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Original Research Article

Association between the use of renin-angiotensin system blockers and development of in-hospital atrial fibrillation in patients with ST-segment elevation myocardial infarction

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ABSTRACT

Background and aim: Atrial fibrillation (AF) is the most common supraventricular arrhythmia following ST-segment elevation myocardial infarction (STEMI). We evaluated the association between use of previous angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers (renin-angiotensin system [RAS] blockers) and started RAS blockers after MI and development of AF in patients presenting with acute STEMI.

Materials and methods: This retrospective study enrolled 1000 patients with acute STEMI who were admitted to the coronary care unit. Patients were divided into groups according to the use of RAS blockers before MI and development of AF rates was compared. Predictors of AF were determined by multiple logistic regression analysis.

Results: Of the 1000 patients presenting with STEMI, 247 received and 753 did not receive RAS blockers. The incidence of AF was 7.9%. The incidence of AF in patients receiving RAS blockers and did not receiving RAS blockers before MI were similar (5.7% vs. 8.6% respectively, $P = 0.13$). On the other hand, AF rate was lower in patients in whom RAS blockers were administered during MI as compared to those in whom these agents were not administered (7.2% vs. 28.6%, $P < 0.001$). Multiple regression analysis results showed that administration of RAS blockers or statins during hospitalization and left atrial diameter were associated with development of AF in patients with acute STEMI.

Conclusions: Previous therapy with RAS blockers does not reduce the incidence of AF in STEMI. Administration of RAS blockers at the hospital may decrease the AF rate in STEMI.

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1. Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia in clinical practice, and its prevalence increases with age. Previous studies have shown that the prevalence of AF is less than 0.5% at the age of 40–50 years and increases to 5%–15% at the age of 80 years [1].

Atrial fibrillation is the most common type of the supraventricular arrhythmia occurring after ST-segment elevation myocardial infarction (STEMI), and its prevalence is even higher in elderly patients with heart failure and severe left ventricular impairment [1]. The incidences of stroke and death have been found to be higher in patients who develop AF after STEMI compared to those who do not develop AF. Some conditions such as left ventricular dysfunction, atrial ischemia or infarction, right ventricular infarction, pericarditis, and excessive catecholamine release can be predisposing factors for the development of AF [1].

Statins, omega-3 polyunsaturated fatty acids, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers and aldosterone antagonists are termed ''upstream'' therapies for the management of atrial fibrillation. These therapies aim to prevent or delay remodeling after myocardial infarction and may prevent the development of new AF (primary prevention), or once established, its rate of recurrence or progression to permanent AF (secondary prevention) [1].

Studies on patients with acute myocardial infarction (MI) and heart failure showed that renin-angiotensin system (RAS) blockers reduce the incidence of new onset AF [2–6]. Studies investigating patients treated with cardioversion showed that angiotensin-converting-enzyme inhibitors facilitate rhythm control and reduce the recurrence of AF [7–10]. In one study, the incidence of AF in patients who received RAS blockers was similar to that in patients who did not receive RAS blockers after cardiac surgery [11]. Another study showed that, the use of RAS blockers was associated with low incidence of postoperative AF [12]. Meta-analyses of randomized studies showed a decreased risk of development of new onset AF associated with RAS blocker therapy [13–15].

In previous studies investigating the development AF after acute MI, RAS blockers were initiated in patients after MI and explored for the development of AF. However, there are no studies in the literature exploring the effects of receiving RAS blockers before MI on the development of AF. Unlike other studies, the aim of our study was to evaluate the effects of angiotensin-converting-enzyme inhibitor and/or angiotensin receptor blocker therapies (RAS blockers) before or after MI on AF in patients presenting with STEMI.

2. Materials and methods

2.1. Study population

The patients who were on follow-up in the coronary intensive care unit with the diagnosis of STEMI were included in the study. A retrospective study design was used in the present study. Approval was obtained from the ethics committee. A total of 1028 patients were included in the study.

The diagnosis of STEMI was based on the presence of at least one of the following criteria: ischemic symptoms with an increase and/or decrease in the cardiac enzyme levels (chest pain longer than 20 min), and significant electrocardiography (ECG) changes (in at least two contagious leads after j point ST-elevation ≥0.2 mV in men, ≥0.15 mV in women in V2-3 leads, or ≥0.1 m in other derivations or new onset left bundle branch block) [16]. The onset time of acute MI was based on the patient-reported onset time.

The exclusion criteria included unstable angina pectoris, non-STEMI, MI occurring after coronary artery bypass graft or invasive cardiac procedures, patients who underwent primary percutaneous coronary intervention, presence of AF on admission, moderate-severe valvular heart disease, hyperthyroidism, advanced chronic obstructive pulmonary disease, sepsis, medical history of malignancy, previous anti-arrhythmic drug use, and the presence of a known severe psychiatric disease. Twenty-eight patients who met the exclusion criteria (hyperthyroidism [$n = 11$], presence of AF upon hospital admission [$n = 7$], severe valvular disease [$n = 5$], primary percutaneous coronary intervention [$n = 4$], and sepsis [$n = 1$]) were excluded from the study.

Patient data including age, gender, time to hospital admission after symptom onset, and cardiac therapies that the patient underwent outside the hospital were recorded. The risk factors for coronary artery disease, previous medical history, presence of arrhythmia and previous medications of the patients were recorded.

Electrocardiography recordings were obtained upon first admission. Subsequent cardiac rhythm monitoring was conducted by continuous monitoring in the coronary intensive care unit and by ECG recordings obtained routinely on a daily basis or upon report of a complaint suggesting arrhythmia. During the follow-up of patients in the cardiology service, cardiac rhythm was monitored by ECG recordings obtained routinely on a daily basis or upon report of a complaint suggesting arrhythmia. The diagnosis of AF was based on the absence of p waves, presence of fine and coarse fibrillation waves, and irregular RR interval.

Sodium, potassium, urea, creatinine, glucose, creatine kinase, creatine kinase-myocardial band and troponin T levels, liver function tests, lipid parameters and complete blood count were retrospectively reviewed.

All patients were treated according to current published guidelines. Routine primary percutaneous coronary intervention was not available at our hospital at the time of patient recruitment. Therefore, patients treated by this method were limited in number, and were excluded from the study.

The patients were divided into groups according to the use of RAS blockers before MI, and the initiation of these therapies after MI.

2.2. Statistical analysis

SPSS version 11 (SPSS Inc., Chicago, IL) software package was used in the statistical analyses of the study. Categorical variables were expressed as frequency (%) and compared with the χ^2 test. A Kolmogorov–Smirnov test was used to test the distribution of numeric variables, and those with normal distribution were expressed as mean ± standard deviation and

were analyzed with the Student t test or analysis of variance as appropriate. On the other hand, those without normal distribution were expressed as median (minimum–maximum) and were compared with the Mann–Whitney U test or Kruskal–Wallis test as appropriate. In all statistical analyses, P values of <0.05 were considered statistically significant. In the comparison of patients with or without atrial fibrillation, variables (smoking, history of hypertension, statin use, initiation of statin therapy in the hospital, initiation of RAS blockers in the hospital, initiation of positive inotropic agents in the hospital, total cholesterol and triglyceride levels, age, left atrial (LA) diameter, and ejection fraction) yielding a P value of <0.10 were included in multiple regression analysis.

3. Results

The mean age of the patients was 61 years (SD, 12 years) and ranged between 26 and 90 years. Amongst the cohort of 1000 patients, 814 (81.4%) were male. The mean length of hospital stay was 6.2 days (SD, 1.5 days).

The patients included in the study were divided into two groups depending on their history of use of RAS blockers. Of the 1000 patients, 247 (24.7%) were already undergoing therapy with RAS blockers, while 753 (75.3%) never received RAS blockers prior to the development of STEMI. The demographic and clinical features of the patients are presented in Table 1.

The mean age of the patients who had previously received RAS blockers was higher. As risk factors for cardiovascular disease, the prevalence of diabetes mellitus, hypertension, and hyperlipidemia was higher in patients who had received RAS blockers previously (all P values of <0.001), and while the prevalence of smokers and the proportion of males were higher in patients who had not received RAS blockers previously (all P values of <0.001) (Table 1). Furthermore, MI, percutaneous coronary intervention, coronary artery bypass grafting, and the history of heart failure were more common in patients who received RAS blockers previously (both P values of <0.05) (Table 1). The use of acetylsalicylic acid, clopidogrel, statins, and beta-blockers were more common in patients who received RAS blockers previously (all P values of <0.05) (Table 1).

During the follow-up, the development of AF was seen in 14 patients who received RAS blockers previously, and 65 patients who did not. No significant difference was observed between the two groups in terms of the incidence of AF (P = 0.13), conversion of normal sinus rhythm (P = 0.28) and the methods used to convert AF into sinus rhythm (P = 0.94).

Of the 1000 patients with STEMI, 965 patients received RAS blocker therapy after hospitalization, while 35 patients did not. The incidence of AF was found to be lower in patients who received RAS blockers after STEMI (69 of 965 patients), compared to patients who did not (10 of 35 patients) (P < 0.001). The incidence of AF was found to be higher in patients who never received RAS blockers therapies before or after STEMI (9 of 31 patients), compared to patients who started this therapy for the first time after developing STEMI (56 of 722 patients, P < 0.001), as well as compared to patients who continued previous therapies after developing STEMI (13 of 243 patients, P < 0.001).

The patients were divided into two groups, one including patients who developed AF and the other who did not. The demographic and clinical features and laboratory data of the patients are presented in Table 2. The patients who developed AF had more advanced age, lower ejection fraction, higher LA diameter, lower triglyceride level, and lower rate of smoking, compared to patients who did not develop AF (all P values of <0.05) (Table 2). Furthermore, the proportion of patients recently put on positive inotropic medications was higher, the mean length of hospital stay was higher, and the proportion of patients put on therapies with statins, and RAS blockers were lower in patients with AF (all P values of <0.05) (Table 2).

In the comparison of patients with or without AF, variables yielding a P value of <0.10 were included in the regression analysis. Positive univariate predictors of AF were age, smoking, LA diameter and initiation of positive inotropic agent at the hospital. Negative univariate predictors of AF were

Table 1 – Demographic and clinical characteristics.

Variable	Non-RAS blockers (n = 753)	RAS blockers (n = 247)	P
Age, mean (SD) years	60 (11)	64 (12)	<0.001
Male gender	643 (85.4)	171 (69.2)	<0.001
Smoking	478 (63.5)	107 (43.3)	<0.001
Diabetes mellitus	120 (15.9)	87 (35.2)	<0.001
Hypertension	226 (30.0)	187 (75.7)	<0.001
Hyperlipidemia	166 (22.0)	95 (38.5)	<0.001
Ejection fraction, mean (SD), %	41 (9)	41 (8)	0.78
Left atrial diameter, mm	39 (4)	40 (4)	0.07
MI localization			0.24
Anterior	361 (47.9)	129 (52.2)	
Others	392 (52.1)	118 (47.8)	0.55
Previous atrial fibrillation	6 (0.8)	3 (1.2)	<0.001
Previous MI	17 (2.2)	25 (10.1)	<0.001
Previous PCI	25 (3.3)	30 (12.1)	0.01
Previous CABG	13 (1.7)	11 (4.5)	0.48
Peripheral artery disease	8 (1.1)	4 (1.6)	0.81
Chronic renal failure	5 (0.7)	2 (0.8)	0.02
Heart failure	19 (2.5)	14 (5.7)	0.28
Cerebrovascular accident	13 (1.7)	7 (2.8)	
Prior therapies			<0.001
Statin	52 (6.9)	45 (18.2)	<0.001
Beta blocker	50 (6.6)	92 (37.2)	<0.001
Acetyl salicylic acid	130 (17.3)	137 (55.5)	0.02
Clopidogrel	19 (2.5)	14 (5.7)	
Initiated therapies			0.48
Beta blocker	721 (95.8)	239 (96.8)	0.37
Statin	637 (84.6)	203 (82.2)	0.06
RAS blockers	722 (95.9)	243 (98.4)	0.98
Acetyl salicylic acid	747 (99.2)	245 (99.2)	0.08
Heparin	753 (100)	246 (99.6)	0.16
Clopidogrel	246 (32.7)	88 (35.6)	0.93
Thrombolysis	569 (75.5)	186 (75.3)	0.99
Coronary angiography	646	203	
Normal coronary	32 (4.2)	10 (4.0)	0.51
Single-vessel disease	254 (33.7)	85 (34.4)	
Multi-vessel disease	360 (47.9)	108 (43.7)	0.39
Length of hospital stay, mean (SD), days	6.2 (1.4)	6.1 (1.5)	

Values are number (percentage) unless otherwise indicated.
CABG, coronary artery bypass graft, MI, myocardial infarction, PCI, percutaneous coronary intervention, RAS, renin-angiotensin system.

Table 2 – Comparison of patients with and without AF during hospitalization.

Variable	Without AF (n = 921)	With AF (n = 79)	P
Age, mean (SD), years	61 (12)	66 (11)	<0.001
Male gender	753 (81.8)	61 (77.2)	0.32
Smoking	548 (59.5)	37 (46.8)	0.03
Diabetes mellitus	191 (20.7)	16 (20.3)	0.92
Hypertension	373 (40.5)	40 (50.6)	0.08
Hyperlipidemia	246 (267)	15 (19)	0.13
Ejection fraction, mean (SD), %	41 (9)	37 (9)	0.001
Left atrial diameter, mean (SD), mm	39 (4)	42 (5)	<0.001
MI localization			0.21
Anterior	446 (48.4)	44 (55.7)	
Others	475 (51.6)	35 (44.3)	0.38
Previous AF	9 (1.0)	0 (0)	0.65
Previous MI	37 (4.0)	4 (5.1)	0.89
Previous PCI	50 (5.4)	4 (5.1)	0.94
Previous CABG	22 (2.4)	2 (2.5)	0.26
Peripheral artery disease	10 (1.1)	2 (2.5)	0.44
Chronic renal failure	7 (0.8)	0 (0)	0.12
Heart failure	28 (3.0)	5 (6.3)	0.63
Cerebrovascular accident	19 (2.1)	1 (1.3)	0.07
Total cholesterol, mean (SD), mg/dL	186 (54)	174 (40)	0.99
HDL cholesterol, mean (SD), mg/dL	41 (10)	41 (13)	0.39
LDL cholesterol, mean (SD), mg/dL	111 (43)	107 (37)	0.04
Triglycerides, mean (SD), mg/dL	149 (93)	126 (63)	
Prior therapies			0.13
RAS blocker	233 (25.3)	14 (7.7)	0.94
Beta blocker	131 (14.2)	11 (13.9)	0.06
Statin	94 (10.2)	3 (3.8)	0.57
Acetyl salicylic acid	248 (26.9)	19 (24.1)	0.29
Clopidogrel	32 (3.5)	1 (1.3)	
Initiated therapies			0.92
Beta blocker	884 (96.0)	76 (96.2)	0.02
Statin	781 (84.8)	59 (74.7)	<0.001
RAS blocker	896 (97.3)	69 (87.3)	0.41
Acetyl salicylic acid	913 (99.1)	79 (100)	0.08
Heparin	921 (100)	78 (98.7)	0.91
Clopidogrel	309 (33.5)	25 (31.6)	0.20
Thrombolysis	700 (76)	55 (69.6)	0.001
Positive inotropic	12 (1.3)	5 (6.3)	
Coronary angiography	793 (86)	56 (71)	0.62
Normal coronary	40 (4.3)	2 (2.5)	
Single-vessel disease	317 (34.4)	22 (27.8)	0.84
Multi-vessel disease	436 (47.3)	32 (40.5)	<0.001
Length of hospital stay, mean (SD), days	6.2 (1.5)	6.8 (1.6)	

Values are number (percentage) unless otherwise indicated.
AF, atrial fibrillation; CABG, coronary artery bypass graft; HDL, high-density lipoprotein cholesterol, LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; RAS, renin-angiotensin system.

ejection fraction, total cholesterol levels, triglycerides levels, initiation of statins at the hospital and initiation of RAS blockers at the hospital. In the multivariate regression analysis, initiation of RAS blockers at the hospital (OR = 0.166; 95% CI, 0.067–0.399; $P < 0.001$), initiation of statins at the hospital (OR = 0.501; 95% CI, 0.285–0.917; $P = 0.028$), and LA diameter (OR = 1.161; 95% CI, 1.096–1.236; $P < 0.001$) were found to be associated with the development of AF (Table 3).

4. Discussion

Atrial fibrillation is the most common supraventricular arrhythmia encountered following the development of STEMI [1]. The patients sustaining STEMI can develop AF in relation to left or right ventricular dysfunction, atrial ischemia, pericarditis, excessive catecholamine release, drugs, acute hypoxia, and hypopotassemia, and through many other mechanisms involved [17]. The sympathetic hyperactivity caused by excessive catecholamine release results in an increase in angiotensin release. Angiotensin II exerts inotropic, chronotropic, contractile, and arrhythmogenic effects on cardiomyocytes [18]. Angiotensin II also increases strain on the myocardial wall by producing arterial vasoconstriction, and provides a basis for left ventricular hypertrophy and atrial dilation [19]. Myocardial infarction is followed by myocardial fibrosis, and interstitial fibrosis is known to be an important factor in the development of AF [1]. The RAS plays a significant role in the structural and electrical remodeling of atrium, and it therefore contributes to the development of arrhythmia [19].

There are no studies in the literature investigating the relationship between the use of RAS blockers before MI and the development of AF. In two studies investigating patients with

Table 3 – Predictors of atrial fibrillation.

Variables	OR	95% CI	P
Positive univariate predictors			
Age	1.036	1.016 to 1.057	<0.001
Smoking	1.668	1.052 to 2.645	0.03
Left atrial diameter	1.154	1.091 to 1.220	<0.001
Initiation of positive inotropic at the hospital	3.331	1.518 to 7.307	0.003
Negative univariate predictors			
Ejection fraction	0.954	0.927 to 0.981	0.001
Total cholesterol	0.994	0.988 to 1.000	0.035
Triglycerides	0.996	0.993 to 1.000	0.035
Initiation of statins at the hospital	0.647	0.464 to 0.903	0.010
Initiation of RAS blockers at the hospital	0.193	0.089 to 0.417	<0.001
Multivariate predictors			
Initiation of RAS blockers at the hospital	0.166	0.067 to 0.399	<0.001
Initiation of statins at the hospital	0.501	0.285 to 0.917	0.028
Left atrial diameter	1.161	1.096 to 1.236	<0.001

RAS, renin-angiotensin system.

acute coronary syndrome, the incidence of developing in-hospital AF was lower among patients receiving RAS blockers before admission [20,21]. However, these studies did not include only STEMI patients. In the present study, the incidence of AF in patients with STEMI, who had a history of usage of RAS blockers prior to STEMI, did not significantly differ from those patients who did not have a history of use of RAS blockers, a finding that is in contrast to that which is reported in the above-mentioned studies.

Similar to studies that evaluated patients sustaining myocardial infarction [2,3], initiation of therapy with RAS blockers in the hospital was accompanied by a reduction in the incidence of AF in the present study. The incidence of AF was found to be higher in patients who never received RAS blockers, neither before nor after STEMI, compared to patients who started these therapies for the first time after STEMI, and compared to patients who continued previous therapies after STEMI. The incidence of AF was similar in patients who started RAS blockers for the first time after STEMI and patients who continued previous therapies with RAS blockers after STEMI. These findings suggest that the reduction in the incidence of AF after STEMI with the use of RAS blockers was independent of the time of initiation of the drug.

The incidence of developing AF in the hospital was similar in patients who received or who did not receive previous therapies with RAS blockers. Although statistically insignificant, heart failure, coronary artery disease, hyperglycemia, hypertension, and advanced age, which are the risk factors for AF, were more common in patients who were already receiving RAS blockers, and the incidence of AF was lower. Based on the current findings, the use of RAS blockers in patients with high risk of development of AF may be suggested to prevent AF following STEMI. In the present study, the initiation of such drugs was found to be associated with a lower incidence of AF.

Statins are pleiotropic agents known to reduce inflammation, which are believed to play a key role in atrial remodeling. Statins are hypothesized to have a benefit against arrhythmias in addition to the well-established benefit of atherosclerotic coronary artery disease and also can be used for primary and secondary prevention of AF development [1]. Studies evaluating patients who have sustained myocardial infarction and acute coronary syndrome [22–24] have shown a reduction in new onset AF with the initiation of statin therapy. Likewise, the present study found a significant reduction in the development of AF associated with the initiation of statin therapy in the hospital.

Previous studies have shown that, LA diameter is an important factor for development of AF [25,26]. Studies evaluating patients with myocardial infarction [27,28] reported an increased incidence of AF in relation to LA enlargement; however, they did not establish LA diameter as an independent predictor for the development of AF. The present study reports a similar association between the LA diameter and the development of AF, and additionally, LA diameter was found to be an independent predictor for the development of AF.

Some study limitations have to be mentioned. The retrospective study design may have caused some errors in the results of the study by affecting the reliability of the collected data along with other biases and methodological errors. However, in our opinion, the results should be considered reliable since great care was taken in maintaining and retaining patient data. Atrial fibrillation was not detected with a highly sensitive method in the present study; the detection was based on ECG monitoring and analyzed through monitored data maintained in the files and retrospective records. This is indeed a factor that may affect the incidence and accuracy of the detection of AF. The Holter ECG monitor offers the highest sensitivity for use for this purpose; however, the use of this technique was technically not feasible due to the retrospective study design. In our center, routine primary percutaneous coronary intervention was not available at the time of patient recruitment, which constituted a significant limitation and may have influenced the study results. Therefore, this study reflects the period of fibrinolysis therapy.

5. Conclusions

The incidence of developing AF in the hospital was found to be similar in patients who had a history of prior use of RAS blockers and those who did not. The initiation of RAS blockers in the hospital reduced the incidence of AF. Furthermore, initiation of statins during the hospital stay and LA diameter appeared to be independent predictors for the development of AF.

Conflict of interest

The authors state no conflict of interest.

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