OPEN

Amiodarone Use Is Associated With Increased Risk of Stroke in Patients With Nonvalvular Atrial Fibrillation

A Nationwide Population-Based Cohort Study

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Abstract: Atrial fibrillation (AF), the most common sustained arrhythmia requiring treatment worldwide, is one of the major causes of ischemic stroke. Although amiodarone is commonly used for rhythm control in AF, its relationship with stroke has rarely been addressed.

We evaluated 16,091 patients who were diagnosed with AF (Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] 427.31 and 427.32) between 1998 and 2011; the date of AF diagnosis was set as the index date. Patients with a history of stroke (ICD-9-CM 430–438) who received amiodarone before the index date or during the following 30 days, or who experienced stroke within 30 days of receiving amiodarone were excluded. Finally, 7548 patients with AF were included in this study and divided into 2 groups according to whether they received amiodarone (Anatomical Therapeutic Chemical code C01BD01) during the study period.

The risk of ischemic stroke in AF patients receiving amiodarone was 1.81-fold (95% confidence interval [CI] 1.52–2.16), 1.79-fold (95% CI 1.50–2.14), and 1.78-fold (95% CI 1.49–2.13) higher than in those who did not receive amiodarone, according to crude, Model 1, and Model 2 Cox proportional hazard regression models, respectively. In a demographically stratified analysis, the risk of ischemic stroke was significantly higher in patients aged <65 years, with no comorbidities, who were also taking digoxin or had a low CHA_2DS_2VASc score.

Amiodarone treatment is associated with an increased risk of stroke in patients with AF, especially in those who have an initial low risk of stroke. Antiplatelet drugs and warfarin could reduce the stroke risk in AF patients receiving amiodarone. However, as the combination of digoxin and amiodarone increases the risk of stroke in these patients, the combination of these 2 drugs should be avoided.

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Abbreviations: AF = atrial fibrillation, ATC = Anatomical Therapeutic Chemical, CAD = coronary artery disease, LHID = Longitudinal Health Insurance Database, NHIRD = National Health Insurance Research Database.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia requiring treatment and is one the major causes of ischemic stroke worldwide.[1] The incidence of ischemic stroke among patients with nonvalvular AF is approximately 5% per year and increases with age, resulting in higher morbidity and mortality[2,3] because AF-induced ischemic stroke is more disabling and fatal than other types of ischemic stroke. The treatment of AF includes rhythm correction, rate control, and anticoagulant therapy, and aims to improve the symptoms and reduce the complications. Although warfarin has been commonly used in the past few decades to reduce stroke risk in patients with AF, recent phase III clinical trials have shown that new oral anticoagulants are superior or noninferior to warfarin, with respect to their efficacy in preventing ischemic stroke and systemic embolism.[3]

A cohort study showed that digoxin, a rate control agent, was associated with an increased risk of stroke in patients with nonvalvular AF.[4] Increased expression of CD62P in platelets and platelet-leukocyte conjugates, and endothelial activation markers, was proposed as a possible mechanism to explain the higher risk of stroke in these patients.[5] Furthermore, although the new rhythm control agent dronedarone restores sinus rhythm and reduces hospitalization or death in AF patients,[6] it also maintains sinus rhythm with an efficacy of approximately 40%[7] but increases the rate of stroke from cardiovascular causes in patients with permanent AF.

Despite these adverse effects, maintenance of sinus rhythm is considered an important goal in AF patients because it improves their prognosis by enhancing cardiac function and relieving symptoms. Rhythm management in patients with AF involves electrical and pharmacological cardioversion.[8] Although electrical cardioversion shows a superior success rate (~88%), it entails a risk of thromboembolism (up to 5.6%) when it is performed without anticoagulation.[8,9] The efficacy of pharmacological cardioversion to maintain sinus rhythm using amiodarone is around 50% to 60% and better than other agents, including dronedarone.[7] However, although neurological effects have been reported,[10] large studies investigating the relationship between amiodarone and ischemic stroke among patients with nonvalvular AF are lacking.

Therefore, in this study we aimed to investigate the association between amiodarone and the risk of stroke among a nationwide population-based cohort of 7548 patients with nonvalvular AF.

MATERIAL AND METHODS

Data Source

For this study, we used data from the Longitudinal Health Insurance Database (LHID), which is a part of the Taiwan National Health Insurance Research Database (NHIRD). The NHIRD was set up on March 1, 1995 by the Bureau of National Health Insurance of Taiwan. The LHID includes all medical claims reported between 1996 and 2011 from 1 million beneficiaries randomly selected from among all insurants. Disease definition was based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), as recorded in the NHIRD. Medication definitions were based on the Anatomical Therapeutic Chemical (ATC) classification system. In accordance with the Personal Information Protection Act, the identities of all beneficiaries were recorded by computer. This study was approved by the institutional review board of the China Medical University Hospital, Taiwan.

Study Subjects, Outcomes, and Covariates

We evaluated 16,091 patients who were diagnosed with AF (ICD-9-CM 427.31 and 427.32) between 1998 and 2011 with the date of AF diagnosis set as the index date. Patients with a history of stroke (ICD-9-CM 430–438) who received amiodarone before the index date or during the following 30 days, or who experienced stroke within 30 days of receiving amiodarone were excluded. Finally, 7548 patients with AF were included in this study and divided into 2 groups according to whether they received amiodarone (ATC code C01BD01) during the study period.

Hospitalized ischemic stroke (ICD-9-CM 433 and 434) was defined as the outcome of interest, and cases due to accident were excluded. The first event of hospitalized ischemic stroke was defined as the endpoint event in our study population. Coding of ischemic stroke in the NHIRD was based on the neurologist's diagnosis, brain computer tomography, or brain magnetic resonance imaging findings. All study subjects were followed from the index date to the date on which the outcome was recorded, to the time at which they withdrew from this insurance program, or to the end of 2011, whichever occurred first.

Covariates in this study included age (<65, 65–74, and 75+ years), sex, comorbidities, and medications. Comorbidities included ischemic heart disease, diabetes, hypertension, heart failure, and hyperlipidemia with ICD-9-CM codes 410–414, 250, 401–405, 428, and 272, respectively. The CHA_2DS_2VASc score was also considered as a covariate in this study. Medications used included the antiplatelet agents aspirin, clopidogrel, and dipyridamole; warfarin; digoxin, with ATC codes B01AC06, B01AC04, B01AC07, B01AA03, and C01AA05, respectively. Cardiac conversion (procedure code 18028B) and transcatheter radiofrequency ablation (procedure code 33091A) were also analyzed.

Statistical Analysis

The χ^2 and Student *t* tests were used to examine differences in categorical and continuous variables respectively, between the 2 groups. As not all patients received amiodarone during the study period, we used a Cox proportional hazard model with time-dependent exposure covariates to reduce the bias resulting from overestimation of the effect of amiodarone on ischemic stroke risk. Model 1 controlled for age, sex, ischemic heart disease, diabetes, hypertension, heart failure, hyperlipidemia, antiplatelet agent, warfarin, and digoxin covariates. Model 2 controlled for CHA_2DS_2VASc score, hyperlipidemia, antiplatelet agent, warfarin, and digoxin covariates. The association between ischemic stroke and amiodarone dosage was also assessed. The age-, sex-, comorbidity-, and CHA_2DS_2VASc-score-specific risks of ischemic stroke in patients who received amiodarone was compared with those who did not receive amiodarone. The joint effect of amiodarone- and AF-associated medications on ischemic stroke was also analyzed. All statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc, Carey, NC).

RESULTS

During the study period, 2587 (34.3%) patients with AF received amiodarone and 4961 (65.7%) did not. The mean age in both the groups was comparable (66.0 vs 65.8 years, respectively) (Table 1). Patients who received amiodarone had more comorbidities than those who did not receive the drug, including ischemic heart disease (50.7% vs 41.9%), hypertension (66.3% vs 58.4%), heart failure (66.3% vs 17.6%), and hyperlipidemia (27.2% vs 23.4%). Moreover, amiodarone-treated patients received more medications, including antiplatelet agents (67.3% vs 45.9%), warfarin (20.2% vs 12.0%), and digoxin (67.4% vs 56.7%), and underwent more cardiac conversions (2.63% vs 1.21%) and transcatheter radiofrequency ablations (4.56% vs 1.65%) than nonamiodarone-treated patients.

Furthermore, the results of the crude, Model 1 and Model 2 Cox proportional hazard regression analyses showed that the risk of ischemic stroke was 1.81-fold (95% confidence interval [CI] 1.52–2.16), 1.81 (95% CI 1.50–2.17), and 1.80-fold (95% CI 1.51–2.15) higher, respectively, in patients who received amiodarone ($P < 0.001$ for all models; Table 2). In Model 1, AF patients aged ≥75 and between 65 and 74 years had an increased risk of stroke compared with those aged <65 years (age ≥75 years, hazard ratio [HR] 2.09, CI 1.71–2.56, $P < 0.001$; age 64–75 years, HR 1.79, CI 1.47–2.17, $P < 0.001$). In addition, AF patients with diabetes or hypertension had a higher risk of ischemic stroke (HR 1.44 and 1.41, 95% CI 1.20–1.73 and 1.17–1.70, $P < 0.001$). Patients who also received digoxin had a 1.69-fold increase in the risk of stroke (95% CI 1.41–2.03), whereas those who received an antiplatelet agent or warfarin had a lower risk (HR 0.71 and 0.66, 95% CI 0.61–0.84 and 0.53–0.82, $P < 0.001$). Moreover, cardiac conversion had no effect, but transcatheter radiofrequency ablation reduced stroke risk (HR 0.33, 95% CI 0.09–0.50). The results of Model 2 show that the risk of stroke increased with increasing CHA_2DS_2VASc scores (scores 2–3, HR 2.44, 95% CI 1.93–2.10, $P < 0.001$; scores 4–5, HR 3.36, 95% CI 2.62–4.30, $P < 0.001$; scores >5, HR 4.78, 95% CI 3.37–6.77, $P < 0.001$) compared with patients with CHA_2DS_2-VASc scores of 0 to 1.

Analysis of the risk of stroke stratified by age, sex, or comorbidity showed that patients who received amiodarone had a significantly higher risk than those who did not (Table 3). Moreover, significant differences were observed between the 2 cohorts when patients were stratified by CHA_2DS_2VASc score, except in those with a CHA_2DS_2VASc score >5.

TABLE 1. Patient Demographic CharacteristicS

	Amiodarone Use				
	Yes (N = 2587)		No (N = 4961)		
	n	%	n	%	*P*
Age, y					<0.0001
<65	1091	42.2	2036	41.0	
65–74	746	28.8	1293	26.1	
75+	750	29.0	1632	32.9	
Mean (SD)	66.0	(13.9)	65.8	(16.3)	0.59
Men	1530	59.1	2851	57.5	0.16
Comorbidity					
Ischemic heart disease	1311	50.7	2078	41.9	<0.0001
Diabetes	475	18.4	871	17.6	0.39
Hypertension	1716	66.3	2898	58.4	<0.0001
Heart failure	562	21.7	871	17.6	<0.0001
Hyperlipidemia	704	27.2	1161	23.4	0.0003
CHA_2DS_2VASc score					0.003
0–1	621	24.0	1422	28.7	
2–3	1024	39.6	1855	37.4	
4–5	794	30.7	1422	28.7	
> 5	148	5.72	262	5.28	
Mean (SD)	2.85	(1.69)	2.70	(1.71)	0.0003
Medication					
Antiplatelet agent	1742	67.3	2276	45.9	<0.0001
Warfarin	522	20.2	597	12.0	<0.0001
Digoxin	1744	67.4	2815	56.7	<0.0001
Transcatheter radiofrequency ablation	118	4.56	82	1.65	<0.0001
Cardioversion	68	2.63	60	1.21	<0.0001

Chi-square test and Student *t* test.

Compared with patients who did not receive amiodarone and an antiplatelet agent, patients receiving amiodarone alone had a higher risk of stroke than those taking amiodarone and antiplatelet agents, but this difference was not significant in Model 1. A similar trend was observed in patients who received amiodarone and warfarin, compared with those who received neither. Furthermore, patients who received amiodarone and digoxin had the highest risk of ischemic stroke, followed by those who only received amiodarone, and those who only received digoxin, an effect seen in both the models.

DISCUSSION

Amiodarone displays multiple effects, including sodium, potassium, and calcium channel blocking, and noncompetitive β-blocking.[2] It is the most commonly used drug for rhythm control with superior effects in restoring and maintaining sinus rhythm, reducing the AF recurrence rate, and improving patient quality of life.[2,11–13] However, cardiac and noncardiac adverse events have been reported in patients receiving amiodarone therapy.[10]

The European Society of Cardiology recommends the use of the CHA_2DS_2VASc score to guide the administration of antithrombotic therapy to patients with AF.[14] This scoring system includes 2 risk factor categories: ''major'' and ''clinically relevant nonmajor'' risk factors for stroke. The 2 major risk factors are age ≥75 years, and prior stroke, transient ischemic attack, or thromboembolism, whereas clinically relevant nonmajor risk factors include congestive heart failure, hypertension, diabetes mellitus, vascular disease (myocardial infarction, complex aortic plaque, and peripheral arterial disease), age 65 to 74 years, and female sex. Similarly, the American College of Cardiology Foundation and American Heart Association (AHA) guidelines include diabetes mellitus, hypertension, dyslipidemia, smoking, obesity, and a family history of premature coronary artery disease (CAD) as classical risk factors for CAD.[15] In our population-based cohort of 7548 patients with nonvalvular AF, we found that amiodarone and digoxin use, age, diabetes, hypertension, and CHA_2DS_2VASc score were independent risk factors for stroke, but the use of antiplatelet agents or warfarin had a protective effect. Although amiodarone use was associated with a 1.81-fold increase in the risk of stroke, a higher daily dose of the drug did not increase this risk. AF patients who were taking amiodarone and had no relative comorbidities had a higher risk of stroke than those who had comorbidities (HR 2.79, 95% CI 1.64–4.74, $P < 0.001$, vs HR 1.72, 95% CI 1.42–2.07, $P < 0.001$, Table 3).

Based on the CHA_2DS_2VASc score, age ≥75 and 65 to 74 years are considered a major and a classical risk factor, respectively.[14] Accordingly, in our study, we found that the risk of stroke increased with age (Table 2). Moreover, after adjustment for sex, comorbidities, and medications used, patients who were aged ≥75 years and received amiodarone treatment had a higher risk of stroke than those aged 65 to 74 years (HR 1.85, 95% CI 1.36–2.51, $P < 0.001$, vs HR 1.49, 95% CI 1.10–2.02, $P < 0.05$, Table 3). However, compared with older patients, those <65 years who received amiodarone had a greater risk of

TABLE 2. HRs and 95% CI for Stroke in Time-Depended Models

	Crude HR (95% CI)	Model 1	Model 2
Amiodarone use	1.81 (1.52–2.16)***	1.81 (1.52–2.17)***	1.80 (1.51–2.15)***
Increased dose of amiodarone, per DDD	1.00 (0.999–1.004)	1.00 (0.999–1.004)	1.02 (0.999–1.004)
Age, y			
<65	1.00	1.00	
65–74	2.23 (1.85–2.68)***	1.79 (1.47–2.17)***	
75+	2.91 (2.41–3.51)***	2.09 (1.71–2.56)***	
Men vs women	0.83 (0.72–0.97)*	0.94 (0.81–1.09)	
Comorbidity			
Ischemic heart disease	1.51 (1.30–1.75)***	1.11 (0.94–1.30)	
Diabetes	1.66 (1.39–1.98)***	1.44 (1.20–1.73)***	
Hypertension	2.12 (1.79–2.51)***	1.41 (1.17–1.70)***	
Heart failure	1.48 (1.24–1.77)***	1.04 (0.86–1.25)	
Hyperlipidemia	1.02 (0.86–1.21)	0.86 (0.71–1.03)	0.85 (0.71–1.02)
CHA_2DS_2VASc score			
0–1	1.00		1.00
2–3	2.55 (2.02–3.21)***		2.44 (1.93–3.10)***
4–5	3.65 (2.88–4.63)***		3.36 (2.62–4.30)***
> 5	5.45 (3.89–7.63)***		4.78 (3.37–6.77)***
Medication			
Antiplatelet agent	1.07 (0.92–1.24)	0.71 (0.61–0.84)***	0.75 (0.64–0.88)***
Warfarin	0.73 (0.59–0.90)**	0.66 (0.53–0.82)***	0.62 (0.50–0.76)***
Digoxin	2.03 (1.70–2.41)***	1.69 (1.41–2.03)***	1.77 (1.47–2.12)***
Transcatheter radiofrequency ablation	0.21 (0.09–0.50)***	0.33 (0.14–0.79)*	0.28 (0.12–0.68)**
Cardioversion	0.65 (0.36–1.18)	—	—

Mode 1 was manually adjusted for amiodarone use, age, sex, comorbidity, and medication used. Model 2 was manually adjusted for amiodarone use, hyperlipidemia, CHA_2DS_2VASc score, and medication used. CI = confidence interval, DDD = defined daily dose, HR = hazard ratio.

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

TABLE 3. HRs and 95% CI for Stroke Stratified by Demographic and Clinical Covariates in Time-Dependent Models

	Amiodarone Used vs Covariates HR (95% CI)	
	Model 1	Model 2
Age, y[a]		
<65	2.17 (1.57–3.00)***	2.26 (1.63–3.11)***
65–74	1.49 (1.10–2.02)*	1.49 (1.10–2.02)*
75+	1.85 (1.36–2.51)***	1.82 (1.34–2.47)***
Sex[b]		
Women	1.89 (1.46–2.46)***	1.93 (1.48–2.50)***
Men	1.70 (1.33–2.18)***	1.71 (1.34–2.18)***
Comorbidity[c]		
No	2.79 (1.64–4.74)***	
Yes	1.72 (1.42–2.07)***	
CHA_2DS_2VASc score[d]		
0–1		2.89 (1.78–4.71)***
2–3		1.80 (1.38–2.36)***
4–5		1.61 (1.19–2.17)**
> 5		1.39 (0.71–2.74)

Mode 1: [a]adjusted for sex, comorbidity, and medication used; [b]adjusted for age, comorbidity, and medication used;
[c]adjusted for age, sex, and medication used. Model 2: [a]adjusted for CHA_2DS_2VASc score, hyperlipidemia, and medication used; [b]adjusted for CHA_2DS_2VASc score, hyperlipidemia, and medication used; [d]adjusted for hyperlipidemia, and medication used. CI = confidence interval, HR = hazard ratio.

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

stroke (HR 2.17, 95% CI 1.57–3.00, $P < 0.001$). The stroke risk remained similar after adjustment for CHA_2DS_2VASc score, hyperlipidemia, and medications used. These results suggest that compared with older patients, amiodarone treatment in patients <65 years of age could be associated with a higher stroke risk. In addition, sex is considered another classical risk factor, with women with AF considered to be at a higher risk of stroke. Our results reflected this effect (Table 2). Furthermore, amiodarone use was associated with a higher risk of stroke in women with AF (Table 3).

According to the CHA_2DS_2VASc score, oral anticoagulation should be used in AF patients with a CHA_2DS_2VASc score ≥ 2.[14] As shown in Table 2, we also found that the stroke risk in AF patients increased significantly with the CHA_2DS_2VASc score. However, focusing on the interaction between amiodarone use and CHA_2DS_2VASc score, amiodarone use in AF patients with a CHA_2DS_2VASc score of 0 to 1 was associated with a higher risk of stroke (HR 2.89, 95% CI 1.78–4.71, $P < 0.001$, Table 3). Furthermore, although the stroke risk associated with amiodarone use in AF patients decreased with increasing CHA_2DS_2VASc scores, the stroke risk was not significant in patients with a CHA_2DS_2VASc score >5 (HR 1.39, 95% CI 0.71–2.74, Table 3). One possible explanation may be that the effect of amiodarone use on stroke risk is weaker in AF patients who are already at a higher risk, including those with more comorbidities, aged ≥75 years, and with a CHA_2DS_2VASc score >5. These findings, that is, the interaction of amiodarone with age, sex, comorbidities, and CHA_2DS_2VASc score suggest that amiodarone should be used with caution in AF patients who have a low risk of stroke because of the higher stroke risk associated with amiodarone use.

Chang et al[4] observed that digoxin use increased the risk of stroke in patients with AF, suspecting that the increase in intracellular calcium levels may contribute to digoxin-mediated platelet activation. Moreover, Chirinos et al[5] observed increased levels of CD62P expression in platelets and platelet-leukocyte conjugates, and endothelial activation markers in patients receiving digoxin. In this study, further examination of the interaction between amiodarone and digoxin revealed that digoxin use was an independent risk factor for stroke in AF patients, whether adjusted for amiodarone use, age, sex, comorbidity, and medication used, or for amiodarone use, hyperlipidemia, CHA_2DS_2VASc score, and medication used (HR 1.69, 95% CI 1.41–2.03, $P < 0.001$; HR 1.77 95% CI 1.47–2.12, $P < 0.001$; Table 2). As shown in Table 4, we found that the combined use of digoxin and amiodarone had a cumulative effect on stroke risk in AF patients. However, although the mechanisms underlying this effect are not yet clear, a possible explanation may be that, due to the multiple effects of amiodarone, a crossover effect with digoxin may enhance intracellular calcium levels, thus contributing to digoxin-mediated platelet activation.[5] As prevention of thromboembolism is an important measure to reduce in AF patients, several guidelines for the administration of antithrombotic therapy have been published to address this issue, including the CHA_2DS_2VASc score published by the European Society of Cardiology. In addition, according to the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation,[16] oral anticoagulant therapy is indicated in AF patients with prior stroke, hypertension, heart failure, and diabetes mellitus, whereas acetylsalicylic acid (aspirin) was recommended to AF patients with CAD but without a history of prior stroke, hypertension, heart failure, and diabetes mellitus. In our study, 44.89% patients had ischemic heart disease (or CAD), and antiplatelet agent use among all patients was around 53.23% (4018/7548). Moreover, we found that the ratio of antiplatelet agent use was proportional to the ratio of patients with ischemic heart disease, a finding that resulted in antiplatelet agents and warfarin having a similar protective effect in decreasing the stroke risk of amiodarone. Furthermore, our results show that when administering amiodarone, AF patients should also receive oral anticoagulation therapy with warfarin or antiplatelet agents according to their CHA_2DS_2VASc score to decrease stroke risk (Table 4).

Furthermore, after analysis of cardiac conversion and transcatheter radiofrequency ablation status, we found that

TABLE 4. HRs and 95% CI for Stroke and Stroke-Associated Medications Used in Time-Dependent Models

		Model 1	Model 2
Amiodarone	Antiplatelet agent		
No	No	1.00	1.00
Yes	No	2.25 (1.65–3.06)***	2.26 (1.66–3.08)***
No	Yes	0.76 (0.64–0.91)**	0.80 (0.67–0.96)*
Yes	Yes	1.24 (0.98–1.56)	1.29 (1.02–1.62)*
Amiodarone	Warfarin		
No	No	1.00	1.00
Yes	No	1.78 (1.47–2.17)***	1.76 (1.45–2.14)***
No	Yes	0.66 (0.51–0.84)***	0.61 (0.47–0.78)***
Yes	Yes	1.21 (0.83–1.76)	1.12 (0.77–1.64)
Amiodarone	Digoxin		
No	No	1.00	1.00
Yes	No	1.74 (1.17–2.57)**	1.84 (1.25–2.73)**
No	Yes	1.68 (1.37–2.06)***	1.80 (1.47–2.21)***
Yes	Yes	3.04 (2.36–3.91)***	3.17 (2.46–4.09)***

Mode 1, manually adjusted for age, sex, comorbidity, and medication used. Model 2, manually adjusted for hyperlipidemia, CHA_2DS_2VASc score, and medication used. CI = confidence interval, HR = hazard ratio.

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

the ratio of patients receiving cardiac conversion and transcatheter radiofrequency ablation was low in our study population. From our results, it appeared that undergoing cardiac conversion had no effect on stroke risk among AF patients, but transcatheter radiofrequency ablation had a protective effect.

Our study had some limitations associated with retrospective cohorts. For example, the AFFIRM study[17] concluded that the majority of strokes in rhythm correction and rate control groups occurred in patients who had stopped taking warfarin or whose international normalization ratio (INR) was subtherapeutic at the time of the stroke. However, although a limitation of our study was that warfarin use status and actual INR level could not be evaluated, even though warfarin was not used by the majority of patients (14.82%, 1119/7548) (Table 1), it had a protective effect in stroke risk among AF patients (Table 2). A second limitation is that smoking status and family history of stroke could not be analyzed because this information was not available in the NHIRD. Third, we could not classify hyperlipidemia based on high-density lipoprotein, low-density lipoprotein, and triglyceride levels because this information was also not available in the NHIRD.

Amiodarone shows the highest rates of conversion to sinus rhythm, and the Cardioversion of Atrial Fibrillation study in the International Registry of Poland reported a success rate of up to 75%. Moreover, maintenance of sinus rhythm leads to a superior prognosis by improving cardiac function and relieving symptoms in AF patients. Although in our study, patients with or without any comorbidity treated with amiodarone had a significantly higher risk of stroke (HR 1.79 and 1.78, 95% CI 1.50–2.14 and 1.49–2.13, $P < 0.001$), the addition of an antiplatelet agent or warfarin appeared to reduce this risk. This finding suggests that the high sinus rhythm conversion rates of amiodarone may not reduce the risk of stroke in AF patients. However, we are not able to fully explain the mechanism by which amiodarone increases stroke risk in AF patients, and further basic science research and randomized controlled studies are needed to understand the underlying mechanisms behind this association.

In conclusion, our results suggest that AF patients receiving amiodarone treatment are at an increased risk of stroke, especially those with an initially low risk, but this risk may be reduced with the addition of antiplatelet drugs and warfarin. However, as the combination of digoxin and amiodarone further increases the risk of stroke, its administration to AF patients should be avoided.

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