9].

The results of studies to date confirm that the proportion of thromboembolic complications after ECV in patients effectively treated with anticoagulant drugs is not high. Among 1613 AF patients treated with NOACs or vitamin K antagonists (VKAs) and undergoing ECV there were no differences in the incidence of stroke or transient ischemic attack (TIA) within the first year after ECV [10]. The results of the study by Frederiksen et al. [11] involving a group of 2150 patients undergoing ECV were consistent with the results of the previous study. Thromboembolic complications were not observed in any of the patients during the 30-day follow-up period of this study, which included 668 patients treated with NOACs before ECV [12]. Also, Barysiene et al. [13] did not acknowledge thromboembolic events in the 30-day follow-up period for a group of 432 patients receiving pertinent anticoagulant therapy prior to ECV. A meta-analysis of four randomized controlled trials comparing NOAC therapy with VKA, including 4517 cardioversions, showed that the thromboembolic complication rate was 0.4% in patients treated with NOACs and 0.6% in patients treated with VKAs [14]. Another meta-analysis

involving seven trials and 7588 patients undergoing ECV showed that NOACs, as compared to warfarin, resulted in similar risks of ischemic stroke (0.19% vs. 0.53%) after ECV [15].

Prevalence of thrombi in the LAA and their risk factors

In AF patients, thromboembolic material localized in the left atrium is most frequently observed in the LAA. The prevalence of LAA thrombus (LAAT) in patients undergoing anticoagulant therapy was assessed in numerous studies (Table 1) [16–30].

Risk factors for LAAT formation are not clearly defined and are not necessarily the same as the risk factors for thromboembolic events in patients with AF. The main pathophysiological theory of atrial thrombogenesis in AF relates to endocardial remodeling [31]. Oxidative stress and inflammation in fibrillating atrial tissue are the main factors influencing up-regulation of thrombogenic proteins at the endocardial surface.

The precursor of LAAT is a spontaneous echo contrast (SEC) described as discrete reflections that are visible in blood inside cardiac cavities, chambers, or vessels. Smoke-like SEC is defined as swirling, amorphous, light gray haze [32]. Its acoustic density and configuration alter within several cardiac cycles. It is possible to notice it in veins, great vessels, and in left and right heart chambers. Smoke-like SEC shows a strong connection to thromboembolic events and stroke [33] and its probable cause is blood stasis [34]. Non-smoke SEC looks like a 'snowstorm' or like discrete dispersed reflections in normal conditions. Respiratory maneuvers can enhance such SEC in the left atrium. Its intensity can be mild to moderate and conditioned by transient stasis, especially in the pulmonary circulation. LAA sludge signalizes a dynamic, viscid, layered echo dense finding without a discrete mass. Its density seems higher than that of SEC and lower than that of a thrombus. Thus, it is believed to be a stage between SEC and thrombus formation [35].

Concomitant diseases such as arterial hypertension, diabetes mellitus, heart failure, and advanced age appear to have an important impact on endocardial remodeling.

In most studies LAAT prevalence was higher in patients with the higher CHA₂DS₂-VASC score. However, it was proven that LAAT appeared in patients without risk factors included in the CHA₂DS₂-VASC score. Therefore, it is necessary to search for LAAT risk factors that are different

Table 1. The prevalence and risk factors of a left atrial appendage thrombus in the selected studies.

Reference, year	No. of patients	Age	Male, %	LAAT, %	Independent factors predisposing to LAAT
Puwanant [16], 2009	1058	57 (11)	80	0.6	LV function
Gunawardene [17], 2017	1658	63 (11)	65.7	0.78	Congestive heart failure CHA ₂ DS ₂ -VASC ≥ 4 LVEF < 30% Hypertrophic cardiomyopathy
Scherr [18], 2009	732	57 (11)	77	1.6	Non-paroxysmal AF CHADS ₂ ≥ 2 LA diameter ≥ 45 mm
McCready [19], 2010	635	59 (12)	67	1.9	Cardiomyopathy Hypertension Age >75
Dorenkamp [20], 2013	329	62 (10)	65	2.1	CHA ₂ DS ₂ -VASC ≥ 4 CHADS ₂ ≥ 3 Diabetes mellitus
Wu [21], 2018	608	65 (58–71)	72	2.8	Congestive heart failure Moderate/severe LA enlargement
Yamashita [22], 2010	446	59 (11)	70	2.9	Persistent AF Structural heart disease
Huang [23], 2017	2695	58 (12)	67.7	3	Advanced age Stroke/TIA Non-paroxysmal AF LV dysfunction LA enlargement Cardiomyopathy
Frenkel [24], 2016	388	65 (58–71)	74	3.6	Heart failure Persistent AF
Han [25], 2020	1102	60.6 (5.8)	67.5	4.36	Hypertension Stroke/TIA/systemic embolism LVEF < 50% LA enlargement GFR < 60 mL/min/1.73 m ²
Gorczyca [26], 2020	1148	62.1	61.9	4.4	CHA ₂ DS ₂ -VASC ≥ 2 Non-paroxysmal AF GFR < 60 mL/min/1.73 m ²
Harada [27], 2018	407	63 (12)	71	4.4	Persistent AF Inappropriate dose reduction of NOACs
Huang [28], 2018	2173	57.8 (11.8)	67.1	4.9	Non-paroxysmal LVEF $\leq 55\%$ LA enlargement
Kapłon-Cieślicka [29], 2019	1033	60 (53–66)	66	5.71	CHA ₂ DS ₂ -VASC score GFR < 56 mL/min/1.73 m ² Non-paroxysmal AF
Merino [30], 2019	1183	–	–	8.2	Heart failure Age

AF — atrial fibrillation; GFR — glomerular filtration rate; LA — left atrial; LAAT — left atrial appendage thrombus; LV — left ventricle; LVEF — left ventricular ejection fraction; NOACs — non-vitamin K antagonist oral anticoagulants; TIA — transient ischemic attack

Table 2. The proposal of a left atrial appendage thrombus risk stratification model: the CHA₂DS₂-VASC-RF score and the left atrial appendage thrombus/spontaneous echo contrast score (LAAT/SEC).

Risk factors	Scales	
	CHA ₂ DS ₂ -VASC-RF [28]	LAAT/SEC score [29]
Congestive heart failure	1	–
Hypertension	1	–
Diabetes mellitus	1	–
Vascular disease	1	–
Age 65–74 years	1	–
Stroke/TIA/systemic embolism	2	–
Age ≥ 75 years	2	–
Female sex	1	–
GFR < 56 mL/min/1.73 m ²	2	–
Persistent AF	4	1
Permanent AF	10	1
LVEF < 55%	–	2
LA enlargement (> 38 mm for women, > 40 mm for men)	–	3
Risk categories		
Low	0–4 points in men 1–5 points in women	0–1 point
Intermediate	–	2–3 points
High	≥ 5 points in men ≥ 6 points in women	4–6 points

AF — atrial fibrillation; GFR — glomerular filtration rate; LA — left atrial; LVEF — left ventricle ejection fraction; TIA — transient ischemic attack

from the classic thromboembolic ones. A study of 1033 patients revealed renal function and AF type as strong and independent predictors of LAAT. This same study suggested the CHA₂DS₂-VASC score be extended and that it might be considered an effective tool for LAAT prevalence assessment (Table 2) [29]. Further studies showed that the CHA₂DS₂-VASC-RF score was a better LAAT prevalence predictor than the CHA₂DS₂-VASC score in patients treated with NOACs [36]. Therefore, using the CHA₂DS₂-VASC-RF score or taking into account all additional factors included in it (renal function, AF type) in the assessment of LAAT prevalence risk may be helpful in making decisions on TEE performance. Huang et al. [23] proposed a new scoring system established as the LAAT/SEC predictive score, in which the following parameters were included: non-paroxysmal AF, left ventricular ejection fraction (LVEF) < 55%, and left atrial enlargement (Table 2).

TEE-guided cardioversion

According to current guidelines issued by the European Society of Cardiology (ESC), early cardio-

version can be done without TEE in patients with AF duration < 48 hours. Suitable oral anticoagulation is recommended for at least 3 weeks before ECV in patients with AF > 48 hours or of unknown duration [37]. This recommendation is the same for all patients, independent of stroke risk, according to the CHA₂DS₂-VASC score. This 3-week period of adequate anticoagulant treatment is necessary, based on the time presumably needed for endothelialization or resolution of possible LAAT. To shorten this time, experts recommended TEE to exclude LAAT as an alternative to a 3-week anticoagulation period when early cardioversion is planned [37]. Recommendations from the ESC and the American Society of Cardiology for the aforementioned issue are consistent [37, 38] with previous ESC guidelines [39].

Tee before ECV in clinical practice

In clinical practice, procedures related to performing TEE in patients using NOACs and undergoing planned ECV are different at individual centers. In the case of patients treated with VKAs, the international normalized ratio value from 3 weeks before ECV proves that anticoagulant

treatment is adequate. Thus far, none of the coagulation parameters were considered to be indicators confirming regular use of NOACs. Therefore, in the absence of laboratory confirmation of regular NOAC use, patients undergo TEE prior to ECV.

Results of the European Heart Rhythm Association survey from 2019 included 54 centers and found that most would also perform TEE in patients with AF lasting ≥ 48 hours in case of no or incomplete information (80% and 78%, respectively) about adequate anticoagulation. Only 12% of the centers would routinely perform TEE before any LA procedure, regardless of the thromboembolic risk [40]. The results of the same survey from 2013 are not consistent with the above-mentioned practice. In 56.5% of centers where patients were not on adequate anticoagulation therapy, TEE was performed. An additional 4.6% of the centers recommended TEE routinely for all patients [41]. In the study including 668 AF patients treated with NOACs before ECV, TEE was performed in 54% of patients [12]. Data from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II showed that 25% of patients had pre-cardioversion TEE [10].

When TEE should be made before ECV: Practical decision algorithm

Data referring to the frequency of TEE procedures in patients with AF treated with NOACs are not consistent and show diverse strategies among individual centers performing ECV.

Current ESC guidelines lack the possibility of standardizing how NOAC action is monitored, indicating the need to search for new patterns that can be used to determine which AF patients would be served with TEE prior to ECV. The data indicates that performing pre-cardioversion TEE in all patients treated with NOACs is not optimal, nor is exempting them all from TEE before ECV.

There is a great deal of evidence indicating that, according to the CHA₂DS₂-VASc score, high risk of thromboembolic complications in patients treated with NOACs is a predictor of LAAT. In the study of Gorczyca et al. [26] the LAAT predicting factor was a CHA₂DS₂-VASc score ≥ 2 points, and in the study of Gunawardene et al. [17] CHA₂DS₂-VASc score ≥ 4 points was predictive. However, using this score alone for patient assessment may not be the most thorough approach possible, given that other conditions also present the same results. In some situations, it is necessary to diagnose LAAT risk based on a patient's detailed clinical characteristics and not the result of a particular score.

Central illustration. The algorithm proposed for assessing indications for transesophageal echocardiography (TEE) before planned electrical cardioversion in patients treated with non-vitamin K oral anticoagulants (NOACs); GFR — glomerular filtration rate; LA — left atrial; LAVI — left atrial volume index; LVEF — left ventricular ejection fraction; TIA — transient ischemic attack.

For the systematic approach to performing TEE before ECV we propose a decision-making algorithm, presented in Central illustration. We have merged widely accessible clinical features, identified in the above-discussed studies as the risk factors of LAAT, in a simple screening path. In patients with AF using NOACs before planned ECV, pre-procedural TEE should be performed in those who had LAAT in the past, regardless of treatment strategy, and also in those with any suspicion of unsystematic NOAC use. In the remaining patients, the necessity for TEE should be decided upon after considering individual thromboembolic risk. According to the presented algorithm, TEE should be performed in patients with any strong LAAT risk factor such as: previous intracardiac

thrombus, irregular use of NOAC, inappropriate dose reduction of NOAC, previous stroke/TIA/systemic embolism, CHA₂DS₂-VASc score ≥ 3 points, glomerular filtration rate < 60 mL/min/1.73 m², reduced LVEF, or moderate or severe left atrial enlargement (Central illustration).

TEE: Limitations of the methods

Transesophageal echocardiography is a minimally invasive procedure that is usually safer when conducted by an experienced physician. However, it is time consuming, carries patient discomfort, is not readily available in all centers, and sometimes it is associated with potential life-threatening complications. Although TEE is regarded as the gold standard to exclude a thrombus in the LAA before scheduled ablation or AF cardioversion, the accuracy of this technique is far from 100%. In patients who present contraindication to TEE or do not agree to have this examination, computed tomography or magnetic resonance imaging can be considered reasonable alternatives to TEE in the identification of LAAT. Multidetector computed tomography provides three-dimensional volumetric data of the entire heart, including the LAA. It is of high spatial and temporal resolution, which allows the identification of LAAT and spontaneous contrast formation similar to the SEC observed by TEE. Cardiac magnetic resonance with its high temporal resolution shows the LAA size and function and can detect LAAT in AF patients. A recently conducted systematic review and meta-analysis of 4 cardiac magnetic resonance and 22 multidetector computed tomography studies juxtaposed TEE with the diagnostic performance of listed methods for LAAT identification. Sensitivity and specificity of multidetector computed tomography were, respectively, 0.99 and 0.94 compared to TEE, with notably increased specificity of the delayed imaging protocols. Cardiac magnetic resonance, in comparison to TEE, demonstrated sensitivity and specificity of 0.80 and 0.98, respectively [42]. It seems that in clinical practice the main limitation of TEE is lack of common TEE accessibility in all centers performing ECV.

Summary

Due to the high risk of LAAT and lack of standardized laboratory tests confirming the efficacy of NOAC, it seems necessary to define guidelines for performing TEE prior to ECV. It appears that risk factors of thromboembolic complications and LAAT

are not the same. In patients with low thromboembolic risk, it is especially important to consider additional factors that increase the risk of LAAT prevalence. The proposed algorithm guarantees a more systematic approach to performing TEE in patients undergoing ECV.

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