Xanthine Oxidase Inhibitors in Heart Failure
Where Do We Go From Here?
Leonardo Tamariz, MD, MPH; Joshua M. Hare, MD

Despite its public health impact, there are relatively few classes of drugs in use for the treatment of heart failure (HF) and left ventricular dysfunction. HF pharmacology is based on relatively few signal transduction pathways, most prominently the sympathetic nervous system and the renin-angiotensin-aldosterone system. Thus, the quest for additional therapeutic targets remains critically important, and oxidative stress/nitroso-redox imbalance is a potential target of long-standing interest.

Several lines of evidence support that this pathway may be of pathophysiological relevance. First, serum uric acid (SUA) is a biomarker of oxidative stress in several cardiovascular diseases, including HF. This elevation of SUA is due primarily to the increased amounts of available xanthine and hypoxanthine after cellular damage, which is then catalyzed into uric acid via xanthine oxidase (XO). XO uses oxygen as a potential electron acceptor, thus forming reactive oxygen species (ROS), resulting in oxidative stress.

Several observational studies and meta-analyses have identified elevations of SUA as an independent marker of poor cardiac function, mortality, poor functional capacity, and the development of atrial arrhythmias in HF. Thus, an active hypothesis is that SUA may represent not only a prognostic biomarker of HF but a potential target for intervention.

A second line of evidence emerges from experimental studies exploring the role of XO in HF, showing first and foremost an upregulation of this enzyme in the cardiovascular system. Furthermore, preclinical animal data supported the use of XO inhibitors in HF, showing greater survival, improved left ventricular function, enhanced mechanoenergetic coupling, attenuation of ventricular remodeling, decreased myocardial oxygen consumption, reduced afterload, and improved ventricular vascular coupling.

In humans, intracoronary and intravenous allopurinol improved myocardial efficiency and increased the concentration of high-energy phosphates within the heart. Therefore, XO inhibitors in animals and humans improve cardiac function, enhancing mechanoenergetic coupling while reducing myocardial oxygen consumption and improving afterload. An important insight, however, is that the enhancement of mechanoenergetic coupling depends on the degree XO overexpression in HF animal models.

A third line of evidence is supported by nested case-control and retrospective cohort studies showing a decrease in HF readmissions and all-cause mortality in patients with gout who receive allopurinol.

Together, these findings have prompted a series of clinical trials examining XO inhibition in patients with HF. In this issue of Circulation, Givertz and colleagues report the results of the Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) trial, a double-blind, multicenter, randomized trial that compared guideline adherent therapy plus allopurinol with guideline-adherent therapy alone in a high-risk HF population with elevated SUA. In this study, XO inhibition with allopurinol did not improve functional capacity, clinical status, or left ventricular ejection fraction. Other randomized studies have reached similar conclusions and are summarized in the Table. The randomized studies of XO inhibition in HF consistently fail to show improvement in clinical composite outcomes. It is important to note, however, that 2 studies, including the EXACT-HF trial, show trends toward improvement in secondary outcomes like hospitalizations and ejection fraction. The results seem to be independent of the severity of the HF, patients enrolled, the use of active metabolites of XO inhibitors and dosages to decrease uric acid, and the use of different clinical composite outcomes. Another potential caveat from the randomized trials is that long-term effects of these medications remain unknown because the trials had relatively short-term follow-up.

The study by Givertz and colleagues is based in part on the Oxyipurinol Therapy for Congestive Heart Failure (OPT-CHF) trial results, which compared XO inhibitors with guideline therapy. In post hoc analysis of this study, oxyipurinol showed a potential benefit in HF patients with elevated SUA, and this benefit correlated to the degree of SUA reduction. This study contributed to the rationale for the present study, which used elevated SUA as an enrollment criterion to select for a group of patients with elevated XO.

Potential epidemiological explanations for the negative findings reported by Givertz et al and others include the possibility that SUA might be just a marker of disease severity and prognosis, not a target for therapy. In addition, a combination of sample size, low event rates, and short follow-up time could have limited the ability
to detect a real long-term effect shown as a trend toward lower hospitalizations in the allopurinol group reported in this study. Another potential but unlikely explanation could be the use of oral medications subject to first-pass-effect metabolism of the liver because the available experimental results in humans used parenteral allopurinol. 3,13

Table. Comparison of Randomized Studies Using XO Inhibition in HF

<table>
<thead>
<tr>
<th>Author</th>
<th>HF Population, n</th>
<th>XO Inhibitor</th>
<th>Follow-Up, wk</th>
<th>Primary Outcome Definition</th>
<th>Primary Outcome Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Givertz et al, 19 2015</td>
<td>253 with SUA &gt;9.5 mg/dL with 1 more high-risk marker</td>
<td>Allopurinol 300–600 mg/d</td>
<td>24</td>
<td>Clinical status: outcomes, medication change, and patient global assessment</td>
<td>13% improved in both the allopurinol and placebo arms</td>
</tr>
<tr>
<td>Greig et al, 19 2011</td>
<td>32 NYHA class II–III</td>
<td>Allopurinol 300 mg/d</td>
<td>4</td>
<td>6-min walk test and oxidative stress markers</td>
<td>No difference in 6-min walk test and improved oxidative markers</td>
</tr>
<tr>
<td>Nasr and Maurice, 19 2010</td>
<td>59 NYHA class III–IV</td>
<td>Allopurinol 300 mg/d</td>
<td>36</td>
<td>Composite endpoint: global cardiac function and mortality/morbidity</td>
<td>Allopurinol did not improve composite endpoint</td>
</tr>
<tr>
<td>Hare et al, 1 2008</td>
<td>405 with a median SUA of 7.8 mg/dL and NYHA class III–IV</td>
<td>Oxypurinol 600 mg/d</td>
<td>24</td>
<td>Clinical status: outcomes, medication change, patient global assessment, or NYHA</td>
<td>43% improved in the oxypurinol arm compared vs 45% in the placebo arm; improved primary outcome in patients with higher uric acid levels</td>
</tr>
<tr>
<td>Cingolani et al, 21 2006</td>
<td>60 NYHA class II–III</td>
<td>Oxypurinol 600 mg/d</td>
<td>4</td>
<td>EF</td>
<td>4.7±2.6% higher EF between the oxypurinol and placebo arms</td>
</tr>
<tr>
<td>Gavin and Struthers, 19 2005</td>
<td>50 NYHA class II–III</td>
<td>Allopurinol 300 mg/d</td>
<td>12</td>
<td>Exercise stress test and 6-min walk test</td>
<td>No difference in exercise performance with a decrease in plasma BNP</td>
</tr>
</tbody>
</table>

BNP indicates brain natriuretic peptide; EF, ejection fraction; NYHA, New York Heart Association; SUA, serum uric acid; and XO, xanthine oxidase.

Figure. Effect of xanthine oxidase (XO) inhibition (XOI) on the nitroso-redox balance. The underlying mechanistic basis for the use of XOs in the failing heart. As shown, XOs act on a key enzyme, XO/xanthine dehydrogenase (XDH), to inhibit reactive oxygen species (ROS) production but has other actions that might detract from full restoration of nitroso-redox balance. XOs decrease serum uric acid and superoxide production by inhibiting XO. Importantly, however, there are other sources of ROS production in the failing heart, including mitochondrial respiration and NADPH oxidases, that are not affected by XOs. In addition, nitric oxide (NO) synthase (NOS) activity may be impaired in heart failure or further disrupted by XOs. In states of inadequate NO production, oxidation or diminished S-nitrosylation of the ryanodine receptor (RyR) receptor and other key proteins involved in excitation-contraction coupling impairs calcium cycling, which drives optimal myocardial performance. Persistent ROS production also consumes NO and leads to peroxynitrite formation, which can cause DNA, protein, and lipid damage. Peroxynitrite oxidizes the calcium ATPase SERCA (sarcoplasmic reticulum [SR] calcium ATPase; responsible for calcium reuptake into the SR). Thus, NO continues to be depleted by XOI, perpetuating nitroso-redox imbalance and causing ineffective excitation-contraction coupling. NOX indicates NADPH oxidases; O−, superoxide; SOD, superoxide dismutase; and XOR, xanthine oxidoreductase.
This is an unlikely theory because there was a significant decrease in SUA.

The nonsignificant findings of EXACT-HF and other studies prompt an examination of the pathophysiological mechanisms that are the basis for this novel therapeutic strategy. A leading possibility explaining the lack of response to XO inhibition could be the fact that this pharmacological strategy addressed only 1 of 2 limbs underlying nitroso-redox imbalance (Figure). In HF, not only are ROS-generating pathways upregulated, but important aspects of reactive nitrogen species production are downregulated.2 Three important factors related to the nitroso-redox balance might have bearing on the findings by Givertz and colleagues.16 First, other enzymes and metabolic pathways contribute to nitroso-redox imbalance, including other enzymes that produce ROS (NADPH oxidase enzymes and the respiratory chain in the mitochondria); superoxide dismutase, which neutralizes superoxide; and the family of nitric oxide (NO) synthases, which produce NO. Selective XO inhibition might be inadequate to curtail the cascade of ROS accumulated in HF, and, very importantly, this is supported by the present study because myeloperoxidase levels did not change. Second, we now know that the nitroso-redox balance is intimately interconnected. This is supported by a series of experiments that found that NO binds superoxide to produce peroxynitrite, NO modulates the expression of XO, NO synthase inhibitors abolish the contractile effect of XO inhibitors, and XO inhibition can actually decrease NO production.6,22 NO synthase 1–deficient animal models have proven an increase in mortality, left ventricular remodeling, and ventricular arrhythmias after myocardial infarction.23,24 Thus, inhibition of XO in the failing circulation may fail to have beneficial effects if NO synthase activity or signaling is also depressed; XO inhibition may affect only 1 limb of the nitroso-redox imbalance.

Thus, the results of EXACT-HF add another important data point in the quest to unravel whether aspects of nitroso-redox imbalance have potential as a therapeutic target. The trial suggests that XO inhibition alone, even in HF patients with high SUA, is inadequate to improve clinical outcomes. As this field progresses, it will be crucial to examine other limbs of this balance and to ask whether augmenting NO production concomitantly with inhibition ROS production will have clinical benefits in HF.

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References


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