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ORIGINAL RESEARCH

Early Risk of Stroke in Patients Undergoing Acute Versus Elective Cardioversion for Atrial Fibrillation

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BACKGROUND: Electrical cardioversion (ECV) is routinely used to restore sinus rhythm in patients with symptomatic atrial fibrillation. The European guidelines have been updated in recent years. Current information on differences in the risk for stroke after acute versus elective ECV is lacking.

METHODS AND RESULTS: All patients with a first-time acute or elective ECV in the Stockholm regional health care data warehouse from 2011 to 2018 were included. Cox regression analyses were performed evaluating ischemic or unspecified stroke within 30 days after ECV with adjustments for the CHA_2DS_2-VASc score, medical treatment, and year of inclusion. The study included 9139 patients, 3094 after acute and 6045 after elective ECV. The mean age was 65.9±11.3 years, 69.5% were men, and the mean CHA_2DS_2-VASc score was 2.4±1.7. Before the intervention, 49.6% of patients with an acute ECV and 96.4% of those with an elective ECV had claimed an oral anticoagulant prescription. Ischemic or unspecified stroke occurred in 26 (0.28%) patients within 30 days. The unadjusted risk was higher after acute compared with elective ECV (hazard ratio [HR], 2.29; 95% CI, 1.06–4.96), whereas there was no difference after multivariable adjustments (adjusted HR, 0.99; 95% CI, 0.36–2.72). Both non–vitamin K oral anticoagulants (adjusted HR, 0.28; 95% CI, 0.08–0.98) and warfarin (adjusted HR, 0.17; 95% CI, 0.05–0.53) were associated with a lower risk for stroke compared with no anticoagulation.

CONCLUSIONS: Acute ECV was associated with a higher unadjusted risk for stroke than elective ECV, but the risk was similar after adjustment for anticoagulant treatment. This study indicates the importance of anticoagulation before ECV according to recent European guidelines.

Key Words: anticoagulant ■ arrhythmia ■ atrial fibrillation ■ cardioversion ■ thromboembolism

Atrial fibrillation (AF) is the most common arrhythmia. Many patients with AF experience disabling symptoms and AF is associated with significant health care consumption including frequent emergency department (ED) visits.[1] Rhythm control therapies like antiarrhythmic drugs and catheter ablation are associated with substantial recurrence rates and not suitable in all patients.[2] Therefore, cardioversion remains an essential tool to restore sinus rhythm in routine AF management.

Electrical cardioversion (ECV) is known to be more effective than medical cardioversion for symptomatic AF. Irrespective of the mode, cardioversion is complicated by thromboembolic complications.[3] Thromboembolic risk can be reduced by adequate anticoagulation treatment[4] or transesophageal ultrasound guided exclusion of left atrial thrombus transesophageal echocardiogram before conversion and by continued anticoagulation 4 weeks afterwards.[5] Non–vitamin K antagonist oral anticoagulants (NOACs) have replaced warfarin to a large extent in clinical practice.[6] NOACs have a rapid onset of anticoagulation effect, fewer drug and food

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CLINICAL PERSPECTIVE

What Is New?

- Electrical cardioversion is a routine procedure both in the acute and elective setup to restore sinus rhythm in patients with symptomatic atrial fibrillation.

What Are the Clinical Implications?

- Risk for stroke is very low after electrical cardioversion when adequate anticoagulation and guideline recommendation follows.

Nonstandard Abbreviations and Acronyms

ECV	electrical cardioversion
NOAC	non–vitamin K oral anticoagulant
OAC	oral anticoagulant

interactions [7] and facilitate shorter waiting times to cardioversion than warfarin.[8]

In some situations, an emergency cardioversion must be performed in patients with AF who are hemodynamically unstable regardless of prior oral anticoagulant (OAC) treatment. However, in the past decade there has been a shift in the European guidelines on acute ECV for hemodynamically stable AF. In 2010, acute ECV for rhythm control was indicated without prior OAC even in the presence of risk factors for stroke if the onset was <48 hours or after a transesophageal echocardiography without a sign of thrombus in the patient with an onset of ≥48 hours.[9] According to the more cautious current European Society of Cardiology guidelines, acute ECV can be considered in patients without prior OAC treatment in AF if the onset was <12 hours and the patient has no history of thromboembolism or within 48 hours if the patient has a low risk for stroke according to CHA_2DS_2-VASc (≤1 for men and ≤2 for women).[10]

Interestingly, the risk of thromboembolic complications associated with acute versus elective conversion of AF has not been studied in greater detail and current data to inform decisions on acute or elective cardioversion from the NOAC era is lacking. We sought to investigate the incidence of ischemic or unspecified stroke and to compare the risk of stroke during the first 30 days in patients who underwent acute ECV compared with elective ECV.

METHODS

There was no direct patient or public involvement in the study, and patients were waived from informed consent. The study was approved by the Regional Ethical Review Board in Stockholm. The authors declare that all supporting data are available within the article.

Study Population

This population-based cohort study included all patients in the Stockholm Region with a first ECV of AF between January 1, 2011, and December 31, 2018. Individuals with mechanical heart valves or a mitral stenosis were excluded (Figure 1). Data were collected from the administrative health data register of the

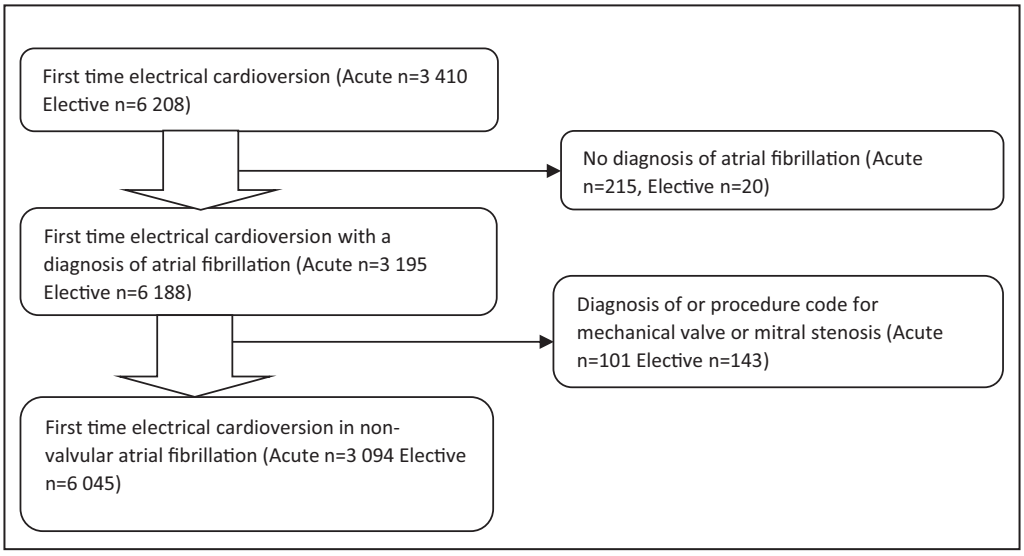

Figure 1. Study inclusion flowchart of 9139 patients with nonvalvular atrial fibrillation with first-time acute or elective electrical cardioversion from 2011 to 2018 in the Stockholm Region.
All instances of atrial fibrillation refer to nonvalvular atrial fibrillation.

Stockholm Region (Vårdanalysdatabasen), that is, the Swedish regional health care data warehouse.[11] This register contains anonymized data for all individuals in the region (2.3 million inhabitants) including diagnoses, age, sex, prescription claims, hospitalizations and other health care consultations, migration, and death. Vårdanalysdatabasen also contains individual level data on all prescription drugs dispensed to inhabitants in the region since July 2010. This information is derived from the Swedish Prescribed Drug Register (National Board of Health and Welfare).[12]

Acute or elective ECV was defined based on procedure codes (Table S1). Comorbidity was defined as at least 1 registration of each diagnosis (*International Classification of Diseases, Tenth Revision* [*ICD-10*] codes) as the main or secondary diagnosis in primary or secondary care (including both outpatient visits and hospitalizations) during the 5 years before the index ECV (Table S2). This information was also used to calculate the CHA_2DS_2VASc score. Transesophageal echocardiography was considered if recorded within 7 days before the ECV. Drugs at baseline were included when claimed within 6 months prior up until the index date (Table 1). Only the last claimed OAC was included.

Management of ECV in the Stockholm Region

Patients with AF considered for elective ECV usually undergo a standardized preprocedural protocol according to regional recommendations based on international guidelines.[13–15] Patients must be on adequate anticoagulation treatment at least 3 weeks before and 4 weeks after ECV either with NOAC or warfarin with an international normalized ratio 2.0 to 3.0. If there is an uncertain duration of AF or any doubt regarding anticoagulation status or if a patient needs early cardioversion, then a transesophageal echocardiography is recommended to exclude left atrial thrombus. According to regional treatment algorithms, warfarin was the first-line recommendation for thromboembolic prophylaxis in AF until 2014, followed by NOAC (most often apixaban).

A maximum of 3 to 4 shocks (150–200 joule) is delivered from a biphasic defibrillator in synchronized mode via self-adhesive electrode pads preferably in the anterior–posterior position.

Based on physician judgment, acute ECV is indicated in case of hemodynamic compromise in an emergency department or inpatient setting and may be considered for patients with symptomatic AF.

Definitions of Outcomes

The primary outcome was ischemic or unspecified stroke (I63 or I64) during the first 30 days after acute or elective ECV. Ischemic and unspecified strokes were included only if they occurred as the main or first secondary diagnosis in inpatient hospital-based acute somatic care as previously described.[16]

Statistical Analysis

Descriptive statistics were used for crude estimates with data presented as proportions or mean values with 95% CIs and standard deviations (SD), as appropriate.

Kaplan–Meier curves were presented for the primary end point. To evaluate the proportional hazard assumption, we visually examined the Kaplan–Meier diagram as well as scatterplot smooths of scaled Schoenfeld residuals. Cox regression analyses were performed for unadjusted and adjusted estimates of the hazard ratios (HRs) evaluating the ischemic or unspecified stroke (I63 or I64) during the first 30 days after acute or elective ECV attributed to AF as primary end point. The multivariable models were adjusted for known major confounders for stroke such as age, sex, congestive heart failure, hypertension, diabetes mellitus, previous transient ischemic attack/stroke or thromboembolism, and previous history of any vascular diseases. Adjustments were made for the CHA_2DS_2-VASc score as a continuous variable, anticoagulant treatment, and year of inclusion. As a sensitivity analysis, we evaluated if adding the use of antiarrhythmic agents would change the results of the multivariable model. Patients were censored at the primary end points, death, migration out of the region, or at the end of follow-up. Furthermore, a sensitivity analysis was performed investigating the risk for stroke during the first 7 days after ECV.

All statistical analyses were performed using SAS Enterprise Guide 8.2 (SAS Institute Inc., Cary, NC), and the 5% level of significance was considered.

RESULTS

There were 9139 patients with a first-time ECV of whom 3094 had an acute and 6045 an elective ECV (Table 1). The number of ECV was stable over the years (Table 2). The patients had a mean age of 65.9±11.3 years and a mean CHA_2DS_2-VASc of 2.4±1.7; 69.5% were men (Table 1). Hypertension was the most common comorbidity followed by heart failure and vascular disease, whereas about 7% had a history of ischemic or unspecified stroke. During the 6 preceding months, 49.6% of patients with an acute ECV and 96.4% of those with an elective ECV had claimed an OAC prescription; 9.2% and 5.7% had claimed antiarrhythmic agents (Table 1). The proportion of patients without OAC decreased from 22.8% to 14.4% during the study period in the whole cohort.

Table 1. Baseline Table of 9139 Patients With Atrial Fibrillation With First-Time Acute or Elective Electrical Cardioversion From 2011 to 2018 in the Stockholm Region

	Total	Elective cardioversion	Acute cardioversion
Number of patients	9139	6045	3094
Age, y	65.9±11.3	67.0±10.0	63.7±13.1
CHA_2DS_2VASc	2.4±1.7	2.5±1.6	2.2±1.8
Male sex	6348 (69.5)	4319 (71.5)	2029 (65.6)
Age 0–64 y	3459 (37.9)	2046 (33.9)	1413 (45.7)
Age 65–74 y	3752 (41.1)	2682 (44.4)	1070 (34.6)
Age 75–79 y	1215 (13.3)	874 (14.5)	341 (11.0)
Age ≥80 y	713 (7.8)	443 (7.3)	270 (8.7)
Heart failure	2108 (23.1)	1548 (25.6)	560 (18.1)
Hypertension	5314 (58.2)	3636 (60.2)	1678 (54.2)
Diabetes mellitus	1190 (13.0)	829 (13.7)	361 (11.7)
Ischemic stroke/TIA or peripheral embolus	638 (7.0)	430 (7.1)	208 (6.7)
Vascular disease	1481 (16.2)	913 (15.1)	568 (18.4)
Other comorbidity			
Cancer	1181 (12.9)	781 (12.9)	400 (12.9)
Dementia	42 (0.5)	21 (0.4)	21 (0.7)
Alcohol abuse	314 (3.4)	220 (3.6)	94 (3.0)
Anemia	576 (6.3)	356 (5.9)	220 (7.1)
Renal disease	321 (3.5)	184 (3.0)	137 (4.4)
Liver disease	110 (1.2)	65 (1.1)	45 (1.5)
Obesity	677 (7.4)	482 (8.0)	195 (6.3)
COPD/emphysema	538 (5.9)	375 (6.2)	163 (5.3)
Gastric/duodenal bleeding	25 (0.3)	15 (0.3)	10 (0.3)
Intracranial bleed	70 (0.8)	40 (0.7)	30 (1.0)
Any severe bleed	299 (3.3)	193 (3.2)	106 (3.4)
Venous thromboembolism	419 (4.6)	274 (4.5)	145 (4.7)
Frequent falls, ≥2 registrations	519 (5.7)	332 (5.5)	187 (6.0)
Prior transesophageal echocardiography	59 (0.7)	0	59 (1.9)
Medication			
Apixaban	2451 (26.8)	1991 (32.9)	460 (14.9)
Dabigatran	1052 (11.5)	795 (13.2)	257 (8.3)
Edoxaban	3 (0.0)	2 (0.0)	1 (0.0)
Rivaroxaban	331 (3.6)	223 (3.7)	108 (3.5)
Warfarin	3526 (38.6)	2816 (46.6)	710 (23.0)
No OAC	1776 (19.4)	218 (3.6)	1558 (50.4)
LMWH	376 (4.1)	241 (4.0)	135 (4.4)
Lipid-lowering treatments	2670 (29.2)	1796 (29.7)	874 (28.3)
Antiarrhythmic agents	632 (6.9)	346 (5.7)	286 (9.2)

Data are provided as mean±SD or number (percentage). COPD indicates chronic obstructive pulmonary disease; LMWH, low molecular weight heparin; OAC, oral anticoagulant; and TIA, transient ischemic attack.

Although warfarin was the most common treatment in 2011 (77.2%) it had been replaced by apixaban in 2018 (68.2%) (Table 2).

In the main analysis, 68 patients were censored. There were 57 deaths (0.62%) and 11 patients who migrated out of the region (0.12%).

Stroke Risk

A total of 26 patients (0.28%; 95% CI, 0.18%–0.39%) experienced the primary outcome of ischemic or unspecified stroke within 30 days after ECV (Table 3). The absolute risk of stroke was 0.45% (95% CI, 0.22%–0.69%) in patients who underwent acute

Table 2. Treatment per Year of Inclusion in 9139 Patients With First-Time Electrical Cardioversion for Atrial Fibrillation From 2011 to 2018

	2011	2012	2013	2014	2015	2016	2017	2018	Total
Warfarin	807 (77.2)	750 (73.6)	601 (56.9)	571 (48.9)	435 (33.0)	176 (15.9)	117 (9.8)	69 (5.6)	3526
Apixaban	0	0	4 (0.4)	23 (2.0)	282 (21.4)	555 (50.1)	749 (62.8)	838 (68.2)	2451
Dabigatran	0	55 (5.4)	208 (19.7)	287 (24.6)	234 (17.7)	103 (9.3)	74 (6.2)	91 (7.4)	1052
Rivaroxaban	1 (0.1)	0	10 (1.0)	38 (3.3)	110 (8.3)	66 (6.0)	55 (4.6)	51 (4.2)	331
Edoxaban	0	0	0	0	0	0	0	3 (0.2)	3
No oral anticoagulant	238 (22.8)	214 (21.0)	233 (22.1)	250 (21.4)	258 (19.6)	208 (18.8)	198 (16.6)	177 (14.4)	1776
Total	1046	1019	1056	1169	1319	1108	1193	1229	9139

Data are provided as number or number (percentage).

ECV and 0.20% (95% CI, 0.09%–0.31%) in patients who underwent elective ECV. The unadjusted risk of stroke was higher in patients who underwent acute compared with elective ECV (HR, 2.29; 95% CI, 1.06–4.96). However, there was no increased risk after multivariable adjustment (adjusted HR, 0.99; 95% CI, 0.36–2.72). Overall, patients on NOAC (adjusted HR, 0.28; 95% CI, 0.08–0.98) and warfarin (adjusted HR, 0.17; 95% CI, 0.05–0.53) had a lower risk of stroke compared with those who were not on OAC. The risk of stroke after ECV decreased continuously from 2011 to 2018 (Table 4).

To confirm the role of oral anticoagulation, we separately analyzed patients who underwent acute ECV. Prior OAC treatment was associated with a lower risk of stroke compared with no treatment after adjustments for CHA_2DS_2-VASc and year of inclusion (adjusted HR, 0.12; 95% CI, 0.03–0.55). The absolute risk of stroke was low (0.21%; 95% CI, 0.00%–0.49%) after acute ECV without OAC at low risk according to CHA2DS2-VASc (≤1 for men and ≤2 for women) but increased at higher CHA2DS2-VASc scores (1.70%; 95% CI, 0.82–3.10). There were 59 transesophageal echocardiograms recorded, and none of these patients had a stroke in the following 30 days.

There were 195 (6.3%) patients who had a new cardioversion within 30 days after acute ECV while 342 (5.7%) patients had a new cardioversion within 30 days after elective ECV.

Most of the outcomes occurred during the first week after ECV (Figure 2). Visual examination of scatterplot smooths of scaled Schoenfeld residuals also indicated some risk of nonproportionality during the first 7 days after ECV. A sensitivity analysis investigating the risk for stroke during the first 7 days after ECV showed similar results as the main analysis (Table S3). Adding antiarrhythmic agents to the multivariable model did not change the associations of the main analysis (Table S4). In addition, to confirm the results, we performed a sensitivity analysis using logistic regression instead of Cox regression to evaluate stroke during the first 30 days after ECV, which showed almost identical associations as the main analysis (Table S5).

DISCUSSION

This population-based cohort study from the Stockholm Region indicates a low risk for stroke within 30 days. However, the risk for stroke was

Table 3. Risk for Ischemic or Unspecified Stroke Within 30 Days After Electrical Cardioversion in 9139 Patients With Atrial Fibrillation

Type of cardioverson	CHA_2DS_2-VASc	No oral anticoagulant: number, percentage (95% CI), or 0/number of cardioversions	NOAC: number, percentage (95% CI), or 0/number of cardioversions	Warfarin: number, percentage (95% CI), or 0/number of cardioversions
Elective		218	3011	2816
	0	0/51	0/379	0/264
	1	0/32	0.48 (0.00–1.02)	0.21 (0.00–0.61)
	2–4	0.88 (0.00–2.61)	0.17 (0.00–0.37)	0.23 (0.00–0.46)
	5–9	0/22	0/285	0/351
Acute		1558	826	710
	0	0.21 (0.00–0.61)	0/64	0/55
	1	0.25 (0.00–0.75)	0/150	0/78
	2–4	1.22 (0.32–2.11)	0/518	0/442
	5–9	2.86 (0.00–6.84)	0/94	1.48 (0.00–3.52)

NOAC indicates non–vitamin K oral anticoagulant.

Table 4. Univariate and Multivariable HRs for Ischemic or Unspecified Stroke Within 30 Days of First-Time Electrical Cardioversion in 9139 Patients With Atrial Fibrillation From 2011 to 2018

	Univariate HR (95% CI)	Multivariable HR (95% CI)	Multivariable HR (95% CI)
Acute vs elective cardioversion	2.29 (1.06–4.96)	2.41 (1.11–5.21)	0.99 (0.36–2.72)
CHA_2DS_2-VASc, per point	1.27 (1.03–1.57)	1.28 (1.04–1.57)	1.36 (1.12–1.65)
Year of inclusion, per y	0.83 (0.70–0.99)	0.82 (0.69–0.98)	0.81 (0.66–1.00)
NOAC vs no oral anticoagulant	0.21 (0.08–0.56)		0.28 (0.08–0.98)
Warfarin vs no oral anticoagulant	0.27 (0.11–0.67)		0.17 (0.05–0.53)

HR indicates hazard ratio; and NOAC, non–vitamin K oral anticoagulant.

substantially higher after acute ECV than elective ECV, probably caused by a lack of protection with OACs. Acute ECV performed without anticoagulant treatment at low CHA_2DS_2-VASc scores according to recent guidelines was associated with a low risk for stroke.

The patients with a first-time ECV in the present study were substantially younger than both the total AF cohort in the region (65.9 versus 75.0) and patients with AF who initiated OAC treatment for the first time (65.9 versus 72.9–74.1).[6,16] This may reflect clinical practice to use ECV preferably in the early course of disease and a preference to rhythm control over rate-control strategies in patients at younger ages. Still, 7.8% of the patients who underwent ECV were aged 80 years or older. From 2011 to 2018, there was an increasing proportion of patients treated with OACs before ECV, reflecting an increase in awareness and following the guideline recommendation. There was also a shift from warfarin to NOAC, which

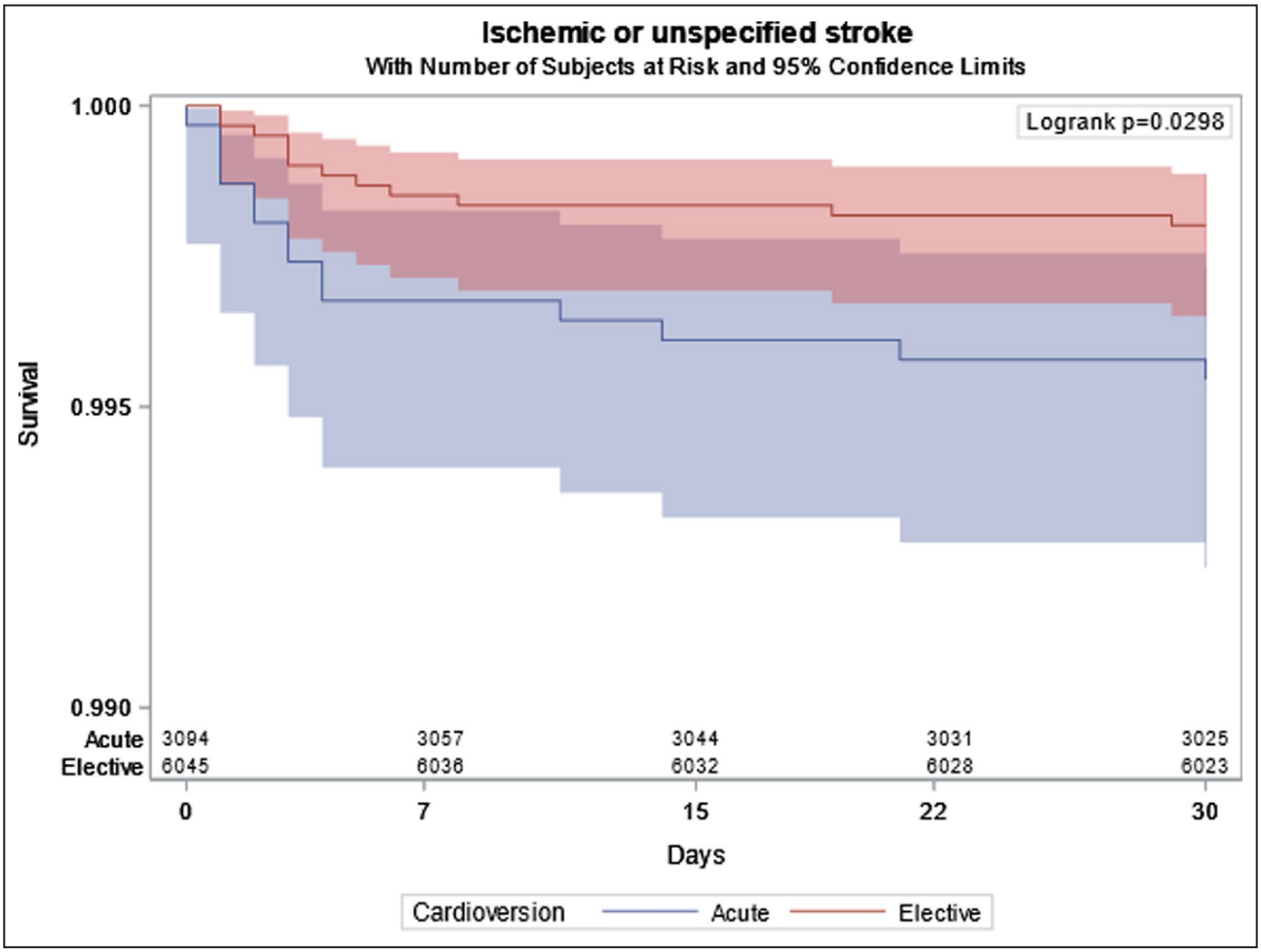

Figure 2. Kaplan–Meier diagram of ischemic or unspecified stroke in 9139 patients with atrial fibrillation with first-time acute or elective electrical cardioversion from 2011 to 2018.

is in line with treatment patterns in the total AF population. Both NOAC and warfarin were associated with a lower risk for stroke than no OAC treatment. The study was inadequately powered to investigate clinically relevant differences between the OACs, but a decreasing risk for stroke after ECV could be seen from 2011 to 2018.

The stroke rate in this study is similar to a previous report comparing ECV and pharmacological cardioversion.[17] Moreover, in a large registry-based cohort study between 2000 and 2008, the incident rate for thromboembolism 30 days after ECV was 4.0 per 100-person years with warfarin and 10.33 without treatment, which corresponds to incidences of thromboembolism of 0.33% and 0.85%, respectively, during the first 30 days, as expected slightly higher than the incidence of ischemic or unspecified stroke in the present study.[18] Similarly, in a Finish study on ECV, the risk for systemic embolism was 0.4% in patients with CHA_2DS_2-VASc scores 0 to 1 without any anticoagulant treatment, slightly higher than in the present study.[19]

The CHA_2DS_2-VASc score and AF duration are known predictors of stroke after ECV.[20] This may partly be linked to atrial stunning after ECV, facilitating the generation of micro thrombus in the atrium and atrial appendage.[21] When atrial contractions restore after EVC, a thrombus may dislodge and thus explain why stroke incidence peaks several hours or days after ECV. Permanent AF is associated with decreased atrial contractile function and increased atrial volumes; 2 features that have been associated with increased risk for stroke.[22] Even patients treated with OACs can have a stroke, but the risk is reduced. One way to minimize the stroke risk after ECV is to perform transesophageal echocardiography to exclude a thrombus in the left atrium and its appendage before ECV. Only a minority of the patients in our cohort had procedure codes for transesophageal echocardiography before ECV, and none of these patients suffered any type of stroke. There were not enough observations to draw any conclusions regarding this procedure in this study.

One important aspect after ECV is to maintain sinus rhythm to prevent the recurrence of AF. Appropriate investigation and management of underlying coronary heart disease, hypertension, and heart failure are of great importance to prevent stroke and death in many of the patients with AF.[23] Antiarrhythmic drugs can help to prevent recurrence of AF and maintain sinus rhythm but have limitations in clinical use for many reasons. In our cohort, only about 7% of the patients had antiarrhythmic medications before the first-time ECV. Similarly, according to recent guidelines, ablation therapy is now an established treatment for rhythm control.[24]

Limitations and Strengths of the Study

The main limitations of our study are, as for all registry-based observational studies, the possibility for misclassification as well as confounding by indication. To address these limitations, only specific procedure codes for AF related ECV were included, patients without an *ICD-10* code for AF were excluded, and appropriate adjustments were made in multivariable models. The risk for residual confounding that we could not control for should be considered. Interpretations of the results must be made in the context of a publicly funded health care setting in a large region comprising both the capital and surrounding suburban and rural areas. Results from the multivariable adjustments should be interpreted cautiously because of the limited number of outcomes. Furthermore, the strength of association between acute versus elective cardioversion and stroke was reduced when considering only strokes within 7 days after ECV, and the reported difference may be attributed to chance alone (Table S3 primary outcome comparison of interest was 95% CI, 0.93–5.63). We do not have any data regarding the duration of AF before ECV. Some strokes that occurred during the first 30 days after ECV might be associated with other factors and thus not caused by the investigated procedure.[25] Other possible ECV complications other than stroke were not investigated.

Nevertheless, the main strength of our study was the population-based large cohort of well-characterized patients with AF with minimal loss to follow-up. The administrative health data register of the Stockholm Region covers both primary and secondary care for the whole population and has been extensively used, notably for other studies of AF.[6,11,14] Although the absolute number of ischemic stroke events in patients with acute ECV was small, we found a clear indication of higher event rates with acute compared with elective ECV, which could be plausibly explained in multivariable models by a lack of anticoagulant treatment and may also be attributed to underlying comorbidities.

In conclusion, this is so far the largest cohort study comparing acute and elective cardioversion. It indicates a low risk for stroke within 30 days after both acute and elective ECV with improvements during the study period. Acute ECV was associated with a higher unadjusted risk for stroke than elective ECV, but the risk was similar after adjustment for anticoagulant treatment. This study supports the importance of anticoagulation before ECV according to recent guidelines.

ARTICLE INFORMATION

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Disclosures

Dr Holzmann received consultancy honoraria from Idorsia. Dr Braunschweig is a consultant to Medtronic and Biotronik and has received speaker honoraria from Boehringer and Pfizer. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S5

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Supplemental Material

Table S1. Definitions of cardioversion and baseline co-morbidities by ICD-10, primary care codes and procedure codes.

Diagnosis or procedure	ICD-code or procedure code beginning with
Alcohol abuse	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714
Anaemia	D50-64
Any severe bleeding	I60-62, I690-I692, S064-S066, I850, I983, K25-28 (sub codes 0-2 and 4-6 only), K625, K922, D500, D629, J942, I312, H431, H356
Atrial fibrillation	I48
Cancer	entire C-series
Cardioversion of atrial fibrillation	Elective: DF026 Acute: DF027
COPD/Emphysema	J43-44
Dementia	F00-F03
Diabetes	E10-E14
Frequent falls (more than one registration)	W00-19
Gastric duodenal bleeding	K25-28 (sub codes 0-2 and 4-6 only)
Heart failure	I50
Hypertension	I10-I15

Ischemic stroke, arterial embolism, and stroke, unspecified	I63, I64, I679, I693, I694, I698, I67-, I69-, Z866A, Z866B, Z867C, G450, G451, G452, G453, G458, G45.9, G45-, I74
Intracranial bleeding	I60-I62, I690-I692, S064-S066
Liver disease	K70-77
Mechanical valve	Z952 Procedure codes: FCA60, FDC10, FGE00, FGE96, FJF00, FJF96, FKD00, FKD96, FMD00, FMD96
Mitral stenosis	I050, I052, I342
Obesity	E65-66
Renal disease	N17, N183, N184, N185, N189
Transesophageal echocardiography	AF064
Vascular disease	I20-I25, I70, I739
Venous thromboembolism	I26, I80 (I80.0 excluded), I82 (I82.1 excluded), I27.82

Table S2. ATC-codes of the studied treatments.

Treatment	**ATC-code beginning with**
Antihypertensive treatments	C03 C07 C08 C09
Antiarrhythmic drugs	C01B
Apixaban	B01AF02
Dabigatran	B01AE07
Dipyridamole	B01AC07
Edoxaban	B01AF03
Lipid lowering treatments	C10
Low molecular weight heparin (LMWH)	B01AB04 B01AB05 B01AB10
Oral anticoagulant (OAC)	B01AE07 B01AF01 B01AF02 B01AF03 B01AA
Rivaroxaban	B01AF01
Warfarin	B01AA

Table S3. Univariate and multivariable hazard rates (HR) for ischemic or unspecified stroke within 7 days of first-time electric cardioversion in 9 139 patients with atrial fibrillation 2011-2018.

	Univariate HR (CI 95)	Multivariable HR (CI 95)	Multivariable HR (CI 95)
Acute vs elective cardioversion	2.18 (0.89-5.36)	2.29 (0.93-5.63)	1.02 (0.31-3.31)
CHA2DS2-VASc (per point)	1.29 (1.01-1.64)	1.29 (1.02-1.64)	1.37 (1.09-1.73)
Year of inclusion (per year)	0.81 (0.66-1.00)	0.80 (0.65-0.99)	0.76 (0.59-0.98)
NOAC vs No oral anticoagulant	0.26 (0.09-0.76)		0.39 (0.09-1.69)
Warfarin vs No oral anticoagulant	0.28 (0.09-0.83)		0.17 (0.04-0.66)

NOAC: Non-vitamin K oral anticoagulants; CI: Confidence interval; HR: Hazard ratio

Table S4. Sensitivity analysis adding antiarrhythmic agents.

	Multivariable HR (CI 95)
Acute vs elective cardioversion	1.02 (0.37-2.87)
CHA2DS2-VASc (per point)	1.35 (1.11-1.65)
Year of inclusion (per year)	0.81 (0.66-1.00)
NOAC vs No oral anticoagulant	0.29 (0.08-1.03)
Warfarin vs No oral anticoagulant	0.18 (0.06-0.58)
Antiarrythmic agents	0

Multivariable hazard rates (HR) for ischemic or unspecified stroke within 30 days of first-time electric cardioversion in 9 139 patients with atrial fibrillation 2011-2018.

NOAC: Non-vitamin K oral anticoagulants; CI: Confidence interval; HR: Hazard ratio

Table S5. Sensitivity analysis using logistic regression.

	Multivariable OR (CI95)
Acute vs elective cardioversion	0.98 (0.35-2.71)
CHA2DS2-VASc (per point)	1.36 (1.11-1.65)
Year of inclusion (per year)	0.81 (0.66-1.00)
NOAC vs No oral anticoagulant	0.28 (0.08-0.99)
Warfarin vs No oral anticoagulant	0.17 (0.05-0.53)

Multivariable odds ratios (OR) for ischemic or unspecified stroke within 30 days of first-time electric cardioversion in 9 139 patients with atrial fibrillation 2011-2018.

NOAC: Non-vitamin K oral anticoagulants; CI: Confidence interval; HR: Hazard ratio