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Impact of Oxypurinol in Patients With Symptomatic Heart Failure

Results of the OPT-CHF Study

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Objectives This study evaluated whether a xanthine oxidase (XO) inhibitor, oxypurinol, produces clinical benefits in patients with New York Heart Association functional class III to IV heart failure due to systolic dysfunction receiving optimal medical therapy.

Background Increased XO activity may contribute to heart failure pathophysiology.

Methods Patients (n = 405) were randomized to oxypurinol (600 mg/day) or placebo. Efficacy at 24 weeks was assessed using a composite end point comprising heart failure morbidity, mortality, and quality of life.

Results The percentage of patients characterized as improved, unchanged, or worsened did not differ between those receiving oxypurinol or placebo. Oxypurinol reduced serum uric acid (SUA) by ~2 mg/dl ($p < 0.001$). In a subgroup analysis, patients with elevated SUA (>9.5 mg/dl, n = 108) responded favorably to oxypurinol ($p = 0.02$ for interaction term), whereas oxypurinol patients with SUA <9.5 mg/dl exhibited a trend towards worsening. In addition, SUA reduction to oxypurinol correlated with favorable clinical response. Within the entire oxypurinol patient cohort, those characterized as either improved or unchanged had significantly greater reductions in SUA compared with patients who worsened (−2.3 ± 2.1 mg/dl vs. −1.0 ± 1.9 mg/dl, $p = 0.0006$). In placebo patients, lower baseline SUA, but not change in SUA, correlated with improved clinical outcome.

Conclusions Oxypurinol did not produce clinical improvements in unselected patients with moderate-to-severe heart failure. However, post-hoc analysis suggests that benefits occur in patients with elevated SUA in a manner correlating with the degree of SUA reduction. Serum uric acid may serve as a valuable biomarker to target XO inhibition in heart failure. (Oxypurinol Compared With Placebo for Class III-IV NYHA Congestive Heart Failure; NCT00063687) (J Am Coll Cardiol 2008;51:2301–9) © 2008 by the American College of Cardiology Foundation

Elevation in the abundance and the enzymatic activity of xanthine oxidase (XO) is described in experimental animals (1–3) and humans (4,5) with heart failure. The upregulation of this pathway contributes to both vasoconstriction and reduced myocardial function, which are hallmarks of congestive heart failure (6). Enhanced activity of this enzyme system may produce increases in oxidative stress and levels of uric acid (7,8), both of which may contribute to the pathophysiology of cardiovascular (CV) disease (9). Previous studies have suggested that XO inhibition may improve endothelial reactivity (9), myocardial function (4), and ejection fraction (10) in patients with congestive heart failure. The purpose of this study was to test whether XO inhibition would produce clinical benefits in patients with systolic dysfunction and symptomatic heart failure treated with a background of optimal heart failure therapies.

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Methods

The design of this multicenter, randomized, double-blind, placebo-controlled, parallel group OPT-CHF study (The Efficacy and Safety Study of Oxypurinol Added to Standard

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Abbreviations and Acronyms

BNP = brain natriuretic peptide
CCE = composite clinical end point
CI = confidence interval
CV = cardiovascular
ITT = intent to treat
MLHF = Minnesota Living with Heart Failure
NYHA = New York Heart Association
PGHFCS = Patient Global Heart Failure Clinical Status
SUA = serum uric acid
XO = xanthine oxidase

Therapy in Patients With New York Heart Association Class III-IV Congestive Heart Failure) is described in detail elsewhere (11).

Patients. Eligible patients were between 18 to 85 years old, had symptomatic heart failure (New York Heart Association [NYHA] functional class III to IV), and left ventricular dysfunction defined as a left ventricular ejection fraction ≤40%. Patients were eligible if they had at least 1 hospitalization for heart failure within 18 months, an emergency room visit resulting in treatment with intravenous therapy for worsening heart failure, or if a new drug class for heart failure was added to their regimen due to lack of medical stability. Patients receiving continuous or intermittent intravenous inotropic or vasodilator agents for a period of at least 4 weeks before entering the study in any dosage (varying dosages allowed) met the criteria for new drug therapy addition. Investigators were asked to ensure each patient was, in their opinion, on an optimum dose of heart failure medication, a requirement for study entry.

Study design. Patients were randomized to oxypurinol or placebo. The initial dose for both active and placebo groups during the first week post-randomization was 1 capsule (100 mg oxypurinol or matching placebo). Subsequently, both groups received 6 capsules (600 mg) daily. Patients with reduced renal function had their study medication titrated based on serum creatinine levels, and those with creatinine >3.0 were excluded (11).

Study drug was initiated after a 2-week run-in period, during which time stability of symptoms and background treatment were assessed and baseline assessments were obtained. Patients were monitored with outpatient visits every 4 weeks for 24 weeks, at which time they received a history and physical examination, NYHA functional class assessment, a 6-min walk test, the Patient Global Assessment of Heart Failure questionnaire, and the Minnesota Living with Heart Failure (MLHF) questionnaire (a quality-of-life assessment).

Patients remained on their assigned dosage until the end of the study, unless the investigator felt an adverse event was drug related and required drug withdrawal, or the patient withdrew consent to continue on study medication. These patients were followed as part of the intent-to-treat (ITT) cohort, and received all protocol-related study procedures through the 24-week time point. Patients who did not return for study procedures after study drug withdrawal were contacted at the conclusion of the trial to determine their mortality status, unless they formally withdrew consent to participate in the study.

Study end points. The primary end point was a composite clinical end point (CCE) that classified subject's clinical status as improved, worsened, or unchanged at week 24, similar to that reported in Packer (12), with a slight modification. The classification followed sequential rules based on the outcomes of the following items: 1) CV death; 2) hospitalization, emergency room, or emergent office/clinic visit for worsening heart failure; 3) administration of a new drug class for heart failure or the administration of intravenous diuretics de novo for worsening heart failure; 4) permanent withdrawal of study drug due to worsening heart failure; 5) NYHA functional class; or 6) Patient Global Heart Failure Clinical Status (PGHFCS). These components were adjudicated by a clinical events committee. A patient was classified as worsened if they died, were hospitalized, visited an emergency room, or experienced an emergent office or clinic visit adjudicated by the clinical events committee to be primarily for treatment of worsening heart failure symptoms. In addition, worsening was defined by a decrement in NYHA functional class at week 24, a PGHFCS assessment at week 24 in which the patient indicated moderately or markedly worse symptoms of heart failure, the addition of a new drug class for heart failure, the administration of intravenous diuretics de novo for worsening heart failure, or permanent discontinuation from study medication due to worsening heart failure. With regards to addition of a new class of drugs, substituting one class for another due to a side effect (e.g., angiotensin receptor blocker for angiotensin-converting enzyme inhibitor) did not constitute this end point. A patient was characterized as improved if none of the above occurred and they improved one or more NYHA functional classes, or if they indicated a moderate or marked improvement in the PGHFCS assessment. Patients who met criteria for neither improving nor worsening were classified as unchanged. Patients were evaluated on an ITT basis.

Secondary efficacy end points included time to first occurrence of CV death or hospitalization for worsening heart failure; change from baseline to week 24 in quality-of-life score as assessed by the MLHF questionnaire, and change from baseline to week 24 in serum uric acid (SUA) levels. Tertiary end points included individual components of the CCE in addition to the 6-min walk test, and the time to all-cause death and all-cause hospitalization.

The study was approved by institutional review boards at all participating centers, and all patients gave written informed consent. Four hundred and five patients were enrolled between March 2003 and December 2004 at 54 centers in Canada and the U.S. Of the 405 randomized patients, 51 patients did not complete the study through to the 24-week visit, 22 withdrew consent, 15 died, and 14 discontinued for other reasons. Where possible, every effort was made to determine the 24-week status of all patients who withdrew from the study.

Subgroup analysis. An additional exploratory analysis was conducted to examine the effect of SUA on the primary CCE outcome. Patients were classified as high SUA if they had a baseline SUA >9.5 mg/dl, and low SUA if they had a baseline SUA ≤9.5 mg/dl, which was a cutoff chosen based on previously published findings (7). In addition, the degree of SUA reduction was assessed within these subgroups.

Statistical methods. All analyses were conducted using the ITT principle. Analysis of the primary efficacy CCE end point utilized the Cochran-Mantel-Haenszel mean score test with modified ridit scores to compare the distributions. Patients who were lost to follow-up were evaluated for all end points using the last value carried forward method. The same approach was applied to the analysis of the change from baseline in NYHA functional class, where subjects were classified as improved by 2 or more categories, improved by 1 category, unchanged, or worsened by 1 category, and the PGHFCS assessment at week 24. Analyses of the time-to-event end points utilized the log-rank test to compare distributions between treatment groups, and a Cox proportional hazards regression model for estimation of the hazard ratios. Analysis of the change from baseline in SUA, MLHF questionnaire score, and the 6-min walk test score was conducted using a repeated measures mixed model, with baseline score as a covariate and treatment, time, and the treatment by time interaction as fixed effects. For the MLHF questionnaire score and the 6-min walk test, the covariance matrix was specified to be autoregressive of order one, while for SUA an unstructured covariance matrix was used. The choice of covariance matrix was examined. Examination of the strength of an association between the

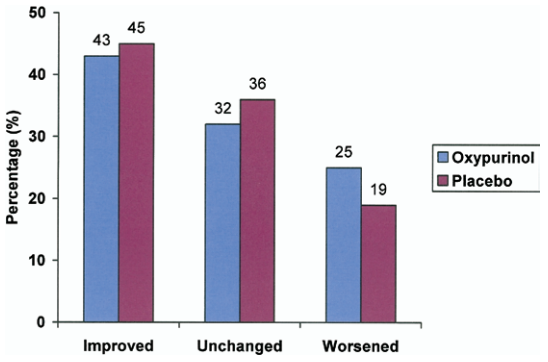

Figure 1 Impact of Oxypurinol on the CCE

As depicted, randomization to oxypurinol failed to increase the proportion of patients improving according to the composite categorization. CCE = composite clinical end point.

Table 1 Baseline Characteristics

	Placebo (n = 202)	Oxypurinol (n = 203)
Age, yrs (mean ± SD)	65 ± 13	64 ± 13
Male gender (%)	70	76
Race (%)		
Caucasian	80	75
Black	15	20
NYHA functional class III (%)	96	96
LVEF (mean ± SD)	27.7 ± 13.4	25.3 ± 13.1
6MWT (m)	278 ± 123	257 ± 118
Medication use (%)		
Diuretics	95	95
ACE inhibitor	75	72
ARB	19	25
Beta-blocker	90	93
Carvedilol	83	84
Digoxin	56	54
Spironolactone	34	36
Nitrates	33	33
Etiology (%)		
Ischemic	60.9	61.1
Idiopathic	22.8	20.2
Hypertensive	5.9	7.4
Entry criteria (%)		
Hospitalized	69.8	68.3
ER visit	24.3	25.2
New HF medication	44.8	45.2
On maximum tolerated medications (%)	99.0	99.5
Median (25th to 75th quartile) SUA (mg/dl)		
Overall	7.8 (6.4–9.2)	7.9 (6.4–9.8)
SUA <9.5	7.1 (5.9–8.3)	7.0 (6.0–8.0)
SUA ≥9.5	10.6 (9.9–11.6)	11.4 (10.3–12.5)
Mean (25th to 75th quartile) BNP (pg/ml)		
Overall	186 (73–402)	234 (81–464)
SUA <9.5	177 (68–403)	187 (66–422)
SUA ≥9.5	225 (80–392)	326 (140–564)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BNP = brain natriuretic peptide; ER = emergency room; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SUA = serum uric acid; 6MWT = 6-min walk test.

Table 2 Components of Primary End Point (ITT Population)

	Placebo (n = 202)	Oxypurinol (n = 203)	p Value
Improved	91 (45.0%)	88 (43.3%)	0.4211
NYHA and PGHFCS improved	28	35	
NYHA improved	36	22	
PGHFCS improved	27	31	
Unchanged	72 (35.6%)	65 (32.0%)	
NYHA and PGHFCS unchanged	72	65	
Worsened	39 (19.3%)	50 (24.6%)	
CV death	4	8	
Hospitalization/ER/office visit for HF	18	29	
Use of new medication for HF	3	1	
Discontinuation due to HF	—	1	
NYHA worsened	—	1	
PGHFCS worsened	7	4	
Lost to follow-up	7	6	

The components were derived based on the sequence as outlined in the Results section.

CV = cardiovascular; ITT = intent to treat; PGHFCS = Patient Global Heart Failure Clinical Status; other abbreviations as in Table 1.

Table 3 Secondary and Tertiary Clinical Events

	Placebo (n = 202)	Oxypurinol (n = 203)	Hazard Ratio (95% CI)*	p Value†
Secondary end points				
All-cause death	6 (3%)	10 (5%)	1.7 (0.6–4.7)	0.2906
CV death	4 (2%)	8 (4%)	2.1 (0.6–6.9)	0.2267
All-cause hospitalization	50 (25%)	59 (29%)	1.2 (0.8–1.7)	0.3405
HF hospitalization	15 (8%)	26 (13%)	1.8 (0.9–3.3)	0.0763
Tertiary end points				
CV death/HF hospitalization	18 (9%)	31 (15%)	1.8 (1.0–3.1)	0.0546
ER/office visit (HF)	4 (2%)	8 (4%)	2.0 (0.6–6.7)	0.2426

*Based on a Cox proportional hazards model with the time to event as the end point; †based on a log-rank test with time to event as the end point.
CI = confidence interval; HF = heart failure; other abbreviations as in Tables 1 and 2.

primary end point and both SUA and brain natriuretic peptide (BNP), as well as between BNP and SUA were conducted using Pearson's correlation test. Brain natriuretic peptide was log transformed for these analyses. All analyses were conducted using SAS version 8.2 (SAS Institute, Cary, North Carolina).

Results

Table 1 depicts the baseline characteristics of patients enrolled in this study. Both groups were comparable across all baseline characteristics. The majority of patients were NYHA functional class III (96%), and virtually all patients (99%) were on maximum tolerated medications for their heart failure.

Primary and secondary study outcomes. The distribution of patients characterized as improved, worsened, and unchanged as assessed by the primary composite end point did not differ between oxypurinol and placebo groups (Fig. 1, Table 2). Improvement was observed in 91 (45%) subjects versus 88 (43%) subjects in the placebo versus oxypurinol groups, respectively; no change was seen in 72 (36%) versus 65 (32%) subjects, respectively, and worsening was seen in 39 (19%) versus 50 (25%) subjects in the placebo versus oxypurinol groups, respectively (p = 0.4211).

Table 3 depicts hazard ratios for secondary and tertiary outcome measures. The majority of secondary and tertiary events, including all-cause or CV mortality, were not different between treatment groups. With regard to CV death or hospitalization for heart failure, 31 (15%) oxypurinol-treated patients and 18 (9%) placebo patients experienced this combined end point, with a trend towards an increased risk (hazard ratio 1.8; 95% confidence interval [CI] 1.0 to 3.1, p = 0.055) in oxypurinol-treated patients.

Quality of life. The change from baseline to week 24 in the MLHF score was not different in placebo (−4.3) and oxypurinol (−5.6) groups. Change from baseline to week 24 in the NYHA functional class, and the PGHFCS assessment at week 24, both components of the primary composite end point, were comparable between treatment groups (Table 4). Finally, the change from baseline in the 6-min walk test was also not different between treatment groups.

SUA subgroup analysis. Oxypurinol produced a significant reduction in SUA after 1 month of therapy, which was maintained through to the end of the trial (Fig. 2). One of the postulated mechanisms of oxypurinol benefit is to inhibit uric acid production. Thus, we examined the impact of the drug in groups of patients dichotomized by high or low SUA using 9.5 mg/dl as a cutoff. Using this cutoff, 108 (21%) of the 405 patients were characterized as high SUA patients: 60 in the oxypurinol group and 48 in the placebo group (Table 5).

Analysis of the primary CCE in the 2 SUA subgroups revealed a significant subgroup by treatment interaction (p = 0.02), indicating that the direction of the response differs within the subgroups (Fig. 3). In the subgroup of patients with a high baseline SUA, there was a trend towards benefit in the oxypurinol group: 31 (52%) versus 16 (33%) improved, 16 (27%) versus 20 (42%) remained unchanged, and 13 (22%) versus 12 (25%) worsened in the oxypurinol and placebo groups, respectively (Table 5). In contrast, analysis of the low baseline subgroup of patients

Table 4 Quality of Life and Clinical Status Outcomes

End Point	Categorical Response	Placebo (n = 202)	Oxypurinol (n = 203)	p Value*
Change from baseline to week 24 in NYHA functional class	Improved by 2 or more categories	6 (3.3%)	2 (1.1%)	0.4
	Improved by 1 category	61 (33.7%)	54 (32.6%)	
	Unchanged	112 (61.9%)	113 (64.6%)	
	Worsened by 1 category	2 (1.1%)	3 (1.7%)	
Week 24 PGHFCS	Markedly improved	18 (10.0%)	24 (14.0%)	0.4
	Moderately improved	43 (23.9%)	44 (25.7%)	
	Mildly improved	49 (27.2%)	39 (22.8%)	
	No change	58 (32.2%)	51 (29.8%)	
	Slightly worse	4 (2.2%)	8 (4.7%)	
	Moderately worse	6 (3.3%)	4 (2.3%)	
	Markedly worse	2 (1.1%)	1 (0.6%)	

*p value was calculated using a Cochran-Mantel-Haenszel mean score test.
NYHA = New York Heart Association; PGHFCS = Patient Global Heart Failure Clinical Status.

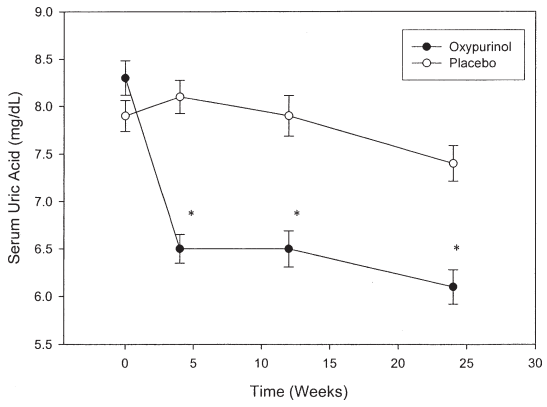

Figure 2 **Impact of Oxypurinol on SUA**

Serum uric acid (SUA) was measured at monthly intervals throughout the 6-month follow-up period. As depicted, oxypurinol effectively lowered SUA by approximately 2 mg/dl, and this effect was evident within 1 month of therapy. *Indicates $p < 0.0001$ versus placebo and is based on a repeated measures mixed model with baseline as a covariate and change from baseline as the dependent variable.

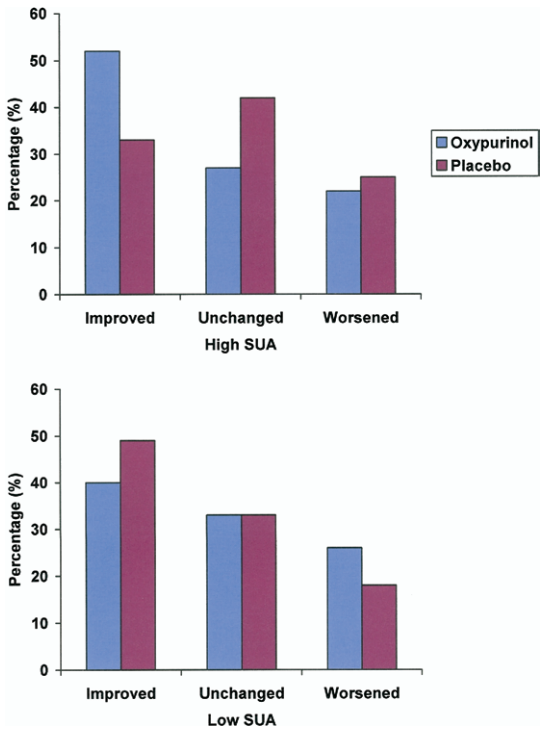

Figure 3 **Impact of Oxypurinol on the CCE in High and Low SUA Subgroups**

p = 0.02 for interaction between high and low serum uric acid (SUA) groups. CCE = composite clinical end point.

suggested worse outcomes due to oxypurinol: 57 (40%) versus 74 (49%) improved, 48 (33%) versus 51 (33%) remained unchanged, and 37 (26%) versus 27 (18%) worsened in the oxypurinol and placebo groups, respectively (Table 5).

Table 6 depicts the secondary and tertiary outcome measures in the 2 SUA subgroups. Oxypurinol-treated patients with a baseline SUA ≥9.5 mg/dl showed a trend towards decreased risk for all-cause (hazard ratio 0.4; 95% CI 0.1 to 2.1) and CV (hazard ratio 0.5; 95% CI 0.1 to 3) death compared with placebo-treated patients. A similar trend was not seen in oxypurinol patients with an SUA <9.5 mg/dl.

Quality of life. Although the change from baseline to week 24 NYHA functional class was no different in the SUA subgroup analysis, the baseline to week 24 PGHFCS end point indicated that oxypurinol-treated patients with a baseline SUA ≥9.5 mg/dl had statistically significant im-

Table 5 **Components of the Primary End Point Within SUA Subgroups (ITT Population)**

	SUA ≥9.5 mg/dl			SUA <9.5 mg/dl		
	Placebo (n = 48)	Oxypurinol (n = 60)	p Value	Placebo (n = 152)	Oxypurinol (n = 142)	p Value
Improved	16 (33%)	31 (52%)	0.1270	74 (49%)	57 (40%)	0.0720
NYHA and PGHFCS improved	7	9		21	26	
NYHA improved	4	6		31	16	
PGHFCS improved	5	16		22	15	
Unchanged	20 (42%)	16 (27%)		51 (33%)	48 (33%)	
NYHA and PGHFCS unchanged	20	16		51	48	
Worsened	12 (25%)	13 (22%)		27 (18%)	37 (26%)	
CV death	3	2		1	6	
Hospitalization/ER/office visit for HF	3	9		15	20	
Use of new medication for HF	—	—		3	1	
Discontinuation due to HF	—	—		—	1	
NYHA worsened	—	1		—	—	
PGHFCS worsened	3	—		4	4	
Lost to follow-up	3	1		4	5	

Abbreviations as in Tables 1 and 2.

Table 6 Secondary and Tertiary Clinical Events by SUA Subgroup (ITT Population)

	Baseline SUA (mg/dl)	Placebo	Oxypurinol	Hazard Ratio (95% CI)
Secondary end point				
CV death/HF hospitalization	<9.5	13 (9%)	20 (14%)	1.7 (0.6–4.6)
	≥9.5	5 (10%)	11 (18%)	1.7 (0.9–3.5)
Tertiary end points				
All-cause death	<9.5	2 (1%)	8 (6%)	4.5 (1.0–21.3)
	≥9.5	4 (8%)	2 (3%)	0.4 (0.1–2.1)
CV death	<9.5	1 (1%)	6 (4%)	6.8 (0.8–55.6)
	≥9.5	3 (6%)	2 (3%)	0.5 (0.1–3.1)
All-cause hospitalization	<9.5	37 (24%)	37 (26%)	1.1 (0.7–1.7)
	≥9.5	12 (25%)	22 (37%)	1.5 (0.7–3.0)
HF hospitalization	<9.5	12 (8%)	17 (12%)	1.6 (0.9–3.3)
	≥9.5	3 (6.3%)	9 (15%)	2.4 (0.6–8.7)
ER/office visit (HF)	<9.5	3 (2%)	8 (6%)	2.9 (0.8–11.0)
	≥9.5	1 (2%)	—	—

CI = confidence interval; other abbreviations as in Tables 1 and 2.

provements compared with placebo-treated patients ($p = 0.02$); a driving force behind the trend seen in the CCE. Oxypurinol patients with baseline SUA levels <9.5 mg/dl did not exhibit in a similar trend (Table 7).

Evaluation of baseline SUA levels in the placebo group supported the notion that increasing levels of SUA correspond with worsening outcome (Table 8). Interestingly, this pattern was not observed in the oxypurinol group, consistent with a treatment response to the drug linked to its impact on SUA.

Within the entire oxypurinol cohort, there was an association between improvement and reduction in SUA ($r = 0.23$; $p = 0.0014$). Patients who improved had an average reduction in SUA of 2.3 ± 2.1 mg/dl, patients who remained unchanged had an average reduction in SUA of 2.2 ± 2.0 mg/dl, and patients who worsened had an average reduction in SUA of 1.0 ± 1.9 mg/dl. Figure 4 shows a scatter plot of the baseline and final SUA measurements by treatment group and response. In addition, in the entire cohort of oxypurinol-treated patients, those experiencing death or hospitalization had lower degrees of SUA reduction (−0.9 vs. −2.1, $p = 0.0026$). Within the oxypurinol high SUA subgroup, patients who improved had an average SUA decrease of 3.5 mg/dl compared with 1.7 mg/dl in the patients categorized as worsened (Fig. 5).

Relationship between SUA and BNP. There was a relationship between the natural logarithm of baseline BNP and baseline SUA ($r = 0.11$; $p = 0.0351$); however, no relationship between change in SUA and change in BNP was seen ($r = -0.03$; $p = 0.6676$ for oxypurinol group and $r = -0.08$; $p = 0.2466$ for placebo). Evaluation of an association between outcome and baseline BNP levels in the oxypurinol and placebo groups showed a significant association between baseline BNP and outcome in the oxypurinol group but not in the placebo group (Table 8). When evaluated based on the change from baseline by CCE outcome, both oxypurinol and placebo-treated patient BNP values decreased with improved outcomes (Table 9).

Table 7 Quality of Life and Clinical Status Outcome by SUA Subgroup (ITT Population)

	SUA ≥9.5 mg/dl			SUA <9.5 mg/dl		
End Point	Placebo (n = 48)	Oxypurinol (n = 60)	p Value	Placebo (n = 152)	Oxypurinol (n = 142)	p Value
Change from baseline to week 24 in NYHA functional class						
Improved by 2 or more categories	2 (4%)	—	0.9318	4 (3%)	2 (1%)	0.3587
Improved by 1 category	9 (19%)	16 (27%)		54 (36%)	44 (31%)	
Unchanged	36 (75%)	40 (67%)		92 (61%)	96 (68%)	
Worsened by 1 category	1 (2%)	4 (7%)		2 (1%)	—	
Week 24 PGHFCS						
Markedly improved	2 (4%)	5 (8%)	0.0166	17 (11%)	20 (14%)	0.4869
Moderately improved	11 (23%)	23 (38%)		35 (23%)	27 (19%)	
Mildly improved	14 (29%)	17 (28%)		38 (25%)	29 (20%)	
No change	14 (29%)	11 (18%)		54 (36%)	53 (37%)	
Slightly worse	3 (6%)	3 (5%)		3 (2%)	6 (4%)	
Moderately worse	2 (4%)	—		4 (3%)	6 (4%)	
Markedly worse	2 (4%)	1 (2%)		1 (1%)	1 (1%)	

Abbreviations as in Tables 1 and 2.

Table 8 Baseline SUA and BNP Values

	Placebo	Oxypurinol
SUA		
Improved	7.6 ± 1.95, r = 0.15	8.4 ± 2.68, r = −0.05
Unchanged	8.0 ± 2.57 (p = 0.0344)	8.2 ± 2.44 (p = 0.5308)
Worsened	8.6 ± 2.46	8.1 ± 2.59
BNP		
Improved	5.2 ± 1.2, r = 0.07	5.0 ± 1.2, r = 0.15
Unchanged	4.9 ± 1.3 (p = 0.3066)	5.1 ± 1.3 (p = 0.0410)
Worsened	5.3 ± 1.2	5.6 ± 1.3

Data are reported as mean ± SD. r is the Pearson correlation coefficient and brain natriuretic peptide (BNP) is reported as the natural log.
SUA = serum uric acid.

Discussion

The OPT-CHF study was designed to test the hypothesis that inhibition of XO with oxypurinol, when added to best conventional therapy, would improve clinical outcomes in patients with symptomatic heart failure due to systolic dysfunction. In this study, patients receiving active therapy did not differ according to the primary outcome composite measure relative to patients randomized to placebo. Accordingly, the study failed to achieve its primary end point. Importantly, when dichotomized by SUA levels, using 9.5 mg/dl as a cutoff, several lines of evidence support the idea that heart failure patients with elevated SUA represent a patient population responsive to therapy with XO inhibition.

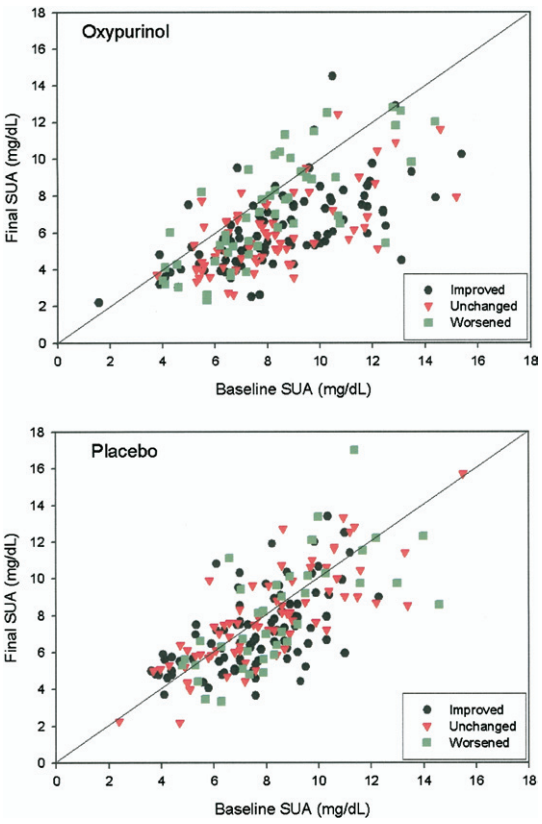

Figure 4 Scatterplot of Baseline SUA to Final SUA by Outcome

Overall, the oxypurinol-treated group had improved final serum uric acid (SUA) compared with their baseline SUA levels when evaluated against the placebo group.

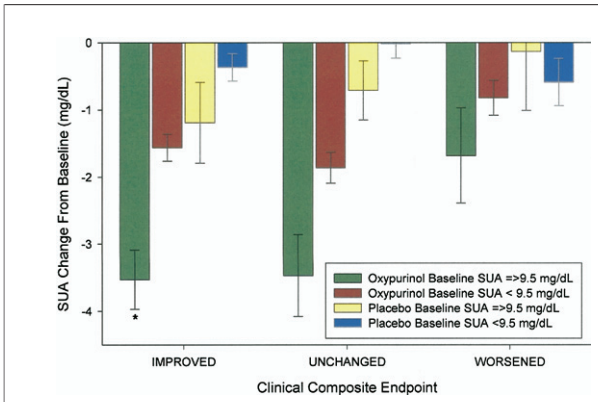

Figure 5 Degree of SUA Reduction in Patients With Low and High SUA

As depicted, the degree of serum uric acid (SUA) reduction was greatest in treated patients classified as improved or unchanged with high baseline SUA. *p < 0.05 versus worsened group.

Examination of secondary and tertiary end points showed little to no impact of oxypurinol therapy. The combined end point of time to CV death plus heart failure hospitalization suggested the possibility of an adverse response to oxypurinol (Table 2). This finding argues against the use of oxypurinol in all patients with symptomatic heart failure due to systolic dysfunction, and prompted an examination of predictors of outcome within the study population.

Subgroup analysis demonstrated that patients with elevated levels of SUA may represent a responsive population. The SUA findings are consistent with a series of reports indicating that elevated SUA is a valuable biomarker of morbidity and mortality in heart failure (8). Anker et al. (7) proposed a cutoff of 9.5 mg/dl based on an analysis of several populations. In the latter analysis, using a cross-sectional study design, high uric acid was demonstrated to be associated with higher mortality and greater need for cardiac transplantation. Importantly, in the present study, the change in SUA response also correlated with clinical outcome. First, in the placebo group, SUA did not change over the 6-month period of

Table 9 Change From Baseline BNP by CCE Outcome

	Placebo	Oxypurinol
Improved	−0.24 ± 0.83, r = 0.17	−0.30 ± 0.84, r = 0.05
Unchanged	0.09 ± 0.67 (p = 0.0125)	0.14 ± 0.74 (p = 0.4828)
Worsened	0.03 ± 0.54	0.03 ± 0.51

Data are reported as mean ± SD; r is the Pearson correlation coefficient, and brain natriuretic peptide (BNP) is reported as the natural log.
CCE = composite clinical end point.

study, and baseline SUA correlated with outcome. Second, in both the entire cohort and the high SUA group, patients who worsened had substantially lower reductions in SUA compared with the other groups. Finally, when relevant secondary or tertiary end points were examined, a failure to decrease SUA correlated with adverse outcome. Together, these analyses strongly suggest that an attenuated response to oxypurinol, as indicated by diminished SUA reduction, predicts failure of clinical response and possibly adverse outcomes.

Whether uric acid is toxic, per se, or is a biomarker of xanthine oxidoreductase activity is currently unclear. Interestingly, most mammalian species have low circulating uric acid due to the presence of uricase, an enzyme inactive in humans, which degrades uric acid (13). Nevertheless, cardiac injury is associated with increased XO activity in many animal models, and one in particular demonstrated the association between XO activity and uric acid in myocardial tissue (14). Collectively, numerous animal models and human studies demonstrate improved cardiac remodeling (3,15), cardiac energetics (16,17), endothelial function (5,9,18,19), and survival after cardiac injury (1,20) in response to XO inhibition. Most recently, George et al. (21) argued against direct toxicity of uric acid, and have demonstrated that the ability of allopurinol to improve endothelial function cannot be attributed to uric acid lowering, per se (21). Together, these experimental and clinical studies suggest that uric acid may represent a valuable biomarker of XO activity in the CV system. Indeed, the fact that approximately one-quarter of the patients in this study had levels of SUA above 9.5 mg/dl argues that this pathway is not addressed by other conventional medications, and represents an unaddressed therapeutic target in a substantial proportion of patients. With regard to usage as a biomarker, it is interesting to note that here we confirm our previous finding that SUA only weakly correlates with the logarithm of BNP and thus may offer additive clinical information (22).

There are several reasons why oxypurinol may not have led to clinical benefits in the broad population of symptomatic, treated patients. First, it is possible that sources of oxidative stress are already inhibited by other medications such as inhibitors of the renin-angiotensin-aldosterone pathway or carvedilol. In this regard, angiotensin II can activate XO directly (23) and indirectly via NADPH oxidase (24). However, it may be argued that patients with high SUA who did not respond to oxypurinol and worsened did so due to lack of efficacy of the medication. Indeed, in this cohort the level of SUA reduction was substantially and significantly less compared with that in patients with high SUA who remained unchanged or who clinically improved. Moreover, findings from retrospective analyses have previously suggested that patients receiving low-dose XO inhibitors may worsen, whereas those receiving high doses may have mortality and hospitalization reductions (25).

Although the post-hoc analysis of SUA is provocative, it is limited. This was not a pre-specified analysis, and the numbers of patients in the high SUA group were small. These results, however, are hypothesis generating, and offer potential explanations for why a hypothesis that was so well supported by pre-clinical work failed to be borne out in humans with advanced heart failure. Future clinical trials are required to prospectively assess the impact of XO inhibition in patients with high SUA.

Conclusions

In summary, this study demonstrates that oxypurinol did not improve a clinical composite score in patients with systolic, symptomatic heart failure, and could potentially cause harm to some patients. Subgroup analysis supports the concept that patients with these clinical characteristics and a high SUA may benefit from XO inhibition. Moreover, the degree of SUA reduction correlated with clinical outcome, such that patients who worsened despite oxypurinol therapy had relatively less reduction in uric acid. Measurements of uric acid may aid in individualizing therapy with XO inhibitors.

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APPENDIX

For a complete list of investigators, please see the online version of this article.