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Impact of Urate-Lowering Therapy after Percutaneous Coronary Intervention on the Long-Term Prognosis of Patients with Hyperuricemia

Background	Hyperuricemia (HUA) frequently coexists with coronary artery disease (CAD) and is linked to adverse cardiovascular outcomes. The long-term impact of urate-lowering therapy (ULT) on clinical outcomes, including all-cause mortality and major adverse cardiovascular events (MACEs), in CAD patients after percutaneous coronary intervention (PCI) has not been determined. That was the aim of this study.
Material and methods	In this retrospective cohort study, we included 649 patients with HUA who underwent PCI between July 2014 and May 2020. Patients who received standardized ULT for at least one month post-PCI were assigned to the treatment group, while those untreated or nonadherent were assigned to the non-treatment group. Outcomes were assessed using Kaplan–Meier survival curves, multivariate Cox regression models, and propensity score matching. Preoperative and postoperative cardiac function, including left ventricular ejection fraction and right ventricular systolic pressure (RVSP), was evaluated.
Results	Over a median follow-up of 6.32 years, the incidence of all-cause mortality was 30.41 per 1,000 person-years, and MACEs occurred at a rate of 45.90 per 1,000 person-years. ULT was associated with a significant reduction in all-cause mortality (hazard ratio [HR]: 0.915; 95% confidence interval [CI]: 0.645–0.998) and MACEs (HR: 0.887; 95% CI: 0.661–0.990). Subgroup and sensitivity analyses confirmed these benefits, regardless of baseline uric acid (UA) concentrations or early UA normalization. Notably, ULT was most effective in reducing cardiovascular mortality and myocardial infarction, with no significant effect on stroke or heart failure. Cardiac function in the treatment group improved post-PCI, with significant improvements in diastolic function and RVSP. In a sensitivity analysis using propensity score matching, the protective effect of ULT on both all-cause mortality and MACEs remained robust, reinforcing the conclusions of the primary analyses.
Conclusion	Early initiation of ULT in patients with HUA after PCI is associated with improved long-term survival, reduced MACEs, and better cardiac function. These findings underscore the clinical value of ULT.

Keywords	Hyperuricemia; percutaneous coronary intervention; urate-lowering therapy; mortality; major adverse cardiovascular even
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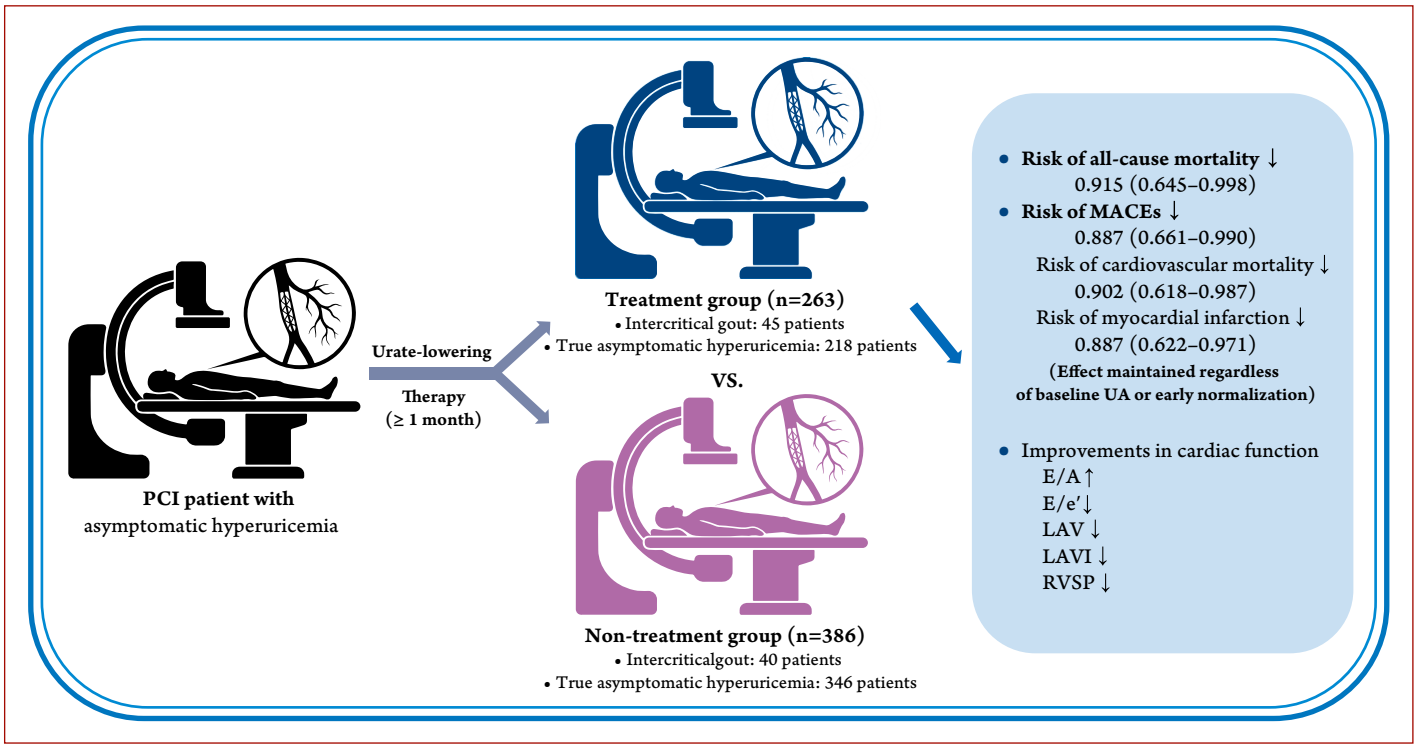
Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality globally, with coronary artery disease (CAD) representing a major contributor [1, 2]. Advances in interventional techniques and stent technologies have positioned percutaneous coronary intervention (PCI) as the primary treatment strategy for CAD, particularly in patients with severe stenosis or total occlusion [3]. Nevertheless, patients continue to experience major adverse cardiovascular events (MACEs) despite these therapeutic advancements [4].

Multiple risk factors have been identified for such adverse outcomes, including advanced age, smoking, diabetes, and elevated low-density lipoprotein cholesterol (LDL–C). Hyperuricemia (HUA) is a frequent comorbidity among individuals with CAD [5–7], and the presence of HUA has been shown to be associated with CVD, including CAD [8–11]. Emerging evidence further suggests that HUA may influence clinical outcomes in patients with CAD following PCI [12, 13]. These findings imply a potential clinical benefit of urate-lowering therapy (ULT) in patients with CAD and concomitant HUA. In a multicenter prospective study, dotinurad, an inhibitor of the renal urate transporter 1 (URAT1), was associated with improvement in vascular stiffness and reduction in markers of oxidative stress in patients with hypertension

Central illustration. Early Urate-Lowering Therapy After PCI Improves Long-Term Survival and Cardiac Function in Hyperuricemia Patients



and HUA [14]. These responses to dotinurad lead to a significant decrease in the cardio-ankle vascular index and a corresponding reduction in atherosclerotic risk. Conversely, a large-scale prospective cohort study reported that allopurinol, a xanthine oxidase inhibitor responsible for converting purines into uric acid, did not reduce mortality during follow-up in patients with acute myocardial infarction [9]. Similarly, in a recent randomized controlled trial, allopurinol did not significantly reduce the incidence of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death compared to no ULT in patients with ischemic heart disease [15]. In contrast, a randomized controlled trial conducted by Ma et al. demonstrated that febuxostat, an xanthine oxidase inhibitor, significantly lowered the risk of contrast-induced nephropathy in patients undergoing coronary intervention [16]. This finding is supported similar results with febuxostat in patients with stage 3 chronic kidney disease undergoing the same coronary procedure [17].

Considering the conflicting results of earlier studies, the impact of ULT on the long-term prognosis of patients with CAD who undergo PCI merits further investigation. Therefore, this retrospective study examined the effect of ULT on long-term clinical outcomes in patients with HUA following PCI.

Material and methods

Study design and participants

This retrospective observational study included patients who underwent PCI between July 2014 and May 2020 at the Department of Cardiology, The Ninth Medical Center, Chinese PLA General Hospital.

The *inclusion criteria* were:

1) Age >18 years;
2) A diagnosis of CAD and successful implantation of a drug-eluting stent following PCI;
3) Serum uric acid (UA) >420 μmol/l in the absence of an acute gout flare. This criteria included both patients with true asymptomatic hyperuricemia and those with a prior history of gout currently in the intercritical period;
4) A follow-up duration of at least one year.

Exclusion criteria:

1) Ongoing urate-lowering treatment;
2) Clinical evidence of an acute gout flare;
3) End-stage renal failure;
4) Malignancy;
5) Premature discontinuation of antiplatelet or statin therapy;
6) Absence of essential baseline data.

Patients who initiated standardized ULT for a minimum of one month following PCI are identified as the treatment group. Those who did not receive therapy or demonstrated poor adherence during follow-up are identified as the non-treatment group. All participants were advised to follow a urate-lowering diet throughout the follow-up period. ULT administered during follow-up included febuxostat, allopurinol, and benzbromarone, another URAT1 transporter. A total of 649 patients were ultimately enrolled in the study. The selection process is illustrated in Figure 1.

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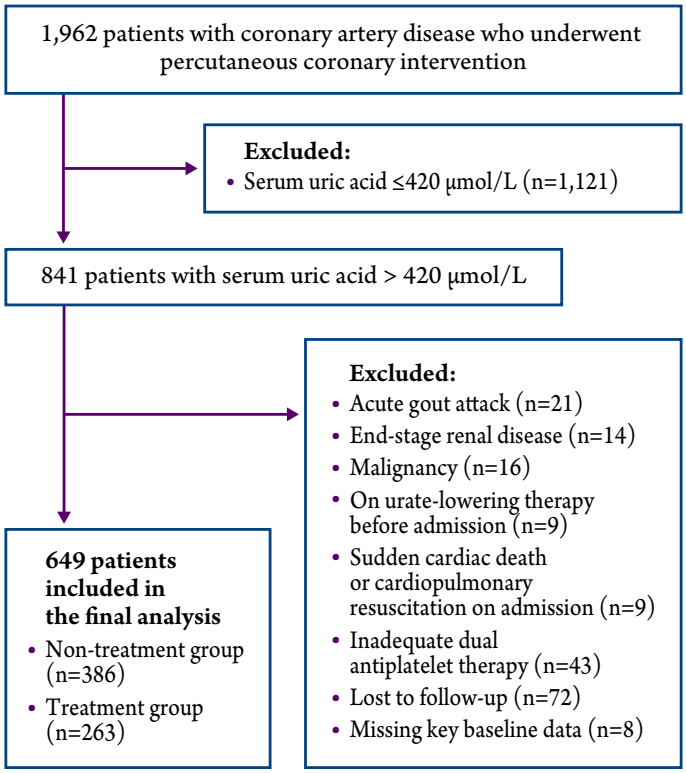
Figure 1. Study flowchart for participant selection



The study protocol was approved by the Ethics Committee of The Ninth Medical Center, Chinese People's Liberation Army General Hospital. Written informed consent was waived due to the retrospective nature of the study (Approval number: LL–LCSY-2024-11).

Data collection

Clinical data were extracted from the hospital's electronic medical record system. These data included cardiovascular risk factors, medication history, echocardiographic parameters, biochemical parameters, and key baseline characteristics, such as age, sex, and findings on physical examination. The estimated glomerular filtration rate (eGFR) was calculated using the modified modification of diet in renal disease equation [18].

Outcomes and follow-up

The primary endpoint was all-cause mortality. The secondary endpoint was the occurrence of MACEs, defined as a composite of cardiovascular mortality, myocardial infarction (MI), heart failure (HF), stroke or transient ischemic attack (TIA). Follow-up assessments were conducted at 1, 3, and 9–12 mos after hospital discharge, and annually thereafter. During the initial three month period, serum UA concentrations, ULT status, and adverse events were recorded. During subsequent follow-up visits, only adverse events were documented. The most recent follow-up is scheduled for June 2024.

Definitions and criteria

The diagnosis of CAD was confirmed by coronary angiography, and was defined as the presence of at least one coronary artery stenosis >50% [19]. HUA was defined as a serum UA concentration >420 μmol/l in accordance with the 2019 Guideline for the Diagnosis and Management of Hyperuricemia and Gout in China [20]. The PCI procedure was performed in accordance with the latest version of the Chinese Guidelines for Percutaneous Coronary Intervention [21].

Statistical analyses

Continuous variables are presented as median with interquartile range (IQR), while categorical variables are expressed as frequency and percentage. Descriptive comparisons were performed using the Mann–Whitney U test for continuous variables and the χ^2 test for categorical variables. For survival analysis, Kaplan–Meier survival curves and multivariable Cox proportional hazards regression models were employed to assess the association between ULT and adverse outcomes, including all-cause mortality and MACEs. The multivariable Cox model was empirically adjusted for age, gender, smoking status, BMI, systolic blood pressure (SBP), left ventricular ejection fraction (LVEF), history of MI, hypertension, diabetes, statin use, beta blocker use, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (ACE-I/ARB) use, N-terminal pro – brain natriuretic peptide (NT-proBNP), fasting blood glucose (FBG), LDL–C, eGFR, and baseline UA concentrations. Subgroup analysis was performed using multivariable Cox regression models stratified by baseline UA concentrations (420–480 μmol/l and ≥480 μmol/l) to explore the association between ULT and adverse outcomes among PCI patients with varying degrees of HUA. A sensitivity analysis was also conducted using 1:1 propensity score matching with a caliper width of 0.02 to evaluate the robustness of the association between ULT and adverse outcomes in PCI patients. All statistical analyses were conducted using Stata version 18.0 (StataCorp LLC, College Station, TX, USA) and R version 4.4.2 (The R Project for Statistical Computing, Vienna, Austria). A two-tailed p-value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

Table 1 summarizes the baseline characteristics of the 649 participants. The total cohort had a median age of 61.0 yrs (IQR: 53.0–72.0), and the majority were male (83.2%). Participants in the treatment group were older compared to those in the non-treatment group. Additionally, the treatment group exhibited a higher prevalence of diabetes mellitus, hypertension, prior MI, and prior

Table 1. Baseline characteristics of included patients stratified by urate-lowering therapy exposure

Baseline characteristics	Total (n=649)	Non-treatment group (n=386)	Treatment group (n=263)	p-value
Age, yrs	61.0 (53.0–72.0)	59.0 (52.0–69.0)	63.0 (54.0–74.0)	0.004
Male	540 (83.2)	322 (83.4)	218 (82.9)	0.860
Current smokers	219 (33.7)	135 (35.0)	84 (31.9)	0.420
BMI, kg/m^2	26.0 (24.0–28.4)	26.1 (24.0–28.4)	26.0 (24.1–28.4)	0.690
SBP, mm Hg	133.0 (121.0–149.0)	135.0 (122.0–150.0)	130.0 (120.0–145.0)	0.100
DBP, mm Hg	76.0 (67.0–84.0)	77.0 (69.0–84.0)	75.0 (66.0–83.0)	0.220
LVEF, %	57.0 (49.0–61.0)	57.0 (50.0–61.0)	56.0 (46.0–61.0)	0.410
Medical history				
Diabetes mellitus	215 (33.1)	112 (29.0)	103 (39.2)	0.007
Hypertension	475 (73.2)	271 (70.2)	204 (77.6)	0.038
Previous MI	145 (22.3)	75 (19.4)	70 (26.6)	0.031
Atrial fibrillation	135 (20.8)	72 (18.7)	63 (24.0)	0.125
Previous true asymptomatic hyperuricemia	466 (71.8)	265 (68.7)	201 (76.4)	0.038
Previous gout *	85 (13.1)	40 (10.4)	45 (17.1)	0.017
Medication				
ACE-I/ARB	295 (45.5)	176 (45.6)	119 (45.2)	0.930
Beta blocker	466 (71.8)	276 (71.5)	190 (72.2)	0.840
Statin	592 (91.2)	349 (90.4)	243 (92.4)	0.380
Warfarin	28 (4.3)	17 (4.4)	11 (4.2)	0.999
DOACs	67 (10.3)	41 (10.6)	26 (9.9)	0.864
Urate-lowering therapy				
Allopurinol	222 (34.2)	43 (11.1)	179 (68.1)	<0.001
Febuxostat	86 (13.3)	19 (4.9)	67 (25.5)	<0.001
Benzbromarone	28 (4.3)	11 (2.8)	17 (6.5)	0.043
Laboratory indicators				
Creatinine, mmol/l	89.5 (76.2–117.9)	89.2 (75.4–114.2)	89.8 (77.7–126.0)	0.150
eGFR, ml/min/1.73m^2	81.8 (55.7–100.1)	83.1 (57.3–101.4)	80.5 (50.6–97.2)	0.160
Glucose, mmol/l	5.8 (5.0–7.5)	5.8 (5.1–7.4)	5.8 (5.0–7.6)	0.450
NT-proBNP, pg/ml	249.8 (70.3–1700.0)	203.1 (73.8–1339.0)	290.4 (62.3–2395.0)	0.300
LDL–C, mmol/l	2.3 (1.7–2.9)	2.2 (1.7–2.9)	2.3 (1.8–3.0)	0.039
HDL–C, mmol/l	0.9 (0.8–1.1)	1.0 (0.8–1.1)	0.9 (0.8–1.1)	0.041
TC, mmol/l	3.8 (3.2–4.6)	3.8 (3.1–4.6)	4.0 (3.3–4.8)	0.025
TG, mmol/l	1.5 (1.0–2.2)	1.5 (1.0–2.1)	1.5 (1.1–2.2)	0.073
Baseline UA, μmol/l	473 (447–517)	466 (442–505)	489 (458–535)	<0.001
UA at 3 months, μmol/l	449 (420–492)	456 (429–489)	433 (382–503)	0.003
UA control at 3 mos	187 (28.8)	70 (18.1)	117 (44.5)	<0.001

Data are median (interquartile range) or number (percentage). * Previous gout: prior diagnosis of gout; all patients were in the intercritical phase at baseline. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DOACs, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; UA, uric acid.

gout attack. In terms of lipid profiles, the treatment group demonstrated elevated concentrations of LDL–C and total cholesterol, whereas HDL–C concentrations were higher in the non-treatment group. The median baseline UA level across the cohort was 473 μmol/l (IQR: 447–517), with significantly higher values observed in the treatment group relative to the non-treatment group. At three months, the median UA level decreased to 449 μmol/l (IQR: 420–492), with lower concentrations noted in the treatment group compared to the non-treatment group. At this time point, 28.8% of participants achieved UA control, with a significantly greater proportion in the treatment group than in the non-treatment group (both p<0.001).

Pre- and postoperative cardiac function assessment

To assess the effects of ULT on heart function after PCI, key echocardiographic parameters were compared between the treatment and non-treatment groups at baseline and again at three months after PCI (Table 2). At follow-up, patients who received at least one month of ULT had significantly lower values in

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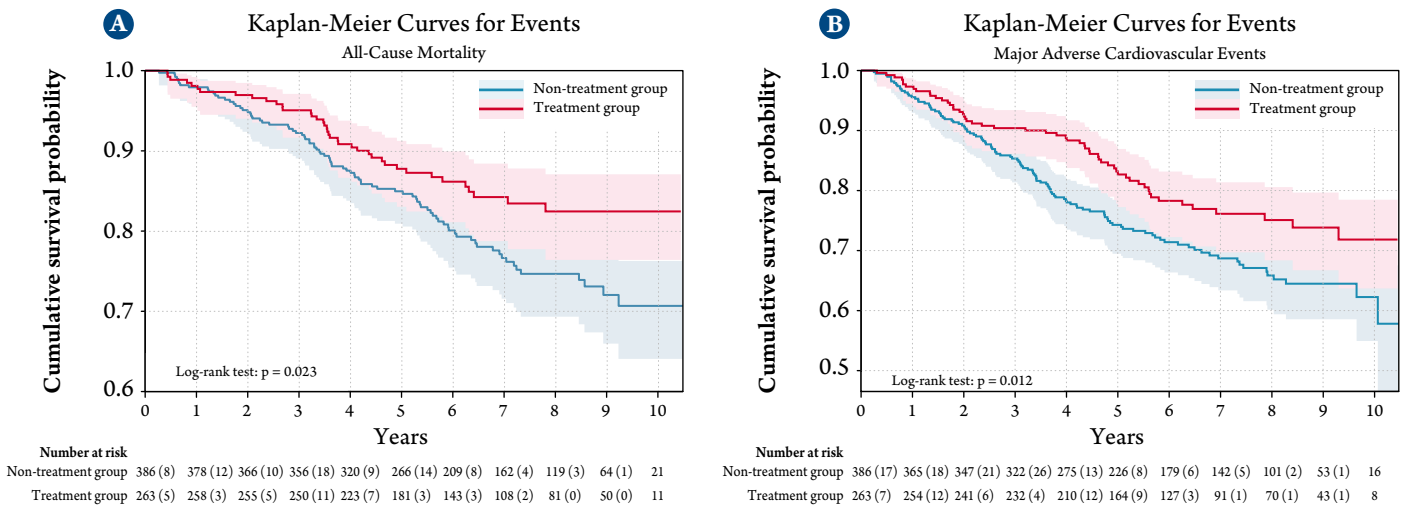
Table 2. Comparison of echocardiographic parameters before and three months post-PCI in the treatment and non-treatment groups

Clinical Parameter/Time Point	Non-treatment group (n=386)	Treatment group (n=263)	p-value
LVEF, %	57.0 (50.0–61.0)	56.0 (46.0–61.0)	0.410
LVEF, 3 mos post-PCI, %	58.0 (52.1–62.7)	59.0 (54.4–63.2)	0.084
E/A	1.0 (0.8–1.3)	1.1 (0.9–1.3)	0.093
E/A, 3 mos post-PCI	1.1 (0.9–1.4)	1.2 (1.0–1.5)	0.015
E/e′	12.3 (10.6–14.1)	12.4 (10.8–14.0)	0.206
E/e′, 3 mos post-PCI	11.0 (9.6–12.5)	9.9 (8.4–11.4)	0.021
LVID, mm	45.0 (42.3–49.6)	45.0 (43.1–49.7)	0.520
LVID, 3 mos post-PCI, mm	43.5 (41.4–47.2)	43.0 (41.2–46.5)	0.340
LVMI	112 (104–121)	113 (106–122)	0.278
LVMI, 3 mos post-PCI	109 (102–117)	107 (99–116)	0.118
RVSP, mmHg	35.0 (30.4–40.8)	34.0 (30.2–39.9)	0.290
RVSP, 3 mos post-PCI, mmHg	33.0 (28.5–37.4)	30.0 (27.2–33.6)	0.001
LAV, ml	50.0 (45.1–55.7)	52.0 (47.6–58.4)	0.150
LAV, 3 mos post-PCI, ml	47.0 (43.3–52.5)	45.0 (42.4–50.9)	0.043
LAVI	36.0 (32.2–40.6)	37.0 (33.1–41.4)	0.152
LAVI, 3 mos post-PCI	34.0 (30.1–38.8)	31.5 (27.3–35.7)	0.036

Data are median (interquartile range). LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; E/A, the ratio of peak early diastolic mitral inflow to late diastolic mitral inflow; E/e′, the ratio of peak early diastolic mitral inflow velocity to the early diastolic mitral annular velocity; LVID, left ventricular internal diameter; LVMI, left ventricular mass index; RVSP, right ventricular systolic pressure; LAV, left atrial volume; LAVI, left atrial volume index.

Figure 2. Kaplan–Meier curves for clinical outcomes in treated and untreated patients with hyperuricemia undergoing percutaneous coronary intervention



Panel **A**: All-cause mortality. Panel **B**: MACEs. The colored background strip of each line represents the confidence interval of the survival curve. ULT, urate-lowering therapy; MACEs, major adverse cardiovascular events.

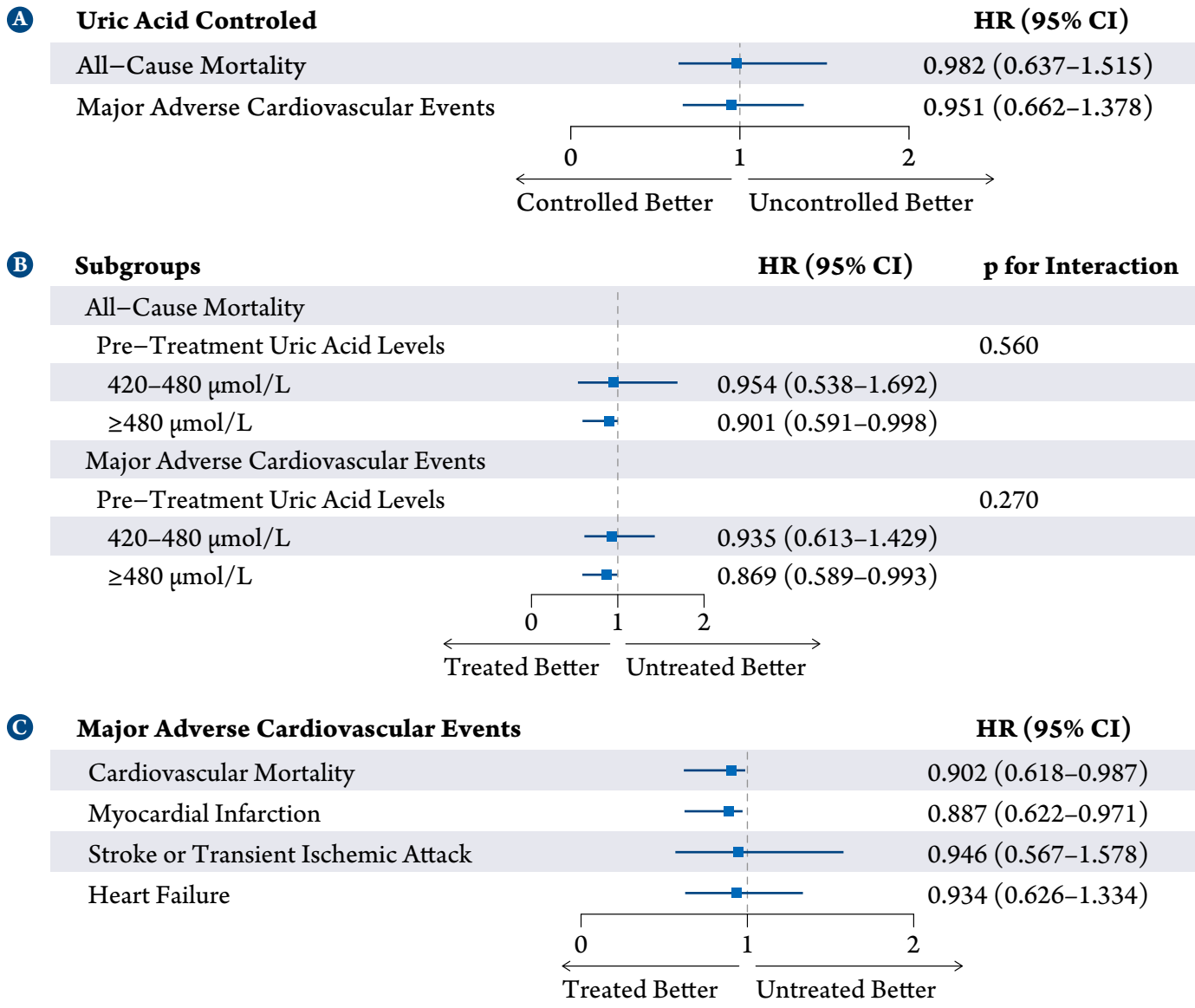
left atrial volume (45.0 ml vs. 47.0 ml, p=0.043), left atrial volume index: (31.5 ml/m² vs. 34.0 ml/m², p=0.036), E/A (1.2 vs. 1.1, p=0.015), E/e′ (9.9 vs. 11.0, p=0.021), and right ventricular systolic pressure: (30.0 mmHg vs. 33.0 mmHg, p=0.001) compared to the non-treatment group.

Effect of uric acid-lowering therapy on all-cause mortality

A total of 649 patients were included in the analysis, with a median follow-up duration of 6.32 years. During this period, 126 patients (19.4%) experienced all-cause mortality. The incidence of all-cause mortality was significantly higher in the non-treatment group compared to the treatment group (Table 3). In the fully adjusted Cox regression model, ULT was independently associated with a reduced risk of all-cause mortality (hazard ratio [HR]: 0.915, 95% confidence interval [CI]: 0.645–0.998) (Table 3 and Figure 2).

Subgroup analysis further demonstrated that the effect of ULT on reducing all-cause mortality was not significantly modified by baseline HUA concentrations (p for interaction = 0.560) (Figure 3A). Additionally, there was no signif-

Figure 3. Subgroup analysis of the association between urate-lowering therapy and outcomes



The model analyses shown in Figures A–C was adjusted for age, gender, smoking status, BMI, SBP, LVEF, history of MI, hypertension, diabetes, statin use, beta blocker use, ACE-I/ARB use, NT-proBNP, FBG, LDL-C, eGFR, and baseline UA concentrations.

Table 3. Association between urate-lowering therapy and clinical outcomes in patients with hyperuricemia undergoing percutaneous coronary intervention

Outcomes	Events/sample size; Incidence per 1,000 PYs (95% CI)	Crude Model Unadjusted HR (95% CI)	Model 1[a] Adjusted HR (95% CI)	Model 2[b] Adjusted HR (95% CI)
All-cause mortality	126/649; 30.41 (25.54–36.21)	—	—	—
Non-treatment group	87/386; 35.46 (28.74–43.75)	Ref	Ref	Ref
Treatment group	39/263; 23.08 (16.86–31.59)	0.861 (0.604–0.992)	0.872 (0.612–0.994)	0.915 (0.645–0.998)
Major adverse cardiovascular events	174/649; 45.90 (39.56–53.25)	—	—	—
Non-treatment group	118/386; 53.20 (44.41–63.71)	Ref	Ref	Ref
Treatment group	56/263; 35.60 (27.40–46.26)	0.860 (0.637–0.996)	0.865 (0.643–0.997)	0.887 (0.661–0.990)

[a] Model 1 adjusted for age and gender; [b] Model 2 adjusted for age, gender, smoking status, BMI, SBP, LVEF, history of MI, hypertension, diabetes, statin use, beta blocker use, ACE-I/ARB use, NT-proBNP, FBG, LDL–C, eGFR, and baseline UA concentrations. PYs, person-years; HR, hazard ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NT-proBNP, N-terminal pro – B-type natriuretic peptide; FBG, fasting blood glucose; LDL–C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UA, uric acid; Ref, reference group.

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Table 4. Baseline characteristics of propensity score-matched patients stratified by urate-lowering therapy exposure

Baseline characteristics	Total (n=310)	Non-treatment group (n=155)	Treatment group (n=155)	p-value
Age, yrs	61.0 (53.0–71.0)	62.0 (53.0–71.0)	58.0 (52.0–72.0)	0.350
Male	262 (84.5)	129 (83.2)	133 (85.8)	0.530
Current smokers	112 (36.1)	52 (33.5)	60 (38.7)	0.340
BMI, kg/m^2	26.1 (24.0–28.4)	25.9 (23.7–28.0)	26.3 (24.7–28.7)	0.170
SBP, mm Hg	133.0 (121.0–145.0)	133.0 (120.0–144.0)	133.0 (122.0–150.0)	0.120
DBP, mm Hg	76.5 (66.0–84.0)	76.0 (66.0–84.0)	77.0 (67.0–84.0)	0.410
LVEF, %	57.0 (51.0–61.0)	57.0 (50.0–61.0)	57.0 (53.0–61.0)	0.490
Medical history				
Diabetes mellitus	112 (36.1)	55 (35.5)	57 (36.8)	0.810
Hypertension	228 (73.5)	115 (74.2)	113 (72.9)	0.800
Previous MI	71 (22.9)	31 (20.0)	40 (25.8)	0.220
Atrial fibrillation	52 (16.8)	27 (17.4)	25 (16.1)	0.879
Previous true asymptomatic hyperuricemia	215 (69.4)	112 (72.3)	103 (66.5)	0.324
Previous gout *	41 (13.2)	18 (11.6)	23 (14.8)	0.502
Medication				
ACE-I/ARB	145 (46.8)	79 (51.0)	66 (42.6)	0.140
Beta blocker	224 (72.3)	113 (72.9)	111 (71.6)	0.800
Statin	289 (93.2)	143 (92.3)	146 (94.2)	0.500
Warfarin	10 (3.2)	5 (3.2)	5 (3.2)	0.999
DOACs	22 (7.1)	10 (6.5)	12 (7.7)	0.825
Urate-lowering therapy				
Allopurinol	85 (27.4)	25 (16.1)	60 (38.7)	<0.001
Febuxostat	45 (14.5)	15 (9.7)	30 (19.4)	0.024
Benzbromarone	15 (4.8)	5 (3.2)	10 (6.5)	0.290
Laboratory indicators				
Creatinine, mmol/l	89.5 (77.0–116.8)	90.3 (76.3–118.2)	87.0 (77.0–114.6)	0.560
eGFR, ml/min/1.73m^2	82.7 (55.5–99.3)	79.9 (53.7–98.3)	86.8 (57.5–100.2)	0.300
Glucose, mmol/l	5.7 (5.0–7.5)	5.8 (5.1–7.4)	5.7 (4.8–7.6)	0.250
NT-proBNP, pg/ml	237.8 (62.3–1328.0)	206.1 (70.3–1262.0)	253.7 (56.6–1532.0)	0.910
LDL–C, mmol/l	2.3 (1.8–2.9)	2.3 (1.7–2.9)	2.3 (1.8–3.0)	0.490
HDL–C, mmol/l	0.9 (0.8–1.1)	1.0 (0.8–1.1)	0.9 (0.8–1.1)	0.190
TC, mmol/l	3.9 (3.3–4.8)	4.0 (3.3–4.9)	3.9 (3.3–4.8)	0.980
TG, mmol/l	1.5 (1.1–2.2)	1.5 (1.0–2.2)	1.5 (1.1–2.2)	0.920
Baseline UA, μmol/l	478 (451–522)	472 (449–516)	488 (451–532)	0.220
UA at 3 months, μmol/l	449 (413–498)	464 (428–498)	423 (372–490)	<0.001
UA control at 3 mos	105 (33.9)	32 (20.6)	73 (47.1)	<0.001

Data are median (interquartile range) or number (percentage). *Previous gout: prior diagnosis of gout; all patients were in the intercritical phase at baseline. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DOACs, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LDL–C, low-density lipoprotein cholesterol; HDL–C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; UA, uric acid.

icant survival benefit associated with the normalization of uric acid concentrations through ULT compared to those with uncontrolled uric acid concentrations (Figure 3B).

Effect of uric acid-lowering therapy on MACEs

174 patients (26.8%) experienced MACEs. The incidence of MACEs was significantly higher in the non-treatment group compared to the treatment group (Table 3). In the fully adjusted Cox regression model, ULT was independently associated with a reduced risk of MACEs (HR: 0.887, 95% CI: 0.661–0.990) (Table 3 and Figure 2).

Subgroup analysis revealed no significant interaction between the effect of ULT and baseline HUA concentrations on the incidence of MACEs (p for interaction = 0.510) (Figure 3A). Additionally, the reduction in MACE risk was consistent regardless of whether patients achieved normal uric acid concentrations or had persistently elevated concentrations (Figure 3B).

Table 5. Association between urate-lowering therapy and clinical outcomes in the propensity score–matched cohort undergoing percutaneous coronary intervention

Outcomes	Events/ sample size; Incidence per 1,000 PYs (95% CI)	Adjusted HR[a] (95% CI)
All-cause mortality	63/310; 31.55 (24.65–40.39)	—
Non-treatment group	41/155; 41.42 (30.50–56.26)	Reference group
Treatment group	22/155; 21.85 (14.39–33.19)	0.935 (0.682–0.997)
Major adverse cardiovascular events	83/310; 45.27 (36.51–56.14)	—
Non-treatment group	51/155; 56.67 (43.07–74.57)	Reference group
Treatment group	32/155; 34.28 (24.24–48.47)	0.911 (0.685–0.992)

[a] Model adjusted for age, gender, smoking status, BMI, SBP, LVEF, history of MI, hypertension, diabetes, statin use, beta blocker use, ACE-I/ARB use, NT-proBNP, FBG, LDL-C, eGFR, and baseline UA concentrations. PYs, person-years; HR, hazard ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NT-proBNP, N-terminal pro–B-type natriuretic peptide; FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UA, uric acid.

When analyzing the individual components of MACE, as shown in Figure 3C, ULT significantly reduced the risk of cardiovascular mortality and MI. However, no significant association was observed for stroke/TIA or HF.

Robustness of uric acid-lowering therapy effects on clinical outcomes: sensitivity analysis after propensity score matching

A sensitivity analysis was conducted following 1:1 propensity score matching, which included 310 patients, with 155 patients in each group. Baseline characteristics according to treatment status are detailed in Table 4. The results from this analysis confirmed that, even after adjusting for all baseline covariates, the protective effect of ULT on both all-cause mortality and MACEs among PCI patients with HUA remained robust (Table 5). Specifically, the association between ULT and reduced mortality risk, as well as the reduction in MACE incidence, persisted, reinforcing the initial findings from the primary analysis. This robustness indicates that the observed benefits of ULT on clinical outcomes are not confounded by baseline differences between treatment groups.

Discussion

This study evaluated the long-term effects of ULT on clinical outcomes in patients with HUA following PCI. The findings demonstrated that ULT significantly reduced the risk of all-cause mortality and MACEs. Subgroup analyses indicated that the protective effects of ULT were consistent across baseline HUA concentrations. Among the individual components of MACEs, ULT was particularly effective in reducing the incidence of cardiovascular mortality and MI. In addition, ULT was associated with significant improvements in cardiac function, as evidenced by reductions in left atrial volume, diastolic filling pressures, and right ventricular systolic pressure at three-month follow-up. Sensitivity analyses further confirmed the robustness of these findings, reinforcing the beneficial role of ULT in improving long-term prognosis in this patient population.

Several previous studies have investigated the association between HUA and CVD, as well as the potential effects of ULT on cardiovascular outcomes. A Japanese study reported that HUA was associated with a significantly increased risk of major adverse cardiovascular events (HR=1.52, 95% CI: 1.23–18.6) and hospitalization for heart failure in patients with chronic coronary syndrome (HR= 2.19, 95% CI: 1.69–2.83) [8]. Zhang et al., using propensity score analysis in a large cohort, demonstrated that HUA was associated with an elevated risk of mortality (HR=1.33, 95% CI: 1.15–1.53), with similar results observed in the propensity score-matched cohort (HR= 1.33, 95% CI: 1.11–1.61). Moreover, the addition of UA to the SYNTAX score II significantly enhanced its predictive accuracy for mortality [10]. A Mexican study likewise identified elevated serum UA concentrations as an independent predictor of short-term mortality in patients with acute myocardial infarction (HR=1.99, 95% CI: 1.08–3.66) [11]. Additional research has shown that HUA is closely associated with adverse long-term outcomes following coronary intervention, with a significantly increased risk of all-cause mortality at both two years (HR = 4.332, 95% CI: 1.990–9.430) and five years (HR = 2.063, 95% CI: 1.186–3.590) post-procedure [12]. A meta-analysis of 12 studies further corroborated these findings, demonstrating that HUA increases the risk of adverse outcomes following coronary intervention (relative risk [RR] = 1.46, 95% CI: 1.29–1.65) [13]. However, prior studies have not shown that ULT significantly reduces the risks of all-cause mortality, cardiovascular death, non-fatal MI, or non-fatal stroke among patients with CAD [9, 15]. Notably, only febuxostat has been reported to lower the risk of contralateral nephropathy in patients undergoing coronary intervention [16, 17]. Therefore, the effect of ULT on long-term prognosis following coronary stent implantation remained unclear.

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In contrast to earlier reports, the present study demonstrated that ULT confers protection against long-term adverse outcomes in patients undergoing PCI, including those with only mildly elevated UA concentrations when ULT is initiated early post-procedure. Further analysis of all patients receiving ULT revealed that, even in cases where UA concentrations had not normalized by the third month, there were no significant differences in clinical outcomes compared to patients whose UA concentrations had reached the normal range, provided that standardized ULT had been administered for at least one month. These findings underscore the clinical value of early initiation of ULT in PCI patients with HUA, and they suggest that the therapeutic benefit is not dependent on the achievement of normouricemia within the initial treatment period. The results highlight the importance of timely ULT initiation, irrespective of baseline UA concentrations or short-term normalization, in improving long-term outcomes in this patient population.

The mechanisms by which ULT confers prognostic benefits in patients undergoing coronary stent implantation remain incompletely understood. In two independent placebo-controlled trials, Doehner et al. demonstrated that allopurinol significantly improves endothelial function and peripheral blood flow in patients with heart failure and concomitant hyperuricemia [22]. Additionally, both clinical studies and meta-analyses have reported that allopurinol may enhance endothelial function across diverse patient populations [23, 24]. A multicenter prospective study further showed that dotinurad reduces vascular stiffness and the expression of oxidative stress-related factors in patients with hypertension and hyperuricemia, leading to a significant reduction in the cardio-ankle vascular index and attenuated atherosclerotic risk [14]. Moreover, a meta-analysis indicated that allopurinol therapy improves markers related to endothelial function and inflammation in patients with stroke [25]. Other investigations have suggested that ULT effectively decreases serum UA concentrations while also reducing the incidence of hyperuricemia and lowering cholesterol and triglyceride concentrations in patients with gout [26, 27]. However, it remained uncertain whether these favorable effects translate to improved outcomes in patients undergoing coronary stent implantation. Notably, previous studies failed to demonstrate a significant protective effect of febuxostat on coronary endothelial function [28, 29], whereas benzbromarone was reported to significantly improve endothelial function in patients with hyperuricemia [30].

In a similar study [31], Tai et al. assessed cardiovascular outcomes in post-MI patients with and without ULT in a population-based, propensity score-matched cohort study. The analysis, which included patients undergoing PCI and coronary artery bypass grafting (CABG), found that ULT was associated with a lower risk of all-cause mortality in post-MI patients, and potentially with a reduced incidence of repeat revascularization procedures among ULT users [31]. Similarly, Kermani-Alghoraishi et al. examined the effects of allopurinol pre-treatment on post-revascularization outcomes in patients admitted with ST-elevation MI (STEMI) [32]. Their findings suggested that allopurinol pre-treatment enhanced coronary perfusion in patients undergoing either primary or rescue PCI for STEMI. Collectively, these limited data suggest that ULT may offer prognostic advantages following PCI in patients with CAD; however, further research is necessary to clarify these potential benefits and elucidate the underlying protective mechanisms.

Strengths and limitations

This study has several notable strengths. To the best of our knowledge, it is the first study to evaluate the impact of ULT in patients undergoing stent implantation. The findings provide evidence supporting the administration of ULT in patients with HU undergoing coronary stenting. Moreover, the study is strengthened by a relatively long follow-up period, which enabled the assessment of ULT's influence on long-term prognosis following stent implantation.

Nonetheless, several limitations should be acknowledged. First, the study was conducted at a single center and employed a retrospective design with a relatively small sample size, which may limit the generalizability of the findings. Moreover, because treatment allocation was not randomized, potential selection bias may also have influenced the results. Second, the study did not differentiate the effects of specific ULT agents, such as febuxostat, allopurinol, and benzbromarone. Additionally, the influence of treatment duration on clinical outcomes was not examined. Future randomized controlled trials are warranted to further investigate the effects of ULT on the clinical prognosis of patients undergoing PCI.

Conclusion

This study demonstrates that, in patients with HUA undergoing PCI, early initiation of ULT is associated with reduced all-cause mortality and a lower incidence of MACEs. This protective effect is maintained irrespective of baseline UA concentrations or whether UA normalization occurs within a brief period. These findings underscore the clinical relevance of timely ULT initiation for improving long-term outcomes in this high-risk population. Further large-scale randomized trials are needed to validate these observations, elucidate the underlying mechanisms, and determine optimal therapeutic strategies.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The Ninth Medical Center, Chinese PLA General Hospital, and patients' written informed consents were waived due to the retrospective nature (Approval number: LL–LCSY-2024-11).

Author contributions

Bei Zhao: Conceptualization, Methodology, and Writing – original draft, review & editing; Zhong Zhang: Formal analysis; Chaosheng Du: Data curation; Ning Li: Methodology; Li Liu: Software and Visualization; Xiaobing Zhao: Data curation and Software; Huihui Xia: Data curation and Software; Shuai Mao: Data curation and Software; Changhui Duo: Data curation and Software; Shouli Wang: Supervision.

No conflicts of interest are reported.

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