Short-Term Outcome of Atrial Fibrillation and Its Affecting Factors

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ABSTRACT

Background: This study aimed to determine the short-term outcome of atrial fibrillation in patients admitted to emergency departments, in order to provide a report of mortality and relapse rates and the factors affecting it, and presenting a detailed picture of the status of conducted therapeutic measures, and their impact on mortality and relapse rates.

Method: In this study, 587 patients aged greater than or equal to 18 with AF who were admitted to five hospitals were evaluated. Initially, the demographic characteristics, underlying diseases and drug history, therapeutic measures and hospital length of stay of patients were determined. Then, the follow-up of three-month outcome of the disease was performed in terms of mortality, relapse and stroke. The chi-square test, Fisher's exact test and risk ratio report were used for analyzing the data; while the level of statistical significance was considered to be $p < 0.05$.

Results: Totally, 506 patients were included in the study, 62.8% of the patients were males and the mean age was 68.7 years. Atrial fibrillation relapsed in 161 patients (31.8%) within three months, and 25 patients (4.9%) died, among them 8 deaths (32.0%) were due to cardiac conditions, 6 deaths (0.24%) were as a result of stroke, and 11 patients (44.0%) died because of other CVAs. Existence of chest pain (RR = 1.6; 95% CI: 1.2-2.1; P = 0.003) and reduced physical capacity (RR = 1.3; 95% CI: 1.06-1.7; P = 0.01) on admission and using digoxin increased the risk of death or relapse of AF up to 2.1 times (RR = 2.1; 95% CI: 1.6-3.8; P = 0.001). While the administration of beta-blockers (RR = 0.45; 95% CI: 0.25-0.81; P = 0.007), amiodarone (RR = 0.51; 95% CI: 0.37-0.89; P = 0.01) and combined administration of LMWH with warfarin (RR = 0.68; 95% CI: 0.5-0.94; P = 0.02)showed a protective effect on the outcome of the disease.

Conclusion: Based on the findings of this study, patients with AF admitted to the emergency department with chest pain and reduced physical capacity should be taken more seriously. However, based on the evidences obtained in the present study, it seems that using digoxin for heart rate control is associated with increased risk of mortality or relapse.

KEYWORDS: Atrial Fibrillation, Treatment, Outcome.

INTRODUCTION

Atrial Fibrillation (AF) is the most common cardiac arrhythmia that affects 1.25-3.0% of the general population (1).The prevalence of AF is increasing and statistics show that in 2005, about 3.2 million people in the United States suffered from AF, and it seems that this figure will be as high as 7.65 million until the year 2050 (2).Mortality and disability due to the disease are associated with the incidence of stroke, thromboembolism and heart failure and leads to outstanding loss of quality of life (3). AF increases stroke risk up to five times and the risk of heart failure up to 3 times, and imposes considerable health care cost burden (4).Over the past 20 years, hospital admissions for AF have increased up to 66%, which is mainly due to aging population on the one hand and the increased incidence of heart diseases on the other hand (5).

Despite all the consequences of this disease, there is so much controversy over the standard treatment procedure and policy that should be adopted during treatment of AF. Accordingly, there is a huge difference in medical interventions undertaken by physicians for treatment of AF in different medical centers. For example, in a study conducted on English and Spanish emergency consultants, significant differences were observed in the management of atrial fibrillation, particularly in relation to cardio version and anticoagulant therapy (1). However, in 2010, European Society of Cardiology (ESC) provided a comprehensive and detailed protocol for management of patients with AF (6).Nevertheless, the studies that constitute a basis for such treatment strategies are of considerable heterogeneity, and the evaluation of such strategies has not been conducted yet. That is why the protocol has not been implemented in many medical centers and there is still so much debate over the management of AF (4, 7-9).

Accordingly, it seems that we still need to monitor and evaluate these methods based on the outcome of AF. Studying the outcome in patients with AF and its relationship with patient's underlying factors, clinical

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symptoms and medical interventions enables us to determine mortality and relapse rates and complications, and to explore the efficacy of existing treatments. Accordingly, the present study aimed to determine the short-term outcome of atrial fibrillation in patients admitted to emergency departments, in order to provide a report of mortality and relapse rates and the factors affecting it and presenting a detailed picture of the status of undertaken medical measures, and their impact on mortality and relapse rates.

METHOD

This is a prospective cohort study conducted from April to October 2011. In this study, 587 patients aged greater than or equal to 18 with AF who were admitted to five training hospitals affiliated with Shahid Beheshti University of Medical Sciences, Tehran (capital of Iran), were evaluated. Research protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences. Inclusion criteria were age ($\geq$ 18 years),presence of AF rhythm, and written Letter of Consent of the patient. Exclusion criteria included the presence of atrial flutter rhythm without atrial fibrillation symptoms and patient reluctance to be included in the study and impossibility of contacting with and conducting follow-up of the patient.

AF was confirmed by definitive diagnosis based on ECG of patients provided by cardiologists' reports. After identification and confirmation of AF patients, emergency medicine specialists collected information using a checklist. Then, three months after discharge, the information regarding the patients' clinical status was obtained by phone contact. The data collected initially was demographic data including age, gender, underlying disease, medication history and stroke history. After collecting the demographic and the baseline information, the medications and treatments prescribed for patients, side effects of prescribed medications or treatment, and length of stay in the emergency department were also included in the checklist. The checklist was prepared by two cardiologists and an epidemiologist and its Cronbach's alpha coefficient was 0.83.

Because this was a multicentric research, before the start of the study, necessary trainings were provided for conducting the research and filling out the checklists to emergency medicine specialists who were resident in target medical centers. In order for monitoring data collection procedure, all checklists were collected monthly, the date entry of the variables into electronic files was performed, incomplete cases were excluded from the study and the emergency specialists were informed concerning the problems.

The sample size required to evaluate the outcome of patients with atrial fibrillation determined by considering the prevalence of relapse for this disease as 31.8%, with the statistical power of 90%, error rate of 5%, and determined to be 334 patients.

Outcome Follow-up

The outcome follow-up in patients included death, relapse and stroke. Three months after discharge of the patient, the death of the patients and its cause was checked by phone call. Existence of a clinical file for definitive AF (during follow-up period) in one of the medical centers was defined as relapse. Follow-up of stroke incidence was conducted based on sudden neurological attacks of vascular origin and supporting imaging evidences. The fatal strokes also were included.

Statistical Analysis

Mortality and relapse rates and stroke incidence were reported for the three-month follow-up. Since all stroke incidences led to death of patients, outcome of the disease was classified as an uncomplicated outcome, relapse and death. Demographic and baseline characteristics of the admitted patients and medical treatments administered in the emergency departments were evaluated depending on disease outcome during 3-month follow-up period using chi-square test or Fisher's exact test. It is worth noting that prior to initiating anticoagulant therapy, CHADS2 scores were used to determine the risk of stroke in AF patients. CHADS2 is an index for determining stroke risk in patients with atrial fibrillation and the range of its score is from 0-6. Higher scores indicate higher risk, and based on a classification provided in previous studies, the patients were divided into three groups based on stroke risk, i.e. low-risk, moderate-risk and high-risk groups (10, 11). After determining CHADS2 scores and studying their distribution, according to the disease outcome and by elaborating a general linear model, Risk Ratio (RR) was provided. The results reported as RR at confidence level of 95%, and the level of statistical significance was considered to be $p < 0.05$.

RESULTS

From the total 587 patients included initially, 79 subjects withdrew from the study and 506 patients were included in the study, 318 of them (62.8%) were male. The mean and standard deviation of age of the patients were 68.7$\pm$6.6 years; 317 patients (62.6%) had a history of atrial fibrillation, 74 patients (14.6%) had a history of CHF, 396 patients (78.3%) had been hospitalized for coronary artery disease, 95 patients (18.8%) had a history of hypertension, 25 patients (4.9%) had experienced stroke, 34 patients (6.7%) had a history of mitral or

tricuspid valve replacement (artificial heart valve), 128 patients (25.3%) had diabetespreviously, and 10 patients (2.0%) had a history of hypothyroidism. Meanwhile, 302 patients (59.7%) had previously taken beta-blockers, 181 of the samples (35.8%) had been given ACEI and 171 patients (33.8%) had taken both aspirin and Plavix. It was understood that 205 patients (40.5%) were at low risk of incidence of stroke, 191 samples (37.8%) were at moderate risk, and 110 patients (21.7%) were at higher risk for stroke. Table (1)presents the demographic and underlying factors of the patients.

The three-month follow-up of patients with AF revealed that 320 patients (63.2%) showed no complication after medical interventions. Atrial fibrillation relapsed in 161 patients (31.8%) during the three-month period, and 25 patient (4.9%) died, among them 8 deaths (32.0%) were due to cardiac conditions, 6 deaths (0.24%) were as a result of stroke, and 11 patients (44.0%) died because of other CVAs.

Persistent AF was observed in 401 patients (79.2%) and paroxysmal AF in 105 patients (20.8%). After studying the type of AF in terms of outcome it was understood that AF outcome is not correlated with the type of AF (P = 0.42), meanwhile chest pain was associated with higher mortality and more relapse of AF,so that 123 patients (35.6%) who experienced chest pain had a history of relapse of AF and among them 18 patients (5.2%) died (P = 0.02). Among those patients with reduced physical capacity,13 patients (8.6%) and 46 patients (30.3%) died or experienced relapse respectively (P = 0.049). Nevertheless, the risk of stroke (P = 0.07), palpitations (P = 0.67), lightheadedness (P = 0.86), systolic pressure lower than 90mmHg (P = 0.60), peripheral embolism symptoms (P = 0.44), heart rate (P = 0.52), EF less than 30% (P = 0.44) and length of stay at emergency department (P = 0.8) and hospital length of stay (P = 0.83) were not associated with AF outcome (Table (2)).

The observed side effects included: 1 case (0.2%) of myocardial infarction, 27 cases (5.3%) of hypotension, 6 cases (1.2%) of bradycardia, 7 cases (1.4%) of ventricular tachycardia, 4 cases (1.3%) of block heart, and 2 cases (0.4%) of cardiac arrest. All patients who experienced medical complications were immediately treated by emergency interventions and survived. It is notable that no relationship was found between complications and outcome in patients (P = 0.17).

Table 1:Demographic variables in patients with AF

Variable	Frequency	Percent
Age (years)		
≥ 50	57	11.3%
60-51	144	28.5%
74 -61	191	37.7%
≥ 75	114	22.5%
Gender		
Male	318	62.8%
Female	188	37.1%
History of ventricular fibrillation	317	62.6%
History of CHF	74	14.6%
History of hospitalization due to coronary artery disease	396	78.3%
History of hypertension	95	18.8%
History of stroke	25	4.9%
History of hypothyroidism	10	2.0%
History of diabetes	128	25.3%
History of medicine		
Blocker	302	59.7%
ACEI	181	35.8%
Cholesterol-lowering medications	109	21.5%
Aspirin	171	33.8%
Coumadin	101	20.0%
Plavix	171	33.8%
CHADS2 score		
Low risk	205	40.5%
Moderate risk	191	37.8%
High risk	110	21.7%

Table 2: Clinical symptoms in patients with AF in terms of outcome

Variable	Uncomplicated	Death	Relapse	P
Type of AF				
Persistence	259 (64.6%) 259	20 (5.0%)	122 (30.4%)	0.42
Paroxysmal	61 (58.1%)	5 (4.8%)	39 (37.1%)	
Palpitation	263 (62.6%)	20 (4.8%)	137 (32.6%)	0.67
Lightheadedness	146 (64.0%)	12 (5.3%)	70 (30.7%)	0.86
Chest pain	205 (59.2%)	18 (5.2%)	123 (35.6%)	0.02*
Reduce physical capacity	93 (61.2%)	13 (8.6%)	46 (30.3%)	0.049*

Systolic pressure < mmHg 90%	63 (60.6%)	7 (6.7%)	34 (32.7%)	0.6
Symptoms of peripheral embolism	11 (73.3%)	1 (6.7%)	3 (20.0%)	0.44
Initial heart rate				
101-120	29 (70.7%)	1 (2.4%)	11 (26.8%)	0.52
> 120	291 (62.6%)	24 (5.2%)	150 (32.3%)	
EF <30%	155 (60.6%)	14 (5.5%)	87 (34.0%)	0.44
Length of stay at emergency department				
≤ 6 hours	132 (62.6%)	12 (5.7%)	67 (31.8%)	0.8
> 6 hours	188 (63.7%)	13 (4.4%)	94 (31.9%)	
Hospital length of stay				
< 6 days	115 (63.9%)	10 (5.7%)	55 (30.6%)	0.83
≥ 6 days	205 (62.9%)	15 (4.6%)	106 (32.5%)	
CHADS2 score				
Low risk	125 (61.0%)	5 (2.4%)	75 (36.6%)	0.07
Moderate risk	127 (66.5%)	14 (7.3%)	50 (26.2%)	
High risk	68 (61.8%)	6 (5.4%)	36 (32.7%)	

Rate control treatment for atrial fibrillation included administration of digoxin in 357 patients (70.6%), beta-blockers in 50 patients (9.9%), amiodarone in 74 patients (14.6%), and calcium channel blockers in 25 persons (0/5%). Remarkably, 95 patients (18.8%) provided no good response to rate control treatment and amiodarone was used in the next step. Fisher's exact test showed a significant relationship between rate control treatment and outcome of AF (P< 0.0001) which means that digoxin is more associated with increased mortality and relapse than other medications.

However, treatment with amiodarone as the second drug to control heart rate caused only 2 deaths (2.0%) and relapse in 14 patients (14.7%) (P< 0.0001), therefore, it was associated with better outcome for patients than digoxin. Anticoagulant therapy was significantly associated with disease outcome; 15 patients (11.0%) treated with warfarin, 8 patients (.8%) treated with aspirin and 2 patients (2.7%) treated with both heparin and warfarin died during the three-month follow-up period while combined administration of low-molecular-weight heparin with warfarin caused no death. Relapse rates in each of these anticoagulant therapies were 57 (41.6%), 33 (19.8%), 33 (44.6%) and 38 (29.7%) respectively (P < 0.0001). It should be noted that discharge treatment was not associated with outcome (P> 0.05).

Table 3: Medical interventions for patients and their impact on disease outcome

Variable	Uncomplicated	Death	Relapse	P
Rate control treatment				
Digoxin	196 (54.9%)	25 (7.0%)	136 (38.1%)	< 0.0001
Beta blocker	40 (80.0%)	0 (0.0%)	10 (20.0%)	
Amiodarone	59 (79.7%)	0 (0.0%)	15 (20.3%)	
Calcium channel blocker	25 (100.0%)	0 (0.0%)	0 (0.0%)	
Amiodarone with other medications	79 (83.2%)	2 (2.1%)	14 (14.7%)	< 0.0001
Cardioversion therapy	1 (9.1%)	2 (18.2%)	8 (72.7%)	< 0.0001
Anticoagulation therapy				
Warfarin (alone)	65 (47.4%)	15 (11.0%)	57 (41.6%)	< 0.0001
Aspirin (alone)	126 (75.4%)	8 (4.8%)	33 (19.8%)	
Intravenous heparin + warfarin	39 (52.7%)	2 (2.7%)	33 (44.6%)	
LMWH + warfarin	90 (70.3%)	0 (0.0%)	38 (29.7%)	
Discharge treatment*				
Aspirin	168 (65.4%)	11 (4.3%)	78 (30.4%)	0.55
Warfarin	152 (61.0%)	14 (5.6%)	83 (33.3%)	0.55
LMWH	35 (64.2%)	2 (3.7%)	17 (31.5%)	0.9
Beta-blocker	289 (63.7%)	22 (4.8%)	143 (31.5%)	0.84
Calcium blocker	29 (58.0%)	3 (6.0%)	18 (36.0%)	0.72
Anti-arrhythmic drugs	58 (61.7%)	4 (4.3%)	32 (34.0%)	0.85
Digoxin	101 (67.3%)	9 (6.0%)	40 (26.7%)	0.24

* Some patients were discharged with two or more medications

The Risk Ratio (RR) calculated in the present study showed that chest pain (RR = 1.6; 95% CI: 1.2-2.1; P = 0.003) and reduced physical capacity (RR = 1.3; 95% CI: 1.06-1.7; P = 0.01) on admission, and rate control

treatment and anticoagulation therapy were four independent factors affecting the three-month outcome of AF patients admitted to the emergency departments. Accordingly, the use of digoxin increased the risk of death or relapse of AF up to 2.1 times (RR = 2.1; 95% CI: 1.6-3.8; P = 0.001). While the administration of beta-blockers (RR = 0.45; 95% CI: 0.25-0.81; P = 0.007), amiodarone (RR = 0.51; 95% CI: 0.37-0.89; P = 0.01) prevented from death or relapse of disease. Combined administration of amiodarone with a rate control medication (RR = 0.38; 95% CI: 0.19-0.75; P = 0.006) and combined administration of LMWH with warfarin (RR = 0.68; 95% CI: 0.5-0.94; P = 0.02) showed a protective effect on the outcome of the disease.

Table 4: Independent factors in determining the outcome of patients with AF

Variable	RR	95%	P
Gender	0.8	0.34-1.01	0.06
Chest pain	1.6	1.2-2.1	0.003
Reduced physical capacity	1.3	1.06-1.7	0.01
Rate control treatment			
Digoxin	1.2	1.6-3.8	0.001
Blocker	0.45	0.25-0.81	0.007
Amiodarone	0.51	0.37-0.89	0.01
Calcium channel blocker	0.75	0.63-1.03	0.09
Combination therapy with amiodarone	0.38	0.19-0.75	0.006
Anticoagulation therapy			
Warfarin (alone)	1.2	0.7-1.9	0.13
Aspirin (alone)	0.8	0.62-1.2	0.36
Intravenous heparin + warfarin	1.1	0.84-1.5	0.77
LMWH + warfarin	0.68	0.5-0.94	0.02
Use of shock	1.7	0.34-7.9	0.23
CHADS2 score	1.04	0.9-1.2	0.57

DISCUSSION

This study examined the outcome of AF, and the results indicated the incidence of death and relapse of AF during three-month period was 4.9% and 31.8% percent respectively. In addition, chest pain and reduced physical capacity on admission and use of digoxin as a treatment for rate control increased the risk of death and relapse. While prescribing beta-blockers and amiodarone (for rate control) and LMWH with warfarin prevented the incidence of death or relapse of disease. Remarkably, in patients who did not respond to other rate control therapies, the use of amiodarone improved outcome of the disease. These findings may be of high clinical significance for the treatment of patients with AF.

The mortality rate reported in the present study is higher than the mortality rate of 4.2% (for one year) reported by the North-American Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trials (12-15), and the mortality rate of 3.7 percent (for one year) as reported by The Strategies of Treatment of Atrial Fibrillation (STAF) Study (7). Nevertheless, a 14-year follow-up of patients with AF aged greater than or equal to 65 reported a mortality rate of 11% and 25% in the first 30 days and in the first year, respectively; these are much higher than the rates in other studies (16). In this study, 8 patients (32.%) lost their lives due to cardiac diseases, 6 patients (24.0%) due to ischemic stroke and 11 patients (44.0%) due to other CVAs. In the AFFIRM study in 2004 (17), the causes of death for a period of 3.5 years included 36.2% due to cardiac diseases and 9.8% because of vascular diseases (stroke and CNS hemorrhage). Furthermore, the incidence of CVA in this study was 3.4% and the patients died in all cases. The rate of CVA is also higher than the rate reported in the previous studies, i.e. 1.8% per year (7).

As it can be seen, there is a significant difference between the incidence and causes of death in these studies. The reason for this difference stems from the fact that medical interventions for AF are highly variable. In each of these studies, each of which has been implemented in a different geographic location and climate, different treatment method has been applied. The various methods of treatment in the studies reflect lack of guidelines for the treatment of AF and show the necessity to address it. Another reason for the difference in results was the differences in duration of follow-up. Accordingly, it can be concluded that short-term mortality in patients with AF is mainly caused by cardiovascular diseases and CVAs. These claims are consistent with the findings from large population-based studies, and show that AF is associated with increased risk of death due to cardiovascular complications (18-21).

Hemodynamic and cardiac consequences and changes of AF are numerous, and this explains the fact that the cardiac factor is the most common cause of death in patients with AF. These changes include uncoordinated atrial and ventricular contractions and ventricular high rate that affects cardiac function and reduces cardiac output (22).Increased risk of cardiomyopathy and heart failure (23), increased myocardial oxygen demand and decreased myocardial perfusion (19, 24) are the other changes that happen after the occurrence of AF. For these reasons, the presence of chest pain and reduced physical capacity were considered as risk factors for death or

relapse, because chest pain and decreased physical capacity are the most visible symptoms of ischemia or other heart disorders. Therefore, these clinical parameters in patients with AF should be taken more seriously, and they can be regarded as prognostic indicators of undesired outcome in patients.

The current study indicates that the use of digoxin for the treatment of AF is associated with increased risk of death and relapse. Clinical guidelines have confirmed the use of digoxin for rate control in patients with AF; however, such recommendations are based on limited and out-of-date information. Recently, several clinical trials indicate that the use of digoxin in patients with AF is associated with increased mortality risk (8, 25). Thus, due to the availability of other treatment options for heart rate control, digoxin role in the management of atrial fibrillation should be re-investigated. However, in treatment guidelines provided by ESC for AF in 2010, digoxin has been given a very limited role in the treatment of AF (6). Therefore, it is recommended that the use of digitalis in the treatment of AF should be entirely excluded from the treatment protocol.

Several studies suggest that amiodarone is highly effective in the treatment of AF and changing it into sinus rhythm. Pharmacological Intervention in Atrial Fibrillation (PIAF) trials showed that success of amiodarone is up to 70% and the Canadian Trial of Atrial Fibrillation (CTAF) demonstrated the effectiveness of the drug up to 69%. According to the proposed protocol by ESC, when a patient does not respond to glycosides, beta-blockers or calcium blockers, amiodarone should be used (6). In addition to these findings, the current study also showed that the use of amiodarone is associated with a desired outcome of disease, and the use of amiodarone leads to mortality reduction in patients and less relapse of AF. Here, 95 patients who had not responded properly to other treatments were treated with amiodarone and all of them recovered. The three-month follow-up of these patients also showed low level of mortality and relapse. Therefore, in cases with AF recurrence or no response to other treatments, amiodarone will be effective as an alternative treatment.

Beta-blockers reduce ventricular rate during rest and activity and are considered as drug intervention for rate control, and are a good treatment choice for AF with rapid ventricular response. These drugs may be useful in the presence of high adrenergic tone or myocardial ischemia associated with AF. During chronic therapy, beta-blocker drugs also are safe and effective drugs in comparison with digoxin and placebo (6). The study findings also suggest that beta-blockers are effective in the treatment of acute AF with negligible mortality prevalence and relapse.

Administrating prophylactic anticoagulant agents is another therapeutic measure underlined in existing treatment protocols. Anticoagulant therapy is conducted based on the risk of thrombotic stroke and thromboembolism. Although extensive researches have been done in this area, which often show that warfarin dose adjustment is more effective in preventing stroke than aspirin (26-28),however, a systematic review concluded that existing studies are so heterogeneous that decision-making on the selection of appropriate anticoagulant is not an easy task (29). In another systematic review aimed to assess the thromboprophylactic effect of aspirin, warfarin and ximelagatran in patients with AF, it was shown that although warfarin has been more effective in reducing mortality rate compared with placebo, but it is not more efficacious than aspirin and Ximelagatran (30). The results of this study also confirm the findings of that review study, i.e. warfarin, aspirin and intravenous heparin had no obvious efficacy on mortality and relapse of AF comparing each other. However, the current study also showed that combination therapy of LMWH and warfarin was associated with less mortality and relapse of AF, and that further studies are needed to confirm these findings.

Limitations

The study's strengths include being prospective, relatively appropriate sample size and being multicentric. Furthermore, this study is among the few studies that have examined the silent AF or asymptomatic AF, because paroxysmal AF samples were also examined, while most studies have only analyzed persistent AF. However, short-term follow-up of patients is among its limitations, because a three-month follow-up can only evaluate the initial outcome in patients. Another limitation of the study is that the patients were followed up by phone. If the three-month follow-up of patients could be performed by visiting them at medical centers, other complications and outcomes of the disease also could be assessed and further clinical evidences could be obtained. Another limitation of this study is the low frequency of the use of calcium antagonists (25 patients) for rate control. Due to such low frequency, the findings presented in this regard are only for the purpose of reporting and any conclusion based on them is not reliable.

Conclusion

Based on the findings of this study, patients with AF, who are admitted to the emergency departments with chest pain and reduced physical capacity, should be taken more seriously, because these two factors increase the risk of death and relapse in such patients. Therefore, it is recommended that in future studies, the relationship of these two factors with the outcome of patients with AF be addressed, and after determining the influence of these factors on treatment protocols of AF and monitoring them, patients with these clinical symptoms to be recognized as a group with a high risk of death or relapse. Meanwhile, based on the evidence obtained in the

present study, it appears that the use of digoxin for rate control is associated with increased risk of death of patients or relapse, therefore, it is proposed that AF treatment protocol be revised. Furthermore, although in the existing guidelines (6), use of oral anticoagulation, especially vitamin K antagonists such as warfarin, have been proposed for stroke prevention, but this study showed that the drug is able to improve the patient's condition and reduce mortality rate due to AF only if it is administered with LMWH. Therefore, it is recommended that in future studies, the effect of LMWH administered in combination with warfarin be examined.

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