The risk of stroke after acute myocardial infarction in patients with and without atrial fibrillation: A nationwide cohort study

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Abstract

Background: Acute myocardial infarction (AMI) and atrial fibrillation (AF) are risk factors for stroke. The risk of stroke after AMI may differ between patients with and without AF. The aim of this study was to evaluate the impact of AF on stroke in patients after the first AMI.

Methods: This was a retrospective, nationwide cohort study. Patients with a primary diagnosis of a first AMI between 2000 and 2012 were included. All patients were followed up until ischemic stroke or transient ischemic attack (TIA), or December 31, 2012, whichever occurred first. Kaplan–Meier cumulative survival curves were constructed to compare ischemic stroke or TIA between AMI patients with and without AF.

Results: A total of 170 472 patients were enrolled in this study. Among them, 8530 patients with AF were identified. The propensity score matching technique was used to match 8530 patients without AF of similar ages and sexes. Overall, the 12-year stroke rate was significantly higher in patients with AF than in those without AF (log-rank $p < 0.001$), including different sexes, ages, and interventional therapy subgroups. Patients with pre-existing AF had higher stroke rates than those with newly diagnosed AF in male sex, age below 65 years, and those receiving interventional therapy subgroups. In Cox proportional-hazard regression analysis, AF was an independent risk factor for stroke after the first AMI (hazard ratio, 1.67; 95% CI: 1.5-1.87).

Conclusion: AF significantly increases stroke risk after the first AMI. In patients with AF, those with pre-existing AF have higher stroke risks in male sex, age below 65 years, and those with interventional therapy than those with newly diagnosed AF.

Keywords: Atrial fibrillation; Myocardial infarction; Stroke

1. INTRODUCTION

Stroke may lead to the disability or even mortality of patients and potentially impact their families, caregivers, and societies enormously.[1] Myocardial infarction (MI) happens when there is evidence of myocardial injury with necrosis in a clinical setting consistent with myocardial ischemia.[2] MI and ischemic stroke may have similar pathophysiology, including inflammation and atherosclerosis of vessels.[3] MI itself may be a possible contributor to stroke through the mechanism of cardiac emboli, either during revascularization[4] or from blood stasis in a poor functioning left ventricle due to acute focal hypokinesia or akinesia after MI.[5] Moreover, stroke and MI may share a number of risk factors such as hypertension, hypercholesterolemia, smoking, diabetes, and age.[6,7] Atrial fibrillation (AF) is a well-known risk factor of stroke due to the possibility of cardiac emboli formation in the left atrium (LA), especially within the LA appendage, due to loss of rhythmic contractility of the LA.[8] MI may be accompanied by AF, either pre-existing or newly diagnosed. According to previous studies, the incidence of AF complicating acute myocardial infarction (AMI) is between 2.3% and 21%.[9] As a result, AF itself has an impact on both stroke and MI. We investigated the risk of stroke after MI in patients with and without AF. The aim of this study was to evaluate the impact of AF on stroke in patients after the first AMI using a retrospective analysis of data from the Taiwan National Health Insurance Research Database (NHIRD).

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2. METHODS

2.1. Data source

In Taiwan, the National Health Insurance Program has financed healthcare for more than 99% of Taiwanese residents since 1995.

The NHIRD includes detailed information from the medical records of patients admitted to hospitals, including age, sex, diagnosis, intervention procedures, and prescribed medications. The NHIRD provides researchers with de-identified data via encryption of the identification codes to preserve patient anonymity and has been extensively used in epidemiologic studies in Taiwan.[10–12] Our use of the NHIRD data and the informed consent waiver was approved by the Human Research Committee of Kaohsiung Veterans General Hospital with the reference number of VGHKS15-CT12-01. All analyses were performed in accordance with the relevant guidelines and regulations.

2.2. Definition of AMI population

All patients admitted to hospitals in Taiwan with a primary diagnosis of AMI (ICD-9: 410-410.92) between January 2000 and December 2012 were enrolled. From this group, those who were younger than 20-years old or older than 120-years old, who had doubtful data, whose ICD-9 codes consisted of both ST-elevated MI (STEMI) and non-ST-elevated MI (NSTEMI), and who had any previous history of ischemic stroke or transient ischemic attack (TIA) (ICD-9: 433-438 or A292-A294) were excluded. All ICD-9 codes used for diagnosis in this study are shown in Table 1.

2.3. Outcome analysis

All enrolled patients were followed up until ischemic stroke or TIA, or December 31, 2012, whichever occurred first. Stroke was defined as the following admission with the first diagnosis code of ischemic stroke or TIA (ICD-9: 433-438 or A292-A294).

2.4. Statistical analyses

Data extraction and statistical analysis were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). Descriptive statistics were calculated for all variables, with categorical data reported as percentile values and continuous variables as the mean. Between-group differences were evaluated by paired *t* test for continuous variables and Chi-squared test for categorical variables, with a *p*-value <0.05 considered statistically significant. Cox proportional-hazard regression analysis was used to calculate the hazard ratio (HR) and the associated 95% CI for significant variables. Kaplan–Meier cumulative survival curves were constructed to compare stroke between AMI patients with and without AF, including subgroup analysis of different sexes, ages, and with or without intervention. Log-rank tests were considered statistically significant at $p < 0.05$.

3. RESULTS

3.1. Descriptive characteristics of study group

Among the 170 472 identified patients with the first hospitalization for AMI, 8530 patients (5%) with diagnosed AF at discharge were identified (Fig. 1). Of the remaining 161 942 patients, patients with any diagnosis of AF prior to admission were excluded, leaving 158 046 control patients for comparison. A propensity score matching technique was used to minimize baseline differences between the control and AF groups. One-to-one matching was based on sex and age. Therefore, the data from 8530 AMI patients with AF and 8530 matched controls were included in our final analysis. Among 8530 AMI patients with AF during admission, 6641 (78%) patients who did not have any prior diagnosis of AF were defined as newly diagnosed AF. The remaining 1889 (22%) patients who had a prior diagnosis of AF were defined as having pre-existing AF (Fig. 1).

Table 1

ICD-9-CM code used for diagnosis in this study

Diagnosis	ICD-9-CM code
ST-elevated myocardial infarction	410.0-410.6 or 410.9
Non-ST-elevated myocardial infarction	410.7 or 410.8
Ischemic stroke and transient ischemic attack	433-438 or A292-A294
Hypertension	401-405
Diabetes	250
Heart failure	428
Dyslipidemia	272
Chronic obstructive pulmonary disease	491, 492, or 496
End-stage renal disease	585
Percutaneous coronary intervention	Procedure codes 36.0, 36.01, 36.02, 36.05, 36.06, or 36.09
Coronary artery bypass graft	Procedure codes 36.10-36.19

The descriptive characteristics of the 8530 patients comprising the AMI with AF group (AF group) and the 8530 matched controls (control group), including the types of AMI, with or without interventional therapies (coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]), comorbidities, CHA_2DS_2-VASc scores, and discharge medications, are listed in Table 2. Groups were comparable on the primary demographic variables of age and sex distribution. The ratio of NSTEMI was higher in the AF group (66.07% vs 62.44%, $p < 0.001$). The ratio of interventional therapy was lower in the AF group (40.47% vs 42.39%, $p = 0.0108$). Comorbidities including hypertension (30.81% vs 35.38%, $p < 0.0001$), diabetes mellitus (DM) (20.2% vs 29.84%, $p < 0.0001$), dyslipidemia (8.84% vs 14.87%, $p < 0.0001$), and end-stage renal disease (ESRD) (1.41% vs 1.79%, $p = 0.0441$) were lower in the AF group. Comorbidities including heart failure (29.57% vs 19.64%, $p < 0.0001$) and chronic obstructive pulmonary disease (COPD) (7.15% vs 6.19%, $p = 0.0119$) were higher in the AF group. Regarding discharge medications, the use of aspirin (82.91% vs 77.95%, $p < 0.0001$), clopidogrel (64.33% vs 59.34%, $p < 0.0001$), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) (66.62% vs 59.5%, $p < 0.0001$), beta blockers (53.22% vs 48.36%, $p < 0.0001$), warfarin (12.26% vs 2.06%, $p < 0.001$), Class III antiarrhythmic drugs (AADs) (37.55% vs 8.56%, $p < 0.0001$), digoxin (27.21% vs 8,19%, $p < 0.001$), and non-dihydropyridine calcium-channel blockers (CCBs) (21.47% vs 11.84%, $p < 0.0001$) were higher in the AF group. In contrast, the use of statins was lower in the AF group (30.6% vs 32.4%, $p = 0.0111$).

We further divided the AF group into newly diagnosed AF and pre-existing AF subgroups (Table 3). There were 6641 patients in the newly diagnosed AF subgroup and 1889 patients in the pre-existing AF subgroup. The proportion of female patients was higher in the pre-existing AF subgroup (41.03% vs 38.01%, $p = 0.0174$). Age was higher in the pre-existing AF subgroup ($p < 0.0001$). The ratio of NSTEMI was higher in the pre-existing AF subgroup (71.89% vs 64.42%, $p < 0.0001$). The interventional therapy ratio was lower in the pre-existing AF subgroup (35.63% vs 41.85%, $p < 0.0001$). Regarding comorbidities, the ratios of hypertension (32.87% vs 30.22%, $p = 0.0275$) and heart failure (35.31% vs 27.93%, $p < 0.0001$) were higher in the pre-existing AF subgroup, and the ratio of dyslipidemia (6.56% vs 9.49%, $p < 0.0001$) was lower in the pre-existing AF subgroup. The CHA_2DS_2-VASc score was higher in the pre-existing AF subgroup ($p < 0.0001$). Regarding discharge medications, the use of aspirin (78.82% vs 84.07%, $p < 0.0001$) and class III AADs (27.37% vs 40.45%, $p < 0.0001$) was lower in the pre-existing AF subgroup. The use of warfarin (19.64% vs 10.16%, $p < 0.0001$), digoxin (34.09% vs 25.25%, $p < 0.0001$), and non-dihydropyridine CCBs (23.13% vs 20.99%, $p = 0.0453$) was higher in the pre-existing AF subgroup.

3.2. Stroke analysis

Overall, the long-term stroke rate was significantly higher in the AF group (including newly diagnosed AF and pre-existing AF) (log-rank $p < 0.001$; Fig. 2A). Among both sexes, the rate of

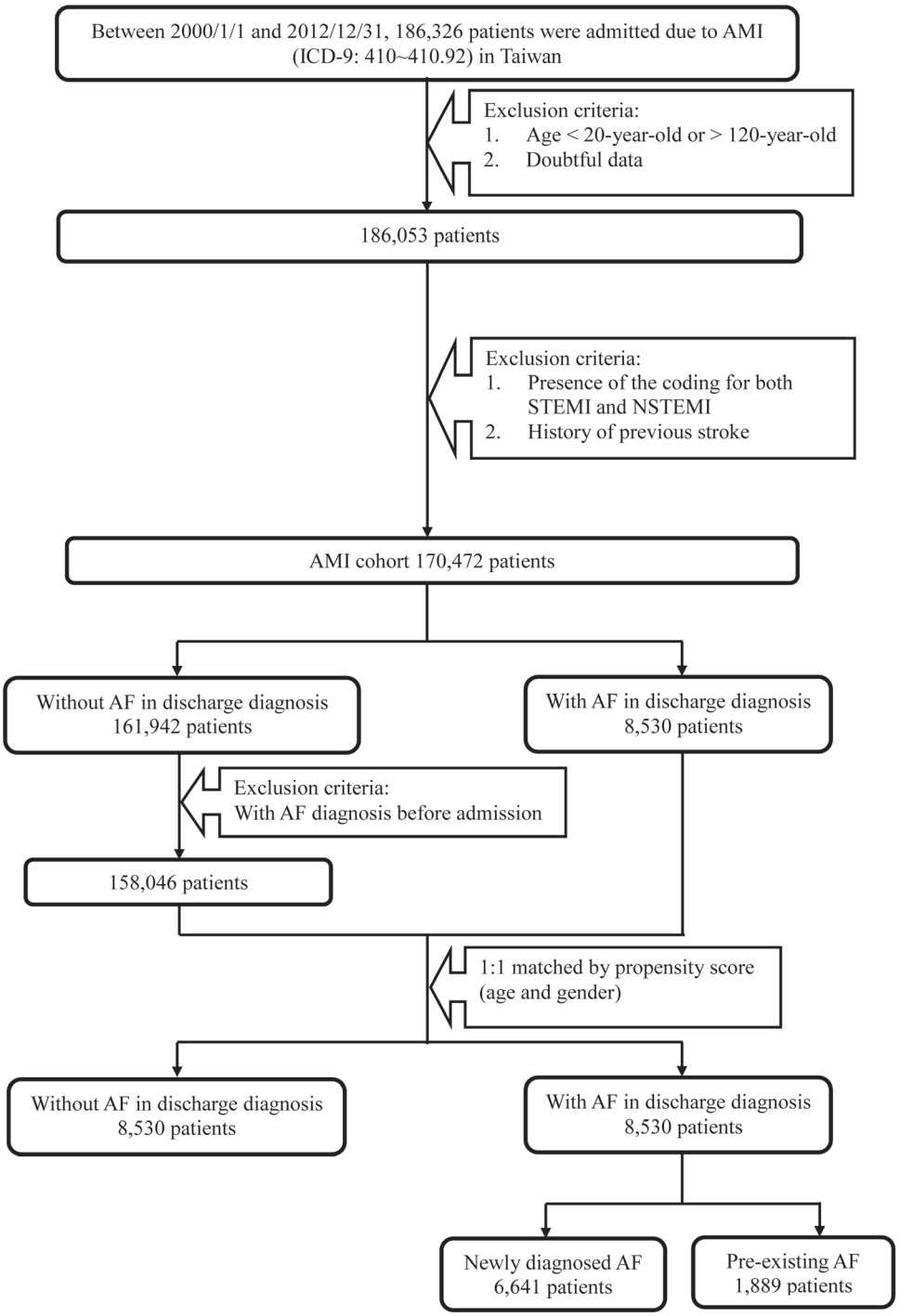

Fig. 1 Flowchart outlining the various study cohorts. There were 186 326 patients in Taiwan between January 2000 and December 2012 with the first diagnosis of AMI. From this group, patients who were ≤20 or ≥120-years old, who had doubtful data, who had the diagnoses of both STEMI and NSTEMI, and who had the history of stroke were excluded, leaving 170 472 patients. Among these 170 472 patients, 8350 patients had AF in discharge diagnosis. In the other 161 942 patients without AF in discharge diagnosis, patients with AF diagnosis before admission were excluded. The final 158 046 patients underwent one-to-one propensity score matching to minimize baseline differences between the two groups. Patients with AF in discharge diagnosis were further divided into newly diagnosed AF or pre-existing AF. AF = atrial fibrillation; AMI = acute myocardial infarction; NSTEMI = non-ST-elevated myocardial infarction; STEMI = ST-elevated myocardial infarction; TIA = transient ischemic attack.

stroke was significantly higher in the AF group (log-rank $p < 0.001$ in both sexes; Fig. 2B and C). Patients were further divided into different age subgroups (age <65 years, age ≥65 and <75 years, and age ≥75 years), and the Kaplan–Meier cumulative curves for stroke were all significantly higher in the AF group in these three age subdivisions (all log-rank $p < 0.001$) (Fig. 3A-C). The rates of stroke were significantly higher in the AF group either with or without interventional therapy (log-rank $p < 0.001$ in both groups; Fig. 4A and B). AF subgroups were further analyzed, including newly diagnosed AF and pre-existing

Table 2

Characteristics of AMI patients with and without AF

Characteristics	Without AF (N = 8530)	With AF (N = 8530)	*p*
Gender			
Female	3299 (38.68%)	3299 (38.68%)	1
Male	5231 (61.32%)	5231 (61.32%)	
Age			
Age <65 years	1961 (22.99%)	1961 (22.99%)	1
65 ≤ age < 75 years	2174 (25.49%)	2174 (25.49%)	
Age ≥75 years	4395 (51.52%)	4395 (51.52%)	
Type of AMI			
NSTEMI	5326 (62.44%)	5636 (66.07%)	<0.0001
STEMI	3204 (37.56%)	2894 (33.93%)	
Interventions			
Without PCI or CABG	4914 (57.61%)	5078 (59.53%)	0.0108
PCI or CABG	3616 (42.39%)	3452 (40.47%)	
Comorbidities			
Hypertension	3018 (35.38%)	2628 (30.81%)	<0.0001
DM	2545 (29.84%)	1723 (20.2%)	<0.0001
Heart failure	1675 (19.64%)	2522 (29.57%)	<0.0001
Dyslipidemia	1268 (14.87%)	754 (8.84%)	<0.0001
COPD	528 (6.19%)	610 (7.15%)	0.0119
ESRD	153 (1.79%)	120 (1.41%)	0.0441
CHA_2DS_2-VASc score			
1	625 (7.33%)	641 (7.51%)	<0.0001
2	1335 (15.65%)	1378 (16.15%)	
3	2190 (25.67%)	2137 (25.05%)	
4	2336 (27.39%)	2437 (28.57%)	
5	1489 (17.46%)	1533 (17.97%)	
≥6	555 (6.51%)	404 (4.74%)	
Medications			
Aspirin	6649 (77.95%)	7072 (82.91%)	<0.0001
Clopidogrel	5062 (59.34%)	5487 (64.33%)	<0.0001
ACEI/ARB	5075 (59.5%)	5683 (66.62%)	<0.0001
Beta blocker	4125 (48.36%)	4540 (53.22%)	<0.0001
Statin	2764 (32.4%)	2610 (30.6%)	0.0111
Warfarin	176 (2.06%)	1046 (12.26%)	<0.0001
Class I AAD	0 (0%)	3 (0.04%)	0.25
Class III AAD	730 (8.56%)	3203 (37.55%)	<0.0001
Digoxin	699 (8.19%)	2321 (27.21%)	<0.0001
Non-dihydropyridine CCB	1010 (11.84%)	1831 (21.47%)	<0.0001

AAD = antiarrhythmic drug; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; CCB = calcium-channel blocker; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; ESRD = end-stage renal disease; NSTEMI = non-ST-elevated myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevated myocardial infarction.

Table 3

Characteristics of AMI patients with newly diagnosed AF and with pre-existing AF

Characteristics	Newly diagnosed AF (N = 6641)	Pre-existing AF (N = 1889)	*p*
Gender			
Female	2524 (38.01%)	775 (41.03%)	0.0174
Male	4117 (61.99%)	1114 (58.97%)	
Age			
Age <65 years	1608 (24.21%)	353 (18.69%)	<0.0001
65 ≤ age < 75 years	1674 (25.21%)	500 (26.47%)	
Age ≥75 years	3359 (50.58%)	1036 (54.84%)	
Type of AMI			
NSTEMI	4278 (64.42%)	1358 (71.89%)	<0.0001
STEMI	2363 (35.58%)	531 (28.11%)	
Interventions			
Without PCI or CABG	3862 (58.15%)	1216 (64.37%)	<0.0001
PCI or CABG	2779 (41.85%)	673 (35.63%)	
Comorbidities			
Hypertension	2007 (30.22%)	621 (32.87%)	0.0275
DM	1362 (20.51%)	361 (19.11%)	0.1817
Heart failure	1855 (27.93%)	667 (35.31%)	<0.0001
Dyslipidemia	630 (9.49%)	124 (6.56%)	<0.0001
COPD	470 (7.08%)	140 (7.41%)	0.619
ESRD	97 (1.46%)	23 (1.22%)	0.4287
CHA_2DS_2-VASc score			
1	554 (8.34%)	87 (4.61%)	<0.0001
2	1135 (17.09%)	243 (12.86%)	
3	1654 (24.91%)	483 (25.57%)	
4	1820 (27.41%)	617 (32.66%)	
5	1172 (17.65%)	361 (19.11%)	
≥6	306 (4.61%)	98 (5.19%)	
Medications			
Aspirin	5583 (84.07%)	1489 (78.82%)	<0.0001
Clopidogrel	4243 (63.89%)	1244 (65.85%)	0.1159
ACEI/ARB	4436 (66.8%)	1247 (66.01%)	0.5241
Beta Blocker	3553 (53.5%)	987 (52.25%)	0.3363
Statin	2055 (30.94%)	555(29.38%)	0.1932
Warfarin	675 (10.16%)	371 (19.64%)	<0.0001
Class I AAD	3 (0.05%)	0 (0%)	1
Class III AAD	2686 (40.45%)	517 (27.37%)	<0.0001
Digoxin	1677 (25.25%)	644 (34.09%)	<0.0001
Non-dihydropyridine CCB	1394 (20.99%)	437 (23.13%)	0.0453

AAD = antiarrhythmic drug; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; CCB = calcium-channel blocker; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; ESRD = end-stage renal disease; NSTEMI = non-ST-elevated myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevated myocardial infarction.

AF subgroups. In the subgroups of male sex, age below 65 years, and with interventional therapy, patients with pre-existing AF had a significantly higher risk of stroke than patients with newly diagnosed AF (Table 4 and Figs. 2-4).

The Cox proportional-hazard regression analysis showed an increased prevalence of stroke after AMI in patients with any one of the following characteristics (Table 5): older age (age ≥65 years and <75 years vs age <65 years: HR 1.49; 95% CI: 1.30-1.71) (age ≥75 years vs age <65 years: HR 2; 95% CI: 1.76-2.28), DM (HR 1.26; 95% CI: 1.13-1.40), heart failure (HR 1.18; 95% CI: 1.05-1.32), and AF (HR 1.67; 95% CI: 1.50-1.87).

Forest plots of HRs were used for the subgroup analysis (Fig. 5). In patients with AMI and AF, HRs for stroke were higher in both male and female patients (*p* for interaction = 0.6314) and age (age <65 years, age ≥65 years and <75 years, and age ≥75 years). Notably, *p* for interaction in different age subgroups was 0.0011 (<0.05), which means that AF has a significantly higher impact on stroke in younger age groups. In patients with AMI, those with AF also had a high risk for stroke either with or without hypertension (*p* for interaction = 0.5991), DM (*p* for interaction = 0.1305), heart failure (*p* for interaction = 0.4387), dyslipidemia (*p* for interaction = 0.1711), and interventional therapy (*p* for interaction = 0.8221). Furthermore, whether the use of aspirin (*p* for interaction = 0.4395), clopidogrel (*p* for interaction = 0.1307), ACEIs/ARBs (*p* for interaction = 0.6296), beta-blockers (*p* for interaction = 0.0939), statins (*p* for interaction = 0.5082) or CCBs (*p* for interaction = 0.9687), and AF also had higher HRs for stroke.

In patients with COPD, AF did not have a significantly higher HR for stroke (HR 1.12; 95% CI: 0.76-1.66) and *p* for interaction in patients with and without COPD was 0.0374 (<0.05).

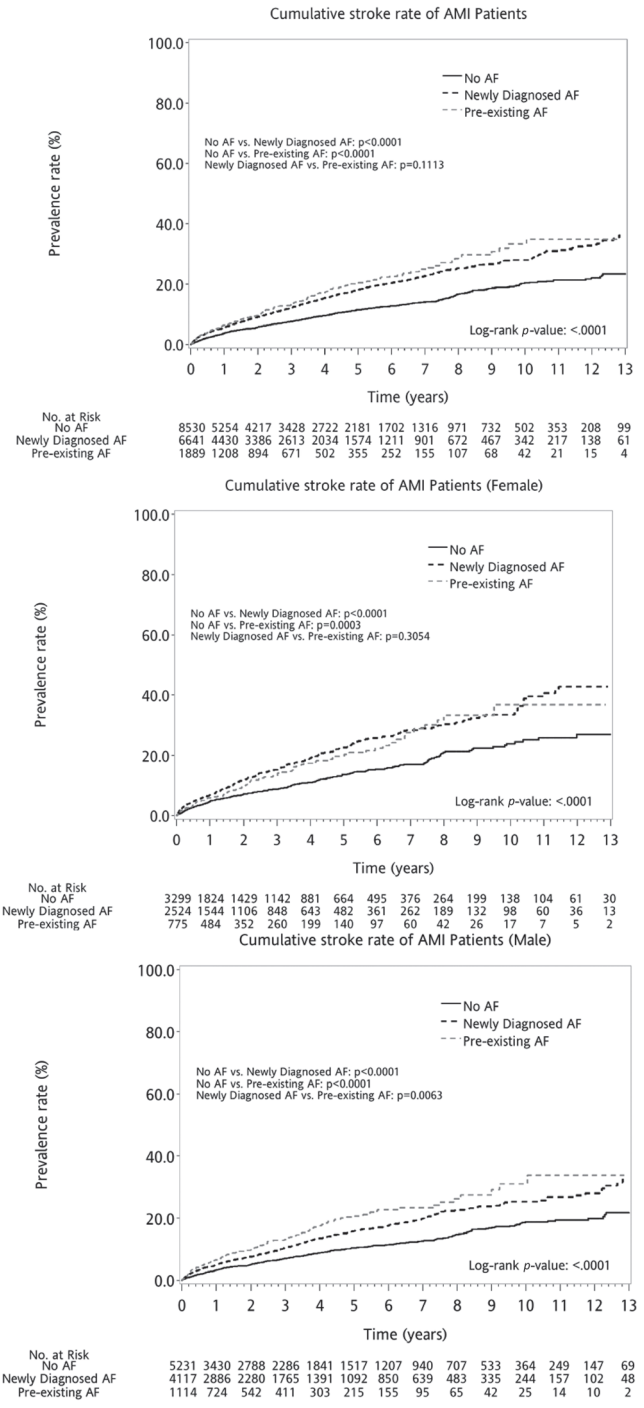

Fig. 2 Kaplan–Meier curve for stroke after the first AMI for all patients and sex subgroups. Overall, the stroke rates were higher in the AF group (A, log-rank $p < 0.0001$), in the male subgroup (B, log-rank $p < 0.0001$) and in the female subgroup (C, log-rank $p < 0.0001$). AF = atrial fibrillation; AMI = acute myocardial infarction.

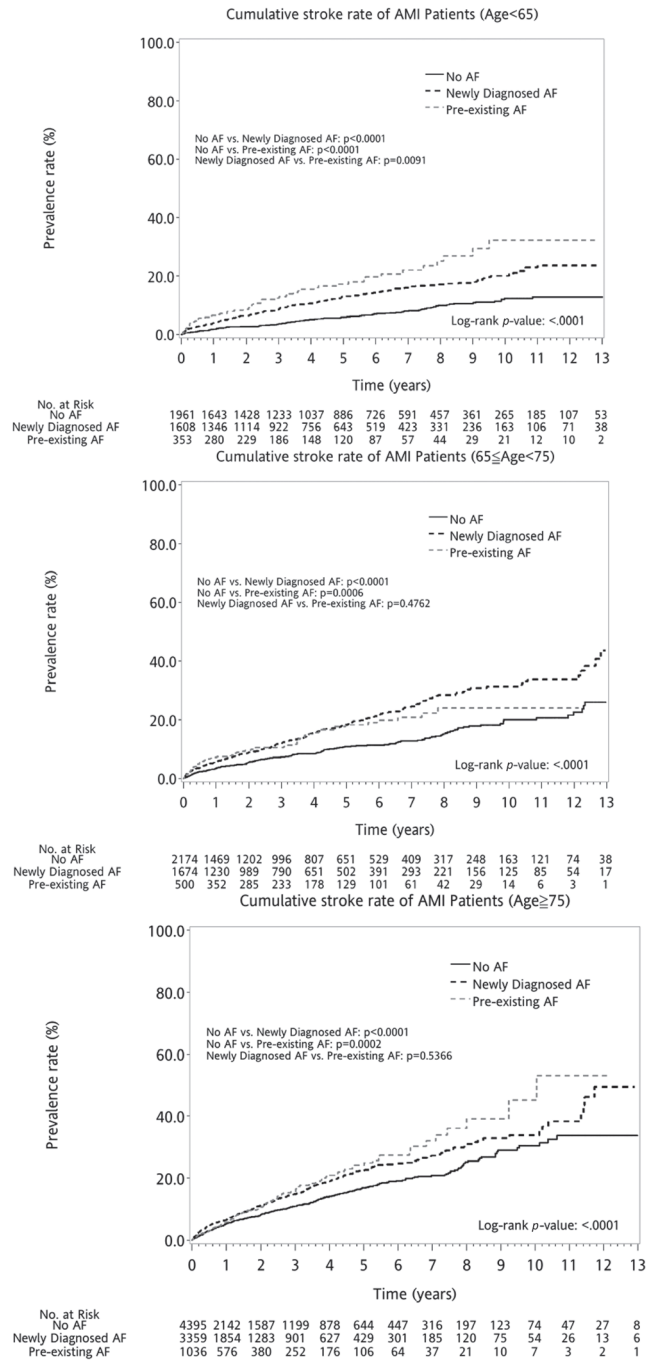

Fig. 3 Kaplan–Meier curve of stroke after the first AMI for age subgroups. Overall, the stroke rates were higher in AF patients in the "age <65 years" subgroup (A, log-rank $p < 0.0001$), in the "age ≥65 years and <75 years" subgroup (B, log-rank $p < 0.0001$), and in the "age ≥75 years" subgroup (C, log-rank $p < 0.0001$). AF = atrial fibrillation; AMI = acute myocardial infarction.

In patients with ESRD, AF did not have a significantly higher HR for stroke (HR 2.62; 95% CI: 0.89-7.69). However, the *p*-value for interaction in patients with and without ESRD was 0.4108 (>0.05). In patients discharged with a warfarin prescription, AF did not have a significantly higher HR for stroke (HR 1.33; 95% CI: 0.82-2.15). However, the *p* for interaction in patients discharged with and without a warfarin prescription was 0.3375 (>0.05). In patients discharged with a Class III AAD prescription, AF did not have a significantly higher HR for stroke (HR 1.15; 95% CI: 0.85-1.53) and *p* for interaction in patients discharged with a Class III AAD prescription was 0.0069 (<0.05). In patients discharged with a digoxin prescription, AF did not have a significantly higher HR for stroke (HR 1.29; 95% CI: 0.98-1.71). However, the *p* for interaction in patients discharged with and without a digoxin prescription was 0.0508 (>0.05).

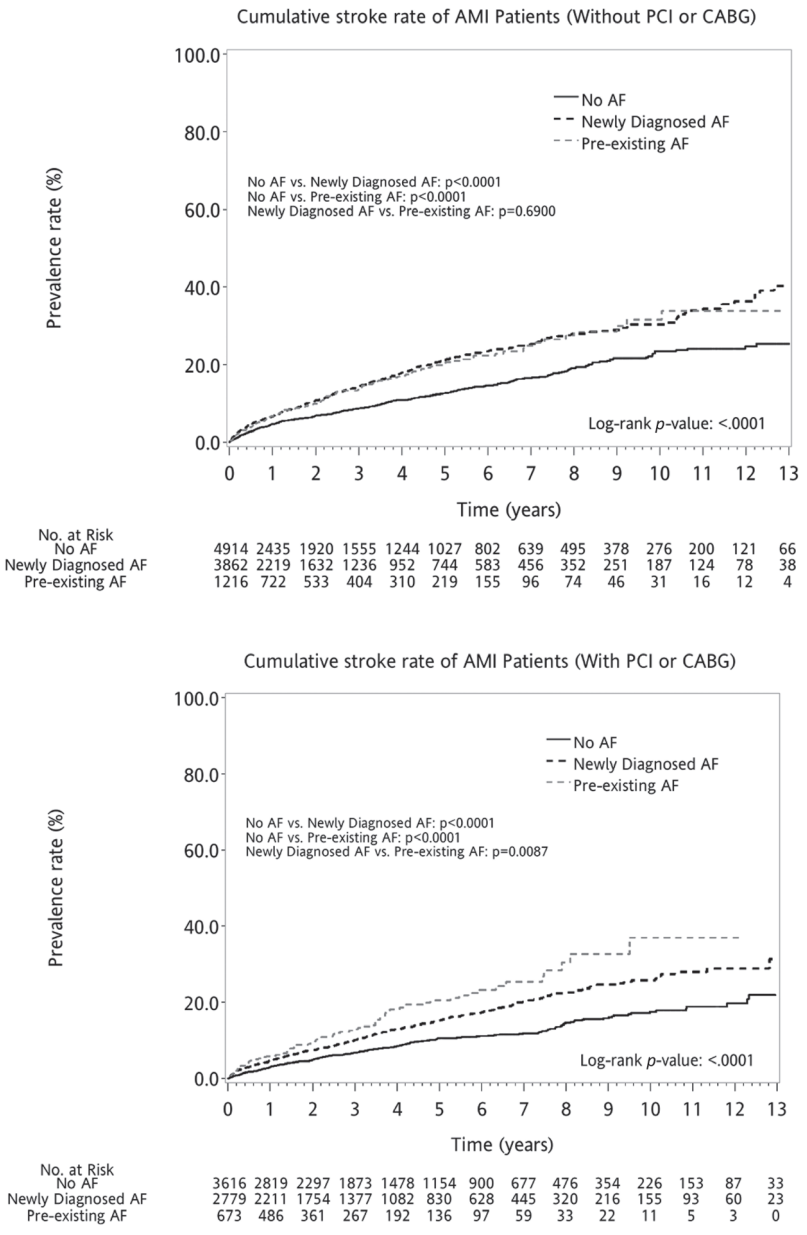

Fig. 4 Kaplan–Meier curve of stroke after the first AMI for interventional therapy subgroups. Overall, the stroke rates were higher in the "without interventional therapy" subgroup (A, log-rank $p < 0.0001$) and in the "with interventional therapy" subgroup (B, log-rank $p < 0.0001$). AF = atrial fibrillation; AMI = acute myocardial infarction.

4. DISCUSSION

This study revealed that the long-term stroke rate in patients after the first AMI was significantly higher in patients with AF than in those without AF. This negative impact remained in both sexes, different ages, and those receiving interventional therapy (PCI or CABG). In patients with AF, those with pre-existing AF had a significantly higher stroke rate than those with newly diagnosed AF in the subgroups of male sex, age below 65 years, and those receiving interventional therapy.

4.1. Newly diagnosed and pre-existing AF in AMI

Our data revealed that the prevalence of AF during hospitalization was 5% (8530 in 170 472 patients) and the pre-existing AF prevalence was 22% (1889 in 8530 patients). Our results are similar to those of previous studies where the prevalence of AF during hospitalization for AMI was reported to be between 2.3% and 21%.[9,13] Previous studies have revealed that the prevalence rate of pre-existing AF in patients with AMI is between 43% and 72%.[14–17] Our data showed a relatively lower prevalence of pre-existing AF and this may possibly be due to ethnicity differences. The majority of our study population was Asian, whereas previous studies focused on Caucasians. The prevalence of AF in the Asian population was around 1%, which is lower than that in Caucasians (approximately 2%).[18]

In a previous study by Zusman et al, new-onset AF following MI was associated with a nearly 35-fold increased risk of stroke during follow-up (mean 41 months; HR 34.6, 95% CI: 4.0-296.8).[19] However, the limited number of patients and events (14 out of 300 patients) made their results seem to be less precise, as evidenced by such a wide 95% CI. In a study using data from the Danish National Patients Registry with a total of

Table 4

Comparison of stroke cumulative prevalence rate in patients with pre-existing AF and newly diagnosed AF

Comparison of stroke cumulative prevalence rate	Log-rank *p*
Overall	
Pre-existing AF vs newly diagnosed AF	0.5366
Male	
Pre-existing AF vs newly diagnosed AF	0.0063*
Female	
Pre-existing AF vs newly diagnosed AF	0.3054
Age <65 years	
Pre-existing AF vs newly diagnosed AF	0.0091*
65 ≤ age < 75 years	
Pre-existing AF vs newly diagnosed AF	0.4762
Age ≥75 years	
Pre-existing AF vs newly diagnosed AF	0.5366
Without interventional therapy	
Pre-existing AF vs newly diagnosed AF	0.69
With interventional therapy	
Pre-existing AF vs newly diagnosed AF	0.0087*

AF = atrial fibrillation.
*p-value < 0.05.

89 703 patients with MI being analyzed and at the end of 5-year follow-up, new onset AF complicating MI was demonstrated as an independent predictor for fatal and non-fatal stroke (HR: 2.34; 95% CI: 2.12-2.57 and HR: 2.47; 95% CI: 2.24-2.73, respectively).[20] Additionally, Luo et al reported a meta-analysis, which showed that new-onset AF was associated with an increased risk of ischemic stroke (risk ratios: 2.84, 95% CI: 1.91-4.23; six studies).[21] Regarding pre-existing AF, Tanne et al reported that chronic AF was associated with significant appearance of stroke or TIA in hospital-discharged survivors of AMI (odds ratio: 5.71, 90% CI: 1.55-21.01).[22] Our data included both patients with newly diagnosed and pre-existing AF, with a longer follow-up duration (up to 12 years) and a high number of patients with AF (8530 patients). The stroke risk after AMI in our study was significantly higher in patients with AF than those without AF, with a HR of 1.67 (95% CI: 1.5-1.87).

Table 5

Cox proportional-hazard regression on stroke of patients after AMI

Characteristics (all, N = 17 060)	HR (95% CI)	*p*
Sex (male vs female)	0.88 (0.79-0.97)	0.0106*
Age (65 ≤ age < 75 vs age < 65)	1.49 (1.3-1.71)	<0.0001*
Age (age ≥ 75 vs age < 65)	2 (1.76-2.28)	<0.0001*
Hypertension (yes vs no)	1.11 (1-1.22)	0.0512
DM (yes vs no)	1.26 (1.13-1.4)	<0.0001*
Heart failure (yes vs no)	1.18 (1.05-1.32)	0.0067*
Dyslipidemia (yes vs no)	0.97 (0.83-1.13)	0.6985
COPD (yes vs no)	1.05 (0.86-1.29)	0.6452
ESRD (yes vs no)	1.03 (0.62-1.72)	0.9153
Intervention (with vs without PCI or CABG)	0.9 (0.81-1.01)	0.063
AF during admission (yes vs no)	1.67 (1.5-1.87)	<0.0001*
Aspirin (yes vs no)	0.93 (0.81-1.07)	0.3379
Clopidogrel (yes vs no)	0.8 (0.72-0.9)	0.0001*
ACEI/ARB (yes vs no)	1.11 (0.99-1.24)	0.0777
Beta blocker (yes vs no)	0.98 (0.88-1.08)	0.6354
Statin (yes vs no)	1.09 (0.97-1.23)	0.1696
Warfarin (yes vs no)	0.99 (0.83-1.17)	0.8583
Class III AAD (yes vs no)	0.91 (0.81-1.03)	0.1369
Digoxin (yes vs no)	1.12 (0.99-1.27)	0.0804
Non-dihydropyridine CCB (yes vs no)	1.05 (0.93-1.19)	0.4222

AAD = antiarrhythmic drug; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; CCB = calcium-channel blocker; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; ESRD = end-stage renal disease; HR = hazard ratios; PCI = percutaneous coronary intervention.
*$p < 0.05$.

There may be a higher prevalence of heart failure and cardiomyopathy in AMI patients with pre-existing AF.[23] On the contrary, newly diagnosed AF during admission of AMI patients may be due to the acute change of heart function at the time of AMI, including left atrial ischemia or overload due to the pumping failure of the left ventricle, as well as neuroendocrine activation and tachycardia due to hemodynamic instability.[13] Therefore, pre-existing AF and newly diagnosed AF may influence outcomes differently. To our knowledge, there is only one report directly comparing pre-existing and newly diagnosed AF in the influence of stroke in patients with AMI; Gourronc et al compared pre-existing AF, new-onset AF, and AF-free patients with AMI. The results show that there is no significant difference regarding stroke between pre-existing AF, new-onset AF, and AF-free patients (2.2%, 0.5%, and 0.8%, respectively, $p = 0.327$).[24] Our data showed that AMI patients with AF, including newly diagnosed and pre-existing AF, had significantly higher stroke rates than those without AF. The difference in our findings compared to those of Gourronc et al may be because we enrolled a larger number of patients (8530 patients in our study compared to 436 patients with AF in their study) and much longer follow-up durations (up to 12 years in our study compared to 1 year in their study).

Our study revealed that in the subgroup of men aged <65 years and with interventional therapy, AMI patients with pre-existing AF had a significantly higher stroke rate than those with newly diagnosed AF (Table 4). In addition, AMI patients with pre-existing AF were predominantly women of older age. Previous studies have reported conflicting results regarding the distribution of ages and sexes in AMI patients with different types of AF.[14–17] Some studies revealed that AMI patients with pre-existing AF tended to be older[15,16] and were predominantly female,[16] while some studies revealed that there were no significant differences in age and sex.[14,17] Our study revealed that AMI patients with pre-existing AF were significantly older and predominantly female.

Moreover, AMI patients with pre-existing AF had a higher rate of NSTEMI and heart failure and a lower rate of receiving interventional therapy. The CHA_2DS_2-VASc scores were also higher in AMI patients with pre-existing AF than in those with newly diagnosed AF. As a result, AMI patients with pre-existing AF tend to be frailer than those with newly diagnosed AF. This could explain why AMI patients with pre-existing AF had a significantly higher rate of stroke in the male, younger, and interventional therapy subgroups than those with newly diagnosed AF.

This study had a few limitations. First, although a previous study confirmed the accuracy of NHIRD as a valid resource for research on cardiovascular disease,[25] the relevant clinical variables such as cardiac biomarkers, left ventricular ejection fraction, and Killip grade were unavailable, and these variables have important influences on the occurrence of stroke. Second, the AF type was not present in this study. However, according to a previous study, the type of AF did not significantly affect the risk of stroke and should not influence the decision to prevent stroke.[26] Third, the anticoagulant used for stroke prevention in AF patients during our study period was mainly warfarin and the percentage of usage was relatively low (12.26% of patients with

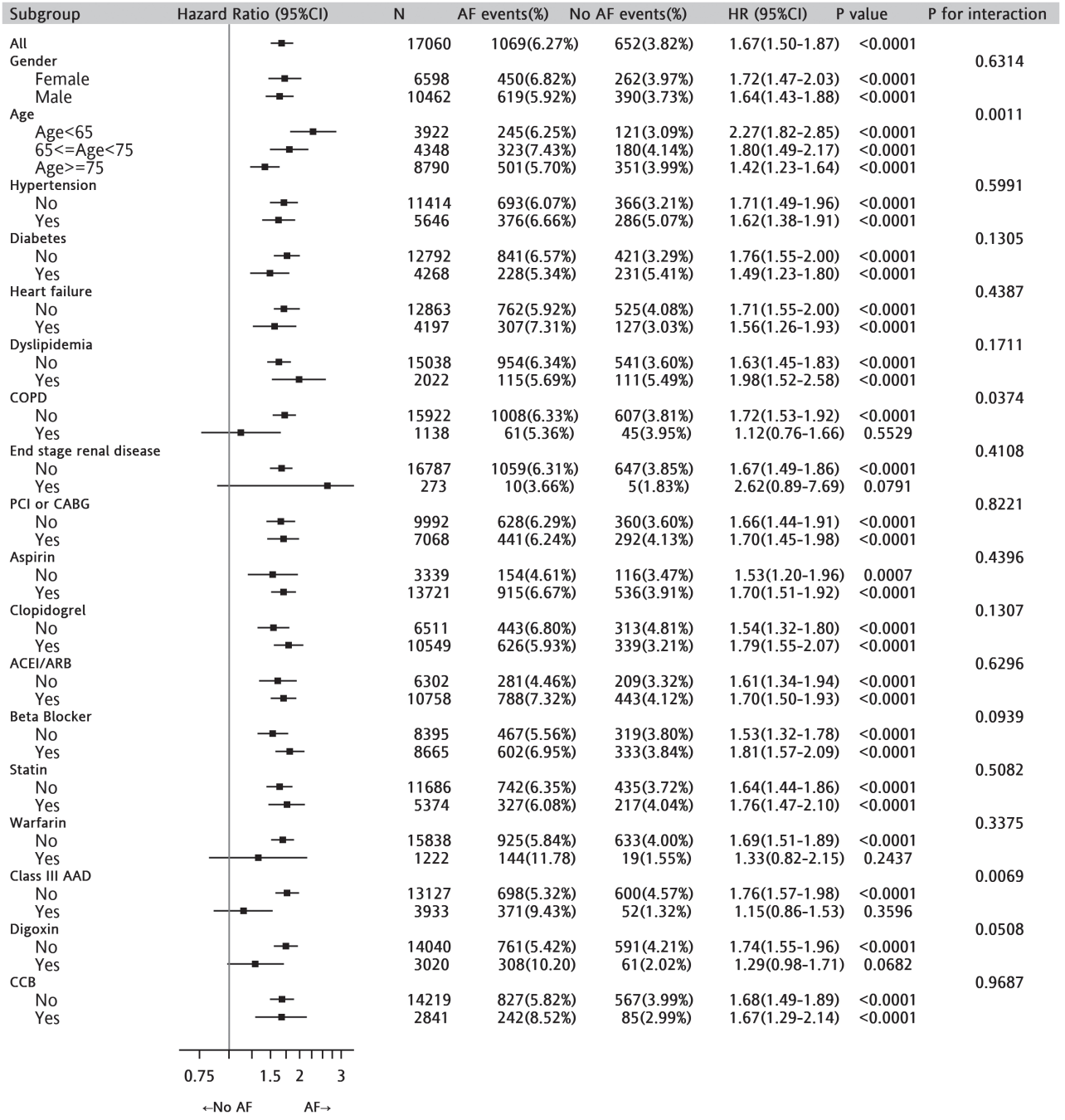

Fig. 5 Forest plot of HR and *p* for interaction for various characteristics in patients with or without AF during admission. AF = atrial fibrillation; HR = hazard ratios.

AF in our study). However, non-vitamin K oral anticoagulants are now widely used in stroke prevention in patients with AF, and the percentage of anticoagulant use has increased enormously in recent years.[18] Current clinical practice may affect the rates of stroke in patients with AF. However, our study revealed that the *p*-value for interaction was 0.3375 (>0.05) in the prescription of warfarin (Fig. 5). This may account for the fact that the prescription of warfarin did not have a significant influence on stroke. This may be due to the low rate of warfarin prescriptions in our study period.

In conclusion, this study demonstrates that the long-term stroke rate in patients after AMI is significantly higher in patients with AF than in those without AF; this remains present in different subgroups, including both sexes, different ages, and those receiving interventional therapy (PCI or CABG). In patients with AF, those with pre-existing AF before admission have a higher risk of stroke in subgroups of male sex, younger age, and those with interventional therapy than patients with newly diagnosed AF during admission.

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REFERENCES

1. Feigin VL, Mensah GA, Norrving B, Murray CJ, Roth GA; GBD 2013 Stroke Panel Experts Group. Atlas of the Global Burden of Stroke (1990-2013): The GBD 2013 Study. *Neuroepidemiology* 2015;**45**:230–6.
2. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al; Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction; ESC Committee for Practice Guidelines (CPG). Third universal definition of myocardial infarction. *Eur Heart J* 2012;**33**:2551–67.
3. Witt BJ, Ballman KV, Brown RD Jr, Meverden RA, Jacobsen SJ, Roger VL. The incidence of stroke after myocardial infarction: a meta-analysis. *Am J Med* 2006;**119**:354.e1–9.
4. Kaarisalo MM, Immonen-Räihä P, Marttila RJ, Salomaa V, Torppa J, Tuomilehto J; FINMONICA MI and Stroke Registry Teams. The risk of stroke following coronary revascularization – a population-based long-term follow-up study. *Scand Cardiovasc J* 2002;**36**:231–6.
5. Lamas GA, Vaughan DE, Pfeffer MA. Left ventricular thrombus formation after first anterior wall acute myocardial infarction. *Am J Cardiol* 1988;**62**:31–5.
6. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;**42**:1289–367.
7. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–77.
8. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498.
9. Schmitt J, Duray G, Gersh BJ, Hohnloser SH. Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. *Eur Heart J* 2009;**30**:1038–45.
10. Wang MT, Tsai CK, Kuo SH, Huang WC, Lin KC, Hung WT, et al. The dipyridamole added to dual antiplatelet therapy in cerebral infarction after first acute myocardial infarction: a nationwide, case-control study. *Front Neurol* 2018;**9**:1003.
11. Liu ES, Chiang CH, Hung WT, Tang PL, Hung CC, Kuo SH, et al. Comparison of long-term mortality in patients with acute myocardial infarction associated with or without sepsis. *Int J Infect Dis* 2019;**79**:169–78.
12. Kuo SH, Hung WT, Tang PL, Huang WC, Yang JS, Lin HC, et al. Impact of hepatitis C virus infection on long-term mortality after acute myocardial infarction: a nationwide population-based, propensity-matched cohort study in Taiwan. *BMJ Open* 2018;**8**:e017412.
13. Jabre P, Roger VL, Murad MH, Chamberlain AM, Prokop L, Adnet F, et al. Mortality associated with atrial fibrillation in patients with myocardial infarction: a systematic review and meta-analysis. *Circulation* 2011;**123**:1587–93.
14. Podolecki T, Lenarczyk R, Kowalczyk J, Kurek T, Boidol J, Chodor P, et al. Effect of type of atrial fibrillation on prognosis in acute myocardial infarction treated invasively. *Am J Cardiol* 2012;**109**:1689–93.
15. Topaz G, Flint N, Steinvil A, Finkelstein A, Banai S, Keren G, et al. Long term prognosis of atrial fibrillation in ST-elevation myocardial infarction patients undergoing percutaneous coronary intervention. *Int J Cardiol* 2017;**240**:228–33.
16. Lau DH, Huynh LT, Chew DP, Astley CM, Soman A, Sanders P. Prognostic impact of types of atrial fibrillation in acute coronary syndromes. *Am J Cardiol* 2009;**104**:1317–23.
17. Poçi D, Hartford M, Karlsson T, Edvardsson N, Caidahl K. Effect of new versus known versus no atrial fibrillation on 30-day and 10-year mortality in patients with acute coronary syndrome. *Am J Cardiol* 2012;**110**:217–21.
18. Chiang CE, Wu TJ, Ueng KC, Chao TF, Chang KC, Wang CC, et al. 2016 Guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation. *J Formos Med Assoc* 2016;**115**:893–952.
19. Zusman O, Amit G, Gilutz H, Zahger D. The significance of new onset atrial fibrillation complicating acute myocardial infarction. *Clin Res Cardiol* 2012;**101**:17–22.
20. Bang CN, Gislason GH, Greve AM, Bang CA, Lilja A, Torp-Pedersen C, et al. New-onset atrial fibrillation is associated with cardiovascular events leading to death in a first time myocardial infarction population of 89,703 patients with long-term follow-up: a nationwide study. *J Am Heart Assoc* 2014;**3**:e000382.
21. Luo J, Li H, Qin X, Liu B, Zhao J, Maihe G, et al. Increased risk of ischemic stroke associated with new-onset atrial fibrillation complicating acute coronary syndrome: a systematic review and meta-analysis. *Int J Cardiol* 2018;**265**:125–31.
22. Tanne D, Goldbourt U, Zion M, Reicher-Reiss H, Kaplinsky E, Behar S. Frequency and prognosis of stroke/TIA among 4808 survivors of acute myocardial infarction. the SPRINT Study Group. *Stroke* 1993;**24**:1490–5.
23. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;**107**:2920–5.
24. Gourronc Y, Grall S, Ingremeau D, Desprets L, Prunier F, Furber A, et al. De novo atrial fibrillation as an independent prognostic marker after ST-segment elevation myocardial infarction: results from the RIMA registry. *J Cardiol* 2019;**74**:123–9.
25. Cheng CL, Lee CH, Chen PS, Li YH, Lin SJ, Yang YH. Validation of acute myocardial infarction cases in the national health insurance research database in Taiwan. *J Epidemiol* 2014;**24**:500–7.
26. Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY, et al. Pattern of atrial fibrillation and risk of outcomes: the Loire Valley Atrial Fibrillation Project. *Int J Cardiol* 2013;**167**:2682–7.