Advances in Heart Failure

Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients
Design and Rationale of the EXACT-HF Study

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According to the most recent National Health and Nutrition Examination Survey, an estimated 5.1 million adult Americans have heart failure (HF), and projections show that by the year 2030 the prevalence of HF in the United States will increase by 25%. Despite guideline-recommended therapy for patients with HF and reduced ejection fraction, the overall 5-year mortality remains ≈50%, and the 1-year mortality in patients with New York Heart Association functional class III to IV HF on maximal medical therapy is 35% to 40%. Given the public health burden of HF, there is a clear need for improved medical therapies.

Oxidant Stress and Progression of HF
Reduced myocardial antioxidant activity and increased oxidant damage have been demonstrated in animal models of HF, and markers of oxidative stress are increased in HF patients. These data support the thesis that reactive oxygen species may contribute to the progression of myocardial failure. Xanthine oxidase (XO) is among the potential stimuli of formation of reactive oxygen species in HF and may be an important target for therapy. Current evidence supports the hypothesis that HF is associated with an increase in the activity of XO, which, in turn, increases production of superoxide and uric acid (UA) during purine metabolism. The resulting nitroso-redox imbalance may be exacerbated by decreased activity of nitric oxide synthase (Figure 1). Significant hyperuricemia (ie, serum UA ≥9.5 mg/dL) is present in ≈25% of patients with HF and reduced ejection fraction. In addition to nitroso-redox imbalance, other contributors to hyperuricemia in HF include activation of proinflammatory cytokines, impaired vascular function, and renal insufficiency, as well as loop diuretic therapy. In patients with HF, there is a strong relationship between elevated UA levels and worsening symptoms, impaired exercise tolerance, and increased mortality. On the basis of these findings, serum UA levels have been included in HF risk scores. Furthermore, observational studies in both chronic and acute HF patients with gout suggest that treatment with allopurinol, an XO inhibitor, is associated with improved survival.

Superoxide decreases nitric oxide signaling and also decreases myofilament sensitivity to calcium and contractility. Decreased contractility leads to hypoperfusion of the heart and other organs, increases anaerobic metabolism, and leads to depletion of ATP and the accumulation of hypoxanthine (the substrate of XO). Allopurinol is a potent XO inhibitor that can reverse these processes, ultimately increasing cardiac contractile efficiency and reducing myocardial oxygen consumption (MVO₂). There are several lines of experimental and clinical data that support the use of XO inhibitors in HF.

Acute XO Inhibition in HF
HF is characterized by an imbalance between left ventricular (LV) performance and MVO₂. Experimental models suggest that oxidant stress resulting from XO activation contributes to mechanoenergetic uncoupling, and that XO inhibition with allopurinol may improve LV efficiency. Cappola et al instrumented patients with idiopathic dilated cardiomyopathy to assess MVO₂, contractility (dP/dt_max and E₉₀), and efficiency (stroke work/MVO₂) before and after intracoronary infusion of allopurinol. Allopurinol caused a significant decrease in MVO₂ (−16±5%; P<0.01) without a parallel decrease in dP/dt_max or E₉₀. The net result was a significant increase in myocardial efficiency (+4±7%; P<0.05). More recently, Hirsch et al used magnetic resonance spectroscopy to determine myocardial concentrations of ATP and the rate of ATP synthesis through creatine kinase flux in vivo. In 16 patients with nonischemic cardiomyopathy, intravenous allopurinol acutely increased myocardial high-energy phosphates and ATP flux, thereby providing a mechanism for the improvement in mechanoenergetic coupling.

Chronic XO Inhibition in HF
Impaired endothelium-dependent relaxation contributes to symptoms and exercise intolerance in HF. An important mechanism underlying endothelial dysfunction is increased...
oxidative stress, in part, because of vascular XO activity. To determine whether chronic XO inhibition would improve endothelial function in HF, Farquharson et al\(^2\) randomized 11 patients with mild to moderate HF in a double-blind, crossover study to receive allopurinol 300 mg once daily or placebo for 1 month. Allopurinol significantly improved endothelium-dependent vasodilation and reduced markers of oxidative stress. In a subsequent study, George et al\(^2\) demonstrated a steep dose–response relationship between allopurinol and its effect on endothelial function. In 30 subjects with chronic HF, allopurinol 600 mg once daily increased forearm blood flow in response to acetylcholine compared to both allopurinol 300 mg once daily and placebo and was well tolerated. Other short-term studies with allopurinol in patients with HF have demonstrated improvements in LV ejection fraction (LVEF),\(^2\) diastolic function, and coronary flow reserve.\(^2\)

**XO Inhibition and Clinical Outcomes in HF**

Oxypurinol is the primary metabolite of allopurinol and, therefore, a potent XO inhibitor. Numerous studies have documented the potential benefits of oxypurinol in experimental and clinical conditions involving oxidative stress. The Oxypurinol Compared With Placebo for Class III to IV New York Heart Association Congestive Heart Failure (OPT-CHF) Trial was designed to test whether oxypurinol produces clinical benefits in patients with moderate to severe HF because of systolic dysfunction receiving optimal medical therapy.\(^2\) In this study, 405 patients with a mean age of 65 years, LVEF of 26%, and UA level of 8.1 mg/dL, who were well treated with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (96%) and β-blocker (92%), were randomized to receive oxypurinol 600 mg once daily or placebo for 24 weeks. Efficacy was assessed using a composite end point comprising HF morbidity, mortality, and quality of life (QOL).\(^2\) Oxypurinol reduced serum UA by ≈2 mg/dL $(P<0.001)$ but did not improve clinical status in unselected patients with HF. In a hypothesis-generating subgroup analysis, patients with elevated UA levels $(>9.5 \text{ mg/dL}; n=108)$ responded favorably to oxypurinol, whereas patients with UA $<9.5 \text{ mg/dL}$ exhibited a trend toward worsening. In addition, UA reduction to oxypurinol correlated with favorable clinical response.

On the basis of these findings, we hypothesize that in patients with symptomatic HF because of LV systolic dysfunction, who have elevated serum UA levels and are not receiving allopurinol for another indication such as gout, treatment with high-dose allopurinol for 24 weeks will improve clinical outcomes compared with placebo treatment. We chose allopurinol over oxypurinol given its wide availability and known safety profile of higher doses.

**Study Design and Patient Population**

The Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) study is a multicenter, randomized (1:1), double-blind, placebo-controlled, 24-week trial of allopurinol in patients with symptomatic HF because of LV systolic dysfunction (LVEF $\leq 40\%$) and elevated serum UA levels $(UA \geq 9.5 \text{ mg/dL})$. The study includes screening, study drug administration, and follow-up phases (Figure 2). A total of 250 patients meeting eligibility criteria (Table 1) will be enrolled in the study. In an effort to enroll a population with an adequate event rate to power a medium-size, proof-of-concept study, patients must have $\geq 1$ additional marker of increased risk, including an acute HF event within 12 months, severe LV dysfunction (LVEF $\leq 40\%$) and elevated serum UA levels $(UA \geq 9.5 \text{ mg/dL})$. The study includes screening, study drug administration, and follow-up phases (Figure 2). A total of 250 patients meeting eligibility criteria (Table 1) will be enrolled in the study. In an effort to enroll a population with an adequate event rate to power a medium-size, proof-of-concept study, patients must have $\geq 1$ additional marker of increased risk, including an acute HF event within 12 months, severe LV dysfunction (LVEF $\leq 40\%$), or an elevated natriuretic peptide level (B-type natriuretic peptide $>250 \text{ pg/mL}$ or N-terminal pro–B-type natriuretic peptide $>1500 \text{ pg/mL}$).\(^2\)

**Active Drug Intervention and Dose Adjustment for Renal Dysfunction**

For patients with gout, allopurinol is typically initiated at a dose of 100 mg once daily and may be titrated to a maximum dose of 800 mg depending on the severity of disease and the target UA level (usual goal $<6.0 \text{ mg/dL}$).\(^2\) The drug is metabolized in the liver to oxypurinol, and the latter is excreted in
the urine. The elimination half-life of oxypurinol is 15 to 25 hours and may be longer in renal failure. Recommendations first proposed in 1984 and maintained in the current allopurinol package insert call for a dose reduction to 200 mg if the estimated glomerular filtration rate is 10 to 20 mL/min and to 100 mg if <10 mL/min. Importantly, EXACT-HF excludes subjects with an estimated glomerular filtration rate of <20 mL/min.

On the basis of this information, active therapy in EXACT-HF consists of allopurinol (target dose, 600 mg daily in divided doses), with dose adjustment for renal function (Table 2). Study drug is given for 24 weeks starting with 300 mg by mouth once daily for 1 week. If that dose is well tolerated, the dose is increased to 600 mg daily for the remaining 23 weeks of the study. Patients unable to tolerate the 600-mg dose are maintained on the 300-mg dose. Patients with a serum creatinine level >2.0 mg/dL at screening are started on 100 mg daily and titrated to 300 mg daily. Patients are instructed to take the study drug with food, and compliance is assessed by phone contact at multiple time points (Figure 2). The rationale for using relatively high doses of allopurinol is based on data reported by George et al showing that allopurinol has dose-dependent effects on both UA lowering and endothelium-dependent vasodilation in patients with HF and is well tolerated (Table 3).

### Table 1. EXACT-HF Inclusion and Selected Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>Age ≥18 y</td>
<td>NYHA functional class II–IV HF because of ischemic or nonischemic cardiomyopathy</td>
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</tr>
<tr>
<td>HF symptoms for 3 mo, despite standard HF treatment with an ACE inhibitor or ARB, and β-blocker (if tolerated)</td>
<td>LVEF ≤40% by echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum UA level ≥9.5 mg/dL†,‡,§</td>
<td>At least one of the following additional markers of increased risk*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization, ER visit, or urgent clinic visit for HF requiring IV diuretics within the previous 12 mo</td>
<td>BNP level &gt;250 pg/mL or NT-proBNP level &gt;1500 pg/mL</td>
<td></td>
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</table>

| Selected exclusion criteria | | | |
| Acute coronary syndrome, PCI, or CABG within 3 mo | VAD or heart transplant likely within the next 6 mo |
| Uncontrolled hypertension (ie, SBP >170 mm Hg or DBP >110 mm Hg) | Serum creatinine >3 mg/dL or estimated GFR <20 mL/min |
| Evidence of active hepatitis with ALT and AST >3× normal | Any condition other than HF which could limit the ability to perform a 6-min walk test (eg, PAD, orthopedic or neurological conditions) |
| Any diseases other than HF which are likely to alter the patient’s global perception of status or quality of life over a period of 6 mo | Receiving treatment with allopurinol currently or within 30 days, or having symptomatic hyperuricemia which requires treatment with allopurinol |

ACE indicates angiotensin-converting enzyme; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; DBP, diastolic blood pressure; ER, emergency room; EXACT-HF, Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients; GFR, glomerular filtration rate; HF, heart failure; IV, intravenous; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; UA, uric acid; and VAD, ventricular assist device.

* Determined at or within 4 wk of screening evaluation.
† Determined at the time of screening evaluation.

### Randomization, Stratification, and Blinding

At the baseline visit, patients who qualify are randomized to treatment using a permuted block randomization scheme stratified by clinical site. Study drug or matching placebo is started within 12 hours of completing the baseline visit. Randomization is performed using an automated web-based system administered by the Data Coordinating Center. Blinding of the study is preserved by the use of matching placebo capsules. Investigators are requested not to measure serum UA levels during the study. Given the well-known safety profile of allopurinol and lack of a specific antidote, it is anticipated that there will be no need to unblind study drug.

### Concomitant HF Medication and Management of Gout

Patients should be receiving a stable treatment regimen for HF for ≥2 weeks before randomization, and in the case of β-blockers for ≥3 months. Regular intermittent use of supplemental diuretic doses (oral or intravenous) is permitted if used.
as part of a regular diuretic treatment regimen at baseline. Patients are excluded if they are taking allopurinol (or oxypurinol) or have taken one of these agents within 30 days of randomization. Patients with a history of gout may enter the trial as long as they are not currently treated with these agents and are unlikely to require these agents during the study. However, it is anticipated that enrollment of hyperuricemic patients with HF will include those at risk for developing gout during the course of the trial. In addition, the initiation of allopurinol itself may precipitate a gout flare. If this occurs and the patient’s physician recommends use of open-label allopurinol (or oxypurinol), study drug will be permanently discontinued and the subject will continue with study visits through 24 weeks.

**Risks of Treatment With Allopurinol**

Allopurinol is a commonly used, Food and Drug Administration–approved medication for the treatment of gout, and chronic treatment is generally safe. The dose being evaluated in this study (600 mg orally in divided doses) is within the current standard of care for patients with gout, although doses used in clinical practice are typically lower, and the side effect profile is well characterized. This dose has also been studied in patients with mild to moderate HF as well as in patients with coronary artery disease and shown to be well tolerated. Uncommon side effects include pruritus (5%), rash (1.5%), nausea or vomiting (1.3%), and renal failure (1.2%). Rare, serious adverse effects (<1%) include Stevens-Johnson syndrome, agranulocytosis, anemia, myelosuppression, and hepatotoxicity.

The allopurinol hypersensitivity syndrome (AHS), which involves progression of skin rash to exfoliative lesions, generalized vasculitis, and irreversible hepatotoxicity, occurs in <0.5% of patients, with a case fatality rate of ≤25%. Risk factors for AHS include renal dysfunction, recent onset allopurinol use, and use in asymptomatic hyperuricemia. The keys to prevention and treatment are early recognition, drug withdrawal, and supportive care. In the event of a new rash, the protocol requires that study drug be held until clinical assessment is made.

**Primary End Point**

The primary end point of EXACT-HF is a composite clinical end point that classifies the subject’s clinical status as improved, worsened, or unchanged at 24 weeks (Table 4), similar to that reported by Packer, with a slight modification as previously described. The classification follows sequential rules on the basis of the outcomes of the following items:

1. Death: All-cause mortality will be used in the composite analysis, and adjudicated as because of HF, other cardiac cause, or noncardiac cause.
2. Hospitalization, emergency room visit, or emergent clinic visit for worsening HF: These events will also be adjudicated as because of HF, other cardiac, or noncardiac cause.
3. Medication change for worsening HF: The investigator must prescribe or concur with (1) the addition of a new drug class for worsening HF, or (2) an increase in diuretic dose or an increase or decrease in β-blocker or renin–angiotensin system inhibitor dose by ≥50% for >1 week. A newly added drug class is defined as the addition of a new pharmacological agent specifically for HF therapy, or generally recognized as effective in the management of HF within current treatment guidelines.
4. Patient global assessment: The 7-point patient global assessment tool asks patients to define their current status relative to baseline as markedly improved, moderately improved, mildly improved, no change, slightly worse, moderately worse, and markedly worse. It will be evaluated at 4, 12, and 24 weeks.

**Secondary End Points**

The principal secondary efficacy criteria in this study include the change in QOL as assessed by the Kansas City Cardiomyopathy Questionnaire and the change in submaximal exercise capacity as assessed by 6-minute walk test, both at 12 and 24 weeks. The Kansas City Cardiomyopathy Questionnaire is a self-administered, 23-item questionnaire developed to provide a better description of health-related QOL in patients with HF. It quantifies physical limitation, symptoms, QOL, social interference and self-efficacy. A clinical summary score is calculated by combining the functional status with the QOL capacity as assessed by 6-minute walk test, both at 12 and 24 weeks.

Because usual daily activities generally require much less than maximal exertion, the measurement of submaximal

**Table 2. Allopurinol Dose Adjustment With Renal Dysfunction**

<table>
<thead>
<tr>
<th>Visit (Time)</th>
<th>SCr ≤2 mg/dL</th>
<th>SCr &gt;2, but ≤3 mg/dL</th>
<th>SCr &gt;3, but &lt;5 mg/dL</th>
<th>SCr ≥5 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (baseline)*</td>
<td>300 mg</td>
<td>100 mg</td>
<td>Excluded</td>
<td>Excluded</td>
</tr>
<tr>
<td>1 (7–10 d)†</td>
<td>600 mg</td>
<td>300 mg</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>2 (4 wk)‡</td>
<td>600 mg</td>
<td>300 mg</td>
<td>100 mg</td>
<td>Discontinue</td>
</tr>
<tr>
<td>4 (12 wk)‡</td>
<td>600 mg</td>
<td>300 mg</td>
<td>100 mg</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

SCR indicates serum creatinine level.
*Screening laboratories used to determine dosing at baseline and visit 1.
†Laboratories are not checked at this visit, which is a telephone call.
‡If renal function improves at visit 2 or 4, subjects remain at established dose (ie, no up-titration).

**Table 3. Rationale for High-Dose Allopurinol in EXACT-HF**

<table>
<thead>
<tr>
<th>Oxyipurinol, mg</th>
<th>Allopurinol, mg</th>
<th>Effect on UA levels</th>
<th>Effect on vascular function</th>
<th>Toxicity</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>600</td>
<td>≈81*</td>
<td>↓ 26%</td>
<td>Mildly improved</td>
<td>Well tolerated</td>
<td>Dose used in OPT-CHF (n=450)</td>
</tr>
<tr>
<td>300</td>
<td></td>
<td>↓ 44%</td>
<td>Moderately improved</td>
<td>Well tolerated</td>
<td>Dose used in vascular study (n=11)</td>
</tr>
<tr>
<td>600</td>
<td></td>
<td>↓ 61%</td>
<td>Markedly improved</td>
<td>Unknown</td>
<td>Dose used in vascular study (n=30)</td>
</tr>
</tbody>
</table>

EXACT-HF indicates Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients; OPT-CHF, Oxyipurinol Compared With Placebo for Class III to IV New York Heart Association Congestive Heart Failure; and UA, uric acid.

*Dose equivalent of oxypurinol 600 mg.
Table 4. Composite Clinical End Point

<table>
<thead>
<tr>
<th>Improved</th>
<th>Worsened</th>
<th>Unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient global assessment moderate or markedly improved</td>
<td>Death</td>
<td>Neither improved or worsened</td>
</tr>
<tr>
<td></td>
<td>Hospitalization, ER visit, or emergent clinic visit for worsening HF</td>
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</tr>
<tr>
<td></td>
<td>Medication change for worsening HF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient global assessment moderate or markedly worse</td>
<td></td>
</tr>
</tbody>
</table>

ER indicates emergency room; and HF, heart failure.

exercise capacity may provide information that is complementary to that provided by maximal exercise testing. The 6-minute walk test is the most common of the fixed-time tests. It is moderately predictive of maximal oxygen consumption and independently predicts morbidity and mortality in HF. Tertiary End Points

Additional parameters that will be assessed for efficacy include New York Heart Association functional class, echocardiographic measures of LV remodeling (LV volumes, stroke volume, ejection fraction, and mass), HF biomarkers (UA, N-terminal pro-B-type natriuretic peptide), measures of renal function (serum creatinine, cystatin C, and estimated glomerular filtration rate), markers of oxidative stress (myeloperoxidase, nitrotyrosine, and allantoin), total number of hospitalizations and hospital days, time to first HF hospitalization, and cardiovascular death. In addition, increased diuretic requirement (defined as an increase in outpatient diuretic dose by ≥50% for >1 week) will be tracked.

Statistical Considerations

All analyses will be conducted using the intention to treat principle with the minor modification as described below. The intention to treat population includes all patients who are randomized. Analysis of the primary efficacy composite clinical end point will use the Cochran–Mantel–Haenszel row mean score test with modified ridit scores to compare the distributions. The study is designed to test whether allopurinol is significantly more effective than placebo in patients with New York Heart Association class II to IV HF and LVEF ≤40% receiving standard background therapy for HF. The test for the superiority of allopurinol versus placebo will be based on a χ² statistic which compares the 2 randomized arms with respect to differences in a linear trend in the proportions of patients that fall into the ordinal categories of the primary end point.

Sample Size and Power Calculation

On the basis of previous data from the OPT-CHF study, which used the same composite end point, it is assumed that the placebo arm will have approximately the following response rates for the primary end point: 33% improved, 42% unchanged, and 25% worsened. We hypothesize that the outcome of the allopurinol arm will be superior, with response rates of ≈52% improved, 37% unchanged, and 11% worsened. To estimate the statistical power of these assumptions, we randomly generated data sets to simulate the clinical trial, computed the Cochran–Mantel–Haenszel row mean score test statistic in each data set, and compared the resulting P value to the 0.05 level of significance. On the basis of 2000 replicate samples, we estimated that a sample size of 250 patients would provide 83% power to detect a statistically significant difference using the row mean score statistic under the assumptions above. Additional calculations confirmed that a sample size of 250 subjects will also provide adequate power for other end points.

Safety

Although interim data analysis for the primary efficacy end point will not be conducted, safety data will be frequently assessed by a Data Safety Monitoring Board. Appointed by the National Heart, Lung, and Blood Institute (NHLBI), this independent committee of individuals with expertise in HF clinical trials will advise the NHLBI on the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial. The Data Safety Monitoring Board will also perform interim reviews of all-cause mortality, using the Haybittle–Peto boundary for interpreting mortality differences between the treatment arms. Information on adverse event definitions and reporting is provided in the online-only Data Supplement.

Other Targets for Therapy

Increasing recognition that nitroso-redox imbalance can affect cardiac structure and function has led investigators to target XO in other cardiovascular disease states. Rekhraj et al randomized 66 patients with ischemic heart disease and LV hypertrophy to receive allopurinol 600 mg daily or placebo for 9 months. Compared with placebo, allopurinol significantly reduced LV mass and volumes (as assessed by cardiac MRI), improved flow-mediated dilation, and was well tolerated. Others have demonstrated benefits of high-dose XO inhibition on symptoms and exercise tolerance in patients with stable angina. Both of these studies suggest that reducing myocardial and vascular XO activity underlies the benefit of allopurinol. However, although a reduction in systemic markers of oxidative stress has been demonstrated, these changes have not uniformly correlated with structural and functional improvements. More work is needed to understand the underlying mechanisms and pathobiology of enhanced XO activity in heart disease. In addition to cardiovascular disorders, allopurinol is currently undergoing investigation in noncardiovascular disease states as diverse as sleep apnea, chronic kidney disease, sarcopenia, and intrauterine growth retardation. Finally, we aim to explore the role of chronic XO inhibition in improving insulin sensitivity in an EXACT-HF substudy (see Material in the online-only Data Supplement).

Conclusions

Accumulating evidence suggests the potential efficacy and safety of XO inhibition in cardiovascular disease states, in general, and HF, in particular. Furthermore, a subgroup of analysis of the OPT-CHF study demonstrated a signal of benefit of XO inhibition in patients with HF and elevated UA.
levels. Against this background, we designed the EXACT-HF study to test the hypothesis that in patients with symptomatic HF because of LV systolic dysfunction, who have elevated serum UA levels, treatment with high-dose allopurinol for 24 weeks will improve clinical outcomes compared with placebo treatment.

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Disclosures

None.

References


Key WORDS: allopurinol • clinical trial • heart failure • xanthine oxidase
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