Original paper

Recurrence of arrhythmia and adverse cardiovascular events within 12 months of electrical cardioversion in patients with atrial fibrillation receiving oral anticoagulation therapy

Nawrót arytmii i niepożądane zdarzenia sercowo-naczyniowe w ciągu 12 miesięcy po kardiowersji elektrycznej u pacjentów z migotaniem przedsionków stosujących doustne leki przeciwzakrzepowe

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Słowa kluczowe: migotanie przedsionków, antykoagulacja, echokardiografia przezprzełykowa, kardiowersja elektryczna, udar mózgu.

Abstract

Introduction: Patients with atrial fibrillation (AF) are at increased risk of cardiovascular diseases and death. Evidence on the comparable effects of rhythm and heart rate control strategies in patients with AF is ambiguous.
Aim of the research: To assess the recurrence of arrhythmia and adverse cardiovascular events within 12 months of electrical cardioversion in patients with AF receiving oral anticoagulation therapy.
Material and methods: This was a prospective, single-centre cohort study. The participants underwent transoesophageal echocardiography before direct current cardioversion (DCC). A total of 226 patients were enrolled. The primary outcome was sinus rhythm (SR) restoration after DCC for AF. All participants were followed up for 12 months to evaluate the incidence of death, systemic thromboembolic events, stroke, acute coronary syndrome, hospitalization due to worsening heart failure (HF), and recurrence of arrhythmia after SR restoration.
Results: SR restoration was achieved after DCC in 197 (87.2 %) patients, of whom 112 (56.9%) experienced arrhythmia relapse. Significant risk factors associated with arrhythmia recurrence were β-adrenergic antagonist therapy, chronic obstructive pulmonary disease, and previous stroke/transient ischaemic attack/thromboembolic events. All enrolled patients were free of acute coronary syndrome, systemic thromboembolic events, and stroke, and none of the patients died during the 12-month follow-up period. Hospitalization with worsening HF occurred in 13 patients with SR and in 10 patients with persistent AF ($p = 0.42$).
Conclusions: The arrhythmia recurrence rate was high; however, cardiovascular complications and deaths did not occur. The incidence of hospitalization for HF was comparable between the AF and SR groups.

Streszczenie

Wprowadzenie: U pacjentów z migotaniem przedsionków (AF) stwierdza się zwiększone ryzyko wystąpienia chorób sercowo-naczyniowych i zgonu. Dowody na porównywalne efekty strategii kontroli rytmu i częstości rytmu serca u pacjentów z AF są niejednoznaczne.
Cel pracy: Ocena nawrotu arytmii i niepożądanych zdarzeń sercowo-naczyniowych w czasie 12 miesięcy po kardiowersji elektrycznej u pacjentów z AF stosujących doustne leki przeciwzakrzepowe.
Materiał i metody: Było to prospektywne, jednoośrodkowe badanie kohortowe. Uczestnicy zostali poddani echokardiografii przezprzełykowej przed kardiowersją elektryczną prądem stałym (DCC). Do badania włączono 226 pacjentów. Pierwszorzędowym punktem końcowym było przywrócenie rytmu zatokowego (SR) po DCC z powodu AF. Wszyscy uczestnicy byli obserwowani przez 12 miesięcy w celu oceny częstości występowania zgonów, systemowych incydentów zakrzepowo-zatorowych, udaru mózgu, ostrego zespołu wieńcowego, hospitalizacji z powodu pogorszenia niewydolności serca (HF) oraz nawrotu arytmii po przywróceniu SR.

Wyniki: Przywrócenie SR po DCC uzyskano u 197 (87,2%) pacjentów, z których u 112 (56,9%) wystąpił nawrót arytmii. Istotnymi czynnikami ryzyka związanymi z nawrotem arytmii były leczenie antagonistami receptorów β-adrenergicznych, przewlekła obturacyjna choroba płuc oraz przebyty udar mózgu lub przemijające niedokrwienie mózgu, lub zdarzenia zakrzepowo-zatorowe. U żadnego z pacjentów włączonych do badania nie wystąpił ostry zespół wieńcowy, systemowe zdarzenie zakrzepowo-zatorowe i udar mózgu, nie stwierdzono też zgonów w czasie 12-miesięcznej obserwacji. Hospitalizacja z powodu zaostrzenia HF wystąpiła u 13 pacjentów z SR i 10 pacjentów z przetrwałym AF (p = 0,42).
Wnioski: Częstość nawrotów arytmii była wysoka, jednak nie pojawiły się powikłania sercowo-naczyniowe i zgony. Częstość hospitalizacji z powodu HF była porównywalna w grupach AF i SR.

Introduction

Atrial fibrillation (AF) is a global healthcare problem, and the prevalence of AF is increasing worldwide. Even with optimal therapy, patients with AF have an increased risk of cardiovascular diseases, such as stroke and heart failure (HF), and death [1]. Prevention of stroke and thromboembolic events remains an essential part of AF treatment according to the recommendations of the European Society of Cardiology and the American Heart Association; however, improved symptom management and optimal cardiovascular and comorbidity management are equally important [2, 3]. There are 2 therapeutic strategies for AF: rhythm and heart rate control strategies [2, 3], but the evidence on the comparable health effects of these strategies is unclear [4]. Previous trials, such as AFFIRM, RACE, STAF, PIAF, and HOT CAFE, have not shown the superiority of rhythm control over rate control in improving cardiovascular outcomes and reducing mortality in patients with AF; however, many post-hoc analyses have disclosed the advantages of sinus rhythm (SR) maintenance, including improved physical capacity [5–14]. The CABANA trial did not confirm that catheter ablation for AF was superior to antiarrhythmic drug therapy in improving the primary composite endpoints of death, disabling stroke, serious bleeding, or cardiac arrest [15]. In contrast, in the EAST-AFNET 4 trial, early rhythm control therapy among patients with a recent diagnosis of AF and concomitant cardiovascular conditions was found to be superior to the usual care in improving cardiovascular outcomes [16].

Aim of the research

Based on this uncertainty, the current study analysed the incidence and predictive factors of arrhythmia recurrence and cardiovascular complications after direct current cardioversion (DCC) in anticoagulated patients with AF.

Material and methods

Study group

Consecutive patients with AF receiving oral anticoagulation (OAC), who were admitted to the cardiology department for DCC, were included in this study. All participants underwent transoesophageal echocardiography (TEE) before DCC. Of the 296 enrolled patients, 226 (76.3%) underwent electrical cardioversion between December 2010 and June 2018. Of the 70 disqualified from cardioversion, 43 had a left atrial appendage thrombus, and the remaining patients had frequent previous relapses of arrhythmia and were finally qualified for a heart rate control strategy. To be eligible, patients had to meet all the following criteria: the presence of arrhythmia with a duration of > 48 h, symptomatic or poorly tolerated arrhythmia, OAC for > 3 weeks, and age ≥ 18 years. The exclusion criteria were the presence of bradycardia (heart rate < 60/min), signs of peripheral hypoperfusion, systolic blood pressure of < 90 mm Hg, signs of aggravated HF, moderate to severe mitral stenosis defined as mean pressure gradient ≥ 5 mm Hg with mitral orifice area ≤ 1.5 cm^2, any prosthetic heart valve, and history of intracardiac thrombus, ablation, and/or electrical cardioversion. All patients were followed up for 12 months from the day of TEE to evaluate the incidence of death, systemic thromboembolic events, stroke, acute coronary syndrome, hospitalization due to worsening HF, and recurrence of arrhythmia after SR restoration.

Anticoagulation therapy

All participants were on OAC therapy, according to the current guidelines: vitamin K antagonist (VKA) therapy with international normalized ratio (INR) ≥ 2.0 or uninterrupted non-vitamin K antagonist oral anticoagulant therapy for at least 3 weeks before study inclusion [17–20]. For patients on a VKA regimen, INR was checked every week for 3 weeks, and the results were expected to be within the therapeutic range. For patients taking apixaban, the required dose was 5 mg twice daily, but 2.5 mg twice daily was also allowed in patients fulfilling at least 2 of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, and serum creatinine level ≥ 1.5 mg/dl. In the case of dabigatran, the required dose was 150 mg twice daily, but 110 mg twice daily was also allowed in patients fulfilling at least one of the following criteria: a HAS-BLED score ≥ 3, an estimated glomerular filtration rate of 30–49 ml/min/1.73 m^2, concomitant use of verapamil, and age ≥ 80 years [18]. For patients on rivaroxaban, the required dose was 20 mg once daily; however, 15 mg once daily was also allowed in patients fulfilling at least one of the following criteria: HAS-BLED score ≥ 3 and estimated glomerular filtration rate of

15–49 ml/min/1.73 m^2. The glomerular filtration rate was evaluated using the MDRD formula [21].

Echocardiographic examination

All echocardiographic examinations were performed by 3 independent certified echocardiography specialists using a Vivid E9 (GE Vingmed Ultrasound AS, Horten, Norway) ultrasound device with a multiplanar transducer, according to an approved protocol [22]. Transthoracic and transoesophageal echocardiographic examinations were performed on all participants. The anteroposterior diameter of the left atrium (LA) was evaluated during end-systole in a plane perpendicular to the long axis of the ascending aorta in the parasternal long-axis view. Left ventricular ejection fraction was assessed using the Simpson's biplane method [23]. All echocardiographic examinations were recorded and stored and were available for reassessment if needed.

Direct current cardioversion

At least 6 h of fasting were required before elective cardioversion. In all patients, electrolytes and thyroid hormones were within normal limits, and digitalis glycosides were not used before the DCC. The maximum time interval between TEE and DCC was 3 h. Synchronized DCC was performed under general anaesthesia with propofol, midazolam, or etomidate, according to contemporary guidelines, and propofol was the most commonly used anaesthetic agent. Oxygen was administered to each patient directly before and during general anaesthesia using a simple face mask. Oxygen saturation of arterial haemoglobin measured using the pulse oximetry method (SpO_2), heart rate, and arterial pressure were controlled until the patients were fully awake at least 60 min after DCC. Defibrillation gels were applied to the electrodes of the external defibrillator to reduce chest impedance and the risk of skin burns. An electric shock was administered through the paddles placed on the chest in the anterolateral position. In the case of cardiac implantable electronic devices (CIEDs), the defibrillation paddles were also placed in the anterolateral position, maintaining at least an 8-cm distance between the paddles and the device generator. Self-adhesive defibrillation pads were not used in the present study. A maximum of 3 discharges of DCCs per patient during one procedure were performed. The discharge energy during cardioversion was selected individually for each patient with the assumption that during the possible second and third discharges, the electric energy must not be lower than that used in the previous discharges. The initial energy was 100–300 J, and the possible subsequent shocks had energies of 150–300 J. Cardioversion was performed using a biphasic external defibrillator (Medtronic Physio Control Lifepak 12). Cardioversion was considered successful if SR was restored and the patient had SR for at least 12 h. The DCC results were documented using 12-lead electrocardiography (ECG).

Antiarrhythmic drug therapy

The patients were discharged after at least 24 h of follow-up in the Department of Cardiology after cardioversion. After cardioversion, antiarrhythmic drug therapy was selected individually for each patient except in the case of sinus bradycardia, defined as heart rate < 60/min. β-blockers, propafenone, amiodarone, sotalol, a combination of β-blocker and propafenone, a combination of β-blocker and amiodarone, and digoxin were used to prevent recurrent arrhythmia. Therapy with amiodarone and a combination of amiodarone and β-blocker was mainly reserved for patients with significant structural heart disease, defined as the presence of left ventricular ejection fraction < 40%, left ventricular wall thickness ≥ 14 mm, and/or significant coronary disease, defined as a history of an acute coronary syndrome in the last 12 months. For participants with or without irrelevant heart disease, antiarrhythmic therapy was chosen from other forms of antiarrhythmic pharmacotherapy. Propafenone has frequently been used in combination with a β-blocker to block conduction in the atrioventricular node due to its potential to convert AF to rapid conduction atrial flutter (AFL) during recurrent arrhythmia. Extended-release metoprolol succinate was administered at an oral dose of 23.75–95 mg once daily or bisoprolol at an oral dose of 1.25–10 mg once daily. Amiodarone was administered orally at a dose of 200 mg three times a day for 4 weeks, then 200 mg twice a day for 4 weeks, and then 200 mg once a day. Sotalol, propafenone, and digoxin were administered orally at a dose of 80–160 mg twice daily, 300 mg three times daily, and 100 mg once daily, respectively.

Recurrence of arrhythmia was defined as the ECG-documented symptomatic AF or AFL that required treatment at the Emergency Department or hospitalization. A standard 12-lead ECG recording was required to establish the diagnosis of recurrent arrhythmia.

Statistical analysis

Numbers and percentages are used to represent qualitative variables. Quantitative data are shown as median and interquartile ranges or standard deviation and arithmetic mean when appropriate. For qualitative data, group comparisons were performed using the χ^2 or Fisher's exact tests. Owing to a violation of the assumption of normality (normality of the distribution was assessed using the Shapiro-Wilk test), the distributions of quantitative data were compared using the Mann-Whitney *U* test. Survival analysis was used in relation to the analysis of arrhythmia recur-

rence after successful cardioversion. Survival curves were constructed using the Kaplan-Meier method. The log-rank test was used to compare the survival curves between the groups. Hazard ratios (HRs) were determined using the Cox proportional hazards model. For all tests, a p-value < 0.05 was considered significant (2-tailed). All statistical tests were performed using the R software package version 3.6.2 (R: language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

The study protocol was approved by the local Ethics Committee (Reg. no. 21/2010). All procedures performed in this trial were conducted in accordance with the Declaration of Helsinki and the ethical standards of the local bioethics committee. Written informed consent was obtained from all the patients.

Results

Effectiveness of electrical cardioversion and recurrence of arrhythmia

A total of 226 patients underwent cardioversion, and SR was restored in 197 patients (Figure 1) with no periprocedural complications. None of these patients required AF or AFL catheter-ablation procedures during a 12-month follow-up. The baseline characteristics according to cardioversion results are described in Table 1, and the baseline characteristics in relation to recurrent arrhythmia are shown in Table 2. All patients received guideline-recommended OACs and therapies for concomitant cardiovascular diseases. Cardioversion was performed for rhythm control, and antiarrhythmic drugs were administered. The most commonly used form of antiarrhythmic drug therapy was a combination of a β-blocker and propafenone (Table 3). Arrhythmia recurrence was detected in 112 (56.9%) patients with the maximum frequency in the first 30 days after cardioversion. In 5 patients in the group with recurrent arrhythmia, arrhythmia recurred as AFL. The survival curves constructed using the Kaplan-Meier method demonstrated the superiority of different antiarrhythmic drug schemas over β-blocker therapy in the reduction of arrhythmia recurrence; however, this reduction in arrhythmia recurrence was statistically significant for propafenone therapy and the combination of the β-blocker with propafenone versus β-blocker therapy (Figure 2). The HRs determined using the Cox proportional hazard model revealed that the risk factors associated with arrhythmia recurrence were β-adrenergic antagonist therapy, chronic obstructive pulmonary disease, and previous stroke/transient ischaemic attack (TIA)/thromboembolic events (Table 4).

Follow-up for cardiovascular conditions

Follow-up was completed for all participants. No cases of acute coronary syndrome, systemic thromboembolic event, stroke, or death were reported during the 12 months following the TEE. Hospitalization due to HF aggravation occurred in 13 patients with SR and in 10 patients with persistent AF (p = 0.42).

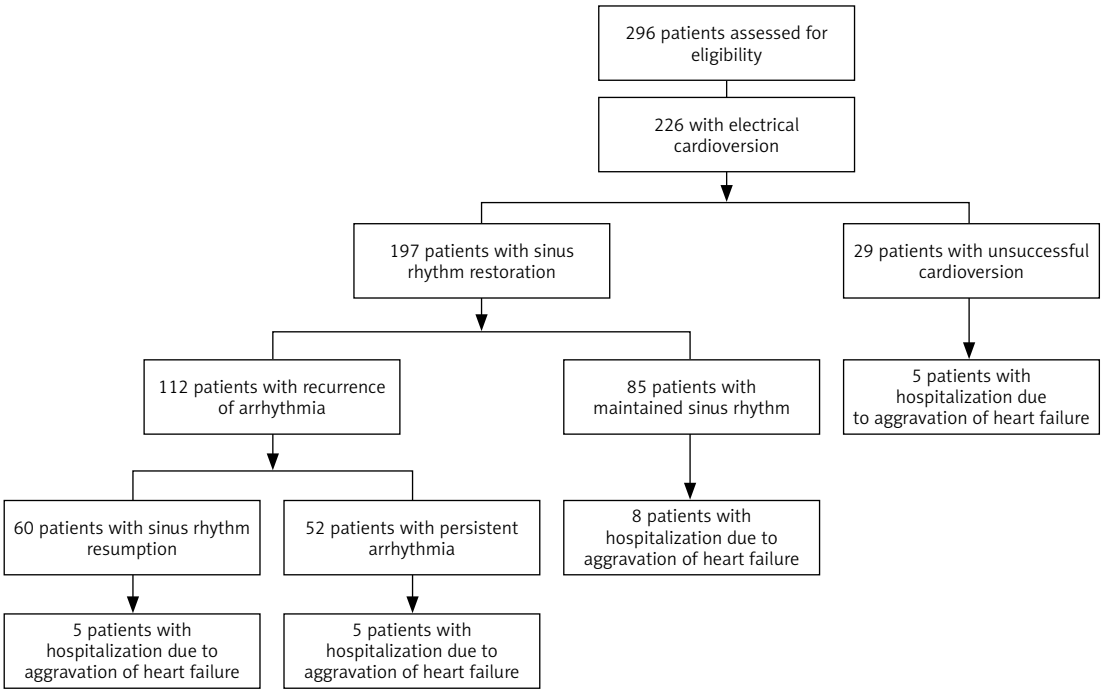

Figure 1. Patient flow chart

Table 1. Baseline characteristics according to the direct current cardioversion result

Variable	DCC successful (*n* = 197)	DCC unsuccessful (*n* = 29)	*P*-value
Age [years], mean (SD)	64.7 (9.3)	60.8 (9.6)	0.03
Age range [years]	27–87	43–77	N/A
Age < 65 y, *n* (%)	85 (43.1)	19 (65.5)	0.06
Age ≥ 65 y, *n* (%)	112 (56.9)	10 (34.5)	0.02
Age ≥ 75 y, *n* (%)	21 (10.7)	3 (10.3)	> 0.99
Female sex, *n* (%)	83 (42.1)	9 (31.0)	0.26
BMI [kg/m^2] mean (SD)	29.5 (4.4)	32.1 (3.7)	< 0.001
BMI range [kg/m^2]	17.3–47.0	25.5–44.5	N/A
BMI ≥ 25 kg/m^2, *n* (%)	173 (87.8)	29 (100.0)	0.051
BMI ≥ 30 kg/m^2, *n* (%)	71 (36.0)	21 (72.4)	< 0.001
SBP [mm Hg] mean (SD)	123.7 (10.3)	123.6 (9.1)	0.92
DBP [mm Hg] mean (SD)	77.1 (7.1)	75.5 (7)	0.17
Heart rate [bpm] mean (SD)	97.1 (19.4)	94 (19.5)	0.35
COPD, *n* (%)	9 (4.6)	0 (0.0)	0.61
Arterial hypertension, *n* (%)	154 (78.2)	20 (69.0)	0.27
Heart failure, *n* (%)	52 (26.4)	9 (31.0)	0.6
Previous myocardial infarction, *n* (%)	11 (5.6)	1 (3.4)	> 0.99
Peripheral artery disease, *n* (%)	2 (1.0)	0 (0.0)	> 0.99
CABG, *n* (%)	2 (1.0)	0 (0.0)	> 0.99
Diabetes mellitus, *n* (%)	31 (15.7)	6 (20.7)	0.59
Stroke/TIA/systemic thromboembolism, *n* (%)	12 (6.1)	4 (13.8)	0.13
Current smoker, *n* (%)	16 (8.1)	4 (13.8)	0.3
eGFR [ml/min/1.73 m^2] mean (SD)	65.2 (15)	70.4 (13.3)	0.049
eGFR range [ml/min/1.73 m^2]	20.9–133.1	42.3–97.4	N/A
LA diameter [mm] mean (SD)	44.4 (4.5)	45.4 (3.8)	0.21
LVEF %, mean (SD)	55.8 (8)	53.9 (9.9)	0.48
LVEF range %	30–76	20–67	N/A
LVEF < 40%, *n* (%)	9 (4.6)	2 (6.9)	0.64
LVEF < 50%, *n* (%)	33 (16.8)	6 (20.7)	0.6
CHA2DS2-VASc score, mean (SD)	2.5 (1.4)	2.3 (1.7)	0.37
CHA2DS2-VASc score range	0–7	0–6	N/A
CHA2DS2-VASc score ≥ 2, *n* (%)	151 (76.6)	16 (55.2)	0.01
β-blocker, *n* (%)	171 (86.8)	27 (93.1)	0.54
ACE inhibitor/ARB, *n* (%)	141 (71.6)	21 (72.4)	0.92
Statin, *n* (%)	125 (63.5)	19 (65.5)	0.83
VKA, *n* (%)	33 (16.8)	8 (27.6)	0.16
Rivaroxaban, *n* (%)	54 (27.4)	10 (34.5)	0.43
Dabigatran, *n* (%)	105 (53.3)	11 (37.9)	0.12
Apixaban, *n* (%)	5 (2.5)	0 (0.0)	> 0.99

Table 1. Cont.

Variable	DCC successful (*n* = 197)	DCC unsuccessful (*n* = 29)	*P*-value
Initial energy for DCC [J] mean (SD)	154.2 (32.4)	156 (37)	0.85
Initial energy for DCC range [J]	100–250	100–300	N/A
Energy to BMI ratio for initial DCC [J/kg/m^2] mean (SD)	5.3 (1.1)	4.9 (1.2)	0.01
Energy to BMI ratio range for initial DCC [J/kg/m^2]	2.8–8.7	3.2–10.1	N/A
Success in initial DCC, *n* (%)	146 (74.1)	0 (0.0)	< 0.001
Final energy for DCC [J] mean (SD)	168.8 (40.1)	200.9 (39.2)	< 0.001
Final energy for DCC range [J]	100–300	150–300	N/A
Energy to BMI ratio for final DCC [J/kg/m^2]	5.8 (1.3)	6.6 (1.6)	0.006
Energy to BMI ratio range for final DCC [J/kg/m^2]	2.8–10.5	4.1–10.1	N/A

ACE inhibitor – angiotensin–converting–enzyme inhibitor, ARB – angiotensin receptor blocker, BMI – body mass index, CABG – coronary artery bypass grafting, CHA2DS2-VASc – scale for stroke and thromboembolic risk assessment, COPD – chronic obstructive pulmonary disease, DCC – direct current cardioversion, eGFR – estimated glomerular filtration rate, ICD – implanted cardioverter–defibrillator, LA – left atrium, LVEF – left ventricular ejection fraction, S/DBP – systolic/diastolic blood pressure, SR – sinus rhythm, TIA – transient ischemic attack, VKA – vitamin K antagonist.

Discussion

In the present study, in patients with AF who were receiving guideline-recommended OAC and therapy for concomitant cardiovascular diseases, rhythm control therapy using cardioversion and antiarrhythmic drug therapy were associated with cardiovascular effects comparable to the effects of heart rate control strategy during a 12-month follow-up period. Interestingly, β-blockers were inferior to other arrhythmic drugs in the prevention of AF recurrence after cardioversion and were significant risk factors for arrhythmia recurrence. Other risk factors for arrhythmia recurrence were chronic obstructive pulmonary disease and previous stroke/TIA/thromboembolic events.

According to the current guidelines for AF [2, 3], the management of this form of arrhythmia includes stroke prevention, reduction of arrhythmia-related symptoms, and optimal cardiovascular and comorbidity treatment. Despite progression in AF therapy, patients with this condition still have an increased risk of cardiovascular events. Restoration of SR and maintenance of rhythm control therapy using antiarrhythmic drugs and/or cardioversion and/or AF ablation are performed to alleviate AF-related symptoms and improve quality of life [2]. It is unclear whether the rhythm control strategy is better than the heart rate control strategy for reducing the risk of cardiovascular events and death rates. Results from 5 randomized trials (PIAF, STAF, RACE, AFFIRM, and HOT CAFE) indicated that the rhythm control strategy did not show superiority over the ventricular rate control (heart rate control) strategy in patients with AF with respect to several specific outcomes such as reduced death or stroke rates; however, these trials had different patient inclusion criteria, therapeutic management techniques, and endpoints, limiting the applicability of their conclusions to all patients with AF [5, 7, 9–11]. In a study by Roy *et al*. involving patients with AF and HF with reduced ejection fraction, a rhythm control strategy did not reduce the rate of death from cardiovascular causes compared with a heart rate control strategy [24]. The CABANA trial assessed the effectiveness of catheter ablation compared with antiarrhythmic drug therapy in reducing the occurrence of primary composite endpoints consisting of death, disabling stroke, serious bleeding, or cardiac arrest among patients with symptomatic AF. In this study, the incidence of recurrent AF and AF burden were lower with ablation than with drug therapy alone, but ablation was not superior to antiarrhythmic drug therapy in improving cardiovascular outcomes during the 5 years of follow-up. However, the primary endpoint was analysed according to the intention-to-treat principle, and therefore the analysis of the study results was based on the initial treatment assignment and not on the treatment eventually received. The principal findings in the trial might have been affected by crossover rates in both directions and the lower-than-expected cardiovascular event rate in the drug arm [15]. According to the "as treated" analysis, AF ablation would have demonstrated superior effectiveness compared with antiarrhythmic drug therapy in terms of mortality [25]. The EAST-AFNET 4 trial was different from other trials, such as CABANA, AFFIRM, and RACE. First, the study population had early AF (defined as AF diagnosed ≤ 12 months before enrolment) in EAST-AFNET 4 compared with the study population with a more sustained AF in other trials. Second, there was a reasonably high rate of

Table 2. Baseline characteristics according to the recurrence of arrhythmia after direct current cardioversion

Variable	Maintained sinus rhythm (*n* = 85)	Recurrent arrhythmia (*n* = 112)	*P*-value
Age [years] mean (SD)	64.9 (8.9)	64.5 (9.5)	0.75
Age range [years]	42–82	27–87	N/A
Age ≥ 65 y, *n* (%)	49 (57.6)	63 (56.2)	0.84
Age ≥ 75 y, *n* (%)	11 (12.9)	10 (8.9)	0.37
Female sex, *n* (%)	37 (43.5)	46 (41.1)	0.73
BMI [kg/m^2] mean (SD)	29.5 (4.3)	29.4 (4.5)	0.98
BMI range [kg/m^2]	21–46.2	17.3–47	N/A
BMI ≥ 25 kg/m^2, *n* (%)	76 (89.4)	97 (86.6)	0.55
BMI ≥ 30 kg/m^2, *n* (%)	29 (34.1)	42 (37.5)	0.62
SBP [mm Hg] mean (SD)	124 (11.1)	122.8 (9.5)	0.17
DBP [mm Hg] mean (SD)	76.5 (7.2)	77.6 (7.1)	0.23
Heart rate [bpm] mean (SD)	94.8 (18.2)	98.8 (20.2)	0.17
COPD, *n* (%)	1 (1.2)	8 (7.1)	0.08
Arterial hypertension, *n* (%)	70 (82.4)	84 (75)	0.21
Heart failure, *n* (%)	24 (28.2)	28 (25)	0.61
Myocardial infarction, *n* (%)	7 (8.2)	4 (3.6)	0.21
CABG, *n* (%)	0 (0)	2 (1.8)	0.51
Diabetes mellitus, *n* (%)	16 (18.8)	15 (13.4)	0.3
Stroke/TIA/systemic thromboembolism, *n* (%)	2 (2.4)	10 (8.9)	0.056
Current smoker, *n* (%)	7 (8.2)	9 (8)	0.96
eGFR [ml/min/1.73 m^2] mean (SD)	67.3 (15.1)	63.6 (14.8)	0.15
eGFR range [ml/min/1.73 m^2]	35.4–133.1	20.9–104.4	N/A
LA diameter [mm] mean (SD)	44.2 (4.7)	44.6 (4.4)	0.38
LA diameter > 40 mm, *n* (%)	71 (83.5)	93 (83)	0.93
LA diameter > 45 mm, *n* (%)	32 (37.6)	46 (41.1)	0.63
LVEF %, mean (SD)	57 (7.7)	54.9 (8.2)	0.11
LVEF range %	35–76	30–68	N/A
LVEF < 50 %, *n* (%)	10 (11.8)	23 (20.5)	0.1
LVEF < 40 %, *n* (%)	3 (3.5)	6 (5.4)	0.73
CHA2DS2-VASc score, mean (SD)	2.6 (1.2)	2.5 (1.6)	0.41
CHA2DS2-VASc score range	0–5	0–7	N/A
CHA2DS2-VASc score ≥ 2, *n* (%)	69 (81.2)	82 (73.2)	0.19
VKA, *n* (%)	13 (15.3)	20 (17.9)	0.63
Rivaroxaban, *n* (%)	24 (28.2)	30 (26.8)	0.82
Dabigatran, *n* (%)	45 (52.9)	60 (53.6)	0.93
Apixaban, *n* (%)	3 (3.5)	2 (1.8)	0.65
ACE inhibitor/ARB before DCC, *n* (%)	64 (75.3)	77 (68.8)	0.31
ACE inhibitor/ARB after DCC, *n* (%)	64 (75.3)	77 (68.8)	0.31

Table 2. Cont.

Variable	Maintained sinus rhythm (*n* = 85)	Recurrent arrhythmia (*n* = 112)	*P*-value
Statin before DCC, *n* (%)	54 (63.5)	71 (63.4)	0.98
Statin after DCC, *n* (%)	54 (63.5)	71 (63.4)	0.98
β-blocker before DCC, *n* (%)	75 (88.2)	96 (85.7)	0.6
β-blocker after DCC, *n* (%)	6 (7.1)	14 (12.5)	0.21
β-blocker and amiodarone after DCC, *n* (%)	13 (15.3)	18 (16.1)	0.88
β-blocker and propafenone after DCC, *n* (%)	56 (65.9)	66 (58.9)	0.32
β-blocker and digoxin after DCC, *n* (%)	0 (0)	1 (0.9)	> 0.99
Amiodarone after DCC, *n* (%)	0 (0)	5 (4.5)	0.07
Propafenone after DCC, *n* (%)	8 (9.4)	5 (4.5)	0.16
Sotalol after DCC, *n* (%)	0 (0)	1 (0.9)	> 0.99
Initial energy for DCC [J] mean (SD)	155.6 (33.5)	153.1 (31.7)	0.6
Initial energy for DCC range [J]	100–250	100–250	N/A
Energy to BMI ratio for initial DCC [J/kg/m^2] mean (SD)	5.3 (1.1)	5.3 (1.1)	0.76
Energy to BMI ratio range for initial DCC [J/kg/m^2]	2.8–8.2	3.2–8.7	N/A
Success in initial DCC, *n* (%)	63 (74.1)	83 (74.1)	> 0.99
Energy in successful DCC [J] mean (SD)	170 (41.7)	167.9 (39.1)	0.78
Energy in successful DCC range [J]	100–300	100–300	N/A
Number of attempts in DCC, mean (SD)	1.3 (0.6)	1.3 (0.5)	0.91
Number of attempts in DCC range	1–3	1–3	N/A

ACE inhibitor – angiotensin-converting-enzyme inhibitor, ARB – angiotensin receptor blocker, BMI – body mass index, CABG – coronary artery bypass grafting, CHA2DS2–VASc – scale for stroke and thromboembolic risk assessment, COPD – chronic obstructive pulmonary disease, DCC – direct current cardioversion, eGFR – estimated glomerular filtration rate, LA – left atrium, LVEF – left ventricular ejection fraction, S/DBP – systolic/diastolic blood pressure, TIA – transient ischaemic attack, VKA – vitamin K antagonist.

Table 3. Antiarrhythmic drugs after successful direct current cardioversion

Without antiarrhythmic drug, *n* (%)	4 (2)
β-blocker, *n* (%)	20 (10.2)
β-blocker and amiodarone, *n* (%)	31 (15.7)
β-blocker and digoxin, *n* (%)	1 (0.5)
β-blocker and propafenone, *n* (%)	122 (62)
Amiodarone, *n* (%)	5 (2.5)
Propafenone, *n* (%)	13 (6.6)
Sotalol, *n* (%)	1 (0.5)

AF ablation (8% at enrolment, 20% by 5 years) in the EAST-AFNET 4 trial. Third, the EAST-AFNET 4 trial results showed that a rhythm control strategy was superior to heart rate control therapy in improving cardiovascular outcomes in patients with early AF and concomitant cardiovascular conditions. In the EAST-AFNET 4 trial, reductions were noted for the achieve-

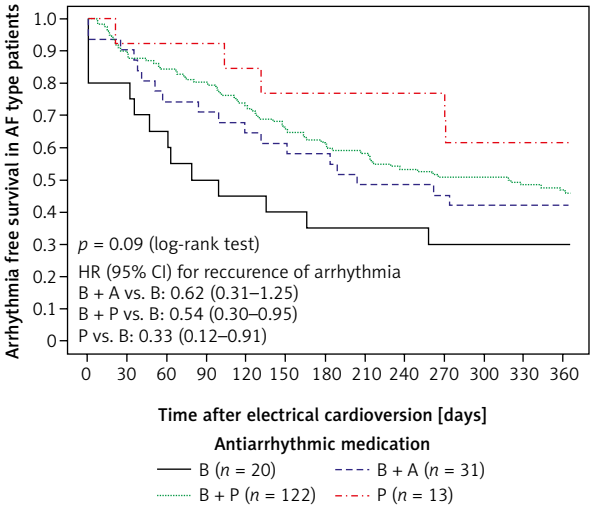

Figure 2. Kaplan-Meier Curves for arrhythmia-free survival in atrial fibrillation patients in the β-blocker (B), β-blocker and Amiodarone (B + A), β-blocker and Propafenone (B + P), and Propafenone (P) groups

Table 4. Cox proportional hazards ratios for the arrhythmia recurrence after the successful direct current cardioversion

Variable	Arrhythmia recurrence		Hazard ratio (95% CI)	*P*-value
	No (*n* = 85)	Yes (*n* = 112)		
Female sex, *n* (%):				
No	48 (56.5)	66 (58.9)	Reference level	
Yes	37 (43.5)	46 (41.1)	0.99 (0.68–1.44)	0.94
Age ≥ 65 y, *n* (%):				
No	36 (42.4)	49 (43.8)	Reference level	
Yes	49 (57.6)	63 (56.2)	1.02 (0.71–1.49)	0.9
Age ≥ 75 y, *n* (%):				
No	74 (87.1)	102 (91.1)	Reference level	
Yes	11 (12.9)	10 (8.9)	0.74 (0.39–1.42)	0.37
BMI ≥ 30 kg/m^2, *n* (%):				
No	56 (65.9)	70 (62.5)	Reference level	
Yes	29 (34.1)	42 (37.5)	1.04 (0.71–1.53)	0.83
COPD, *n* (%):				
No	84 (98.8)	104 (92.9)	Reference level	
Yes	1 (1.2)	8 (7.1)	2.7 (1.31–5.57)	0.007
Arterial hypertension, *n* (%):				
No	15 (17.6)	28 (25)	Reference level	
Yes	70 (82.4)	84 (75)	0.77 (0.5–1.18)	0.23
Heart failure, *n* (%):				
No	61 (71.8)	84 (75)	Reference level	
Yes	24 (28.2)	28 (25)	0.95 (0.62–1.46)	0.81
Myocardial infarction, *n* (%):				
No	78 (91.8)	108 (96.4)	Reference level	
Yes	7 (8.2)	4 (3.6)	0.63 (0.23–1.71)	0.37
Diabetes mellitus, *n* (%):				
No	69 (81.2)	97 (86.6)	Reference level	
Yes	16 (18.8)	15 (13.4)	0.69 (0.4–1.18)	0.17
Stroke/TIA/systemic thromboembolism, *n* (%):				
No	83 (97.6)	102 (91.1)	Reference level	
Yes	2 (2.4)	10 (8.9)	2.1 (1.1–4.03)	0.02
eGFR < 60 ml/min/1.73 m^2, *n* (%):				
No	57 (67.1)	67 (59.8)	Reference level	
Yes	28 (32.9)	45 (40.2)	1.3 (0.89–1.89)	0.18
eGFR < 50 ml/min/1.73 m^2, *n* (%):				
No	76 (89.4)	95 (84.8)	Reference level	
Yes	9 (10.6)	17 (15.2)	1.39 (0.83–2.34)	0.21
PPM, *n* (%):				
No	77 (90.6)	101 (90.2)	Reference level	
Yes	8 (9.4)	11 (9.8)	0.97 (0.52–1.82)	0.94

Table 4. Cont.

Variable	Arrhythmia recurrence		Hazard ratio (95% CI)	*P*-value
	No (*n* = 85)	Yes (*n* = 112)		
Current smoker, *n* (%):				
No	78 (91.8)	103 (92)	Reference level	
Yes	7 (8.2)	9 (8)	0.88 (0.44–1.73)	0.71
Former smoker, *n* (%):				
No	61 (71.8)	93 (83)	Reference level	
Yes	24 (28.2)	19 (17)	0.66 (0.4–1.08)	0.09
Non-smoker, *n* (%):				
No	31 (36.5)	28 (25)	Reference level	
Yes	54 (63.5)	84 (75)	1.46 (0.95–2.25)	0.08
LA diameter > 40 mm, *n* (%):				
No	14 (16.5)	19 (17)	Reference level	
Yes	71 (83.5)	93 (83)	1.01 (0.62–1.65)	0.97
LA diameter > 45 mm, *n* (%):				
No	53 (62.4)	66 (58.9)	Reference level	
Yes	32 (37.6)	46 (41.1)	1.18 (0.81–1.72)	0.39
LVEF < 50%, *n* (%):				
No	75 (88.2)	89 (79.5)	Reference level	
Yes	10 (11.8)	23 (20.5)	1.54 (0.97–2.44)	0.06
LVEF < 40%, *n* (%):				
No	82 (96.5)	106 (94.6)	Reference level	
Yes	3 (3.5)	6 (5.4)	1.22 (0.54–2.78)	0.63
CHA2DS2-VASc score ≥ 2, *n* (%):				
No	16 (18.8)	30 (26.8)	Reference level	
Yes	69 (81.2)	82 (73.2)	0.76 (0.5–1.15)	0.19
Before DCC: β-blocker, *n* (%):				
No	10 (11.8)	16 (14.3)	Reference level	
Yes	75 (88.2)	96 (85.7)	0.88 (0.52–1.49)	0.63
Before DCC: ACE inhibitor/ARB, *n* (%):				
No	21 (24.7)	35 (31.2)	Reference level	
Yes	64 (75.3)	77 (68.8)	0.81 (0.55–1.21)	0.31
Before DCC: Statin, *n* (%):				
No	31 (36.5)	41 (36.6)	Reference level	
Yes	54 (63.5)	71 (63.4)	0.99 (0.67–1.45)	0.95
Before DCC: VKA, *n* (%):				
No	72 (84.7)	92 (82.1)	Reference level	
Yes	13 (15.3)	20 (17.9)	1.1 (0.68–1.78)	0.7
Before DCC: Rivaroxaban, *n* (%):				
No	61 (71.8)	82 (73.2)	Reference level	
Yes	24 (28.2)	30 (26.8)	0.96 (0.63–1.45)	0.84

Table 4. Cont.

Variable	Arrhythmia recurrence		Hazard ratio (95% CI)	*P*-value
	No (*n* = 85)	Yes (*n* = 112)		
Before DCC: Dabigatran, *n* (%):				
No	40 (47.1)	52 (46.4)	Reference level	
Yes	45 (52.9)	60 (53.6)	1.01 (0.69–1.46)	0.98
After DCC: ACE inhibitor/ARB, *n* (%):				
No	21 (24.7)	35 (31.2)	Reference level	
Yes	64 (75.3)	77 (68.8)	0.81 (0.55–1.21)	0.31
After DCC: Statin, *n* (%):				
No	31 (36.5)	41 (36.6)	Reference level	
Yes	54 (63.5)	71 (63.4)	0.99 (0.67–1.45)	0.95
After DCC: β-blocker, *n* (%):				
No	79 (92.9)	98 (87.5)	Reference level	
Yes	6 (7.1)	14 (12.5)	1.77 (1.01–3.11)	0.04
After DCC: β-blocker and amiodarone, *n* (%):				
No	72 (84.7)	94 (83.9)	Reference level	
Yes	13 (15.3)	18 (16.1)	1.06 (0.64–1.75)	0.83
After DCC: β-blocker and propafenone, *n* (%):				
No	29 (34.1)	46 (41.1)	Reference level	
Yes	56 (65.9)	66 (58.9)	0.76 (0.52–1.11)	0.15
After DCC: Propafenone, *n* (%):				
No	77 (90.6)	107 (95.5)	Reference level	
Yes	8 (9.4)	5 (4.5)	0.53 (0.22–1.3)	0.17

ACE inhibitor – angiotensin–converting–enzyme inhibitor, ARB – angiotensin receptor blocker, BMI – body mass index, CHA2DS2-VASc – scale for stroke and thromboembolic risk assessment, COPD – chronic obstructive pulmonary disease, DCC – direct current cardioversion, eGFR – estimated glomerular filtration rate, LA – left atrium, LVEF – left ventricular ejection fraction, PPM – permanent pacemaker, TIA – transient ischaemic attack, VKA – vitamin K antagonist.

ment of composite endpoints consisting of death from cardiovascular causes, stroke, or hospitalization with worsening HF or acute coronary syndrome, as well as death from cardiovascular causes and stroke. Fourth, most patients in the EAST-AFNET 4 trial in both treatment groups continued to receive anticoagulation, rate control therapy, and treatment of concomitant cardiovascular conditions in contrast to medical management in the other trials [16]. The results of the CASTLE-AF trial showed that AF ablation in patients with HF was associated with a lower rate of achievement of the composite endpoint consisting of hospitalization for worsening HF or death from any cause, compared with medical therapy [26]. In the AATAC trial, enrolled patients had persistent AF and HF. The results of this study show that AF ablation was superior to amiodarone therapy in improving the maintenance of SR during a long-term follow-up period and reducing unplanned hospitalization and mortality. Additionally, a substantial improvement in the 6-minute walk distance and left ventricular ejection fraction was observed in recurrence-free patients [27].

In the present study, one of the predictors of unsuccessful DCC was young age. The relationship between "age" and "BMI" variables was assessed because BMI could affect the bioelectrical resistance of the chest, thereby affecting the result of DCC [4], and no significant relationship was found between these factors. In this case, analysis of the total duration of the arrhythmia and assessment of the total electrical impedance of the chest seem important to elucidate the age-related variations in the context of ineffective DCC. Data regarding unsuccessful DCC in young patients are lacking.

Unfortunately, in the present study, we did not collect data on the total duration of AF before study inclusion and AF burden. Moreover, data collection on arrhythmia recurrence concerned symptomatic

arrhythmia that required medical care or hospitalization. Thus, the arrhythmia recurrence rate might have been underestimated. Additionally, the follow-up period was short (12 months), and the sample size was small. However, all consecutive patients were included, and all participants received anticoagulation and treatment for concomitant cardiovascular diseases. Moreover, in the present study, we investigated antiarrhythmic drugs and cardioversion but not AF ablation. These limitations may explain the results of this study.

In the previous studies, antiarrhythmic drugs were moderately effective in maintaining SR after conversion of AF, as in the present study. Despite the reduction in arrhythmia recurrence, AF still relapsed in 30.4% to 67% of people treated with antiarrhythmics. The use of these drugs can also be associated with serious side effects and proarrhythmic effects [28–30]. Because safety is of paramount concern, antiarrhythmic agents should be used cautiously. Despite a high incidence of AF recurrence, many patients remain free from arrhythmia recurrence, and DCC, as part of the heart rhythm control strategy, is useful to alleviate AF-related symptoms and improve quality of life. However, the effects of the rhythm control strategy on the important clinical endpoints of mortality, stroke, and HF are still unknown.

In view of the high rate of recurrent arrhythmia in the present study, we analysed the potential risk factors for arrhythmia recurrence. Previous studies have shown that the predisposing factors for AF recurrence after cardioversion are old age, long AF duration before cardioversion, early relapses of arrhythmia, LA enlargement or impairment, coronary artery disease, and mitral valve disease. The risk of AF recurrence may be increased by premature atrial contractions, increased heart rate, and atrial conduction disturbances [17, 31, 32]. Previous small trials suggested a positive effect on the maintenance of SR and a low arrhythmia recurrence rate with β-blockers among patients with AF [32–36]; however, most evidence pleads against the significant role of β-blockers in preventing AF [29, 30] Despite this, in the European registry published in 2013, β-blockers were recommended as the first-choice treatment for secondary prevention of AF recurrence, followed by other drugs such as amiodarone, sotalol, flecainide, propafenone, and dronedarone [37]. In the present study, β-blockers were inferior to other arrhythmic therapies in preventing recurrent arrhythmia. Moreover, they were significant risk factors for arrhythmia recurrence, and the explanation for this might be that β-blockers were compared to de facto antiarrhythmic drugs, which were more effective.

During the 12-month follow-up in the present study, no cases of acute coronary syndrome, stroke, systemic thromboembolic events, or death were recorded, but there was a comparable incidence of hospitalization with worsening of HF in patients with and without AF.

Conclusions

The present study demonstrated comparable effects of rhythm control and heart rate control therapies on cardiovascular events during a follow-up period of 12 months in patients with AF. Antiarrhythmic therapy with a β-blocker after cardioversion, chronic obstructive pulmonary disease, and previous stroke/TIA/thromboembolic events were associated with an increased risk of arrhythmia recurrence.

The main clinical implications of the results are that DCC seems highly effective for converting AF to SR, whereas antiarrhythmic drugs may be moderately effective for the maintenance of SR. However, whether the rhythm control strategy is superior to heart rate control therapy in improving cardiovascular outcomes in patients with AF remains unclear.

Conflict of interest

The authors declare no conflict of interest.

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