

Original Article



Impact of Allopurinol on early and one-year outcomes of patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: A randomized controlled trial

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Summary

Background: Due to the potential benefits of allopurinol in ischemic reperfusion injury, this randomized control trial was performed to evaluate the pretreatment allopurinol effect on major adverse cardiovascular events (MACE) in patients undergoing primary percutaneous coronary intervention (pPCI).

Methods: A randomized controlled trial was performed on 170 first-time ST-elevation myocardial infarction (STEMI) patients undergoing pPCI. Before the procedure, patients in intervention group (n=85) received 300 mg dose of allopurinol and control group (n=85) received placebo. Then, for the next 28 days, 100 mg of allopurinol was given to allopurinol group and placebo to the other group. Patients were compared regarding the baseline characteristics, clinical findings and one-year MACE.

Findings: Our findings showed that patients receiving allopurinol had significantly longer door-to-balloon time than the control group (60.76±19.38 vs. 50.06±16.38, *P* value: 0.001). During one year of follow-up, heart failure (HF), cerebrovascular event (CVA) and mortality occurred more frequently in allopurinol group but differences were not statistically significant. No significant difference was also seen between the two groups regarding MACE during follow-up or hospitalization (*P*=0.179, 0.330 respectively). Kaplan-Meier curve could not show a significant difference between the two groups in terms of mortality and MACE (*P*=0.317 and 0.128 respectively).

Conclusion: According to findings of this trial allopurinol had no cardioprotective effect against adverse cardiovascular events or death in patients undergoing pPCI.

Trial Registration: Identifier: IRCT20140512017666N2; <https://irct.behdasht.gov.ir/>.

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Introduction

Coronary artery disease (CAD) is the number one cause of mortality in most countries. CAD can lead to acute myocardial infarction (MI), especially ST elevation MI (STEMI), the most severe type.¹ The World Health Organization (WHO) estimates that annually 7.3 million deaths worldwide occur due to MI.² MI leads to significant long-term morbidity among survivors due to complications such as heart failure (HF) and raised risks of death, cerebrovascular event (CVA), and recurrent MI.^{3,4}

It is essential to seek proper therapies to enhance the clinical outcomes of MI patients. The current standard treatment for acute STEMI is myocardial reperfusion, primarily done through primary percutaneous coronary intervention (pPCI).³

One of the enzymes involved in producing reactive oxygen species (ROS) is the xanthine oxidase (XO).

ROS may lower the contractility of cardiac muscles, leading to HF.⁵ They are also implicated in ischemia-reperfusion injury, atherosclerosis, hypertension (HTN), and thrombosis.⁶ Allopurinol is a common XO inhibitor prescribed mainly to treat hyperuricemia. Allopurinol can prevent ROS production, unlike other antioxidants that reduce free radicals after production.⁷ The cardiovascular benefits of allopurinol have been suggested to occur through three fundamental mechanisms. The first action is increasing local tissue availability of oxygen and adenosine triphosphate by interfering with purine catabolism.^{8,9} The second one is reducing uric acid serum concentration, which is a pro-inflammatory factor.^{10,11} The third mechanism is inhibiting ROS generation, which promotes endothelial dysfunction and atherosclerosis plaque instability.^{12,13}

Past considers investigating the impact of allopurinol



on ventricular action, infarct size, reperfusion injury, and arrhythmia event have driven to conflicting results, and the results have not been collectively positive.^{5,14-16}

Given the doubts about allopurinol's benefits for preventing major adverse cardiovascular events (MACE) in cardiac patients, we aimed to evaluate the impact of allopurinol in patients with acute STEMI undergoing pPCI by comparing the incidence of HF, death, and CVA in patients enrolled in this randomized controlled trial (RCT).

Methods

This study was carried out at the Shahid Madani Heart Hospital in Tabriz, Iran from March 2020 to March 2021. The Tabriz University of Medical Sciences Ethics Committee approved the study protocol (IR.TBZMED.REC.1398.487), and written informed consent was obtained from all patients. Protocol of this trial was also registered in the Iranian Registry of Clinical Trials (IRCT: IRCT20140512017666N2, Registration date: 2019-10-15) and has been carried out in accordance with Declaration of Helsinki.

Study population and design

This RCT enrolled patients with STEMI who were admitted within 12 hours of symptom onset and underwent pPCI. Inclusion criteria required patients to be over 18 years old, have a confirmed diagnosis of first-time STEMI, and achieve successful pPCI, defined as post-angiographic stenosis of less than 25%. STEMI was defined as at least two continuous leads with ST-segment elevation of more than 2.5 mm in males under 40, 2 mm in men over 40, or 1.5 mm in women in leads V2-V3 and/or 1 mm in the remaining leads.¹⁴ Patients with any evidence of intimal dissection within 24 hours from admission were excluded. Other exclusion criteria were the presence or history of ventricular tachycardia or fibrillation, any kind of bundle block, previous HF or MI and history of revascularization, patients with severe valve disease, those who had contraindications for allopurinol use, patients with cardiogenic shock at the time of admission or history of previous CVA, and finally those who were candidates just for percutaneous old balloon angioplasty (POBA) were also excluded. We used the results of our previous study¹⁵ to determine the sample size. Considering $\alpha = 0.05$ and a power of 80%, 80 patients in each group and a total of 160 patients were calculated for this study. One hundred eighty-four individuals were initially included in the study due to the potential of missing data and attrition. Random numbers were generated using the RANDLIST 1.2 software, and patients were divided into intervention and placebo groups based on sample size. Before the PCI, patients in each group received either a 300 mg dose of allopurinol or a placebo. Then, for the next 28 days, 100 mg of allopurinol was given to intervention group and

placebo (which contained starch and was in the form of tablets) to control group. Aspirin 325 mg and clopidogrel 300 mg were given orally, along with weight-adjusted intravenous heparin, as part of the normal pretreatment protocol for pPCI. All pPCIs were performed out by expert interventional cardiologists using the standard technique, and none of the staff members in the catheterization lab were aware of the groups.

Laboratory and clinical measurements

Baseline findings were recorded in all patients including demographic information like age, gender, and medical history including HTN, diabetes mellitus (DM), hyperlipidemia, smoking, and family history of MI. On admission, venous blood samples were taken and placed in citrated tubes with ethylenediaminetetraacetate (EDTA) potassium salt additive. The hospital laboratory received and examined blood samples. To achieve laboratory results, a daily-calibrated automated Coulter CBC H1 counter was used. Measurements were performed for hemoglobin, creatinine, uric acid, and cardiac troponin I (cTnI). During the first 48 hours of hospitalization, the blood levels of cTnI were monitored every 6 hours, and their peak values were recorded. At admission and 90 minutes after pPCI, a standard 12-lead ECG was taken, and 20 milliseconds after the end of the QRS complex, the ST-E sum was measured for the affected leads. At the time of admission and 40 days following pPCI, the left ventricle ejection fraction (LVEF) was measured echocardiographically using the modified Simpson's rule.

Follow-up

Throughout the one-year follow-up period, patients were monitored for occurrence of MACE. There were no patients lost to follow-up during the study period. Calls were made one, six, and 12 months after discharge to check on the patients. Re-hospitalizations due to HF and stroke at our hospital or other hospitals were detected and recorded through regular clinic visits. Diagnosis and assessment of HF in the hospital and clinic were done by an experienced cardiologist. Finally, patients' information during one year of follow-up was collected and compared between the placebo and intervention groups.

Outcomes

MACE was defined as a composite of mortality, HF, and CVA during hospitalization and follow-up. The principal aim of the study was to evaluate the effect of allopurinol use on one-year MACE. Comparison of HF, CVA, and mortality separately between two groups during the follow-up period was the secondary outcome of this study.

Statistical analysis

All statistical analysis were conducted using SPSS (Version 21.0; IBM SPSS Corporation, Chicago, IL). The

Kolmogorov-Smirnov test was used to verify the normal distribution assumption for continuous data. While qualitative data were provided as frequency and percent (%), quantitative data were shown as mean (SD). For continuous variables, an independent samples t-test was utilized. The chi-square test, as appropriate, was used to analyze categorical variables. Calculations were made to determine relative risks (RRs) and their confidence intervals (CIs). The Kaplan-Meier curve was used in survival analysis to compare the mortality and follow-up MACE between the two groups. *P* values < 0.05 were considered statistically significant.

Results

Of 184 patients diagnosed with anterior STEMI who were eligible to participate in this study, 14 patients were not enrolled according to the exclusion criteria as shown in Figure 1. Eventually, 170 patients were randomly divided into group A, the allopurinol-treated group (*n*=85), or group B, the placebo group (*n*=85). The baseline characteristics and demographics of the patients are shown in Table 1. The mean age of the whole population was 56.51 ± 11.66 years and the majority of

the patients were men, however, there was no significant difference between the two groups regarding age and gender. Furthermore, the baseline features of patients including LVEF, hemoglobin, creatinine, uric acid, and cTnI concentrations did not statistically differ between the two groups. The most common risk factor in eligible participants was HTN (39.4%) followed by smoking (38.2%) and diabetes (20%). No significant difference was there in total ischemic time and ST elevation (*P*=0.863, 0.172 respectively). The intervention group had significantly longer door-to-balloon time than the control group (60.76 ± 19.38 vs. 50.06 ± 16.38 , *P*=0.001). More than half of the patients (58.8%) had one vessel disease and almost all of them (98.8%) had TIMI (thrombolysis in MI) flow 3, but there was no significant difference between the two groups (*P*=0.837 and 0.884, respectively). LVEF of the patients was compared after 40 days of pPCI and there was no significant difference between the two groups (mean: 37.79 ± 8.08 vs. 32.21 ± 4.89 ; *P*=0.118). The mean left ventricular diastolic diameter (LVDD) was 51.05 ± 4.90 mm 40 days after MI. Approximately 70% of the patients had ST resolution of more than 50% after PCI although the difference between the two groups was not

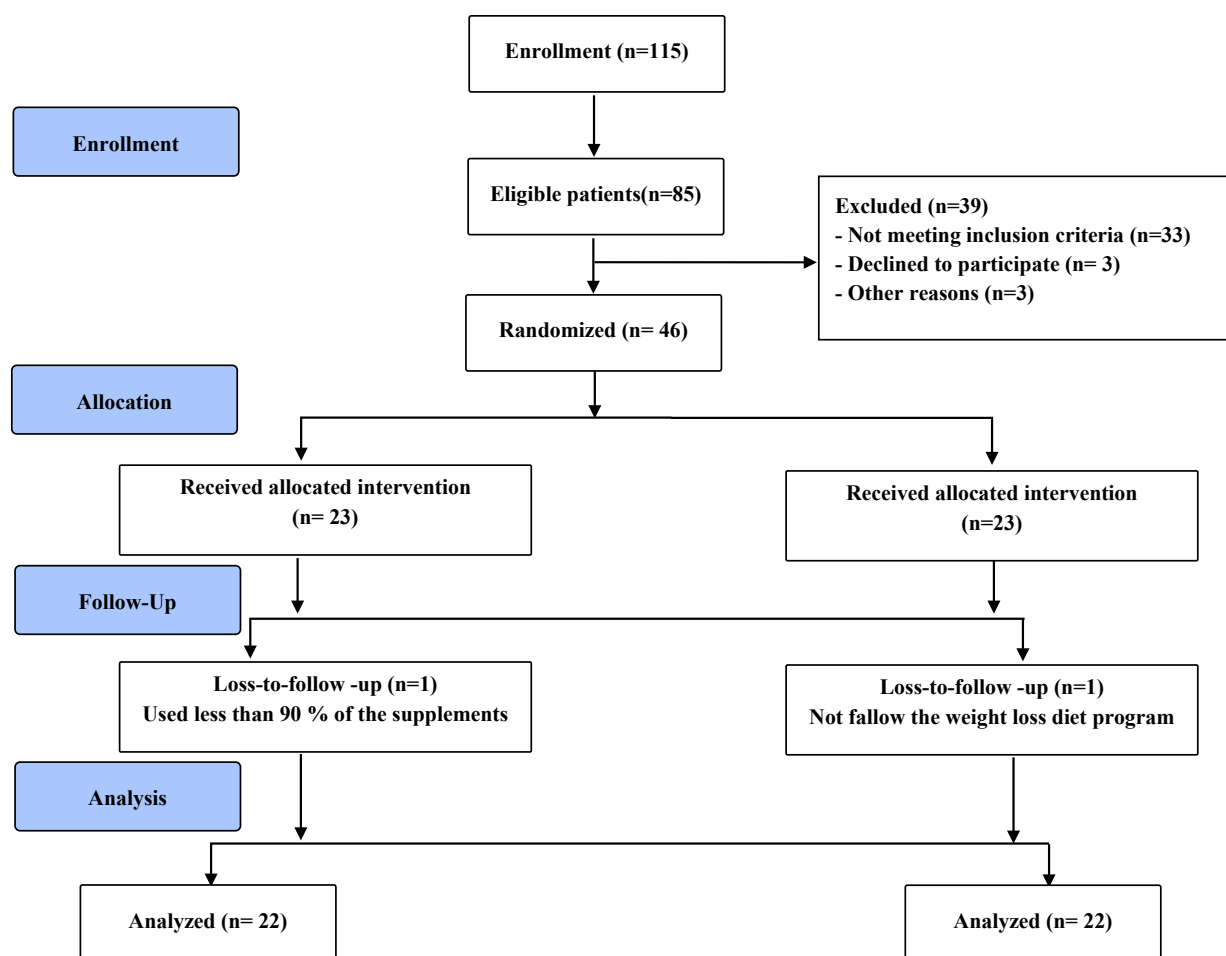


Figure 1. Flow diagram of the study

Table 1. Baseline characteristics of the patients

Finding	All patients (N=170)	Allopurinol (n=85)	Placebo (n=85)	P value
Age, year	56.51 ± 11.66	55.23 ± 11.05	57.78 ± 12.16	0.154
Gender				0.193
Male	145 (85.3%)	76 (89.4%)	69 (81.2%)	
Female	25 (14.7%)	9 (10.6%)	16 (18.8%)	
Ejection fraction (%)	32.21 ± 4.89	31.76 ± 4.67	32.65 ± 5.09	0.241
Hemoglobin (g/dL)	15.01 ± 1.92	15.06 ± 1.98	14.97 ± 1.87	0.757
Creatinine (mg/dL)	1.02 ± 0.20	1.03 ± 0.19	1.02 ± 0.22	0.826
Uric acid (mg/dL)	5.15 ± 1.26	5.02 ± 1.29	5.28 ± 1.22	0.168
Peak CTNI (ng/dL)	14.56 ± 9.68	14.98 ± 10.50	14.13 ± 8.82	0.568
Diabetes	34 (20%)	18 (21.2%)	16 (18.8%)	0.848
Hypertension	67 (39.4%)	32 (37.6%)	35 (41.2%)	0.754
Hyperlipidemia	25 (14.7%)	15 (17.6%)	10 (11.8%)	0.387
Smoking	65 (38.2%)	37 (43.5%)	28 (32.9%)	0.207
Familial history	9 (5.3%)	5 (5.9%)	4 (4.7%)	0.732
TIT (min)	273.59 ± 145.81	271.65 ± 153.74	275.53 ± 138.33	0.863
DBT (min)	55.44 ± 18.69	60.76 ± 19.38	50.06 ± 16.38	0.001
Total STE (mm)	13.74 ± 8.41	14.62 ± 8.81	12.85 ± 7.95	0.172

TIT: Total ischemic time, DBT: Door to balloon time, STE: ST elevation.

For continuous variables, an independent samples t-test was utilized. The chi-square test, as appropriate, was used to analyze categorical variables.

significant ($P=0.869$).

Post-angiographic outcomes of patients are shown in Table 2. As shown in the table, none of the measured outcomes differs significantly between the two groups.

Table 3 shows the clinical outcomes of the whole population. Based on our findings 12 (14.1%) patients in the allopurinol group and 7 (8.2%) patients in the placebo group experienced in-hospital MACE (RR: 1.83, 95% CI: 0.68-4.90, $P=0.330$). During the one-year follow-up, HF was the most common adverse event (16.5%) followed by CVA (3.5%) in all patients, with no significant difference between the two groups. Four (2.4%) patients died during the follow-up time and there was no statistically significant difference between the two groups regarding the follow-up mortality ($P=0.621$). Thirty-four patients experienced MACE during the follow-up, of which 21 (24.7%) of them were in the allopurinol group (RR: 1.81, 95% CI: 0.84-3.92, $P=0.179$).

Also, we performed a survival analysis to compare the mortality and MACE during the one-year follow-up between the two groups. As shown in Figure 2 and Figure 3 there was no significant difference between the two groups in terms of both mortality and MACE ($P=0.317$ and 0.128 , respectively).

Discussion

In the present study, we evaluated the effect of allopurinol on the incidence of MACE, HF, CVA, and mortality in adult patients undergoing pPCI. We did not find any significant difference in in-hospital MACE and in HF, CVA, mortality separately or follow-up MACE between the group receiving allopurinol after pPCI and the

placebo group. While rates of these complications were higher in the intervention group, none of the differences were statistically significant. There were no significant differences in baseline characteristics between two groups except door to balloon time (DBT), which was longer in the intervention group. The results of this research are supported by the context of literature within this field. In a meta-analysis by Bredemeier et al¹⁶ 65 RCTs for MACE and 74 RCTs for death were included in the analysis of the efficacy of purine-like XO inhibitors for prevention of cardiovascular events and mortality in patients from different settings. This study failed to establish a significant effect for these medications in the prevention of cardiovascular events and mortality. Data of off-treatment follow-up periods were excluded from this study. However, another meta-analysis by Singh et al.¹⁷ analyzing allopurinol efficacy in reducing the incidence of MI following coronary artery bypass grafting (CABG) showed cardioprotective effects for allopurinol. However, only six studies published before 2000 satisfied the eligibility criteria of this meta-analysis. Ullah et al¹⁸ addressed a similar question by analyzing nine studies, of which five of them were the same as the study of Singh et al.¹⁷ Ullah et al¹⁸ could not find any long-term benefits in terms of secondary prevention of acute coronary syndrome or mortality in patients undergoing CABG. Considering the findings of previous studies reporting the potential cardioprotective effects of allopurinol against MACE or death, no consensus has been established and many newer studies have reported contradictory findings on survival-increasing effects for allopurinol in

Table 2. Post-angiographic outcomes of patients

Finding	Total (N = 170)	Allopurinol (n = 85)	Placebo (n = 85)	P value
EF 40 days after MI	37.79 ± 8.08	36.82 ± 8.12	38.76 ± 7.97	0.118
LVDD 40 days after MI	51.05 ± 4.90	51.78 ± 3.52	50.32 ± 4.31	0.052
STR > 50%	116 (68.2%)	59 (69.4%)	57 (67.1%)	0.869
1 vessel disease	100 (58.8%)	51 (60%)	49 (57.6%)	0.837
2 vessel disease	44 (25.9%)	21 (24.7%)	23 (27.1%)	
3 vessel disease	26 (15.3%)	13 (15.3%)	13 (15.3%)	
TIMI flow				0.884
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	
2	2 (1.1%)	0 (0.0%)	2 (2.3%)	
3	168 (98.8%)	85 (100%)	83 (97.6%)	
MR				0.454
negative	78 (45.9%)	37 (43.5%)	41 (48.2%)	
+ 1	60 (35.3%)	32 (37.6%)	28 (32.9%)	
+ 2	29 (17.1%)	13 (15.3%)	16 (18.8%)	
+ 3	2 (1.2%)	2 (2.4%)	0 (0%)	
+ 4	1 (0.6%)	1 (1.2%)	0 (0%)	
Stent diameter	3.15 ± 0.43	3.15 ± 0.43	3.14 ± 0.44	0.958
Stent length	21.21 ± 6.91	21.36 ± 7.30	21.07 ± 6.54	0.782

EF: Ejection fraction, LVDD: Left ventricle diastolic diameter, STR: ST resolution, TIMI: Thrombolysis in myocardial infarction, MR: mitral regurgitation. For continuous variables, an independent samples t-test was utilized. The chi-square test, as appropriate, was used to analyze categorical variables.

Table 3. In-hospital MACE and one-year outcomes of patients

Finding	All patients (N = 170)	Allopurinol (n = 85)	Placebo (n = 85)	RR	95% CI	P value
In-hospital MACE	19 (11.2%)	12 (14.1%)	7 (8.2%)	1.83	0.68-4.90	0.330
HF	28 (16.5%)	17 (20.0%)	11 (12.9%)	1.68	0.73-3.84	0.301
CVA	6 (3.5%)	5 (5.9%)	1 (1.2%)	5.25	0.60-45.92	0.210
Mortality	4 (2.4%)	3 (3.5%)	1 (1.2%)	3.07	0.31-30.15	0.621
Follow-up MACE	34 (20.0%)	21 (24.7%)	13 (15.3%)	1.81	0.84-3.92	0.179

MACE: major adverse cardiovascular events, HF: heart failure, CVA: cerebrovascular accident; RR, relative risk. Multivariate analysis was done to determine the RR and P values.

cardiovascular disorders.¹⁹⁻²¹ However, allopurinol has been reported to positively affect HTN,²²⁻²⁴ endothelial function,²⁵⁻²⁷ left ventricular mass,²⁸⁻³⁰ rate of progression of kidney disease,³¹ and perinatal hypoxia-induced free radical formation.^{32,33} In a study by Goicoechea et al,³¹ 107 patients with chronic kidney disease were divided into two groups and followed up for five years. They found that long-term treatment with allopurinol can slow the rate of progression of kidney disease and reduce cardiovascular risk in patients with chronic kidney disease. Kanbay et al³⁴ analyzed 11 trials that treated HF patients with uric acid-lowering agents, which were allopurinol in most of the studies. They found these agents were associated with worse mortality outcomes and higher LVEF but did not significantly affect hospitalizations. In another study by Weisman et al³⁵ mortality and cardiovascular outcomes in an allopurinol-treated diabetes cohort of the elderly were assessed. Allopurinol was found to reduce all-cause mortality and cardiovascular events in this group of patients. Singh et al³⁶ also found similar results in patients

with gout and diabetes. It can be concluded that certain patient populations or patients with specific comorbidities might benefit from allopurinol and studies so far have not been able to uniformly prove the positive effects of allopurinol on the survival of the general population with cardiovascular disorders. Therefore, further research on the survival-increasing effects of allopurinol needs to focus on specified populations to determine which populations and subsets of patients benefit the most from adding allopurinol to their medication regimen. Besides the uncertainty of around prescribing allopurinol to patients, there is also no consensus on whether patients will benefit from higher doses. Some studies have found higher dosages to be harmful and some beneficial. Bredemeier et al¹⁶ found that the use of high doses of allopurinol (>300 mg/d), especially with furosemide, may lead to worse cardiovascular outcomes than treatment with lower dosages. Rekhraj et al²⁸ found high-dose allopurinol to regress left ventricle hypertrophy, and improve endothelial function in patients with

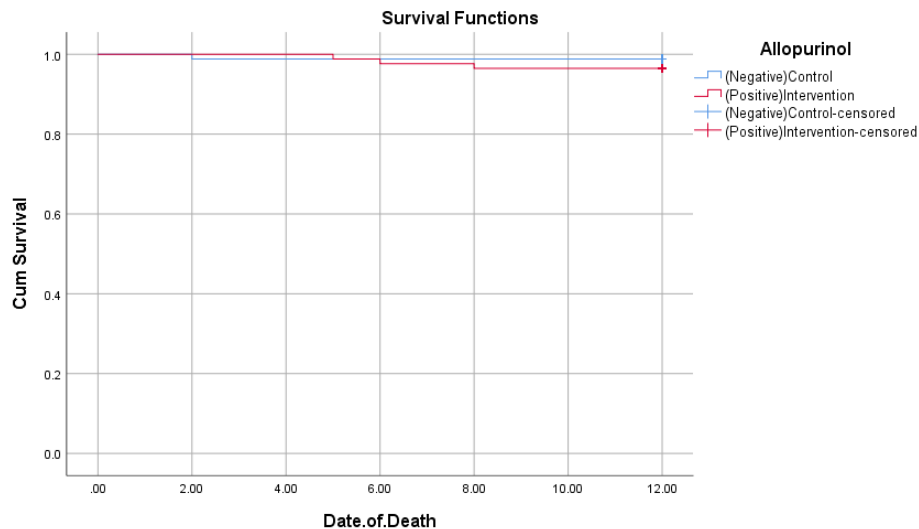


Figure 2. Kaplan-Meier curve for patients' mortality ($P=0.317$)

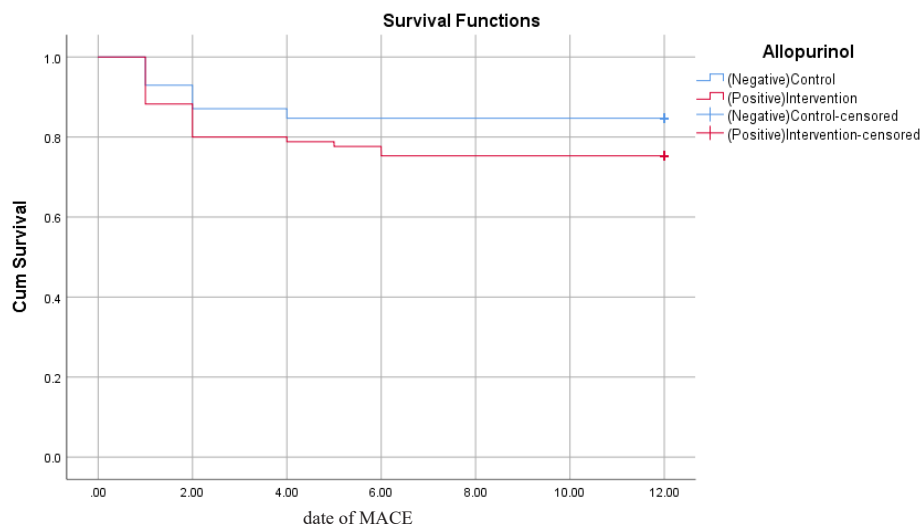


Figure 3. Kaplan-Meier curve for follow-up MACE ($P=0.128$)

ischemic heart disease. Rajendra et al³⁷ also found that high-dose allopurinol (600 mg/d) can decrease vascular tissue oxidative stress in optimally treated CAD patients. Therefore, the dosage of allopurinol should also be taken into account when interpreting its effect and indication.

Strengths of this study include its similar patient groups and accurate follow-up, as well as blinding of the patients and assessors. On the other hand, this study occurred in a single center and only included patients from the Caucasian race, which can make generalization of our findings to other races difficult. In addition, we only followed up the patients for a year and outcomes might have changed if there was a longer follow-up period. Therefore, future studies need to recruit more patients and follow them for longer, however, it is suggested to do so in patient populations with specific characteristics or comorbidities that might benefit from the effects of xanthine inhibitors.

Conclusion

Our findings show that allopurinol, despite possessing beneficial features in the treatment of other diseases, might not help patients undergoing pPCI with overall survival or occurrence of adverse outcomes. Therefore, it is recommended to thoroughly review the possible benefits of allopurinol before considering it as a possible choice for improving survival.

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Competing Interests

Authors declare that there is no competing of interests.

Ethical Approval

All methods were carried out following relevant guidelines and regulations. The data is anonymized, and no information regarding patients' identities was disclosed. The study was performed in accordance with the Helsinki Declaration. The protocol of this study was reviewed by the Ethics Committee of Tabriz University of Medical Sciences (ID: IR.TBZMED.REC.1398.487) and registered in the Iranian Registry of Clinical Trials (identifier: IRCT20140512017666N2).

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