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Late recurrence of atrial fibrillation and flutter in patients referred for elective electrical cardioversion

Aim	The primary aim was to ascertain long-term rates of atrial fibrillation (AF) recurrence in this all-comer patient population undergoing elective electrical cardioversion (DCR). Secondary aims included procedural DCR success, clinical predictors of long-term maintenance of sinus rhythm (SR) and AF related hospitalizations.
Material and Methods	A retrospective cohort study was conducted. Consecutive patients (n=316) undergoing elective DCR were included.
Results	Successful immediate reversion to SR was attained in 266 (84%) of patients. 224 (84%) patients were followed up for a median period of 3.5 years (IQR 2.7–4.3). Most patients (150 [67%]) had recurrence of AF/flutter at a median time of 240 days. Clinical predictors of AF recurrence included a history of AF (HR 0.63, p=0.038) and a dilated left atrium (HR 4.13, p=0.048). Maintenance of SR was associated with fewer unplanned hospitalizations for AF (HR 3.25, p<0.01).
Conclusion	There was high procedural success post DCR. However, long-term rates of AF recurrence were high, and AF recurrences were associated with increased hospitalizations. These findings underscore the importance of clinical vigilance and multi-modal management as part of a comprehensive and effective rhythm control strategy.

Keywords	Atrial Fibrillation; cardioversion
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Introduction

Atrial fibrillation (AF) and atrial flutter are common cardiac arrhythmias. Progression from paroxysmal to persistent AF occurs due to adverse electrical and structural atrial remodelling and is associated with increased risk of heart failure (HF) and stroke [1]. Compared to patients in sinus rhythm (SR), patients with AF have increased rates of cardiac mortality, stroke [2] and reduced quality of life [3]. If left untreated, AF can cause further structural heart disease, such as left ventricular (LV) systolic impairment or atrial dilatation resulting in valvular regurgitation [4]. AF presents a significant burden on the healthcare system, since 10–40% of patients with AF are hospitalized each year [2, 5]. AF may be treated with a rate control strategy where the goal is to control the ventricular rate and accept longstanding AF. An alternative is a rhythm control strategy which aims to restore SR by a multidisciplinary approach with non-pharmacological interventions for modifiable risk factors combined with pharmacotherapy and procedures such as electrical cardioversion (DCR) and ablation procedures [2, 6]. The major benefit of a successful rhythm control strategy is improved symptoms [3]. This which must be balanced against higher rates of hospitalization and adverse events arising from more intensive anti-arrhythmic medications, procedures, and potential complications [7].

DCR aims to immediately restore SR, and it may additionally clarify the contribution of AF in patients with multifactorial symptoms [2, 6]. Initial DCR procedural success rates are typically very high [8], with SR maintained for up to one month in many series [8–11]. However, there is little information regarding longer term maintenance of sinus rhythm and how this relates to outcomes, such as hospitalization.

The aim of this retrospective cohort study was to determine longer term maintenance of SR of patients undergoing elective DCR for persistent AF and atrial flutter. Secondary outcomes included: DCR success rates, clinical predictors of AF recurrence, periprocedural safety, and other clinical outcomes including hospitalization for HF or AF and all-cause mortality.

Material and Methods

A retrospective cohort study was undertaken of 316 consecutive patients with persistent AF or flutter, who

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from January 2016 to December 2018, were referred for elective DCR at a tertiary hospital in Melbourne, Australia. The institutional ethics department advised that ethical approval was not required due to the nature of the collected data.

The baseline characteristics of the patients are shown in Table 1. The study protocol, including DCR success and follow-up rates, is illustrated in Figure 1. DCR was performed under general anaesthesia using a biphasic defibrillator and up to three applications at an energy up to 200 Joules. Recurrence of AF was determined by a combination of clinical review, ECG analysis, ambulatory ECG monitoring, and interrogation of an implantable cardiac electronic device.

Left atrial (LA) size and LV systolic function were evaluated with transthoracic echocardiography. LV function was quantified according to standard definitions, with LV ejection fractions of 41–51%, 30–40%, and <30% for males and 41–53%, 30–40%, and <30% for females defined as mildly, moderately, and severely depressed LV systolic function, respectively. Indexed LA volumes of 35–41 mL/m^2, 42–48 mL/m^2 and >48 mL/m^2 were defined as mildly, moderately, and severely dilated, respectively [12].

Survival curves for freedom from AF recurrence were determined using the Kaplan-Meier method, and the median and interquartile range values are reported. Baseline characteristics are reported as either numbers (percentage), mean ± standard deviation (SD), or median (interquartile range (IQR)). Predictors of an immediately successful cardioversion were compared using logistic regression analysis and are reported as odds ratios (OR) with 95% confidence intervals (CI). Predictors of AF recurrence were compared using the log-rank test, and univariate predictors with $p<0.05$ were included in a multivariate model using Cox proportional hazards regression and are reported using a hazard ratio (HR) with 95% confidence intervals. Statistical analyses were performed with STATA version 13.1 (STATAcorp, College Station, TX, USA).

Results

Review of medical records identified 316 eligible patients (mean age 66±11 yrs, 72% male, Table 1). The median waitlist time from referral to cardioversion was 69 days (range 4–251 days). Successful reversion to SR was attained in 266 (84%) patients. Among patients who had successful reversion to SR, complete follow-up data were available for 224 (84%) patients, who were followed up for a median period of 42 mos (IQR 2.7–4.3). The majority of patients (150 [67%]) had recurrence of AF or flutter at a median time of 240 days (IQR 49–497) (Figures 1 and 2).

Atrial Flutter

64 patients were in atrial flutter at the time of their DCR, and a successful reversion to SR was obtained in 60 (94%). Of those, 51 (85%) patients completed follow-up with 32 (63%)

Figure 1. Number of patients undergoing DCR and included in the study protocol

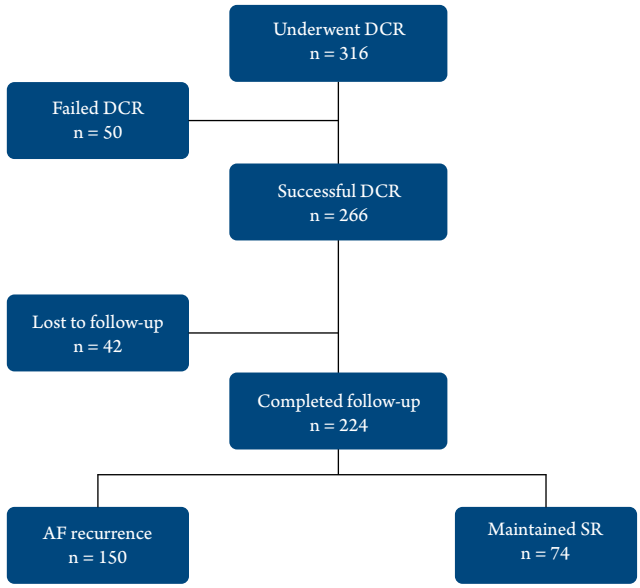


Figure 2. Kaplan-Meier curve for AF recurrence free survival in the entire population

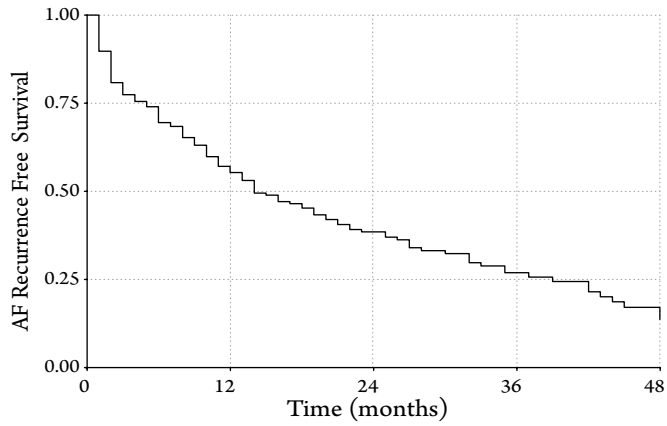


Figure 3. Kaplan-Meier curve for AF recurrence free survival in the entire population, comparing patients with new-onset AF to those with a past history of AF, unadjusted $p<0.01$

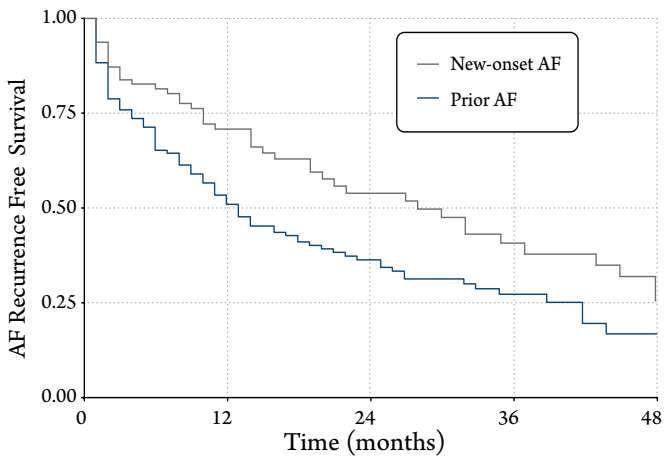


Table 1. Baseline characteristics and clinical outcomes

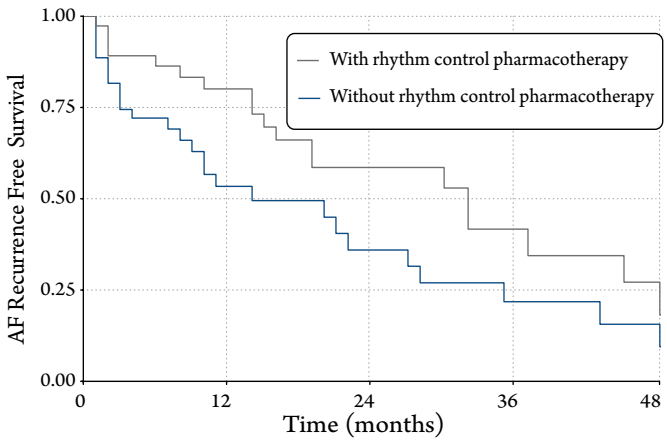
Clinical characteristic or outcome	n=316
Age (years)	66±12
Male	226 (72%)
Atrial flutter	65 (21%)
$CHADS_2$-VASc	2.5±1.6
New-onset AF	130 (41%)
Prior DCR	82 (26%)
Prior ablation	16 (5.1%)
Waitlist time (days)	69±46
Heart Failure	122 (39%)
Ischemic heart disease	79 (25%)
Hypertension	187 (59%)
Diabetes	63 (20%)
Stroke/TIA	22 (7.0%)
Chronic kidney disease (eGFR <30mL/min/1.73m²)	43 (14%)
Body mass index (kg/m²)	30.3±12
Obstructive sleep apnea	51 (16%)
High Alcohol Intake (≥4 standard drinks per day)	44 (14%)
LA dilatation (N = 199)	
≥ mild	183 (94%)
≥ moderate	123 (63%)
≥ severe	36 (18%)
LV systolic dysfunction (N = 199)	
≥ mild	93 (47%)
≥ moderate	50 (25%)
≥ severe	2 (12%)
Anti-arrhythmic therapy	
Amiodarone	93 (29%)
Sotalol	76 (24%)
Flecainide	6 (1.9%)
Beta blocker (excluding sotalol)	170 (54%)
Cardiac selective calcium channel blocker	27 (8.5%)

Data are number (percentage) or mean ± SD.

Table 2. Univariable analysis of risk factors predicting immediate cardioversion failure (n=316)

Clinical characteristic	Odds Ratio (95% CI)	p value
Age	1.00 (0.97-1.02)	0.87
Male gender	0.19 (0.32-1.13)	0.11
Atrial flutter	0.29 (0.10-0.84)	0.02
CHA_2DS_2-VASc	0.86 (0.71-1.05)	0.13
New-onset AF	1.80 (0.97-3.33)	0.07
Prior DCR	0.57 (0.07-4.6)	0.60
Prior ablation	1.85 (0.57-6.04)	0.31
Waitlist time (per day)	1.00 (0.94-1.01)	0.56
Heart Failure	1.07 (0.57-1.97)	0.84
Ischaemic heart disease	0.52 (0.23-1.16)	0.11
Hypertension	0.85 (0.46-1.56)	0.60
Diabetes	0.61 (0.26-1.42)	0.25
Stroke/ TIA	0.83 (0.24-2.90)	0.77
Chronic kidney disease (eGFR <30 mL/min/1.73m²)	0.36 (0.11-2.21)	0.10
Body mass index	0.99 (0.96-1.01)	0.87
Obstructive sleep apnoea	1.14 (0.52-2.51)	0.75
High alcohol intake	1.23 (0.59-2.58)	0.58
CHA_2DS_2-VASc score	0.86 (0.71-1.045)	0.13
HATCH score	0.93 (0.74-1.16)	0.49
FINCV score	1.05 (0.87-1.27)	0.59
LA dilatation (≥ mild)	0.96 (0.20-4.61)	0.96
LV systolic dysfunction (≥ mild)	0.66 (0.31-1.40)	0.28
Rhythm control pharmacotherapy	1.15 (0.63-2.13)	0.65

Figure 4. Kaplan-Meier curve for AF recurrence free survival in patients with new-onset AF (n=87), comparing those prescribed rhythm control pharmacotherapy (amiodarone, sotalol or flecainide) to those not prescribed rhythm control pharmacotherapy, unadjusted p=0.028



experiencing recurrence of AF/flutter at a median time of 296 (IQR 75–655) days.

New-onset AF

124 patients had no prior history of AF/flutter. 107 (86%) of these underwent a successful reversion to SR, and 91 (85%) completed follow-up with 51 (56%) patients experiencing a recurrence of AF/flutter at a median time of 311 (IQR 87–669) days (Figure 3).

Predictors of successful DCR

Patients in atrial flutter were significantly more likely to undergo a successful cardioversion (OR 0.29 [95% CI 0.10–0.84], p=0.023) than patients in atrial fibrillation (Table 2). Other patient factors and pharmacotherapy were not statistically significant. Within the subgroup of patients with atrial flutter, there was a trend toward successful

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cardioversion for patients referred after their first episode of flutter, p=0.05.

Predictors of AF recurrence

Univariate analysis showed that new-onset AF was the only significant protective factor (HR 0.57, [95% CI 0.40–0.81], p=0.0015.). LA dilatation on a pre-DCR echocardiogram (available in 199 [85%] patients) (HR 3.85 [95% CI 0.928–16.0], p=0.045) and a prior DCR (HR 1.55 [95% CI 1.07–2.23], p=0.020) were significant predictors of AF recurrence (Table 2). Multivariate analysis showed that LA dilatation (HR 4.13 [95% CI 1.01–16.8], p=0.048) and initial AF presentation (HR 0.63 [95%CI 0.40–0.97], p=0.038) remained significant predictors of AF recurrence (Table 3).

In patients presenting with new-onset AF, the only significant univariate predictor of reduced AF recurrence was rhythm control pharmacotherapy with amiodarone, sotalol, or flecainide (HR 0.51 [95% CI 0.28–0.94], p=0.03, Figure 4). No such trend was observed in patients with a prior history of AF (HR 0.97 [95% CI 0.65–1.46], p=0.89).

Clinical outcomes

Of the 224 patients who underwent a successful DCR and completed follow-up; there were 14 hospital presentations with symptomatic AF, three presentations with symptomatic bradycardia requiring pacemaker insertion, and 16 heart failure presentations of which four were related to AF recurrence. 24 patients died of which four were due to cardiac causes. Maintenance of SR was associated with fewer hospitalizations for AF (HR 3.25, 95%CI 1.87–5.65, p<0.01), but not for HF hospitalizations, cardiac specific, or all-cause mortality (Table 2).

Procedural complications

Of the 316 patients who underwent DCR; one (0.3%) patient survived an asystolic cardiac arrest requiring emergent pacing support and another two (0.6%) patients developed significant bradycardia and required inpatient permanent pacemaker insertion in a non-emergent setting. One patient was non-compliant with anticoagulation and suffered a stroke thirteen days after DCR.

Discussion

The three major findings of our study are:

1) AF recurrence is common within one year after elective DCR (Figure 2).
2) AF recurrence was significantly more common in patients with a previous diagnosis of AF, as well as those with a dilated LA (Figure 2 and Table 3).
3) Patients with an AF recurrence experienced a higher rate of unplanned AF-related hospitalization (Table 3).

While a successful DCR resulting in immediate restoration of sinus rhythm is typical, our study has shown that most patients

Table 3. Univariable and multivariable analysis of risk factors predicting AF recurrence in patients who underwent a successful DCR and completed follow-up (n=224)

Clinical characteristic	Univariable		Multivariable	
	Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value
Age	1.00 (0.99–1.01)	0.92	–	–
Male gender	0.75 (0.53–1.06)	0.097	–	–
Atrial flutter	0.75 (0.51–1.12)	0.15	–	–
CHA_2DS_2-VASc	0.99 (0.90–1.16)	0.88	–	–
New-onset AF	0.57 (0.40–0.81)	<0.01	0.63 (0.40–0.97)	0.04
Prior DCR	1.55 (1.07–2.21)	0.02	1.25 (0.80–1.95)	0.32
≥2 shocks	1.18 (0.80–1.76)	0.41	–	–
Prior ablation	1.32 (0.65–2.7)	0.44	–	–
Waitlist time (per day)	1.00 (1.00–1.01)	0.37	–	–
Heart failure	0.82 (0.59–1.18)	0.25	–	–
Ischaemic heart disease	0.85 (0.59–1.22)	0.38	–	–
Hypertension	1.08 (0.78–1.59)	0.62	–	–
Diabetes	0.89 (0.60–1.30)	0.57	–	–
Stroke/TIA	0.92 (0.46–1.81)	0.80	–	–
Chronic kidney disease (eGFR 30 mL/min/1.73 m^2)	1.09 (0.70–1.72)	0.69	–	–
Body mass index	0.99 (0.97–1.02)	0.93	–	–
Obstructive sleep apnoea	1.11 (0.72–1.76)	0.62	–	–
High alcohol intake	1.21 (0.77–1.93)	0.42	–	–
LA dilatation (≥ mild)	3.85 (0.93–16.09)	0.04	4.13 (1.01–16.83)	0.04
LV systolic dysfunction (≥mild)	0.89 (0.61–1.39)	0.57	–	–
Rhythm control pharmacotherapy	0.75 (0.52–1.11)	0.11	–	–
CHA_2DS_2-VASc score	0.99 (0.90–1.1)	0.88	–	–
HATCH score	0.93 (0.82–1.05)	0.21	–	–
FINCV score	1.04 (0.94–1.15)	0.49	–	–
Clinical outcome				
HF hospitalization	1.02 (0.55–1.91)	0.94	–	–
AF hospitalization	3.25 (1.92–5.71)	<0.01	–	–
Mortality (all cause)	1.35 (0.78–2.31)	0.28	–	–

experience an AF recurrence. Such recurrences occur due to the presence of an abnormal atrial myocardial substrate and ongoing triggered activity, which leads to disease progression and persistent AF. Therefore, the principles of a rhythm control strategy include risk factor modification, pharmacological therapy, and indicated DCRs and electrophysiological ablation procedures [6]. The high rates of AF recurrence we observed highlight the importance of long-term clinical follow-up and utilization of these multi-modal therapies. Potential benefits from a rhythm control strategy include improved symptoms [3] which must be balanced against the increased incidence of adverse drug-reactions and procedural complications. The major risk of DCR is bradycardia requiring permanent pacemaker implantation, which occurred in three patients (1%) of our series. In addition, a DCR with restoration of sinus rhythm can clarify the contribution of AF with multifactorial symptoms and guide whether a rate-control or rhythm-control strategy is later pursued, depending on the short-term symptomatic response [2].

Predictors of DCR success and AF recurrence

As AF progresses, electrical and structural remodelling of the atrial myocardium results in progressive LA dilatation, which can be measured by transthoracic echocardiography. Indeed, our study identified that a dilated LA is a significant predictor of AF recurrence, as is consistent with previous studies [13]. Conversely, early restoration of sinus rhythm can partially reverse pathophysiologic changes and reduce LA dilatation [14], as evidenced by the significant reduction in recurrence we observed in patients with newly diagnosed AF. LA strain, as measured by speckle-tracking echocardiography, is a novel technique that promises to identify early atrial myopathy in patients with normal LA volume. It may be a further predictor of AF recurrence [14].

Regarding other predictors of AF recurrence; previous studies have reported that a higher arrhythmic burden correlated with cardiovascular and epidemiological risk factors [8–10], although this was not particularly evident in our study, (Table 2). While there is a consensus that traditional cardiovascular risk factors contribute to AF recurrence, the magnitude of their individual contributions varies across studies. This reflects the variety of scoring systems developed to stratify probability of DCR success or short-term risk AF recurrence, including CHA_2DS_2-VASc [9, 15], HATCH [16], AF-CVS [8], and FinCV [10], none of which were significant in our study, (Table 2 & 3). Notably, none of these scoring systems include assessments of LA size. Other studies have shown that increased LA size and AF duration are the major determinants of AF recurrence [11, 13], This was the case when adjustment were made for cardiovascular risk factors on multivariate analysis, as it is these risk factors that drive the underlying pathological process of atrial remodelling and the development of an arrhythmic substrate. However, this does not lessen the importance of risk factor modification, which is an increasingly recognized component of AF management. In fact, non-pharmacological interventions, such as weight loss [17] and alcohol cessation [18] have demonstrated efficacy in reducing AF recurrence in randomized trials. Also, treatment of obstructive sleep apnoea has shown to be beneficial in observational trials [19].

Regarding pharmacotherapy, we have demonstrated that rhythm control drugs, including amiodarone, sotalol and flecainide significantly reduce AF recurrence in patients with a new diagnosis of AF (HR 0.51 [95% CI 0.28–0.94], p 0.028). In contrast, such medications did not reduce AF recurrence in patients with an established diagnosis of AF. This was likely due to a correlation between such pharmacotherapy and increasing disease severity and atrial remodelling. Notably, 142 (46%) patients were not prescribed a rhythm control agent at the time of their DCR. We speculate this was to avoid the well-known increased risk of adverse drug reactions or that such patients may have been intolerant of pharmacotherapy and instead underwent aggressive risk factor modification and/or early consideration of ablation procedures. While previous studies have shown a mortality signal for patients taking rhythm control pharmacotherapy [20], this was not observed in our small study for either all cause or cardiac specific mortality.

AF related hospitalizations and clinical outcomes

We report a three-fold increase in AF related hospitalizations in patients who failed to maintain sinus rhythm at one year. The 14 patients with symptomatic AF outnumbered three patients who presented with symptomatic bradycardia requiring pacemaker implantation. Given that around 15% of all hospitalizations are AF related [5], any intervention which can reduce this has clear implications for healthcare resource utilization.

Limitations

This study has all of the limitations inherent to its observational, retrospective and single-centre design. Our reliance on documented AF recurrences reflects current clinical practice but under-estimates the true arrhythmic burden as episodes in the community may be asymptomatic or under-reported. Emerging wearable devices with continuous heart rate monitoring capability lead to increased detection of subclinical AF recurrence [21] and are likely to redefine standards of care as they increase in popularity [22].

Conclusion

Consistent with previous studies, we found high procedural and short-term DCR success. The major findings of this study are that long term rates of AF recurrence were high, and such recurrences were associated with increased hospitalizations.

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Predictors of AF recurrence included a prior history of AF, as well as a dilated LA. This reinforces the importance of ongoing clinical vigilance, risk factor modification, pharmacotherapy, timely referral for repeat DCR, and indicated AF ablation procedures as elements of a comprehensive rhythm control strategy to prevent the otherwise inexorable progression to permanent AF.

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