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Risk Factors Influencing Long Term success of Electrical Cardioversion for Patients with Atrial Fibrillation–A Retrospective Service Evaluation

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Abstract

Atrial Fibrillation (AF) is a common arrhythmia associated with decreased quality of life and increased mortality. Treatment options include electrical cardioversion (ECV) to restore sinus rhythm. However, success rates at one year have been reported to be low and influenced by a range of factors. The aim of this study was to determine which factors influence patients' chance of being AF-free for one-year post-ECV in a real-world cohort. Consecutive patients were retrospectively identified from a database of patients undergoing ECV. Demographic data, clinical factors reported to influence AF-free following ECV (identified from an initial literature review) along with cardiac-rhythm at one year were recorded. From this data, univariate and multivariate logistical regression analysis were performed. A total of 195 patients met the inclusion and exclusion criteria. At one year 68 (34.4%) patients were AF-free. In univariate analysis, the absence of left atrial (LA) enlargement was the only significant factor (p=0.012) reduced likelihood of being AF-free. However, in multivariate analysis, 3 factors where associated with improved outcomes, the presence of hypertension (p=0.038), lack of LA enlargement (p=0.027), and the use of rate-control medication prior to ECV (p=0.025). Despite the world literature describing multiple factors influencing long-term maintenance of sinus rhythm following ECV, this study only identified 3 factors; hypertension, prior-medication with rate-control medications and lack of LA enlargement significantly increased being AF-free one year.

Keywords: DC cardioversion, Atrial fibrillation, Sinus rhythm, Outcomes.

Abbreviations and Acronyms: ACEi: Angiotensin Converting Enzyme inhibitor, AF: Atrial Fibrillation, CABG: Coronary Artery Bypass Graft, CAD: Coronary Artery Disease, CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, ECG: Electrocardiogram, ECV: Electrical Cardioversion, IHD: Ischaemic Heart Disease, LA: Left Atrial, LV: Left Ventricle, LVH: Left Ventricular Hypertrophy, MI: Myocardial Infarction, OSA: Obstructive Sleep Apnoea, RHD: rheumatic heart disease, SCI: Scottish Care Information, SR: Sinus Rhythm, TIA: Transient Ischaemic Attack.

Introduction

Atrial Fibrillation (AF) is the most common heart rhythm disorder in the developed world affecting 1–2% of the population [1-3]. Symptoms

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such as palpitations, breathlessness and reduced exercise tolerance can reduce quality of life, but importantly, intra-cardiac thrombi can develop causing embolic events such as stroke and ischaemic bowel [4]. Patients with an AF-related stroke have higher mortality, morbidity and length of hospital admission [5,6] and thus optimizing AF treatment is crucial.

The main clinical decision in AF management is whether to pursue rhythm control (aim for return to sinus rhythm) or a rate control (accepting permanent AF) strategy. Rate control is usually achieved by medication whereas rhythm control may be achieved by medication but may also need interventions such as electrical cardioversion (ECV). Rhythm control is usually indicated in patients who remain symptomatic despite adequate rate control therapy [3]. One advantage of ECV is that it has a high immediate success rate (greater than 90%), even for long lasting AF [7]. However, although initially successful, at the end of one year only 30-40% of patients will still be in sinus rhythm (SR) with the remainder needing further ECV within a year or alternate treatment strategies [8,9].

Many factors have been described that predict the maintenance of SR following ECV, which include, but are not limited to, the duration of AF [10-15], cardiac morphology such as atrial remodelling with left atrial (LA) enlargement [10-18], underlying coronary artery disease [10], significant valve disease [18], and age [8,10,12,14]. This study aimed to determine which of the risk-factors described in the literature influence the maintenance of long-term SR in a real-life cohort of patient undergoing ECV, by assessing cardiac rhythm at 1 year.

Methods

This was a retrospective cohort study carried out at a remote regional hospital in the North of Scotland serving a dispersed population of approximately 300,000. Consecutive patients attending for ECV over a 4-year period between April 2010 and March 2014 were included only the most recent ECV was assessed so that each patient was only included in the analysis once. Only patients with at least 1 year follow up data and outpatient ECV attempts which were included. Patients who were listed in the records but who cancelled the appointment were excluded.

To determine risk factors for long term success of ECV, a literature review was undertaken [19] which guided which factors were reported to influence maintenance of SR after ECV (Table 1). These identified factors were then collected from the patients' records and echocardiography database.

The initial data were collected prospectively in a proforma by the cardioversion specialist nurse. Verification and further data were collected from the digital Scottish Care information (SCI) store, containing immediate and final discharge letters, clinic letters, test results and any other correspondence. Any further data were then obtained from written case notes. The data were then analyzed in SPSS version 24. Sample characterization descriptive statistics with frequency tables for categorical data and normality tests for continuous data were performed. After checks of distribution for the continuous variables 'age' and 'duration of AF prior to referral' they were transferred into binary data. The cut-off point was chosen after considering the median of each variable. Therefore 'age' was categorized as 70 years or older, duration of AF prior to referral' was categorized in 3 or more months. The duration of AF prior to cardioversion procedure was from the first documented diagnosis of AF. 'Symptomatic vascular disease' was positive if there was any record of myocardial infarct (MI), angioplasty, ischaemic heart disease (IHD), coronary artery disease (CAD), stenting, coronary artery bypass grafting (CABG), transient ischaemic attack (TIA) or stroke in the medical history. Renal impairment was defined for eGFR <60 mL/min/m^2 or chronic kidney disease (CKD) stage 3 onwards. Rhythm control medications included amiodarone or dronedarone (no patients were on any additional rhythm control medications). Risk factors that occurred in very few cases (obstructive sleep apnoea (OSA), rheumatic heart disease (RHD), Chronic Obstructive Pulmonary Disease (COPD), prior ablation, number of shocks greater than 1) were not included in further analysis. Left ventricular (LV) impairment was defined as an ejection fraction less than 55% and left ventricular hypertrophy (LVH) was defined as intraventricular septum thickness in diastole greater than 1.2 cm. LV impairment and LVH were collapsed into one combined factor to avoid multi-collinearity as those two independent variables were highly inter-correlated. Left atrial enlargement was defined as LA diameter greater than 2.3 cm/m^2. Valvular disease included an echocardiographic evidence of any mitral (moderate or above), aortic, tricuspid, or pulmonary regurgitation (Table 1).

The primary outcome was AF-free at 1 year following ECV. A 5-week electrocardiogram (ECG) was carried out post-ECV but no further routine follow-up was organized afterwards. ECG's one 1 year after were analyzed to assess whether in sinus rhythm. Patients who had prior ECV were included and when patients had more than one ECV, then only the most recent appointment was recorded. Therefore, the duration was determined from the date of recurrence of AF after the previous appointment. If no information was found regarding recurrence of AF, the patient was assumed to still be in sinus rhythm at one year follow up.

All risk factors for the first model were cross-tabulated with the outcome 'AF free for one year' using Chi-square test of association, except in cases where more than 80% of expected frequencies were of value 5 or less, when Fisher's exact test was used instead. For all 2 × 2 tables continuity correction was used instead of Pearson Chi-Square. Unadjusted odds ratios for each risk factor against 'AF free for one year' were conducted using binary logistic regression.

Direct logistic regression was performed to assess the impact of a number of factors on the likelihood that patients would be AF free for one year after ECV. The model contained fifteen risk-factor variables (age, gender, smoking history, symptomatic vascular disease hypertension, diabetes, renal impairment, hyperthyroid disease duration greater or equal

to 3 months, LV impairment and/or LVH, valvular disease, LA enlargement, no rhythm control medication, no rate control medication). For the multivariate analysis, logistic regression was performed with all variables included, despite not showing strong association in the univariate analysis.

For this study, Caldicott Approval was obtained to access to patients' medical information and the protocol was confirmed to be a service evaluation by the NHS Highland Research & Development Office.

Results

Risk and influencing factors included in the service evaluation for the long-term success of being AF free are shown in Table 1 and baseline characteristics are shown in Table 2.

Every patient who met the inclusion criterion was identified from the patient records at the Cardioversion clinic. From initially 364 consecutive cases, 169 patients were excluded for reasons such as delayed ECV, further repeated ECV, cancelled, left area or died, ablation performed alternatively, spontaneous return to sinus rhythm and no follow-up data at one year (Figure 1).

Of the 195 patients, 34.9% (n=68) were in sinus rhythm (SR) (38.0% (n=54) of males and 26.4% (n=14) of females) at 1 year. Significantly more female patients suffered from renal impairment ($p<0.001$) and hyperthyroid disease ($p<0.001$). In addition, men were more likely to have received an ACEi medication ($p=0.04$) but there was no observed difference in rate or rhythm control medication or presenting with prolonged AF greater than 3 months (Table 3). There were no cases of valvular AF such as mitral stenosis or patients with artificial heart valves.

Of the general risk factors thought to determine maintenance of sinus rhythm, the three most prevalent baseline factors were found to be LA enlargement (66.7%, n=130) hypertension (58.0%, n=111)) and age>70 years (41.5%, n=81).

While all of the 15 factors were assumed to influence the patients' chance to be AF free for one year after ECV, only LA enlargement showed statistically significant influence on the outcome (OR 0.451; $p=0.012$) in the univariate analysis (Table 3). Using multivariate analysis; treated hypertension (OR 2.197; $p=0.038$), use of rate control medication (OR 0.195; $p=0.050$) and lack of LA enlargement (OR 0.446; $p=0.027$) where the only significant factors influencing being AF free at one-year post ECV (Table 4).

Discussion

This study assessed clinical risk factors that influenced outcome following ECV for AF in a real-world cohort. Our findings demonstrated that relatively few of the traditional risk factors previously reported to influence AF risk actually influenced SR at one year. These results suggest that a greater proportion of patients that previously indicated may be suitable for ECV. Alternatively, it could be argued that patients that were thought to be good candidates through lack of risk factors, have similar chances of success compared to those with more risk factors. In any case, this shows that each patient's case should be considered carefully for ECV.

In contrast to previous studies, no significant impact on being AF-free effect was found with age, gender, smoking status, symptomatic vascular disease, diabetes, renal impairment, hyperthyroid disease, duration of AF more than 3 months, LV impairment/hypertrophy, valvular disease, rhythm control or presence of ACE inhibitors. Fewer patients than expected had diagnosed diabetes or COPD, which could be due to symptoms that seem due to COPD or clinicians are less likely to refer them for ECV (as these conditions often co-exist with frailty), as they think maintenance of sinus rhythm would be less likely to be successful [14].

In the multivariate analysis, the finding that presence of treated hypertension was associated with the patient being AF free ($p=0.038$) might be explained due to hypertension

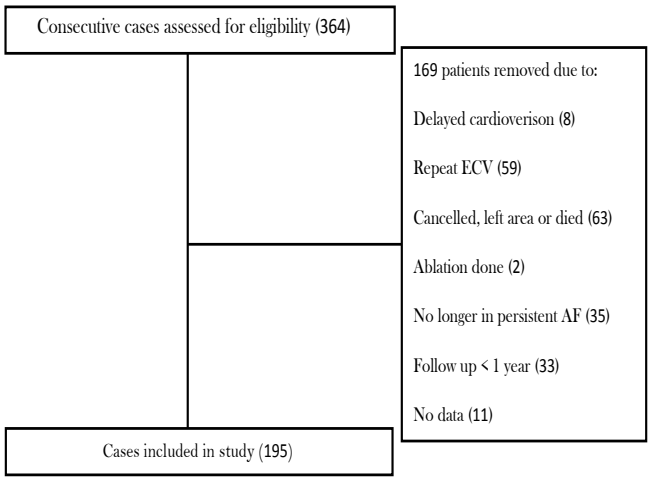

Figure 1: Consort diagram for exclusion criteria.

Table 1: Clinical factors included in service evaluation.

Patient factors
Gender
Age
Smoking Status
Co-morbidities
COPD
Hypertension
Symptomatic vascular disease
Diabetes
Hyperthyroidism
Renal disease
Echocardiographic factors
Left ventricular impairment
Left ventricular hypertrophy
Valvular disease
Increase left atrial size
Medication
Use of rate-control medication (beta-blocker)
Use of rate-control medication (calcium-channel blocker)
Use of rhythm-control medication (amiodarone / dronedarone)
Angiotensin converting enzyme inhibitor
AF factors
Duration of AF

Table 2: Patient demographics and gender differences.

Risk factors	Total % (n)	male (m) % (n)*	female (f) % (n)*	p-value (m vs. f)
AF free after one year	34.9 (68)	38 (54)	26.4 (14)	0.179
Male gender	72.8 (142)	n/a	n/a	n/a
Age >70	41.5 (81)	35.2 (50)	58.5 (31)	0.06
Smoker/ex-smoker	14.4 (28)	16.9 (24)	7.5 (4)	0.153
COPD**	2.6 (5)	3.5 (5)	0 (0)	0.326
Hypertension	58.0 (111)	56.7 (80)	58.5 (31)	0.954
Symptomatic vascular disease	28.9 (56)	30.3 (43)	25.0 (13)	0.589
Diabetes	12.8 (25)	13.4 (25)	11.3 (6)	0.887
Hyperthyroidism**	7.7 (15)	2.8 (4)	20.8 (11)	<0.001
Renal disease**	7.7 (15)	2.8 (4)	20.8 (11)	<0.001
LV impairment	26.7 (52)	28.9 (41)	20.8 (11)	0.338
LV hypertrophy	2.6 (5)	3.5 (5)	0 (0)	0.382
Valvular disease	20.5 (40)	17.6 (25)	28.3 (15)	0.148
LA enlargement*	66.7 (130)	63.4 (90)	75.5 (40)	0.172
Beta-blocker*	70.3 (137)	71.4 (100)	74.0 (37)	0.869
Calcium-channel blocker*	23.1 (45)	22.7 (32)	25.5 (13)	0.833
ACEi*	39.5 (77)	44.4 (63)	27.8 (14)	0.040
Rhythm-control medication*	25.1 (49)	24.1 (34)	28.8 (15)	0.629
Duration of AF >3 months*	26.2 (51)	26.1 (37)	26.4 (14)	1.000
Prior ECV	30.8 (60)	30.3 (43)	32.1 (17)	0.759

*valid percent excluding missing cases (LA enlargement=1, beta-blocker=5, calcium channel blocker=3, Angiotensin converting enzyme inhibitor (ACEi)=5, rhythm medication=2. **Fisher`s exact test used instead of Chi-square test of association.

Table 3: Univariate analysis for odds-ratio of being AF free at 1 year.

Risk/influence factor	% (n)	OR (95% CI)	p-value
Male Gender	72.8 (142)	1.709 (0.850-3.437)	0.132
Age >70 years	36.0 (81)	0.977 (0.537-1.777)	0.940
Smoker	14.4 (28)	1.487 (0.658-3.357)	0.340
HTN	57.2 (111)	1.779 (0.964-3.280)	0.065
Symptomatic vascular disease	28.9 (56)	1.076 (0.561-2.061)	0.826
Diabetes	12.8 (25)	1.058 (0.441-2.540)	0.899
Hyperthyroidism	7.7 (15)	0.653 (0.200-2.136)	0.481
Renal impairment	7.7 (15)	0.449 (0.122-1.651)	0.228
AF duration ≥ 3month	75.4 (51)	0.805 (0.399-1.622)	0.544
LV impairment and/or LVH	28.2 (55)	0.781 (0.400-1.522)	0.467
Valvular disease	20.5 (40)	1.155 (0.561-2.375)	0.696
LA enlargement	67.0 (130)	0.451 (0.242-0.839)	0.012
No rate control	7.9 (14)	0.287 (0.062-1.323)	0.109
No rhythm control	25.1 (49)	0.912 (0.467-1.798)	0.799
No ACE inhibitor	40.5 (77)	1.408 (0.763-2.599)	0.274

Table 4: Multivariate analysis for odds-ratio for being AF free in 1 year.

Risk/influence factor	% (n)	OR (95% CI)	p-value
Male gender	26.2 (47)	0.636 (0.261-1.553)	0.321
Age >70 years	38.5 (75)	0.866 (0.407-1.842)	0.708
Smoking	14.5 (26)	0.830 (0.315-2.188)	0.707
Symptomatic vascular disease	28.5 (51)	1.153 (0.315-2.188)	0.720
Hypertension	57.0 (102)	2.197 (1.046-4.615)	0.038
Diabetes	12.8 (23)	0.676 (0.241-1.901)	0.458
Renal impairment	8.4 (15)	0.356 (0.078-1.625)	0.183
Hyperthyroidism	6.7 (12)	0.720 (0.093-2.663)	0.414
AF duration ≥ 3month	25.7 (46)	0.720 (0.320-1.616)	0.425
LV impairment and/or LVH	29.6 (53)	0.657 (0.297-1.452)	0.299
Valvular disease	20.1 (36)	2.053 (0.782-5.391)	0.144
LA enlargement	65.9 (118)	0.446 (0.218-0.913)	0.025
No rate control medication	7.8 (14)	0.195 (0.038-1.002)	0.050
No rhythm control medication	75.4 (135)	0.611 (0.273-1.365)	0.230
No ACEi	59.2 (106)	2.014 (0.957-4.240)	0.065

being a treated condition in this cohort as shown by the percentage of patients who are on additional medication such as ACE inhibitors, calcium-channel blockers and beta-blockers [8,13,14,17,20,21] (92.9%). In addition, the significance of the lack of rate-control medication on the chance of being AF-free at one year (p=0.050) suggesting that appropriate medication has a large role in determining maintaining sinus rhythm.

LA enlargement was the most prevalent echocardiographic risk factor affecting over two thirds (67.9%) of the patients and our study showed that this factor significantly decreases AF-free outcomes one year after ECV (p=0.027). This effect is possibly be explained by atrial remodelling favouring perpetuation of AF [22] and thus with shorter duration of AF, LA enlargement is less significant influencing factor as seen in previous literature [23,24]. In addition, the cycle of atrial remodelling may create a substrate for AF and AF perpetuating more remodelling [25].

This study has several limitations. This was a retrospective study in a relatively small population. Given the negative findings for traditional risk factors, one explanation is type 2 error from the limited sample size. However, the population was consecutive and thus representative of 'real life' within a predominantly Caucasian population. Another limitation was that sinus rhythm was assumed at one year if there was no documentation of reverting back to AF. This might have the impact of missing some patients who had atrial fibrillation, thus the one-year success of ECV may possibly be less than we have quoted.

Overall, the long-term success rate was low, and this study demonstrates the need for the development of a risk score for long term success of ECV to provide a better tool for cardiologists to select the most suitable candidates for ECV. Additionally, these findings add to the current

limited evidence to help guide patients and staff about the realistic chance of long-term success after ECV and thus the appropriateness of this intervention.

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