

Efficacy and safety of direct oral anticoagulants in patients undergoing elective electrical cardioversion: A real-world patient population



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ABSTRACT

Background: Direct oral anticoagulants (DOACs) have emerged as the preferred choice of oral anticoagulation in patients with atrial fibrillation. Randomized trials have demonstrated the efficacy and safety of DOAC in patients undergoing electrical cardioversion (ECV); however, there is limited real-world data.

Objective: To evaluate the outcome of patients undergoing an elective ECV for atrial tachyarrhythmia in a tertiary referral center who were treated with DOAC or vitamin K antagonist (VKA) without routine trans esophageal echocardiography (TEE).

Methods: This was a retrospective single-center cohort study of consecutive patients undergoing an elective ECV for atrial tachyarrhythmia from January 2013 to February 2020. The primary endpoints were thromboembolism (composite of stroke, transient ischemic attack or systemic embolism) and major bleeding events within 60 days. **Results:** A total of 1431 ECV procedures were performed in 920 patients. One-third of the procedures were performed under DOAC ($N = 488$, 34%) and the remainder of the procedures was performed under VKA ($N = 943$, 66%). There were no differences between groups with regard to demographic variables (mean age 62.4 ± 11.7 , 72% men) and mean CHA₂DS₂-VASc score (2.3 ± 1.6); however, the VKA group had a higher proportion of patients with co-morbidity. Thromboembolism occurred in 0.41% in the DOAC group versus 0.64% in the VKA group ($P = 0.72$). Major bleeding events occurred in 0.41% in the DOAC group versus 0.11% in the VKA group ($P = 0.27$).

Conclusion: In a real-world population, the rates of thromboembolism and major bleeding events were low after elective ECV in patients using DOAC or VKA, even without routine TEE.

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1. Introduction

Direct oral anticoagulants (DOACs) are currently the preferred choice of oral anticoagulation in patients with atrial fibrillation (AF) for long-term stroke prevention [1]. Electrical cardioversion (ECV) play an important role in a rhythm control strategy, therefore it is not surprising that many patients undergoing ECV are treated with a DOAC. For patients with AF of >48 h duration, it is recommended to use therapeutic oral anticoagulation at least 3 weeks before and 4 weeks after ECV [2]. An advantage of DOAC is that therapeutic oral anticoagulation can be achieved rapidly, which is especially relevant for anticoagulation naïve patients. However, it is important to ensure adherence to the DOAC intake, as there is no coagulation assay available providing information on effective anticoagulation over the past 3 weeks.

Post-hoc subgroup analysis from large phase 3 stroke prevention trials have shown a good safety profile of DOACs pericardioversion with a thromboembolic risk of <1% [3–6]. Furthermore, prospective randomized controlled trials (RCTs) in patients requiring elective ECV demonstrated low and similar thromboembolic and bleeding rates when comparing factor Xa inhibitors to vitamin K antagonists (VKA) [7–9]. It is important to note that all RCTs were not powered to demonstrate noninferiority. In addition, the majority (>50%) of patients in the RCTs underwent transesophageal echocardiography (TEE) to guide cardioversion, which is not routine practice in many centers.

There is limited real-world data of DOACs in patients undergoing elective ECV outside the scope of highly controlled RCT [10–18]. The availability of real-world data is important as it reflects actual clinical practice. For example, in many centers it is not common practice to have a preprocedural TEE before an elective ECV. We evaluated the efficacy and safety of DOACs versus VKA in patients undergoing elective ECV for atrial tachyarrhythmia in a large tertiary referral center without routine preprocedural TEE.

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2. Methods

2.1. Study cohort

We retrospectively evaluated all consecutive adult patients who underwent an elective ECV for sustained atrial tachyarrhythmia (>48 h) from January 2013 to February 2020 at the department of Cardiology of the Erasmus MC, University Medical Center Rotterdam, the Netherlands. Atrial tachyarrhythmias comprised atrial fibrillation, atrial flutter and atrial tachycardia. Patients who had an emergency ECV or received an ECV for an atrial tachyarrhythmia with a duration <48 h were not included in the study. Patients were identified by screening all scheduled ECV procedures in the study period. If the patient did not undergo an ECV for any reason, then this patient was excluded from the final analysis. Furthermore, patients who had <60 days of follow-up after the procedure, except when death occurred, were excluded. Data were collected from the electronic medical records.

2.2. Anticoagulation regimen

All patients required therapeutic oral anticoagulation for at least 3 weeks prior to ECV. In patients using VKA, the International Normalized Ratio (INR) level had to be in the therapeutic range (≥ 2.0) in the 3 weeks prior to the procedure. The INR was rechecked on the day of the procedure. Patients using DOAC had to use them continuously for at least 3 weeks. Compliance was evaluated by asking the patient whether they did not miss a dose in the previous 3 weeks. If abovementioned conditions were not met, we usually postponed the procedure. If required (e.g., inadequate INR, doubt about DOAC adherence, symptom-driven), a TEE-guided ECV was performed. Thus, not all patients with an inadequate oral anticoagulation received a TEE. Patients continued their oral anticoagulation for a minimum of 4 weeks after the ECV procedure. Continuation of oral anticoagulation after this 4-week period was based on the CHADS-VASc score or other indication for oral anticoagulation (e.g., mechanical heart valves).

2.3. Electrical cardioversion

Electrical cardioversion was performed in the holding area or on the ward under the supervision of a nurse practitioner or cardiologist. The procedures were performed under monitored anaesthesia care. The placement of the external patches was usually posterior-anterior. For patients in atrial fibrillation a synchronized ECV was performed with a biphasic shock of 200 J. For patients in atrial flutter a lower dose was used (usually 100 J). A cardioversion was repeated when necessary.

2.4. Study endpoints

The primary efficacy endpoint was a composite of stroke, transient ischemic attack (TIA), and systemic embolic event (SEE) within 60 days. The primary safety endpoint was major bleeding within 60 days. Major bleeding was defined according to the International Society of Thrombosis and Haemostasis (ISTH) criteria and included clinically overt bleeding accompanied by a decrease in the haemoglobin level of at least 20 g/L (1.24 mmol/L) or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death [19]. TIA and stroke were diagnosed by a neurologist. The secondary efficacy endpoints were death from any cause, stroke, TIA, SEE, and a composite of stroke and SEE (excluding TIA).

2.5. Statistical analysis

Continuous parameters were tested for normality before analysis and are expressed as mean \pm standard deviation (SD) or median [interquartile range], as appropriate. Categorical data are presented as frequencies and percentages. Comparisons between groups were

performed with an independent Student *t*-test, chi-square tests, Fisher exact test, or a Mann-Whitney *U* test, as appropriate. All analyses were two-tailed; a *p*-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (SPSS, version 25; IBM, Chicago, Illinois).

2.6. Ethics

The Medical Ethics Committee reviewed the study (MEC-2019-0405), and this retrospective single-center study was not subjected to the Dutch Medical Research Involving Human Subjects Act. The study was carried out according to the ethical principles for medical research involving human subjects established by Declaration of Helsinki, protecting the privacy of all the participants and the confidentiality of their personal information.

3. Results

3.1. Patient population and cardioversion

A total 1570 elective ECV procedures were scheduled in the study period. In 94 cases (6.0%) no ECV was performed and 45 cases (2.9%) had insufficient follow-up after an ECV (Fig. 1). Preprocedural TEE was performed in 23 patients (1.5%) and a left atrial thrombus was suspected in 5 cases resulting in postponement of the procedure (Appendix A). Final analysis was performed in the remaining 1431 ECV procedures among 920 patients. Almost two-third of the patients received one ECV procedure during the study period (*n* = 610), while

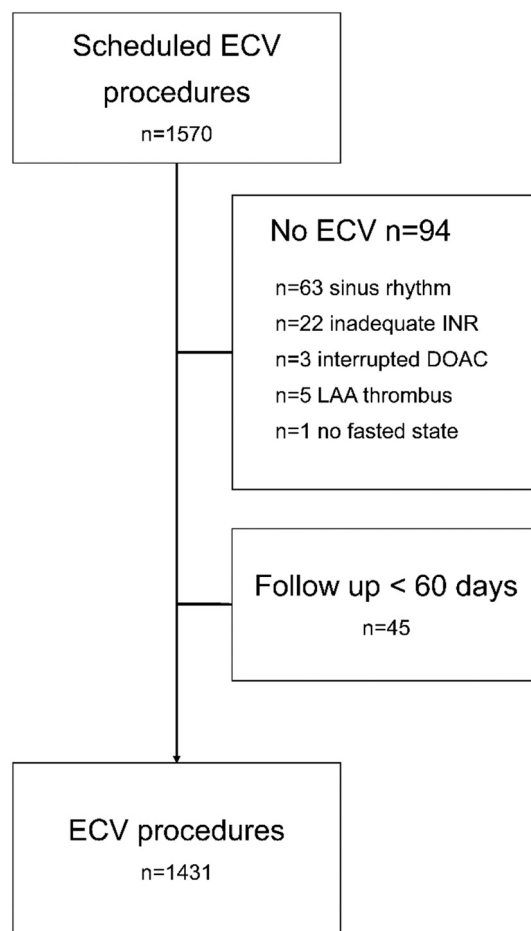


Fig. 1. Abbreviations: DOAC = direct oral anticoagulant, ECV = electrical cardioversion, INR = International Normalized Ratio, LAA = left atrial appendage.

the remaining one-third received ≥ 2 ECV procedures ($n = 310$). These 310 patients with multiple ECV procedures had a total of 511 repeat ECV procedures. Repeat ECV procedures were performed more often in the VKA group in comparison to the DOAC group (39% versus 28%, $P < 0.001$). The reason for a repeat ECV was recurrence of atrial tachyarrhythmia ($n = 450$, 88%) or a prior not successful ECV ($n = 61$, 12%), this was similar for both groups.

Periprocedural DOAC was used in 488 (34%) procedures, while in the remainder of the procedures ($n = 943$, 66%) periprocedural VKA was used. Of the 488 cardioversions performed on DOAC, dabigatran was used in 225 of 488 procedures (46%); apixaban in 114 procedures (23%); rivaroxaban in 81 procedures (17%); and edoxaban in 68 procedures (14%). Periprocedural VKAs used were acenocoumarol ($n = 846$) or phenprocoumon ($n = 97$). The use of DOAC increased steadily over the years during the study period, increasing from 5% in 2013 to 73% in 2020 (Fig. 2). Since 2018, DOAC was used in more than half of the procedures.

There were differences in baseline characteristics between the VKA and DOAC group (Table 1). The VKA group comprised a more complex patient population with a higher proportion of patients with congenital heart disease, congestive heart failure, coronary heart disease, diabetes mellitus, LV dysfunction and renal insufficiency. This is also reflected by a higher proportion of patients with a HAS-BLED bleeding score ≥ 3 and American Society of Anaesthesiologists (ASA) physical status classification system score ≥ 3 . The acute cardioversion success was similar between groups (92% for both groups, $P = 0.70$).

3.2. Primary endpoints

In total, 8 patients (0.56%) had a thromboembolic event and 3 patients (0.21%) had an ISTH major bleeding event during the 60-day follow-up period. There were no differences in the primary efficacy and safety endpoints between both groups (Table 2). A detailed overview of

endpoints is presented in Appendix B. A thromboembolic event occurred in 6 (0.64%) and 2 (0.41%) patients in the VKA and DOAC group, respectively ($P = 0.72$). The timing of thromboembolic events was similar between groups (VKA: median 19 [10,25] days; DOAC: 13 [4,22] days, $P = 0.64$). In the 8 patients with a thromboembolic event, 5 patients (63%) had a medical history of prior stroke or TIA (Appendix B). All patients with a TIA after ECV had an uneventful recovery. The patients who had experienced a stroke had a modified Rankin scale [20] ranging from 0 to 2. No SEE occurred in the study population.

Major bleeding occurred in 1 (0.11%) and 2 (0.41%) patients in the VKA and DOAC group, respectively ($P = 0.27$) (Table 2, Appendix B). One patient had a trauma-related subdural hematoma and had a modified Rankin scale of 4. The two other patients experienced a gastrointestinal bleeding requiring blood transfusion and had an uneventful recovery.

3.3. Secondary endpoints

In total, 8 patients (0.56%) died within 60 days after the ECV procedure. There were no differences in the all-cause mortality rate between both groups (Table 2, Appendix B). Also, when looking at the individual endpoints there was no difference between groups with regard to stroke, TIA or SEE. For comparison with RCTs, the composite endpoint of stroke and SEE was also presented. The 30-day rate of the composite endpoint of stroke and SEE and major bleeding after ECV was comparable to the results of the 3 RCTs focusing on the efficacy and safety of pericardioversion DOAC (Appendix C).

4. Discussion

The present study demonstrates that DOACs are associated with low thromboembolic and bleeding rates (both $< 0.5\%$) in patients

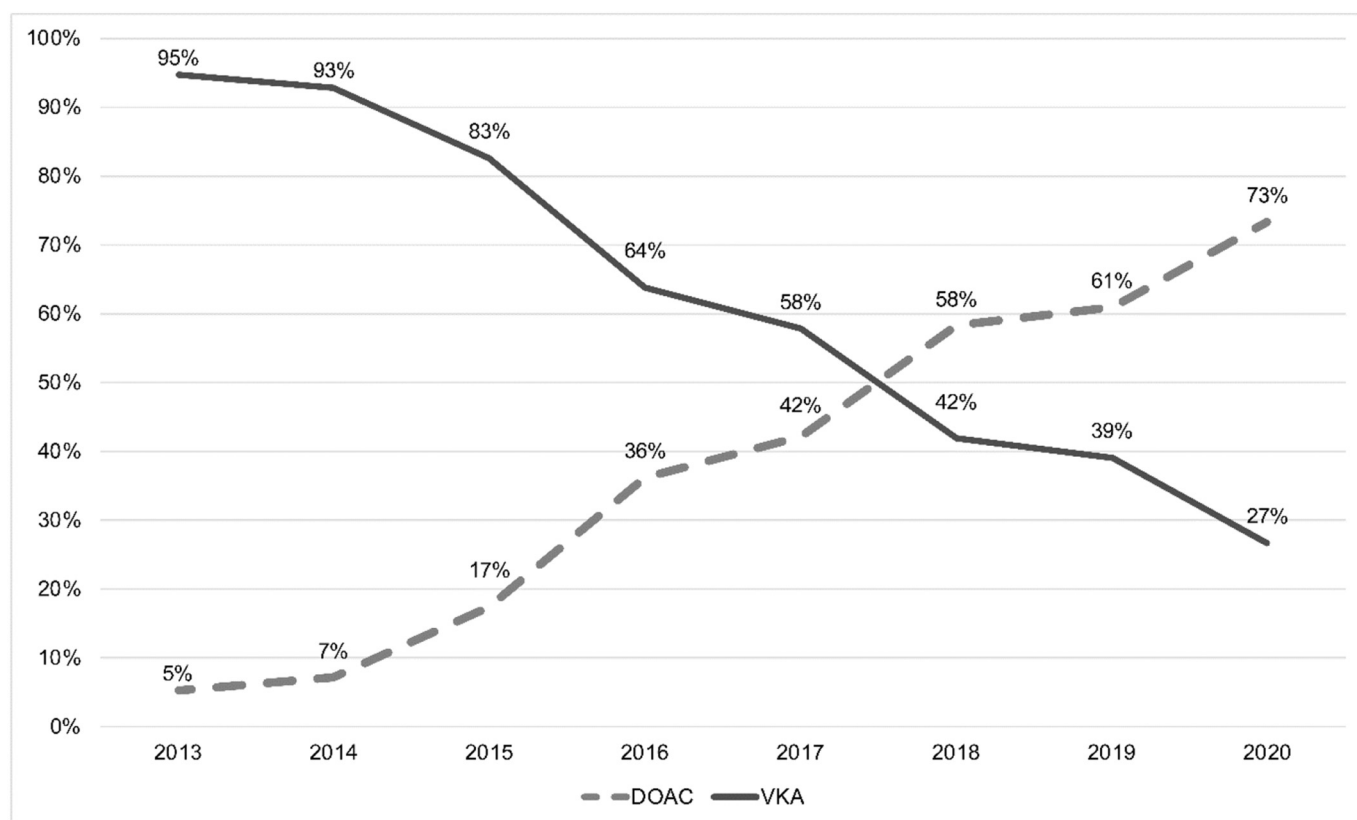


Fig. 2. Type of periprocedural oral anticoagulation during the study period. Abbreviations: DOAC = direct oral anticoagulant, VKA = vitamin K antagonist.

Table 1
Baseline characteristics.

Characteristic	Total n = 1431	VKA group n = 943	DOAC group n = 488	p-value
Age (years), mean ± SD	62.4 ± 11.7	62.1 ± 11.6	62.8 ± 12.0	0.32
Male gender	1032 (72.1)	669 (70.9)	363 (74.4)	0.17
BMI, mean ± SD	28.3 ± 5.4	28.3 ± 5.5	28.3 ± 5.1	0.98
TEE	18 (1.3)	13 (1.4)	5 (1.0)	0.80
Medical history				
Prior TIA	111 (7.8)	71 (7.5)	40 (8.2)	0.65
Prior stroke	106 (7.4)	72 (7.6)	34 (7.0)	0.65
Prior intracranial bleeding	17 (1.2)	15 (1.6)	2 (0.4)	0.069
Prior extracranial bleeding	64 (4.5)	48 (5.1)	16 (3.3)	0.14
Arterial hypertension	612 (42.8)	402 (42.6)	210 (43.0)	0.88
Renal insufficiency*	342 (23.9)	266 (28.2)	76 (15.6)	<0.001
Congestive heart failure	333 (23.3)	250 (26.5)	83 (17.0)	<0.001
Coronary artery disease	323 (22.6)	239 (25.3)	84 (17.2)	<0.001
LVEF ≤40%	304 (21.3)	227 (24.1)	77 (15.8)	<0.001
Diabetes mellitus	209 (14.6)	151 (16.0)	58 (11.9)	0.036
Vascular disease	175 (12.2)	119 (12.6)	56 (11.5)	0.53
Congenital heart disease	114 (8.0)	90 (9.5)	24 (4.9)	0.002
Type of atrial tachyarrhythmia				
Atrial fibrillation	1094 (77.2)	724 (77.7)	370 (76.3)	0.55
Atrial flutter	262 (18.5)	163 (17.5)	99 (20.4)	0.18
Atrial tachycardia	61 (4.3)	45 (4.8)	16 (3.3)	0.22
Scores				
ASA ≥3	774 (56.3)	543 (59.2)	231 (50.4)	0.002
CHA ₂ DS ₂ -VASC, mean ± SD	2.3 ± 1.6	2.4 ± 1.7	2.2 ± 1.6	<0.001
CHA ₂ DS ₂ -VASC ≥2	935 (65.3)	625 (66.3)	310 (63.5)	0.30
HAS-BLED, mean ± SD	1.3 ± 1.1	1.4 ± 1.1	1.1 ± 1.0	<0.001
HAS-BLED ≥3	176 (12.3)	132 (14.0)	44 (9.0)	0.007
Antiplatelet therapy				
Acetylsalicylic acid	105 (7.3)	81 (8.6)	24 (4.9)	0.12
Clopidogrel	53 (3.7)	35 (3.7)	18 (3.7)	0.98
Persantin	2 (0.1)	2 (0.2)	–	0.55
Ticagrelor	1 (0.1)	1 (0.1)	–	1.00
Triple therapy	14 (1.0)	10 (1.1)	4 (0.8)	0.78
Antiarrhythmic therapy				
Amiodaron	356 (24.9)	271 (28.7)	85 (17.4)	<0.001
Sotalol	335 (23.4)	208 (22.1)	127 (26.0)	0.093
Digoxin	286 (20.0)	210 (22.3)	76 (15.6)	0.003
Flecainide	95 (6.6)	53 (5.6)	42 (8.6)	0.031
Verapamil	30 (2.1)	24 (2.5)	6 (1.2)	0.10
Diltiazem	15 (1.0)	9 (1.0)	6 (1.2)	0.63
Propafenone	3 (0.2)	3 (0.3)	–	0.56

All data depicted as n (%) unless stated otherwise. * eGFR <60 ml/min/m². Abbreviations: ASA = American Society of Anaesthesiologists physical status classification system, DOAC = direct-acting oral anticoagulation; LVEF = left ventricular ejection fraction, TEE = transesophageal echocardiogram; VKA = vitamin K antagonist.

undergoing elective ECV for atrial tachyarrhythmia in the setting of a tertiary referral center. Furthermore, the study period was a transition time in our center where DOAC use pericardioversion increased from 5% in 2013 to 73% in 2020.

In non-anticoagulated patients, ECV is associated with an increased risk of stroke (5–7%) [21]. This risk is mitigated (<1%) if patients use oral anticoagulation. The 2016 ESC AF guidelines recommends the use of therapeutic oral anticoagulation at least 3 weeks before and 4 weeks after ECV [2]. The use of VKA has its limitations, the most important being its narrow therapeutic window requiring regular INR assessments, delayed onset of action and certain drug-drug interactions [11,22]. Considering these limitations, DOACs has become an attractive alternative for VKA [1]. In the Netherlands, there was initially a conservative policy with regard to DOAC mainly due to concerns about the lack of an antidote, patient adherence, lack of monitoring and increased health care costs [23]. In the Netherlands there was a slower uptake of DOAC use in comparison to other Western European countries [24]. Since 2016 there is a steady increase in the use of DOAC in the Netherlands and this is reflected in a higher proportion of patients

Table 2
Study outcomes <60 days after ECV.

	Total n = 1431	VKA group n = 943	DOAC group n = 488	p-value
Primary efficacy endpoint				
Stroke, TIA and SEE	8 (0.56)	6 (0.64)	2 (0.41)	0.72
Primary safety endpoint				
Major bleeding	3 (0.21)	1 (0.11)	2 (0.41)	0.27
Secondary endpoints				
All-cause death	8 (0.56)	5 (0.53)	3 (0.61)	1.00
Stroke	3 (0.21)	2 (0.21)	1 (0.20)	1.00
TIA	5 (0.35)	4 (0.42)	1 (0.20)	0.67
SEE	–	–	–	–
Stroke and SEE	3 (0.21)	2 (0.21)	1 (0.20)	1.00

All data depicted as n (%) unless stated otherwise. DOAC = direct-acting oral anticoagulant; ECV = electrical cardioversion; SEE = systemic embolic event; TIA = transient ischemic attack; VKA = vitamin K antagonist.

with DOAC undergoing an elective ECV in our center in the second half of the study period. Nowadays, DOAC is the most commonly used oral anticoagulant pericardioversion. An advantage of the use of DOAC in the setting of ECV is that it can avoid delays or postponement of ECV due to inadequate INR levels with VKA [9,11]. Avoiding postponement and rescheduling of ECV procedures by using DOAC has been shown to be cost-effective in comparison to VKA [25].

RCTs and meta-analysis have demonstrated the safety and efficacy of DOAC in patients undergoing ECV [7–9,26–28]. Our results are in line with the outcome of the 3 RCTs focusing on pericardioversion DOAC (Appendix C). The mean CHA₂DS₂-VASC score and the proportion of patients with moderate to high thromboembolic risk (CHA₂DS₂-VASC score ≥ 2) in our study population was comparable to the RCTs (Appendix C). These randomized trials are important, but the study populations and pre-procedural work-up do not always reflect clinical practice. For example, the EMANATE trial only included anticoagulation naïve patients (<48 h of anticoagulation before randomization) [8]. Furthermore, >50% of patients in the RCTs underwent cardiac imaging to rule out thrombus in the left atrial appendage before ECV. Previous observational studies have shown that in 1.4–3.6% of therapeutically anticoagulated patients a TEE prior to ECV or AF ablation revealed a LAA thrombus [29,30]. The incidence of LAA thrombus seems to correlate with the CHADS-VASC score [29]. In many centers, however, preprocedural imaging is not standard practice. Therefore, availability of real-world studies of pericardioversion DOAC is important [10–18]. Of these real-world studies, 2 single-center studies had a larger sample size than our study, however, in both studies approximately one-fifth of procedures were guided by TEE [11,17]. Coleman et al. retrospectively evaluated 4647 cardioversions in the Cleveland Clinic (USA) in the period 2009 to 2013, of which only 20% were performed under DOAC [17]. The thromboembolic event rate under DOAC was relatively high, 1.62% within 8 weeks of follow-up, but this was similar to the VKA group (0.97%, P = 0.16). Frederiksen et al. retrospectively evaluated 2150 cardioversions from the Regional Hospital Central Jutland (Denmark) in the period 2011 to 2016 [11]. This study showed a low thromboembolic event rate within 60 days with either DOAC or VKA (0.15% versus 0.14%). Our study also demonstrates a low thromboembolic event rate in procedures performed under DOAC and VKA in a routinely non-TEE-guided strategy.

4.1. Study limitations

The present study has the known limitations inherent to an observational study. Selection bias may play a role, as DOAC are not used in patients with severe renal dysfunction or mechanical valves. This is partly reflected by a higher proportion of patients with comorbidity in the VKA group. Furthermore, the low event rates precluded a thorough statistical analysis between groups.

5. Conclusions

During the past years, DOAC has replaced VKA as the most commonly used oral anticoagulant in patients undergoing elective ECV for atrial tachyarrhythmias. The use of pericardioversion DOAC was associated with low rates of thromboembolic and bleeding complications (both <0.5%) and was comparable to the use of VKA in a real-world population without routine TEE.

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Conflicts of interest

None to declare.

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