Fluvastatin therapy could not decrease progression of paroxysmal atrial fibrillation in non-valvular disease patients

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Abstract

Objective: This study aimed to evaluate whether fluvastatin therapy could decrease the probability of atrial fibrillation (AF) progression from paroxysmal AF to permanent AF and decrease the recurrence frequency of AF.

Methods: Analyses were performed using two-tailed Student's t test or Mann-Whitney U tests. Categorical variables were compared with the χ^2 statistics or Fisher's exact test. Patients with paroxysmal AF were randomized case-control, prospective into either the fluvastatin group (n=61) or control group (n=57). Patients were followed up for 24 months. The primary endpoint event was paroxysmal AF that progressed to permanent AF. Secondary endpoints were AF recurrence, cardiac dysfunction, stroke, or death.

Results: There were no differences in AF progression (fluvastatin group, 8.19% vs. control group, 12.51%; p>0.05) and stroke (fluvastatin group. 6.55% vs. control group. 8.77%; p>0.05). Patients in the fluvastatin group had a lower rate of AF recurrence (fluvastatin group, 24.59% vs. control group, 49.12%; p<0.05) and a lower rate of cardiac dysfunction (fluvastatin group, 6.55% vs. control group, 19.29%; p<0.05). Death did not occur in both the groups. After 1 week of fluvastatin therapy, C-reactive protein (CRP) and homocysteine (HCY) levels were lower in the fluvastatin group than in the control group. At 24 months of follow-up, CRP and HCY levels remained lower in the fluvastatin group than in the control group. The number of endothelial progenitor cells (EPCs) increased in the fluvastatin group compared with that in the control group (fluvastatin group, 72.27±12.49 counts/10^5 vs. control group, 57.45±8.24 counts/10^5, p=0.001).

Conclusion: Fluvastatin therapy could not decrease AF progression. However, it could decrease the recurrence frequency of paroxysmal AF and cardiac dysfunction. This may occur because of depressing inflammation and improving circulating EPCs. *(Anatol J Cardiol 2017; 17: 000-00)*

Keywords: inflammation; fluvastatin; atrial fibrillation; endothelial progenitor cell

Introduction

Atrial fibrillation (AF) is the most common arrhythmia worldwide and confers a high risk of mortality and morbidity that occur because of complications such as stroke and heart failure (HF) (1-2). AF usually develops as paroxysmal AF (PAF) and transforms into permanent AF (3). Antiarrhythmic agents such as beta-blockers and amiodarone have limited efficacy in preventing AF progression/recurrence. Therefore, "upstream" therapy of AF such as statin therapy is proposed to reduce PAF progression or recurrence. In addition to reducing cholesterol levels, statins have pleiotropic effects such as improving endothelial function, reducing thrombogenesis, and suppressing oxidative stress and inflammation (4). Prior studies suggest that the use of statins reduces AF incidence or progression (5). However, the current data are controversial.

This study aimed to evaluate whether fluvastatin therapy could decrease the probability of AF progression from PAF to permanent AF and decrease the recurrence frequency of AF.

Methods

Study population

Patients with non-valvular PAF who were scheduled for regular clinical examination between October 2012 and September 2014 were enrolled. Inclusion criteria were as follows, 1) Patients had a history of initial AF episode, defined as the first electrocardiogram (ECG) or Holter monitoring confirmed AF occurrence, followed by documented sinus rhythm. AF history was no longer than 6 months. 2) Left ventricular ejection fraction (LVEF) of >50%. 3) Patients were aged 25–79 years. 4) They had not received statins in previous 2 weeks. There was no restriction regarding other medication. Exclusion criteria were as follows: 1) established coronary artery diseases, including acute myocardial infarction and angina pectoris; 2) persistent or permanent AF (6); 3) surgical or interventional indications of valvular heart disease; 4) left ventricular dysfunction (ejection fraction of <50%); 5) carcinoma; and 6) serious liver dysfunction (ALT or AST, >120 U/L). A total of 316 patients were evaluated/screened for inclusion, and 126 patients were finally enrolled.

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Accepted Date: 03.03.2017 **Available Online Date:** 10.04.2017

DOI:10.14744/AnatolJCardiol.2017.7664

Anatol J Cardiol 2017; 17: 000-000
DOI:10.14744/AnatolJCardiol.2017.7664

This study was approved by the Ethics Committee, and all patients provided written informed consent before participation.

AF types were defined as suggested by the guideline (1): PAF as terminating within 7 days of onset; persistent AF as being sustained for more than 7 days; and permanent AF as a decision to stop attempting to restore or maintain sinus rhythm.

Study therapy

This trial was double blinded. Patients were randomized to either the fluvastatin group (80 mg fluvastatin once daily; n=63) or the control group (placebo once daily; n=63) by the random number method. No dose adjustments were performed during the study period, and the patients remained on the same allocation if they continued throughout the study. In both the groups, other medications included beta-blocker, aspirin or warfarin. and ACEI/ARB. Amiodaron or another antiarrhythmic drug was not used in both the groups. If there was medical indication for these drugs, eight patients were required to quit the trial.

Follow-up

Patients were followed up for 24 months (1 week, 3 months, 6 months, 12 months, 18 months, and 24 months). The primary endpoint was PAF that progressed to permanent AF. Second endpoints were AF recurrence, cardiac dysfunction (NYHA III or IV), stroke, or death. Patients were instructed to contact the study team if they experienced symptoms that suggested AF between their scheduled visits. AF recurrence included PAF and persistent AF.

At each visit, a 12-lead ECG and a list of ongoing medications were obtained. Holter monitoring was performed at the 12- and 24-month visits. C-reactive protein (CRP) and homocysteine (HCY) levels were measured at baseline, 1 week, and 24 months after the therapy. CRP levels were measured using an immunoturbidimetric assay, and HCY levels were measured using an enzyme-linked immunosorbent assay. Echocardiography was performed at baseline and 24 months after the therapy. Transthoracic echocardiography (vivid 7, GE, Wuxi, China) was performed to evaluate the left atrial diameter (LAD), left ventricular diameter (LVD), and LVEF. All procedures and analyses were performed by an experienced researcher who was blinded to the therapy.

Quantification of circulating EPCs

Circulating EPC levels were measured at baseline and 24 months after the therapy by flow cytometry, as previously described (7). In brief, 500 µL of peripheral blood samples were collected. Red blood cells were lysed using the lysis buffer (BD Pharmingen, Lake Franklin, USA). Single-cell suspensions of peripheral blood mononuclear cell (PBMNC) (1×10^5 cells) were then resuspended in PBS for staining with an FITC-conjugated mouse anti-human CD34 antibody (BD Pharmingen) and a PE-conjugated mouse anti-human KDR antibody (BD Pharmingen). IgG1-FITC isotype controls (BD Pharmingen) served as the negative controls. All antibody incubations were conducted for 30 mins at 4°C in the dark. The cells were then analyzed by fluorescence-activated cell sorting (FACS) using a FACS Calibur flow cytometer and Cell Quest software (BD Biosciences, Lake Franklin, USA). For each sample, the fluorescence intensity of 50.000 cells was quantified.

Table 1. Clinical characteristics of the two groups

	Fluvastatin group (n=61)	Control group (n=57)	*P*
Age, years	66.51±10.35	66.28±11.01	0.706
Sex, M/F	33/28	30/27	0.873
Smoking, %	13 (21.31%)	15 (26.31%)	0.523
Diabetes, %	7 (11.47%)	6 (10.52%)	0.869
Hypertension, %	24 (39.34%)	22 (38.59%)	0.900
Creatine, µmoL/L	73.37±13.49	81.06±42.61	0.242
Glucose, mmoL/L	5.99±1.48	5.67±1.33	0.254
ACEI/ARB user, %	21 (34.42%)	19 (33.33%)	0.412
Beta-blocker user, %	52 (85.24%)	49 (85.96%)	0.912
Warfarin user, %	6 (9.83%)	5 (8.77%)	0.843
TC, mmol/L	4.61±1.21	4.52±0.97	0.707
TG, mmol/L	2.21±1.41	2.09±1.18	0.406
LDL-C, mmol/L	2.88±0.93	2.75±0.81	0.706
HDL-C, mmol/L	0.91±0.37	0.94±0.32	0.257
CRP, mg/L	2.58±1.91	2.55±1.28	0.915
HCY, µmol/L	16.93±5.81	16.05±7.81	0.958
LVD, mm	50.07±6.43	48.54±7.04	0.269
LA, mm	40.07±5.76	42.27±6.96	0.140
LVEF, %	64.47±9.35	62.21±11.67	0.295
EPC counts/10^5	57.21±13.91	55.45±15.73	0.064

CRP - C-reactive protein; EPC - endothelial progenitor cell; HCY - homocysteine; HDL-C - high-density lipoprotein cholesterol; LAD - left atrial diameter; LDL-C - low-density lipoprotein cholesterol; LVD - left ventricular diameter; LVEF - left ventricular ejection fraction; TC - total cholesterol; TG - triglyceride. Analyses were performed using two-tailed Student's *t*-test or Mann–Whitney U test for between-group comparisons (CRP and EPC). Categorical variables were compared with χ^2 statistics

Statistical analysis

All statistical analyses were performed using the SPSS 17 software (SPSS, Chicago, IL, USA). Continuous variables were expressed as mean±standard deviation of the mean. Shapiro–Wilk test was used to assess the normality of distribution. Between-group comparisons were performed using two-tailed Student's t-test or Mann–Whitney U test where appropriate. Categorical variables were compared with the χ^2 statistics or Fisher's exact test. Plots of the Kaplan–Meier curves for time to AF progression and AF recurrence were performed. The survival distributions between the two groups were compared using the log rank test. A p value of <0.05 was considered to be statistically significant.

Results

Patient characteristics

Baseline clinical characteristics are shown in Table 1. The two groups were similar with respect to age, sex, hypertension,

Table 2. Follow-up characteristics of the two groups

	Fluvastatin group (n=61)	Control group (n=57)	*P*
TC, mmoL/L, 24 months	3.59±0.71	4.24±0.62	0.008
TG, mmoL/L, 24 months	1.37±0.75	1.51±1.01	0.412
LDL-C, mmoL/L, 24 months	1.92±0.67	2.31±0.62	0.039
HDL-C, mmoL/L, 24 month	0.96±0.29	0.93±0.36	0.135
CRP, mg/L, 1 weeks	1.34±0.91	1.70±0.91	0.037
CRP, mg/L, 24 months	0.73±0.32	0.98±0.74	0.021
HCY, μmoL/L, 1 weeks	11.79±2.79	15.05±4.81	0.004
HCY, μmoL/L, 24 month	11.41±3.12	14.65±8.21	0.039
LVD, mm, 24 months	50.86±6.78	49.30±6.37	0.257
LA, mm, 24 months	41.71±5.89	42.59±6.46	0.140
LVEF, %, 24 months	63.76±8.96	61.52±10.50	0.259
EPC, counts/10^5, 24 months	72.27±12.49	57.45±8.24	0.001

CRP - C-reactive protein; EPC - endothelial progenitor cell; HCY - homocysteine; HDL-C - high-density lipoprotein cholesterol; LAD - left atrial diameter; LDL-C - low-density lipoprotein cholesterol; LVD - left ventricular diameter; LVEF - left ventricular ejection fraction; TC - total cholesterol; TG - triglyceride. Analyses were performed using two-tailed Student's *t*-test or Mann–Whitney U test for between-group comparisons (CRP and EPC)

smoking, and diabetes mellitus. There were no significant differences regarding laboratory characteristics such as total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). There was no difference with regard to the echocardiography parameters such as LVD, LAD, and LVEF.

Follow-up and clinical outcomes

The follow-up period was 24 months. Eight patients quit the trial during the follow-up period because of medical indication for amiodaron. The final number of patients in the fluvastatin group was 61 and that in the control group was 57.

As shown in Table 2, there was no difference with respect to LVEF, LVD, and LAD between the two groups after 24 months of follow-up. Patients who received fluvastatin therapy had lower serum TC and LDL-C levels.

Our results in Table 3 indicate that there were no differences regarding AF progression (fluvastatin group, 8.19% vs. control group, 12.51%; p>0.05); however, patients in the fluvastatin group had a lower rate of AF recurrence (four cases of persistent AF and 11 of PAF in the fluvastatin group; seven cases of persistent AF and 21 of PAF in the control group; p<0.05). Kaplan–Meier

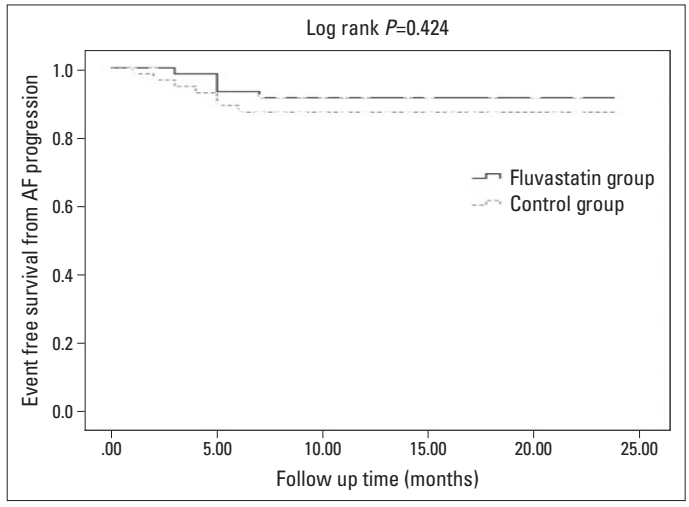

Figure 1. Kaplan–Meier analysis for the event-free survival from AF progression in both the groups

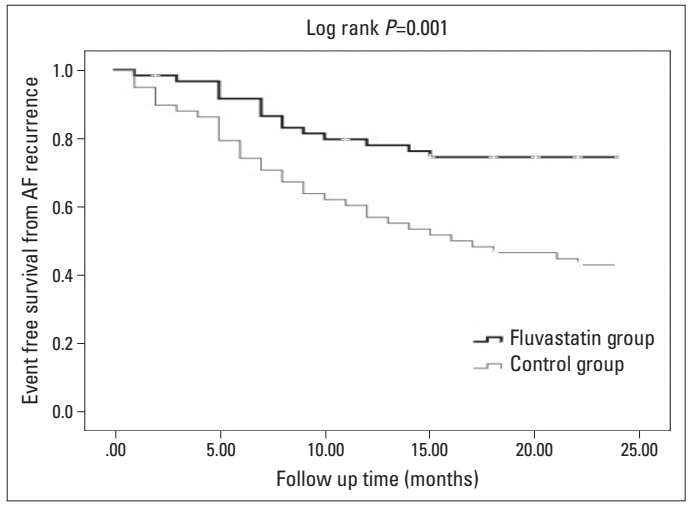

Figure 2. Kaplan–Meier analysis for the event-free survival from AF recurrence in both the groups

curves demonstrate that there was no difference concerning the time to AF progression between the two groups (log rank, p>0.05; Fig. 1). Fluvastatin therapy could increase the event-free survival from AF recurrence compared with the controls (Fig. 2).

As shown in Table 3, the fluvastatin group had a lower rate of cardiac dysfunction (EF-preserved cardiac dysfunction, NYHA III or IV) (fluvastatin group, 6.55% vs. control group, 19.29%; p<0.05). There was no statistical difference with respect to stroke (fluvastatin group, 6.55% vs. control group, 8.77%, p>0.05). Death did not occur in both the groups.

Table 3. Clinical outcomes of the two groups

	Progression	Recurrence	Cardiac dysfunction	Stroke	Death
Fluvastatin group	8.19% (5/61)	24.59% (15/61)	6.55% (4/61)	6.55% (4/61)	0
Control group	12.5% (7/57)	49.12% (28/57)	19.29% (11/57)	8.77 (5/57)	0
P value	0.463	0.006	0.038	0.615	–

Analyses were performed using χ^2 statistics

Anatol J Cardiol 2017; 17: 000-000
DOI:10.14744/AnatolJCardiol.2017.7664

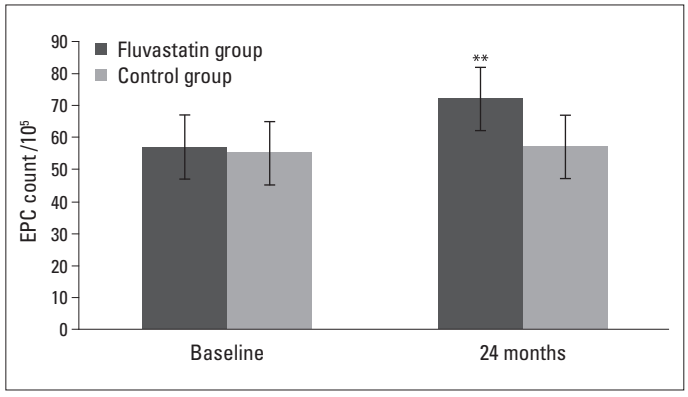

Figure 3. Comparison of circulating endothelial progenitor cell (EPC) levels in both the groups. After 24 months of follow-up, EPC levels were significantly increased in the fluvastatin group

CRP and HCY levels

After 1 week of fluvastatin therapy, CRP levels significantly decreased in the fluvastatin group. After 24 months of follow-up, CRP levels were significantly lower in the fluvastatin group than in the control group (Table 2). Fluvastatin therapy also significantly decreased HCY levels at 1 week and 24 months after the therapy.

Quantification of circulating EPCs

As shown in Table 1, there were no difference regarding circulating EPC levels (measured as CD34+KDR+ cells by flow cytometry) between the two groups at baseline (fluvastatin group, 57.21±13.91 counts/10^5 vs. control group, 55.45±15.73 counts/10^5, p=0.604). After 24 months of follow-up (Table 2 and Fig. 3), flow cytometry analysis revealed that the number of EPCs was increased in the fluvastatin group compared with that in the control group (fluvastatin group, 72.27±12.49 counts/10^5 vs. control group, 57.45±8.24 counts/10^5; p=0.001).

Discussion

This study demonstrated that fluvastatin therapy could not decrease AF progression but could decrease PAF recurrence and cardiac dysfunction incidence; this may occur because of anti-inflammation and increasing circulating EPC levels.

Although AF pathogenesis is incompletely understood, inflammation is believed to play a key role in initiating and maintaining AF. Several studies (8,9) indicate a close association between inflammation and AF. Inflammatory infiltrates, myocyte necrosis, and fibrosis have been observed in multiple atrial biopsy specimens from patients who had AF only (10). Serum levels of inflammatory biomarkers such as CRP and interleukin-6 are increased in patients with AF. Inflammation might participate in atrial structural remodeling, inducing cellular degeneration, apoptosis, and subsequent atrial fibrosis and dilation. The initiation of AF may be a consequence of necrosis and fibrosis caused by inflammation, making inflammation one of the many possible cofactors of AF.

Because there is a close correlation between inflammation and AF, anti-inflammation therapy may have protective effects in patients with AF. However, the efficacy of anti-inflammatory interventions for AF remains controversial. Folkeringa et al. (11) found that the use of statin could not reduce AF incidence after cardiac valvular surgery. In another study (12), patients with AF were randomized to receive either 80 mg atorvastatin (n=62) or placebo (n=63) for 3 months. The result indicated that theory with 80 mg/day atorvastatin following AF ablation did not decrease the risk for AF recurrence. However, a meta-analysis (13) (including five trials with 524 patients) showed that statin therapy was likely to provide a benefit for decreasing the frequency of AF recurrence in patients aged <65 years (RR=0.58; p=0.0005) and in those with a mean LAD of no less than 45 mm (RR=0.64; p=0.006). In our study, we observed that fluvastatin therapy decreased AF recurrence. We also found that fluvastatin users had lower serum CRP and HCY levels. CRP is a representative inflammatory biomarker, which is primarily synthesized in the liver in response to inflammatory cytokines (14). The circulating CRP level is increased in patients with AF compared with those with a sinus rhythm. Higher CRP levels are also associated with AF recurrence following electrical cardioversion and catheter ablation (15). Our results indicated that the protective effect of fluvastatin may occur because of depressing inflammation and oxidative stress.

Recent studies (3,16) suggested that persistent or permanent AF was associated with worse prognosis than PAF. However, this study showed that fluvastatin did not reduce AF progression. A prior study (16) indicated that patients with a larger left atrial chamber size (LAD, >50 mm) and severe mitral valve regurgitation are more likely to progress to persistent or permanent AF. Our follow-up data showed that both the groups had a relative low AF progression rate, possibly because patients with shorter AF history and smaller left atrial chamber size (mean LAD, <45 mm) were enrolled. Moreover, we excluded patients with a severe valvular disease. If patients with longer AF history and larger LAD were enrolled, we may obtain different results. The association of statin use with AF progression requires further investigation.

Although there was no significant difference with regard to LAD, LVD, and LVEF between the two treatment arms, namely either at the beginning or at the end of this study, a significant reduction in cardiac dysfunction occurrence in fluvastatin-treated patients was observed. This result may indicate that fluvastatin therapy could prevent LVEF-preserved HF in patients with AF. The mechanism of fluvastatin and HF prevention remain unclear; however, there is maybe an association among endothelial dysfunction, statin therapy, and HF prevention in patients with AF and preserved LVEF. Our study also provided new information by focusing on circulating EPC levels in patients with AF. Prior study indicated that AF caused turbulent flow in the atrium that may induce endothelial damage/dysfunction, possibly leading to HF (17). As a precursor of endothelial cells, EPCs are mobi-

lized from the bone marrow, differentiate into mature endothelial cells, and maintain endothelial function (18). Endothelial damage may exhaust circulating EPCs. Siu et al. (19) found that patients with persistent AF had reduced number of circulating EPCs compared with normal control with sinus rhythm. In this study, the result showed that fluvastatin therapy increased circulating EPC levels. Endothelial dysfunction has been shown to be related to cardiovascular events in patients with AF. This result indicates that fluvastatin may improve endothelial function and reduce cardiac dysfunction by improving circulating EPC levels.

Study limitations

First, AF recurrence was diagnosed using 12-lead ECG, and patients with undiagnosed AF recurrence could not be identified. Second, the study size was small, and we did not exclude patients with hypertension, diabetes, and chronic renal disease, possibly affecting circulating EPC levels. Third, we did not perform Cox regression analysis to compute univariate and multivariate hazard ratios for the study endpoints in the two treatment arms.

Conclusion

In this study, we found that fluvastatin therapy could not decrease AF progression but could decrease the frequency of AF recurrence and cardiac dysfunction in patients with PAF. The mechanism may occur because of depressing inflammation and improving circulating EPC levels.

Acknowledgments: The study was conducted at the Department of Cardiology, the first hospital of Qinhuangdao, Qinhuangdao, Hebei, China. The study was supported by Qinhuangdao technical fund.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – Q.T.; Design – Q.T.; Supervision – Q.T.; Materials-S.Z.; Data collection &/or processing – X.Z., J.Z., J.H., Q.S.; Analysis &/or interpretation – Q.T.; Literature search – Q.T.; Writing – Q.T.; Critical review – Q.T., S.Z.

References

1. Lip G, Laroche C, Ioachim PM, Rasmussen LH, Vitali-Serdoz L, Petrescu L, et al. Prognosis and treatment of atrial fibrillation patients by European cardiologists: One year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry).Eur Heart J 2014; 35: 3365-76.
2. Galea R, Cardillo MT, Caroli A, Marini MG, Sonnino C, Narducci ML, et al. Inflammation and C-reactive protein in atrial fibrillation: cause or effect? Tex Heart Inst J 2014; 41: 461-8.
3. Im SI, Chun KJ, Park SJ, Park KM, Kim JS, On YK. Long-term Prognosis of paroxysmal atrial fibrillation and predictors for progression to persistent or chronic atrial fibrillation in the Korean population. J Korean Med Sci 2015; 30: 895-902.
4. Harada M, Van Wagoner DR, Nattel S. Role of inflammation in atrial fibrillation pathophysiology and management. Circ J 2015; 79: 495-902.
5. Warita S, Kawasaki M, Tanaka R, Ono K, Kojima T, Hirose T, et al. Effects of pitavastatin on cardiac structure and function and on prevention of atrial fibrillation in elderly hypertensive patients. A prospective study of 2-Years' Follow-up. Circ J 2012; 76: 2755-62.
6. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Heart Rhythm 2012; 9: 632-96.
7. Tan Q, Wang Q, Zhang S, Qi X, Li Y. Circulating endothelial progenitor cells were increased in patients with thin-cap fibroatheroma. Clin Lab 2016; 62: 2233-40.
8. Polovina MM, Ostojic MC, Potpara TS. Relation of biomarkers of infammation and oxidative stress with hypertension occurrence in lone atrial fibrillation. Mediators Inflamm 2015; 2015: 653026.
9. Kusayama T, Furusho H, Kashiwagi H, Kato T, Murai H, Usui S, et al. Inflammation of left atrial epicardial adipose tissue is associated with paroxysmal atrial fibrillation. J Cardiol 2016; 68: 406-11.
10. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation 1997; 96: 1180-4.
11. Folkeringa RJ, Tieleman RG, Maessen JG, Prins MH, Nieuwlaat R, Crijns H. Statins do not reduce atrial fibrillation after cardiac valvular surgery: A single centre observational study. Neth Heart J 2011; 19: 17-23.
12. Suleiman M, Koerstler C, Lerman A, Lopez-Jimenez F, Herges R, Hodge D, et al. Atorvastatin for prevention of atrial fibrillation recurrence following pulmonary vein isolation: a double-blind, placebo-controlled, randomized trial. Heart Rhythm 2012; 9: 172-8.
13. Yan P, Dong P, Li Z, Cheng J. Statin therapy decreased the recurrence frequency of atrial fibrillation after electrical cardioversion: A meta-analysis. Med Sci Monit 2014; 20: 2753-8.
14. Watanabe E, Arakawa T, Uchiyama T, Kodama I, Hishida H. High-sensitive C-reactive protein is predictive of successful cardioversion for atrial fibrillation and maintenance of sinus rhythm after conversion. Int J Cardiol 2006; 108: 346-53.
15. Wu N, Xu B, Xiang Y, Wu L, Zhang Y, Ma X, et al. Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: A meta-analysis. Int J Cardiol 2013; 169: 62-72.
16. Thacker EL, Jensen PN, Psaty BM, Mackighet B, Longstreth WT, Dublin S, et al. Use of statins and antihypertensive medications in relation to risk of longstanding persistent atrial fibrillation. Ann Pharmacother 2015; 49: 378-86.
17. Skalidis EI, Zacharis EA, Tsetis DK, Pagonidis K, Chlouverakis G, Yarmenitis S, et al. Endothelial cell function during atrial fibrillation and after restoration of sinus rhythm. Am J Cardiol 2007; 99: 1258-62.
18. Padfield GJ, Tura-Ceide O, Freyer E, Barclay GR, Turner M, Newby DE, et al. Endothelial progenitor cells, atheroma burden and clinical outcome in patients with coronary artery disease. Heart 2013; 99: 791-8.
19. Siu CW, Watson T, Lai WH, Lee YK, Chan YH, Ng KM, et al. Relationship of circulating endothelial progenitor cells to the recurrence of atrial fibrillation after successful conversion and maintenance of sinus rhythm. Europace 2010; 12: 517-21.