Atrial fibrillation and the risk of myocardial infarction : a nation-wide propensity-matched study

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Atrial fibrillation and the risk of myocardial infarction : a nation-wide propensity-matched study

Directed by Professor Boyoung Joung

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<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Atrial fibrillation and the risk of myocardial infarction
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Objective In addition to being an established complicating factor for myocardial infarction (MI), recent studies have revealed that atrial fibrillation (AF) increased risk of MI. This study is to evaluate the risk of MI associated with AF in general population.

Methods We examine the association between AF and incident MI in 497,366 adults [mean age 47.6 ± 14.3 years, 250,569 women (50.0%)] from the Korean National Health Insurance Service database, who were free of AF and MI at baseline. AF group (n=3,295) was compared with propensity matched no-AF group (n=13,159).

Results Over 4.2 years of follow up, 137 MI events occurred. AF was associated with 3-fold increased risk of MI (HR, 3.1; 95% CI, 2.22-4.37) in both men (HR, 2.91; 95% CI 1.91-4.45) and women (HR, 3.52; 95% CI 2.01-6.17). The risk of AF-associated MI was higher in patients free of hypertension, diabetes, ischemic stroke, and dyslipidemia at baseline. The cumulative incidence of AF-associated MI was lower in patients on anticoagulant and statin therapies.

Conclusions AF was associated with an increased risk of MI, with its incidence lower in anticoagulants and statin users. Our finding suggests that AF complications beyond stoke should extend to total mortality to include MI.

Key Words: atrial fibrillation, myocardial infarction, nation-wide cohort.

I. INTRODUCTION

The significance of atrial fibrillation (AF) as a major public health problem comes from its increasing prevalence and strong association with morbidity and mortality.[1,2] Patients with AF have 5 times the risk of stroke and double the risk of mortality compared with those without AF.[3,4] AF has known to complicate acute myocardial infarction (MI).[5] In addition to being an established complicating factor for MI, recent studies have revealed that AF increased the risk of MI.[6,7] In the Atherosclerosis Risk in Communities (ARIC) study, AF was associated with an increased risk of non-ST segment elevation MI (NSTEMI), especially in women.[6] In the Reasons for Geographic and Racial Difference in Stroke (REGARDS) study, AF was associated with a 70% increased risk of incident MI, the risk being higher in women than in men and in blacks than in whites.[7] However, the risk of MI in association with AF in the general population has not been previously investigated, and the mechanisms explaining these associations are yet to be validated.

Thus, we examined the association between AF and MI by analyzing a recently developed Korean National Health Insurance Service–national sample cohort (NHIS-NSC) database, which includes over five hundred thousand individuals. In addition, the beneficial effects of the commonly prescribed medications for AF patients on the occurrence of MI have not been elucidated. Herein, we also analyzed the association of medications with incident MI in AF patients.

II. MATERIALS AND METHODS

1. Source of study data

The national health insurance service (NHIS) in Korea is a single-payer program and is mandatory for all residents in South Korea.[8] All Koreans residing in South Korea are covered under medical coverage of NHIS, which includes the following three categories: employee insured, self- employed insured, and medical aid beneficiary.[9] The NHIS database represents the entire Korean population.[10] The NHIS released the National Sample Cohort database in 2015. It consists of 1,025,340 Koreans as an initial 2002 cohort and follows the subjects through 2013. This represents about 2.2% of the source population in 2002 (46,605,433). This is a semi-

dynamic cohort database; the cohort has been followed up to either the time of the participant's disqualification of health services due to death or emigration or the end of the study period. The database contains eligibility and demographic information regarding health insurance and medical aid beneficiaries, medical bill details, medical treatment, disease histories, and prescriptions.

In this cohort, the subjects' disease information was classified according to the 10th revision of the International Classification of Diseases (ICD-10) codes obtained from the Korean National Statistical Office (Supplementary table 1). This study was approved by the Institutional Review Board (IRB) of Yonsei University College of Medicine in Seoul, Korea. The IRB waived the requirement to obtain informed consent, and this study was conducted in accordance with the tenets of the Declaration of Helsinki.

2. Study population

A total of 506,805 patients, who had a health check-up between 2009 and 2013, were enrolled and follow-up data were reviewed until December 2014. AF cases were identified by ICD-10 codes of I48.[11] Valvular AF cases, which were defined from any diagnoses or operation of mitral stenosis (ICD-10: I05.0, I05.2, I34.2, Z95.2-4), were excluded. To ensure accuracy of diagnosis, we defined patients as AF only when it was a discharge diagnosis or was confirmed more than twice in the outpatient department. To further evaluate the accuracy of the definition of AF, a validation study was performed in 628 randomly selected patients with ICD-10 code of I48 in 2 separate hospitals. Their electrocardiograms (ECGs) were reviewed by two physicians. Patients were determined to have AF if documented by ECG. The positive predictive value was 94.1%. The clinical end point was the first occurrence of MI during follow up. MI cases were identified by ICD-10 codes of I21or I22, and were ascertained when the diagnosis was confirmed by hospitalization or death from MI. To evaluate the accuracy of our definition of MI, we conducted a validation study with medical records of two independent tertiary hospitals from 2006-2013. A total of 4,688 patients were found to have ICD codes of I21 or I22. Data of clinical history, cardiac biomarkers, ECGs and the results of coronary angiography were reviewed by two cardiologists. The positive predictive value was 86.5%.

Supplementary table 1. International Classification of Disease 10th codes for comorbidities

Diagnosis of Comorbidities		
Atrial fibrillation	Defined from diagnosis*	ICD10: I48
Ischemic stroke	Defined from diagnosis*	ICD10: I63, I64
Heart failure	Defined from diagnosis*	ICD10: I11.0, I50, I97.1
Diabetes mellitus	Defined from diagnosis*	ICD10: E10, E11, E12, E13, E14
Hypertension	Defined from diagnosis*	ICD10: I10, I11, I12, I13, I15
Myocardial infarction	Defined from diagnosis*	I21, I22, I25.2
Peripheral arterial obstructive disease	Defined from diagnosis*	ICD10: I70.0, I70.1, I70.2, I70.8, I70.9, I73.9, I79.2
Dyslipidemia	Defined from diagnosis*	ICD10: E78
Chronic obstructive lung disease	Defined from diagnosis*	J42, J43(except J43.0), J44
Chronic renal failure	Defined from eGFR	eGFR <60 mL/min per 1.73 m^2
End state renal disease	Defined from national registry for severe illness.	Patients with ESRD undergoing chronic dialysis or received a kidney transplant.
Malignancy	Defined from diagnoses of cancer (non-benign)	ICD10: C00-C97
Potential absence of non-valvular atrial fibrillation	Defined from any diagnoses or operation of mitral stenosis	ICD10: I05.0, I05.2, I34.2, Z95.2-4
Chronic Liver disease	Defined from diagnosis of chronic liver disease, cirrhosis, and hepatitis	ICD10: B18, K70, K71, K72, K73, K74, K76.1

*To ensure accuracy, comorbidities were established based on one inpatient or two outpatient records of ICD-10 codes in the database.

Of the 8,296 patients with AF, patients who had AF or MI before 2009 (n=4,976) and who suffered an MI before AF (n=25) were excluded. Finally 3,295 patients were enrolled in the AF group. Among those without AF (n=498,509), 494,071 patients were enrolled in the no-AF group after excluding the patients who suffered an MI before 2009 (n=4,438). Given the differences in the baseline characteristics and the risk of cardiovascular diseases between the AF and control

groups, we used 1:4 propensity score matching and calculated the propensity score, with predicted probability of AF occurrence conditional on baseline covariates, by multivariable logistic regression (Table 1).[12] We attempted to match each patient in the AF cohort with a patient in the control cohort with a similar propensity score, based on nearest-neighbor matching without replacement, using a caliper width equal to 0.05 of the standard deviation of the logit of the propensity score. Pre- and post-match absolute standardized differences were presented as Love Plots.[13]

The following variables were entered: age, sex, and a history of congestive heart failure, hypertension, diabetes mellitus, chronic kidney disease (CKD) or end-stage renal disease (ESRD), dyslipidemia, ischemic stroke, peripheral artery occlusive disease (PAOD), chronic obstructive pulmonary disease (COPD), history of malignancy, anemia, smoking history, blood pressure, body mass index, waist circumference, body surface area, cholesterol level, serum creatinine, and estimated –glomerular filtration rate (eGFR). Covariates included in propensity matching were the data from baseline examination, and the definition of comorbidity was based on ICD codes. The matching procedure was performed using R packages (R Foundation for Statistical Computing, Vienna, Austria), including Matchit, RItools, and CEM.[14] Finally, a total of 3,295 AF patients and 13,159 no-AF patients were evaluated in this study (Figure 1).

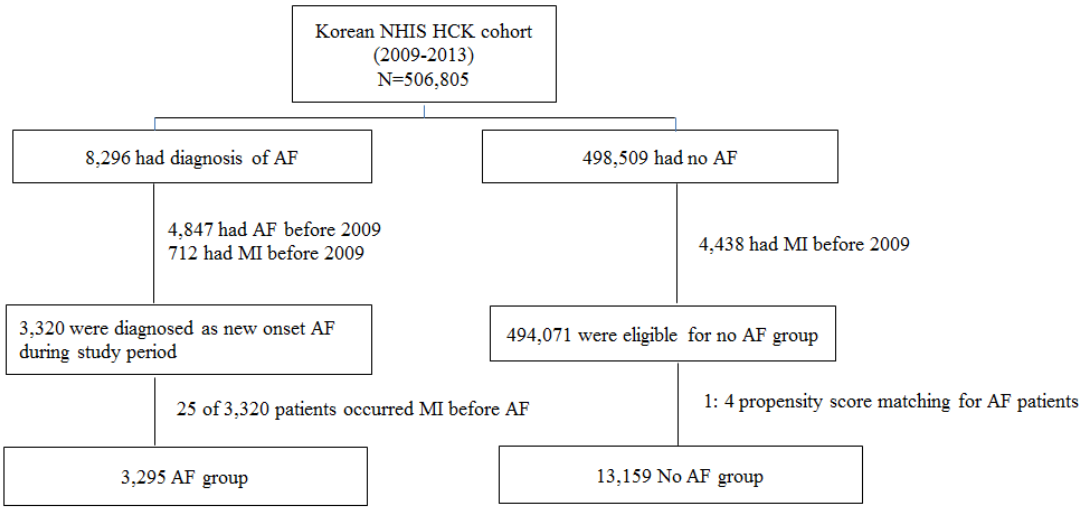

Figure 1. Study population. AF, atrial fibrillation; MI, myocardial infarction; NHIS HCK, National Health Insurance Service-health check-up. Medical records of all participants were reviewed from 2002 till 2013.

3. Statistical analysis

Data were presented as mean ± SD for normally distributed continuous variables and as proportions for categorical variables. Age-adjusted incidence rate of MI per 1000 person-years in patients with and without AF was calculated in the propensity matched population and in the sex subgroup. Person-time for the incidence rate in the AF group was calculated from AF diagnosis to the occurrence of MI or censoring. The exclusion method was used to account for the guarantee-time bias in the AF group.[15] In the no-AF group, person-time was calculated from baseline to MI occurrence or censoring. Cumulative incidence of MI was plotted using a Kaplan-Meier method, with statistical significance examined using log-rank test by AF status. The risk of MI was assessed using Cox regression analysis. Statistical analysis was performed using SPSS 21.0 statistical software (SPSS Inc., Chicago, IL, USA). All p-values were two tailed, and values less than 0.05 were considered statistically significant.

III. RESULTS

1. Baseline characteristics

The mean age of matched patients was 63 years (range, 19-98 years) and 58% of the patients were male. Table 1 shows the baseline characteristics of the study population stratified by AF status. In the full pre-match cohort, patients with AF were older, had a higher body mass index, a higher prevalence of heart failure (HF), hypertension, diabetes, CKD or ESRD, dyslipidemia, ischemic stroke, PAOD, and COPD (all $P<0.001$). Mean CHA_2DS_2-VASc score was 2.6 ± 1.9 in the AF group and 1.2 ± 1.3 in the no-AF group ($P<0.001$). Covariates with significant imbalances in the pre-matched cohort which were well balanced after propensity matching are displayed in Table 1. Absolute standardized differences in all measured covariates were less than 5%, suggesting substantial covariate balance across the groups (Figure 2).

Table 1. Baseline characteristics by AF status before and after propensity score matching

	Before propensity matching				After propensity matching		
	No AF (n=494,071)	AF (n=3,295)	Standard, mean, Difference	p	No AF (n=13,159)	AF (n=3,295)	Standard, mean, Difference
Age, years	47.4±14.2	62.8±12.9	1.194	<0.001	62.9±12.9	62.8±12.9	-0.006
Female, %	50.1	42	-0.173	<0.001	42.1	42.0	-0.003
Systolic BP, mmHg	122.1±15.3	128.3±16.9	0.366	<0.001	128.5 ±16.1	128.3 ±16.8	-0.012
Diastolic BP, mmHg	76.0±10.2	78.6±10.6	0.245	<0.001	78.8 ±10.2	78.6 ±10.7	-0.012
Body mass index, kg/m2	23.7±3.3	24.3±3.4	0.190	<0.001	24.3 ±3.2	24.3 ±3.4	0.003
Waist circumference, cm	79.9± 9.3	83.9± 9.1	0.449	<0.001	84.0 ±8.6	84.0 ±9.1	0.003
Heart failure, %	1.9	11.5	0.299	<0.001	10.1	11.5	0.038
Hypertension, %	20.7	57	0.732	<0.001	56.5	57	0.009
Diabetes, %	12.3	32.1	0.426	<0.001	31.3	32.1	0.017
CKD or ESRD, %	5.6	17.3	0.309	<0.001	16.6	17.3	0.015
Dyslipidemia, %	18.6	38.1	0.400	<0.001	38.2	38.1	-0.003
Ischemic stroke, %	2.4	9.3	0.239	<0.001	9.1	9.3	0.005
PAOD, %	6.9	19.4	0.315	<0.001	19.2	19.4	0.005
COPD, %	6.0	17.3	0.298	<0.001	16.6	17.3	0.015
History of malignancy, %	6.6	14.1	0.218	<0.001	13.7	14.1	0.011
Anemia, %	11.8	16.7	0.245	<0.001	16.3	16.2	-0.004
Smoking, %	37.6	39.4	0.021	0.042	38.4	39.4	0.004
Total cholesterol, mg/dl	195.1±37.2	192.9±39.4	-0.054	0.001	192.9 ±37.8	192.9 ±39.3	0.002
Triglyceride, mg/dl	131.9±94.1	139.2±88	0.088	<0.001	139.6 ±86.7	139.2 ±88.2	-0.004
HDL-cholesterol, mg/dl	56.5±27.9	55.1±36.5	-0.028	0.025	54.8 ±35.3	55.1 ±36.5	0.006
LDL-cholesterol, mg/dl	113.8±37.6	112.4±38.7	-0.031	0.038	112.8 ±38.8	112.4 ±38.7	-0.007
Serum creatinine, mg/dl	1.0±1.1	1.1±1.2	0.079	<0.001	1.09 ±1.2	1.10 ±1.2	0.007
eGFR-CKD-EPI	89.5±21.1	76.7±21.1	-0.601	<0.001	77.4 ±20.5	77.1 ±20.9	-0.010
$CHADS_2$	0.5 ± 0.9	1.4 ± 1.4	0.995	<0.001	1.4 ± 1.4	1.4 ± 1.4	0.029
CHA_2DS_2-VASc	1.2 ± 1.3	2.6 ± 1.9	1.073	<0.001	2.5 ± 2.0	2.6 ± 2.0	0.026

AF, atrial fibrillation; $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR-CKD-EPI, estimated glomerular filtration rate-chronic kidney disease-epidemiology collaboration; ESRD, end–stage renal disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAOD, peripheral artery obstructive disease; VASc, Vascular disease, age 65-75 years, sex category

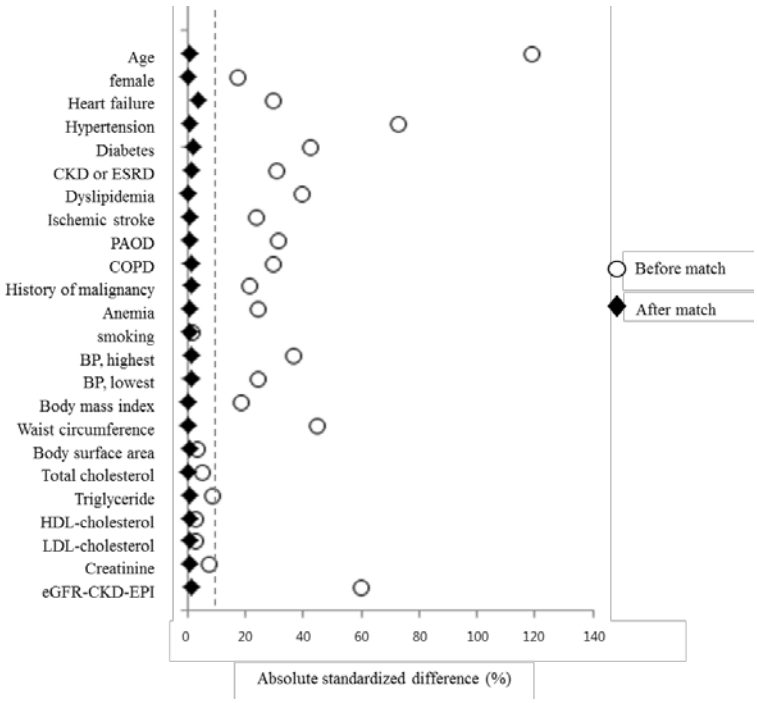

Figure 2. Love plots for absolute standardized difference for baseline covariate between patients with and without atrial fibrillation, before and after propensity score matching. CKD, chronic kidney disease; ESRD, end–stage renal disease; PAOD, peripheral artery obstructive disease; COPD, chronic obstructive pulmonary disease; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR-CKD-EPI, estimated glomerular filtration rate-chronic kidney disease-epidemiology collaboration

Aspirin, oral anticoagulants (OACs), statin, digoxin, beta blocking agent (BB), and calcium channel blocker (CCB) were more frequently prescribed in AF patients; aspirin (50.3% vs. 27.5%, P<0.001), anticoagulant (20.9% vs. 0.3%, P<0.001), statin (38.2% vs. 28.5%, P<0.001), digoxin (13.4% vs. 0.9%, P<0.001), BB (43.1% vs.16.1%, P<0.001), and CCB (11.4% vs. 2.5%, P<0.001).

2. AF and the risk of MI

Over 4.2 years of follow up, 137 MI events occurred. The mean ± SD time from AF diagnosis to MI in those with AF was 4.1 ± 1.0 years (median, 3.9 years). Figure 3 shows the unadjusted cumulative incidence of MI stratified by baseline AF status in the entire cohort (Figure 3A) and the matched cohort (Figure 3B). Patients with AF had a higher incidence of MI than those without AF in both the entire cohort and the matched cohort (log rank p<0.001 for both cohorts).

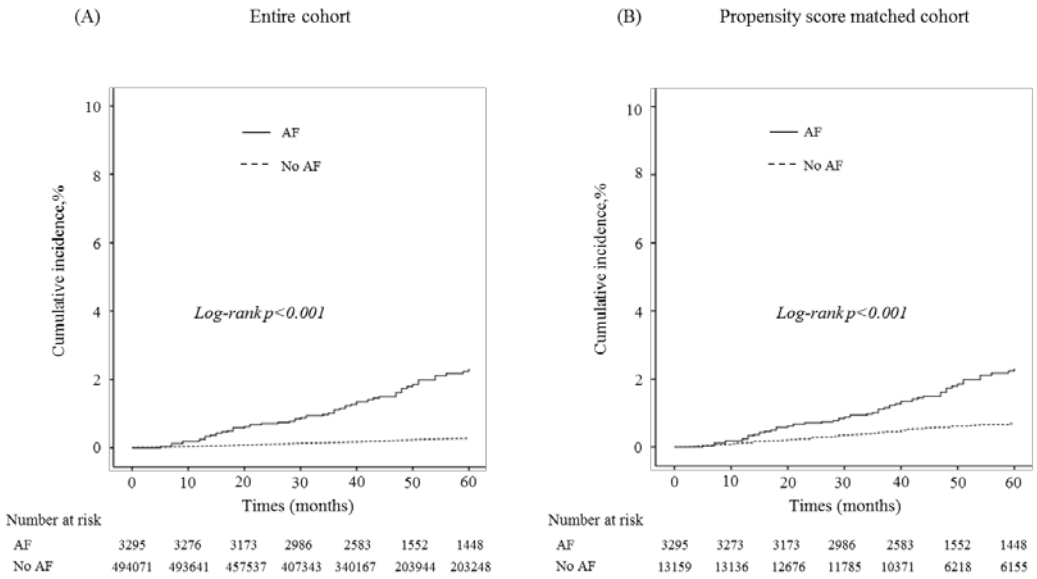

Figure 3. Unadjusted cumulative incidence of myocardial infarction by baseline atrial fibrillation (AF) status in the entire cohort (A) and in the propensity scored matched cohort (B).

The age adjusted incidence rate of MI among participants was higher in those with AF than in those without AF (4.42 vs 1.42 per 1000 person-years), with an incidence rate ratio (IRR) of 3.12 [95% CI, 2.23-4.36]. In a sex stratified analysis, IRR of age-adjusted MI stratified by AF status was higher in women (IRR, 3.65; 95% CI, 2.09-6.38) than in men (IRR, 2.88; 95% CI, 1.89-4.39) (Figure 4).

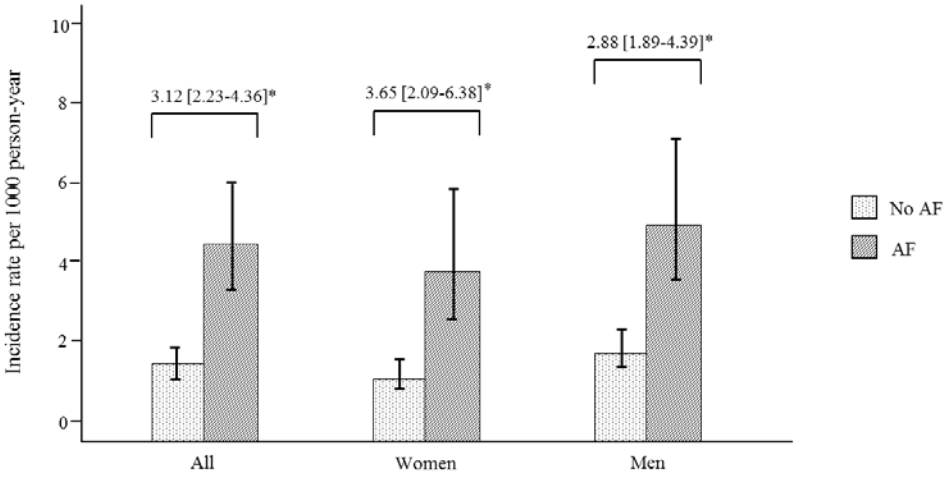

Figure 4. Age-adjusted incidence rate and incidence rate ratios of myocardial infarction by atrial fibrillation (AF) status. *Age adjusted incidence rate and incidence rate ratios were based on the average of the cohort.

In a Cox proportional hazards model of the matched cohort, AF was an independent risk factor for MI [Hazard ratio (HR), 3.12; 95% CI, 2.23-4.37, p<0.001]. Other risk factors were hypertension (HR, 1.87; 95% CI, 1.30-2.69, p<0.001), diabetes (HR, 1.79; 95% CI, 1.28-2.51, p<0.001), HF (HR, 2.04; 95% CI, 1.32-3.14, p=0.003), CKD or ESRD (HR, 2.70; 95% CI, 1.09-3.85, p<0.001), and dyslipidemia (HR, 1.45; 95% CI, 1.04-2.03, p=0.031) (Table 2).

Table 2. The independent clinical predictors of myocardial infarction in propensity score matched cohort

	HR	95% CI	p-value
Age, per 1 year	1.05	1.03-1.07	<0.001
Atrial fibrillation	3.12	2.23-4.37	<0.001
Heart failure	2.04	1.32-3.14	0.003
Hypertension	1.87	1.30-2.69	<0.001
Diabetes	1.79	1.28-2.51	<0.001
CKD or ESRD	2.70	1.90-3.85	<0.001
Dyslipidemia	1.45	1.04-2.03	0.031
Ischemic stroke	1.71	1.05-2.77	0.030
COPD	2.18	1.51-3.15	<0.001
Anemia	1.54	1.02-2.30	0.038
Waist circumference	1.03	1.01-1.05	0.011

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end stage renal disease

3. Association of AF with MI in subgroups

The associations of AF with MI among various subgroups of patients are displayed in Figure 5. The risk of hospitalization or death due to MI was significantly higher in the AF group than in the no-AF group, regardless of age (p for interaction=0.1), sex (p for interaction=0.6), comorbidities with HF (p for interaction=0.11), and CKD or ESRD (p for interaction=0.56) at baseline. On the other hand, we found that the risk of AF associated incident MI was higher in patients free of hypertension [HR, 7.87 (95% CI, 4.13-15.0) vs. 2.06 (95% CI, 1.35-3.14), p for interaction=0.001], diabetes [HR, 4.89 (95% CI, 3.13-7.67) vs. 1.66 (95% CI, 0.72-3.84), p for interaction=0.003], ischemic stroke [HR, 3.50 (95% CI, 2.44-5.03) vs. 1.407 (95% CI, 0.51-3.91), p for interaction=0.002], and dyslipidemia [HR, 4.49 (95% CI, 2.84-7.09) vs. 1.98 (95% CI, 1.18-3.35), p for interaction=0.021] at baseline.

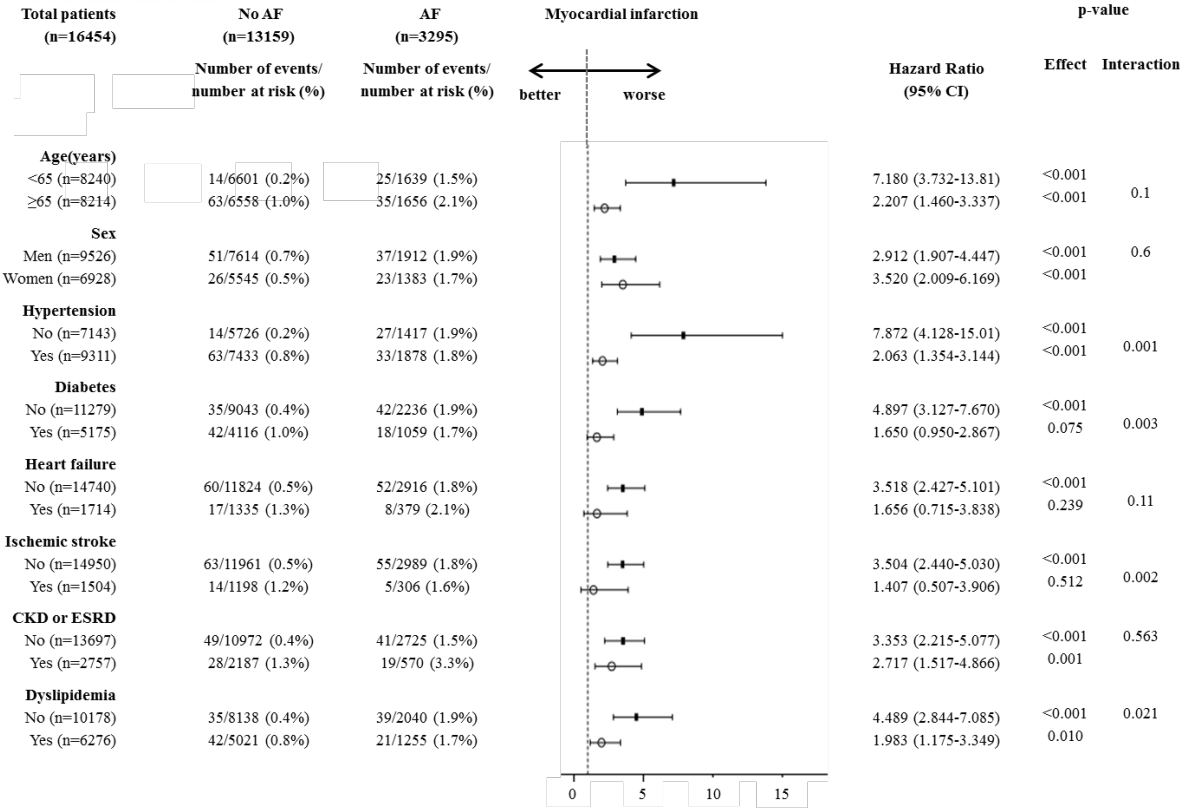

Figure 5. Association of atrial fibrillation with hospitalization or death due to myocardial infarction in subgroups of propensity score matched cohort.

4. Risk of MI in association with medications in AF patients

Medications analyzed in this study were aspirin, OACs, statin, digoxin, BB and CCB. Anticoagulants included in the analysis were warfarin, direct thrombin inhibitor and factor Xa inhibitors.

Figure 6 shows the effect of OACs on the occurrence of MI in AF patients. OACs were prescribed in 688 of the 3,295 AF patients and cumulative incidence of MI was lower in AF patients on OACs than in those without OACs (Figure 6A, p=0.004). Subgroup analyses were conducted to focus on the effects of OACs according to CHA_2DS_2-VASc scores. In patients with AF with a CHA_2DS_2-VASc score of 0 or 1 (n=1,191), OACs were prescribed in 213 (17.9%) patients and cumulative incidence of MI did not significantly differ between the patients on OACs and no OACs (Figure 6B,

p=0.385). In patients with CHA_2DS_2-VASc ≥ 2 (n=2,104), OACs were prescribed in 475(22.6%) patients and cumulative incidence of MI was significantly lower in patients on OACs than in no OCAs. (Figure 6C, p=0.004).

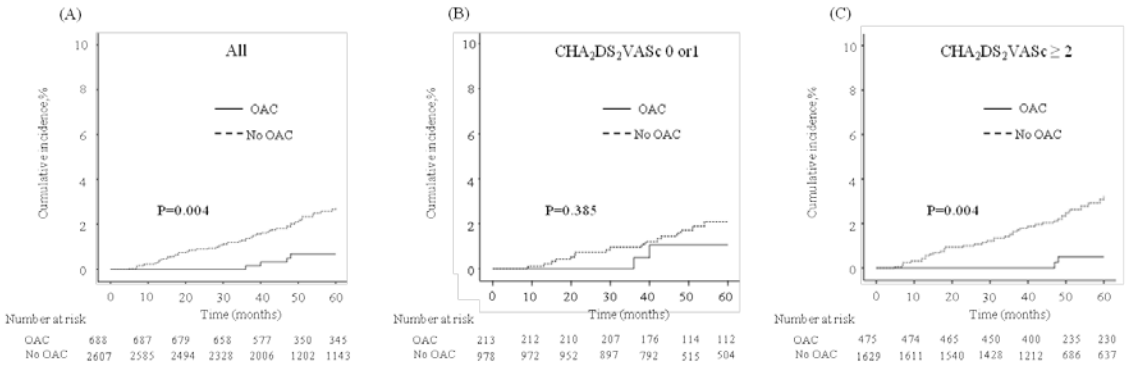

Figure 6. The effect of oral anticoagulants on the occurrence of atrial fibrillation (AF) associated myocardial infarction. In all AF patients (A), in patients with CHA_2DS_2-VASc score of 0 or 1 (B), and in patients with CHA_2DS_2-VASc score ≥ 2 (C).

Statins were prescribed in 1,259 of the 3,295 AF patients cumulative incidence of MI was lower in AF patients on statin than in those without statin (Figure 7A, p=0.039). Aspirin users showed a similar trend, which did not reach statistical significance (Figure 7B, p=0.058). The most commonly prescribed rate control agent was BB, followed by digoxin and CCB. MI events did not differ between patients who were taking digoxin (Figure 7C), BB (Figure 7D), and CCB (Figure 7E) and those who were not taking these medications. Overall death, regardless of the mode of death, occurred more often in patients with MI than in those without MI during the follow up period (35.8% vs 4.6%, p<0.001).

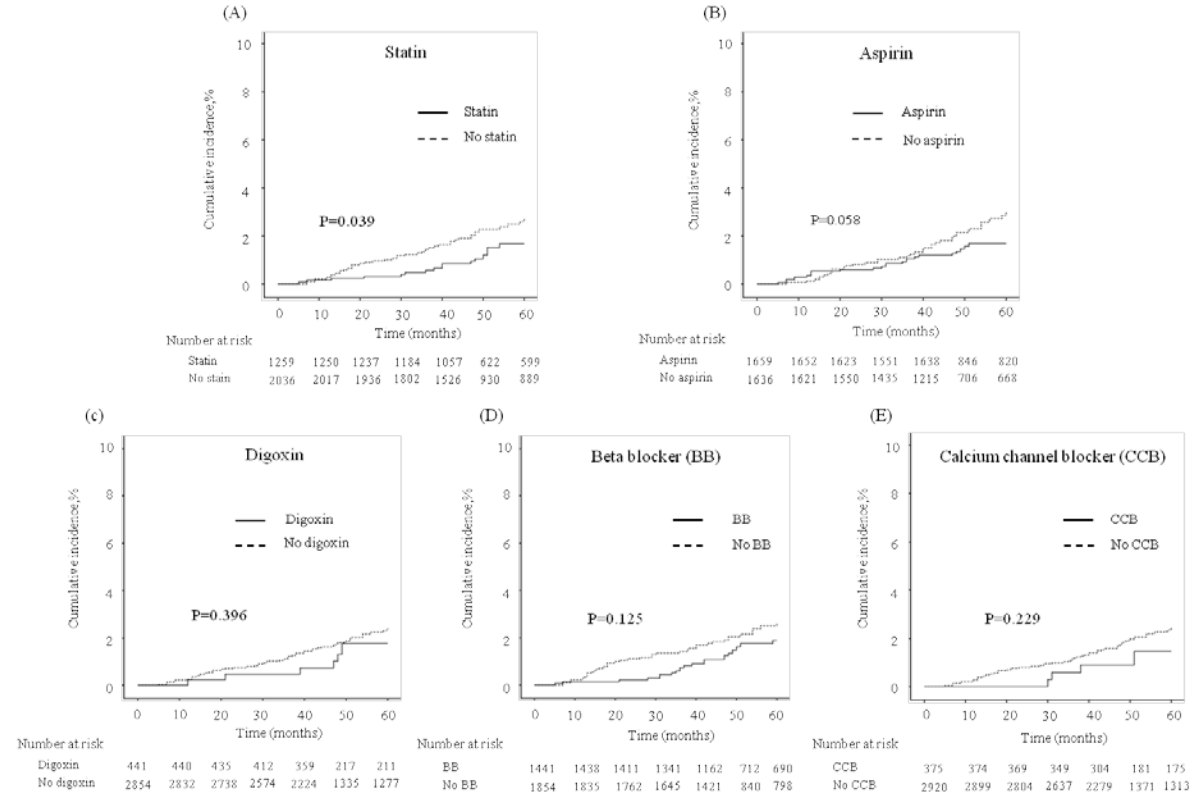

Figure 7. Risk of incident myocardial infarction associated with medication in patients with atrial fibrillation.

IV. DISCUSSION

1. Main findings

In this study from NHIS, a nationwide population based cohort, our principal findings are as follows: (1) AF was significantly associated with increased risk of incident MI. (2) Association between AF and the risk of MI did not differ by sex. (3) The risk of AF associated incident MI was higher in patients free of hypertension, diabetes, ischemic stroke, and dyslipidemia, which were well known risk factors for MI. (4) The incidence of AF associated incident MI was lower in patients on anticoagulant and statin therapies.

2. AF and the risk of MI

In this study, AF was associated with an increased risk of MI in both the entire cohort and the propensity matched cohort. In the time dependent Cox analysis using survival time from 2009 to the occurrence of MI, the risk of AF associated incident MI was similar (HR, 3.02; 95% CI, 2.17-4.41, p<0.001). The well-known risk factors and potential confounders for MI were included in the matching and the association was stronger in women than in men. These findings were in accordance with the recently reported findings in the REGARDS and ARIC studies which showed AF as an independent risk factor for MI, with sexual and racial differences.[6,7,16] In another study, association between AF and inflammation has been reported.[17] The well-known pathophysiology of MI is plaque rupture in atherosclerotic coronary arteries and subsequent thrombus formation in infarct related arteries. A number of histologic observations have shown that a ruptured plaque contains more inflammatory cells and activated in the vessel wall.[18] These findings may shed light on similar underlying mechanisms in both AF and MI. Our observation that there is a higher AF-associated risk of MI in women than in men provides evidence for gender difference in cardiovascular disease outcomes and the potential differences in the impact of risk factors among sexes. It is less likely that sex difference in MI occurrence was confounded by the difference in AF-associated co-morbidities because we adjusted for the potential confounders in propensity matching as covariates.

3. Association of AF with MI in subgroups

Notably, we confirmed that the risk of MI was significantly higher in patients with AF free of overt cardiovascular disease-hypertension, diabetes, ischemic stroke, and dyslipidemia-than in subjects without AF. Previous study from Olmsted County revealed that lone AF in the absence of overt cardiovascular disease has a benign clinical course with a comparable risk of embolic events and mortality to the general population.[19,20] In contrast, recent studies from Brand and Chao showed that patients with AF without cardiovascular co-morbidities had an increased risk of cardiovascular events and mortality.[21,22] These interactions with established risk factors for MI suggest that shared underlying risk factors for MI is not the only mechanisms explaining the association between AF and MI. There are plausible explanations for why AF patients with less co-morbidity were predisposed to MI. In high risk patients, who already have established risk factors for MI, AF may

contribute less to the occurrence to MI, compared with those who were previously healthy. In our study, anticoagulants showed beneficial effect against AF associated incident MI, especially in patients with CHA_2DS_2-VASc score ≥ 2. Accordingly, embolic events to coronary arteries are another possible explanation. Statin use, and also, is higher in patients with established cardiovascular diseases, which may decrease the incident MI. Further study is needed in this regard.

4. Risk of MI in association with medications in AF patients

In this analysis stratified by medications after AF diagnosis, the risk of incident MI was less in anticoagulant users. Previously, it was reported that warfarin might have a protective effect against MI after acute coronary syndrome.[23] The pathophysiology and pharmacokinetics related to the protective effect of warfarin against MI in AF patients have not been fully understood. Even though the actual incidence of coronary embolism is not known and it is considered to be rare, sporadic cases of thromboembolic MI have been reported in patients with AF.[24,25] Prizel *et al.*[26] reported that AF was the underlying disease predisposing to coronary embolism in 24% of these cases. Prevention of thrombus formation with use of warfarin, in part, might be a plausible explanation for the beneficial effect against MI in AF patients. In our study, the anticoagulants analyzed were direct thrombin inhibitor, factor Xa inhibitors, as well as warfarin, and the protective effect of each medication against AF-associated MI was not evaluated. Further investigation is needed.

Clinical trials have already demonstrated a clear beneficial effect of statin for primary and secondary prevention of coronary heart disease.[27,28] In accordance with these studies, this study revealed that the risk of AF-associated incident MI was less in statin users than in non-users.

Type 2 MI can occur due to the episode of poorly controlled ventricular response in AF patients.[29] The rate control strategy in AF patients is expected to reduce the occurrence of type 2 MI, by reducing the oxygen demand and by increasing the diastolic filling time of coronary arteries. However, the result of this study was not in accordance with this common belief, suggesting that type 2 MI is less likely to be the main mechanism by which AF leads to MI.

5. Clinical implications

Our study revealed that AF increased the risk of MI. Considering MI as a known risk factor for AF,[30] this result suggests a bidirectional relationship between AF and MI. The possible explanation for this

bidirectional relationship comes from the fact that AF and MI share similar risk factors. The pathophysiology of AF is complex and incompletely understood. An association between AF and abnormal prothrombotic plasma markers suggests that arrhythmia itself may contribute to the development of pro-thrombotic status.[31] Recently, it was reported that various inflammatory markers such as C-reactive protein, tumor necrosis factor-α, and interleukins are related to the presence or the outcome of AF.[17] In our study, anticoagulants and stain showed beneficial effects against incident MI in AF patients. It is conceivable that the antithrombotic effect of anticoagulants and the anti-inflammatory effect of statin contributed to the favorable outcome.

The prevalence of AF doubles with each additional decade of life.[32] With an increasing older population, the occurrence of AF itself and AF-associated morbidity and mortality is expected to increase as well. From a preventive perspective, the notion should suggest that AF potentiates the risk of MI. In addition, genetic difference and socioeconomic status of those who are predisposed to MI should be investigated further.

6. Limitations

There are several limitations to this study. Although we ascertained AF cases with ECGs as well as ICD codes, it is possible that paroxysmal or asymptomatic AF cases were not detected. Also, we could not analyze paroxysmal, persistent and permanent AF separately. Second, because MI cases were identified by ICD-10 code, data for cardiac markers, ECGs, and coronary angiography were not available, which could have provided further information about the type of MI.[29] We could not analyze the association of AF with different types of MI. Third, even though the NHIS recommends biennial health check-up to all health insurance subscribers, it is not compulsory and there is a possibility that healthier and more educated subjects could have participated in this study. Fourth, potentially uncontrolled covariates may exist because comorbidities included in propensity matching are the data from baseline examination. They may be absent at baseline, but may have developed during the follow-up. Fifth, similar to other studies, considerable confounders may remain although propensity-score matching was well balanced. Despite the limitations, this study is the nation-wide cohort based observational studies providing the further evidence for a link between AF and MI, and the effects of medications on the occurrence of AF related incident MI.

V. CONCLUSION

AF is associated with an increased risk of MI in the Korean population, with the age adjusted incidence rate of MI being higher in women than in men. Anticoagulants and statin showed beneficial effects against MI in AF patients. Our finding suggests that AF complications beyond stroke should extend to total mortality to include MI.

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ABSTRACT(IN KOREAN)

심방세동과 연관된 심근경색의 위험성
: 성향점수 매칭을 통한 전국적 코호트 연구

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이 혜 영

목적 : 심방세동은 심근경색 환자에서 그 예후에 좋지 않은 영향을 미치는 요인으로 이미 알려져 있다. 최근 연구에서 심방세동이 심근경색의 위험을 높인다고 보고한 바 있다. 본 연구는 심방세동과 연관된 심근 경색의 위험도를 전체 인구를 대상으로 하여 조사하고자 하였다

방법 : 한국 국민건강보험 자료를 분석하여 기존에 심방세동이나 심근경색의 기왕력이 없는 497,366 명(평균연령 47.6 세, 250,569 여성)을 5 년간 추적 관찰하였으며 이 기간동안 심방세동이 새로 발생한 3,295 명과 성향점수 매칭으로 선별된 심방세동이 없는 13,159 명을 대상으로 심근경색 발생율을 비교 분석하였다.

결과 : 4.2 년의 추적관찰 기간 동안 총 137 건의 심근경색이 발생하였으며 심방세동 진단시점에서 심근경색 발생까지의 기간은 4 년이었다. 연령 보정 심근경색 발생율은 심방세동이 있는 군에서 그렇지 않은 군보다 더 높았다 [발생율, 4.42 (95% 신뢰구간; 3.25-5.98 대 1.42 (95% 신뢰구간. 1.07-1.87)/1000 인년]. 심방세동은 심근경색 발생 위험을 3 배 증가시키며 [위험비율, 3.25 (95% 신뢰구간; 2.24-4.7), 추적 기간 동안

심근경색의 누적 발생율은 항응고제와 지질 강하제를 복용한 군에서 그렇지 않은 군에 비해 유의하게 작았다.

결론 : 심방세동은 심근경색의 위험을 증가시키며, 그 위험도는 항응고제와 지질 강하제의 사용에 의해 감소된다. 본 연구의 결과는 심방세동의 합병증이 뇌졸중뿐만 아니라 심근경색에 의한 사망률까지 고려해야 함을 시사한다.

핵심되는 말 : 심방세동, 심근경색, 전국민 코호트