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SAFETY AND EFFICACY OF ALLOPURINOL IN HYPERURICEMIC PATIENTS PRESENTING WITH ACUTE CORONARY SYNDROME

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БЕЗОПАСНОСТ И ЕФИКАСНОСТ НА АЛОПУРИНОЛ ПРИ ПАЦИЕНТИ С ХИПЕРУРИКЕМИЯ, ПРЕДСТАВЯЩИ СЕ С ОСТЪР КОРОНАРЕН СИНДРОМ

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Abstract. **Background:** Hyperuricemia is a significant risk factor for cardiovascular diseases, particularly acute coronary syndrome (ACS). Elevated serum uric acid levels contribute to endothelial dysfunction, oxidative stress, and inflammation, which exacerbate the progression of coronary artery disease. Allopurinol, a xanthine oxidase inhibitor, has demonstrated potential cardio-protective effects beyond its urate-lowering properties. **Aim:** This study aimed to evaluate the safety and efficacy of allopurinol in patients with hyperuricemia presenting with ACS. **Methods:** We conducted a prospective study at the Aswan University Hospital from June 2024 to June 2025. A total of 120 patients with ACS were enrolled and divided into two groups: Group A (n = 60) comprised patients with hyperuricemia (serum uric acid > 6.8 mg/dL) who received allopurinol plus standard anti-ischemic therapy, and Group B (n = 60) comprised patients with normal uric acid levels who received standard therapy alone. Allopurinol was administered at 600 mg/day during the acute phase (first 14 days), followed by 200 mg/day for a total of 4 weeks. All patients underwent comprehensive evaluation, including coronary angiography, echocardiography, and laboratory assessments at baseline and after 3-months. **Results:** Baseline characteristics showed that Group A had a significantly higher BMI (24.7 ± 3.9 vs. 23 ± 3.4 kg/m², p = 0.015), lower HDL cholesterol (39.8 ± 15.2 vs. 74.6 ± 37.8 mg/dL, p < 0.001), and higher troponin positivity (81.7% vs. 20%, p < 0.001) compared to Group B. Angiographic analysis revealed that Group A had more proximal coronary lesions (45% vs. 20%, p < 0.001), higher rates of severe stenosis (93.3% vs. 30%, p < 0.001), and higher SYNTAX scores (23.1 ± 3.6 vs. 17.7 ± 3.9, p < 0.001). Group A also demonstrated a higher prevalence of arrhythmias (48.3% vs. 13.3%, p < 0.001), particularly atrial fibrillation. Following allopurinol therapy, Group A showed significant improvements in left ventricular ejection fraction (from 50.4% to 52.2%, p < 0.001), reduction in left atrial volume index (from 38 to 32.8 m², p < 0.001), and decreased incidence of arrhythmias (from 48.3% to 25%, p = 0.008). Only three patients experienced mild adverse effects (mood and sleep disturbances), with no treatment discontinuation reported. **Conclusion:** Allopurinol is safe and efficacious in hyperuricemic patients with ACS, demonstrating significant improvements in cardiac function, a reduction in arrhythmic events, and favorable modification of echocardiographic parameters. These findings support the incorporation of uric acid screening and targeted allopurinol therapy in the comprehensive management of ACS patients with hyperuricemia.

Key words: hyperuricemia, allopurinol, acute coronary syndrome, xanthine oxidase inhibitor

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Резюме. **Въведение:** Хиперурикемията е значителен рисков фактор за сърдечно-съдови заболявания, по-специално за остър коронарен синдром (ОКС). Повишените нива на пикочна киселина в серума допринасят за ендотелиална дисфункция, оксидативен стрес и възпаление, които ускоряват прогресирането на коронарната болест. Алопуринолът, инхибитор на ксантиноксидазата, е показал потенциални кардиопротективни ефекти, които надхвърлят неговите свойства за понижаване на нивата на урат. **Цел:** Настоящото проучване имаше за цел да оцени безопасността и ефикасността на алопуринола при пациенти с хиперурикемия, при които се наблюдава ОКС. **Методи:** Проведохме проспективно проучване в Университетската болница в Асуан от юни 2024 г. до юни 2025 г. Общо 120 пациенти с ОКС бяха включени в проучването и разделени на две групи: Група А (n = 60) включваше пациенти с

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хиперурикемия (серумна пикочна киселина > 6,8 mg/dL), които получаваха алопуринол в комбинация със стандартна антиишемична терапия, а Група Б (n = 60) включваше пациенти с нормални нива на пикочна киселина, които получаваха само стандартна терапия. Алопуринолът се прилагаше в доза 600 mg/ден през острата фаза (първите 14 дни), последвана от 200 mg/ден за общо 4 седмици. Всички пациенти бяха подложени на цялостна оценка, включваща коронарна ангиография, ехокардиография и лабораторни изследвания в началото на проучването и след 3 месеца. **Резултати:** Характеристиките в началото на проучването показаха, че група А имаше значителнопо-висок ИТМ (24,7 ± 3,9 спрямо 23 ± 3,4 kg/m², p = 0,015), по-нисък HDL холестерол (39,8 ± 15,2 спрямо 74,6 ± 37,8 mg/dl, p < 0,001) и по-висока честота на положителни резултати за тропонин (81,7% спрямо 20%, p < 0,001) в сравнение с група Б. Ангиографският анализ показа, че група А има повече проксимални коронарни лезии (45% спрямо 20%, p < 0,001), по-висока честота на тежки стенози (93,3 спрямо 30%, p < 0,001) и по-високи SYNTAX-резултати (23,1 ± 3,6 спрямо 17,7 ± 3,9, p < 0,001). Група А също така показа по-висока честота на аритмии (48,3 спрямо 13,3%, p < 0,001), по-специално предсърдно мъждене. След терапията с алопуринол група А показа значително подобрение на фракцията на изтласкване на лявата камера (от 50,4 до 52,2%, p < 0,001), намаляване на индекса на обема на лявото предсърдие (от 38 до 32,8 m², p < 0,001) и по-ниска честота на аритмии (от 48,3 до 25%, p = 0,008). Само трима пациенти изпитаха леки нежелани реакции (нарушения на настроението и съня), като не бяха отчетени случаи на преустановяване на лечението. **В заключение:** Алопуринолът е безопасен и ефикасен при пациенти с хиперурикемия и ОКС, като показва значително подобрение на сърдечната функция, намаляване на аритмичните събития и благоприятна промяна в ехокардиографските показатели. Тези резултати подкрепят включването на скрининг за нивото на пикочната киселина и целенасочена терапия с алопуринол в комплексното лечение на пациенти с ОКС и хиперурикемия.

Ключови думи: хиперурикемия, алопуринол, остър коронарен синдром, инхибитор на ксантиноксидазата

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Introduction

Hyperuricemia, characterized by elevated serum uric acid (UA) levels, has emerged as a significant biomarker and potential mediator of cardiovascular disease. Observational studies have consistently linked hyperuricemia with an increased risk of major adverse cardiovascular events (MACE) and poorer prognosis following acute coronary syndrome (ACS) [1]. The underlying pathophysiological mechanisms are multifactorial, involving endothelial dysfunction, increased oxidative stress via xanthine oxidase (XO) activity, activation of the inflammasome, and systemic inflammation, all of which contribute to the progression of atherosclerosis and myocardial injury [2].

Allopurinol, a well-established XO inhibitor, is primarily used to manage gout and hyperuricemia. In addition to its urate-lowering effects, allopurinol exhibits pleiotropic cardiovascular properties. By inhibiting XO, the production of reactive oxygen species (ROS) and uric acid is reduced, thereby potentially improving endothelial function, reducing vascular inflammation, and attenuating myocardial ischemia-reperfusion injury [3]. These mechanisms suggest a promising therapeutic role for allopurinol in high-risk cardiac populations.

Despite this compelling biological rationale, clinical evidence regarding the efficacy and safety of allopurinol initiated during the acute phase of ACS remains inconclusive and limited in terms of quantity. While some studies suggest potential benefits on endothelial function and cardiovascular outcomes [4], others have failed to demonstrate a significant impact on major cardiovascular events in patients with ischemic heart disease [5]. This inconsistency highlights a critical gap in knowledge and underscores the need for targeted clinical evaluations.

Therefore, this study aimed to investigate the safety and efficacy of allopurinol in hyperuricemic patients presenting with ACS. Specifically, we sought to evaluate whether the addition of allopurinol to standard anti-ischemic therapy improves clinical and echocardiographic outcomes, reduces arrhythmic burden, and influences coronary artery disease severity as assessed by angiography and the SYNTAX score, compared to ACS patients with ACS with normal uric acid levels.

Methods

This was a prospective study conducted at the Cardiology Department of Aswan University Hospital, Egypt, from June 2024 to June 2025. The study included 120 patients diagnosed with Acute Coronary Syndrome (ACS) and underwent coronary angiography during hospital course and then divided into two groups based on level of uric acid. Group A comprised 60 Patients with ACS and hyperuricemia (serum uric acid > 6.8 mg/dL) who received allopurinol in addition to standard anti-ischemic therapy, Group B comprised 60 Patients with ACS and normal uric acid levels (≤ 6.8 mg/dL) who received only standard anti-ischemic therapy. Patients with hypersensitivity to allopurinol, thyroid disorders, hepatic or renal insufficiency, acute gout attack were excluded from the study.

All patients received guideline-directed medical therapy for ACS, including antiplatelet agents, anticoagulants, beta-blockers, statins, and ACE inhibitors/ARBs, as indicated.

Group A: Received allopurinol at a dose of 600 mg/day during the acute phase (first 14 days), followed by 200 mg/day for the remaining 4 weeks (total treatment duration: 4 weeks), as adapted from previous protocols [6]. Group B: Received standard care without the use of allopurinol.

All patients were subjected to

1. Clinical Evaluation including detailed history, physical examination, and documentation of risk factors.
2. **Electrocardiography (ECG):** Performed on admission and after 3 months of treatment to detect ischemic changes and arrhythmia.
3. **Echocardiography:** A comprehensive 2D echocardiogram (GE Vivid E9) was performed within 48 h of admission and after 3months of treatment to assess:
   – Left ventricular ejection fraction (LVEF)
   – Left atrial volume index (LAVI)
   – Wall motion abnormalities
   – Diastolic dysfunction (graded I–III)
   – Valvular lesions
   – Speckle-tracking-derived global longitudinal strain (GLS)
4. **Coronary Angiography:** Performed during hospitalization to evaluate
   – Number of diseased vessels
   – Lesion location (proximal, mid, distal, ostial).
   – Stenosis severity (mild: 20-49%; moderate: 50-69%; severe: 70-99%)
   – SYNTAX score (for multi-vessel disease)
5. **Laboratory investigations included:** serum uric acid, troponin, lipid profile, renal function, HbA1c, and complete blood count.
6. **Follow-up Assessment was done at 3 months to assess:** ECG changes, echocardiographic parameters modification such as (LVEF, LAVI and diastolic dysfunction), uric acid level, any MACE and re-hospitalization with heart failure or acute coronary syndrome.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows (version 24.0; IBM Corp., Armonk, NY, USA). The data are presented descriptively according to the variable type and distribution. Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables are reported as frequencies and percentages. Baseline characteristics and outcomes of Group A (ACS with hyperuricemia receiving allopurinol) and Group B (ACS with normouricemia receiving standard care) were compared using appropriate inferential tests. The normality of continuous variables was evaluated using the Shapiro-Wilk test and visual assessment of the Q-Q plots. Normally distributed continuous variables were compared using the independent samples t-test, while the non-parametric Mann-Whitney U test was used for non-normally distributed variables. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test for 2 × 2 tables with expected cell counts < 5. To assess the longitudinal effects of allopurinol on clinical and echocardiographic outcomes, repeated-measures analysis of variance (ANOVA) was employed. This model was tested for within-subject changes over time, as well as the interaction between time and treatment group, to determine whether the trajectory of change differed significantly between groups. Mauchly's test was used to assess sphericity, with the Greenhouse-Geisser correction applied when the assumption was violated. For all analyses, a two-tailed p-value of < 0.05 was considered statistically significant.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee of the Aswan University. Written informed consent was obtained from all the participants. Confidentiality was maintained, and patients were free to withdraw from the study at any time without prejudice.

Results

A total of 120 patients with Acute Coronary Syndrome (ACS) were enrolled and allocated into two groups: Group A (n = 60) comprised hyperuricemic patients (serum uric acid > 6.8 mg/dL) who received allopurinol in addition to standard anti-ischemic therapy, and Group B (n = 60) included normouricemic patients who received standard therapy alone.

Baseline Characteristics and Laboratory Findings

The mean age was comparable between groups A (59.9 ± 11.3 years) and B (58.8 ± 9.6 years) ($p = 0.573$). There were no significant differences in sex distribution or traditional cardiovascular risk factors, such as diabetes mellitus, hypertension, or prior ischemic heart disease (all $p > 0.05$). However, Group A had a significantly higher body mass index (24.7 ± 3.9 vs. 23.0 ± 3.4 kg/m², $p = 0.015$) and a lower proportion of smokers (15% vs. 60%, $p < 0.001$).

As expected, serum uric acid levels were markedly higher in Group A (10.8 ± 2.38 mg/dL) than in Group B (4.92 ± 0.99 mg/dL) ($p < 0.001$). Group A also exhibited lower high-density lipoprotein (HDL) (39.8 ± 15.2 vs. 74.6 ± 37.8 mg/dL, $p < 0.001$) and lower triglyceride levels (154.3 ± 40.3 vs. 190 ± 45 mg/dL, $p < 0.001$). Troponin positivity was significantly more frequent in Group A (81.7% vs. 20%, $p < 0.001$), suggesting greater myocardial injury at presentation. No significant differences were observed in other laboratory parameters, including HbA1c, creatinine and lipid profile ($p > 0.05$) (Table 1).

Baseline echocardiographic parameters, including left ventricular ejection fraction (LVEF), left ventricular end-dia-

stolic diameter (LVEDD) did not differ significantly between the groups (p > 0.05). However, the left atrial volume index (LAVI) was significantly higher in Group A (38 ± 4.4 ml/m²) than in Group B (32.8 ± 2.8 ml/m², p < 0.001), indicating greater atrial remodeling, Valvular lesions were also more common in Group A (68.3% vs. 43.3%, p = 0.006).The incidence of arrhythmia was significantly higher in Group A (48.3% vs. 13.3%, p < 0.001), with atrial fibrillation being the most prevalent type (48.3% vs. 37.5%, though not statistically different in subtype analysis) (Table 2).

Table 1. Demographic data, Clinical presentation and Laboratory data between studied groups

Variable	Group A (N = 60)	Group B (N = 60)	P- value
Sex	Male: 53.3%, (n = 32)	Male: 70% (n = 42)	0.06
	Female:46.7%, (n = 28)	Female: 30% (n = 18)	
Age (years)	59.9 ± 11.3	58.8 ± 9.6	0.573
BMI (kg/m²) (Mean ±SD)	24.7 ± 3.9	23 ± 3.4	0.015
Risk Factors			
Diabetes Mellitus (DM)	68.3%	55%	0.133
Hypertension (HTN)	53.3%	53.3%	1.0
Ischemic Heart Disease (IHD)	18.3%	23.3%	0.5
Smoking	15%	60%	1.0
Acute Coronary Syndrome	Unstable Angina: 16.7%	Unstable Angina: 18.3%	0.810
	NSTEMI: 55%	NSTEMI: 48.3%	0.465
	STEMI: 28.3%	STEMI: 33.3%	0.53
NSTEMI Risk	High: 81.8%	High: 96.6%	0.067
	Very High: 18.2%	Very High: 3.4%	
Uric Acid (mg/dL) (Mean ±SD)	10.8 ± 2.38	4.92 ± 0.99	< 0.001
HbA1C (%) (Mean ±SD)	7.72 ± 2.47	7.87 ± 2.85	0.756
Creatinine (mg/dL) (Mean ±SD)	1.07 ± 0.29	1.11 ± 0.46	0.673
Urea (mg/dL) (Mean ±SD)	35.1 ± 12.8	40 ± 17.7	0.081
Hemoglobin (g/dL) (Mean ±SD)	12.7 ± 1.7	12.6 ± 2	0.750
Cholesterol (mg/dL) (Mean ±SD)	208.2 ± 38.6	195.9 ± 30.1	0.053
Triglycerides (mg/dL) (Mean ±SD)	154.3 ± 40.3	190 ± 45	< 0.001
LDL (mg/dL) (Mean ±SD)	119.5 ± 33	131.7 ± 42.6	0.081
HDL (mg/dL) (Mean ±SD)	39.8 ± 15.2	74.6 ± 37.8	< 0.001
Non-HDL (mg/dL) (Mean ±SD)	170.6 ± 45.7	161.9 ± 47	0.301
Troponin	Positive: 81.7%	Positive: 20%	1.0
	Negative: 18.3%	Negative: 80%	

SD = Standard deviation, BMI = body mass index, NSTEMI = non ST segment elevation myocardial infarction, STEMI = ST segment elevation myocardial infarction, HBAIC = hemoglobin AIC, p value < 0.05 = significant, p value > 0.05 = non-significant.

Table 2. Comparison between studied groups as regard arrhythmias and Echocardiographic Parameters

Variable	Group A (N = 60)	Group B (N = 60)	P- value
Arrhythmia (Overall)	No : 51.7% (n = 31)	No: 86.7% (n = 52)	< 0.001
	Yes: 48.3% (n = 29)	Yes: 13.3% (n = 8)	
Types of Arrhythmia			
Atrial Fibrillation	48.3%	37.5%	0.588
Ventricular Fibrillation (VF)	6.9%	0%	0.445
Ventricular Tachycardia (VT)	5%	3.9%	0.619
Extra-systole	20.7%	37.5%	0.326
Complete heart block (CHB)	6.9%	0%	0.445
(LVEF %) (Mean ±SD)	50.4 ± 9.5	49.1 ± 10.7	0.512
LVEDD (cm) (Mean ±SD)	4.57 ± 0.61	4.73 ± 0.93	0.286
LVESV (cm) (Mean ±SD)	3.83 ± 0.4	4.04 ± 0.72	0.052
LAVI (ml/m²) (Mean ±SD)	38 ± 4.4	32.8 ± 2.8	< 0.001
Diastolic dysfunction (DD)	Grade I: 63.3% (n = 38)	GradeI: 68.3% (n = 41)	0.684
	Grade II: 33.3% (n = 20)	Grade II: 26.7% (n = 16)	
	Grade III: 3.3% (n = 2)	Grade III: 5% (n = 3)	
Valvular Lesions	Yes: 68.3% (n = 41)	Yes: 43.3% (n = 26)	0.006
	No: 31.7% (n = 19)	No: 56.7% (n = 34)	
	No: 80% (n = 48)	No: 50% (n = 30)	

SD = standard deviation, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end diastolic diameter, LVESD = left ventricular end diastolic diameter, LAVI = left atrial volume index, p value < 0.05 = significant, p value > 0.05 = non-significant.

Coronary angiography revealed no significant intergroup differences in the number of diseased vessels. However, Group A had a higher prevalence of proximal (45% vs. 20%) and ostial lesions (26.7% vs. 5%), whereas Group B had more distal lesions (43.3% vs. 10%) ($p < 0.001$). Stenosis severity was significantly worse in Group A, with 93.3% classified as severe compared to 30% in Group B ($p < 0.001$). Accordingly, the SYNTAX score, reflecting coronary lesion complexity, was significantly higher in Group A (23.1 ± 3.6) than in Group B (17.7 ± 3.9, $p < 0.001$) (Table 3).

At the 3-month follow-up, group A demonstrated significant improvements in several echocardiographic parameters compared to baseline: LVEF increased from 50.4 ± 9.5% to 52.2 ± 8.1% ($p < 0.001$), LAVI decreased from 38 ± 4.4 to 32.8 ± 4 ml/m² ($p < 0.001$), and the proportion of patients with diastolic dysfunction improved significantly ($p = 0.004$). The incidence of arrhythmia also decreased from 48.3% to 25% ($p = 0.008$) (Table 4). Also group B showed significant improvement in LVEF (49.1 ± 10.7% to 52.3 ± 8.5%, $p < 0.001$) and LAVI (32.8 ± 2.8 to 36.3 ± 5.1 ml/m², $p < 0.001$) but no significant change in arrhythmia incidence was observed ($p = 0.104$) (Table 5). We noticed also no significant difference between group A and group B as regard LVEF (P value 0.9) but there was significant improvement in LAVI in group A in comparison with group B after 3 months of treatment (p value 0.001), also there was significant improvement in diastolic function in group A better than group B (p value 0.01), clinically, there was a trend toward fewer cardiovascular events at 3 months in Group A (20% vs. 50% in Group B), although this did not reach statistical significance ($p = 0.099$). The re-hospitalization rates were similar between the groups ($p = 0.729$) (Table 6). The allopurinol treatment was well tolerated. Only three patients (5%) reported mild mood or sleep disturbances, which did not necessitate discontinuation. No cases of severe hypersensitivity, hepatotoxicity, or hematological adverse effects were observed.

Table 3. Comparison of coronary angiography between studied groups

Variables		Group A (N = 60)		Group B (N = 60)		P-value
Number of diseased vessels	Mean ±SD	2.15 ± 0.94		2.3 ± 1.01		0.401
	Range	0-4		1-4		
Site of lesion	Proximal	27	45%	12	20%	< 0.001
	Mid	11	18.3%	19	31.7%	
	Distal	6	10%	26	43.3%	
	Ostial	16	26.7%	3	5%	
Stenosis severity	Low	1	1.7%	7	11.7%	< 0.001
	Moderate	3	5%	35	58.3%	
	Severe	56	93.3%	18	30%	
Syntax score	Mean ±SD	23.1 ± 3.6		17.7 ± 3.9		< 0.001
	Range	16-30		10-24		

SD = standard deviation, p value < 0.05 = significant, p value > 0.05 = non-significant.

Table 4. comparison of echocardiographic data and risk of arrhythmia (before & after TTT) in group A

Variables	Group A	Before (N = 60)		After (N = 60)		P-value
LVEF (%)]	Mean ±SD	50.4 ± 9.5		52.2 ± 8.1		< 0.001
	Range	25 - 67		30 - 67		
LAVI	Mean ±SD	38 ± 4.4		32.8 ± 4		< 0.001
	Range	30-54		29-52		
Arrhythmia	No	31	51.7%	45	75%	0.008
	Yes	29	48.3%	15	25%	
LVDD	Grade I	38	63.3%	53	88.3%	0.004
	Grade II	20	33.3%	7	11.7%	
	Grade III	2	3.3%	0	0%	

SD = standard deviation, LVEF = left ventricular ejection fraction, LVDD = left ventricular diastolic dysfunction, LAVI = left atrial volume index, p value < 0.05 = significant, p value > 0.05 = non-significant.

Table 5. Comparison of echocardiographic data and risk of arrhythmia (before & after TTT) in group B

Variables	Group B	Before (N = 60)		After (N = 60)		P-value
LVEF (%)	Mean ±SD	49.1 ± 10.7		52.3 ± 8.5		< 0.001
	Range	20-67		29-67		
LAVI	Mean ±SD	32.8 ± 2.8		36.3 ± 5.1		< 0.001
	Range	28-42		29-50		
Arrhythmia	No	52	86.7%	45	75%	0.104
	Yes	8	13.3%	15	25%	
LVDD	No	0	0%	8	13.3%	0.004
	Grade I	41	68.3%	43	71.7%	
	Grade II	16	26.7%	9	15%	
	Grade III	3	5%	0	0%	

SD = standard deviation, LVEF = left ventricular ejection fraction, LVDD = left ventricular diastolic dysfunction, LAVI = left atrial volume index, p value < 0.05 = significant, p value > 0.05 = non-significant.

Table 6. Comparison between studied groups as regard cardiovascular events and echocardiographic parameters after 3 months of treatment

Variables		Group A (N = 60)		Group B (N = 60)		P-value
Symptoms (cardiovascular events)	No	48	80%	20	50%	0.099
	Yes	12	20%	20	50%	
LAVI	Mean ±SD	32.8 ± 4		36.3 ± 5.1		< 0.001
	Range	29 - 52		29 - 50		
LVEF	Mean ±SD	52.2 ± 8.1		52.3 ± 8.5		0.947
	Range	30-67		29-67		
LVDD	No	0	0%	8	13.3%	0.01
	Grade I	53	88.3%	43	71.7%	
	Grade II	7	11.7%	9	15%	
Hospital re-admission	No	55	91.7%	56	93.3%	0.729
	Yes	5	8.3%	4	6.7%	

SD = standard deviation, LVEF = left ventricular ejection fraction, LVDD = left ventricular diastolic dysfunction, LAVI = left atrial volume index, p value < 0.05 = significant, p value > 0.05 = non-significant

Discussion

Our study offers substantive evidence supporting the therapeutic potential of allopurinol in patients with hyperuricemia presenting with acute coronary syndrome (ACS). Our findings delineate two principal narratives: first, hyperuricemia is independently associated with a more severe and complex coronary disease phenotype; and second, short-term adjunctive treatment with allopurinol confers measurable improvements in cardiac structure and function, along with a favorable safety profile.

The observed demographic and clinical profile of our hyperuricemic cohort (Group A – characterized by higher BMI, dyslipidemia (elevated triglycerides and reduced HDL), and a greater incidence of arrhythmias – corroborates the established notion that elevated serum uric acid (SUA) levels are frequently embedded within a metabolic syndrome framework [7]. However, its role extends beyond that of a simple biomarker. At supra-physiological concentrations, UA transitions from an antioxidant to a potent pro-oxidant, instigating a cascade of deleterious cardiovascular effects [8].

The significantly higher prevalence of atrial fibrillation (AF) in Group A (48.3% vs. 37.5% in Group B) was particularly noteworthy. The pathophysiological link may be multifactorial: UA-induced oxidative stress promotes atrial fibrosis and electrical remodeling, whereas activation of the NLRP3 inflammasome leads to the release of IL-1β and IL-18, which are known to destabilize atrial cardiomyocyte electrophysiology [9]. This finding aligns with population studies, such as the Framingham Heart Study, which identified hyperuricemia as an independent risk factor for AF development[10].

Angiographic findings further underscore the severity of the disease in hyperuricemic patients. The predominance of proximal lesions and higher SYNTAX scores in Group A suggest a more aggressive and unstable form of atherosclerosis. This is mechanistically plausible because UA crystals can activate vascular endothelial cells and promote the expression of adhesion molecules, whereas XO-derived reactive oxygen species (ROS) contribute to endothelial dysfunction, lipid peroxidation, and plaque vulnerability [11]. Our results are consistent with those of **He et al. (2019) and Kaya et al. (2010)**, who similarly reported positive correlations between serum UA levels and angiographic disease complexity.

The clinical benefits observed in Group A following allopurinol therapy – improved LVEF, reduced LAVI, ameliorated diastolic dysfunction, and decreased arrhythmia burden – can be attributed to its dual pharmaco-dynamic action: xanthine oxidase inhibition and consequent reduction in oxidative stress and inflammation.

Improvement in Ventricular Function and Remodeling: The significant increase in LVEF and reduction in LAVI post-treatment highlighted allopurinol's role in mitigating adverse cardiac remodeling. XO is a major source of ROS in the ischemic heart. By inhibiting XO, allopurinol reduces oxidative damage to cardiomyocytes, improves calcium handling, and preserves mitochondrial function [12]. The reduction in LAVI, a robust marker of left atrial pressure and chronic diastolic burden, suggests improved ventricular compliance and filling pressures, likely secondary to reduced myocardial fibrosis and inflammation [3].

Antiarrhythmic Effects: The marked reduction in overall arrhythmia prevalence, particularly AF, from 48.3% to 25% in Group A, was a compelling finding. In addition to lowering UA, allopurinol's inhibition of XO reduces the production of ROS, which are known to disrupt cardiac ion channel function (e.g., Kv1.5) and promote triggered activity [9]. Furthermore, by attenuating the inflammatory milieu (indirectly evidenced by improved clinical outcomes), allopurinol may reduce the substrate for atrial fibrillation.

Plaque Stabilization and Endothelial Protection: While study did not directly measure endothelial function or plaque characteristics, the observed trend towards fewer recurrent cardiovascular events in Group A (20% vs. 50% in Group B, $p = 0.099$) hints at systemic vascular benefits. Allopurinol has been shown to enhance nitric oxide (NO) bioavailability, reduces endothelial apoptosis, and decreases levels of inflammatory cytokines, such as TNF-α and hs-CRP [13]. These effects contribute to improved endothelial function and potentially greater plaque stability in the arteries.

Our positive results are consistent with those of several mechanistic and clinical studies. **Kanbay et al.** (2007) demonstrated that allopurinol improved flow-mediated dilatation (a measure of endothelial function) in hyperuricemic patients [14]. **Similarly, Huang et al.** (2017) found that allopurinol reduced infarct size and inflammatory markers in patients with ACS [3]. Our findings extend this evidence by demonstrating tangible improvements in standardized echocardiographic and clinical parameters in a real-world ACS cohort. However, we acknowledge the contradictory results of some large-scale outcome trials. The **EXACT-HF trial** [5] found no improvement in exercise capacity or clinical status with allopurinol in patients with heart failure, and the **ALL-HEART study** [15] reported no reduction in cardiovascular events with allopurinol in patients with ischemic heart disease. Several critical distinctions may explain these discrepancies: 1-Patient Population: Our study exclusively enrolled hyperuricemic ACS patients, a group experiencing an acute inflammatory and oxidative burst, where XO inhibition might be most impactful. In contrast, ALL-HEART included patients with

stable IHD regardless of uric acid levels. 2-Timing and Duration: We initiated allopurinol treatment during the acute phase of ACS (within 14 days), targeting a period of heightened XO activity and reperfusion injury. Many negative trials have used allopurinol for secondary prevention in the chronic stable phase. 3-Outcome Measures: We focused on intermediate endpoints (echocardiographic function and arrhythmias), which may be more sensitive to the biological effects of allopurinol over a short period than hard clinical endpoints, such as mortality, which require larger sample sizes and longer follow-up.

The safety profile of allopurinol was excellent in our acute setting. The reported side effects were minor and did not lead to treatment discontinuation in any case. This is crucial because concerns regarding allopurinol hypersensitivity syndrome often deter its use. Our protocol, which excluded patients with renal or hepatic impairment, likely contributed to this safety profile. The dosing regimen (600 mg/day acute, then 200 mg/day maintenance) was adapted from prior cardiovascular studies [6] and was proven feasible.

Limitations

Our study had some limitations as a single-center trial; the external validity may be constrained and the 3-month follow-up while sufficient to detect functional changes was too short to assess the effects on mortality or MACE.

The lack of serial measurements of oxidative stress (e.g., MDA) and inflammatory biomarkers (e.g., hs-CRP, IL-1β) is a missed opportunity for mechanistic confirmation.

Conclusion

Our study demonstrated that allopurinol is safe and effective in hyperuricemic patients with acute coronary syndrome. Treatment with allopurinol resulted in significant improvements in cardiac function, a reduction in arrhythmia burden, and favorable modification of echocardiographic parameters. Patients with hyperuricemia and ACS presented with more severe and complex coronary artery disease, highlighting the importance of uric acid assessment in this population.

Recommendations

1. Based on our findings, we recommend the following:

2. Serum uric acid levels should be measured in all patients with ACS for enhanced risk stratification.

3. Consider allopurinol therapy in hyperuricemic ACS patients, particularly those with complex coronary diseases or arrhythmias.

4. Allopurinol should be initiated during the acute hospitalization phase when feasible.

5. Integrating uric acid management into comprehensive cardiac rehabilitation programs is essential.

6. Increased awareness among cardiologists regarding the cardiovascular implications of hyperuricemia is required.

7. Support further investigations into the mechanisms and long-term benefits of xanthine oxidase inhibition in cardiovascular disease.

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