Cardiology

AF and Stroke: Research Article

Cardiology 2024;149:571–579
DOI: 10.1159/000540007

Received: October 26, 2023
Accepted: June 18, 2024
Published online: August 1, 2024

Elective Direct Current Cardioversion of Atrial Fibrillation: Silent Brain Infarction and Health-Related Quality of Life

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Keywords
Atrial fibrillation · Silent cerebral ischaemia · Thromboembolic stroke · Cardioversion · Health-related quality of life

Abstract

Introduction: Atrial fibrillation (AF) increases the risk for stroke, dementia, and impaired health-related quality of life (HRQL). Elective direct current cardioversion (ECV) is often used to restore sinus rhythm but is associated with thromboembolism. While larger strokes usually produce symptoms, subclinical ones may go unrecognized and may cause cognitive and functional decline over time. In the current study, we sought to evaluate the effects of ECV on silent brain infarctions and HRQL in patients with AF. ***Methods:*** Patients with AF (n = 46) underwent brain magnetic resonance imaging (MRI) and HRQL assessment using the EuroQL-5D5L questionnaire before and after ECV. Implantable loop recorders (ILRs) were used to observe the rate of early AF recurrences within the first 30 days. All patients were treated with anticoagulants according to guidelines. The primary endpoint was silent brain infarction assessed by brain MRI within the first 2 weeks after ECV. Secondary endpoints were the change in HRQL and its association with AF recurrence at follow-up and by ILR recordings. ***Results:*** New silent brain infarction after ECV was detected in 1 patient. At follow-up visit after 19.1 days AF recurrence was detected by 12-lead ECG in 13 patients (28.3%), whereas 27 patients (58.7%) had AF recurrence recorded by ILR within the first 30 days after ECV. European Heart Rhythm Association (EHRA) symptom score and the EuroQL-5d5L score were improved after ECV. ***Conclusion:*** Silent brain infarctions may occur after ECV despite anticoagulation treatment. Early AF recurrence is frequent. ECV positively affects HRQL mainly in those patients with sustained sinus rhythm at follow-up.

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Plain Language Summary

Electric shock treatment is safe and well tolerated in the most common form of heart arrhythmia. The most common form of heart arrhythmia in humans is called AF. This affects up to 1/3 of the general population in their lifetime. Many people with this condition develop symptoms such as breathlessness and chest pain. Even worse, this arrhythmia increases the risk of developing stroke dramatically. Common treatments include medicines that prevents the blood from clotting and thereby forming strokes and small, timed electric impulses to restore a regular rhythm. However, the transition from arrhythmia to a regular heart rhythm increases the risk for stroke as well, albeit only for a short time. Moreover, not all small strokes are necessarily immediately symptomatic. In this work, researchers used advanced imaging diagnostic to find out how often this may happen. They found out, that most people really felt better, though 1/3 of the patients may develop a relapse of their arrhythmia. Small strokes after the procedure were not a regular finding. However they may still develop, as seen in one patient in this study despite appropriate medicine to prevent blood clots.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide [1–4]. It implicates an increased risk of thromboembolic events, heart failure, depression, dementia, impaired health-related quality of life (HRQL) and increased mortality [5–7]. Anticoagulation and especially the use of non-vitamin-K oral anticoagulants have contributed to a significant reduction in thromboembolic events [8, 9]. The reduction in HRQL may be even more pronounced than in other chronic cardiovascular conditions and can be cumbersome to treat [10–13]. The restoration of sinus rhythm by elective direct current cardioversion (ECV) is often used as an immediate symptomatic remedy, but also to evaluate the true symptomatic burden of AF [6]. Recently, it has been shown that early restoration and maintenance of sinus rhythm may even have favourable prognostic consequences [14]. However, ECV is associated with a small but relevant risk of thromboembolism, both immediately after ECV and during the so-called stunning phase of days to weeks that atrial function takes to recover [15]. While the frequency of strokes is comparatively easy to estimate based on pertinent clinical trials and by analysis of medical coding in large-scale real-world registries, silent brain infarction, defined as magnetic resonance imaging findings that imply recent or prior ischemia without acute symptoms, is more difficult to investigate [16]. However, silent brain infarctions may be a major contributing factor to dementia and cognitive impairment in AF patients [16–19]. The aim of our current study was to evaluate the effects of ECV on silent brain infarction, the rate of early recurrences and the changes in HRQL in patients with AF.

Methods

Study Population

We conducted a single centre prospective study. Fifty-eight eligible adult patients scheduled to ECV were screened for eligibility between September 2018 and January 2022, and 46 patients were finally included (Fig. 1). Inclusion was paused due to the global COVID-19 pandemic between January 2020 and August 2021. Inclusion criteria were confirmed AF, age <80 years, CHA_2DS_2-VASc risk score ≤4 (congestive heart failure [1], hypertension [1], age ≥75 [2], diabetes [1], stroke [2], vascular disease [1], age 65–74 years [1] and female sex [1]) at inclusion, and planned direct-current cardioversion. Patients with CHA2DS2-VASc scores above 4 were excluded, to alleviate the confounding by concurrent risk for stroke and quality of life measures. Especially since the study protocol included a follow-up of 12 months. Exclusion criteria consisted of a life expectancy less than 1 year, nonresident patients or concurrent disease potentially affecting follow-up and outcome. Patients with prior clinical stroke were not excluded as older lesions could be identified in the brain-magnetic resonance imaging (MRI) examination prior to the ECV as well as by the imaging technique used after ECV.

Written informed consent was obtained from all participants. The study was registered and approved by the regional Norwegian Ethics Board and by the local patient data protection regulation council.

Study Design

All patients underwent clinical examination. Demographics and family history for defined cardiovascular pathology (AF or flutter, sudden cardiac death, coronary heart disease, heart failure, or valve disease) medical history, clinical characteristics, and current medications were recorded.

MRI of the brain was performed before and within 2 weeks after ECV. A 3T machine was utilized in all but those patients in whom implants only allowed for 1.5T use (Siemens MAGNETOM Skyra 3T or Aera 1.5 T; Siemens Medical Solutions, Erlangen, Germany). A 20-channel head/neck coil was utilized. Sagittal T1, transversal T2, 3D dark fluid T2 FLAIR and diffusion weighted (DW) transversal sequences (b50 and b800) were obtained. Image interpretation was performed by one experienced neuroradiologist. Echocardiography was obtained on GE Vivid machines (General Electric Healthcare, Horten, Norway) by four experienced sonographers before and directly after ECV as well as at the follow-up visit 2–4 weeks after ECV to allow for complete resolution of atrial stunning. A strict protocol for a complete echocardiographic examination was followed to assure comparability. Loops of standardized projections were stored for later processing. A usual 12 lead ECG, European Heart Rhythm Association (EHRA) symptom score and the European Quality of Life foundation 5-dimensional, 5-level health-related quality of life scale (EQ-5D-5L) questionnaire were obtained at visits prior to ECV and at the follow-up visit. Furthermore, patients were clinically assessed for focal neurological deficits using the National Institutes of Health Stroke Scale (NIHSS) at the same visits. EHRA symptom score is defined as I: no symptoms, II: mild symptoms, III: severe symptoms and IV: disabling symptoms [20] and assessed by trained physicians. The EQ-5D-5L

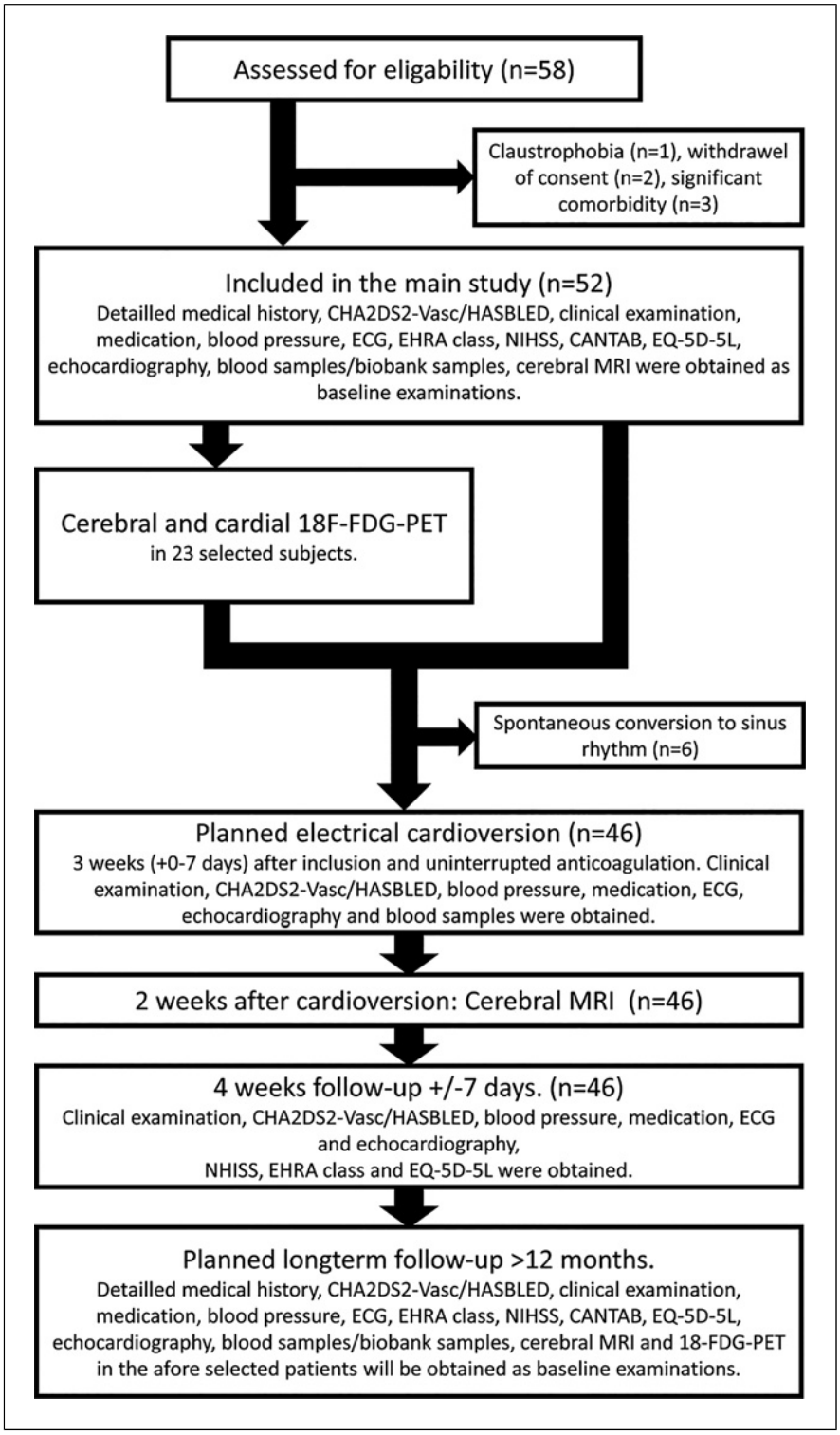

Fig. 1. Flowchart.

score is a six-item questionnaire that includes five different domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as well as one visual analogue scale on global health. Each domain is scored based on a 5-point Likert scale between "without problems" and "not possible due to serious problems," and a global score can be calculated from these five domains. The overall visual analogue scale (VAS) is scored on a scale between 0 and 100 whereby 0 indicates the worst possible general health and 100 the best

Table 1. Concomitant diagnoses at inclusion and their association to early recurrence

Concomitant diagnosis	Absolute number (valid percent)	Relative risk for early recurrence
Hypertension (known diagnosis)	26 (56.5)	0.6 (0.3–1.3)
Hypercholesterolaemia (known diagnosis or LDL more than 2.59 mmol/L untreated)	32 (69.6)	1.3 (0.7–2.7)
Obesity (BMI ≥30)	13 (28.3)	2.1 (0.7–6.0)
Diabetes (known or HbA1c >46 mmol/mol (6.4%))	11 (23.9)	1.2 (0.5–2.8)
Prediabetic state (HbA1c 39–46 mmol/mol)	15 (32.6)	1.5 (0.7–3.5)
CKD (KDIGO), further analysed as CKD 0–1 versus CKD ≥2		
CKD 1	15 (32.6)	1.3 (0.6–3.1)
CKD 2	29 (63.0)	0.7 (0.3–1.7)
CKD 3	1 (2.2)	
CKD 4	0 (0)	
CKD 5	1 (2.2)	
Heart failure (known diagnosis)	9 (19.6)	1.3 (0.5–3.5)
Cancer (known diagnosis)	6 (13.0)	0.8 (0.3–1.9)
Inflammatory disease (known diagnosis)	9 (19.6)	0.9 (0.4–2.1)
History of CVI	3 (6.5)	0.6 (0.3–1.4)
Tobacco use	14 (30.4)	0.6 (0.3–1.2)
Valvular heart disease (known diagnosis)	4 (8.7)	0.5 (0.3–1.0)
Coronary heart disease (known diagnosis)	8 (17.4)	0.8 (0.4–1.8)
OSAS (known diagnosis)	6 (13.0)	2.7 (0.4–16.7)

LDL, low density lipoprotein; BMI, body mass index; CKD, chronic kidney disease; KDIGO, Kidney Disease Improving Global Outcome; CVI, cerebro-vascular insult; OSAS, obstructive sleep apnoea syndrome.

general health the participant could imagine [21]. ECV was conducted in propofol anaesthesia following the established local procedure using ECG trigger and starting at 150 J with escalation to 200 J when required. Patch placement was usually anterior-posterior. A maximum of three discharges were applied per session. We considered all shocks delivered on the same day as one cardioversion attempt. Cardioversion was considered successful if sinus rhythm was restored and maintained at least for 3 h. All patients received at least 3 weeks of uninterrupted anticoagulation prior to and 4 weeks after ECV. Afterwards individual anticoagulation was based on the CHA_2DS_2-VASc score. The reliability of the therapeutic non-interruption was verified by independent thorough anamnesis by a doctor and a nurse using patient logbooks. Implantable loop recorders (ILRs) were employed to objectify AF recurrences and were implanted directly after ECV in the same session (Reveal LINQ™; Medtronic, Minneapolis, MN, USA). AF detection was set to 2 min, and burden was automatically calculated at a remote readout 30 days after ECV as percentage of absolute time elapsed. Echo, ILR data, a neurocognitive test (CANTAB-neurocognitive test battery) and 18 FDG-PET data were collected and will be analysed after a 12-month follow-up period.

Outcome

Primary endpoint was new-onset cerebral ischemia as demonstrated on brain MRI within the first 2 weeks after ECV. Radiologic criteria were high signal intensity on DW imaging (DWI) and low signal intensity on corresponding apparent diffusion coefficient (AECV) maps. Secondary endpoints were the change in EHRA class and EQ-5D-5L, the recorded rhythm at follow-up and AF recurrences on the ILR recordings.

Statistics

Descriptive statistics were used to characterize the study cohort. Mean and standard deviation were calculated for continuous, and frequencies for nominal variables. Absolute frequencies and number of patients experiencing improvement and deterioration are provided for HRQL measures. However, even though CHA_2DS_2VAsc, EHRA, and EQ-5D-5L scores are ordinal in character, we provided mean and standard deviation as well. Means for HRQL measures pre and post-ECV were compared using a paired sample *t*-test as well as Wilcoxon signed-rank test. Significance of differences was assessed from the test result. The level of significance for the paired-sample *t* tests was set at a p value ≤ 0.05 and $p \leq 0.025$ for the one sided Wilcoxon signed-rank test. Adjustment for multiple comparisons was not performed. The relative risk (RR) for early recurrence was calculated for concomitant diagnoses. The odds ratio (OR) was calculated for nominal independent characteristics of the finally included cohort and logarithmic regression was used to calculate the OR for ordinal and continuous characteristics of the finally included cohort. All analyses were performed using SPSS, version 28 (IBM, Chicago, IL, USA).

Results

A total of 46 Caucasian patients (six females) were included in the study. Patient concomitant diagnoses are shown in Table 1, and characteristics in Table 2. Mean

Table 2. Characteristics of the finally included cohort and their association to early recurrence

Characteristics	Absolute number (valid percent)	Mean (standard deviation)	OR for early recurrence
Age, years		63.5 (11.7)	1.0 (0.97–1.07)
Sex			
Female	6 (13)		1.5 (0.27–8.4)
Male	40 (87)		
BMI		29.1 (7.00)	1.15 (0.99–1.33)
CHA2DS2-Vasc pre ECV	Score of 0: 8 (17.4) Score of 1: 8 (17.4) Score of 2: 15 (32.6) Score of 3: 6 (13) Score of 4: 9 (19.6)	2.00 (1.4)	Compared to CHA2DS2Vasc of 0 7 (0.57–86.32) 0.875 (0.16–4.87) 5 (0.39–64.39) 0.8 (0.12–5.4)
EHRA pre EEC	Score of 1: 5 (10.9) Score of 2: 30 (65.2) Score of 3: 11 (23.9)	2.1 (0.6)	Compared to EHRA score of 1 0.21 (0.03–1.54) 0.17 (0.16–1.78)
Antiarrhythmic therapy at cardioversion			
Class I	4 (8.7)		all experienced recurrence
Class II	40 (87)		1.5 (0.27–8.4)
Class III	12 (26.1)		0.14 (0.03–0.62)
Class IV	0 (0)		n.s.
Clearance by CKD-EPI, mL/min/1.73 m^2		82.2 (20.7)	1.01 (0.98–1.04)
NTpro-BNP, ng/L		1,434 (1,374.2)	0.68 (0.42–1.12)
Troponin I, ng/L		9.9 (23.6)	0.99 (0.97–1.02)
CRP, mg/L		6.2 (3.0)	0.97 (0.87–1.07)
Statin use	17 (37.0)		0.69 (0.2–2.3)
RAAS antagonist use	20 (43.5)		1.1 (0.34–3.6)
Family history of specified cardiac condition	29 (63.1)		3.94 (1.1–14.7)

BMI, body mass index; CHA2DS2VASC, congestive heart failure [1], hypertension [1], age ≥75 [2], diabetes [1], stroke [2], vascular disease [1], age 65–74 years [1] and female sex [1]; EHRA, European Heart Rhythm Association atrial fibrillation symptom score; CKD, chronic kidney disease; CRP, C-reactive protein; RAAS, renin-angiotensin-aldosterone-system.

age was 63.5 years (+/− 11.7 years). Mean CHA_2DS_2-VASc was 2.0 (+/− 1.4). Mean body mass index was 29.1 kg/m^2 (+/− 7.0 kg/m^2). None of the included patients reported any missing doses of anticoagulants within the 3 weeks prior to ECV and the 4 weeks after ECV. The most frequently used agent was apixaban in 37 patients (80.4%), followed by rivaroxaban in 6 patients (13.0%). 2 patients (4.3%) received warfarin, and 1 patient (2.2%) was treated with low molecular weight heparin. ECV was initially effective in 43 patients (93.5%). The remaining 3 patients were converted in a second session. No symptomatic side effects of ECV were noted during the procedure or at follow-up. No patient developed a worsening of focal neurological deficits assessed by NIHSS. One patient received Brain MRI examination by 1.5T MRI by indication at both baseline and follow-up examinations (2.1%), 2 patients received 1.5T MRI on baseline by error (4.2%). Follow-up brain MRI examination was performed after a mean of 14.3 days (+/− 8.5 days) after ECV. One patient (2.2%) undergoing 3 T brain-MRI examinations suffered a silent brain infarction in temporal relation to the ECV by comparison to the pre-ECV brain-MRI.

Sinus rhythm on the 12-lead ECG at follow-up after 19.1 days (10.0) was seen in 32 patients (72.7%), while ILR data showed that only 19 patients (41.3%) were free of AF recurrence after 30 days. An improvement of EHRA class was seen in 24 patients (54.5%), 21 patients (65.6%) in the subgroup with sustained sinus rhythm and 3 patients (25.0%) in the subgroup with recurrence at follow-up. Missing and errand data were observed in 2 patients. An improvement in EQ-5D-5L was seen in 24 patients

Table 3. Health-related quality-of-life measures prior and post-ECV of AF

	All patients: mean (SD) (n = 46)		Patients with sustained SR: mean (SD) (n = 32)		Patients with AF recurrence at follow-up: mean (SD) (n = 14)	
EHRA score prior to ECV	2.1 (0.6)	$p < 0.001$	2.3 (0.5)	$p < 0.001$	1.8 (0.6)	$p = 0.59$
EHRA score after ECV	1.5 (0.6)		1.4 (0.7)		1.7 (0.5)	
EQ-5D-5L prior to ECV	7.9 (3.1)	$p < 0.001$	8.1 (3.2)	$p < 0.001$	7.3 (2.8)	$p = 0.7$
EQ-5D-5L after ECV	6.6 (2.3)		6.8 (2.5)		6.0 (1.1)	
VAS global prior to ECV	65.8 (18.6)	$p < 0.001$	66.7 (19.3)	$p < 0.001$	67.6 (18.8)	$p = 0.678$
VAS global after ECV	77.7 (16.5)		79.0 (14.7)		70.2 (21.4)	

p values are given for paired sample t tests. No difference in significance was observed using Wilcoxon signed-rank test. EHRA, European Heart Rhythm Association atrial fibrillation symptom score; EQ-5D-5L, EUROQOL research foundation 5-dimensional 5-level health-related quality-of-life scale; VAS, visual analogue scale of global well-being; SR, sinus rhythm; AF, atrial fibrillation; SD, standard deviation; VAS, visual analogue scale on patient's global health perception.

(58.3%), 20 patients (64.5%) in the subgroup with sinus rhythm at follow-up and 4 patients (40.0%) in the subgroup with AF recurrence at follow-up with missing or errand data in 5 patients. The change of mean HRQL measures in the total group, as well as in the group with sinus rhythm and AF recurrence at follow-up are shown in Table 3. Use of class III antiarrhythmic drugs was associated with an OR of 0.14 (0.03–0.62) for early recurrence as shown on the ILR data, while family history for specific cardiac conditions was associated with a higher risk for recurrence, OR 3.94 (1.1–14.7).

Discussion

In this single-centre prospective observational study we showed that silent brain infarction after ECV may occur despite guideline compliant anticoagulation. However, the primary outcome was observed in only 1 patient who underwent 3T MRI 14 days after ECV. To the best of our knowledge, no other study has investigated the risk of silent brain infarction after ECV with serial 3T brain MRI examinations, considering the time interval for atrial function to recover. In addition, we obtained objective ILR data on early recurrence and HRQL after ECV in each patient. Early AF recurrence was frequent but significantly less so in patients receiving class III antiarrhythmic drugs. HRQL measures improved especially in patients with sustained sinus rhythm at follow-up. As shown in many clinical trials, non-vitamin-K oral anticoagulants are as safe as vitamin-K antagonists to reduce the risk of clinical stroke after ECV [18, 19, 22–27]. Only one other study has investigated the risk of silent brain infarction after ECV by serial brain MRI [28]. In this study Vásquez et al. [28] found that none of the 62 patients suffered from silent stroke. However, in this study 1.5T MRI was employed and follow-up was performed already after 24 h, thus not comprising the atrial stunning phase of increased thromboembolic risk [29]. Furthermore, this study only included patients treated with vitamin K-antagonists. Few studies have investigated the direct effects of ECV and sustainment of sinus rhythm on HRQL with ambiguous results [10, 30, 31]. Different HRQL questionnaires have been used to assess the highly variable symptoms of AF [6]. We chose to use the most common clinical tool, the EHRA symptom score that enables clinicians to estimate the impacts of the patient's symptoms on daily life. The EHRA symptom score is very easy to obtain and is regarded as a quality measure of AF management [6, 32]. According to guidelines, EHRA symptom score should therefore be obtained at every AF visit [6]. Our data showed that patients with sustained sinus rhythm at follow-up reported significantly better EHRA scores after ECV compared with patients in AF at follow-up which is in line with findings in the literature [32]. In addition to the EHRA symptom score, we used a non-disease specific questionnaire, the EQ-5D-5L that previously has been proposed for use in AF patients [6]. EQ-5d-5L offers a broad comparability to HRQL in other diseases, allows for calculation of quality adjusted life-year and cost-utility analysis and is validated in Norwegian, though disease specific tools such AFEQT, AF-Qo, ASTA, or AFSS might give more nuanced overview of AF related impairment of HLQL [6]. All five domains of the EQ-5D-5L improved after ECV. The overall score improved significantly mainly driven by significant improvements in the self-care, anxiety/depression, and mobility domains in patients with sustained sinus rhythm at follow-up. Also, the VAS on

global health improved significantly after ECV but only in patients with sustained sinus rhythm at follow-up.

ILR data showed that more than half of the patients experienced early relapse. Only about 60% of patients that suffered early relapses could be identified with conventional ECG at follow-up. It has been proposed that rhythm control may improve HRQL despite shorter AF recurrences (<24 h) [6]. In concordance, we could not demonstrate an association between HRQL improvement and ILR recurrence, while 12 lead ECG-confirmed sinus rhythm at follow-up showed a significant association with HRQL improvements. Class III antiarrhythmic drugs did significantly improve the rate of relapse-free sinus rhythm on ILR. A family history for defined cardiovascular pathology (AF or flutter, sudden cardiac death, coronary heart disease, heart failure or valve disease) increased the risk of AF recurrence after EC in our small cohort.

Limitations

The results should be interpreted in the light of several limitations of our study: Due to the extensive protocol with a multitude of investigations for every included patient relative few patients were included. As in any observational study, there was potential for selection bias and residual confounding factors. Further, the changes in primary and secondary outcomes were not compared to a control group. All patients were recruited and followed up at a single centre. Institutional bias can therefore not be excluded. As in all studies on HRQL that contain active questionnaires, the awareness of being investigated may alter the way participants behave with respect to outcome measures. Disease specific questionnaires for AF might have given a more nuanced view on the specific problems patients encounter during AF episodes. Finally only few women and no non-Caucasians could be included in this study. While this represents the typical referred patient at the only site of inclusion, it may impair generalizability.

Conclusion

This prospective pre- and post-ECV brain-MRI study revealed that silent brain infarction may occur despite guideline-compliant anticoagulation with DOAC. In our cohort, 1 patient (2.2%) developed silent brain infarction without clinical neurologic consequences. Early recurrence of AF was frequent. ECV positively affected HRQL in patients who maintained sinus rhythm at follow-up.

Acknowledgments

We thank Mari Brathovde at the medical faculty of Oslo University for statistical assistance.

Statement of Ethics

This study was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants. The trial was registered at and approved by the regional board for medical and health related research ethics (REK sør-øst C, nr.2016/133, id: 28217) and the local personal data safety board PV (16/04009). This work is conducted in line with the COPE guidelines.

Conflict of Interest Statement

Peter M. Andel received compensation for lectures and consulting from SOBI, AstraZeneca, and Novartis. Anne Hege Aamodt has received unrestricted research grants from Boehringer Ingelheim and compensation for lectures and consulting from Teva, Novartis, Abbvie, Roche, Pfizer, and Lundbeck. Dan Atar has received compensation for lectures and consulting from Amgen, Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Chiesi, BMS, MSD, Novartis, NovoNordisk, Pfizer, Pharmacosmos, Philips, Roche-Diagnostics, Sanofi, Takeda, and Vifor. He has received institutional grant support from BMS/Pfizer, Medtronic, Bayer, Roche-Diagnostics. Jostein Gleditch, Erik Melin, Mona Elisabeth Rootwelt-Revheim, Kjetil Steine have no conflicts of interest.

Funding Sources

This independent research was sponsored by the Bristol Myers Squibb-Pfizer Alliance.

Author Contributions

Peter M. Andel planned the outline of the manuscript, did the literature research and wrote the draft. Anne Hege Aamodt planned the research project and reviewed/contributed to the manuscript. Jostein Gleditsch helped evaluate the MRI examinations and reviewed/contributed to the manuscript. Erik Melin evaluated the MRI examinations and reviewed/contributed to the manuscript. Mona Elisabeth Rootwelt-Revheim was involved in planning the research project and reviewed/contributed to the manuscript. Kjetil Steine reviewed/contributed to the manuscript. Dan Atar planned the research project and reviewed/contributed to the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available as they contain information that could compromise the privacy of research participants as well as they are subject to ongoing research. The original data are available from the corresponding author (P.M.A.) upon reasonable request, except where restricted by GDPR liabilities.

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