# Impact of Elevated Serum Uric Acid Level on Target Lesion Revascularization After Percutaneous Coronary Intervention for Chronic Total Occlusion

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**Elevated serum uric acid (SUA) level is reportedly associated with subsequent cardiovascular events including revascularization in patients with coronary artery disease. However, the impact of SUA level on revascularization in patients with chronic total occlusion (CTO), one of the highest risk subsets in coronary artery disease, is unclear. The aim of this study was to evaluate the impact of SUA level on target lesion revascularization (TLR) in contemporary percutaneous coronary intervention (PCI) for CTO. A total of 165 patients who underwent successful PCI with new-generation drug-eluting stent for CTO under intravascular ultrasound guidance were included. Patients were classified into 3 groups according to the tertiles of SUA level at baseline. Coronary angiography was qualitatively and quantitatively assessed, and gray-scale intravascular ultrasound was also analyzed. The primary end point was TLR. The tertiles of SUA level were as follows: low tertile, ≤5.2 mg/dl; intermediate tertile, 5.3 to 6.4 mg/dl; and high tertile, ≥6.5 mg/dl. During a median follow-up of 34 months, TLR was observed in 5 patients (8.8%) in the low tertile, in 5 (9.4%) in the intermediate tertile, and in 14 (25.5%) in the high tertile ($p = 0.02$). Kaplan-Meier analysis demonstrated a significantly higher incidence of TLR in patients with high tertile than the low and intermediate groups. Multivariable analysis showed SUA ≥6.5 mg/dl, diabetes mellitus, and longer CTO length as independent predictors of TLR. In conclusion, in patients who underwent PCI with drug-eluting stent, elevated SUA level was associated with TLR after successful recanalization of CTO.**  **(Am J Cardiol 2019;124:1827−1832)**

Chronic total occlusion (CTO) in coronary arteries is considered as the final stage of coronary atherosclerosis, and it is observed in up to 30% of patients with coronary artery disease.[1] Successful recanalization of CTO by percutaneous coronary intervention (PCI) is reported to be associated with better long-term survival compared with failed recanalization.[2] Despite remarkable advances in PCI for CTO, in-stent restenosis (ISR) is still clinical issue even in the era of drug-eluting stent (DES). Previous studies demonstrated that the rate of ISR and subsequent target lesion revascularization (TLR) was higher in vessels with CTO compared with those without CTO.[3−6] Significant relation has been found between serum uric acid (SUA) level and coronary atherosclerosis,[7,8] or its surrogate marker such as inflammation and endothelial dysfunction.[9,10] In the bare metal stent era, higher SUA level was reported to be an independent predictor of ISR in patients with stable and unstable angina.[11] However, the relation between SUA level and ISR or subsequent revascularization in CTO patients treated with DES is unknown. The aim of this study was to evaluate the impact of SUA level on TLR in contemporary PCI for CTO.

## Methods

From July 2013 to July 2016, a total of 204 patients underwent PCI for CTO with new-generation DES under intravascular ultrasound (IVUS) guidance and were successfully recanalized at Tokushima Red Cross Hospital. In our institution, follow-up coronary angiography was routinely performed at 8 to 12 months after PCI. CTO was defined as a lesion with a thrombolysis in myocardial infarction flow grade of 0 for at least 3 months. Patients were considered eligible for this study when SUA measurement on admission was available. Major criteria for exclusion were PCI without coronary stent at index procedure ($n = 7$), patients receiving antihyperuricemic agents on admission ($n = 18$), and hemodialysis ($n = 14$). Thus, 165 patients were included in the present study. They were classified into 3 groups according to tertiles of SUA level. Written informed consent for the procedures was obtained from all patients, and the ethics committee of Tokushima Red Cross Hospital approved this study. The primary end point of the present study was TLR, defined as any percutaneous or surgical revascularization procedure of the target lesion.

Coronary angiography at index procedure was qualitatively and quantitatively analyzed by QAngio XA (Version 7.3, Medis Medical Imaging System BV, Leiden, the Netherlands). Intracoronary isosorbide dinitrate was administered before each angiogram. Coronary segments were analyzed by a program automatically. Lesion length was measured during simultaneous anterograde and retrograde injection of contrast or after vessel recanalization. Calcification was identified as readily apparent radiopacities

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within the vascular wall at the site of the occlusion and was classified as none/mild, moderate (radiopacities noted only during the cardiac cycle before contrast injection), and severe (radiopacities noted without cardiac motion before contrast injection generally compromising both sides of the arterial lumen). Collateral filling of the recipient artery was assessed according to the Rentrop classification. We defined grade 3 as good collateral flow. Coronary perfusion after PCI was assessed according to thrombolysis in myocardial infarction criteria. The J-CTO score was calculated as a marker of case complexity.[12]

All IVUS examinations were performed after intracoronary administration of isosorbide dinitrate. IVUS imaging data were acquired with a commercially available IVUS imaging system: Opticross (Boston Scientific, Massachusetts); ViewIT (Terumo Corp., Tokyo, Japan); and Navifocus WR (Terumo Corp., Tokyo, Japan). All IVUS measurements were performed by an experienced cardiologist, who was unaware of the patients' clinical characteristics, according to the expert consensus document.[13] Offline IVUS analysis was performed using a computerized system (QIVUS, Medis Medical Imaging Systems, North Carolina). Stent, lumen, and external elastic membrane cross-sectional areas (CSA) were manually traced to assess stent, lumen, vessel, and plaque areas. The minimal stent area (MSA) was the smallest CSA measured within the stented segment. At the MSA site, the CSA of the external elastic membrane area was also measured, defined as vessel area. Plaque area was defined as vessel area minus MSA, and plaque burden was calculated as (plaque area/vessel area) × 100.

All analyses were performed using the JMP Pro statistical software package (SAS Institute, Cary, North Carolina). Data are expressed as the mean ± standard deviation, median (interquartile range), or frequency as appropriate. Categorical variables were compared by Fisher's exact test. Comparisons of multiple continuous variables were carried out using analysis of variance or Kruskal-Wallis test. Kaplan-Meier analysis with the log-rank test was used to assess TLR-free survival rates. The associated variables in univariable analyses ($p < 0.10$) and estimated glomerular filtration rate were included in the multivariable model to identify the independent predictors of TLR, presented as odds ratio with 95% confidence intervals. A value of $p < 0.05$ was considered significant.

## Results

A total of 165 patients were grouped into tertiles according to preprocedural SUA level. The tertiles of SUA level were as follows: low tertile, ≤5.2 mg/dl; intermediate tertile, 5.3 to 6.4 mg/dl; and high tertile, ≥6.5 mg/dl. Table 1 lists baseline patient characteristics. There were no significant differences among the 3 groups except for gender, renal function, and lipid profiles. Table 2 shows lesion characteristics. Following successful recanalization of CTO with PCI, 24 (14.5%) patients had TLR during a median follow-up of 34 (22 to 48.5) months. The median follow-up duration was 34 (22.5 to 48.5) months in the low tertile group, 34 (23 to 49) in the middle tertile group, and 33 (13 to 48) in the high tertile group ($p = 0.48$), with the median time from index PCI to TLR of 13 (11.5 to 34), 13 (6 to 31.5), and 13 (8.5 to 27.75) months, respectively ($p = 0.56$). TLR was observed in 5 patients (8.8%) in the low tertile, in 5 (9.4%) in the intermediate tertile, and in 14 (25.5%) in the high tertile group ($p = 0.02$). Kaplan-Meier analysis

Table 1
Baseline patient characteristics

| Variable | All (n = 165) | Low (n = 57) | Intermediate (n = 53) | High (n = 55) | p Value |
|---|---|---|---|---|---|
| Men | 137 (83%) | 39 (68%) | 49 (92%) | 49 (89%) | 0.002 |
| Age (years) | 68.2 ± 10.3 | 69.3 ± 9.9 | 68.3 ± 9.8 | 67.1 ± 11.1 | 0.52 |
| Body mass index (kg/m$^2$) | 24.5 ± 4.0 | 24.3 ± 3.5 | 24.7 ± 5.1 | 24.6 ± 3.2 | 0.83 |
| Hypertension | 121 (73%) | 37 (65%) | 43 (81%) | 41 (75%) | 0.15 |
| Diabetes mellitus | 62 (38%) | 20 (35%) | 22 (42%) | 20 (36%) | 0.77 |
| Dyslipidemia | 137 (83%) | 46 (81%) | 46 (87%) | 45 (82%) | 0.67 |
| Previous myocardial infarction | 79 (48%) | 26 (46%) | 22 (42%) | 31 (56%) | 0.28 |
| Previous coronary intervention | 91 (55%) | 37 (65%) | 25 (47%) | 29 (53%) | 0.16 |
| Previous coronary bypass | 6 (4%) | 3 (5%) | 1 (2%) | 2 (4%) | 0.64 |
| eGFR (ml/min/1.73 m$^2$) | 65.0 ± 15.6 | 70.7 ± 15.2 | 65.4 ± 13.5 | 58.7 ± 17.8 | 0.002 |
| Triglyceride (mg/dl) | 147 ± 82 | 128 ± 67 | 145 ± 75 | 170 ± 100 | 0.03 |
| HDL-cholesterol (mg/dl) | 48 ± 11 | 50 ± 11 | 48 ± 11 | 45 ± 11 | 0.04 |
| LDL-cholesterol (mg/dl) | 93 ± 25 | 95 ± 26 | 92 ± 25 | 91 ± 25 | 0.79 |
| CRP (mg/dl) | 0.20 ± 0.33 | 0.16 ± 0.29 | 0.16 ± 0.32 | 0.28 ± 0.38 | 0.16 |
| Medications on discharge | | | | | |
| Antiplatelet therapy | 161 (98%) | 56 (98%) | 52 (98%) | 53 (96%) | 0.88 |
| Anticoagulant | 15 (9%) | 3 (5%) | 5 (10%) | 7 (13%) | 0.39 |
| $\beta$-blocker | 44 (27%) | 13 (23%) | 11 (21%) | 20 (36%) | 0.15 |
| ACE-I or ARB | 101 (61%) | 31 (54%) | 33 (62%) | 37 (67%) | 0.37 |
| Statin | 132 (80%) | 48 (84%) | 39 (74%) | 45 (82%) | 0.35 |
| Diuretic | 19 (12%) | 5 (9%) | 3 (6%) | 11 (20%) | 0.06 |

Values are mean ± standard deviation or n (%). ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2
Lesion characteristics

| Variable | All (n = 165) | Low (n = 57) | Intermediate (n = 53) | High (n = 55) | p Value |
|---|---|---|---|---|---|
| Target coronary artery | | | | | 0.65 |
| Right | 77 (47%) | 26 (46%) | 24 (45%) | 27 (49%) | |
| Left anterior descending | 68 (41%) | 24 (42%) | 20 (37%) | 24 (44%) | |
| Left circumflex | 20 (12%) | 7 (12%) | 9 (17%) | 4 (7%) | |
| Good collateral flow | 131 (79%) | 45 (79%) | 42 (79%) | 44 (80%) | 0.99 |
| Occluded length (mm) | 19.0 ± 13.1 | 17.7 ± 12.4 | 19.1 ± 10.4 | 20.3 ± 15.8 | 0.59 |
| Calcification | | | | | 0.29 |
| None/mild | 106 (64%) | 36 (63%) | 35 (66%) | 35 (64%) | |
| Moderate | 38 (23%) | 10 (18%) | 12 (23%) | 16 (29%) | |
| Severe | 21 (13%) | 11 (19%) | 6 (11%) | 4 (7%) | |
| J-CTO score | 1 (1-2) | 1 (1-2) | 1 (0-2) | 2 (1-2) | 0.34 |
| Retrograde approach | 34 (21%) | 12 (21%) | 9 (17%) | 13 (24%) | 0.69 |
| Post-PCI TIMI flow grade 3 | 157 (95%) | 54 (95%) | 50 (94%) | 53 (96%) | 0.87 |
| Total stent length (mm) | 57.0 ± 25.4 | 57.0 ± 24.4 | 56.2 ± 25.2 | 57.9 ± 26.6 | 0.94 |
| False lumen stenting | 23 (14%) | 8 (14%) | 9 (17%) | 6 (11%) | 0.66 |
| Post-PCI QCA analysis | | | | | |
| Reference LD (mm) | 2.81 ± 0.54 | 2.78 ± 0.51 | 2.83 ± 0.55 | 2.83 ± 0.57 | 0.85 |
| In-stent minimum LD (mm) | 2.37 ± 0.51 | 2.30 ± 0.48 | 2.39 ± 0.48 | 2.43 ± 0.57 | 0.58 |
| Diameter stenosis (%) | 15.4 ± 8.9 | 17.0 ± 9.5 | 15.0 ± 9.3 | 14.2 ± 7.7 | 0.32 |
| Post-PCI IVUS analysis | | | | | |
| Minimum stent area ($mm^2$) | 4.94 ± 2.12 | 4.65 ± 1.62 | 4.76 ± 2.12 | 5.43 ± 2.53 | 0.31 |
| Vessel area ($mm^2$) | 9.91 ± 4.43 | 9.67 ± 3.88 | 9.89 ± 4.52 | 10.16 ± 4.86 | 0.96 |
| Plaque burden (%) | 51.5 ± 9.8 | 50.4 ± 10.4 | 49.5 ± 9.7 | 54.4 ± 9.3 | 0.052 |

Data are expressed as mean ± standard deviation, median (interquartile range), or n (%). Good collateral flow is defined as Rentrop grade 3. CTO = chronic total occlusion; IVUS = intravascular ultrasound; LD = lumen diameter; PCI = percutaneous coronary intervention; QCA = quantitative coronary arteriography; TIMI = thrombolysis in myocardial infarction.

demonstrated a significantly higher incidence of TLR in patients with high tertile than the low and intermediate groups (Figure 1). Multivariable analysis showed SUA ≥6.5 mg/dl, diabetes mellitus, and longer CTO length as independent predictors of TLR (Table 3).

## Discussion

The present study showed that TLR was found in 14.5% in patients who underwent successful CTO PCI with new-generation DES under IVUS guidance during a median follow-up of 34 months. Patients in the high tertile group (SUA ≥6.5

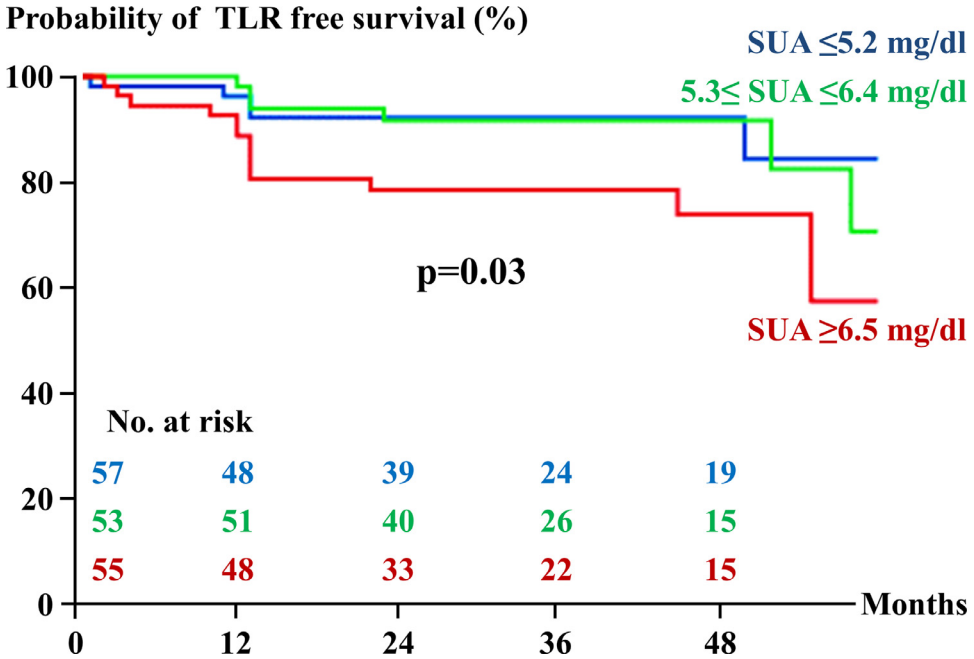


Figure 1. Kaplan-Meier analysis for the probability of TLR-free survival. TLR = target lesion revascularization; SUA = serum uric acid.

Table 3
Predictors of target lesion revascularization

| Variable | Univariable | | Multivariable | |
|---|---|---|---|---|
| | OR (95% CI) | p Value | OR (95% CI) | p Value |
| Men | 1.59 (0.44-5.74) | 0.48 | | |
| Age (years) | 0.96 (0.92-1.00) | 0.04 | 1.00 (0.95-1.06) | 0.85 |
| Hypertension | 2.87 (0.81-10.15) | 0.10 | | |
| Diabetes mellitus | 2.71 (1.12-6.56) | 0.03 | 3.51 (1.14-10.81) | 0.03 |
| Dyslipidemia | 5.45 (0.70-42.13) | 0.10 | | |
| eGFR (ml/min/1.73 $m^2$) | 1.02 (0.99-1.05) | 0.14 | 1.03 (0.99-1.07) | 0.06 |
| Serum uric acid ≥6.5 (mg/dl) | 3.41(1.40-8.31) | 0.006 | 6.74 (2.05-22.11) | 0.002 |
| Occluded length (mm) | 1.04 (1.01-1.07) | 0.01 | 1.04 (1.00-1.08) | 0.04 |
| Minimum stent area ($mm^2$) | 0.79 (0.60-1.02) | 0.07 | 0.80 (0.61-1.05) | 0.11 |

CI = confidence interval; eGFR = estimated glomerular filtration rate; OR = odds ratio.

mg/dl) had a higher rate of TLR (25.5%) than those in the low tertile (8.8%) and the intermediate tertile (9.4%). Multivariable analysis demonstrated that SUA ≥6.5 mg/dl was significantly associated with TLR, in addition to history of diabetes mellitus, and longer CTO length. To the best of our knowledge, this is the first report investigating the impact of SUA level on TLR in contemporary CTO PCI.

The ISR and subsequent TLR rates after PCI of CTO lesions are known to be higher than non-CTO lesions. In the early DES era, the reported incidence of angiographic restenosis at 6 to 12 months was 20% to 25%.[3,5] The j-Cypher registry showed that TLR rate was significantly and consistently higher in CTO PCI than non-CTO PCI at 1 year (9.6% vs 6.5%), 3 years (16.4% vs 10.9%), and 5 years (20.7% vs 14.8%) in the real-world clinical settings.[4] Even in the new-generation DES era, the LEADERS all-comers trial demonstrated that CTO PCI was associated with increased risk of TLR at 5-year follow-up compared with non-CTO PCI (21.0% vs 12.6%, p = 0.03).[6] The TLR rate at 3 years from the j-Cypher registry is consistent with our results, and the TLR rates in the j-Cypher registry and the LEADERS all-comers trial at 5 years were similar. In addition, a meta-analysis indicated that new-generation DES rather than the first-generation DES was associated with reduced risks of myocardial infarction and stent thrombosis, but not with TLR.[14] These findings reinforce the high TLR rate in CTO PCI as clinical concerns even in the new-generation DES era. Thus, the identification of clinical and/or angiographic characteristics predicting restenosis and TLR after CTO PCI is of importance. Previous studies have indicated several factors as predictors of ISR and TLR following CTO PCI with DES, including diabetes mellitus, in-stent CTO, longer lesion length and more stents, higher J-CTO score, subintimal tracking and re-entry technique, smaller MSA, and smaller stent expansion ratio.[3,12,15,16] Furthermore, the use of IVUS was associated with reduced risk of TLR in CTO PCI, especially in long lesions.[17] However, simple indices for predicting revascularization that can be used before PCI procedure are scarce.

Endothelial dysfunction, inflammatory stimuli, and subsequent smooth muscle cell (SMC) proliferation are considered to play important roles in the occurrence of ISR after PCI.[18,19] Endothelium regulates intravascular homeostasis, vascular tone, vascular permeability, inflammation, and SMC proliferation.[20] Endothelial dysfunction progresses the atherosclerotic changes within vascular wall with excessive production of reactive oxygen species and reduction of activity of endothelial nitric oxide synthase, which promotes SMC proliferation.[21] In this context, previous studies showed that SUA level is inversely correlated with endothelial function.[10] Additionally, experimental and clinical investigations have suggested that inflammation is also a key factor in the pathogenesis of intimal hyperplasia after arterial injury.[19,22] Previous study demonstrated that SUA stimulates inflammatory markers, such as high-sensitivity C-reactive protein (CRP), white blood cells, interleukin-1, interleukin-6, interleukin-10, interleukin-18, endothelin-1, and tumor necrosis factor-alpha, all of which contribute ISR.[9,23] In the present study, there was a trend of positive correlation between SUA level and CRP (r = 0.15, p = 0.056), which might suggest that SUA is associated with inflammation as previously reported. Moreover, SUA has been reported to directly stimulate vascular SMC proliferation and the neointimal formation in the surface of the stent mediated by the activation or induction of extracellular signal-regulated kinase mitogen-activated protein kinases, cyclooxygenase-2, and platelet-derived growth factor.[23,24] Based on these findings, it is plausible that SUA may increase the risk of ISR through proinflammatory status, deteriorating endothelium function, and proliferation of vascular SMC.

The present study showed that preprocedural SUA level may be useful to identify the patients at high risk for TLR in CTO PCI. In the bare metal stent era, Turak et al reported that the higher preprocedural SUA level was one of the independent predictors of ISR in patients with stable or unstable angina.[11] The best cut-off value of SUA level in that study was 5.5 mg/dl, which is numerically lower than the highest tertile in the present study. Furthermore, SUA was also indicated as a predictor of DES restenosis in patients with diabetes mellitus.[25] According to the results of the present study, close monitoring and appropriate secondary prevention should be considered in patients with higher SUA levels who underwent contemporary CTO PCI. Larger sized clinical studies are warranted to determine whether SUA level is causally associated with restenosis.

There is no clinical study examining the efficacy of SUA lowering therapy to reduce coronary events after PCI. Xanthine oxidase inhibitors such as allopurinol have been shown to improve endothelial function and oxidative

stress in patients with stable coronary artery disease[26] and reduce the levels of CRP in patients with high SUA level.[27] A previous randomized study also found that allopurinol significantly reduced the carotid intima-media thickness progression in the placebo-controlled setting.[28] Although a recent randomized control trial did not show the benefit of SUA lowering therapy with a xanthine oxidase inhibitor in reducing coronary events,[29] active intervention on high SUA level might reduce coronary revascularization. Further study is needed to confirm the relation between SUA level and TLR and elucidate whether the reduction of SUA level and/or inhibition of xanthine oxidase contribute to the improvement of prognosis in patients who underwent CTO PCI.

There are some limitations in the present study. First, this was a retrospective single-center analysis, and the number of patients was relatively small. Second, the duration of the occlusion was not clear. Third, although oxidative stress is the one of the key factors of the process of endothelium function, serum oxidative stress marker (e.g., isoprostanes, 8-hydroxy-2′-deoxyguanosine, and thiobarbituric acid reactive substances) was not obtained in the present study. Fourth, multivariable analysis was performed in this study, however, unmeasured factors (e.g. platelet reactivity) might confound TLR rate.

## Disclosures

The authors have no conflicts of interest to disclose.


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