e-ISSN:2320-1215
p-ISSN:2322-0112

Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences

Fluvastatin Combined with Benazepril May Contribute to Favorable Prognosis of Auricular Fibrillation

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Research Article

Received date: 29/04/2016
Accepted date: 10/05/2016
Published date: 15/05/2016

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Keywords: Fluvastatin, Benazepril, Atrial fibrillation, Conversion rate of sinus, hs-CRP, Renin, Ang II, IL-6, TNF-αConversion rate of sinus, hs-CRP, Renin, Ang II, IL-6, TNF-α

ABSTRACT

Objective: To observe the clinical significance of Fluvastatin combined with benazepril therapy on atrial fibrillation (AF).

Methods: A total of 92 AF patients were randomly assigned into a case group (n=46) in which the patients were treated Fluvastatin plus benazepril and a control group (n=46) in which the patients were treated Fluvastatin.

Results: Conversion rate of sinus was higher in the case group than the control group (P<0.05). The case group had more patients with significant efficacy than the control group, with less ineffective patients (P<0.05). The LVEDd, LVESd, LAD, and LVEF indexes in the case group were lower than the control group after 6 months of treatment (all P<0.05). The hs-CRP was decreased in the case group in comparison with the control group after 1 month of treatment (P<0.05). After 12 months, the renin and Ang II were lower in the case group than the control group (both P<0.05). Significant differences of IL-6 and TNF-α were found between the two groups after 1 month, 6 months, and 12 months of treatment (all P<0.05). Compared with the control group, the TC, triglyceride, LDL-C in the case group were lower after 6 and 12 months of treatment (all P<0.05), while the HDL was higher (P<0.05).

Conclusions: Fluvastatin combined with benazepril treatment further increases conversion rate of sinus and remarkably improves life quality and prognosis of AF patients.

INTRODUCTION

Atrial fibrillation (AF) is a common type of arrhythmia that results from considerably different pathophysiological processes in the atria [1]. AF is consistently associated with increased mortality and morbidity in critically-ill patients [2], which also can contribute to an increased risk of stroke, heart failure, dementia and death [3]. It has been reported that the prevalence of AF increases with age, affecting 0.4%-1% in the general population and 9% in the individuals aged over 80 years [4]. Many risk factors can promote the development of AF, including advanced age, obesity, hypertension, valvular heart disease, heart failure as well as hyperthyroidism [5]. Interestingly, there are some results suggesting that ischemic injury during open-heart surgery may be a therapeutic target for a reduced risk of AF due to its significant role in the development of AF after cardiac surgery [6]. Recently, antiarrhythmic medications have been a mainstay in the treatment of AF, which can reduce the frequency as well as duration of arrhythmia episodes and the hospitalizations and mortality AF [7].

e-ISSN:2320-1215
p-ISSN:2322-0112

Fluvastatin is a common kind of statins that has been already established as a secondary prevention for atherosclerotic coronary artery disease [8]. Statins have been one of the most impactful treatments to reduce the incidence rate of cardiovascular disease across the world for a few years, which is also potentially beneficial to decrease the risk of AF in patients with sinus rhythm [9,10]. Due to good safety and cost reduction of statins, it functions as direct anti-arrhythmic or anti-inflammatory drugs in the future [11]. Benazepril is a kind of angiotensin converting enzyme (ACE) inhibitor which is favorable to pharmacodynamics as well as pharmacokinetic properties and exhibits good tolerability and antihypertensive effects [12]. Although ACE inhibitor is not an anti-arrhythmia drug, it can prevent the synthesis of angiotensin II from angiotensin [13]. It has been reported that patients who were treated with ACE inhibitors eventually required fewer defibrillation experiments for successful cardio version than those receiving other treatments [14]. Collectively, we hypothesize that fluvastatin combined with benazepril in the treatment of atrial fibrillation can have good curative effect. Therefore, this study explores the effect of fluvastatin with benazepril in the treatment of atrial fibrillation in comparison with single use of fluvastatin for the treatment of AF, in order to find out better drug therapy to treat atrial fibrillation.

MATERIALS AND METHODS

Study Population

A total of 92 patients diagnosed with AF were admitted to the First Affiliated Hospital of Harbin Medical University between August 2013 and February 2014, including 48 male and 44 female, with a mean age of 63.67 ± 10.30 years. Inclusion criteria: The diagnosis of AF was made based on electrocardiogram and dynamic electrocardiogram; no renal insufficiency and renal artery stenosis, or hyperkalemia as contraindications of angiotensin-converting enzyme inhibitor (ACEI) drugs; patients are informed consent and willing to take part in the clinical observation and follow up. Exclusion criteria: Congenital heart disease and rheumatic heart disease; LVEF <40%; hyperthyroidism; severe valvular disease, such as severe mitral insufficiency and over moderate aortic valve insufficiency; chronic inflammatory diseases or connective tissue diseases, including chronic obstructive pulmonary disease and rheumatoid arthritis; experienced acute infection, hemorrhage in any tissue or organ, trauma and surgery within 3 months; major organ failure, such as lung, liver and kidney failure; allergic to ACEI and statins; All experimental procedures were conducted following the medical ethics standard and approved by the Institutional Review Board/Ethics Committee of XXX. Written informed consent was obtained for all patient samples.

Groups and Treatments

The patients were randomly assigned into two groups. A case group has 46 patients who were treated by combination of fluvastatin and benazepril. A control group also has 46 patients, treated with fluvastatin.

Treatment methods: (1) The case group: taking orally 80 mg fluvastatin (Novartis pharmaceutical Co. Ltd. Beijing, China) once daily before sleeping; taking orally 10 mg benazepril (Novartis pharmaceutical Co. Ltd. Beijing, China.) once daily in the morning. (2) The control group: taking orally 80 mg fluvastatin (Novartis pharmaceutical Co. Ltd. Beijing, China.) once daily before sleeping. The patients in these two groups had 1-year treatment and maintained the usage of medicine for a long term. The patients would be withdrawn if ones failed to tolerate treatment or presented any adverse reactions.

Observation and Assessment

The patients received electrocardiogram (MAC1200ST, GE Medical Systems Co. Ltd., USA), dynamic electrocardiogram (Beneware Medical Equipment Co. Ltd., Zhejiang, China), and ultrasonic cardiogram (UCG) (GE Vivid E9, GE Medical Systems Co. Ltd., USA) examinations before and after treatment. The morning fasting venous blood from all patients was obtained to detect blood lipid, blood routine, liver and kidney function. A radioimmunoassay kit (Beijing Beifang Immune Reagent Institute, China) was applied to exam renin and angiotensin. Enzyme-linked immunosorbent assay (ELISA) kit (Tianjin Union Medical Technology Co. Ltd., China) was used to detect IL-6 and TNF-a. All patients received the treatment for 1 month, 6 months and 12 months, and the fasting venous blood was obtained. Detection was performed as same as previous procedures.

The criterion of efficacy: significantly effective: paroxysmal AF disappears or occasionally occurs; persistent AF turns into sinus rhythm or paroxysmal AF; effective: paroxysmal AF is decreased by 30% in terms of time and frequency and persistent AF turns into paroxysmal AF; ineffective: patients fail to meet the effective criterion.

Statistical Analysis

Data were analyzed using the statistical package for the social sciences (SPSS) version 21.0 (SPSS Inc.; Chicago, IL, USA). Continuous data were displayed as mean ± standard deviation, and the differences between two groups were analyzed by *t* test. Categorical data were expressed as ratio or percentage and Chi-square test was conducted. $P < 0.05$ was regarded as statistically significant.

RESULTS

Clinical Characteristics of Subjects

A total of 92 AF patients underwent the treatment, with 63 cases of persistent AF and 29 cases of paroxysmal AF. All the

e-ISSN:2320-1215
p-ISSN:2322-0112

subjects in the case group (n=46) and control group (n=46) exhibited no significant difference regarding age, gender, body mass index (BMI), course of disease, smoking and other diseases like hypertension, diabetes, coronary, and hyperlipidemia, persistent AF ratio as well as paroxysmal AF ratio (all *P*>0.05) **(Table 1).**

Table 1. Clinical information of the patients in the case group and control group.

Clinical parameters	Case group (n=46)	Control group (n=46)	t/χ2	P
Age	63.61 ± 11.94	63.72 ± 8.43	0.051	0.959
Gender	26/20	22/24	0.697	0.404
BMI (Kg/m^2)	24.90 ± 3.14	24.66 ± 2.32	0.417	0.678
Course of disease (year)	3.56 ± 1.12	3.51 ± 1.09	0.217	0.829
Smoking	17 (37.0)	14 (30.4)	0.438	0.508
Hypertension	15 (32.6)	16 (34.8)	0.049	0.825
Diabetes	19 (41.3)	22 (47.8)	0.396	0.529
Coronary disease	12 (26.1)	16 (34.8)	0.821	0.365
Hyperlipidemia	10 (21.7)	11 (23.9)	0.062	0.804
Persistent AF ratio	33 (71.7)	30 (65.2)	0.453	0.501
Paroxysmal AF ratio	13 (28.3)	16 (37.8)	0.453	0.501
Note: BMI, Body Mass Index; AF, atrial fibrillation.				

Sinus Rhythm Conversion and Efficacy

Among the 92 AF patients, 45 (48.9%) restored to sinus rhythm with 28 (60.9%) in the case group, significantly higher than 17 (37.0%) in the control group (*P*<0.05, **(Table 2).** Compared with the total effective rate of 69.5% in the control group, the case group had an elevated rate of 87.0% (*P*<0.05), which explained that the effect of fluvastatin + benazepril surpassed fluvastatin alone.

Table 2. Efficacy conditions of the patients in the case group and control group.

	Case group	Control group	P
Sinus rhythm conversion			
Restored sinus rhythm	28 (60.9)	17 (37.0)	
Non-restored sinus rhythm	18 (39.1)	29 (63.0)	
Cardioversion rate (%)	60.9	37	0.036
Efficacy			
Significantly effective	31 (67.4)	22 (47.8)	
Effective	9 (19.6)	8 (17.4)	
Ineffective	6 (13.0)	16 (34.8)	
Total effective rate (%)	87	65.2	0.046
Note: Total effective rate = Excellent rate + Effective rate			

The Cardiac Ultrasonic Changes

No significant difference was found concerning LVEDd, LVESd, LAD and LVEF indexes before treatment and 1 month after treatment both in the case group and control group (all *P*>0.05). The LVEDd, LVESd, LAD and LVEF indexes 6 and 12 months after treatment in the case group were lower than those in the control group (all *P*<0.05). In the case group, LVEDd, LVESd and LAD indexes were gradually declined (all *P*<0.05), while LVEF was on the rise (*P*<0.05). There was no significant difference in terms of LVEDd, LVESd, LAD and LVEF indexes between 6 months and 12 months after treatment (all *P*>0.05). Moreover, in the control group, the LVEDd, LVESd and LAD indexes were gradually decreased 6 months after treatment when compared with those before treatment (all *P*<0.05), while the LVEF was increased till to 12 months after treatment (all *P*<0.05). And there was no significant difference in terms of LVEDd, LVESd, LAD and LVEF indexes between 6 months and 12 months after treatment (all *P*>0.05) **(Table 3).**

Table 3. The cardiac ultrasonic changes of patients in the case group and control group.

Index	Group	Before the treatment	1 month after the treatment	6 month after the treatment	12 month after the treatment
LVEDd (mm)	Case group	58.1 ± 4.3	55.3 ± 4.0$^{\#}$	49.5 ± 3.8$^{*\#\&}$	48.6 ± 3.4$^{*\#\&}$
	Control group	57.6 ± 3.8	56.7 ± 3.9	54.5 ± 4.1$^{\#\&}$	53.1 ± 3.7$^{\#\&}$
LVESd (mm)	Case group	47.9 ± 4.1	44.8 ± 3.7$^{\#}$	41.3 ± 3.8$^{*\#\&}$	41.0 ± 3.8$^{*\#\&}$
	Control group	47.1 ± 3.9	45.9 ± 4.0	45.3 ± 3.7$^{\#}$	44.8 ± 3.5$^{\#}$
LAD (mm)	Case group	42.5 ± 4.2	38.6 ± 3.6$^{\#}$	34.2 ± 2.9$^{*\#\&}$	33.9 ± 2.7$^{*\#\&}$
	Control group	41.7 ± 4.6	39.9 ± 4.2	39.0 ± 3.7$^{\#}$	38.7 ± 3.4$^{\#}$
LVEF (%)	Case group	38.8 ± 5.5	46.5 ± 4.3$^{\#}$	57.3 ± 3.8$^{*\#\&}$	58.4 ± 3.9$^{*\#\&}$
	Control group	39.3 ± 4.5	45.2 ± 4.0$^{\#}$	49.7 ± 4.1$^{\#\&}$	51.2 ± 3.6$^{\#\&}$

e-ISSN:2320-1215
p-ISSN:2322-0112

Note: LVEDd, left ventricular end-diastolic dimension; LVESd, left ventricular end-systolic dimension; LAD, 1eft atrial diameter; LVEF, left ventricular ejection fraction; *, compared with the control group, *P*<0.05; #, compared with index before treatment *P*<0.05; &, compared with index 1 month after treatment, *P*<0.05.

Comparison of hs-CRP, Renin, AngII, IL-6 and TNF-a

Before treatment, the hs-CRP, renin, AngII, IL-6 and TNF-a indexes between the case group and control group showed no significant difference (all *P*>0.05, **(Table 4).** And the hs-CRP, IL-6 and TNF-a indexes in the case group were lower than those in the control group during 1-12 months after treatment (all *P*<0.05), and the renin and AngII indexes was lower than those in the control group only 12 months after treatment (both *P*<0.05). Compared with the hs-CRP, IL-6 and TNF-a indexes before treatment, those indexes 1 month after treatment was decreased (all *P*<0.05), and the renin and AngII indexes was declined 6 months after treatment compared with those before treatment (both *P*<0.05). In the case group, the hs-CRP, renin and IL-6 indexes achieved best effect 12 months after treatment (both *P*<0.05), while the AngII and TNF-a indexes revealed no significant change between 6 months and 12 months after treatment (both *P*>0.05). In the control group, the hs-CRP and IL-6 indexes were gradually decreased 1 months after the treatment (both *P*<0.05), but the IL-6 changes 12 months after treatment were not significant in comparison with its volume 6 months after treatment (*P*>0.05). The renin and AngII indexes in the control group were significantly dropped 12 months after treatment compared with those before treatment (both *P*<0.05), while TNF-a indicated no significant difference at any time point (*P*>0.05).

Table 4. hs-CRP, renin, AngII, IL-6 and TNF-a of the patients in the case group and control group.

Index	Group	Before treatment	1 month after treatment	6 month after treatment	12 month after treatment
hs-CR*P* (mg/L)	Case group	6.14 ± 0.16	4.69 ± 0.16$^{*\#}$	3.18 ± 0.17$^{*\#\&}$	2.99 ± 0.12$^{*\#\&\$}$
	Control group	6.11 ± 0.21	5.75 ± 0.28$^{\#}$	4.23 ± 0.29$^{\#\&}$	3.92 ± 0.31$^{\#\&\$}$
Renin (ng/mL.h)	Case group	0.68 ± 0.19	0.62 ± 0.25	0.52 ± 0.25$^{\#}$	0.39 ± 0.23$^{*\#\&\$}$
	Control group	0.65 ± 0.15	0.61 ± 0.28	0.56 ± 0.29	0.52 ± 0.26$^{\#}$
Ang Ⅱ (*P*g/mL)	Case group	71.26 ± 28.68	63.42 ± 27.34	56.26 ± 29.84$^{\#}$	48.76 ± 24.64$^{*\#\&}$
	Control group	72.42 ± 24.89	67.25 ± 24.12	63.19 ± 23.17	61.21 ± 22.37$^{\#}$
IL-6 (ng/L)	Case group	57.64 ± 5.91	50.35 ± 5.03$^{*\#}$	45.31 ± 4.71$^{*\#\&}$	39.22 ± 4.62$^{*\#\&\$}$
	Control group	58.61 ± 5.82	54.16 ± 5.32$^{\#}$	51.37 ± 5.12$^{\#\&}$	50.03 ± 4.91$^{\#\&}$
TNF-a (ng/L)	Case group	43.67 ± 4.91	40.16 ± 4.23$^{*\#}$	38.17 ± 4.05$^{*\#\&}$	37.02 ± 3.71$^{*\#\&}$
	Control group	44.16 ± 4.28	43.64 ± 4.16	42.85 ± 4.18	41.10 ± 3.99

Note: hs-CRP, High-sensitivity C-reactive Protein; AngII, angiotensin II; IL-6, interleukin-6; TNF-a, Tumor Necrosis Factor-a; *, compared with the control group, *P*<0.05; #, compared with index before treatment *P*<0.05; &, compared with index 1 month after treatment, *P*<0.05; $, compared index 12 months after treatment, *P*<0.05

Biochemical Indexes

The indexes of liver and kidney function including alanine aminotransferase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN) and serum creatinine (Cr) revealed no significant difference before and after treatment (all *P*>0.05, **(Table 5).** The total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) also implied no significant difference 1 month after treatment in comparison with those before treatment (all *P*>0.05). Comparing the biochemical indexes between 6 and 12 months after treatment, the TC, TG and LDL-C indexes were lower in the case group than those in the control group (all *P*<0.05), while the HDL-C was higher (*P*<0.05). In the case group, the TC and LDL-C indexes 6 months after treatment were decreased than those before treatment (both *P*<0.05), and the TG and HDL-C indexes 1 months after treatment were significantly different from those before treatment (both *P*<0.05). The TG, LDL-C and HDL-C were improved best 12 months after treatment (all *P*<0.05), while the TC index changes were not significant between 6 and 12 months after treatment (*P*>0.05). In the control group, compared with the indexes before treatment, the TG index 6 months after treatment was significantly different (*P*<0.05), while the LDL-C and HDL-C indexes revealed significant differences only 12 months after treatment (both *P*<0.05). Furthermore, the TG and LDL-C in the control group presented the best improvement 12 months after treatment (both *P*<0.05), while the TG and HDL-C were not significantly different 6 and 12 months after treatment (both *P*>0.05) **(Table 5).**

Table 5. Biochemical indexes of the patients in the case group and control group.

Index	Group	Before treatment	1 month after treatment	6 month after treatment	12 month after treatment
TC (mmol/L)	Case group	5.39 ± 1.13	4.94 ± 1.17	4.07 ± 1.56$^{*\#\&}$	3.45 ± 1.54$^{*\#\&}$
	Control group	5.21 ± 1.12	5.09 ± 1.24	4.95 ± 1.53	4.86 ± 1.63
TG (mmol/L)	Case group	2.35 ± 0.44	2.06 ± 0.48$^{\#}$	1.51 ± 0.41$^{*\#\&}$	1.15 ± 0.38$^{*\#\&\$}$
	Control group	2.38 ± 0.32	2.19 ± 0.33$^{\#}$	2.16 ± 0.35$^{\#}$	2.01 ± 0.37$^{\#\&}$
LDL-C (mmol/L)	Case group	3.81 ± 1.78	3.29 ± 1.25	2.45 ± 0.87$^{*\#\&}$	1.71 ± 0.18$^{*\#\&\$}$
	Control group	3.83 ± 1.22	3.65 ± 1.02	3.42 ± 0.94	3.30 ± 0.29$^{\#\&}$
HDL-C (mmol/L)	Case group	0.92 ± 0.20	1.02 ± 0.24$^{\#}$	1.15 ± 0.23$^{*\#\&}$	1.27 ± 0.20$^{*\#\&\$}$
	Control group	0.90 ± 0.17	0.94 ± 0.18	0.96 ± 0.19	0.99 ± 0.21$^{\#}$

ALT (U/L)	Case group	21.16 ± 7.10	21.18 ± 7.14	21.16 ± 7.15	21.12 ± 7.16
	Control group	20.91 ± 7.09	20.99 ± 7.10	21.13 ± 7.19	21.21 ± 7.23
AST (U/L)	Case group	23.91 ± 7.79	23.97 ± 7.81	24.02 ± 7.99	24.01 ± 7.54
	Control group	24.23 ± 7.39	24.72 ± 7.43	24.16 ± 7.27	23.93 ± 7.25
BUN (mmol/L)	Case group	5.29 ± 1.48	5.37 ± 1.52	5.34 ± 1.56	5.35 ± 1.46
	Control group	5.49 ± 1.42	5.43 ± 1.43	5.32 ± 1.38	5.31 ± 1.27
Cr (umol/L)	Case group	68.02 ± 11.29	68.16 ± 11.49	68.34 ± 12.14	68.31 ± 12.28
	Control group	67.46 ± 12.08	67.89 ± 11.87	68.46 ± 11.45	68.41 ± 12.29

Note: TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; ALT, Alanine aminotransferase; AST, Aspartate transaminase; BUN, blood urea nitrogen; Cr, Serum creatinine; *, compared with the control group, $P<0.05$; #, compared with index before treatment $P<0.05$; &, compared with index 1 month after treatment, $P<0.05$; $, compared index 12 months after treatment, $P<0.05$

DISCUSSION

AF is the most common sustained cardiac arrhythmia. Current treatments for this disease are various and performed depending on specific situations, such as symptom severity and age of the patient [15]. Among those, antiarrhythmic and rate control pharmacotherapy is one of the most effective ways that aims at maintaining and restoring sinus rhythm [16]. Through observing the clinical efficacy of the therapy combining fluvastatin and benazepril, our study is committed to identify new potential way that may promote the treatment of AF. It was shown in our study that, compared with the fluvastatin monotherapy, the combination therapy of fluvastatin and benazepril was more productive in enhancing Sinus converting rate, reducing the left atrial diameter, and bring down the level of serum hs-CRP, renin, Ang Ⅱ, IL-6, TNF-a. It has a pivotal clinical significance for ameliorating the life quality and prognosis of patients suffering from AF.

Our finding illustrated that the therapy combining fluvastatin and benazepril was apparently superior to the fluvastatin monotherapy in improving the sinus converting rate. The pathophysiology of AF is complex, but recent study suggested that an array of factors participate in its development, including the tissue mechanisms that maintain the arrhythmia, ion channel and transporter abnormalities that lead to ectopic impulse formation, electric and structural remodeling, atrial and ventricular dysfunction and the atrial thromboembolism [17]. The activation of renin-angiotensin system (RAS) leads to calcium overload and fibrosis of atrial muscle, which usually serve as contributors for atrial electrical remodeling [18,19]. Benazepril, belonging to ACEI, can limit or prevent the progressive atrial structural remodeling induced by AF via reversing left atrial dilatation and reducing atrial fibrosis and accumulation of extracellular matrix [20] Fluvastatin, belonging to statins, was significantly associated with a decreased rate of AF with the ability to influence atrial remodeling and electrical remodeling [8]. Statins can decrease the prevalence of AF in coronary artery disease by improving endothelial nitric oxide (NO) availability and reducing oxidative stress as well as inflammation [21]. The fact that statins can inhibit the activation of HMG-CoA reductase inhibitors and also result in the reduction of cholesterol synthesis and resistance to energy metabolism, which collectively affect the myocardial systolic and atrial pressure load [22,23]. Similarly, Kumagai et al. demonstrated that statin therapy can improve vascular endothelial function and inhabit platelet aggregation, which collectively prevent thromboembolism in patients, promote the formation of collagen tissue and the stability of fibrous cap and plaque, and further cut down on AF-related complication [24].

Interestingly, our finding also demonstrated that the renin, Ang II, TG, TG and LDL-C in the case group was lower than that in the control group, while the HDL-C was higher than control group, which kept consistent with the result of study by Piero et al. where fluvastatin reduced total LDL-C and apolipoprotein B versus benazepril-valsartan alone in the treatment against chronic Proteinuric Nephropathy [25]. Besides, the present study discovered that LVEDd, LVESd, LAD and LVEF, were in lower level in the case group than those in the control groups after six months of treatment. This was also consistent with studies that advocate fluvastatin effectively decreases levels of P-selectin, one member of the cellular adhesion molecules, in treating essential hypertension, and statins induce prevention or regression of LVH that was an increased risk of cardiovascular morbidity [26,27]. In addition, the present study showed that, after one month of treatment, the hs-CRP in the case group turned to be lower than that in the control group. Linked with our study, Wai et al. reported that flucastatin played a key role in the reduction of inflammation response in patients with chronic kidney disease by decreasing CRP levels [28].

CONCLUSION

Our study provides evidence that, compared with the fluvastatin monotherapy, the combination therapy of fluvastatin and benazepril is more productive in enhancing sinus converting rate, reducing the left atrial diameter, and bring down the level of serum hs- CRP, renin, Ang II, IL-6, TNF-a. This has a pivotal clinical significance for ameliorating the life quality and prognosis of patients suffering from AF. However, it has yet been thoroughly elucidated that how the therapeutic mechanism works and by which way fluvastatin and benazepril decrease the level of hs- CRP, renin, Ang II, IL-6, TNF-a. Therefore, deeper studies are expected on the road ahead.

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