Cardiovascular Events of Electrical Cardioversion Under Optimal Anticoagulation in Atrial Fibrillation: The Multicenter Analysis

Dong Geum Shin[1]*, Iksung Cho[1]*, Bríain ó Hartaigh[2,3], Hee-Sun Mun[4], Hye-Young Lee[5], Eui Seock Hwang[6], Jin-Kyu Park[1], Jae-Sun Uhm[1], Hui-Nam Pak[1], Moon-Hyoung Lee[1], and Boyoung Joung[1]

[1]Division of Cardiology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea;
[2]Department of Radiology, NewYork-Presbyterian Hospital and the Weill Cornell Medical College, New York, NY, USA;
[3]Department of Internal Medicine/Geriatrics, Yale School of Medicine, Adler Geriatric Center, New Haven, CT, USA;
[4]Division of Cardiology, Kangnam Sacred Heart Hospital, Hallym University Medical Center, Seoul;
[5]Division of Cardiology, Sanggye Paik Hospital, Inje University College of Medicine, Seoul;
[6]Division of Cardiology, Myongji Hospital, Kwandong University College of Medicine, Goyang, Korea.

Purpose: Electric cardioversion has been successfully used in terminating symptomatic atrial fibrillation (AF). Nevertheless, large-scale study about the acute cardiovascular events following electrical cardioversion of AF is lacking. This study was performed to evaluate the incidence, risk factors, and clinical consequences of acute cardiovascular events following electrical cardioversion of AF.
Materials and Methods: The study enrolled 1100 AF patients (mean age 60±11 years) who received cardioversion at four tertiary hospitals. Hospitalizations for stroke/transient ischemic attack, major bleedings, and arrhythmic events during 30 days post electric cardioversion were assessed.
Results: The mean duration of anticoagulation before cardioversion was 95.8±51.6 days. The mean International Normalized Ratio at the time of cardioversion was 2.4±0.9. The antiarrhythmic drugs at the time of cardioversion were class I (45%), amiodarone (40%), beta-blocker (53%), calcium-channel blocker (21%), and other medication (11%). The success rate of terminating AF via cardioversion was 87% (n=947). Following cardioversion, 5 strokes and 5 major bleedings occurred. The history of stroke/transient ischemic attack (OR 6.23, 95% CI 1.69–22.90) and heart failure (OR 6.40, 95% CI 1.77–23.14) were among predictors of thromboembolic or bleeding events. Eight patients were hospitalized for bradyarrhythmia. These patients were more likely to have had a lower heart rate prior to the procedure (*p*=0.045). Consequently, 3 of these patients were implanted with a permanent pacemaker.
Conclusion: Cardioversion appears as a safe procedure with a reasonably acceptable cardiovascular event rate. However, to prevent the cardiovascular events, several risk factors should be considered before cardioversion.

Key Words: Atrial fibrillation, cardioversion, cardiovascular events, safety

INTRODUCTION

Atrial fibrillation (AF) is the most common form of sustained cardiac arrhythmia.[1] The prevalence of AF in the general population increase with age, and is estimated to affect over 4% of the population above the age of 60 years.[2-4] Foremost, electrical and chemical cardioversions have been successfully utilized for rhythm control in AF.[5] However, it has been reported that cardioversion in patients with AF is associated with complications including thromboembolic events (5–7%) and bradyarrhythmias (0.8–1.5%).[6-8] Adequate anticoagulation may, in part, attenuate the risk associated with thromboembolic events;

in patients with adequate anticoagulation, the event rate is reported to be between 0.7% and 0.8%.[9-12]

Current guidelines advocate for patients with AF lasting more than 48 hours to achieve therapeutic International Normalized Ratio (INR) for 3 weeks prior to cardioversion and maintain anticoagulation treatment for at least 4 weeks following cardioversion. If patient has not been anticoagulated for the preceding 3 weeks, it is reasonable to perform a transesophageal echocardiography (TEE) prior to cardioversion.[1,13] However, given these recommendations generally stem from small observational studies, therefore, there is a need for additional verification via larger sized datasets of varying study samples. Furthermore, in terms of bradyarrhythmia, the paucity of data regarding the predictors of cardioversion complications remains equivocal to date.[14-16] Hence, the comprehensive safety analysis including thromboembolic, bleeding, and arrhythmic events from electric cardioversion in recurrent and persistent AF in various ethnicities requires further clarification. In the current study, we explored the presence of risk factors and their association with thromboembolic, major bleeding, and arrhythmic events following electrical cardioversion of AF lasting beyond 48 hours with appropriate anticoagulation following current guidelines.

MATERIALS AND METHODS

The present study comprised a retrospective analysis of 1100 patients from January 2005 through August 2013 at four tertiary hospitals in Korea. Although the number of cardioversion was 1597, this study evaluated only the initial cardioversion in each patient. Patients with AF with the duration of 48 hours or more taking warfarin and underwent electric cardioversion were enrolled for evaluation. Patients taking new oral anticoagulant were excluded. All case records were reviewed following the standardized data collection protocol for the purpose of obtaining information: baseline characteristics including age, gender, diabetes, hypertension, heart failure, and history of stroke or myocardial infarction; medication use; management of patients during the initial cardioversion and the 30-day follow-up period after cardioversion. The CHADS$_2$ score [Congestive heart failure, Hypertension, Age ≥75, Diabetes, prior ischemic Stroke, transient ischemic attack (TIA) or thromboembolism (doubled)], CHA$_2$DS$_2$-VASc score [Congestive heart failure or left ventricular dysfunction Hypertension, Age ≥75 (doubled), Diabetes, prior ischemic Stroke, TIA or thromboembolism (doubled), Vascular disease, Age 65−74, gender category (female)], and HAS-BLED (Hypertension, Abnormal renal or liver function, Stroke, Bleeding tendency or predisposition, Labile INRs, Elderly, Drugs or alcohol abuse) were calculated as indices of thromboembolic or major bleeding risks. Before patients begin taking warfarin, INR was checked and warfarin was prescribed considering patient's body weight,

age, and laboratory test result. Then, the dose was modulated according to the target INR level between 2.0 and 3.0 at 1 or 2 weeks interval. When INR level remained same for at least 1 to 2 weeks, INR level was measured once a month.

Diagnosis of AF was based on a 12-lead electrocardiogram (ECG) characterized by the absence of discrete P waves and an irregular ventricular rate. For the majority of patients, a single ECG was sufficient to secure diagnosis, assuming the patient is in AF at the time of the ECG. For the remaining patients, AF was diagnosed by employing a heart rhythm recording such as telemetry strip or Holter monitor. Synchronized direct-current cardioversions were performed according to the current guidelines with the monitoring of ECG, pulse rate, oxygen saturation, and cardiac telemetry under sedation with intravenous injection of pentothal sodium. Cardioversion energy was set to 100 to 200 joules for biphasic devices. Cardioversion was defined as successful if sinus rhythm was obtained and patient was discharged from the cardioversion unit in sinus rhythm. If first cardioversion had failed, second or third cardioversion was performed. To reduce the risk of thromboembolism following cardioversion, anticoagulation was performed according to current guidelines three to four weeks before and after cardioversion. Alternatively, TEE was performed to evaluate the presence of existing intra-cardiac thrombus within 24 hours before electrical cardioversion depending on the physician's decision. In some patients with lower INR levels, intravenous unfractionated heparin was administered at the time of cardioversion.

The outcome in this study was hospitalization due to cardiovascular events after cardioversion during 30 days, which comprised the following: 1) thromboembolic (stroke/TIA, systemic embolism), 2) major bleedings, and 3) arrhythmic events. Stroke was defined as the sudden onset of a focal neurological deficit in a location consistent with the territory of a major cerebral artery and categorized as ischemic, hemorrhagic, or unspecified. Hemorrhagic transformation of ischemic stroke was not considered hemorrhagic stroke. Intracranial hemorrhage consisted of hemorrhagic stroke and subdural or subarachnoid hemorrhage. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ documented by means of imaging, surgery, or autopsy. Major bleeding was defined as a reduction in the hemoglobin level of at least 20 g/L, transfusion of at least 2 unit blood, or symptomatic bleeding in a critical area or organ. Patients with symptomatic significant bradycardia were hospitalized. Significant bradycardia was defined as bradycardia requiring medication or pacing, heart rate lower than 40 beats per minute, or asystole lasting longer than 5 seconds. Other arrhythmic events including ventricular tachycardia and fibrillation also evaluated.

Continuous variables are reported as mean±standard deviation, and were analyzed using independent t-test. Categorical variables were reported as counts and proportions, and analyzed using Pearson's chi-square tests or Fisher's exact test, as

appropriate. We performed univariate analysis and, with variables found to be statistically significant on univariate analysis, multivariate logistic regression analysis was performed to evaluate independent predictors for cardiovascular events. The SPSS statistical package (SPSS Inc., Chicago, IL, USA) was used to perform all statistical evaluations. A *p* value of <0.05 was considered statistically significant. The study protocol was approved by the Institutional Review Boards. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

RESULTS

The clinical characteristics of patients according to the thromboembolic or bleeding events are presented in Table 1. The average duration of anticoagulation before cardioversion was 96±52 days. Mean INR were 2.43±0.89 and 2.38±0.92 at the time of cardioversion and 30-day follow-up, respectively. The proportion of patients with INR ≥2 at the time of cardioversion

were 89% (n=893). The antiarrhythmic drugs used at the time of cardioversion were flecainide (n=494, 45%), amiodarone (n=445, 40%), beta-blocker (n=585, 53%), calcium-channel blocker (n=226, 21%) and others (n=119, 11%). Cardioversion was successful in 947 patients (87%). In 1080 (98%) patients, follow-up more than 30 days were possible.

Thromboembolism and bleeding events

After cardioversion, five stroke events (0.5%) and five major bleeding events (0.5%) occurred during 30-days follow-up period. Patients with thromboembolic and bleeding events were older (67±11 years vs. 60±11 years, *p*=0.042) and had previous stroke (50% vs. 13%, *p*=0.006) than those without events. Patients with high CHADS$_2$ (≥3) and CHA$_2$DS$_2$-VASc score (≥6) were more common in the event group compared with the non-event group (*p*=0.015 and *p*<0.001, respectively). Also, HAS-BLED score of the event group was significantly higher than the non-event group (*p*<0.001). There was no significant difference in INR at the time of cardioversion between event and non-event groups (2.3±0.6 vs. 2.4±0.9, *p*=0.59) (Table 1).

Table 1. Baseline Characteristics of Study Population According to Hospitalization due to Thromboembolic or Bleeding Events at Follow Up 30-Days after Cardioversion

Variables	Total (n=1100)	Thromboembolic or bleeding		*p* value
		Yes (n=10)	No (n=1090)	
Age	60±11	67±11	60±11	0.042
Gender, female	284 (26)	2 (20)	282 (26)	1.0
Diabetes	267 (25)	3 (30)	264 (24)	0.713
Hypertension	686 (63)	7 (70)	679 (63)	0.752
History of stroke/TIA	147 (13)	5 (50)	142 (13)	0.006
Heart failure	163 (15)	5 (50)	158 (15)	0.009
Myocardial infarction	38 (4)	1 (10)	37 (3)	0.299
CHADS$_2$ score	1.3±1.1	2.6±1.8	1.3±1.1	0.044
CHADS$_2$ score ≥3	151 (14)	4 (40)	147 (14)	0.015
CHA$_2$DS$_2$-VASc score	1.7±1.4	3.9±2.7	1.7±1.4	0.029
CHA$_2$DS$_2$-VASc ≥6	14 (1)	4 (40)	10 (1)	<0.001
HAS-BLED score	2.0±1.2	3.4±1.2	1.9±1.2	<0.001
HAS-BLED score ≥4	114 (10)	6 (60)	108 (10)	<0.001
TEE prior to cardioversion	162 (15)	3 (30)	159 (15)	0.172
INR at cardioversion	2.4±0.9	2.3±0.6	2.4±0.9	0.586
Cardioversion success	947 (87)	8 (80)	939 (87)	0.376
Medications				
Flecainide	494 (45)	5 (50)	489 (45)	0.760
Amiodarone	445 (40)	5 (50)	440 (40)	0.537
Beta-blocker	585 (53)	4 (40)	581 (53)	0.529
Calcium-channel blocker	226 (21)	1 (10)	225 (21)	0.697
Others	119 (11)	0	119 (11)	0.612

CHADS$_2$, Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, and prior ischemic Stroke or transient ischemic attack (doubled); CHA$_2$DS$_2$-VASc, Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes mellitus, and prior ischemic Stroke, transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74, Sex category (female); HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding tendency or predisposition, Labile INR, Elderly (e.g. >65), Drugs (e.g., aspirin, clopidogrel or non-steroidal antiinflammatory drug), alcohol abuse; INR, International Normalised Ratio; TEE, transesophageal echocardiography; TIA, transient ischemic attack.
Numbers in parenthesis represent percentage.

Details of the patients hospitalized due to thromboembolic or bleeding events are presented in Table 2. Patients with stroke had a high CHADS$_2$ score ≥2. The level of INR was below 2 in a patient who suffered a stroke within a week after electric cardioversion. Conversely, patients suffering a stroke beyond one week after cardioversion had an INR of more than 2. All five patients with major bleeding presented with a HAS-BLED score equal or above than 3. In only one patient, the INR level was above 3. On multivariate logistic regression analysis for thromboembolic or bleeding events within 30 days after cardioversion, heart failure [odds ratio (OR) 6.40, 95% confidence interval (CI) 1.77–23.14, $p=0.005$] and history of stroke/TIA (OR 6.23, 95% CI 1.69–22.90, $p=0.006$) were found to be independent predictors (Table 3).

Arrhythmic events

Eight (0.7%) patients were hospitalized for bradyarrhythmia. Baseline characteristics of patients according to the arrhythmic events are summarized in Table 4. Heart rate pre- and post-cardioversion was lower in patients hospitalized with bradycardia than those without ($p=0.01$, $p=0.045$, respectively). The number of antiarrhythmic drugs before cardioversion was not significantly different between 2 groups (2.1±1.1 vs. 1.7±0.8, $p=0.11$). The types of arrhythmia were as follows: junctional bradycardia (n=3), sinus bradycardia (n=2), sinus pause (n=2), and tachybradycardia (n=1) (Table 5). Three patients received permanent pacemaker implantation, while the other patients were managed by changing or discontinuation of antiarrhythmic drugs.

Table 2. Characteristics of Patients with Hospitalization due to Thromboembolic or Bleeding Events in 30 Days after Electric Cardioversions

No.	Sex/age	Event characteristics	Days after cardioversion	CHADS$_2$/ CHA$_2$DS$_2$-VASc	HAS-BLED	INR at cardioversion	INR at admission	Type of anticoagulation/ drugs	Management
				Thromboembolic events					
1	M/70	Ischemic stroke, left occipital multiple lacuna	2	2/3	3	2.5	1.8	Warfarin, aspirin	Increase the target level of INR
2	M/43	Lt. renal infarction	2	2/2	1	2.0	1.15	Warfarin	Renal artery thrombectomy and Increase the target level of INR
3	M/68	Ischemic stroke, right basal ganglia, hemorrhagic transformation	3	4/6	4	2.1	1.7	Warfarin, aspirin	Restart of warfarin and aspirin after the resolution of hemorrhage
4	M/75	Ischemic stroke, left basal ganglia, and corona radiata	9	6/8	4	3.0	3.2	Warfarin, aspirin	Add cilostazole to warfarin
5	F/77	Ischemic stroke, right frontal lobe	15	5/6	4	2.7	2.8	Warfarin	Increase the target level of INR
				Bleeding events					
6	M/82	Vocal cord edema and bleeding	1	5/7	4	2.5	2.5	Warfarin	Discontinuation of warfarin
7	M/69	Gastrointestinal bleeding	1	1/3	3	2.4	2.0	Warfarin	Discontinuation of warfarin
8	M/54	Hematoma at iliopsoas and iliacus muscle	4	1/1	5	2.5	3.7	Warfarin	Discontinuation of warfarin
9	F/72	Gastrointestinal bleeding	7	2/3	4	2.2	1.9	Warfarin	Discontinuation of warfarin
10	M/63	Gastrointestinal bleeding	30	2/2	3	2.6	2.9	Warfarin	Discontinuation of warfarin

F, female; M, male; No., patient number; INR, International Normalised Ratio; CHADS$_2$, Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, and prior ischemic Stroke or transient ischemic attack (doubled); CHA$_2$DS$_2$-VASc, Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes mellitus, and prior ischemic Stroke, transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74, Sex category (female); HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding tendency or predisposition, Labile INR, Elderly (e.g. >65), Drugs (e.g., aspirin, clopidogrel or non-steroidal antiinflammatory drug), alcohol abuse.

In the univariate logistic model for arrhythmic events within 30 days after cardioversion, heart rate pre- (OR 0.95, 95% CI 0.89−0.99, p=0.046) and post- (OR 0.88, 95% CI 0.80−0.97, p=0.008) cardioversion were independent predictors of arrhythmic events after cardioversion.

DISCUSSION

Main findings
In this study, we examined the presence of risk factors and their

association with cardiovascular events following electrical cardioversion of AF. The cardiovascular events rate of elective cardioversion for AF using current consensus recommendation was low. Of 1100 patients, there were 18 (1.6%) cases of cardiovascular events related hospitalizations. Heart failure and history of stroke/TIA were strong predictors of thromboembolic or bleeding events. There was a low heart rate pre- and post-cardioversion in those who experienced an arrhythmic event.

Thromboembolism and bleeding events
The success rate of cardioversion was 87% in this study, which

Table 3. Univariate and Multivariate Analysis of Predictors of Thromboembolic or Bleeding Events after Cardioversion

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.07 (1.00–1.14)	0.04	1.05 (0.98–1.12)	0.15
History of stroke/TIA	6.62 (1.89–23.15)	0.003	6.23 (1.69–22.90)	0.006
Heart failure	5.85 (1.67–20.43)	0.006	6.40 (1.77–23.14)	0.005

OR, odds ratio; CI, confidence interval; TIA, transient ischemic attack.

Table 4. Baseline Characteristics of Study Population According to Hospitalization due to Arrhythmic Events at Follow Up 30-Days after Cardioversion

Variables	Bradyarrhythmia		p value
	Yes (n=8)	No (n=1092)	
Age	55±15	60±11	0.234
Gender, female	4 (50)	280 (26)	0.216
Diabetes	2 (25)	265 (24)	1.0
Hypertension	3 (38)	683 (63)	0.156
Heart failure	2 (25)	161 (15)	0.341
History of stroke	1 (13)	146 (14)	1.0
History of MI	0	38 (4)	1.0
Heart rate at pre-cardioversion	64±12	77±19	0.045
Heart rate at post-cardioversion	49±7	61±12	0.01
TEE prior to cardioversion	0	162 (15)	0.613
Unsuccessful cardioversion	0	138 (13)	0.275
Medications			
Flecainide	6 (75)	488 (45)	0.150
Amiodarone	2 (25)	443 (41)	0.485
Beta-blocker	6 (75)	579 (53)	0.295
Calcium-channel blocker	1 (13)	225 (21)	1.0
Others	2 (25)	117 (11)	0.211

TEE, transesophageal echocardiography; MI, myocardial infarction.
Numbers in parenthesis represent percentage.

Table 5. Characteristics of Patients with Hospitalization due to Arrhythmic Events in 30 Days after Electric Cardioversions

No.	Sex/age	Characteristics (ECG findings)	Days after cardioversion	Antiarrhythmic drug	Management
1	M/73	Sick sinus syndrome (Junctional bradycardia)	0	Diltiazem, amidarone	Discontinuation of AAD
2	F/79	Sick sinus syndrome (Junctional bradycardia)	0	Flecaininde, digoxin	Discontinuation of AAD
3	M/66	Sick sinus syndrome (Sinus bradycardia)	1	Metoprolol, amidarone	Discontinuation of AAD
4	F/44	Sick sinus syndrome (Sinus pause)	1	Flecainide, atenolol	Permanent PM
5	M/47	Sick sinus syndrome (Junctional bradycardia)	3	No	Permanent PM
6	F/49	Sick sinus syndrome (Sinus bradycardia)	4	Flecainide, verapamil,	Permanent PM
7	F/39	Sick sinus syndrome (Sinus pause)	6	Flecainide, atenolol	Discontinuation of AAD
8	M/46	Tachybrady syndrome	26	Flecainide, propranolol	Discontinuation of AAD

AAD, antiarrhythmic drug; ECG, electrocardiography; M, male; F, female; PM, pacemaker.

was lower than those reported by previous studies.[16,17] However, this study included the majority of AF >48 hours. A study, which included the majority of AF >48 hours, showed successful rate similar to this study.[14]

Earlier studies[7,18,19] reported the risk of thromboembolism in the absence of adequate anticoagulation to be highest during the first week following cardioversion (5.6%).[8] In the present study, stroke was observed during the first week in patients with low INR less than 2 at the time of admission due to a event. The use of anticoagulation in the setting of cardioversion has not adequately been evaluated in randomized prospective trials, and the current recommendation of therapeutic anticoagulation with warfarin for at least 3 weeks before and 4 weeks after cardioversion is based on small, nonrandomized observational and retrospective studies.[8,11,20] Prospective therapeutic warfarin data from the ACUTE and RE-LY trials have demonstrated 30-day post cardioversion clinical thromboembolism rates of 0.5 and 0.6 percent, respectively.[21,22] Others, however, have failed to show an agreement on predictors for these events.[14,16,17] On the other hand, the present study demonstrated that patients with higher $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores with a prior history of stroke/TIA and heart failure presented with a higher risk of thromboembolic or bleeding events after cardioversion, therefore, warrants careful attention.

As the risk of bleeding tends to be higher among Asians compared to Caucasians, some studies recommended maintenance of a lower target INR for prophylactic anticoagulation in Asian patients with AF.[23-25] Nevertheless, the present study found that maintaining an INR of between 2 to 3 did not result in a higher risk of major bleeding, implying that it is perhaps safe to maintain an INR value as recommended for cardioversion in AF.

Arrhythmic events

Previously, the prevalence of bradyarrhythmic events post-cardioversion has been reported to be between 0.8 and 1.5%.[15,26-28] In comparison, however, the prevalence of arrhythmic events related to hospitalization in the present study was relatively lower. Unlike previous studies, our present study restricted the outcome to only serious arrhythmic events requiring hospitalization, which may, in part, explain the disparity in findings observed. In our study, 38% of patients hospitalized for bradyarrhythmic events underwent permanent pacemaker insertion. Consistently, Grönberg, et al.[16] reported that permanent pacemaker was implanted in 44% of patients hospitalized for bradyarrhythma. The heart rate before cardioversion was significantly lower in patients with bradyarrhythmic events. This result suggests that we should consider reducing the dosage of rate control drugs in patients with bradycardia before cardioversion.

Study limitation

This study was cross-sectional in nature and limits any interpretation of a causal inference. Inclusion of only Asian patients limits the generalizability and applicability of our findings to other ethnic populations with AF. However, given that most of the previous investigations exploring AF cardiovascular events were performed in Caucasian populations, the findings from this study in Asian population are important to report. In addition, the study population was representative of patients referred for cardioversion at four tertiary care centers. The numbers of events that occurred may be insufficient in identifying a significant relationship between the presence of risk factors and greater risk of adverse cardiovascular events following electrical cardioversion in AF. On the other hand, however, this fact points out the fact that cardioversion according to current guideline has a low cardiovascular events rate. Further studies aimed at validating the current study findings in other well-defined populations are needed.

Conclusion

In this study, the incidence of stroke/TIA, major bleedings, and arrhythmic events requiring a hospitalization following cardioversion was found to be low. These observations indicate that the current electric cardioversion guidelines following optimal anticoagulation for more than 4 weeks is safe and represents a low cardiovascular events rate, at least in an Asian population.

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