REVIEWS

The role of uric acid in cardiovascular diseases

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Summary: In recent years, a lot of clinical and epidemiological studies have highlighted the association between increased serum levels of uric acid and metabolic syndromes, diabetes mellitus, hypertension, coronary artery disease[1], cerebrovascular disease[2], evolution with cardiovascular events[3] and death[2]. Some of the clinical studies found that hyperuricemia is an independent cardiovascular risk factor or a risk factor for the development of cardiovascular events and other similar studies have considered hyperuricemia as a "confounding factor" due to it is frequent association with various cardiovascular risk factors[4]. Increased levels of seric uric acid have been linked to heart failure and have been found as an independent predictor of severe prognosis in patients with chronic heart failure[2]. In this context hyperuricemia may become a therapeutic target in the strategy for preventing chronic heart failure. Impact of hyperuricemia treatment with xanthine-oxidase inhibitors on the morbidity and mortality of patients with chronic heart failure is now evaluated in ongoing clinical trials.
Keywords: hyperuricemia, cardiovascular risk factors, heart failure, xanthine oxidase inhibitors.

Rezumat: În ultimii ani numerose studii clinice şi epidemiologice pun în discuţie asocierea nivelelor crescute ale acidului uric cu sindromul metabolic, diabetul zaharat, hipertensiunea arterială, boala coronariană[1], boala cerevbrovasculară[2], evoluţia cu evenimente cardiovasculare[3] şi deces[2]. Rezultatele studiilor clinice şi epidemiologice care apreciaza hiperuricemia ca factor independent de risc cardiovascular sau ca factor de risc al evoluţiei cu evenimente cardiovasculare sunt contrabalansate de rezultatele unor studii similare care au apreciat hiperuricemia drept „confounding factor", datorită asocierii frecvente a acesteia cu diferti factori de risc cardiovascular[4]. În insuficienţa cardiacă nivelele crescute ale acidului uric au fost implicate în patogeneza insuficienţei cardiace şi au fost apreciate ca predictor independent al prognosticului grav[2]. În acest context hiperuricemia devine o ţintă terapeutică la pacienţii cu incuficienţă cardiacă. Date recente sugerează introducerea tratamentului hiperuricemiei în strategia de prevenţie a apariţiei şi progresiei insuficienţei cardiace. Impactului tratamentului hiperuricemiei cu inhibitori ai xantinoxidazei asupra evoluţiei pacienţilor cu insuficienţă cardiacă este în evaluare în trialuri clinice ce au ca obiectiv aprecierea influenţei acestui tratament asupra morbidităţii şi mortalităţii pacienţilor cu insuficienţă cardiacă.
Cuvinte cheie: hiperuricemia, factor de risc cardiovascular, insuficienta cardiaca, inhibitori ai xantinoxidazei

HYPERURICEMIA

Hyperuricemia is defined as the increase of seric uric acid (UA) levels >7 mg/dl and it is reported in 2-20% of the population, depending on age, sex and other factors[6]. The increasing prevalence of hyperuricemia is associated both with the increasing prevalence of obesity and metabolic syndrome, as well as with the increased usage of drugs which can lead to the increase of seric levels of uric acid (UA) (thiazide diuretics and low doses of aspirin)[7].

The seric level of UA is determined by the balance between the endogenous production of uric acid (UA) and the exogenous intake on one hand and renal excretion and UA catabolization on the other. In humans UA catabolism is absent due to the lack of uricase (urate oxidase) - the loss of this enzyme is the result of ancestral genetic mutations. The endogenous production of uric acid determines 70% of the UA "pool", resulting from the purine catabolism under the action of xanthine oxidase, whereas the exogenous intake represents 30%.

The increase in the endogenous production can be determined by an excess in purine levels (severe cytolytic syndrome - rhabdomyolysis, tumor cell destruction) or by an increased activity of xhantine oxidase (XO). An increase in the activity of xanthine oxidase (found in important quantities in the liver and intestine) was incriminated in hyperuricemias from gout and the up-

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regulation of XO activity also described in the myocardium and vascular endothelium was associated with endogenous hyperuricemias found in dilatative cardiomyopathies and heart failure[8]. Endogenous hyperuricemia was also incriminated in the development of hyperuricemia in patients diagnosed with obesity, diabetes, or associated with increased levels of triglycerids, low levels of HDL-c, increased seric levels of C reactive protein. Leptin[9] and insulin regulate UA levels[10].

A diet rich in purines was assessed in clinical trials and revealed an increase in UA levels - meat and seafood, alcohol (beer) or industrial diet food, rich in fructose[11]. A decrease in UA levels was identified in connection with diets rich in dairy products, due to their uricosuric effect[12]. Recent data emphasizes the difficulties in appreciating the intervention of certain foods in the increase of UA levels and the low impact of the quality of the diet, without pointing out a specific element from the diet which can have a predictive value for the increase of UA levels[13]. The kidney excretes 10% of the UA "pool" on a daily basis. A decrease of UA renal excretion can be the consequence of renal failure/dysfunction, but also a result of affections concerning the different stages of renal UA excretion. In healthy subjects the glomerular filtration of UA is followed by an almost complete reabsorption in the proximal convoluted tubule, then by its secretion in the proximal convoluted tubule (50% of the quantity of UA reabsorbed) and in the end the postsecretion reabsorption of 40% of the UA secreted in the tubules[14]. The increase of UA renal excretion under the influence of estrogens explains lower levels of UA in women[15]. A decrease in the renal plasma flow, without variations of the glomerular filtration was associated with increased levels of UA. It is possible that the genetic polymorphism of UA "transtubule" transporters can be responsible for hyperuricemia in young people[16] and that drug interferences with UA transtubule transporter proteins (aspirin)[17] can lead to lower, or higher values of UA renal excretion (losartan)[18].

The uric acid paradox and cardiovascular disease

Uric acid is the main hydrophilic antioxidant in the human body. Acute and moderate increases in UA levels have antioxidant properties directly linked to UA, which intervenes through the oxygen free radicals clearance (peroxynitrite) and by favoring the activity of superoxide dismutase[19]. However, chronic increases in UA levels are associated with the increase of intracellular oxidative stress, a phenomenon known as "the UA oxidant-antioxidant paradox"[20]. The oxidative stress associated with a chronic increase in UA values by an enhanced XO activity, directly involves the activity of XO in the increased production of reactive oxygen types (ROT)[21]. Thus, endogenous chronic hyperuricemia is associated with a larger production of oxygen free radicals. This phenomenon is important in an "atherosclerotic" environment[22]. Studies based on clinical observation and animal disease models have shown that chronic hyperuricemia determines endothelial dysfunction by increasing the oxidative stress[23], as well as low grade systemic inflammation by directly stimulating the production of IL-6 and IL-1[24,25]. Both conditions are important in the onset and progression of atherosclerotic cardiovascular disease, from risk factors to heart failure.

Data referring to the relationship between increased levels of UA and cardiovascular disease has shown that it is not linear, being influenced by age and associated diseases, mainly diabetes and chronic renal disease. Meta analyses conducted on studies which enrolled over 400000 patients have presented the increase of UA serum level as a predictive factor for coronary diseases[26]. Recently published, the results of the NHANES III study have excluded UA as an independent predictive risk factor for multiethnic populations without cardiovascular disease or diabetes[27]. However, these results do not exclude the possibility that increased levels of UA may be useful for predicting increased cardiovascular risk for population subgroups such as the elderly, patients diagnosed with diabetes or those with heart failure, for which previous studies have already proven that increased levels of UA are independent predictive factors. The SHEP study has shown that increased levels of UA in elderly people diagnosed with arterial hypertension represent an independent predictor for cardiovascular events[28]. Hyperuricemia was also appreciated to be an independent predictor for cardiovascular risk[29]. The clinical studies which have reported the UA levels as an independent predictor for cardiovascular events support the need to evaluate the efficiency of XO inhibitor treatment for hyperuricemia concerning cardiovascular risk, mainly for the population subgroups for which increased levels of UA were independent cardiovascular risk factors[29].

Hyperuricemia in heart failure

Hyperuricemia was reported in 50-60% of the patients diagnosed with heart failure[30].

Pathogenetic mechanisms

The rise of seric UA levels in patients diagnosed with heart failure was mainly correlated with the up-regula-

tion of XO activity, including the myocardium[31,32] and with a reduction in renal excretion. The decrease in renal excretion of UA is the consequence of a reduction of the renal plasmatic flow and its tubular secretion. The reduction of the renal plasmatic flow is involved in the rise of UA serum levels found in type-1 cardiorenal syndrome, encountered in the evolution of chronic heart failure. The decrease of tubular secretion is secondary to the renal ischemia provoked by heart failure, combined with the direct effect of the lactate[33]. However, the rise of UA seric levels in heart failure has components independent of renal dysfunction or diuretic treatment.

Hyperuricemia was involved in the onset and progression of heart failure[4,35]. The Framingham Offspring Study has shown that hyperuricemia is a risk factor for heart failure in the community starting from sUA levels of >6.3 mg/dl[4]. Studies conducted on animal disease models have shown that XO inhibition reduces cardiac remodeling[36] and suggests that the reduction of serum UA levels might influence in a positive manner cardiac remodeling, thus preventing the onset of heart failure. The potential mechanisms through which hyperuricemia is involved in the onset of heart failure include the alteration of the energetic metabolism[37] and the release of calcium from myocytic endoplasmic reticulum[38], as well as the reduction in the myofibrile's sensitivity to Calcium[39] and apoptosis. The vascular mechanisms involving hyperuricemia in the progression of heart failure include endothelial dysfunction, provoked by a high oxidative stress (modulated through the activity of extracellular superoxide dismutase[40]) and vascular remodeling with the intervention of the rennin-angiotensin-aldosterone system[41].

The rise of sUA levels is progressive and simultaneous with the functional class of the heart failure. In patients suffering from heart failure and cachexia sUA levels are significantly higher than in patients diagnosed with heart failure, without cachexia[42].

Data published over a decade ago has shown that in heart failure high seric uric acid levels are a prognostic factor independent from the renal function, Sodium levels or age[43]. Later, solid data was published proving that in acute and chronic heart failure the rise of sUA levels can predict the rise of mortality and morbidity[44]. Values of sUA levels >9.50 mg/dl appear to be independent predictors for cardiovascular events in patients with heart failure[43]. UA levels predict a severe prognostic in association with systolic dysfunction (the decrease of the left ventricle's EF) and the functional status of the heart (effort oxygen consumption)[45] The HFSS score, useful for prognostic stratification, can be optimized for the prognostic of patients with heart failure by introducing UA levels next to the other 7 prognostic factors for heart failure[45].

Some studies have even presented the rise of UA levels as a predictive factor for mortality overall[46] and for the need for heart transplantation[45,47]. The predictive value of sUA levels >9.50 mg/dl is also supported by studies which have shown that oxypurinol therapy reduced the rate of cardiovascular events in patients with heart failure only in the patient population with sUA levels >9.50 mg/dl[43].

Anker's study described a gradual relationship between the level of sUA and the survival rate of patients with heart failure. Patients suffering from heart failure and UA levels <400 μmol/L had a better survival rate than those with levels between 400 and 600 μmol/L, 600 and 800 μmol/L and >800 μmol/L[43].

XO inhibitor treatment

The prognostic implications of the rise of seric UA levels in heart failure lead to the legitimate question whether or not lowering UA levels should become a therapeutic goal for these patients and what are the therapeutic means to achieve this goal.

Clinical studies have revealed the fact that allopurinol treatment administered to patients with heart failure brings benefits regarding the correction of endothelial dysfunction[48,49], the reduction of myocardial oxygen consumption, improving contraction[50], reverse cardiac remodeling and the reduction of systolic dysfunction (the increase of the left ventricle's ejection fraction)[51,52].

The results of the studies evaluating allopurinol treatment in patients with heart failure and hyperuricemia were conflicting in regard to the effect of this treatment on the heart's functional capacity (appreciated by the 6 minute walking test[53]), morbidity and mortality[54]. There is some data suggesting a reduction of cardiovascular events in patients with heart failure and hyperuricemia undergoing treatment with allopurinol[55]. The EXACT trial (*Xanthine Oxidase Inhibition for Hyperuricemic HF Patients*) sponsored by The National Heart, Blood and Lung Institute is ongoing and will assess the impact of allopurinol therapy on the heart failure patient's hospitalization[56].

Oxypurinol therapy was, however, able to induce a reduction of cardiovascular events when the evaluation was done on patients with sUA levels >9.50 mg/dl. For these patients, the rise of sUA levels was an independent predictor for the evolution with cardiovascular events[54,57]. The OPT-CHF (*Efficacy and Safety Study*

of Oxypurinol Added to Standard Therapy in Patients with NYHA Class III-IV Congestive Heart Failure) is an ongoing study and will appreciate the safety and efficiency of adding oxypurinol to the standard therapy for patients with heart failure and its effects on morbidity, effort capacity and mortality[58].

Conflict of interest: none declared.

References

1. Tuttle KR, Short RA, Johnson RJ. Sex differences in uric acid and risk factors for coronary artery disease. Am J Cardiol 2001;87:1411-4.
2. Harzand A, Tamariz L, Hare JM. Uric acid, heart failure survival, and the impact of xanthine oxidase inhibition. Congest Heart Fail. 2012; 18:179–82.
3. Takahashi MM, de Oliveira EP, de Carvalho AL, Dantas LA, Burini FH, Portero-McLellan KC, Burini RC: Metabolic Syndrome and dietary components are associated with coronary artery disease risk score in free-living adults: a cross-sectional study, Diabetol Metab Syndr 2011;3:7.
4. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med 1999;131:7-13.
5. Tom M Palmer, Børge G Nordestgaard, Marianne Benn, Anne Tybjærg-Hansen, George Davey Smith, Debbie A Lawlor, Nicholas J TimpsonAssociation of plasma uric acid with ischaemic heart disease and blood pressure: mendelian randomisation analysis of two large cohorts. BMJ 2013;347:f4262.
6. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. Arthritis Rheum. 2011; 63:3136–41.
7. Scott JT. Drug-induced gout. BailliÃ¨re's Clinical Rheumatology 1991;5 (1): 39-60
8. Saavedra WF, Paolocci N, St John ME, et al. Imbalance between xanthine oxidase and nitric oxide synthase signaling pathways underlies mechanoenergetic uncoupling in the failing heart. Circ Res. 2002; 90: 297–304.
9. Fruehwald-Schultes B, Peters A, Kern W, Beyer J, Pfutzner A: Serum leptin is associated with serum uric acid concentrations in humans. Metabolism 1999, 48:677-680.
10. Facchini F, Chen YD, Hollenbeck CB, Reaven GM: Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA 1991; 266: 3008-3011.
11. Erick Prado de Oliveira, Roberto Carlos Burin. High plasma uric acid concentration: causes and consequences. Diabetology & Metabolic Syndrome 2012; 4:12.
12. Yu KH, See LC, Huang YC, Yang CH, Sun JH: Dietary factors associated with hyperuricemia in adults. Semin Arthritis Rheum 2008; 37:243-250.
13. Erick Prado de Oliveira, Fernando Moreto, Liciana Vaz de Arruda Silveira,Roberto Carlos Burin. Dietary, anthropometric, and biochemical determinants of uric acid in free-living adults. Nutrition Journal 2013; 12:11.
14. Bergamini C, Cicoira Mariantonietta, Rossi Andrea, Vassanelli Corrado. Oxidative stress and hyperuricaemia: pathophysiology, clinical relevance, and therapeutic implications in chronic heart failure. Eur J Heart Fail 2009; 11:444-452.
15. Adamopoulos D, Vlassopoulos C, Seitanides B, Contoyiannis.P, Vassilopoulos P. The relationship of sex steroids to uric acid levels in plasma and urine. Acta Endocrinol (Copenh) 1977;85:198-208.
16. Chaves FJ, Corella D, Blesa S, et al. Xanthine oxidoreductase polymorphisms: influence in blood pressure and oxidative stress levels. Pharmacogenet Genomics 2007; 17:589-96.
17. Scott JT. Drug-induced gout. BailliÃ¨re's Clinical Rheumatology 1991; 5(1):39-60.
18. Hoieggen A, Alderman MH, Kjeldsen SE, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int 2004; 65:1041-9.
19. Hink HU, Santanam N, Dikalov S, et al. Peroxidase properties of extracellular superoxide dismutase: role of uric acid in modulating in vivo activity. Arterioscler Thromb Vasc Biol. 2002; 22:1402-1408.
20. Sautin YY, Johnson RJ: Uric acid: the oxidant-antioxidant paradox. Nucleosides Nucleotides Nucleic Acids 2008; 27:608-619 Corry DB, Eslami P, Yamamoto K, et al. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. J Hypertens 2008; 26:269-75.
21. Terada LS, Guidot DM, Leff JA, et al. Hypoxia injures endothelial cells by increasing endogenous xanthine oxidase activity. Proc Natl Acad Sci U S A. 1992; 89:3362-3366.
22. Nieto FJ, Iribarren C, Gross MD et al – UA and serum antioxidant capacity: a reaction to atherosclerosis? Atherosclerosis 2000; 148:131-139.
23. Yu Wang and Xiaorong Bao Effects of uric acid on endothelial dysfunction in early chronic kidney disease and its mechanisms. European Journal of Medical Research 2013; 18:26.
24. Kanellis J, Kang DH: Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. Semin Nephrol 2005; 25:39-42.
25. Ruggiero C, Cherubini A, Ble A, et al. Uric acid and inflammatory markers. Eur Heart J 2006; 27:1174-81.
26. Kim SY, Guvara JP, Kim KM, et al. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2010; 62:170-8.
27. Sandip K Zalawadiya, Vikas Veeranna, Sagar Mallikethi-Reddy, Chirag Bavishi, Abhishekh Lunagaria, Anupama Kottam, Luis Afonso. Uric acid and cardiovascular disease risk reclassification: findings from NHANES III. European Journal of Preventive Cardiology January 15, 2014 2047487313519346.
28. Lonneke V. Franse, Marco Pahor, Mauro Di Bari, Ronald I. Shorr, Jim Y. Wan, Grant W. Somes and William B. Applegate Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). J Hypertens 2000; 18:1149-1154.
29. The Osaka Health Survey. Yuki Taniguchi, Tomoshige Hayashi, Kei Tsumura, Ginji Endo, Satoru Fujii and Kunio Okada Serum uric acid and the risk for hypertension and Type 2 diabetes in Japanese men. Journal of Hypertension 2001; 19:1209-1215.
30. Tamariz L, Harzand A, Palacio A, et al. Uric acid as a predictor of all-cause mortality in heart failure: a meta-analysis. Congest Heart Fail 2011; 17:25-30.
31. Saugstad OD. Role of xanthine oxidase and its inhibitor in hypoxia: reoxygenation injury. Pediatrics. 1996; 98:103-107.
32. Charlat MI, O'Neill PG, Egan JM, et al. Evidence for a pathogenetic role of xanthine oxidase in the "stunned" myocardium. Am J Physiol. 1987; 252:H566-H577.
33. Watanabe S, Kang DH, Feng L, et al. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. Hypertension. 2002; 40:355-360.
34. Leyva F, Anker SD, Godsland IF, et al. UA in chronic HF: a marker of chronic inflammation. Eur Heart J. 1998; 19:1814-22.
35. Eswar Krishnan, Ali Hariri, Omar Dabbous, Bhavik J. Pandya. Hyperuricemia and the Echocardiographic Measures of Myocardial Dysfunction. Congestive Heart Failure 2012; 3(18):138-143.
36. Minhas KM, Saraiva RM, Schuleri KH, et al. Xanthine oxidoreductase inhibition causes reverse remodeling in rats with dilated cardiomyopathy. Circulation research 2006; 98:271-9.
37. Cappola TP, Kass DA, Nelson GS, et al. Allopurinol improves myocardial efficiency in patients with idiopathic dilated cardiomyopathy. Circulation. 2001; 104:2407-2411.
38. Barouch LA, Harrison RW, Skaf MW, et al. Nitric oxide regulates the heart by spatial confinement of nitric oxide synthase isoforms. Nature. 2002; 416:337-340.
39. Pérez NG, Gao WD, Marbán E. Novel myofilament calcium-sensitizing property of xanthine oxidase inhibitors. Circ Res. 1998; 83:423-430.

40. Hernan Alcaino, Douglas Greig, Mario Chionga, Hugo Verdejo et al. Serum uric acid correlates with extracellular superoxide dismutase activity in patients with chronic heart failure. European Journal of Heart Failure 10 (2008) 646-651.
41. Dalila B. Corrya, Pirooz Eslamib, Kei Yamamotob, Michael D. Nybyb, Hirofumi Makinob, and Michael L. Tuckb, Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin–angiotensin system. Journal of Hypertension 2008; 26:269-275.
42. Doehner W, Rauchhaus M, Florea VG, Sharma R, Bolger AP, Davos, CH, Coats AJS, Anker SD. Uric acid in cachectic and non-cachectic CHF patients - relation to leg vascular resistance. Am Heart J. 2001; 141:792-799
43. Stefan D. Anker, Wolfram Doehner, Mathias Rauchhaus, Rakesh Sharma et al.Uric Acid and Survival in Chronic Heart Failure.Validation and Application in Metabolic, Functional, and Hemodynamic Staging. Circulation. 2003; 107:1991-1997
44. Thanassoulis G, Brophy JM, Richard H, Pilote L. Gout, allopurinol use, and heart failure outcomes. Arch Intern Med. 2010; 170:1358-64.
45. Anker S, Doehner W, Rauchaus M, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation. 2003; 107:1991-1997.
46. Harzand A, Tamariz L, Hare JM. Uric acid, heart failure survival, and the impact of xanthine oxidase inhibition. Congest Heart Fail. 2012; 18:179-82.
47. Hare JM, Mangal B, Brown J, et al. Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. J Am Coll Cardiol 2008; 51:2301-975
48. Doehner W, Schoene N, Rauchhaus M, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. Circulation 2002; 105:2619-24.
49. Duşceac D, Ilieşiu A, Câmpeanu A, Uscoiu Gabriela, Cristea A, Marta DS, Moldoveanu E. "Efectele alopurinolului in doze mari asupra disfuncţiei endoteliale, acidului uric seric, stresului oxidativ si inflamatiei în insuficienţa cardiacă cronica". Medicina moderna, 2013; vol. XX(1):7-12, ISSN:1223-0472;
50. Cappola TP, Kass DA, Nelson GS, et al. Allopurinol improves myocardial efficiency in patients with idiopathic dilated cardiomyopathy. Circulation 2001; 104:2407-11.
51. Minhas KM, Saraiva RM, Schuleri KH, et al. Xanthine oxidoreductase inhibition causes reverse remodeling in rats with dilated cardiomyopathy. Circulation research 2006; 98:271-9.
52. Uscoiu Gabriela, Câmpeanu A, Ilieşiu A,Duşceac D, Cristea A. "Efectele allopurinolului în doze mari asupra acidului uric seric şi funcţiei cardiace în insuficienţa cardiacă". Medicina moderna, 2013; vol. XX(3), ISSN:1223-0472;
53. Greig D, Alcaino H, Castro PF, Garcia L, Verdejo HE, Navarro M et al (2011) Xanthine-oxidase inhibitors and statins in chronic heart failure: effects on vascular and functional parameters. J Heart Lung Transplant 30(4):408-413.
54. Hare JM, Mangal B, Brown J, et al. Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. J Am Coll Cardiol 2008; 51:2301-9. 75.
55. Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincon A, et al. Effect of allopurinol in chronic kidney diseas e progression and cardiovascular risk. Clin J Am Soc Nephrol 2010; 5:1388-93.
56. Wei L, Mackenzie IS, Chen Y, Struthers AD, MacDonald TM (2011) Impact of allopurinol use on urate concentration and cardiovascular outcome. Br J Clin Pharmacol 71(4):600-607.
57. Harzand A, Tamariz L, Hare JM. Uric acid, heart failure survival, and the impact of xanthine oxidase inhibition. Congest Heart Fail 2012; 18:179-82.
58. Anker S, Doehner W, Rauchaus M, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation. 2003; 107:1991-1997.