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Analysis of clinical risk factors of failed electrical cardioversion in patients with persistent atrial fibrillation or atrial flutter

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Abstract

Background Although rhythm control could be the best for symptomatic atrial fibrillation (AF), some patients fail to achieve sinus rhythm (SR). This study aimed to identify clinical risk factors of failed electrical cardioversion (ECV).

Methods A total of 248 patients who received ECV for persistent AF or atrial flutter (AFL) were retrospectively reviewed. Patients were divided into three groups: Group 1 maintained SR for > 1 year, group 2 maintained SR ≤ 1 year after ECV, and group 3 failed ECV. SR maintenance was assessed using regular electrocardiography or Holter monitoring.

Results Patients were divided into group 1 (73, 29%), group 2 (146, 59%), and group 3 (29, 12%). The mean age of patients was 60 ± 10 years, and 197 (79%) were male. Age, sex, and baseline characteristics were similar among groups. However, increased cardiac size, digoxin use, heart failure (HF), and decreased left ventricular ejection fraction (LVEF) were more common in group 3. Univariate analysis of clinical risk factors for failed ECV was increased cardiac size [hazard ratio (HR) 2.14 (95% confidence interval [CI], 1.06–4.34, $p = 0.030$)], digoxin use [HR 2.66 (95% CI, 1.15–6.14), $p = 0.027$], HF [HR 2.60 (95% CI, 1.32–5.09), $p = 0.005$], LVEF < 40% [HR 3.45 (95% CI, 1.00–11.85), $p = 0.038$], and decreased LVEF [HR 2.49 (95% CI, 1.18–5.25), $p = 0.012$]. Among them, HF showed clinical significance only by multivariate analysis [HR 3.01 (95% CI, 1.13–7.99), $p = 0.027$].

Conclusions Increased cardiac size, digoxin use, HF, LVEF < 40%, and decreased LVEF were related to failed ECV for persistent AF or AFL. Among these, HF was the most important risk factor. Further multi-center studies including greater number of participants are planned.

Keywords Atrial fibrillation, Atrial flutter, Electrical cardioversion

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia and a major cause of morbidity and mortality worldwide. The prevalence of AF is rapidly increasing along with the aging process, which is a big burden on patients, physicians, and healthcare systems [1, 2]. Prevention of stroke, rate, or rhythm control strategies are the three major constituents of AF management [2]. Among them, rhythm control strategy has received increasing attention on the basis of improving catheter performance, ablation techniques, and clinical outcomes in patients with persistent AF with heart failure (HF) in several studies [3, 4]. However, successful rhythm control could not be achieved in some AF patients, even with several ablation tools, the medical team's efforts, patients' agony, and high cost. Serious procedure-related complications including pacemaker implantation or clinical adverse events such as myocardial infarction (MI), stroke, HF, or death sometimes occur due to the cost of rhythm control strategy for AF [5, 6]. Additionally, the guideline does not provide clear consensus regarding the management approach for persistent AF without HF, and controversy remains regarding suitable candidates for rhythm control for persistent AF [5]. Therefore, suitable patient selection is crucial for the successful rhythm control of AF. Electrical cardioversion (ECV) is a relatively simple, safe, and economical method for initial rhythm control strategy for AF or atrial flutter (AFL), and failed ECV could be a simple and useful marker for failed rhythm control strategy [7]. From these perspectives, we aimed to identify clinical risk factors related to failed ECV, which may facilitate suitable patient selection for rhythm control strategy of persistent AF.

Methods

Patients aged ≥ 20 years who underwent ECV for persistent AF or AFL were reviewed for evaluation, and 248 patients were retrospectively selected from two centers from 2010 to 2019. We excluded patients who (1) were aged < 20 years, (2) had no baseline electrocardiography (ECG) before ECV, (3) had insufficient medical records of follow-up for least 1 year after ECV, (4) underwent catheter or surgical ablations for AF or AFL, and (5) were implanted with a permanent pacemaker, implantable cardioverter defibrillator (ICD), or cardiac resynchronization therapy (CRT). The study was approved by the institutional review board of each participating center, and all patients provided written informed consent for ECV and management.

Administration of antiarrhythmic medications before and after ECV was left to the treating physician's discretion. Anticoagulation therapy was administered as recommended by the guidelines available at the time of enrollment; persistent AF or AFL was treated with warfarin for at least 3 weeks before ECV with an international normalized ratio (2.0–3.0) or non-vitamin K-dependent oral anticoagulants, followed by at least 4 weeks of anticoagulation after ECV. Transesophageal echocardiography was performed before ECV whenever possible. If thrombi were detected, ECV was delayed. After confirming complete thrombus resolution with anticoagulation, ECV was performed.

ECV was performed under sedation, according to contemporary guidelines. Initial energy (200 J) of biphasic shock was mainly chosen for the first shock and increased to 250–360 J for subsequent shocks, depending on the physician's discretion. If needed, amiodarone infusion was selected for subsequent shocks of failed ECV. External shocks are applied either in an anteroposterior or anterolateral electrode position [7]. ECV was considered successful if sinus rhythm (SR) was temporarily restored with or without medications. When the SR did not recover, the version was classified as failed ECV. According to the results, patients were divided into 3 groups: Group 1 maintained SR for > 1 year, group 2 maintained SR for ≤ 1 year, and group 3 was failed ECV. SR maintenance was assessed using regular ECG or Holter monitoring at an outpatient clinic. Diagnosis of HF was based on patient's symptoms and signs caused by a cardiac disorder and supported by elevated natriuretic peptide levels and/or objective finding of pulmonary or systemic vascular congestion regardless of left ventricular ejection fraction (LVEF). The cardiothoracic ratio is measured on a postero-anterior view of chest X-ray, and maximal horizontal cardiac and thoracic diameter is chosen. The cutoff values for cardiac size (159.11 mm) and LVEF (59.5%) were chosen on the receiver operating characteristic curve for maximized sensitivity and specificity. Major adverse cardiovascular events (MACEs) included requiring temporary or permanent pacemaker for bradyarrhythmias, ICD or CRT implantation for serious ventricular arrhythmias or combined HF management, hospitalization for HF, thromboembolic events [stroke, transient ischemic attack (TIA), or systemic embolism], brain hemorrhage, major bleeding, MI, sustained ventricular tachycardia/fibrillation (VT/VF), and death during or after the procedure until 1 year.

Statistical analysis

Continuous variables are expressed as mean ± SD. Data were compared using ANOVA. Categorical variables, expressed as numbers and percentages, were compared using the chi-square or Fisher's exact test. Univariate and multivariate logistic models were used to identify significant risk factors of failed ECV. The duration of AF was dichotomized at 5 years (≤ 5 years and > 5 years).

Controlling variables included increased cardiac size, digoxin use, existence of HF, LVEF < 40%, decreased LVEF, and AF duration. Odds ratio (OR) and 95% confidence interval (CI) for failed ECV were computed. All tests of significance were two-tailed, and $p < 0.05$ was considered significant. All statistical analyses were performed using SPSS software (version 25.0; SPSS Inc., Chicago, IL, USA).

Results

Patients' baseline clinical characteristics are listed in Table 1. The mean age was 60 ± 10 years, and 197 (79%) patients were male. Patients were distributed into group 1 (73, 29%), group 2 (146, 59%), and group 3 (29, 12%). Age, sex, and baseline characteristics were similar among groups. However, HF incidence was highest in group 3 [group 1: 19 (26%), group 2: 22 (15%), and group 3: 12 (41%) patients, $p = 0.004$]. LVEF decreased [group 1: 59 ± 9, group 2: 59 ± 8, and group 3: 54 ± 13, $p = 0.021$], and cardiac size increased in group 3 compared with the other groups [group 1: 155 ± 17, group 2: 157 ± 15, and group 3: 164 ± 18, $p = 0.029$]. Previous stroke/TIA was less developed in group 1 [group 1: 1 (1%), group 2: 18 (7%), and group 3: 2 (7%) patients, $p = 0.022$].

Table 1 Baseline clinical characteristics of study patients

Variable	Group 1 (*N* = 73)	Group 2 (*N* = 146)	Group 3 (*N* = 29)	*p* value
Age (years)	60 ± 9	60 ± 10	61 ± 10	0.885
Males (%)	56 (77)	118 (81)	23 (79)	0.777
Hypertension (%)	39 (53)	56 (38)	16(55)	0.052
Diabetes mellitus (%)	8 (11)	26 (18)	7 (24)	0.220
Heart failure (%)	19 (26)	22 (15)	12(41)	0.004
Previous stroke/TIA (%)	1 (1)	18 (7)	2 (7)	0.022
Previous MI/CAD (%)	4 (5)	10 (7)	2 (7)	0.652
C-V score	1.6 ± 1.0	1.6 ± 1.4	2.1 ± 1.4	0.174
Hyperthyroidism (%)	9 (12)	11(8)	1(3)	0.285
LVEF (%)	59 ± 9	59 ± 8	54 ± 13	0.021
LVEF < 40% (%)	5 (7)	5 (3)	4 (14)	0.067
LA diameter (mm)	45 ± 6	45 ± 6	47 ± 6	0.415
LA volume index	44 ± 19	41 ± 20	45 ± 23	0.410
LV mass index	85 ± 34	77 ± 32	81 ± 33	0.317
TEE	71 (97)	140 (97)	27 (93)	0.717
HR on ECG	85 ± 17	84 ± 17	84 ± 15	0.819
HR on Holter	85 ± 15	79 ± 17	78 ± 12	0.138
Cardiac size (mm)	155 ± 17	157 ± 15	164 ± 18	0.029
Cardiothoracic ratio	0.52 ± 0.06	0.52 ± 0.57	0.54 ± 0.06	0.347

Values are presented as *n* (%) or mean ± SD. *AF* atrial fibrillation, *AFL* atrial flutter, *CAD* coronary artery disease, *C-V* CHA_2DS_2-VASc, *HR* heart rate, *LA* left atrium, *LV* left ventricle, *LVEF* Left ventricular ejection fraction, *TEE* trans-esophageal echocardiography, *TIA* transient ischemic attack

The characteristics of AF or AFL among groups are described in Table 2. The form of AF or AFL did not differ among groups, and most patients had only AF. The duration of AF or AFL was different among groups, and most patients in group 1 had duration of < 5 years (68/69, 99%) compared with group 2 (101/125, 81%) and group 3 (21/26, 81%). The duration of anticoagulation was not different among groups. MACEs were more frequent in groups 2 and 3 during the 1-year follow-up, but there was no statistically significant difference among groups [group 1: 1 (1%), group 2: 8 (6%), and group 3: 2 (7%), $p = 0.300$]. Intergroup difference was group 1 versus 2 ($p = 0.278$) and group 1 versus 3 ($p = 0.194$). Major adverse cardiovascular events of study patients are listed in Table 3. A permanent pacemaker was implanted in group 1 (one patient). In group 2, a temporary pacemaker was implanted in one patient. Three patients were implanted with permanent pacemakers; among them, one patient died of sudden VT/VF, and the other patient was converted to ICD due to sudden VT/VF. ICD was implanted in three other patients, and intracranial hemorrhage developed in one other patient. In group 3, two patients received CRT. Baseline medications were not different among groups, except digoxin [group 1: 7 (10%), group 2: 6 (4%), and group 3: 5 (28%), $p = 0.030$] and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker [group 1: 26 (36%), group 2: 41 (28%), and

Table 2 Atrial fibrillation or atrial flutter characteristics of study patients

Variable	Group 1 (*N* = 73)	Group 2 (*N* = 146)	Group 3 (*N* = 29)	*p* value
Form of AF or AFL				0.252
AF	68 (93)	135 (93)	29 (100)	
AFL	3 (4)	2 (1)		
AF and AFL (mixed)	2 (3)	9 (6)	0 (0)	
Duration of AF or AFL			0 (0)	0.000
Less than 1 year	48 (66)	53 (36)		
From 1 to 2 year	10 (14)	16 (11)	6 (21)	
From 2 to 5 year	10 (14)	32 (22)	6 (21)	
From 5 to 10 year	1 (1)	16 (11)	9 (31)	
Over 10 year	0 (0)	8 (6)	3 (10)	
Unidentified	4 (6)	21 (14)	2 (7)	
Duration of anticoagulation			3 (10)	0.886
Under 1 month	10 (14)	16 (11)	4 (14)	
From 1 to 2 month	14 (19)	23 (16)	6 (21)	
Over 2 month	48 (66)	102 (70)	19 (66)	
None	1 (1)	5 (3)	0 (0)	
MACE (%)	1 (1)	8 (6)	2 (7)	0.300

Values are presented as *n* (%). *AF* atrial fibrillation, *AFL* atrial flutter, *MACE* major adverse cardiovascular event

Table 3 Major adverse cardiovascular events of study patients

Groups	Sex/age	Major adverse cardiovascular events
Group 1 (1 case)	M/49	Implantation of a permanent pacemaker
Group 2 (8 cases)	M/55	Intracranial hemorrhage
	M/63	Implantation of a temporary pacemaker
	M/61	Implantation of a permanent pacemaker. Expired by VT/VF
	M/52	Implantation of a permanent pacemaker, which was changed to an ICD by VT/VF
	F/86	Implantation of a permanent pacemaker by VT/VF
	F/63	Implantation of an ICD
	M/65	Implantation of an ICD
	M/56	Implantation of an ICD
Group 3 (2 cases)	M/78	Implantation of a CRT
	M/77	Implantation of a CRT

CRT cardiac resynchronization therapy, *F* female, *ICD* implantable cardioverter defibrillator, *M* male, *VF* ventricular fibrillation, *VT* ventricular tachycardia

Table 4 Baseline medications of study patients

Variable	Group 1 (*N* = 73)	Group 2 (*N* = 146)	Group 3 (*N* = 29)	*p* value
ACEI/ARB	26 (36)	41 (28)	16 (55)	0.017
Amiodarone	14 (19)	24 (16)	6 (21)	0.800
Beta blocker	39 (53)	69 (47)	13 (45)	0.623
Digoxin	7 (10)	6 (4)	5 (28)	0.030
Diltiazem	8 (11)	14 (10)	1 (3)	0.488
Dronedarone	5 (7)	3 (2)	1 (3)	0.202
Flecainide	4 (6)	12 (8)	2 (7)	0.760
Pilsicainide	2 (3)	1(1)	0 (0)	0.346
Propafenone	2 (3)	18 (12)	2 (7)	0.058
Sotalol	0 (0)	5 (3)	0 (0)	0.168
Total (class I + III) antiarrhythmics	27 (37)	62 (43)	11 (38)	0.710
NOACs	40 (55)	85 (58)	22 (76)	0.137
Warfarin	30 (41)	56 (38)	7 (24)	0.265
Heparin	2 (3)	0 (0)	0 (0)	0.089
Low molecular weight heparin	0 (0)	2 (1)	0 (0)	0.494
No antithrombotics	1 (1)	3 (2)	0 (0)	0.711

Values represent *n* (%). *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *NOACs* non-vitamin K-dependent anticoagulants

group 3: 16 (55%), $p = 0.017$]. The use of antiarrhythmics including classes I and III, beta blockers, and non-dihydropyridine calcium channel blockers was not different among groups (Table 4).

Univariate analysis of clinical risk factors of failed ECV was increased cardiac size [hazard ratio (HR) 2.14 (95% confidence interval [CI], 1.06–4.34), $p = 0.030$], digoxin use [HR 2.66 (95% CI, 1.15–6.14), $p = 0.027$], existence of HF [HR 2.60 (95% CI, 1.32–5.09), $p = 0.005$], LVEF < 40% [HR 3.45 (95% CI, 1.00–11.85), $p = 0.038$], and decreased LVEF [HR 2.49 (95% CI, 1.18–5.25), $p = 0.012$]. When AF duration was dichotomized at 5 years (≤ 5 years and > 5 years), AF duration (> 5 years) was not a risk factor of failed ECV. Multivariate analysis of clinical risk factors of failed ECV showed that only HF had clinical significance [HR 3.01 (95% CI, 1.13–7.99), $p = 0.027$] (Table 5).

Discussion

The main findings of this study are as follows: (1) Increased cardiac size, digoxin use, HF, LVEF < 40%, and decreased LVEF were related risk factors of failed ECV for persistent AF or AFL. (2) Among these, HF was suggested to be the most important risk factor. An optimal rhythm control strategy for persistent AF or AFL could be guided by considering these risk factors together with patient status.

Diverse clinical outcomes depending on the nature of AF lead to the importance of prehension regarding AF characterization. The 2020 European Society of Cardiology (ESC) guideline recommends the 4S-AF scheme as a structured characterization of AF, which contains assessment of stroke risk, severity of symptoms, severity of AF burden, and substrate severity characterization (class IIa) [2]. AF management including prevention of stroke, rate, or rhythm control should be individualized as indicated by these results. Among them, rhythm control strategy has received increasing attention and is supported by several studies to improve clinical outcomes of AF. The Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial showed a survival benefit and lower hospitalization rate for worsening HF in the catheter ablation group for AF. Some other trials have reported improvement in symptom scores in

Table 5 Univariate and multivariate analysis of clinical risk factors of electrical cardioversion failure

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Cardiac size	2.14 (1.06–4.34)	0.030	1.72 (0.68–4.32)	0.249
Digoxin	2.66 (1.15–6.14)	0.027	2.28 (0.61–8.53)	0.221
Heart failure	2.60 (1.32–5.09)	0.005	3.01 (1.13–7.99)	0.027
LVEF	2.49 (1.18–5.25)	0.012	2.12 (0.79–5.70)	0.138
LVEF < 40%	3.45 (1.00–11.85)	0.038	0.76 (0.17–3.32)	0.716
AF duration (> 5 years)	1.07 (0.90–1.26)	0.376	2.01 (0.64–6.38)	0.234

AF atrial fibrillation, *LVEF* left ventricular ejection fraction

persistent AF with HF [3, 4]. According to these positive results, the 2020 ESC guideline suggests that AF ablation should be considered in symptomatic patients with AF and HF with reduced LVEF [2]. However, the guideline does not provide clear consensus on the management of persistent AF without HF. Additionally, there remains controversy regarding the selection of rhythm control strategy for persistent AF [5]. Although understanding AF mechanisms, development of three-dimensional mapping system, use of intra-cardiac echocardiography, and improved ablation catheter, device, and ablation techniques have led to successful rhythm control compared with that in the past, some patients still develop persistent AF or AFL. Sometimes, serious complications including implantation of a permanent pacemaker or adverse clinical events occur. Therefore, suitable patient selection is an important issue for successful rhythm control of AF [5, 6].

ECV is a relatively simple, safe, and economical method for initial rhythm control for AF or AFL, and timely ECV is important for the management of AF [1, 7]. ECV has a different purpose for paroxysmal and persistent AF. Most cases of paroxysmal AF are spontaneously terminated; therefore, ECV is only useful for unstable vital signs or uncontrolled symptomatic states. For persistent AF, a considerable number of patients have no or mild symptoms; therefore, ECV is performed to help unmask the underlying rhythm status, identify the true impact of AF, and provide long-term SR status even without medications [1, 8]. Successful conversion rate after ECV is reported as 67–90% for persistent AF [9, 10]. However, ECV for AF could be associated with serious complications such as thromboembolic events, bradyarrhythmias, or severe dysrhythmias [6, 11, 12]. Acute adverse events were reported in 3.6% and late adverse events were reported in 8.2% of patients after ECV of AF, which are expected to happen more frequently in patients with severe underlying heart disease [9]. Therefore, identification of risk factors of ECV failure has important clinical significance [13, 14]. Additionally, when ECV fails, the patient has little chance to maintain SR even with a catheter ablation. Therefore, a failed ECV may be a simple and useful marker for predicting failed rhythm control.

In this study, increased cardiac size, digoxin use, HF, LVEF < 40%, and decreased LVEF were predicted risk factors of failed ECV for persistent AF or AFL. Among these, HF is the most important risk factor. These factors are connected to one another and are clues for judging AF chronicity. The outcome of ECV could be influenced by other factors such as age, sex, and enlarged left atrium or left ventricle. However, these risk factors were excluded from risk analysis. They showed no statistically significant difference among groups, and we focused to analyze the most relevant and selected risk factors of ECV failure in this study. Although previous studies showed positive clinical outcomes in the catheter ablation group for AF with HF, HF manifestation is widely variable from mild to severe [3, 4]. Acute or subacute HF with tolerable substrate characteristics and evident reversible aggravating factors such as tachycardia, anemia, inappropriate medications, infections, or metabolic causes has much potential to recover heart function by controlling aggravating risk factors. In contrast, longstanding chronic HF with advanced substrate characteristics, severe cardiomegaly or pulmonary hypertension, decreased LVEF, or valvular dysfunction could have a lower chance of recovering heart function. Rhythm control strategy for persistent AF or AFL could be best for HF with recent onset, minimal remodeling, and reversible causes. On the contrary, HF with aggravated, severely decompensated, massive cardiac remodeling, and New York Heart Association class III–IV symptoms requiring digoxin treatment may show failure of rhythm control. Failed ECV was mainly observed in patients with HF using digoxin in this study, which could be evidence of this assertion. Advanced HF with persistent AF or AFL suggests atrial cardiomyopathy and fibrosis with structural, architectural, contractile,

or electrophysiological changes, which might be related to failed ECV [2]. Therefore, careful assessment before ECV is requisite when persistent AF or AFL is combined with HF, especially in advanced stages. For some selected patients, rate control strategy may be the proper approach to AF management.

Furthermore, rhythm control strategy could be dangerous or inappropriate for some cases of severely decompensated HF, which could expose the underlying sick sinus syndrome, provoke pro-arrhythmic events, aggravate tachycardia-induced cardiomyopathy due to AF organization, or combine with procedure-related complications [5, 15]. Economic burden, patients' agony, and medical teams' efforts are other problems. Even so, rhythm control is still a better treatment option for controlling patients' symptoms and clinical outcomes of most AF combined with other forms of HF. Active search and treatment of patients with persistent AF or AFL with potential to recover SR should be continued.

Study limitations

This study had several limitations. First, this was a retrospective observational study conducted at two centers, and the number of recruited patients was relatively small. As a result, there may be selection bias and residual or unmeasured confounding factors. Second, this study only suggests risk factors of failed ECV for persistent AF or AFL and does not contraindicate ECV. The selection between rhythm and rate control is dependent on the physician's discretion. Third, AF duration (≤ 5 years and > 5 years), cutoff value of LVEF, and cardiac size were based on statistical analyses in this study, so the values are not absolute cutoff points but just references. Calculation of AF duration was ambiguous in some patients and was based on vague patients' symptoms or medical records. As a considerable number of patients with persistent AF or AFL have cardiomegaly or decreased LVEF, the absolute cutoff value might have little clinical significance, and whether these risk factors exist could be a clinical issue. Fourth, although adverse clinical events occurred, we could not identify related risk factors because of the small number of cases. Finally, because we tried to identify adverse clinical outcomes for 1 year after ECV, prolonged analysis of clinical outcomes was not our intention.

Conclusion

Increased cardiac size, digoxin use, HF, LVEF < 40%, and decreased LVEF were related to failed ECV for persistent AF or AFL. Among these, HF was the most important risk factor. An optimal rhythm control strategy for persistent AF or AFL could be guided by considering these risk factors together with patient status. Further studies, including more number of participants from multiple centers, are planned. As there is no clear consensus for selecting rhythm control strategy for persistent AF with diverse forms of HF, patient selection is an ongoing clinical question. Discussion and collaboration between the medical team and patients is required for optimal treatment of persistent AF.

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Author contributions
KHK wrote the manuscript; HYC, JP, YJS, SK, DKK, SHS, DIK reviewed the articles and PSY, HEL, JP, JMS, JA, SHL, SIL performed data analyses; JYK reviewed the literature; and all authors reviewed the manuscript.

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Competing interests
The authors declare that they have no competing interests.

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