Original article

Serum uric acid levels correlate with atrial fibrillation in patients with chronic systolic heart failure

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Keywords: *atrial fibrillation; uric acid; chronic heart failure; diuretics*

Background Studies have shown that increased levels of serum uric acid (SUA) are associated with atrial fibrillation (AF). However, less is known about the prognostic value of SUA levels for AF in patients with chronic heart failure (CHF). The aim of the study was to examine the prognostic value of SUA levels for AF in patients with CHF.

Methods Sixteen thousand six hundred and eighty-one patients diagnosed with CHF from 12 hospitals were analyzed. Patients were categorized into AF group and non-AF group, death group, and survival group according to the results of the patients' medical records and follow-up. Univariate and multivariate Cox proportional hazards analyses were performed to examine the risk of AF. The sensitivity and specificity of SUA level in predicting the prognosis were examined by multivariate Cox models and receiver operating characteristic (ROC) curves.

Results The results of univariate predictors in overall patients showed that the higher SUA level was associated with AF. SUA level (HR, 1.084; 95% *CI*, 1.017–1.144; *P* <0.001), diuretics (HR, 1.549; 95% *CI*, 1.246–1.854; *P* <0.001), and New York Heart Association (NYHA) (HR, 1.237; 95% *CI*, 1.168–1.306; *P* <0.001) function class were the independent risk factors for AF. The sensitivity and specificity of the models were 29.6% and 83.8% respectively for predicting AF. When SUA level was added to these models, it remained significant (Wald χ^2, 1494.88; *P* <0.001 for AF); 58.8% (95% *CI*, 57.7%–60.0%) of the observed results were concordant with the separate model.

Conclusion Higher SUA level is associated strongly with AF in patients with CHF. SUA level can increase the sensitivity and specificity in predicting AF.

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Atrial fibrillation (AF) and chronic heart failure (CHF) are common and related conditions, each promoting the other and both associated with increased mortality.[1] AF is a common atrial arrhythmia in patients with CHF caused by left ventricular dysfunction and is associated with significant morbidity.[2] The mechanisms by which CHF promotes AF are incompletely understood. There seem to be trigger- and substrate-dominant mechanisms, and atrial fibrosis appears to play a key role in the development of a substrate for AF in CHF.[3]

Recent studies have demonstrated the implication of inflammation and oxidative stress in the pathophysiology of CHF.[4,5] In addition, there is emerging data to support the association between inflammation and AF.[6] Elevated serum uric acid (SUA) levels are a marker of inflammation, metabolic disturbances, oxidative stress, and endothelial dysfunction.[7] It has a pathophysiologic significance in the progression of CHF and is independently associated with poor prognosis and increased mortality.[8] However, less is known about SUA as a potential prognostic risk factor for AF in patients with CHF. Thus, we investigated the association between AF and SUA levels in patients with CHF, as well as the relative impact of diuretics.

METHODS

Patients and study protocol

We conducted a retrospective study referred to the Cardiology Department of 12 hospitals in Hubei province in China between January 2000 and May 2010. Forty-eight thousand nine hundred and sixty-four consecutive patients' medical records meeting all of the inclusion criteria were included in the study. Inclusion criteria were echocardiographic evidence of a left ventricular ejection fraction (LVEF) of ≤50%, over 18 years of age, and a diagnosis of chronic systolic heart failure (CSHF). The diagnosis of CSHF was based on the European Society of Cardiology criteria.[9] Patients were excluded if they had a history of myocardial infarction in the last 12 months, cardiac surgery or congenital heart disease, and the history of cancer.

All baseline demographic and clinical characteristics were carefully recorded. A transthoracic echo-cardiographic examination was performed in each individual. The LVEF was measured according to the

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biplane Simpson rule. The severity of valvular regurgitation and stenosis was measured by two-dimensional and Doppler echocardiography. Laboratory examinations, including complete blood count and biochemical investigations, were performed in the fasting state. SUA level was measured by standard analytical method (uricase enzymatic test). AF was identified by ECG or Holter or discharged diagnosis.

Statistical analysis

We used χ^2, *t*, and analysis of variance (ANOVA) tests for descriptive analyses to compare baseline characteristics between the AF group and the non-AF group. Univariate and multivariate Cox regression analyses were used on selecting demographic, clinical variables, and therapy methods of AF. A logarithmic conversion was performed for non-normal distribution of variables, such as SUA levels. The associations between SUA levels and AF were assessed using Cox proportional hazards analysis (both single predictor and multivariable models). The Cox models were developed that used the demographic, clinical variables, and therapy methods, with and without the SUA levels, to assess the incremental additive information from this variable in predicting AF. Variables were entered into the model in multiple steps. Sensitivity and specificity analyses were performed on both of these models, and receiver operating characteristic (ROC) curves were generated. All statistical tests were evaluated with the use of two-tailed 95% CI, and tests with $P<0.01$ were considered significant. Data analyses were performed with the use of SPSS for Windows, release 15, 2006 (SPSS Inc, Chicago).

RESULTS

Baseline characteristics

Among the 48 964 patients' files, 9362 patients had one time hospitalization and 10 897 patients had more than one time hospitalization. The first and the last files of those patients were investigated. Finally, 20 259 patients were enrolled in the present study (Figure 1).

During follow-up, 1735 (8.10%) patients were lost and 1843 patients were excluded because of cardiac surgery. Finally, data of 16 681 patients were entered into the Epi info™ software and analyzed. Patients with AF (6807) and without AF (9874) in the overall population were assigned AF group A and non-AF group A, respectively. The demographic characteristics of the overall study population are summarized in Table 1.

There were 10 897 patients who had a history of more than one time hospitalization, among whom 4570 were with AF and 6327 were without AF during the first hospitalization. The last files of the patients without AF showed that 2404 patients had AF (AF group B) and 3923 patients were without AF (non-AF group B). The first and last clinical characteristics of the patients who had more than one time hospitalization are shown in Table 2.

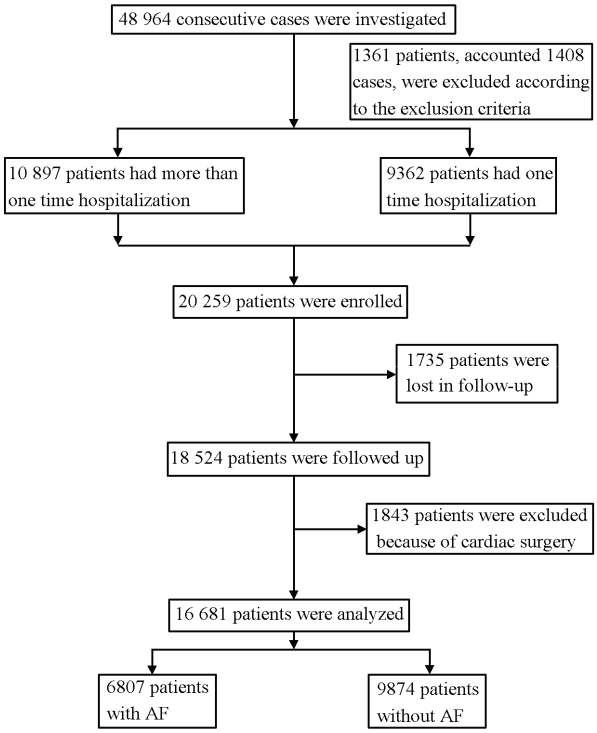

Figure 1. The flow diagram of the present study.

Table 1. The baseline characteristics of CHF patients with and without AF

Parameters	AF group A (*n*=6807)	Non-AF group A (*n*=9874)	*P* values
Female (*n* (%))	3324 (48.83)	3861 (39.10)	<0.001
Age (years)	64.54±13.61	62.19±15.07	<0.001
Systolic blood pressure (mmHg)	126.12±23.85	132.56±26.33	<0.001
Diastolic blood pressure (mmHg)	78.25±14.36	80.05±14.95	<0.001
LVEF (%)	37.43±12.72	38.42±13.96	<0.001
Heart rate (bpm)	90.95±26.59	81.05±18.89	<0.001
NYHA class III-IV (*n* (%))	5547 (81.49)	7121 (72.12)	<0.001
Diabetes mellitus (*n* (%))	1612 (23.68)	1088 (11.02)	<0.001
Hypertension (*n* (%))	2844 (41.78)	5095 (51.60)	<0.001
Alanine transarninase (U/L)	1.440±0.40	1.42±0.38	<0.001
Aspartate aminotransferase (U/L)	1.53±0.34	1.46±0.31	<0.001
Sodium (mmol/L)	138.87±5.00	139.94±10.05	<0.001
Potassium (mmol/L)	4.05±0.66	4.06±0.60	0.445
Calcium (mmol/L)	2.23±0.25	2.25±0.26	<0.001
Creatinine (μmol/L)	1.97±0.21	1.96±0.23	0.038
Blood urea nitrogen (mmol/L)	0.86±0.22	0.84±0.22	<0.001
Uric acid (μmol/L)	2.58±0.24	2.56±0.23	<0.001
NT-proBNP (ng/dl)	3.46±0.61	3.01±0.60	<0.001
hs-CRP	1.14±0.16	0.93±0.10	<0.001
Left atrial end-diastolic diameter (mm)	45.68±10.47	40.70±7.00	<0.001
Left ventricular end-diastolic diameter (mm)	54.03±11.11	53.45±9.89	<0.001
Angiorensin-converting enzyke inhibitors (*n* (%))	3291 (48.35)	4972 (50.35)	0.011
β-receptor blocker (*n* (%))	2819 (41.41)	4605 (46.64)	<0.001
Angiotensin II receptor blocker (*n* (%))	1022 (15.01)	1741 (17.63)	<0.001
Digitalis (*n* (%))	3812 (56.00)	3553 (35.98)	<0.001
Diuretics (*n* (%))	5071 (74.50)	6123 (62.01)	<0.001
Statins (*n* (%))	875 (12.85)	2643 (26.77)	<0.001

In the overall study population, patients had a median age of 63 years (54–74 years). Compared with patients in the non-AF group A, those in AF group A had a higher

Table 2. The baseline characteristics of CHF patients without AF at enrollment and after follow-up

Parameters	AF group B		Non-AF group B		*P* values*			
	At enrollment (*n*=2404)	After follow-up (*n*=2404)	At enrollment (*n*=3923)	After follow-up (*n*=3923)	*P*1	*P*2	*P*3	*P*4
Female (*n* (%))	1322 (54.99)		2512 (64.04)		<0.001			
Age (years)	64.47±15.10	69.39±13.18	61.04±14.98	66.47±14.98	<0.001	<0.001	<0.001	<0.001
Systolic blood pressure (mmHg)	132.21±25.89	127.21±24.05	132.71±26.40	129.21±26.72	0.461	<0.001	<0.001	<0.001
Diastolic blood pressure (mmHg)	79.85±15.197	74.16±14.41	80.14±15.197	76.85±15.20	0.461	<0.001	<0.001	<0.001
LVEF (%)	37.02±9.86	32.92±7.00	38.69±8.50	34.86±7.69	<0.001	<0.001	<0.001	<0.001
Heart rate (bpm)	81.36±18.66	90.77±16.28	79.87±18.93	84.77±18.26	0.002	<0.001	<0.001	<0.001
NYHA class III–IV (*n* (%))	2024 (84.19)	2169 (90.22)	2532 (64.54)	2796 (71.27)	<0.001	<0.001	<0.001	<0.001
Diabetes mellitus (*n* (%))	554 (23.04)	571 (23.75)	763 (12.49)	526 (13.41)	<0.001	<0.001	0.479	0.113
Hypertension (*n* (%))	1811 (75.33)	1860 (77.37)	1451 (36.99)	1683 (42.90)	<0.001	<0.001	0.042	<0.001
Alanine transarninase (U/L)	1.43±0.37	1.43±0.42	1.42±0.38	1.39±0.34	0.305	<0.001	1.000	<0.001
Aspartate aminotransferase (U/L)	1.47±0.30	1.52±0.35	1.45±0.31	1.45±0.30	0.012	<0.001	<0.001	1.000
Sodium (mmol/L)	139.14±10.68	139.23±14.74	140.42±10.02	140.14±15.60	<0.001	0.021	0.808	0.344
Potassium (mmol/L)	4.04±0.59	4.06±0.65012	4.07±0.60	4.09±0.58	0.052	0.034	0.302	0.102
Calcium (mmol/L)	2.25±0.26	2.24±0.23	2.25±0.26	2.27±0.21	1.000	<0.001	0.309	0.002
Creatinine (μmol/L)	1.97±0.23	2.07±0.22	1.96±0.23	2.02±0.23	0.093	<0.001	<0.001	<0.001
Blood urea nitrogen (mmol/L)	0.84±0.21	0.87±0.22	0.84±0.21	0.84±0.21	1.000	<0.001	<0.001	1.000
Uric acid (μmol/L)	2.57±0.19	2.59±0.20	2.55±0.16	2.56±0.18	<0.001	<0.001	<0.001	0.014
NT-proBNP (ng/dl)	3.11±0.61	3.02±0.64	2.96±0.60	2.99±0.69	<0.001	0.085	<0.001	0.040
hs-CRP	0.93±0.11	0.97±0.14	0.92±0.10	0.94±0.11	<0.001	<0.001	<0.001	<0.001
LAD (mm)	41.77±7.05	45.13±9.81	40.96±6.98	42.67±7.05	<0.001	<0.001	<0.001	<0.001
LVDD (mm)	55.56±9.97	56.63±11.46	52.06±8.13	53.86±11.67	<0.001	<0.001	<0.001	<0.001
ACEI (*n* (%))	1131 (47.05)	1322 (54.99)	2056 (52.41)	2097 (53.45)	<0.001	<0.001	<0.001	<0.001
β-receptor blocker (*n* (%))	1096 (45.59)	1060 (44.09)	1854 (47.26)	1985 (50.60)	<0.001	<0.001	0.194	<0.001
ARB (*n* (%))	377 (15.68)	424 (17.64)	739 (18.84)	858 (21.87)	<0.001	<0.001	0.026	<0.001
Digitalis (*n* (%))	973 (40.47)	1468 (61.06)	1305 (33.27)	1453 (37.04)	<0.001	<0.001	<0.001	<0.001
Diuretics (*n* (%))	1814 (75.46)	1861 (77.41)	2108 (53.73)	2398 (61.13)	<0.001	<0.001	0.047	<0.001
Statins (*n* (%))	628 (26.12)	738 (30.70)	1066 (27.17)	1269 (32.35)	0.252	<0.001	<0.001	<0.001
Follow-up time (years)		4.36±0.73		4.38±0.81		0.323		

*P1, Comparison between the AF and Non-AF group B at enrollment; *P*2, Comparison between the AF and Non-AF group B after follow-up; *P*3, Comparison between the enrollment and follow-up in AF group B; *P*4, Comparison between the enrollment and follow-up in Non-AF group B.

median age ((64.54±13.61) vs. (62.19±15.07) years, *P* <0.001), lower systolic blood pressure (SBP; (126.12±23.85) vs. (132.56±26.33) mmHg, *P* <0.001), lower LVEF (37.43±12.72 vs. 38.42±13.96, *P* <0.001), faster heart rate ((90.95±26.59) vs. (81.05±18.89) beats/min, *P* <0.001), and higher prevalence of New York Heart Association (NYHA) class III-IV (81.49% vs. 72.12%, *P* <0.001; Table 1). Furthermore, patients with AF had higher levels of SUA ((2.58±0.24) vs. (2.56±0.23) mmol/L, *P* <0.001), high sensitivity C-reactive protein (hs-CRP) (1.14±0.16 vs. 0.93±0.10, *P* <0.001), and a larger left atrial diameter ((45.68±10.47) vs. (40.70±7.00) mm, *P* <0.001).

Compared with patients in the non-AF group B, the baseline clinical characteristics of AF group B showed that patients with AF had a higher SUA level ((2.57±0.19) vs. (2.55±0.16) mmol/L, *P* <0.001), hs-CRP (0.93±0.11 vs. (0.92±0.10), *P* <0.001), and larger left atrial diameter ((41.77±7.05) vs. (40.96±6.98) mm, *P* <0.001).

Factors associated with AF

Factors that were independently associated with AF are shown in Figure 2. In multivariate Cox regression analysis, the results showed that SUA level (HR, 1.084; 95% *CI*, 1.017–1.144; *P* <0.001), diuretics (HR, 1.549; 95% *CI*, 1.246–1.854; *P* <0.001), left atrial diameter (LAD) (HR, 1.032; 95% *CI*, 1.016–1.046; *P* <0.001), left ventricular end diastolic dimension (LVDD) (HR, 1.044; 95% *CI*, 1.020–1.065; *P* <0.001), and NYHA (HR, 1.237; 95% *CI*, 1.168–1.306; *P* <0.001) function class were the independent risk factors for AF.

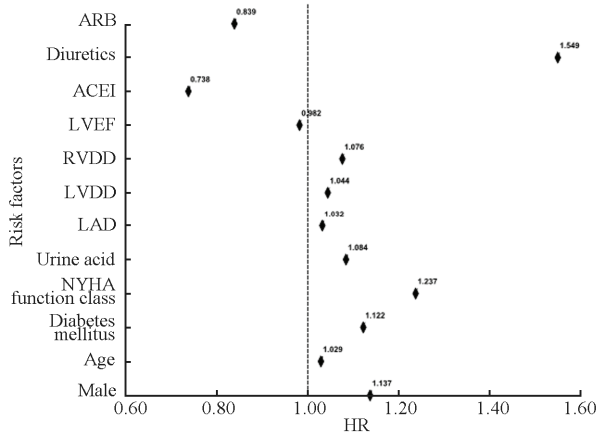

Figure 2. The independent risk factors of AF for CHF patients. The result of multivariate Cox regression analysis shows that several variables including SUA and diuretics are the independent risk factors of AF.

Effect of SUA level on the sensitivity and specificity of predicting models for AF

To determine the sensitivity and specificity of the prognostic value of SUA, Cox models and ROC curves were developed. The Cox models included demographic characters, clinical variables, and therapy methods except

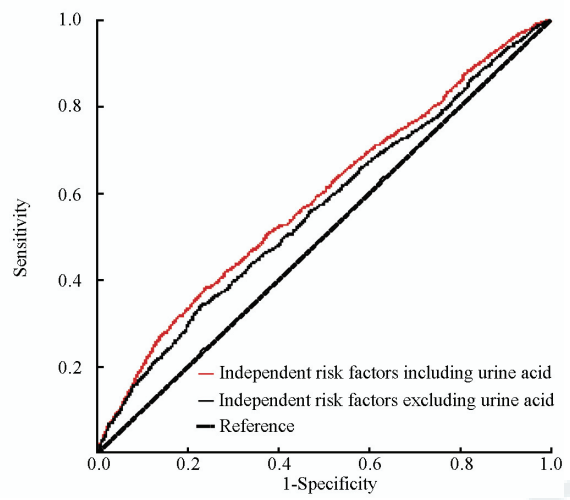

Figure 3. ROC curves of sensitivity and specificity of SUA in predicting AF. To determine the sensitivity and specificity of the prognostic value of SUA, Cox models and ROC curves were developed. The Cox models included demographic characters, clinical variables, and therapy methods except SUA, which were very significant predictors of AF (Wald χ^2 1546.69; P <0.001); 56.3% (95% *CI*, 55.1–57.4) of the observed responses were concordant with the model. The sensitivity and specificity of the models were 24.0% and 77.3%, respectively. When SUA was added to the model, it remained significant (Wald χ^2 1494.88; P <0.001) for AF; 58.8% (95% *CI*, 57.7–60.0) of the observed results were concordant with the separate model. The sensitivity and specificity of the models were 29.6% and 83.8%, respectively.

SUA (Figure 2), and these models were very significant predictors of AF (Wald χ^2, 1546.69; P <0.001). The sensitivity and specificity of the models were 24.0% and 77.3% respectively for predicting AF; 56.3% (95% CI, 55.1–57.4) of the observed results were concordant with the model (Figure 3). When SUA was added to these models, it remained significant (Wald χ^2 1494.88; P <0.001 for AF); 58.8% (95% *CI*, 57.7–60.0) of the observed results were concordant with this model (Figure 3). The sensitivity and specificity of the models were 29.6% and 83.8% respectively for predicting AF.

DISCUSSION

The major and novel finding of the present study was that SUA level and diuretics were the independent predictors of AF in a large group of patients with CHF. Increased SUA has relationship with the diuretics administration in patients with CHF. In addition, we found that the SUA level could increase the sensitivity in predicting AF.

AF and CHF are morbid conditions that share common risk factors and frequently coexist. Studies have amassed regarding the nature of the relations between AF and CHF.[10] The notion that the inflammatory process plays a role in AF has garnered much attention in many recent studies and is now a well-established connection. Inflammation has been considered to be an independent risk factor for the initiation and maintenance of AF.[11-13] Furthermore, patients with CHF remain plagued by a poor prognosis that is thought to be linked to underlying inflammation and oxidative stress.[14,15] Uric acid is the end point of the metabolism of purine compounds, produced in the liver from the degradation of dietary and endogenously synthesized purine compounds via the xanthine oxidase reaction, which irreversibly oxidizes xanthase to uric acid. Numerous studies have demonstrated that uric acid is a marker of oxidative stress and myocardial damage, and the increased serum levels can be a manifestation of toxic myocardium.[16,17] Recently, a clinical study indicates an independent association between increased levels of uric acid and permanent AF.[18] A potential explanation could be that uric acid levels reflect more selectively the increased atrial oxidative stress. To the best of our knowledge no study to date has examined the role of uric acid in the AF setting in patients with CHF.

In the present study, we identified several characteristics that were significantly associated with AF, including diabetic status, heart rate, age, and NYHA class. Use of diuretics and higher levels of SUA were also associated with AF. Furthermore, we found that the SUA level could increase the sensitivity of separate predicting model in predicting AF. The results indicate that SUA level provides additional prognostic information beyond that of readily available clinical variables. The potential mechanism for the higher levels of SUA in patients with CHF may have relationship with the diuretics administration. The elevated SUA level may relate to cardiac dysfunction and progression of heart failure through oxidative stress by increased xanthine oxidase activity in patients with CHF.[19,20] The results of depressed cardiac function and oxidative stress can induce cardiac remodeling and atrial fibrosis, as well as increase the vulnerability of AF.

Limitations

Our study has several limitations. It is a retrospective and observational study. The retrospective nature of the study precluded definite conclusions about cause-effect relations and prognostic implications of the variables in this study. Before and after follow-up, AF was identified by ECG or Holter or discharged diagnosis. Some patients with paroxysmal AF will be missed diagnosis. This result may be confounding and would have resulted in attenuated risk estimates, but the large sample size of the present study can correct it. Furthermore, during the follow-up, whether patients had regular and continuous time to take medicines such as diuretics was unknown. Because all patients were followed up by telephone, it was difficult to define the causes of death. Hence, in the present study, we investigated the relationship between SUA and all-cause death. Whether SUA level can increase the sensitivity in predicting cardiovascular mortality should be further investigated.

In conclusion, The higher SUA level is associated strongly with the vulnerability of AF in a large group of

patients with CHF. SUA can increase the sensitivity in predicting AF.

REFERENCES

1. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003; 107: 2920-2925.
2. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med 1982; 306: 1018-1022.
3. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol 2008; 51: 802-809.
4. Torre-Amione G, Kapadia S, Lee J, Durand JB, Bies RD, Young JB, et al. Tumor necrosis factor-alpha and tumor necrosis factor receptors in the failing human heart. Circulation 1996; 93: 704-711.
5. Mary K, Amir G, Michael JS. Increased oxidative stress in patients with congestive heart failure. J Am Coll Cardiol 1998; 31: 1352-1356.
6. Engelmann MD, Svendsen JH. Inflammation in the genesis and perpetuation of atrial fibrillation. Eur Heart J 2005; 26: 2083-2092.
7. Strazzullo P, Puig JG. Uric acid and oxidative stress: relative impact on cardiovascular risk? Nutr Metab Cardiovasc Dis 2007; 17: 409-414.
8. Jankowska EA, Panikowska B, Majda J, Zymlinski R, Trzaska M, Reczuch K, et al. Hyperuricemia predicts poor outcome in patients with mild to moderate HF. Int J Cardiol 2007; 115: 151-155.
9. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC Committee for Practice Guidelines ESC. Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Eur Heart J 2008; 29: 2388-2442.
10. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003; 91: D2-D8.
11. Conway DS, Buggins P, Hughes E, Lip GY. Prognostic significance of raised plasma levels of interleukin-6 and C-reactive protein in atrial fibrillation. Am Heart J 2004; 148: 462-466.
12. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001; 104: 2886-2891.
13. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, et al. Inflammation as a risk factor for atrial fibrillation. Circulation 2003; 108: 3006-3010.
14. Hamid T, Gu Y, Ortines RV, Bhattacharya C, Wang G, Xuan YT, et al. Divergent tumor necrosis factor receptor-related remodeling responses in heart failure: role of nuclear factor-kappaB and inflammatory activation. Circulation 2009; 119: 1386-1397.
15. Kalantar-Zadeh K, Anker SD, Horwich TB, Fonarow GC. Nutritional and anti-inflammatory interventions in chronic heart failure. Am J Cardiol 2008; 101: E89-E103.
16. Strasak AM, Kelleher CC, Brant LJ, Rapp K, Ruttmann E, Concin H, et al and VHM&PP Study Group. Serum uric acid is an independent predictor for all major forms of cardiovascular death in 28,613 elderly women: a prospective 21-year follow-up study. Int J Cardiol 2008; 125: 232-239.
17. Hare JM, Johnson RJ. Uric acid predicts clinical outcomes in heart failure. Circulation 2003; 107: 1951-1953.
18. Letsas KP, Korantzopoulos P, Filippatos GS, Mihas CC, Markou V, Gavrielatos G, et al. Uric acid elevation in atrial fibrillation. Hellenic J Cardiol 2010; 51: 209-213.
19. Glantzounis GK, Tsimoyiannis EC, Kappas AM, Galaris DA. Uric acid and oxidative stress. Curr Pharm Des 2005; 11: 4145-4151.
20. Dawson J, Walters M. Uric acid and xanthine oxidase: future therapeutic targets in the prevention of cardiovascular disease? Br J Clin Pharmacol 2006; 62: 633-644.

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