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CLINICAL RESEARCH
Atrial fibrillation

Cardioversion of atrial fibrillation in a real-world setting: non-vitamin K antagonist oral anticoagulants ensure a fast and safe strategy compared to warfarin

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Aims Non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly used as thromboembolic prophylaxis in cardioversion. We examined the waiting time to cardioversion and the outcomes in patients with non-valvular atrial fibrillation (AF) of > 48 h of duration who were treated with either NOACs or warfarin.

Methods and results Anticoagulation was handled in a structured, multidisciplinary AF-clinic. The objectives were the waiting time to cardioversion, and thromboembolism and major bleeding events within 60 days. In total, 2150 electrical cardioversions were performed; 684 (31.8%) of patients were on NOACs and 1466 (68.2%) were on warfarin. The waiting time to non-TOE-guided cardioversion was significantly shorter in the NOAC group compared with the warfarin group for all cardioversions ($P < 0.001$ for log-rank test) and for first-time cardioversions ($P < 0.001$ for log-rank test). For all non-TOE-guided cardioversions, 80% of procedures on NOACs and 67% of procedures on warfarin were performed within 25 days ($P < 0.001$). Thromboembolism occurred in one patient (0.15%) receiving NOAC and in two patients (0.14%) receiving warfarin (risk ratio (RR) 1.07; 95% confidence interval (CI) 0.10–11.81). Major bleeding events occurred in four patients (0.58%) in the NOAC group and 11 patients (0.75%) in the warfarin group (RR 0.78; 95% CI 0.25–2.43).

Conclusion In a real-world clinical setting with anticoagulation handled in a structured multidisciplinary AF clinic, the waiting time to cardioversion was shorter with NOACs compared to warfarin. The rates of thromboembolism and major bleeding events were low, with NOACs shown to be as effective and safe as warfarin.

Keywords Atrial fibrillation • AF clinic • Cardioversion • Non-vitamin K antagonist oral anticoagulants • Warfarin Stroke • Thromboembolism

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with a prevalence of approximately 3% in adults aged 20 years or older.[1] Electrical cardioversion is an effective method to restore sinus rhythm and relieve the symptoms of persistent AF. The process of restoring sinus rhythm is associated with an increased risk for thromboembolic events, regardless of the cardioversion method (electrical or pharmacological). Without preceding anticoagulation, cardioversion carries a 5–7% risk of thromboembolic complications[2]. However, this procedure related thromboembolic risk can be reduced to 0.5–1.6% using appropriate anticoagulation.[3–6] Patients who have been in AF for longer than 48 h represent a particularly high-risk group, and current guidelines recommend adequate

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What's new?

- Non-vitamin K antagonist oral anticoagulants are increasingly used in patients with non-valvular atrial fibrillation (AF) and reduce the waiting time to cardioversion when compared to patients who were prescribed warfarin.
- Structured multidisciplinary AF-care ensures optimal anticoagulation and allows for a fast and safe cardioversion strategy with low risk for thromboembolism and major bleeding events.

anticoagulation for at least 3 weeks before and 4 weeks after cardioversion in such patients.[1] The 3-week period of anticoagulation prior to cardioversion can be shortened if a transoesophageal echocardiography (TOE) rules out left atrial thrombus.[4]

Recently, non-vitamin K antagonist oral anticoagulants (NOACs) have been approved for thromboembolic prophylaxis in the treatment of patients with non-valvular AF. NOACs have been shown to be at least as effective as warfarin for stroke prevention in patients with AF and they have all proven to be associated with a lower risk for intracranial haemorrhage.[7–9]

In the setting of cardioversion, *post hoc* analyses from large randomized controlled trials have shown that Dabigatran (RE-LY), Rivaroxaban (ROCKET-AF) and Apixaban (ARISTOTLE) are at least as effective and safe as warfarin with a thromboembolic risk below 1%, and without an increased risk for bleeding.[10–12] So far, the X-VeRT trial and the ENSURE-AF study are the only prospective randomized controlled trials that have examined the effectiveness of NOACs compared to warfarin in patients who require cardioversion.[13,14] Both studies showed low and similar peri-procedural stroke and bleeding risks when comparing rivaroxaban and edoxaban to warfarin.

A major shortcoming of warfarin is its delayed onset of action and labile international normalized ratio (INR) very common during the initiation of warfarin therapy, which may prolong the time until adequate anticoagulation is achieved, because of the requirement of a weekly INR value between 2.0 and 3.0 for at least three consecutive weeks before cardioversion can be attempted[15] On the other hand, NOACs achieve a maximal effect promptly after initiation and have predictable pharmacokinetics and pharmacodynamics, which may be particularly beneficial in the setting of cardioversion in terms of shortening the waiting time.

The X-VeRT trial found that rivaroxaban was associated with a significantly shorter waiting time to cardioversion compared to the traditional treatment with warfarin.[13] However, there are limited real-world data on the significance of NOACs vs. warfarin, concerning the waiting time to cardioversion and the effectiveness in preventing peri-procedural thromboembolism.[16–19]

This study had two objectives. First, we aimed to investigate the waiting time to cardioversion in patients with non-valvular AF of >48 h of duration treated with either NOACs or warfarin. Second, we aimed to examine the effectiveness and safety of NOACs compared to warfarin in cardioversion in relation to the risk for thromboembolism and major bleeding events in a real-world setting with anticoagulation handled in a structured, multidisciplinary AF-clinic peri-cardioversion.

Methods

Study cohort

In this retrospective cohort study, we included patients with non-valvular AF of >48 h of duration who underwent electrical cardioversion at the Regional Hospital Central Jutland (Viborg Regional Hospital and Silkeborg Regional Hospital), in Denmark from August 2011 through March 2016. Data were systematically collected from electronic medical records.

Patients were treated with anticoagulation for at least three weeks or underwent a TOE to rule out left atrial thrombus prior to cardioversion. All patients were treated with at least 4 weeks of anticoagulation therapy after the procedure, which was continued lifelong in patients with permanent risk factors for stroke.[1]

Patients in the present study were followed in a structured, multidisciplinary AF-clinic with an integrated nurse-operated anticoagulation clinic that focus on adequate anticoagulation and compliance to the therapy peri-cardioversion. A dedicated team of specialist nurses maintained anticoagulation therapy as supervised by cardiologists. The team thoroughly described the importance of anticoagulation and correct adherence to the prescribed regimen to the patients. To ensure optimal patient management, nurses provided patient education that was intended to supply the patients with a basic knowledge and understanding of their condition and medical treatment. The patients were seen routinely for follow-up in the AF clinic 60 days after the procedure with a careful clinical examination, assessment of heart rhythm, adherence to antocoagulation, and assessment of any thromboembolic and bleeding events.

Anticoagulation-therapy consisted of either NOAC or dose-adjusted warfarin. Compliance with NOACs was assessed according to patient self-report. In the case of a missed dose, the waiting time for cardioversion was prolonged for another 3 weeks. Depending on comorbidities, patients were treated with dabigatran 110/150 mg twice daily, rivaroxaban 15/20 once daily or apixaban 2.5/5 mg twice daily according to national recommendations. In Denmark, edoxaban was approved for use from June 2016 and therefore not available during the study period. In the case of TOE-guided cardioversion, low-molecular-weight heparins were given under warfarin initiation until target INR of 2.0 was achieved. Anticoagulation with warfarin was confirmed with weekly INR values of at least 2.0 for at least three consecutive weeks prior to cardioversion and for 4 weeks after. The choice of anticoagulant (warfarin or NOAC, type of NOAC) was made on the basis of patient characteristics, kidney function, co-medications, cost and patient preference.

Study outcomes

This study was performed in order (i) to assess the waiting time to cardioversion defined as the number of days from the decision to perform cardioversion was made to the date of the cardioversion procedure, and (ii) to determine the risk of thromboembolism (i.e. stroke, transient ischaemic attack (TIA), and systemic embolism) and major bleeding events after cardioversion. Since complete recovery of mechanical function of the atria after cardioversion may take several days, we ascertained information on effectiveness and safety outcomes 60 days after the procedure.

Stroke was defined as sudden onset of a new, focal neurological deficit in a location consistent with the territory of a major cerebral artery, confirmed by imaging techniques, with symptoms that persisted for at least 24 h. TIA was classified as a brief episode of a focal neurological deficit with symptoms that lasted <24 h. Systemic embolism was defined as an ischaemic episode with an acute vascular occlusion of the artery of an extremity or organ documented by imaging, surgery, or autopsy.

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Major bleeding events were defined according to criteria identified by The International Society of Thrombosis and Haemostasis which included fatal bleeding, symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), and any bleeding causing a decrease in the haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to the transfusion of two or more units of whole blood or packed red blood cells.[20] However, haemoglobin was only measured in the case of clinically overt bleeding.

Statistics

Categorical data are presented as numbers and percentages and were compared using χ^2 tests. Continuous data are presented as medians [interquartile range (IQR)] or mean [standar deviation (SD)] and were compared using Wilcoxon rank-sum tests. We used a Kaplan–Meier estimator to compute the cumulative incidence of cardioversions, and compared the cumulative incidence functions using the log-rank test. Cardioversions performed on the same day as the day of the decision are included with a waiting time of 0.1 day. We estimated percentages of procedures with 95% CI performed within 25 days after decision for non-TOE-guided cardioversions. We tested for a trend between median waiting time to cardioversion and calendar year using a non-parametric test for trending. We used binary regression to estimate the risk ratio (RR) of a thromboembolic event and a major bleeding event between NOACs and warfarin. We used cluster-robust standard errors in the binary regression and applied each patient as a cluster. To account for observational dependency and differences in clinical courses, we performed analyses on all procedures and patients with no prior cardioversions.

All analyses were performed using STATA version 14.2, College Station, TX, USA.

Ethics

The study was approved by the Danish Data Protection Agency (1-16-02-427-15) and the Danish Health and Medicines Authority (3-3013-1165/1). According to Danish law approval from the Ethics Committee was not required.

Results

Patient population and cardioversion

A total of 2150 electrical cardioversions were performed on 1129 patients during the study period. Of the 684 cardioversions performed on NOACs, 291 were performed on patients taking dabigatran (13.5%), 219 on patients taking apixaban (10.2%), and 174 on patients taking rivaroxaban (8.1%). Warfarin was used in 1466 (68.2%) procedures. First-time procedures accounted for 756 cardioversions and 1394 had a history of one or more prior cardioversions. No patients were lost to follow-up. Two patients died of disseminated malignancy during the follow-up period.

Table 1 presents the baseline characteristics for all procedures stratified by treatment. The mean CHA_2DS_2-VASc score was 2.4 in the NOAC group and 2.5 in the warfarin group ($P = 0.31$). Left atrial enlargement and heart failure was predominant in the warfarin group. TOE-guidance was used in 451 (21.0%) of all cardioversions and was performed more frequently in patients receiving NOACs (24.0%) than in patients treated with warfarin (19.6%) ($P = 0.02$).

Figure 1 shows the cumulative incidence curves of cardioversions stratified by TOE and anticoagulation treatment for all procedures and first-time procedures, respectively. The use of NOACs was associated with a significantly shorter waiting time to non-TOE-guided cardioversion compared with the use of warfarin for all cardioversions ($P < 0.001$ for log-rank test) and first-time cardioversions ($P < 0.001$ for log-rank test). For all non-TOE-guided cardioversions, 80% of procedures on patients treated with NOACs and 67% of procedures on patients treated with warfarin were performed within 25 days ($P < 0.001$). Among first-time procedures, 65% of cardioversions in the NOAC group and 39% in the warfarin group were performed within 25 days ($P < 0.001$). With a TOE-guided strategy, NOACs allowed for cardioversion after a shorter waiting time compared with warfarin for all cardioversions ($P = 0.04$ for log-rank test) and first-time cardioversions ($P = 0.03$ for log-rank test).

The use of NOACs steadily increased for each year during the study period beginning with 1.2% in 2011, 7.7% in 2012, 25.6% in 2013, and 40.1% in 2014, and accounted for more than half of the procedures at the end of the period (50.8% and 51.2% in 2015 and 2016, respectively) (*Figure 2*). During the study period a corresponding decrease in the waiting time to non-TOE-guided cardioversion was observed (*Figure 3*).

Cardioversion resulted in immediately restoration of sinus rhythm in 92.3% of cases and was similar between NOAC (90.9%) and warfarin users (93.0%) ($P = 0.10$). Maintenance of sinus rhythm at 60 days of follow-up was observed more frequently in the NOAC group (47.5%) than in the warfarin group (42.4%) ($P = 0.03$).

Thromboembolism

Few thromboembolic events occurred during the 60-day follow-up period. Thromboembolism occurred in one of 684 patients (0.15%) receiving NOAC and two of 1466 patients (0.14%) receiving warfarin (RR 1.07; 95% CI 0.10–11.81).

Event 1

A 63-year-old male with a history of prior TIA, coronary artery disease and congestive heart failure (EF 35%) had a CHA_2DS_2-VASc score of 4 and a HAS-BLED score of 0. Successful cardioversion was performed after starting the patient on 150 mg of twice daily dabigatran with no missed doses for at least three weeks. Three days after the procedure the patient developed left-sided hemiparesis, and magnetic resonance imaging showed an infarction of the right middle cerebral artery.

Event 2

A 76-year-old male with a history of hypertension, coronary artery disease and severe systolic dysfunction (EF 20%) had a CHA_2DS_2-VASc score of 5 and a HAS-BLED score of 2. The patient had undergone major cardiac surgery (i.e. coronary artery bypass surgery, biological aortic valve replacement, and a Maze procedure) 11 days prior to the performance of TOE-guided cardioversion, which was performed while the patient was on warfarin. Sinus rhythm was achieved. Two days after the procedure the patient developed paralysis of the left arm with a rapid regression of symptoms within a few minutes. The event most likely originated from a severe (90%) right-sided carotid artery stenosis demonstrated on ultrasound, and the patient underwent emergency surgical intervention on the carotid artery.

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Table 1 Baseline characteristics of all procedures stratified by treatment

	All procedures *N* = 2150	Warfarin *N* = 1466 (68.2%)	NOAC *N* = 684 (31.8%)	*P*-value
Age, years	67 (61–73)	67 (61–73)	67 (60–73)	0.54
Female sex, *n* (%)	647 (30.1)	430 (29.3)	217 (31.7)	0.26
Weight, kg	88 (75–100)	89 (76–101)	87 (75–100)	0.05
BMI, kg/m^2	27.8 (24.9–31.4)	28.0 (25.1–31.3)	27.2 (24.7–31.5)	0.02
Anticoagulation-naïve (%)	480 (22.7)	218 (15.2)	262 (38.6)	<0.001
Prior AF ablation, *n* (%)	558 (26.0)	472 (32.2)	86 (12.6)	<0.001
Ejection fraction, %	60 (40–60)	60 (40–60)	60 (45–60)	0.46
TOE, *n* (%)	451 (21.0)	287 (19.6)	164 (24.0)	0.02
Heart rate, min^{-1}	92 (76–114)	92 (76–113)	92 (75–115)	0.75
Systolic blood pressure, mmHg	128 (115–142)	128 (115–142)	129 (117–142)	0.52
Diastolic blood pressure, mmHg	83 (74–92)	82 (74–92)	74 (75–92)	0.46
Left atrial enlargement (>4 cm), *n* (%)	1356 (68.7)	944 (71.5)	412 (63.1)	<0.001
$CHADS_2$, mean (SD)	1.4 (1.1)	1.4 (1.1)	1.3 (1.1)	0.03
$CHADS_2$	1 (1–2)	1 (1–2)	1 (1–2)	0.03
CHA_2DS_2-VASc, mean (SD)	2.5 (1.6)	2.5 (1.6)	2.4 (1.7)	0.31
CHA_2DS_2-VASc	2 (1–4)	2 (1–4)	2 (1–3)	0.31
CHA_2DS_2-VASc, *n* (%)				0.02
0	214 (10.0)	128 (8.7)	86 (12.6)	
1	459 (21.4)	319 (21.8)	140 (20.5)	
≥2	1477 (68.7)	1019 (69.5)	458 (67.0)	
HAS-BLED, mean (SD)	1.0 (0.8)	1.0 (0.8)	0.9 (0.8)	0.05
HAS-BLED	1 (0–1)	1 (0–1)	1 (0–1)	0.05
HAS-BLED, *n* (%)				0.08
0	637 (29.6)	427 (29.1)	210 (30.7)	
1	1020 (47.4)	681 (46.5)	339 (49.6)	
2	401 (18.7)	287 (19.6)	114 (16.7)	
≥3	92 (4.3)	71 (4.8)	21 (3.1)	
Heart failure, *n* (%)	605 (28.2)	441 (30.1)	164 (24.0)	0.003
Hypertension, *n* (%)	1331 (62.0)	907 (62.0)	424 (62.0)	0.99
Diabetes, *n* (%)	226 (10.5)	166 (11.3)	60 (8.8)	0.08
Stroke/TIA/embolism, *n* (%)	222 (10.3)	155 (10.6)	67 (9.8)	0.58
Vascular disease, *n* (%)	409 (19.0)	280 (19.1)	129 (18.9)	0.90
Haemoglobin, mmol/L	9.0 (8.3–9.6)	8.9 (8.2–9.6)	9.0 (8.4–9.6)	0.03
Platelets, 10^9/L	221 (185–263)	217 (183–259)	228 (190–269)	0.003
Creatinine, μmol/L	87 (75–103)	89 (76–104)	84 (74–99)	0.001
eGFR, mL/min	70 (58–83)	70 (57–83)	71 (61–84)	0.02
TSH, 10^{-3}/L	1.6 (1.0–2.5)	1.6 (1.0–2.5)	1.6 (1.0–2.3)	0.96
Antiplatelet or NSAID treatment	334 (15.5)	264 (18.0)	70 (10.2)	<0.001

BMI, body mass index; AF, atrial fibrillation; TOE, transoesophageal echocardiogram; TIA, transient ischaemic attack; eGFR, estimated glomerular filtration rate; TSH, thyroid-stimulation hormone; NSAID, non-steroidal anti-inflammatory drug.
Categorical variables are shown with number (%) and were compared using χ^2 tests. Unless otherwise shown, other variables are presented as median (IQR) and were compared using Wilcoxon ranksum tests.

Event 3

A 74-year-old male with a history of coronary artery disease, congestive heart failure (EF 35–40%) and peripheral artery disease had a CHA_2DS_2-VASc score of 3 and a HAS-BLED score of 1. The patient was on stable anticoagulation with warfarin with an INR score within the range of 2.0–3.0 for at least three consecutive weeks prior to successful cardioversion. The patient was re-admitted with acute lower extremity ischaemia 4 days after the cardioversion and an acute surgical intervention with embolectomy was performed. The following day the patient developed sudden symptoms of stroke with aphasia and right-sided hemiparesis. An emergency computer tomography showed an infarction of the left middle cerebral artery.

Bleeding events

Major bleeding occurred in 4 out of 684 (0.58%) patients treated with NOACs and in 11 out of 1466 (0.75%) patients treated with

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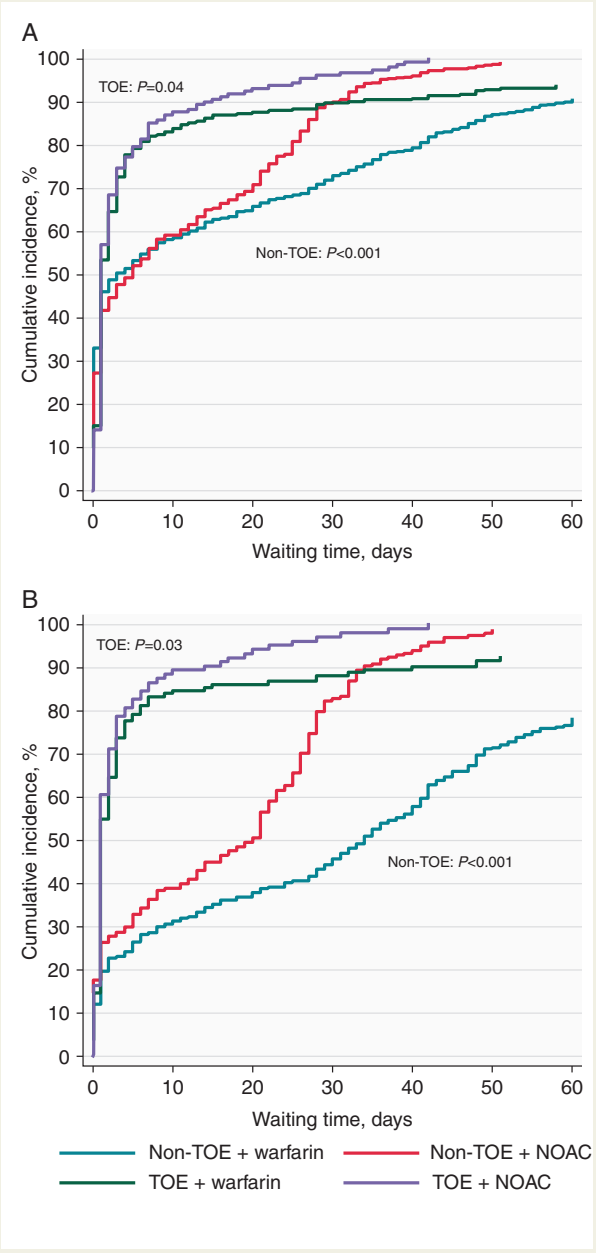

Figure 1 Cumulative incidence curves of cardioversion stratified by TOE and anticoagulation. (*A*) All cardioversions. (*B*) First-time cardioversions.

warfarin (RR 0.78; 95% CI 0.25–2.43) (*Table 2*). Bleeding events were dominated by gastrointestinal bleeding and a majority of patients received concomitant antiplatelet therapy. These events required hospitalization, blood transfusion and in one case acute surgical intervention. Three bleeding events were directly related to a previous invasive procedure. No intracranial or fatal bleedings occurred.

Discussion

In this real-world study anticoagulation with NOACs was associated with a shorter waiting time to cardioversion than warfarin. This supports the data from the X-VeRT study, where rivaroxaban was associated with a significantly shorter time to cardioversion compared with warfarin, particularly in the group who had delayed cardioversion.[13] By contrast, the ENSURE-AF trial resulted in no difference in time to cardioversion between edoxaban and warfarin, probably because edoxaban was compared with an optimized standard-of-care group where enoxaparin bridging was required to minimise the time to achieve the therapeutic range on warfarin.[14] The difference in waiting time in our study might have been non-excisting if low-molecular-weight heparins had been used for bridging in the warfarin arm as in the ENSURE-AF trial.

Only a few studies have investigated the time to cardioversion in a real-world population.[18,19] In a retrospective Swedish study, anticoagulation with dabigatran shortened the time to cardioversion compared to standard care. However, the control group of warfarin-treated patients was small ($n = 166$).[18] The tendency of a shorter time to cardioversion on dabigatran was also noted in a nationwide Danish study. This study included oral anticoagulation-naïve patients with first-time non-valvular AF, and showed a waiting time to cardioversion that was 3 weeks longer in the warfarin group compared to the dabigatran group.[19]

A major disadvantage of warfarin is its delayed onset of action and the narrow therapeutic window that requires frequent INR measurements. In clinical practice, long-term treatment with warfarin is often challenging and the time to cardioversion is delayed because of subtherapeutic INR levels. This delay postpones the alleviation of AF-related symptoms, which is usually the primary goal of cardioversion. Furthermore, fast cardioversion may benefit the maintenance of sinus rhythm on the long run due to the adage that AF begets AF. Due to their rapid onset of action (2–4 h) and predictable pharmacokinetics and pharmacodynamics, the advantages of NOACs in the handling of patients undergoing cardioversion are obvious and allow for patients to be cardioverted within shorter time periods. At a practical level, this means that a newly diagnosed and anticoagulation-naïve patient with AF can be started on a NOAC and can be scheduled for elective cardioversion 3 weeks later. The more rapid cardioversion strategy showed recently to reduce healthcare costs and increase patient-reported treatment satisfaction.[21] Despite the use of TOE, the NOAC group had a shorter time to cardioversion in the present study. This might reflect an easier access to TOE with a minimum of delay at the end of the study period, where NOACs were more prominent used compared to warfarin. More patients receiving NOACs had maintained sinus rhythm at follow-up. This might be explained by the shorter waiting time combined with the fact that patients in the NOAC group had a significantly smaller left atrium at baseline.

Another major finding of this study was the low incidence of thromboembolic and major bleeding events. This supports the

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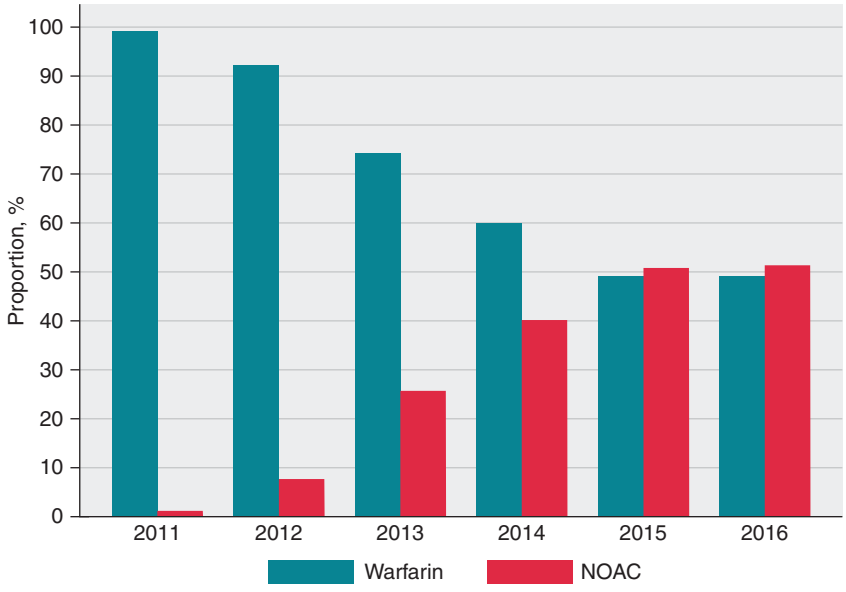

Figure 2 Use of warfarin and NOACs stratified by calendar year.

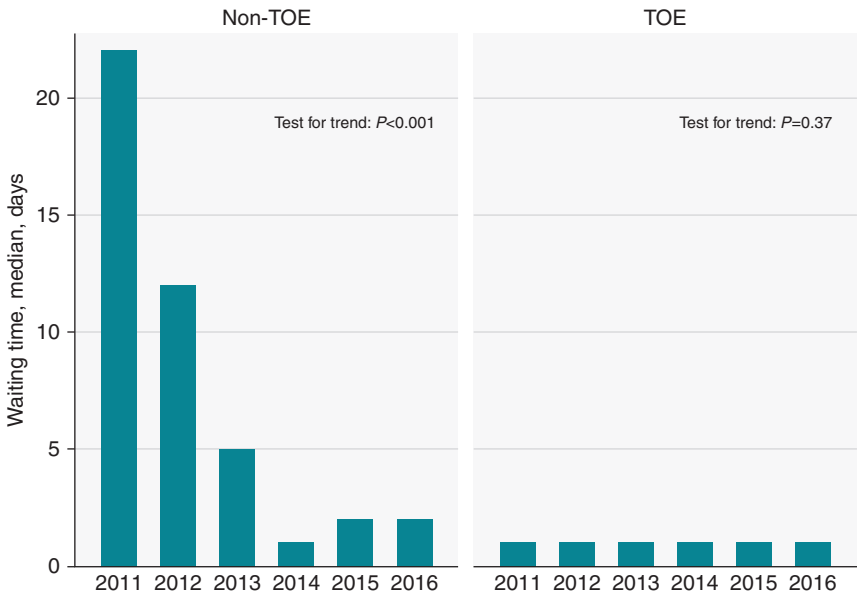

Figure 3 Waiting time (median) stratified by year and TOE.

findings in clinical trials with NOACs being an equivalent alternative to warfarin in the prevention of thromboembolic events peri-cardioversion without an increased risk for bleeding.

So far, experience with NOACs as thromboembolic prophylaxis in cardioversion mainly exists in the form of *post hoc* analyses from the large randomized clinical trials and from the two prospective randomized X-VeRT and ENSURE-AF trials, all of which state that NOACs are at least as effective and safe as warfarin in preventing thromboembolic events without and increased risk for bleeding.

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Table 2 Major bleeding events

Case	CHA_2DS_2-VASc	HAS-Bled	Anticoagulation	Antiplatelet/NSAID[a]	Bleeding event
1	3	3	Warfarin	Aspirin	Gastrointestinal
2	6	4	Warfarin	Aspirin	Gastrointestinal
3	5	4	Warfarin	Aspirin	Gastrointestinal
4	2	2	Warfarin	Clopidogrel	Gastrointestinal
5	2	1	Rivaroxaban, 20 mg × 1	None	Gastrointestinal
6	4	2	Warfarin	None	Gastrointestinal
7	5	4	Warfarin	Clopidogrel	Gastrointestinal
8	0	0	Warfarin	None	Gastrointestinal + haematuria (procedure related)[b]
9	3	1	Warfarin	Aspirin Clopidogrel	Inguinal haematoma (procedure related)[c]
10	5	2	Dabigatran, 150 mg × 2	None	Gastrointestinal (procedure related)[d]
11	4	3	Apixaban, 2.5 mg × 2	Aspirin	Gastrointestinal
12	0	1	Rivaroxaban, 20 mg × 1	Daily use of Ibuprofen	Gastrointestinal
13	6	3	Warfarin	None	Gastrointestinal
14	5	2	Warfarin	Aspirin	Gastrointestinal
15	5	2	Warfarin	Aspirin	Gastrointestinal

[a]Non-steroidal anti-inflammatory drug.
[b]Prostate biopsy.
[c]Coronary angiography.
[d]Colonoskopy with polypectomy.

Clinical randomised trials represent an extremely controlled patient population and clinical setting, with strictly specified inclusion and exclusion criteria and close patient follow-up, which does not reflect a real-world patient population. However, limited real-world data exist on the outcomes following cardioversion in patients receiving NOACs as anticoagulation.[16–19] In the present study, the frequency of thromboembolic events was low compared to these studies. No patients were lost to follow-up, which eliminated the risk of missed events. The previously mentioned nationwide Danish study included 1230 oral anticoagulation naïve patients and found that 0.7% in the dabigatran group and 1.4% in the warfarin group had a composite event of stroke, major bleeding or death within 30 weeks after cardioversion.[19] In a retrospective Swedish study with 786 elective cardioversions performed on dabigatran an incidence of 0.53% of tromboembolism was observed.[18] A large real-life single-centre study from Cleveland, Ohio compared NOACs to warfarin for peri-procedural anticoagulation, and showed an event rate for thromboembolism of 1.62% in the NOAC group and 0.97% in the warfarin group.[16] Compared to our analysis, the Cleveland study had a higher sample-volume, with a total of 5320 cardioversions. However, 13% of patients were lost to follow-up and anticoagulation-therapy was predominated by traditional warfarin therapy, which was used in 80% of the procedures.

We suggest that the low frequency of thromboembolic events in this study reflects the clinical setup with a structured multidisciplinary AF clinic focusing on adequate anticoagulation and compliance to medication peri-cardioversion. An integrated nurse-coordinated anticoagulation clinic is a central part of the AF-clinic, and the effort made by the anticoagulation clinic might be responsible for the low event rate seen in this study. Hence, our study population represent a well-informed patient-population who plays a proactive role in their own treatment process and anticoagulation compliance.

Information regarding compliance to NOAC therapy does represent a potential challenge in everyday clinical practice, since no reliable method currently exists to effectively detect non-compliant patients. In the X-VeRT-trial anticoagulation was considered sufficient if pill-counts were >80% prior to cardioversion for three consecutive weeks, thereby allowing for a few missed doses of Rivaroxaban.[13] In our AF-clinic, anticoagulation is strictly controlled particularly peri-cardioversion and even one missed dose of a NOAC results in postponement of the scheduled cardioversion for an additional 3 weeks.

Limitations

Our study had some limitations. First, patients were not randomly assigned to NOAC or warfarin groups, which inevitably introduced both calendar and selection bias. Second, since no pill-counts were performed, the adherence to NOAC was only assumed. However, the purpose of the study was to investigate cardioversion in a real-world setting. Third, the present study cohort included only Caucasians, and our findings of few complications cannot uncritical be generalized to other clinical settings or other races.

Conclusion

The present study showed that NOAC utilization has increased, with NOACs being the preferred treatment choice in over half of all cardioversion procedures. Introduction of the NOACs has reduced the waiting time to cardioversion. In this real-world setting with patients managed in a structured, multidisciplinary AF-clinic, the risk of thromboembolism within 60 days of cardioversion was low without increased risk of bleeding.

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Conflict of interest: Andi Eie Albertsen has been on the speaker bureaus of both BMS and Pfizer. Lars Frost has been an advisory board member for Pfizer in relation to non-interventional studies and has been on the speaker bureaus for Bayer, BMS, Boehringer Ingelheim, MSD and Pfizer. Dorthe Svenstrup Møller has been on the speaker bureaus for Bayer, BMS, Boehringer Ingelheim, and Pfizer.

References

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B *et al*. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–78.
2. Bjerkelund C, Orning O. The efficacy of anticoagulant therapy in preventing embolism related to D. C. electrical conversion of atrial fibrillation. *Am J Cardiol* 1969;**23**:208–16.
3. Stellbrink C, Nixdorff U, Hofmann T, Lechmacher W, Daniel W, Hanrath P *et al*. Safety and efficacy of enoxaparin compared with unfractionated heparin and oral anticoagulants for prevention of thromboembolic complications in cardioversion of nonvalvular atrial fibrillation: the Anticoagulation in cardioversion using enoxaparin (ACE) trial. *Circulation* 2004;**109**:997–1003.
4. Klein A, Grimm R, Murray R, Apperson-Hansen C, Asinger R, Black I *et al*. Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001;**344**:1411–20.
5. Apostolakis S, Haeusler K, Oeff M, Treszi A, Andresen D, Borggrefe B *et al*. Low stroke risk after elective cardioversion of atrial fibrillation: An Analysis of the Flec-SL trial. *Int J Cardiol* 2013;**168**:3977–81.
6. Hansen ML, Jepsen RM, Olesen JB, Ruwald MH, Karasoy D, Gislason GH *et al*. Thromboembolic risk in 16 274 atrial fibrillation patients undergoing direct current cardioversion with and without oral anticoagulant therapy. *Europace* 2015;**17**:18–23.
7. Connolly S, Ezekowitz M, Yusuf S, Eikelboom J, Oldgren J, Parekh A *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–51.
8. Patel M, Mahaffey K, Garg J, Pan G, Singer D, Hacke W *et al*. Rivaroxaban versus warfarin in non-valvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–91.
9. Granger C, Alexander J, McMurray J, Lopes R, Hylek E, Hanna M *et al*. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–92.
10. Nagarakanti R, Ezekowitz M, Oldgren J, Yang S, Chernick M, Aikens T *et al*. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation* 2011;**123**:131–6.
11. Piccini J, Stevens S, Lokhnygina Y, Patel M, Halperin J, Singer D *et al*. Outcomes following cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial. *J Am Coll Cardiol* 2013;**61**:1998–2006.
12. Flaker G, Lopes R, Al-Khatib S, Hermosillo A, Hohnloser S, Tinga B *et al*. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE trial (apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation). *J Am Coll Cardiol* 2014;**63**:1082–7.
13. Cappato R, Ezekowitz M, Klein A, Camm A, Ma C, Le Heuzey J *et al*. Rivaroxaban versus vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J* 2014;**35**:3346–55.
14. Goette A, Merino J, Ezekowitz M, Zamoryakhin D, Melino M, Jin J *et al*. Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *Lancet* 2016;**388**:1995–2003.
15. Ryman J, Frick M, Frykman V, Rosenqvist M. Duration of warfarin sodium therapy prior to electrical cardioversion of atrial fibrillation. *J Intern Med* 2003;**253**:76–80.
16. Coleman C, Khalaf S, Mould S, Wazni O, Kanj M, Saliba W *et al*. Novel oral anticoagulants for DC cardioversion procedures: utilization and clinical outcomes compared with warfarin. *Pacing Clin Electrophysiol* 2015;**38**:731–7.
17. Kochhäuser S, Khaykin Y, Beardsall J, Juta R, Hache P, Trought K *et al*. Comparison of outcomes after cardioversion or atrial fibrillation ablation in patients with differing periprocedural anticoagulation regimens. *Can J Cardiol* 2014;**30**:1541–6.
18. Johansson A, Juhlin T, Engdahl J, Lind S, Hagwall K, Rorsman C *et al*. Is one month treatment with dabigatran before cardioversion of atrial fibrillation sufficient to prevent thromboembolism? *Europace* 2015;**17**:1514–7.
19. Pallisgaard J, Lindhardt T, Hansen M, Schjerning A, Olesen J, Staerk L *et al*. Cardioversion and risk of adverse events with dabigatran versus warfarin-a nationwide cohort study. *PLoS One* 2015;**10**:e0141377.
20. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;**3**:692–4.
21. Hornloser S, Cappato R, Ezekowitz M, Evers T, Sahin K, Kirchhof P *et al*. Patient-reported treatment satisfaction and budget impact with rivaroxaban vs. standard therapy in elective cardioversion of atrial fibrillation: a post hoc analysis of the X-VeRT trial. *Europace* 2016;**18**:184–90.

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