Are three weeks of oral anticoagulation sufficient for safe cardioversion in atrial fibrillation?

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Abstract:

Background: Patients with atrial fibrillation (AF), lasting >48 h, considered for cardioversion, are recommended ≥3 weeks of oral anticoagulation before sinus rhythm restoration because of high risk of development of left atrial thrombosis (LAT) and stroke. However, the optimal duration of anticoagulation in the presence of overt LAT is unknown.

Methods: An open-label study, aiming to investigate the prevalence of spontaneous echo contrast (SEC) and LAT before and after 3 weeks of direct oral anticoagulant (DOAC) treatment. We included 51 consecutive patients (50.9% males), mean age 69.3±7.4 years with paroxysmal/unknown duration of AF, considered for cardioversion, who agreed to have transesophageal echocardiography at enrollment and 3 weeks later.

Results: At baseline SEC was present in 26 (50.9%) and LAT in 10 (19.6%) of 51 patients. After 3 weeks on DOAC, SEC persisted in 12 (25.0%) and LAT in 7 (14.5%) of 48 patients, p<0.05 vs baseline. Factors, associated most strongly with persistence of SEC/LAT were left atrial appendage (LAA) emptying velocity <20 cm/s (OR=2.82), LAA lobes >2 (OR=1.84) and indexed left atrial volume ≥34 ml/m2 (OR=1.37).

Conclusions: The recommended minimal period of 3 weeks of oral anticoagulation lead to SEC/LAT resolution in 47% of our patients. To our opinion, LA/LAA morphology and function should be taken into account when determining the duration of DOAC treatment before planned cardioversion.

Keywords: anticoagulant; atrial; thrombosis; dabigatran; monitoring

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in humans with estimated prevalence ~3% among the general population aged >20 years: 1 in 4 middle-aged adults will develop at least 1 episode of this rhythm disorder [1]. In addition, AF is a strong and independent risk factor (RF) for ischemic stroke and/or peripheral arterial thromboembolic events [1-4]. Even short/rare episodes of AF possess certain risk of stroke, that should not be neglected, and the risk increases significantly with AF duration, ageing and in the presence of other concomitant diseases such as arterial hypertension, heart failure, chronic kidney disease, diabetes, etc. [1-4].

Many patients with episodes of paroxysmal/persistent AF are referred for pharmacological/electrical cardioversion: rhythm control is a part of the symptom control strategy (together with rate control) [1-3]. However, cardioversion (pharmacological or electrical) is associated with 5-7% risk of thromboembolic events within 30 days in non-anticoagulated patients. Thromboembolic rates are highest within the first 7 days after cardioversion (>80% of events), with 70% of them occurring the first 2 days [2, 5-9].

Clinical trials show that anticoagulation prior, at the time and post-cardioversion can reduce the 30-days thromboembolic risk significantly (<1%) [2, 5, 10]. For this reason, the current European Society of Cardiology (ESC) guidelines recommend a minimal period of 3 weeks of oral anticoagulation (OAC) to patients with AF lasting ≥48 h or AF with unknown duration or AF duration 12-48 h with CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, and female gender) score ≥2 for males and ≥3 for females, if the patients are considered for cardioversion, but left atrial thrombosis (LAT) cannot safely be excluded by a transesophageal echocardiography (TEE) [1]. It has to be mentioned, that these recommendations are not based on results from randomized clinical trials [1, 2, 11]. In addition, there are a lot of reports of peri-/post-cardioversion strokes even in well-coagulated (according to the guidelines) patients with low CHA2DS2-Vasc score [5-7]. Many of these events are due to LAT that have been formed before initiation of OAC and persisting after the recommended minimal period of anticoagulation [8, 9, 13].

Data about the real prevalence of LAT in patients with paroxysmal/persistent AF as well as the prevalence of spontaneous echo contrast (SEC) - a very risky finding, predisposing to LAT formation, are still insufficient [7-15]. The traditional therapeutic approach to these patients is treatment with parenteral anticoagulants or vitamin K antagonists (VKAs), mostly Warfarin [1, 8, 12]. The current ESC guidelines also suggest that the direct oral anticoagulants (DOACs) could be as efficient and safer as VKAs, however robust data from randomized clinical trials (RCTs) are lacking [10-19].

Giving the importance of optimal OAC in AF patients, considered for cardioversion, we conducted a study, aiming to investigate the prevalence of SEC/LAT in patients with paroxysmal/unknown duration of AF, before DOAC treatment and 3 weeks later, thus evaluating the potential of DOACs to resolve these pathological conditions.

2. Materials and Methods

This prospective, open-label study was conducted in the period May, 2016-October, 2017. We included 51 consecutive out-hospital patients with paroxysmal, non-valvular AF, planned for pharmacological/electrical cardioversion (26 males - 50.9%, P males/females = N.S.), mean age 69.3 ± 7.4 (61-86) years. All patients were examined with transesophageal echocardiography (TEE) at baseline, before DOAC initiation and 3 weeks later. The conductance of our study was in accordance with the ethical standards of the Institutional or Regional Responsible Committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. A written informed consent was obtained from all patients before their enrolment in the study, which was approved by the local Ethics Committee.

Patients' selection

The following eligibility criteria were considered for enrolment in the study.

Inclusion criteria: 1. Age≥ 18 years; 2. Paroxysmal AF according to the classification of this arrhythmia in 2016 ESC Guidelines for diagnosis and treatment of AF (not changed in 2020 Guidelines) or AF with unknown duration, considered for rhythm control; 3. Hemodynamic stability; 4. Fulfilled criteria for DOAC treatment of AF patients according to 2016 ESC Guidelines; 5. Signed written informed consent by the patients;

Exclusion criteria were: 1. AF other than paroxysmal/persistent, not considered for sinus rhythm restoration (pharmacological or/and electrical); 2. Patient's disagreement to be treated with a DOAC or to be followed up for the study period; 3. Documented prior stroke, transient ischemic attack or peripheral embolic event; 4. Planned elective procedure of any kind, requiring interruption of the DOAC during the study period; 5. DOAC treatment, initiated before inclusion in the study; 6. Mentally disabled patients, unable to understand the written informed consent or any other patients unwilling to sign the informed consent for participation in the study for any reason.

All screened patients were prescribed a DOAC according to the 2016 ESC Guidelines (not changed in 2020 Guidelines). The choice of the type of a DOAC and its dosage was made by the treating physician based on patient's clinical and instrumental findings, DOAC prescription rules and individual preference.

At baseline all participating patients had the following instrumental investigations: electrocardiography (ECG), transthoracic echocardiography (TTE), TEE and routine laboratory parameters. A control TEE was performed 3 weeks later in 48 of the patients (3 patients refused re-assessment).

TTE and TEE were done in a standard manner with GE Vivid E95 (GE Healthcare, Chicago, Illinois, USA). Before TEE we applied light conscious sedation and topical anesthesia). Multiplane transducer was used for TEE imaging: depending on the image quality, the frequency and gain settings were carefully adjusted to minimize gray-noise artifact, especially when assessing for SEC. The echocardiographic images were acquired using the standard procedure and digitally stored. A thrombus was defined as an echo dense mass and SEC was considered present when dynamic "smoke-like" echoes were seen in the left atrium. In addition, the LA appendage flow velocity was also obtained by the pulsed Doppler method with the sample volume placed 1 cm distally from the opening of the appendage.

Patients' information was collected in a structured questionnaire form (demographic characteristics, socio-economic data, history about clinical presentation, risk factors, comorbidities and medical treatment). We gathered the necessary data directly from the patient's medical history and/or from the available medical documentation.

The design of our study is shown in Figure 1.
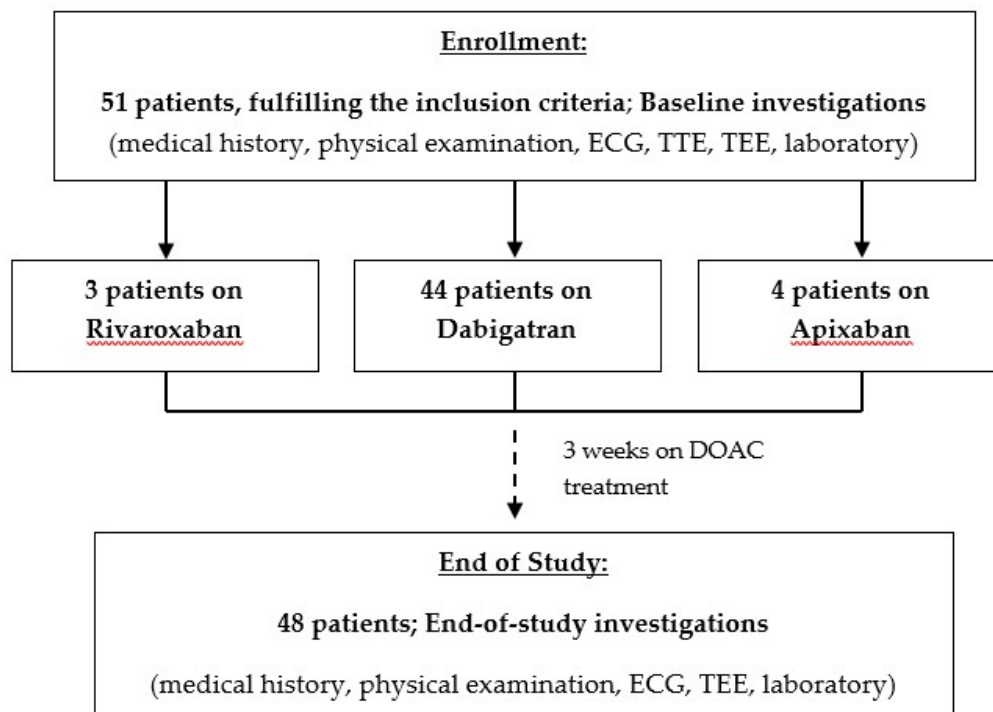
Figure 1. Study design: patient's enrolment and follow-up schedule; ECG – electrocardiography, TEE – transesophageal echocardiography; TTE – transthoracic echocardiography

Statistical analysis

The statistical analysis was performed by SPSS statistical package, version 16.0 (SPSS Inc, Chicago, IL). The data were summarized by frequencies and percentages for categorical variables and by minimal, maximal, mean values and standard deviation for continuous ones. For comparison of categorical variables, we used independent χ2-test and Fisher's exact test. The normality of distribution of continuous data was assessed by Shapiro-Wilk test. T-test and ANOVA were used for comparison of parametric data and the Mann–Whitney U test (with Bonferroni correction when necessary) – for non-parametric data. Univariate and multivariate logistic regression was performed to identify factors, associated strongly with persistence of SEC/LAT after DOAC treatment with odds ratio (OR), demonstrating the strength of each factor. All results were considered to be statistically significant at p-values <0.05.

3. Results

The most important baseline characteristics of the enrolled patients are shown in Table 1. There were no statistically significant gender differences in terms of the age, body mass index, concomitant diseases, stroke and bleeding risk, and other analyzed variables in our study population.

Table 1. Baseline characteristic of the enrolled population

Parameters	Total	Males	Females	
	n = 51	n = 26	n = 25	p
Age (years)	67.3 ± 7.4	66.4 ± 5.7	68.6 ± 6.1	0.126
Body mass index	28.8 ± 3.4	28.7 ± 5.2	29.5 ± 4.9	0.472
HTN, n (%)	46 (90.2%)	22 (84.6)	24 (96.0)	0.160
Type 2 DM, n (%)	10 (19.6)	4 (15.4)	6 (24.0)	0.048
Vascular disease*#, n (%)	6 (11.8)	3 (11.5)	3 (12.0)	0.742
VHD&, n (%)	2 (3.9%)	1 (3.9)	1 (4.0)	0.778
CHA2DS2-VASc (points)	3.92 ± 1.12	3.86 ± 1.04	4.17 ± 0.96	0.010
HAS-BLED (points)	2.33 ± 0.88	2.47 ± 1.07	2.26 ± 0.66	0.622
CrCl (ml/min.)	57.4 ± 7.02	54.1 ± 6.23	59.7 ± 8.16	0.276
Indexed LA volume (mL/m^2)	31.8 ± 6.44	30.2 ± 5.04	32.6 ± 7.38	0.213
LVEF (%)	64.8 ± 6.46	66.2 ± 7.22	62.9 ± 8.17	0.381
Dabigatran 150 b.i.d	38 (74.5)	18 (69.2)	20 (80.0)	0.340
Dabigatran 110 b.i.d	6 (11.8)	4 (15.4)	2 (8.0)	0.220
Apixaban 5 mg b.i.d	3 (5.9)	1 (3.8)	2 (8.0)	0.338
Apixaban 2.5 mg b.i.d	1 (2.0)	0 (0)	1 (4)	0.191
Rivaroxaban 20 o.d	3 (5.9)	3 (11.5)	0 (0)	0.083

CHA2DS2-VASc – Stroke risk score in atrial fibrillation (C - chronic heart failure, H - hypertension, A - age ≥ 75 years, D- type 2 diabetes mellitus, S -suffered stroke or transient ischemic attack, VA – vascular disease, Sc – sex category); CrCl – creatinine clearance, calculated by the Cockroft-Gault original formula; DM – type 2 diabetes mellitus; HAS-BLED – bleeding risk score for patients with atrial fibrillation on oral anticoagulation (H- uncontrolled hypertension, A – abnormal renal or liver function, S – prior stroke, B – bleeding, L – labile international normalized ratio, E – elderly, aged ≥65 years, D – drugs or alcohol); HTN- arterial hypertension; LA – left atrial; LVEF – left ventricular ejection fraction, measured by transthoracic echocardiography; VHD – valvular heart disease; *Documented coronary artery disease (including post-myocardial infarction), peripheral arterial disease and/or aortic plaque; #Concomitant atherosclerotic cerebro-vascular disease was an exclusion criterion; & Any moderate to severe VHD except for moderate to severe mitral stenosis or a prosthetic valve (contraindications for DOACs)

Baseline TEE showed SEC in the left atrial appendage (LAA) of 26 out of 51 patients (50.9%) and a thrombus in other 10 (19.6%). In terms of grading, SEC was mild (grade 1+) in 6 (23.1%), mild to moderate (grade 2+) in 8 (30.8%), moderate (grade 3+) in 7 (26.9%) and severe (grade 4+) in 5 (19.2%)

Table 2 presents the baseline TEE findings of the patients with and without SEC/LAT, before initiation of a DOAC (n = 51).

Table 2. Baseline TEE results

Parameters	SEC/LAT (-) n = 15	SEC/LAT (+) n = 36	p
Indexed LA volume (mL/m^2)	27.8 ± 10.2	35.4 ± 8.6	< 0.001
LAA filling velocity (cm/s)	43.4 ± 7.2	39.5 ± 10.6	0.218
LAA emptying velocity (cm/s)	29.4 ± 11.3	18.7 ± 14.4	0.033
Number of LAA lobes, n (%)			
- 1	10 (66.7)	5 (13.9)	<0.001
- 2	3 (20.0)	13 (36.1)	0.045
- 3	2 (13.3)	12 (33.3)	0.012
- >3	0 (0)	6 (16.7)	<0.001

LA – left atrial, LAA – left atrial appendage, LAT – left atrial thrombosis; SEC – spontaneous echo contrast, TEE – transesophageal echocardiography

A repeated TEE was performed to 48 patients – 3 patients who had no SEC/LAT at baseline refused to have a second TEE. Among the patients with baseline SEC/LAT, after 3 weeks on DOAC treatment SEC persisted in 12 (46.2%) of 26 patients (p < 0.001 versus baseline SEC prevalence): it was mild in 7 (58.3%), mild to moderate in 4 (33.3%) and moderate in 1 (8.3%). A thrombus was present in 7 (70%) of 10 with baseline LAT (p = 0.024 versus baseline TEE). In 4 of these patients there was reduction of thrombus size and in the other 3 - no visual changes after the DOAC treatment. Among the patients free of SEC/LAT at baseline TEE, there were no newly developed findings of this kind at the repeated echo investigation.

Table 3 presents the TEE findings at Week 3 of the patients who were diagnosed with SEC/LAT at baseline. All patients with resolution of these findings after 3 weeks of DOAC treatment were on Dabigatran (all of them on 150 mg b.i.d).

Table 3. TEE parameters of patients who had baseline SEC/LAA thrombus after 3 weeks of DOAC treatment in therms of persistence of these findings (n = 48).

Parameters	SEC/LAA thrombus * (-) n = 29	SEC/LAA thrombus (+) n = 19	p
Indexed LA volume (mL/m^2)	32.3 ± 6.2	37.4 ± 9.5	0.020
LAA filling velocity (cm/s)	40.4 ± 8.1	33.6 ± 9.5	0.014
LAA emptying velocity (cm/s)	24.8 ± 7.1	15.6 ± 9.2	<0.001
Number of LAA lobes, n (%)			
- 1	13 (44.8)	0 (0)	<0.001
- 2	12 (41.4)	4 (21.1)	<0.001
- 3	4 (13.8)	9 (47.4)	0.040
- >3	0 (0)	6 (31.6)	<0.001

LA – left atrial, LAA – left atrial appendage, LAT – left atrial thrombosis; SEC – spontaneous echo contrast, TEE – transesophageal echocardiography; * 3 patients free of SEC/LAT at baseline, refused to have a repeated TEE (2 of these patients had unilobular LAA and 1 – three-lobular LAA according the results from the baseline TEE)

Table 4 shows parameters that have been found to be significantly associated with the risk of non-reversal of SEC/LAA thrombus after 3 weeks of DOAC treatment (mostly dabigatran).

Table 4. Association between some of the examined TEE parameters and the risk of non-resolution of SEC/LAT after DOAC treatment

Variable	OR	95% confidence interval for OR		p
		Lower limit	Upper limit	
Indexed LA volume ≥34 ml/m² vs 34 ml/m²	1.37	1.28	1.88	0.036
LAA emptying velocity <20 cm/s vs ≥20 cm/s	2.82	1.94	4.38	<0.001
Number of LAA lobes >2 vs ≤2	1.84	1.42	2.93	0.042

LA – left atrial, LAA – left atrial appendage, LAT – left atrial thrombosis; SEC – spontaneous echo contrast, OR – odds ratio; TEE – transesophageal echocardiography, vs - versus

During the follow-up period no cerebro-vascular or peripheral arterial ischemic events were observed in our study population. No other new cardiac (myocardial infarction, decompensation of HF, etc.) or non-cardiac complications occurred either. The DOAC treatment was well tolerated with compliance and persistence >80%.

4. Discussion

In our study we investigated the prevalence of SEC/LAT in AF patients with non-valvular paroxysmal or of unknown duration AF, scheduled for pharmacological or electrical cardioversion. We performed TEE at baseline and 3 weeks later aiming to disclose predictors, associated with high risk of non-resolution of these findings after the recommended by the ESC guidelines minimal period on OAC treatment before cardioversion (3 weeks) [1]. Transesophageal echocardiography is currently the modality of choice for evaluation of the LAA [9, 20, 21]. It allows complete delineation of the LAA anatomy, assessment of its function and detection of LAT [9, 21]. The TEE confirmed SEC/LAT in 36 (70.6%) of all studied AF patients: 26 (51%) with SEC of different degree and 10 (19,6%) patients with LAA thrombus.

In previous TEE investigations LAT was observed in 5–30% of all AF patients [2-5]. In a study with 262 non-rheumatic AF patients, TEE revealed intracardiac thrombi in 8% of patients, all of which were within the LAA [22]. Another study showed similar results: 8.8% of patients with non-valvular AF on a VKA with sub-therapeutic oral anticoagulation therapy were diagnosed with LAT, whereas a thrombus was observed in 3.6% of patients with sufficient anticoagulation therapy [8]. The presence of LAT was associated with higher CHA2DS2 -VASc score and presence of SEC [8]. The mean CHA2DS2-VASc score of our study population was also very high (3.92) and that could explain to some extent the high baseline prevalence of SEC/LAT among our non-anticoagulated AF patients [8]. Another factor contributing to this prevalence is the possible long duration

(much longer than 48 h) of the patients with AF of unknown duration in our study [8]. In a meta-analysis of 72 studies (20,516 AF patients) LAT was found in 9.8 % and its presence was associated with a higher age (OR 2.56), female gender (OR 1.35), HTN (OR 1.78), DM (OR 1.86) and chronic HF (OR 3.67) [5].

It has to be mentioned that observational and prospective data have not shown a different thrombus incidence in patients treated with DOACs or VKAs [5, 10-15].

Most of the published TEE data from AF patients focus on the presence of LAT, but not on SEC which is much more prevalent and probably a strong predictor of stroke too [1, 2, 6]. The real prevalence of SEC in AF patients is largely unknown. In our study it was found in every second patient, considered for restoration of sinus rhythm. The factors that promote progression of SEC to LAT in different patients with similar clinical risk profile (including LAA morphology) remain unclear. In our study population, analysis did not disclose any factors/conditions to be significantly associated with increased risk of SEC progression to LAT.

Another important issue about AF and SEC/LAT is how to treat these patients: there are no comprehensive hard clinical endpoint data on the best anticoagulant strategy. Previously, VKA therapy was recommended as a standard of care with strict follow-up and INR monitoring until resolution of LAT (with heparin bridging if necessary) [1-5]. It is now generally admitted that DOACs may be an option for LAT resolution, where VKAs are not well tolerated or sufficient INR control cannot be obtained [1, 10-16]. However, little is also known about the incidence of LAT after anticoagulation therapy: in clinical practice TEE is not routinely performed in short-term AF (<48 h) or after sufficient OAC therapy (>3 weeks) [2, 3, 11]. Among our patients with baseline SEC/thrombosis, after 3 weeks of DOAC treatment (mostly with Dabigatran) SEC had been completely resolved in 14/26 (53.8%) but LAT in 3/10 (30%) only. In our study LAA emptying velocity <20 cm/s was associated most strongly with the risk of persistence of SEC/LAA, followed by indexed LA volume >40 ml/m^2 and presence of >2 LAA lobules. X-TRA study indicated LAT resolution rate of 41.5% with rivaroxaban (20 mg o.d), comparable to the retrospective CLOT-AF registry in which LAT resolution was observed in 62.5% in heparin/warfarin treated patients [23]. In the EMANATE trial, thrombus resolution rate was similar in patients treated with apixaban (52%) as with conventional therapy (56%, 10/18) [24]. Collins et al. performed TEE before and after 4-week on OAC in 18 patients with nonvalvular AF and reported that LAT was resolved in 16 (89%) of them [25].

Study limitations

There were several limitations of our study: 1. The number of patients was relatively small, especially of patients with LAT. Therefore, our findings could not be extrapolated to the entire AF population, treated with DOAC for the same period of time; 2. Most of our patients were treated with Dabigatran and we could not make general conclusions for the other DOACs; 3. The 3-weeks DOAC treatment showed improvement of SEC and reduction of LAT size in some patients, although they persisted – if longer follow-up was performed the number of patients free of LAT and particularly of SEC could be higher; 4. We have investigated some, but not all factors, that might be related to the persistence of SEC/LAT after sufficient period of anticoagulation.

5. Conclusions

Our study demonstrated that: 1. SEC/LAT disappeared in 47% of patients after 3 weeks on DOAC treatment; 2. LAA emptying velocity <20 cm/s, multi-lobular LAA (≥2 lobes) and LA volume >34 ml/m^2 were the most important predictors for persistence of SEC/LAT despite 3 weeks of DOAC treatment in our study population. To our opinion, LA/LAA morphology and function should be taken into account in decision making for the duration of DOAC treatment before planned cardioversion in AF patients.

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Data Availability Statement: All materials supporting reported results are available with Nikolay Runev, e-mail: nrunev@abv.bg, Department of Internal Diseases "Prof. St. Kirkovich", Medical University of Sofia, Bulgaria;

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