

A comparison of early versus delayed elective electrical cardioversion for recurrent episodes of persistent atrial fibrillation: A multi-center study

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ABSTRACT

Background: Due to barriers to accessing timely elective electrical cardioversion (CV) for persistent AF (PeAF), we adopted a policy of instructing patients to present directly to the Emergency Department (ED) for CV.

Objective: We compare a strategy of Emergency CV (ED-CV) versus Elective CV (EL-CV) for treatment of symptomatic PeAF.

Methods: Between 2014 and 7, we evaluated 150 patients undergoing CV for PeAF. ED-CV patients were provided an AF action plan for recurrent symptoms and advised to present to ED within 36 h. EL-CV patients followed standard care, including cardiologist referral and placement on an elective hospital waiting list. Follow-up was 12 months.

Results: We included 75 consecutive ED-CV patients and 75 consecutive EL-CV patients. ED-CV patients had a significantly shorter median AF duration prior to CV (1 day vs 3 months; $p < 0.01$) and less overall AF-related symptoms at 12 months (modified EHRA symptom score ≥ 2 in 44% vs 72%; $p = 0.005$). Time to next AF recurrence was longer in the ED-CV group (295 ± 15 vs 245 ± 15 days; logrank $p = 0.001$), as was time to AF ablation referral (314 ± 13 vs 276 ± 15 days; logrank $p = 0.01$). Baseline LA area was similar (ED-CV 27 ± 4 cm² vs EL-CV 28 ± 11 cm²; $p = 0.67$), however EL-CV had larger atria at follow-up (31 ± 8 vs 26 ± 6 cm²; $p = 0.01$). There were no complications in either group.

Conclusion: ED-CV is an acceptable strategy for symptomatic PeAF. In addition to reduced time spent in AF and improved symptom scores, this strategy may also slow progression of atrial substrate & delay onset of next AF episode.

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1. Background

As an emerging epidemic of cardiovascular disease, increasing numbers of patients are utilizing electrical cardioversion (CV) for treatment of symptomatic persistent atrial fibrillation (PeAF). The timing of CV following AF recurrence is dictated by a combination of factors, including patient symptoms, physician preference and resource availability. In addition to adverse effects on quality of life from prolonged AF duration,

progressive adverse electrical and structural changes occur in the atria at different time points following arrhythmia onset [1]. The clinical implications of delayed CV for intermittent PeAF are not well categorized, although some studies suggest these patients are at higher risk of AF recurrence [2]. Due to barriers to accessing early elective cardioversion, including time taken to see a family physician, obtain specialist referral and wait for a scheduled CV, we adopted a policy of instructing patients to present directly to the Emergency department for early cardioversion.

We sought to compare a strategy of early 'Emergency' CV versus delayed 'Elective' CV for treatment of intermittent PeAF. We hypothesized that benefits of early CV may extend beyond symptoms, including prevention of adverse remodelling, reduction in recurrence risk and potentially lower utilization of AF ablation.

Abbreviations: AF, Atrial fibrillation; PeAF, Persistent atrial fibrillation; CV, Electrical cardioversion; LA, Left atrium; SD, Standard deviation; ED, Emergency department; ED-CV, Emergency cardioversion; EL-CV, Elective cardioversion.

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2. Methods

2.1. Study design

In this observational retrospective cohort study, we evaluated 150 patients presenting with symptomatic PeAF presenting to two centres in metropolitan Melbourne between 2/2014 and 7/2017. All included patients had a history of persistent AF, as defined by a previous or current episode of AF lasting longer than 7 days. We sought to compare two patient groups – those treated with Emergency vs Elective cardioversion strategies and included 75 consecutive patients from each group. Follow-up occurred over 12 months.

Exclusion criteria included: (1) persistent AF with prior early re-initiation of AF within 1 month; (2) paroxysmal AF, with a prior history of spontaneous reversion within 7 days or chemical reversion; (3) atrial flutter as the only documented rhythm; (4) permanent AF, where sinus rhythm was unable to be restored; (5) asymptomatic or minimally symptomatic patients as they are frequently unsure of time of symptom onset; (6) previous AF ablation; and (7) decompensated heart failure.

2.2. Emergency cardioversion (ED-CV) group

Patients with a past history of CV for symptomatic PeAF were provided an AF action plan during their outpatient visit to follow in the event of recurrent symptoms. Patients were advised to document time of symptom onset and present to the emergency department within 36 h, and fast for 6 h prior to arrival. Consistent with guidelines, CV is routinely performed in un-anticoagulated patients within 48 h of symptom onset without transesophageal echocardiography guidance or if anticoagulation is uninterrupted in those with AF onset >48 h. An emergency department physician assessed each patient and propofol was administered for sedation during CV. Additional antiarrhythmics were advised at clinician discretion. Patients with unclear onset of AF who were not consistently anticoagulated for the preceding 4 weeks were not cardioverted due to potential risk of left atrial appendage thrombus, as transesophageal echocardiography is not routinely available in the emergency department.

2.3. Elective cardioversion (EL-CV) group

Patients in this group were managed in an elective fashion consistent with usual care. This included new or repeat referral to a cardiologist, outpatient review, followed by placement on an elective hospital waiting list.

2.4. Anticoagulation

Anticoagulation was managed according to CHA₂DS₂-VASc score as per guidelines [3]. All those with AF >48 h in the elective group required a minimum of 4 weeks oral anticoagulant (AC) prior or a pre-cardioversion TEE. All in this group also required a minimum of 4 weeks AC post-DCR if they were not already on long-term oral AC. Patients with a CHA₂DS₂-VASc score of ≥2 (or =1 at physician's discretion) were on long term oral anticoagulants.

2.5. Follow-up and endpoints

Follow up for 12 months following cardioversion included 12-lead ECG at onset of symptoms and during outpatient review at 3 months post-discharge and 6 months thereafter. Holter monitors were performed at 6 and 12 months or for symptoms. Referral for AF ablation was routinely initiated for symptomatic AF despite 1–2 antiarrhythmic agents. Medical records, including specialist and family physician visits, emergency and inpatient discharge summaries were reviewed for recurrences and subsequent referrals for AF ablation.

The primary endpoint was time to persistent AF recurrence. Secondary endpoints included AF duration prior to CV, changes in left atrial (LA) size on echocardiography from baseline to follow-up, modified European Heart Rhythm Association (EHRA) score at 12 months and time to referral for AF ablation.

2.6. Statistical analysis

Baseline characteristics and outcome measures are summarized as mean ± standard deviation or median, where appropriate. The Shapiro-Wilk test was performed to confirm normal distribution of data. The chi-square test was used to compare categorical variables, and Wilcoxon rank-sum test or Student's *t*-tests used for continuous variables. With respect to analysis of 'time to AF recurrence' and 'time to referral for AF ablation', these were performed using time-to-event methods with outcomes in the two study groups to be compared with the use of hazard ratios and 95% confidence intervals using a Cox proportional-hazards regression model. Multiple linear regression analysis was performed to determine independent clinical predictors of AF-free survival at follow-up. Duration of AF-free survival was used as the continuous dependent variable.

Data analysis was performed using Statistical Package for the Social Sciences for Windows (SPSS version 23, IBM). *p* values <0.05 were considered statistically significant. The study was approved by the Alfred and Melbourne Health Human Research Committees and complies with the Declaration of Helsinki. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12618001425280).

3. Results

A total of 150 patients were included from two public hospitals in Melbourne, Australia with all undergoing CV for intermittent PeAF between 1/2014 and 7/2017. A CONSORT flow diagram for included patients is shown in Supplementary Appendix 1. Baseline characteristics for 75 consecutive Early and 75 consecutive Elective CV are presented in Table 1. Patients were similar with respect to age, gender, co-morbidities and baseline left atrial size. However, the ED-CV cohort had a longer history of AF and more prior cardioversions. As expected, the ED-CV patients had a markedly shorter median AF duration prior to CV: median 1 day (IQR 1–3 days) vs 3 months (IQR 2–7 months; *p* < 0.001). Two ED-CV patients were hypotensive on presentation and required emergent cardioversion.

A transesophageal echocardiogram (TEE) was performed in 25/75 (33.3%) prior to CV in the EL-CV group. There were no complications from CV in either group. Average length of hospital stay was 7.3 ± 1.5 h in the EL-CV group and 8.0 ± 4.4 h in the ED-CV group (*p* = 0.59).

All patients were followed up for 12 months. At follow-up, patients managed with the ED-CV strategy had less AF-related symptoms than the EL-CV group. Modified EHRA symptom scores assessed at the 12-month time point are shown in Fig. 1. Modified EHRA symptom score was reported as at least mild (≥2a) in 44% of the ED-CV group vs 72% in the EL-CV group (*p* = 0.005) and at least moderate (≥2b) in 12% of ED-CV vs 42% of EL-CV (*p* = 0.001).

At 12-months, 42/75 (56%) in the EL-CV cohort and 25/75 (33%) in the ED-CV cohort developed recurrent AF (*p* = 0.005). Time to AF recurrence is shown in Fig. 2A and was longer in the ED-CV group (295 ± 15 vs 245 ± 15 days; logrank *p* = 0.001). Referral for catheter ablation was undertaken in 32/75 (45%) of EL-CV patients vs 21/75 (28%) of ED-CV patients (*p* = 0.06) during the 12 month follow-up period. Time to AF ablation referral was significantly different between the two groups (314 ± 13 ED-CV vs 276 ± 15 days EL-CV; logrank *p* = 0.01), as shown in Fig. 2B.

Changes in LA area on serial echocardiography (baseline and follow-up) are shown in Fig. 3. Baseline LA size was similar between the two groups (EL-CV 28 ± 11 cm² vs ED-CV 27 ± 4 cm²; *p* = 0.67). LA size significantly increased from baseline by 12% in the EL-CV group (*p* = 0.046) while there was a non-significant reduction in LA size by 4% in the ED-CV group (*p* = 0.31). The EL-CV group had larger LA area at follow-up (31 ± 8 vs 26 ± 6 cm²; *p* = 0.007).

Table 1
Baseline characteristics.

| Parameter | Elective CV (n = 75) | Emergency CV (n = 75) | <i>p</i> -Value |
|--|-------------------------|--------------------------|-----------------|
| Age (years) | 63 ± 12 | 59 ± 14 | 0.11 |
| Gender (% male) | 72% | 72% | 1.0 |
| Weight (kg) | 90 ± 29 | 86 ± 20 | 0.43 |
| Body mass index (BMI) | 31 ± 6 | 28 ± 7 | 0.12 |
| Hypertension (%) | 37% | 41% | 0.56 |
| Dyslipidemia (%) | 24% | 23% | 0.85 |
| Diabetes mellitus (%) | 15% | 12% | 0.54 |
| Valvular heart disease (%) | 14% | 15% | 0.92 |
| CHA ₂ DS ₂ -VASc score | 1.7 ± 1.2 | 1.6 ± 1.5 | 0.76 |
| Time from first AF diagnosis (years) | 2.3 ± 4.0 | 5.1 ± 3.6 | 0.03 |
| Number of previous cardioversions | 0.7 ± 0.9 | 1.9 ± 1.3 | 0.001 |
| Antiarrhythmic therapy | 61% | 65% | 0.57 |
| Amiodarone | 28% | 22% | 0.43 |
| Sotalol | 24% | 36% | 0.12 |
| Flecainide | 8% | 6% | 0.73 |
| Baseline echocardiographic data | | | |
| Left atrial area (cm ²) | 27 ± 11 | 28 ± 4 | 0.82 |
| LVEF (%) | 53 ± 12 | 50 ± 17 | 0.29 |
| Mean E/E' | 10 ± 6 | 10 ± 4 | 0.94 |

Abbreviations: AF – atrial fibrillation, CV – electrical cardioversion, LVEF – left ventricular ejection fraction. Bold data indicates statistically significance at *p* < 0.05.

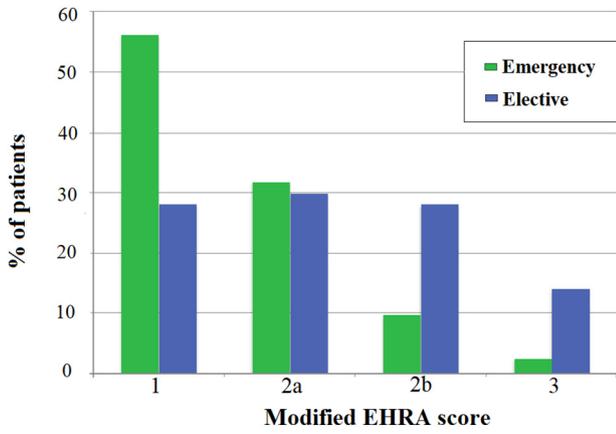


Fig. 1. Comparison of AF symptom severity at 12-months between both groups.

Multiple linear regression analysis was performed to determine multivariate clinical predictors of AF-free survival at 12 months post-CV. Elective cardioversion (standardized β -coefficient = 0.23;

$p = 0.019$) and female gender (standardized β -coefficient = -0.20 ; $p = 0.047$) significantly predicted earlier AF recurrence. Age ($p = 0.84$), diabetes ($p = 0.89$), hypertension ($p = 0.98$), body mass index ($p = 0.13$), class I/III antiarrhythmic use ($p = 0.53$), dyslipidemia ($p = 0.45$) and valvular heart disease ($p = 0.74$) were not statistically significant.

4. Discussion

This study compared a strategy of Emergency versus Elective CV for intermittent symptomatic PeAF in a cohort of 150 patients managed at two tertiary referral centres. Early cardioversion patients presented immediately to an ED for CV while elective patients waited for referral to and an appointment with a managing cardiologist.

There are several key findings:

First, the strategy of ED cardioversion was associated with a significantly lower risk of AF recurrence at one year. This translated into a lower likelihood of referral for invasive and costly AF ablation.

Second, ED cardioversion was associated with a much shorter period of time spent in AF (1 day vs 3 months). As a result, patients with

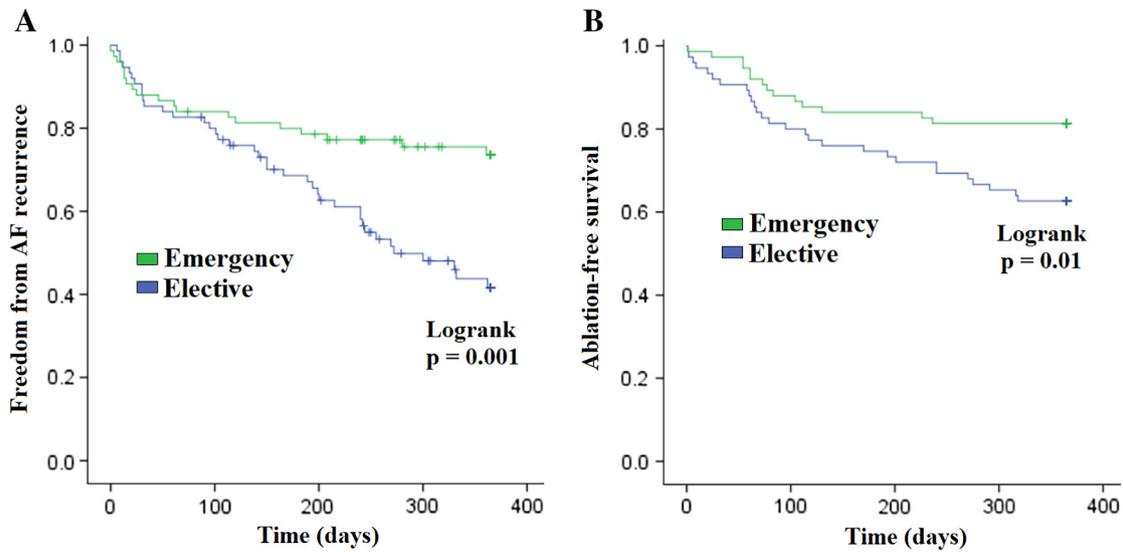


Fig. 2. A. Comparison of time to first AF recurrence between both groups. B. Comparison of time to referral for AF ablation between both groups.

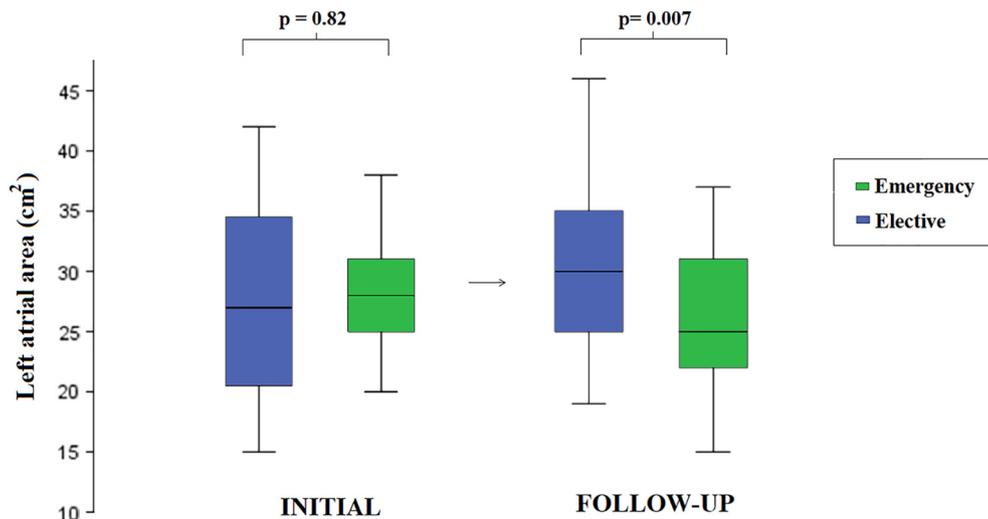


Fig. 3. Comparison between both groups with respect to atrial size at baseline and follow-up.

recurrent persistent AF more frequently found this an acceptable management strategy with significantly less overall impact on quality of life.

Finally, there was less progression of remodelling with ED compared with Elective cardioversion thus providing a rationale for the observation that sinus rhythm begets sinus rhythm in this patient population.

4.1. Improvement in quality of life

The impact of AF on quality of life and mood has been observed to be greater in persistent compared to paroxysmal AF patients [4], and addressing these factors is central in AF management. The reduction in AF burden from 3 months to 1 day in the current study represents a dramatic change and no doubt is a key factor in QoL improvement. However, reduction in AF burden may not be the only factor responsible for the observed reduction in AF symptom severity in the ED-CV cohort [5–6]. The impact of an unpredictable and recurrent condition associated with perceived loss of control has significant psychological impacts on patients [7]. Patient education, development of an AF ‘action plan’ and empowerment were likely responsible for some of the reduction in morbidity observed in the ED-CV group, as other studies have demonstrated [8–9].

4.2. AF begets AF. Does sinus rhythm beget sinus rhythm?

The concept that AF begets AF was first demonstrated in a classic study by Wijffels et al. who showed significant shortening of the atrial effective refractory period and thereby easier AF inducibility after 2–4 weeks of AF, all of which completely resolved within 1 week of sinus rhythm [10]. However, when AF was allowed to continue for 4-months, structural remodelling persisted even 4 months after resumption of sinus rhythm [11]. These pre-clinical studies of AF mediated atrial remodelling were subsequently supported by clinical studies with similar findings [12–13]. Metabolic and electrophysiological ‘adaptations’ occur within hours to days following AF onset, the process by which electrical and structural remodelling ensues and become ‘irreversible’ begins to occur over many weeks to months [1].

On the basis of these observations, a number of prior clinical studies investigated whether the reverse would be true and that repeated early resumption of sinus rhythm would lead to sinus stabilisation (i.e. sinus rhythm begets sinus rhythm). These studies yielded divergent results. Fynn et al. found no improvement in maintenance of sinus rhythm with a policy of early repeated cardioversion within the first month in persistent AF patients [14]. In a study of 15 patients with long-standing drug-resistant persistent AF using patient-activated atrial defibrillators, only 2 (13%) had a decreasing frequency of AF recurrences [15]. In contrast, Bertaglia et al., using a similar protocol of repeated cardioversion within the first month observed a greater proportion of patients in SR at 1 year in those who had repeat CV [16]. We hypothesize that one reason for this variability relates to the activity of triggering foci. In the current study we excluded patients who had demonstrated a tendency to early (within 1 month) AF recurrence post-cardioversion. In doing so we excluded patients with particularly active triggers. Maintenance of sinus rhythm in persistent AF patients is dependent upon the critical interaction between triggers and substrate [17]. In patients with early recurrent AF, active triggering foci will prevent the possibility of reverse substrate remodelling. However, in patients with less active triggers, our study demonstrates that a policy of early return to SR (EL-CV median duration 3 months vs ED-CV of 1 day) not only improves the patients overall quality of life, but may prevent progression of remodelling. Thus this strategy is only applicable to that phenotype of persistent AF which has a “meaningful period” of sinus rhythm after successful cardioversion.

The advent of smartphone technology enabling characterisation of AF onset is likely to aid implementation of a more aggressive CV strategy by emergency department physicians [18]. Close collaboration between cardiology and ED departments, appropriate patient selection,

education of patients and physicians and resource allocation remain vital to successful implementation of ED-CV for intermittent PeAF.

Current guidelines state that it is reasonable to perform repeated CV in PeAF if a clinically meaningful period exists between procedures [19]. The current study demonstrates the benefits of performing this in a timely fashion. Utilizing the Emergency Department as part of an AF action plan focussing on documentation of symptom onset, anticoagulation plan, patient education and empowerment led to a markedly shorter AF duration. This resulted in improvement in overall quality of life, prevented the progression of LA remodelling and delayed both onset of the next AF episode and referral for ablation.

4.3. Potential financial implications

While earlier studies in the ‘pre-ablation’ era did not demonstrate financial savings with respect to earlier CV [20], the reduction in subsequent referral rates for AF ablation by 34% (in addition to lower recurrence rates) observed in our study may be associated with cost savings to the health system. In a study of AF-related healthcare costs in five European countries, catheter ablation was over 30 times more expensive than cardioversion [21]. Moreover, a management strategy of cardioverting patients then discharging them directly from ED has been associated with significant hospital cost savings compared with inpatient admission (\$5460 vs \$23,202) [22].

This study highlights the benefits of restoring sinus rhythm within an appropriate timeframe. Rather than creating an excessive burden on emergency department resources, innovative models of care are required. These may include rapid-access AF clinics that incorporate patient education, AF (and anticoagulation) action plans and timely elective cardioversion.

4.4. Limitations

Like other non-randomized studies, the benefits observed in the ED-CV group may be related to confounding and selection bias whereby clinicians were more likely to employ this strategy in ‘healthier’ patients, or in those with more severe symptoms. One may postulate that the longer time from first AF diagnosis in the ED-CV group suggests these patients may have had closer follow up and been more compliant with medical therapy. While patients in both groups appeared to be similar with respect gender, age and comorbidities, there was a trend towards EL-CV patients being older and more overweight, with the study underpowered to detect small differences in these variables which may have subsequently impacted recurrence rates. The authors should discuss how this issue could have influenced the selection of included patients. The clinical applicability of this study’s findings to patients with asymptomatic AF is unclear as these patients were excluded from this study. Recent studies suggest that these patients have a higher risk of stroke and all-cause mortality [23]. The emergency of new technologies incorporated into smartphones and smartwatches may enable earlier detection and treatment of AF in these patients.

Despite our attempts to exclude true paroxysmal AF patients based on prior history (from both this analysis and the ED-CV treatment strategy), we are unable to definitively exclude that some of the patients electrically cardioverted in ED would not have spontaneously reverted without CV. Of those excluded from the study shown in the Supplementary Appendix, two were excluded due to spontaneous reversion in the Emergency department while 3/7 patients managed with rate control in the ED and discharged were found to be in sinus rhythm at follow-up.

5. Conclusion

In symptomatic patients with intermittent episodes of persistent AF, a strategy of early presentation for cardioversion to the emergency department appears to be an acceptable long-term management strategy for patients with clinically meaningful periods between episodes.

Early ED cardioversion resulted in a lower rate of AF recurrence at 1 year. Furthermore, this strategy is associated with improved quality of life and slowing of disease progression. Delays in sinus rhythm restoration may accelerate adverse atrial remodelling, leading to earlier arrhythmia recurrence and accelerating referral for AF ablation.

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Disclosures/relationship(s) with industry

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