

# Allopurinol, is the Next General Drug for Chronic Heart Failure? A Review Based on 19 Clinical Trials

Yan Chen<sup>1\*</sup>, Wei Zhu<sup>5\*</sup>, Ting Jiang<sup>1</sup>, Weiwei Wang<sup>1</sup>, Chunyu Li<sup>1</sup>, Baoli Zhu<sup>2</sup>, Bing Gu<sup>3</sup>, Jinsong Zhang<sup>1</sup> and Zhijun Han<sup>4</sup>

<sup>1</sup>Emergency Center, The First Affiliated Hospital of Nanjing Medical University, China

<sup>2</sup>Institute of Occupational Disease Prevention and Treatment, Jiangsu Provincial Center for Disease Prevention and Control, China

<sup>3</sup>Department of Laboratory Medicine, The Affiliated Hospital of Xuzhou Medical College, China

<sup>4</sup>Department of Laboratory Medicine, Wuxi Second People's Hospital of Nanjing Medical University, China

<sup>5</sup>Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, China

## Abstract

**Introduction:** Allopurinol, a xanthine oxidase inhibitor, has been reported to have therapeutic value in patients with chronic heart failure, besides its routine effect of decreasing uric acid level.

**Objective:** To better understand the evidence of the treatment effects with allopurinol in patients with chronic heart failure.

**Methods:** We searched Pubmed for clinical trials published between January 2001 and November 2014, based on which, a review was performed to determine whether allopurinol could benefit patients with chronic heart failure. Information of patient characteristics, treatment administration and main evaluation end-points was taken into consideration when assessing the therapeutic effects.

**Results:** Out of 18 articles, 19 clinical trials were included. In most studies, the relevant signs, symptoms, laboratory and other special tests of chronic heart failure were observed to change better with the treatment of allopurinol, yet they failed to draw definite conclusions as the existence of some negative ones affected the consistency of the results.

**Conclusion:** Allopurinol is ought to be helpful to patients with chronic heart failure. But more high-quality studies are required for its better use.

**Keywords:** Chronic heart failure; Allopurinol; Xanthine oxidase; Uric acid, Clinical trial

**Abbreviations:** BNP: B-type Natriuretic Peptide; NT-proBNP: N-Terminal pro-Brain Natriuretic Peptide; CHF: Chronic Heart Failure; NYHA: New York Heart Association; UA: Uric Acid; XO: Xanthine Oxidase

## Introduction

Chronic heart failure is a typically heterogeneous syndrome in which abnormalities of cardiac structure and function are in charge of the impaired ability of the heart to pump blood. The syndrome is characterized by signs and symptoms of intravascular and interstitial volume overload (dyspnea, edema) or manifestations of inadequate tissue perfusion (impaired exercise tolerance, fatigue, renal dysfunction), or both. As a common end stage of various cardiovascular diseases such as heart valve disease, coronary artery disease, hypertension, chronic lung disease, CHF has been one of the leading causes of death and a significant health burden worldwide. Based on an epidemiological investigation, the global number of HF patients has approached to 23 million, which is still increasing at an annual rate of 2 million. In China, according to a recent survey in 2003, the number of adult patients with heart failure was 4 million, estimated with a prevalence of 0.9% [1]. Though its treatments have been revolutionized over the last two decades, the 5-year survival rate of patients with chronic heart failure is comparable to that of cancer patients.

Uric acid is the final product of purine metabolism. And xanthine oxidase is the important enzyme in the metabolic process that catalyzes the oxidation of hypoxanthine to xanthine and uric acid. The balance between the breakdown of purines and the rate of UA excretion controls the level of serum UA in the body, and if broken, it may cause hyperuricemia and gout attack. To manage gout and conditions

associated with hyperuricemia, allopurinol, a well-known inhibitor of XO, has been widely used in the clinical for several decades. But since the first introduction of the association between serum UA and cardiovascular diseases in 1951, a number of epidemiologic studies have indicated that serum uric acid levels have negligible relationships with many diseases, such as coronary artery disease [2], hypertension [3,4], kidney disease [5], metabolic syndrome [4], Parkinson's Disease [6] and preeclampsia [7]. As a result, a burst of clinical research activities has been prompted to determine whether allopurinol could serve as a possible choice for CHF treatment, just described as "A old drug with new tricks".

Apart from the fact that allopurinol had reached positive results in animal models of cardiovascular diseases, allopurinol has also shown significant therapeutic values other than lowering uric acid in clinical studies of chronic heart failure. However, the mechanism of allopurinol in human chronic heart failure hasn't been fully understood. Thus, the purpose of this review was to comprehensively analyze and evaluate the current evidence of allopurinol treatment effects in CHF patients, hoping to find something special to help the clinic.

**\*Corresponding author:** Yan Chen, Emergency Center, The First Affiliated Hospital of Nanjing Medical University, China, Tel: +86 25 8686 2618; E-mail: [chenyandoc@163.com](mailto:chenyandoc@163.com)

**Received** March 30, 2015; **Accepted** April 13, 2015; **Published** April 20, 2015

**Citation:** Chen Y, Zhu W, Jiang T, Wang W, Li C, et al. (2015) Allopurinol, is the Next General Drug for Chronic Heart Failure? A Review Based on 19 Clinical Trials. Pharm Anal Acta 6: 360. doi:10.4172/2153-2435.1000360

**Copyright:** © 2015 Chen Y, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

## Methods

### Identification of eligible studies

Pubmed was searched using the following search strategies (last search was updated on December 2, 2014): “allopurinol” AND “heart failure”, “xanthine oxidase inhibitor” and “heart failure”. In addition, more searches were carried out with the search terms as “allopurinol” and “cardiomyopathy” and “xanthine oxidase inhibitor” and “cardiomyopathy”. No limitations were made in case of any omissions. ClinicalTrials.gov website, a registry and results database of publicly as well as privately supported clinical studies of human participants conducted all over the world, was also necessary to be reviewed for valuable information. All relevant publications were also examined and duplications of articles were eliminated. What's more, the investigators hand-searched the articles in the reference lists for potentially related publications. The search was conducted individually by two investigators. Any disagreements were resolved by discussion or consensus with the involvement of the third author.

### Inclusion and exclusion criteria

All human-associated studies, regardless of the CHF etiologies, were included once they met the criteria below: age  $\geq 18$  years, monotherapy with allopurinol or combined therapy with other drugs (besides the regular therapies), and sufficient data of clinical outcomes. Relevant exclusion criteria were listed as follows: patients currently suffered from chronic kidney disease, stroke, gout attack or any other acute diseases; any recent cardiac surgeries involving coronary artery bypass grafts and percutaneous coronary intervention; full texts unable to obtain. What's more, studies focusing on the changes of cardiac function among patients with diabetes, or the long-term effect of allopurinol on mortality and cardiovascular hospitalizations, were also removed to guarantee the quality.

### Date extraction

Two investigators extracted the relevant data independently to prevent possible unintentional errors. All items had reached a consensus before analysis. For each study, the following information was collected: first author, year of publication, country of the first author, the number of total and evaluated patients, median age, gender, New York Heart Association classification, etiologies of CHF, names of allopurinol or other combined drugs, dose regimen, administration time as well as clinical evaluation end-points.

## Results

### Literature search

The process of literature search and evaluation was roughly reflected in Figure 1. According to the search details, a total of 458 published articles were selected, 200 of which were excluded because of duplicates. Then, 27 reviews and 193 non-clinical trials were removed through reviewing the titles and abstracts. Among the remaining clinical trials, 13 focused on infants or other unrelated diseases, five aimed to determine the role of allopurinol in cardiac surgeries; one trial hadn't been finished yet. Moreover, there were three articles depending on a same trial, and as one was completely contained in another, the rest two were taken into analysis. Besides, two articles both reported double separated clinical trials, but one was ruled out owing to nonuse of any XO inhibitors. Thus, there were finally 18 articles, 19 clinical trials satisfying the inclusion criteria. It was important to mention that there were two studies conducted among angina patients that were reserved on account of the close connection with CHF. Due to

the irreversible heterogeneity of patients, primary diseases, regimens, clinical settings and various outcome measurements used in these trials, pooling of data for meta-analysis was inappropriate. Results were, therefore, summarized qualitatively.

### Study characteristics

Details from the 19 eligible trials published between 2001 and 2013 were listed in Table 1. Within the countries of first authors, UK was undoubtedly on the top with seven trials, followed by Germany with four, USA and Greece with two both, and there was one each from Chile, Egypt, Turkey and China. The numbers of recruited volunteers ranged from 9 to 80, with the median ages from 46 to 69.7 years. The numbers of male and female were obviously unbalanced, which reached consensus in all data-provided trials. And the New York Heart Association functional classification of patients covered all four classifications with the middle two class accounted for about 80% of the given data. Besides, details of the etiologies of CHF were not completely given, which, as seen, consisted of ischemic and non-ischemic heart diseases, such as dilated cardiomyopathy, valvular heart diseases, and so on.

### Treatment administration

Details of eligible trials with monotherapy or combination therapy of allopurinol were summarized in Table 2. Whether or not to accept the allopurinol treatment, all enrolled patients continued their original medication therapies, for example, angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), beta-blocker, diuretic, aspirin. Among the 14 placebo-controlled monotherapeutic trials with relevant information provided, except one that infused 400 mg oxypurinol into the femoral vein at a rate as 26 mg/min [8], all tested allopurinol as the kind of xanthine oxidase inhibitors, though different dosage regimens and periods of administration were applied. There were three trials that allopurinol was particularly administered intravenously, in one of which the drug was directly intracoronary infused with a gradual increase in concentration [9], while the other two were distinguished because of the different doses, one-time injection of 300 mg [10] or persistent coinfusion with acetylcholine or nitroglycerin at a rate of 600  $\mu\text{g}/\text{min}$  [11]. In one else study, the daily dose of allopurinol depended upon the value of creatinine, as 300 mg/d or 100 mg/d if blood creatinine  $> 150 \mu\text{mol}/\text{L}$  or  $< 150 \mu\text{mol}/\text{L}$ , respectively [12]. Besides, six of the rest seven CHF-associated studies adopted a routine dose at 300 mg/d with a period ranged from more than one week to 36 weeks, and the does was doubled in the left one trial. And for the studies concentrated on stable angina [13,14] the therapeutic regimens of allopurinol were 600 mg/d for 6 weeks in one,

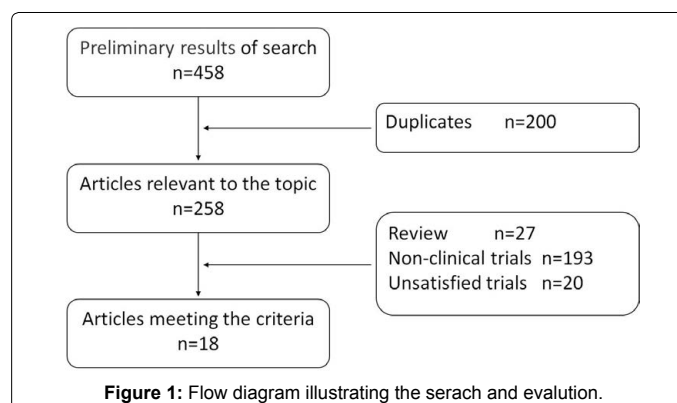


Figure 1: Flow diagram illustrating the search and evaluation.

Trial	Publication information			Patient characteristics				Diseases ( Etiology)
	Author	Year	Country	Total number	average age (years)	Gender (M/F)	NYHA FC (I/II/III/IV)	
1	Abdullah et al.	2001	UK	19(16 <sup>s</sup> )	67	13/3	0/9/5/2	IHD, DCM
2	Thomas et al.	2001	USA	9	46	7/2	1/2/5/1	IDCM
3	Colin et al.	2002	UK	11	67.5	10/1	0/6/5/0	CAD
4	Wolfram et al.	2002	Germany	19	57.2	19/0	-	ICM, DCM
5				15(14 <sup>s</sup> )	68.4	15/0	-	ICM, DCM
6	Gavin et al.	2004	UK	50(43 <sup>s</sup> )	67	34/9	0/31/12/0	IHD, CM, VHD, et al.
7	Jacob et al.	2006	UK	30(29 <sup>s</sup> )	69.7	25/5	0/18/12/0	IHD
8	Stephan et al.	2006	Germany	26	65.3	25/1	0/0/14/6	ICM
9	Dimitris et al.	2010	Greece	42	67	39/3	0/35/7/0	IHD, NIHD
10	Douglas et al.	2010	Chile	74	59.5	61/13	0/41/31/2	IHD, IDCM, et al.
11 <sup>#</sup>	Gamela et al.	2010	Egypt	79	-	-	0/ - / - /0	IHD, IDCM
12 <sup>#</sup>	S von Haehling	2010	Germany	16	68	-	0/10/5/1	IHD, NIHD
13	Dimitris et al.	2011	Greece	60	65.3	55/5	0/49/11/0	IHD, NIHD
14	Dogan et al.	2012	Turkey	42(39 <sup>s</sup> )	-	25/14	- / - / - /0	IDCM
15	Glenn et al.	2012	USA	16(13 <sup>s</sup> )	47.8	9/4	0/10/3/0	NICM
16	Chao Liu et al.	2013	China	34	50.2	30/4	0/0/5/29	CAD, IDCM
17	Sushma et al.	2013	UK	66(60 <sup>s</sup> )	64.5	54/6	-	IHD
18 <sup>*</sup>	Awsan et al.	2010	UK	65(60 <sup>s</sup> )	64.6	50/10	9/42/9/0	CAD
19 <sup>*</sup>	Narasimharajapura et al.	2011	UK	80	65.5	64/16	-	CAD

# Healthy individuals as control

\$ The number of patients eligible for the assessment of clinical outcomes

\* Angina was the study object

- No related information was provided.

et al.. Not all etiologies were provided.

ACM: alcoholic cardiomyopathy; CAD: coronary artery disease; CM: cardiomyopathy; DCM: dilated cardiomyopathy; ICM: ischemic cardiomyopathy; IDCM: idiopathic dilated cardiomyopathy; IHD: ischemic heart disease; NICM: non-ischemic cardiomyopathy; VHD: valvular heart disease

**Table 1:** Characteristics of the included clinical trials.

and 300 mg/d for 4 weeks followed by 600 mg/d for 4 weeks in the other. As for the three trials [15-17] controlled with other drugs and the only trial [17] with combined treatment, allopurinol was used at the routine dose and lasted for 4 weeks. What's more, in addition to the specially noted routes of administration, allopurinol was regarded as taken orally.

### Evaluation end-points

The primary and secondary end-points to evaluate the therapeutic values of allopurinol were various in the included clinical trials, just as given in Tables 2 and 3. Similarly, P value < 0.5 was considered statistically significant in all studies.

There were two studies that focused on myocardial energy metabolism, although its abnormalities had been observed in nearly all experimental models and patients of HF. In one trial [10], intravenously administered allopurinol was discovered to improve the myocardial high-energy phosphates and adenosine triphosphate (ATP) energy flux through CK in falling hearts but not for ischemia, assessed by a noninvasive method as <sup>31</sup>P magnetic resonance spectroscopy (MRS). And the other study showed that the oxygen cost of left ventricular (LV) contraction was decreased due to the short-term therapy of allopurinol [9].

Completely different from above, endothelial function improvement benefited from allopurinol attracted great attention to itself, that 9 clinical trials chose it as an end-point was an evidence [11,14,16,18,19-22]. Among these studies, endothelial function was directly evaluated by Forearm blood flow (FBF) or Flow-mediated dilation (FMD). Despite of the diverse etiologies and treatment regimens, all results came out

with statistically significant improvements in endothelial function. However, opposite conclusions appeared when further analysis was done, particularly with respect to the correlation between dose and effect. Jacob et al. identified that only high-dose allopurinol improved endothelial dysfunction in CHF [20], while Colin et al. indicated that low-dose allopurinol also contributed to the improvement of endothelium-dependent vasodilation [19]. Moreover, the endothelial function was indirectly evaluated through the number of circulating Endothelial progenitor cells (EPCs) which was significantly increased by statin but not allopurinol [9], and Augmentation index (Alx) that improved significantly with allopurinol [14,22].

As an important factor leading to endothelial dysfunction, oxidative stress markers appeared in the end-points as well. Among the patients undergoing treatments with allopurinol, the levels of plasma Malondialdehyde (MDA), extracellular superoxide dismutase (ecSOD) activity, allantoin, appeared to significantly reduced [18,19,21]. Furthermore, biomarkers of adaptive heart remodeling, Matrix metalloproteinases (MMPs) and Tissue inhibitors of metalloproteinases (TIMMPs), were evaluated without notable changes [15,18].

There were seven studies concentrated on the changes in B-type natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) before and after treatment. Except one that failed to find any difference [20], reductions of BNP as well as NT-proBNP caused by allopurinol were observed among the remaining studies, although two changes included fell short of statistically significance [14,17]. Additionally, a series of other parameters were monitored at the same time, for example, hemodynamic indicators (heart rate, blood pressure) and laboratory tests (uric acid, urea, creatinine (Cr),

Trial	Treatment administration			Main evaluation end-points
	Drugs	Dose regimen	Duration	
1	Allopurinol vs placebo	300mg/d (creatinine<150mmol/L) 100mg/d(creatinine>150mmol/L)	2 months	Heart rate variability(HRV), arrhythmia
2	Allopurinol	0.5, 1.0, 1.5ug/min each for 15 minutes*	45 minutes	Left ventricular efficiency, hemodynamic measurements
3	Allopurinol vs placebo	300mg/d	1 month	Endothelial function, oxidase stress, hemodynamic measurements
4	Allopurinol vs placebo	600ug/min**	-	Endothelial function, biochemical parameters
5	Allopurinol vs placebo	300mg/d	≥7 days	Endothelial function, oxidase stress, biochemical parameters
6	Allopurinol vs placebo	300mg/d	3 months	BNP, exercise capacity, biochemical parameters
7	Allopurinol vs placebo	300mg/d 600mg/d	1 month	Endothelial function, BNP, biochemical parameters
8	oxypurinol vs glucose	400mg**	15 minutes	Left ventricular function, biochemical parameters
9	Allopurinol vs rosuvastatin	Allo: 300mg/d Rosu: 10mg/d	1 month	Heart remodeling, NT-pro BNP
10	Allopurinol + atorvastatin vs placebo + atorvastatin	Allo: 300mg/d Ator: 20mg/d	4 weeks	Endothelial function, oxidase stress, heart remodeling, exercise capacity
11	Allopurinol	300mg/d	36 weeks	Left myocardial function, biochemical parameters
12	Allopurinol	-	-	Endothelial function, oxidase stress, hemodynamic measurements
13	Allopurinol vs rosuvastatin vs placebo	Allo: 300mg/d Rosu: 10 mg/d	1 month	Endothelial function, myeloperoxidase(MPO), NT-pro BNP, biochemical parameters
14	Allopurinol	300mg/d(only for the elevated UA)	3 months	Left ventricular function, coronary microvascular function
15	Allopurinol vs placebo	300mg**	-	Myocardial energy metabolism, hemodynamic measurements
16	Allopurinol vs prednisone	Allo: 300mg/d Pred: 1mg/kg/d	4 weeks	NT-proBNP, NYHA functional class, biochemical parameters
17	Allopurinol vs placebo	600mg/d	9 months	Left ventricular mass, endothelial function
18	Allopurinol vs placebo	600mg/d	6 weeks	BNP, exercise capacity, biochemical parameters
19	Allopurinol vs placebo	300mg/d 4W + 600mg/d 4W	8 weeks	Endothelial function, oxidase stress, BNP, biochemical parameters

\*Allopurinol was administered directly into the left coronary artery. \*\*Allopurinol was administered through intravenous injection - No related information was provided.  
BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide

Table 2: Treatment administration and clinical outcomes of the studies.

cholesterol, low- and high-density lipoprotein (LDL, HDL), C-reactive protein (CRP). As would be expected, the levels of UA decreased significantly after treatments in most UA-measured studies, and the only negative one was highly because of the one-time administration [18]. Whereas, rarely notable changes were reported on hepatic, renal, thyroid function and hemodynamic indicators, which suggested that allopurinol was a safe medicine without significant adverse effects.

Left myocardial dysfunction, the most common pathogenic mechanism in CHF, was taken into account to evaluate the therapeutic effects in a total of four trials. And disappointedly, allopurinol was failed to significantly improve the Left ventricular ejection fraction (LVEF) in either of the two studies [23,24], despite the fact that the average of LVEF increased slightly. However, high-dose allopurinol was discovered to regress LV hypertrophy (LVH) and reduce LV end-systolic volumes in patients with IHD [22]. Moreover, Stephan et al. demonstrated that oxypurinol did improve LV function in individuals with ICM, owing to a reduction in end-systolic volumes and an increase in LVEF [18]. Arrhythmia was also common in patients suffering from CHF, but no significant change was found after allopurinol treatment [12].

Apart from all described above, some important indicators with subjective assessment were also tested. New York heart association (NYHA) functional class was one of the most widely-used ones, which changed for the better in allopurinol-treated CHF patients in the clinical trial conducted by Chao Liu et al. [17]. Exercise tolerance, assessed by 6 Minute walk test (6MWT), modified Bruce exercise protocol, total exercise time or time to symptoms, was likely to improve due to the use of allopurinol, as two positive and one negative outcomes were presented [13,17,18]. Particularly, the Minnesota living with heart failure questionnaire was surveyed in one study but no special change occurred with allopurinol.

## Discussion

Chronic heart failure is a clinical symptom diagnosed by a careful history and physical examination and characterized by increased vasoconstriction and a reduced vasodilator response during exercise. Xanthine oxidase is the key to catalyze the oxidation of hypoxanthine to xanthine and uric acid, which controls the level of UA and is the main source of oxygen free radicals formation. Excessive oxygen free radicals may cause oxidative damage, resulting in impaired endothelium dependent vasodilator capacity via scavenging and premature degradation of endothelium derived Nitric oxide (NO) to peroxynitrate. In the end, cardiac dysfunction and impaired tissue perfusion occur. As a result, some interesting and meaningful discoveries have been found from researches about xanthine oxidase, uric acid and chronic heart failure in the past decade. One important was the solid evidence that uric acid was an independent predictor of cardiovascular outcomes. Moreover, in 2012 Israel et al. demonstrated that increased UA levels and an increase in UA during follow-up were independent predictors of increased morbidity and mortality in patients with CHF [25]. And a newly published study suggested that serum UA level was commonly elevated in patients hospitalized for worsening chronic heart failure and reduced ejection fraction, especially in men and blacks [26]. Furthermore, a double-blind placebo-controlled crossover preliminary study especially suggested that it was upregulated XO activity rather than UA itself that actively involved in hemodynamic impairment in CHF [27].

Allopurinol is a traditional agent serving as the cornerstone therapy for hyperuricemia with the ability to inhibit the key enzyme for uric acid formation (Figure 2). When oxidized by xanthine oxidase, allopurinol forms the active metabolite oxypurinol, which is also a XO inhibitor. In the past, two clinical studies drew similar conclusions

Trial	Main evaluation end-points	Specific parameters
1	Heart rate variability(HRV), arrhythmia	SDNN, SDANN, SDNNi, rMSSD, TI
2	Left ventricular efficiency, hemodynamic measurements	MVO <sub>2</sub> , dP/dtmax, SW, dP/dtmax/MVO <sub>2</sub> , SW/MVO <sub>2</sub> , heart rate, blood pressure
3	Endothelial function, oxidase stress, hemodynamic measurements	FBF, plasma MDA, blood pressure
4	Endothelial function, biochemical parameters	endothelium-dependent vasodilator capacity, creatinine, heart rate, blood pressure
5	Endothelial function, oxidase stress, biochemical parameters	arms and legs blood flow, allantoin, UA
6	BNP, exercise capacity, biochemical parameters	BNP, 6MWT, cholesterol, UA, creatinine, CRP, blood pressure
7	Endothelial function, BNP, biochemical parameters	FBF, BNP, UA, creatinine, cholesterol, CRP
8	Left ventricular function, biochemical parameters	LVEF, end-systolic and end-diastolic volumes, UA
9	Heart remodeling, NT-pro BNP	MMP-2, MMP-9, TIMP-1, TIMP-2, NT-pro BNP
10	Endothelial function, oxidase stress, heart remodeling, exercise capacity	MDA, ecSOD activity, FDD, MMP-2, MMP-9, TIMP-1, 6MWT, UA
11	Left myocardial function, biochemical parameters	SUA, LVEF, E/A ratio, LVM, Tei index
12	Endothelial function, oxidase stress, hemodynamic measurements	ADMA, FBF, allantoin, UA, heart rate, blood pressure
13	Endothelial function, myeloperoxidase(MPO), NT-pro BNP, biochemical parameters	EPCs, myeloperoxidase(MPO), FMD, NT-pro BNP, UA, CRP, ox-LDL
14	Left ventricular function, coronary microvascular function	LVEF, coronary flow reserve, UA
15	Myocardial energy metabolism, hemodynamic measurements	PCr, PCr/ATP, ADP, CK flux, ΔG <sub>-ATP</sub> , heart rate, blood pressure
16	NT-proBNP, NYHA functional class, biochemical parameters	UA, creatinine, eGFR, daily urine output, NT-proBNP, NYHA functional class
17	Left ventricular mass, endothelial function	LV mass, LV mass index, FMD, Alx
18	BNP, exercise capacity, biochemical parameters	time to ST depression, total exercise time, time to chest pain, BNP, UA, Cr, CRP
19	Endothelial function, oxidase stress, BNP, biochemical parameters	FMD, Alx, UA, creatinine clearance, BNP, ox-LDL

6MWT: 6 minute walk test; ADP: adenosine diphosphate; ATP: adenosine triphosphate; ADMA: asymmetric dimethylarginine; Alx: augmentation index; BNP: B-type natriuretic peptide; CK: creatine kinase; dP/dtmax: peak rate of rise of left ventricular pressure; CRP: C reactive protein; ecSOD: extracellular superoxide dismutase; eGFR: estimated glomerular filtration rate; EPCs: Circulating endothelial progenitor cells; FBF: forearm blood flow; FMD: flow-mediated dilation; FDD: flow-dependent endothelial-mediated vasodilation; ΔG<sub>-ATP</sub>: free energy of adenosine triphosphate hydrolysis; LVEF: left ventricular ejection fraction; MDA: malondialdehyde; MMPs: matrix metalloproteinases; MVO<sub>2</sub>: myocardial oxygen consumption; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; oxLDL: oxidized low-density lipoprotein; PCr: creatine phosphate; rMSSD, root-mean-square of the successive normal sinus RR interval difference; SDANN, standard deviation of the averaged normal sinus RR intervals for all 5 min segments; SDNN, standard deviation of all normal sinus RR intervals over 24 h; SDNNi, mean of the standard deviations of all normal sinus RR intervals for all 5 min segments; Tei index: left ventricular total isovolumic ejection index; TI, triangular index; SW: stroke work; TIMPs: tissue inhibitors of metalloproteinases; UA: uric acid

**Table 3:** Main evaluation end-points and specific parameters of the studies

that long term high-dose allopurinol use had a lower risk of mortality in patients with CHF [28,29]. However, one study indicated that allopurinol did not produce significant clinical and functional improvement in unselected patients with moderate-to-severe heart failure, but it was inapplicable in volunteers with elevated serum UA [23]. Similarly, to some degree, another study published in 2012 reported that treatment with allopurinol was associated with improved survival in CHF patients with evaluated UA [25]. Meanwhile, animal experiments of allopurinol reached satisfactory results. In 2004, a study in a model of experimental myocardial infarction revealed that treatment with allopurinol attenuated LV remodeling processes and dysfunction [30]. Soon afterwards, Jennifer et al. and Virginie et al. both identified that allopurinol could preserve cardiac function, which meant to alter the progression of heart failure, in mouse and rat models, respectively [31,32]. Hence, allopurinol has attracted great attention to the probability to act as a cardiovascular drug in the clinical. And the probability seems to be great, at least from the available evidences now, despite the pre-treatment levels of uric acid and the therapeutic regimens still remain controversial.

As seen in the clinical trials involved, allopurinol is effective for the abnormalities of myocardial energy metabolism. But obviously, more researches are warranted to confirm these results due to the limited researches. As for endothelial dysfunction, there is a growing in evidence suggesting that it plays an important role in the pathogenesis of CHF [33]. The balance of NO and ET released by endothelial cells is broken, causing endothelium-dependent systolic and diastolic dysfunction, which results in increased arterial resistance, myocardial necrosis and fibrosis, cardiac hypertrophy, and finally the pump function is impaired, and the significant symptoms start to appear,

most obviously is the reduced exercise capacity. Moreover, endothelial function influences the long-term cell repair of blood vessels, the preponderant endothelial cell growth factors tend to cause the vessel wall remodeling, resulting in changes in vascular structures. Within this review, endothelial function was reported to be improved statistically significantly with the treatment of allopurinol in most involved studies. However, the doses and routes of administration to take effect were different. There even were totally opposite conclusions from trials with same dose of allopurinol. Some possible reasons were summarized as follows. Firstly, the sizes of samples were not large enough to remove errors. Secondly, the durations of administration as well as follow-up were too short to reflect the comparatively objective effects. Thirdly, conditions of recruited volunteers were different, such as the etiologies of CHF, uric acid levels, other accompanied diseases, medications and so on. Fourthly, from the 19 studies, a phenomenon was observed as allopurinol had more likely to be effective when the patients received high dose or had hyperuricemia, which showed a potential that allopurinol might work with a dose-effect relationship and work easier when XO activity was up-regulated.

Dissimilar to the significant improvements of oxidative stress and endothelial function with allopurinol, the biomarkers of heart remodeling didn't show meaningful changes. This was highly because that all recruited individuals in this review received the regular therapies for CHF at the same time, including Angiotensin converting enzyme inhibitors (ACEI) or Angiotensin receptor blocker(ARB), β blockers, which had been proved to inhibit the ventricular remodeling, as nobody would want to be treated without these drugs. Thus, the therapeutic value of short term allopurinol was hard to reflect on the patients.

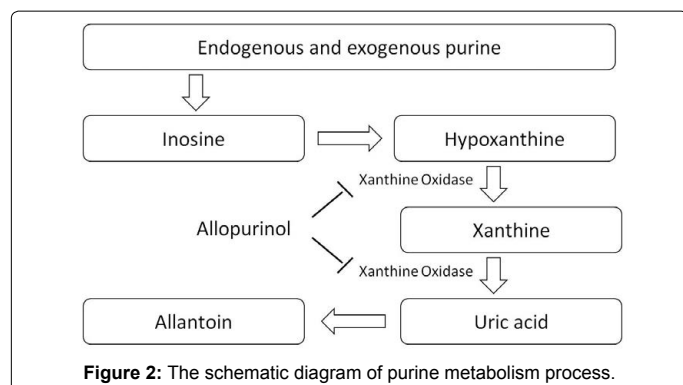


Figure 2: The schematic diagram of purine metabolism process.

BNP, NT-proBNP, LVEF, NYHA functional classification, 6-minute walk test and some other evaluations are most commonly used in the clinic. Indeed, from the included studies, allopurinol was discovered to decrease the levels of BNP as well as NT-proBNP, increase the averages of LVEF, improve the NYHA functional classification and exercise capacity. But the changes in the symptoms and signs haven't reached a consensus, at least regarding the published trials at present. It is true that few studies adopted these end-points. And understandably, compared with the laboratory examinations, the symptoms, signs and other tests are not sensitive enough to reflect small changes caused by allopurinol. It's still probable that the advantages made by allopurinol and other medications may overlap each other, making it difficult to reflect on the specific parameters.

Finally, there are some limitations needed to be mentioned. Till now, most published studies are small and with short follow-up time, large-scale multi-center randomized controlled trials are warranted for the evidence-based medicine. And in part of the studies, patients with different etiologies of CHF were analyzed together, which seemed to accordant with the theory that the pathophysiology processes of chronic heart failure are in common, regardless of various etiologies. Furthermore, since allopurinol is a traditional agent to reduce the high levels of uric acid that don't present in all CHF patients, it's waited to be solved that allopurinol is suitable for all CHF patients or just those accompanied with up-related UA levels. Therefore, researches on each etiologies and different accompanied stations are expected to be conducted to clearly determine the indications of allopurinol. In addition, more clinical indicators commonly used in the clinic, especially recommended in the guidelines for chronic heart failure, are hoped to be evaluated for the efficacy assessments.

## Conclusion

In conclusion, this review provided evidence from 18 clinical trials that took allopurinol as a single-agent and one trial that adopted a combination with atorvastatin. Allopurinol is ought to be effective for chronic heart failure patients, with meaningful changes in signs, symptoms, laboratory and other special tests. But there are still some controversies on the therapeutic regimens and outcomes remaining to be solved. Owing to the limitations, it's a challenge to determine that these differences are meaningful or just some errors. More high-quality studies are needed for the better understanding of the clinical effects of XO inhibitors, which require the efforts of researchers worldwide.

## Acknowledgment

This work was supported by the National Natural Science Foundation of China (NO. 81372035), the Foundation of the Health Department of Jiangsu Province (NO. H201301), the Open Project Program of State Key Laboratory of Natural Medicines, China Pharmaceutical University (No. SKLNMKF201408).

## References

- Gu dong-feng, Huang guang-yong, Tang Q, Chen BD, Gao X, et al. (2003) Investigation of prevalence and distributing feature of chronic heart failure in Chinese adult population. *Chin J Cardiol* 31: 3-6.
- Gazi E, Temiz A, Altun B, Kurt T, Ozcan S, et al. (2014) The association between serum uric acid level and heart failure and mortality in the early period of ST-elevation acute myocardial infarction. *Turk Kardiyol Dern Ars* 42: 501-508.
- Wang J, Qin T, Chen J, Li Y, Wang L, et al. (2014) Hyperuricemia and risk of incident hypertension: a systematic review and meta-analysis of observational studies. *PLoS One* 9: 114259.
- Li LX, Dong XH, Li MF, Shen J, Bao YQ, et al. (2014) Serum uric acid levels are associated with hypertension and metabolic syndrome but not atherosclerosis in Chinese in patients with type 2 diabetes. *J Hypertens* 33: 482-490.
- Chou YC1, Kuan JC, Yang T, Chou WY, Hsieh PC, et al. (2014) Elevated uric acid level as a significant predictor of chronic kidney disease: a cohort study with repeated measurements. *J Nephrol*.
- Qin XL, Zhang QS, Sun L, Hao MW, Hu ZT (2014) Lower Serum Bilirubin and Uric Acid Concentrations in Patients with Parkinson's Disease in China. *Cell Biochem Biophys* 2014.
- Livingston JR, Payne B, Brown M, Roberts JM, Cote AM, et al. (2014) Uric Acid as a predictor of adverse maternal and perinatal outcomes in women hospitalized with preeclampsia. *J Obstet Gynaecol Can* 36: 870-877.
- Baldus S, Mullerleile K, Chumley P, Lund GK, Staude HJ, et al. (2006) Inhibition of xanthine oxidase improves myocardial contractility in patients with ischemic cardiomyopathy. *Free Radic Biol Med* 41: 1282-1288.
- Cappola TP, Kass DA, Nelson GS, Kobeissi ZA, Marban E, et al. (2001) Allopurinol improves myocardial efficiency in patients with idiopathic dilated cardiomyopathy. *Circulation* 104: 2407-2411
- Hirsch GA, Bottomley PA, Gerstenblith G, Weiss RG (2012) Allopurinol acutely increases adenosine triphosphate energy delivery in failing human hearts. *J Am Coll Cardiol* 59: 802-808.
- Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, et al. (2002) 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* 105: 2619-2624.
- Shehab AM, Butler R, MacFadyen RJ, Struthers AD (2001) A placebo-controlled study examining the effect of allopurinol on heart rate variability and dysrhythmia counts in chronic heart failure. *Br J Clin Pharmacol* 51: 329-334.
- Noman A, Ang DS, Ogston S, Lang CC, Struthers AD (2010) Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomized, placebo controlled crossover trial. *Lancet* 375: 2161-2167.
- Rajendra NS, Ireland S, George J, Lang CC, Struthers AD, et al. (2011) Mechanistic insights into the therapeutic use of high-dose allopurinol in angina pectoris. *J Am Coll Cardiol* 58: 820-828.
- Tousoulis D, Andreou I, Tentolouris C, Gounari P, Kotrogiannis I, et al. (2010) Comparative effects of rosuvastatin and allopurinol on circulating levels of matrix metalloproteinases and tissue inhibitors of metalloproteinases in patients with chronic heart failure. *Int J Cardiol* 145: 438-443.
- Tousoulis D, Andreou I, Tsiatas M, Tentolouris C, Siasos G, et al. (2011) Effects of rosuvastatin and allopurinol on circulating endothelial progenitor cells in patients with congestive heart failure: the impact of inflammatory process and oxidative stress. *Atherosclerosis* 214: 151-157.
- Liu C, Zhao Q, Zhen Y, Wang L, Ji L, et al. (2013) Prednisone in Uric Acid lowering in Symptomatic Heart Failure Patients With Hyperuricemia (PUSH-PATH) study. *Can J Cardiol* 29: 1048-1054.
- Greig D, Alcaïno H, Castro PF, Navarro M, Lopez R, et al. (2011) Xanthine-oxidase inhibitors and statins in chronic heart failure: effects on vascular and functional parameters. *J Heart Lung Transplant* 30: 408-413.
- Greig D, Alcaïno H, Castro PF, 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: 408-413.
- George J, Carr E, Davies J, Belch JJ, Struthers A. (2006) High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. *Circulation* 114: 2508-2516.

21. Haehling S, Bode-Böger SM, Martens-Lobenhoffer J, Rauchhaus M, Schefold JC, et al. (2010) Elevated levels of asymmetric dimethylarginine in chronic heart failure: a pathophysiologic link between oxygen radical load and impaired vasodilator capacity and the therapeutic effect of allopurinol. *Clin Pharmacol Ther* 88: 506-512.
22. Rekhraj S, Gandy SJ, Szwejkowski BR, Lang CC, George J, et al. (2013) High-dose allopurinol reduces left ventricular mass in patients with ischemic heart disease. *J Am Coll Cardiol* 61: 926-932.
23. Nasr G, Maurice C. (2010) Allopurinol and global left myocardial function in heart failure patients. *J Cardiovasc Dis Res* 1: 191-195.
24. Erdogan D, Tayyar S, Uysal BA, Ozaydin M, Dogan A, et al. (2012) Effects of allopurinol on coronary microvascular and left ventricular function in patients with idiopathic dilated cardiomyopathy. *Can J Cardiol* 28: 721-727.
25. Gotsman I, Keren A, Lotan C, Zwas DR (2012) Changes in uric acid levels and allopurinol use in chronic heart failure: association with improved survival. *J Card Fail* 18: 694-701.
26. Vaduganathan M, Greene SJ, Ambrosy AP, Maggioni AP, Swedberg K, et al. (2014) Relation of Serum Uric Acid Levels and Outcomes Among Patients Hospitalized for Worsening Heart Failure With Reduced Ejection Fraction (from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan Trial). *Am J Cardiol* 114: 1713-1721.
27. Ogino K, Kato M, Furuse Y, Kinugawa T, Igawa O, et al. (2010) Uric acid-lowering treatment with benzbromarone in patients with heart failure: a double-blind placebo-controlled crossover preliminary study. *Circ Heart Fail*. 3: 73-81.
28. Struthers AD, Donnan PT, Lindsay P, McNaughton D, Broomhall J, et al. (2002) Effect of allopurinol on mortality and hospitalisations in chronic heart failure: a retrospective cohort study. *Heart* 87: 229-34.
29. Wei L, Fahey T, Struthers AD, MacDonald TM. (2009) Association between allopurinol and mortality in heart failure patients: a long-term follow-up study. *Int J Clin Pract* 63: 1327-1333.
30. Engberding N, Spiekermann S, Schaefer A, Hilfiker-Kleiner D, Hornig B, et al. (2004) Allopurinol attenuates left ventricular remodeling and dysfunction after experimental myocardial infarction: a new action for an old drug? *Circulation* 110: 2175-2179.
31. Duncan JG, Ravi R, Stull LB, Murphy AM (2005) Chronic xanthine oxidase inhibition prevents myofibrillar protein oxidation and preserves cardiac function in a transgenic mouse model of cardiomyopathy. *Am J Physiol Heart Circ Physiol* 289: 1512-1518.
32. Mellin V, Isabelle M, Oudot A, Monteil C, Di Meglio B, et al. (2005) Transient reduction in myocardial free oxygen radical levels is involved in the improved cardiac function and structure after long-term allopurinol treatment initiated in established chronic heart failure. *Eur Heart J* 26: 1544-1550.
33. Berezin AE, Kremzer AA, Samura TA, Martovitskaya YV (2014) Circulating endothelial-derived apoptotic microparticles in the patients with ischemic symptomatic chronic heart failure: relevance of pro-inflammatory activation and outcomes. *Int Cardiovasc Res J* 8: 116-23.