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*Percutaneous Coronary Intervention*

# Clinical Impact of High-Sensitivity Cardiac Troponin T on the Chronic Phase of Stable Angina after a Successful Initial Percutaneous Coronary Intervention

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***Background:*** The purpose of this study was to investigate the clinical significance of elevated plasma high-sensitivity troponin T (hs-TnT) in the chronic phase in patients with stable angina pectoris (SAP) who underwent a successful percutaneous coronary intervention (PCI).

***Methods:*** This study enrolled 158 consecutive SAP patients who underwent routine follow-up coronary angiography 9 months after a successful PCI with the implantation of a second-generation drug-eluting stent. Patients with previous coronary artery bypass graft and renal dysfunction were excluded. Patients were divided into two groups according to hs-TnT plasma level at follow-up: elevated hs-TnT (≥ 0.015 ng/ml) group and non-elevated hs-TnT group.

***Result:*** Among the 158 subjects, 42 had an elevated hs-TnT level at follow-up. The elevated hs-TnT group had a significantly higher rate of any coronary lesion (in-stent restenosis and de novo lesions) in follow-up CAG (coronary angiography) than the non-elevated group (28.6% vs. 10.3%, $p < 0.05$). Multivariate analysis also showed that hs-TnT elevation was independently associated with the presence of significant coronary stenosis in the chronic phase (odds ratio: 3.99, 95% confidence interval: 1.38 to 11.53). The best cut-off value of the hs-TnT level at 9 months after a successful PCI to predict the presence of significant coronary stenosis was 0.016 ng/ml (sensitivity: 50.0%; specificity: 82.1%; area under the receiver operating characteristic curve: 0.67).

***Conclusions:*** hs-TnT elevation was independently associated with the presence of coronary stenosis in the chronic phase in SAP patients with successful PCI. Routine measurement of hs-TnT in the chronic phase may be useful to refine the risk of patients after PCI.

**Key Words:** Coronary stenosis • High-sensitivity troponin T • Stable angina

## INTRODUCTION

Cardiac troponins are the most commonly used biomarkers for the diagnosis of acute coronary syndrome.[1] High-sensitivity troponin T (hs-TnT) assays enable the detection of even minor myocardial damage.[2,3] In patients with stable angina pectoris (SAP), elevation of hs-TnT before and immediately after a percutaneous coronary intervention (PCI) has been associated with the incidence of revascularization, heart failure, and cardiovascular death, thereby, providing prognostic information. However, the value of hs-TnT level in the chronic phase after a successful initial PCI in patients with

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SAP remains unclear. Therefore, the aim of this study was to investigate the clinical significance of elevated plasma levels of hs-TnT in the chronic phase in patients with SAP who underwent a successful PCI.

## METHODS

### Patient population

This study was a cross-sectional study that enrolled consecutive SAP patients who underwent routine follow-up coronary angiography 9 months after a successful PCI with the implantation of a second-generation drug-eluting stent (DES) at Kawasaki Medical School Hospital between September 2014 and July 2017. We excluded patients with previous coronary artery bypass graft (CABG) and renal dysfunction [estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 $m^3$]. SAP was defined as non-progressive typical chest pain occurring with physical exercise and significant stenosis (> 75%) on coronary angiography. Silent ischemia was included as SAP and was defined as significant stenosis (> 75%) based on either myocardial scintigraphy or fractional flow reserve. The demographic and clinical characteristics, procedural information, laboratory data, and angiographic outcomes were systematically collected. This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the hospital (approval number: 2784).

### Biochemical analyses

Plasma levels of hs-TnT (Elecsys troponin T assay hs; Roche Diagnostics, Tokyo, Japan) were measured during routine follow-up angiography at 9 months after a successful PCI. This hs-TnT assay had a lower limit of detection of 0.003 ng/ml and a 99$^{th}$ percentile upper reference limit of 0.014 ng/ml. Other routine laboratory measurements were also performed.

### Clinical outcomes and definitions

Patients were divided into two groups according to the hs-TnT level at 9 months of follow-up as the elevated hs-TnT (≥ 0.015 ng/ml) group and non-elevated hs-TnT group. Based on follow-up coronary angiography, we evaluated the presence of both restenosis of the index target lesion as well as progression of luminal stenosis at non-target lesions as clinical outcomes. Restenosis was defined as an angiographic narrowing of > 50% stenosis in in-stent lesions. A progressive lesion was defined as a*de novo* angiographic narrowing of > 75% stenosis in a non-target lesion.

### Statistical analysis

All statistical analyses were performed with JMP version 13 (SAS Institute Inc., Cary, North Carolina, USA). Categorical variables were expressed as number (%) and were compared with the $\chi^2$ test or Fisher's exact test, as appropriate. Continuous variables were expressed as mean ± standard deviation and were compared using the unpaired t-test or Mann-Whitney U-test according to their distributions. Univariate analysis was performed to evaluate associations between hs-TnT elevation and characteristics or variables. To compare the relationship between hs-TnT elevation and the incidence of any significant coronary stenosis, we performed two additional analyses. First, univariate and multivariate logistic regression analyses were performed to identify characteristics or variables independently associated with any significant coronary stenosis. From the univariate analysis, characteristics and variables were entered into the multivariate model: age, sex, hs-TnT, multi-lesion coronary interventions, number of stents per patient, total stent length and AHA/ACC type B2/C lesion. Second, a receiver operating characteristic (ROC) curve was used to determine the best cut-off value of hs-TnT level at 9 months after a successful PCI to predict any significant coronary stenosis. All reported p values were 2-sided, and $p < 0.05$ was regarded as being statistically significant. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated.

## RESULTS

### Patient characteristics

A total of 158 SAP patients who underwent PCI were analyzed in this study, including 42 in the group with hs-TnT elevation and 116 in the group without hs-TnT elevation (Figure 1). The frequency distribution of the hs-TnT levels is shown in Figure 2, and the median hs-TnT level of all patients was 0.011 ng/ml. The clinical characteristics at 9 months after a successful PCI are

summarized in Table 1. Compared to the group without hs-TnT elevation, the group with hs-TnT elevation was significantly older and had significantly higher rates of diabetes, statin use, and anti-diabetic agent use. Laboratory characteristics showed a significantly lower Hb level and significantly higher hemoglobin A1c (HbA1c) and brain natriuretic peptide (BNP) levels in the elevated hs-TnT group than in the non-elevated group (Table 2). The ejection fraction on echocardiography was not significantly different between the two groups. Lesion characteristics at baseline before PCI are shown in Table 3. The patients with hs-TnT elevation more frequently underwent PCI of ACC/AHA type B or C lesions and had significantly longer stent length compared to the patients without hs-TnT elevation (Table 3).

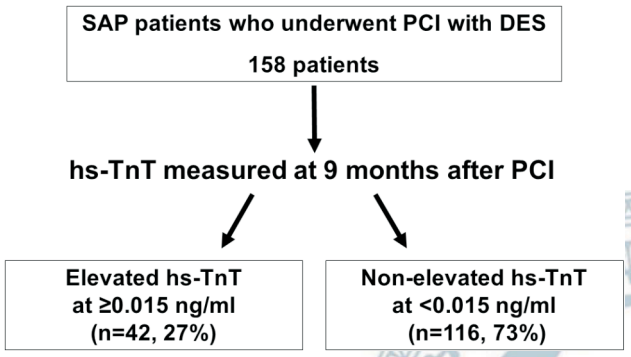


***Figure 1.*** *Schematic presentation of the study design. DES, drug-eluting stent; hs-TnT, high-sensitivity troponin T; PCI, percutaneous coronary intervention; SAP, stable angina pectoris.*

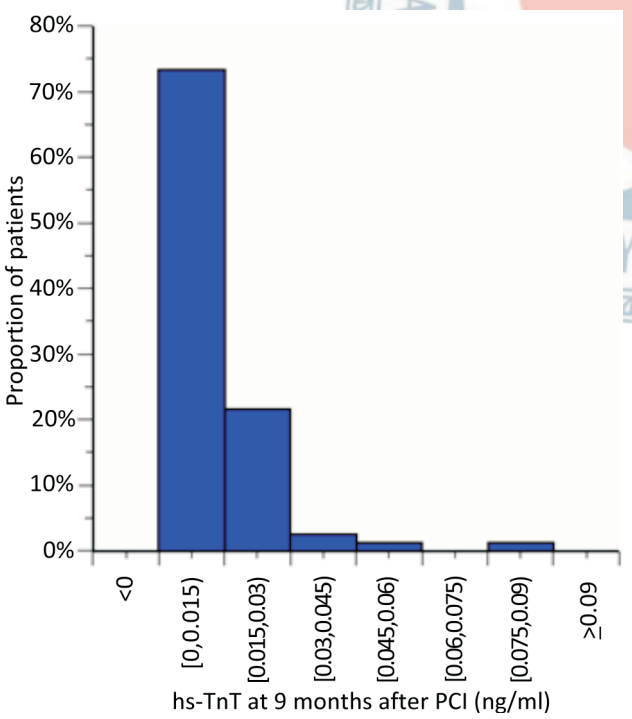


***Figure 2.*** *Proportion of patients across the incremental values of hs-TnT at 9 months after a successful PCI. hs-TnT, high-sensitivity troponin T; PCI, percutaneous coronary intervention.*

**Table 1.** Clinical characteristics of patients according to the hs-TnT levels at 9 months after a successful PCI

| Variable | hs-TnT elevated (n = 42) | hs-TnT not elevated (n = 116) | p value |
|---|---|---|---|
| Age (years) | 75 ± 10 | 68 ± 10 | < 0.01 |
| Male, n (%) | 28 (67) | 91 (78) | 0.13 |
| Diabetes, n (%) | 26 (62) | 46 (40) | 0.013 |
| Dyslipidemia, n (%) | 38 (90) | 109 (94) | 0.46 |
| Hypertension, n (%) | 37 (88) | 100 (86) | 0.75 |
| OMI, n (%) | 18 (43) | 44 (38) | 0.58 |
| Medications | | | |
| ACEI/ARB, n (%) | 30 (71) | 75 (65) | 0.42 |
| Beta-blocker, n (%) | 21 (50) | 46 (40) | 0.24 |
| Anti-diabetics, n (%) | 25 (60) | 43 (37) | 0.012 |
| Statin, n (%) | 33 (79) | 110 (95) | < 0.01 |
| CCB | 22 (50) | 62 (53) | 0.90 |
| Aspirin | 42 (100) | 116 (100) | - |
| Clopidogrel/prasugrel/ticlopidin | 32/4/2 | 96/19/1 | 0.20 |
| Anticoagulation, n (%) | 4 (10) | 8 (7) | 0.51 |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; hs-TnT, high-sensitivity troponin T; OMI, old myocardial infarction; PCI, percutaneous coronary intervention.

**Table 2.** Laboratory tests and echocardiography finding according to the hs-TnT levels at 9 months after a successful PCI

| Variable | hs-TnT elevated (n = 42) | hs-TnT not elevated (n = 116) | p value |
|---|---|---|---|
| Laboratory data | | | |
| Hb (g/dl) | 12.5 ± 1.7 | 13.5 ± 1.5 | 0.013 |
| CRP (mg/dl) | 0.23 ± 0.05 | 0.17 ± 0.31 | 0.35 |
| HbA1c (%) | 6.7 ± 1.2 | 6.2 ± 0.7 | < 0.01 |
| LDL-cholesterol (mg/dl) | 88 ± 24 | 89 ± 20 | 0.85 |
| BNP (pg/ml) | 176 ± 284 | 64 ± 81 | < 0.01 |
| eGFR (ml/min/1.73 $m^2$) | 63 ± 22 | 73 ± 20 | < 0.01 |
| LVEF (%) | 58 ± 11 | 59 ± 9 | 0.62 |

BNP, brain natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1c, hemoglobin A1c; hs-TnT, high-sensitivity troponin T; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

**Table 3.** Lesion characteristics according to the hs-TnT levels at 9 months after a successful PCI

| Variable | hs-TnT elevated (n = 42) | hs-TnT not elevated (n = 116) | p value |
|---|---|---|---|
| Multivessel coronary disease | 26 (61.9%) | 72 (62.1%) | 0.99 |
| Multilesion coronary intervention | 13 (31.0%) | 21 (18.1%) | 0.09 |
| Stent number per patient | 1.71 ± 1.04 | 1.55 ± 1.12 | 0.41 |
| Total stent length (mm) | 37.5 ± 29.1 | 32.3 ± 22.6 | 0.24 |
| Target coronary vessel (n) | 58 | 161 | – |
| LAD/LCX/RCA | 30/15/13 | 87/41/33 | 0.94 |
| AHA/ACC type B2/C lesion | 44 (75.8%) | 98 (60.9%) | < 0.05 |
| Stent number per lesion | 1.26 ± 0.48 | 1.11 ± 0.43 | < 0.05 |
| Stent length per lesion (mm) | 27.2 ± 17.1 | 23.8 ± 12.9 | 0.12 |
| Mean stent diameter per lesion (mm) | 2.78 ± 0.42 | 2.69 ± 0.40 | 0.14 |

AHA/ACC, American College of Cardiology/American Heart Association; hs-TnT, high-sensitivity troponin T; LAD, left anterior descending artery; LCX, left circumflex coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery.

### Clinical outcomes

Among the 158 subjects, 42 had an elevated hs-TnT level at follow-up. The patients with hs-TnT elevation had a significantly higher rate of any coronary lesions (in-stent restenosis and de novo lesions) in follow-up CAG (coronary angiography) than the patients without hs-TnT elevation (28.6% vs. 10.3%, p < 0.05). With regards to the incidence of the individual outcomes, restenosis was significantly higher in the non-elevated hs-TnT group than in the elevated group, but progression in non-target lesions was not different between the two groups (Figure 3).

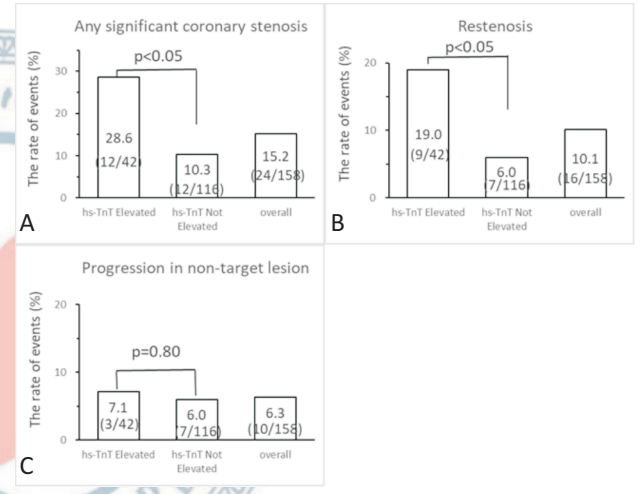


***Figure 3.*** *Clinical outcome at 9 months after successful PCI. Incidence of (A) Any significant coronary stenosis, (B) Restenosis and (C) Progression in non-target lesion between groups with or without hs-TnT elevation. Patients with hs-TnT elevation had significantly higher rate of any coronary lesions (restenosis and progression in non-target lesion) and restenosis than patients without hs-TnT elevation. hs-TnT, high-sensitivity troponin T; PCI, percutaneous coronary intervention.*

### Univariate and multivariate analyses of any significant coronary stenosis

Table 4 shows the results of univariate and multivariate analyses of any significant coronary stenosis. In univariate analysis, there were significant differences in hs-TnT, multi-lesion coronary interventions, number of stents per patient, total stent length and AHA/ACC type B2/C lesions between the two groups. Multivariate analysis also showed that hs-TnT elevation was independently associated with the presence of significant coronary stenosis in the chronic phase (OR: 3.99, 95% CI: 1.38 to 11.53).

### Prediction of the presence of any significant coronary stenosis

The best cut-off value of hs-TnT level at 9 months after a successful PCI to predict the presence of significant coronary stenosis was 0.016 ng/ml (sensitivity: 50.0%; specificity: 82.1%; area under the ROC curve: 0.67) (Figure 4).

## DISCUSSION

The main findings of this study can be summarized as follows: 1) the hs-TnT level in the chronic phase after PCI was elevated in 42 patients (27%); 2) patients with elevated hs-TnT had a significantly higher rate of significant coronary stenosis than the patients without hs-TnT

**Table 4.** Univariate and multivariate logistic regression analysis on any significant coronary stenosis

| Variable | Univariate | | | | Multivariate | |
|---|---|---|---|---|---|---|
| | Any significant coronary stenosis + (n = 24) | Any significant coronary stenosis - (n = 134) | OR (95% CI) | p value | OR (95% CI) | p value |
| Age (years) | 68.7 ± 13.3 | 70.1 ± 10.2 | 0.99 (0.95-1.03) | 0.57 | 0.95 (0.91-1.00) | 0.036 |
| Male, n (%) | 20 (83.3) | 99 (73.9) | 1.77 (0.56-5.53) | 0.31 | 1.45 (0.45-4.70) | 0.529 |
| Diabetes, n (%) | 13 (54.2) | 60 (44.8) | 1.46 (0.61-3.49) | 0.40 | | |
| Dyslipidemia, n (%) | 24 (100) | 123 (91.8) | Infinity | 0.15 | | |
| Hypertension, n (%) | 22 (91.7) | 115 (85.8) | 1.82 (0.39-8.37) | 0.41 | | |
| OMI, n (%) | 10 (41.7) | 52 (38.8) | 1.13 (0.47-2.72) | 0.79 | | |
| Medications | | | | | | |
| ACEI/ARB, n (%) | 16 (66.7) | 89 (66.4) | 1.01 (0.40-2.54) | 0.98 | | |
| Beta-blocker, n (%) | 14 (58.3) | 53 (39.6) | 2.14 (0.89-5.17) | 0.08 | | |
| Anti-diabetics, n (%) | 10 (41.7) | 59 (44.0) | 0.91 (0.38-2.19) | 0.83 | | |
| Statin, n (%) | 24 (100) | 119 (88.8) | Infinity | 0.08 | | |
| CCB | 16 (66.7) | 68 (50.7) | 2.19 (0.88-5.46) | 0.10 | | |
| Aspirin | 24 (100) | 134 (100) | – | – | | |
| Clopidogrel/prasugrel/ticlopidin | 20/3/1 | 112/20/2 | – | 0.71 | | |
| Anticoagulation, n (%) | 1 (4.2) | 11 (8.2) | 0.49 (0.06-3.95) | 0.49 | | |
| Laboratory data | | | | | | |
| Hb (g/dl) | 13.3 ± 2.0 | 13.2 ± 1.5 | 1.06 (0.81-1.39) | 0.67 | | |
| CRP (mg/dl) | 0.26 ± 0.40 | 0.18 ± 0.31 | 1.89 (0.64-5.56) | 0.27 | | |
| HbA1c (%) | 6.5 ± 1.2 | 6.3 ± 0.9 | 1.26 (0.83-1.92) | 0.27 | | |
| LDL-cholesterol (mg/dl) | 94.6 ± 28.0 | 87.6 ± 19.3 | 1.02 (1.00-1.04) | 0.13 | | |
| BNP (pg/ml) | 103.5 ± 109.5 | 91.0 ± 175.1 | 1.00 (0.998-1.003) | 0.74 | | |
| eGFR (ml/min/1.73 $m^2$) | 64.7 ± 26.1 | 71.1 ± 20.2 | 0.99 (0.96-1.01) | 0.17 | | |
| hs-TnT (ng/ml) | 12 (50.0) | 30 (22.4) | 3.47 (1.41-8.50) | < 0.05 | 3.99 (1.38-11.53) | 0.010 |
| LVEF (%) | 58.9 ± 9.9 | 58.3 ± 9.4 | 1.01 (0.96-1.06) | 0.76 | | |
| Multivessel coronary disease (%) | 16 (66.7) | 82 (61.2) | 1.27 (0.51-3.17) | 0.61 | | |
| Multilesion coronary intervention (%) | 9 (37.5) | 25 (18.7) | 2.62 (1.03-6.65) | < 0.05 | 1.81 (0.42-7.90) | 0.433 |
| Stent number per patient | 2.1 ± 1.4 | 1.5 ± 1.0 | 1.48 (1.05-2.06) | < 0.05 | 1.10 (0.51-2.37) | 0.801 |
| Total stent length (mm) | 48.4 ± 33.4 | 31.0 ± 21.7 | 1.02 (1.01-1.04) | < 0.05 | 1.02 (0.99-1.06) | 0.195 |
| Lesion characteristics at baseline | 27 | 192 | – | – | | |
| LAD/LCX/RCA | 15/5/7 | 102/51/39 | – | 0.60 | | |
| AHA/ACC type B2/C lesion (%) | 23 (85.2) | 119 (62.0) | 3.53 (1.17-10.61) | < 0.05 | 1.99 (0.57-6.93) | 0.268 |
| Stent number per lesion | 1.2 ± 0.4 | 1.1 ± 0.5 | 1.38 (0.66-2.88) | 0.38 | | |
| Stent length per lesion (mm) | 26.0 ± 12.1 | 24.3 ± 13.5 | 1.02 (0.99-1.04) | 0.18 | | |
| Mean stent diameter per lesion (mm) | 2.6 ± 0.4 | 2.7 ± 0.4 | 0.68 (0.24-1.93) | 0.46 | | |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AHA/ACC, American College of Cardiology/ American Heart Association; BNP, brain natriuretic peptide; CCB, calcium-channel blocker; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1c, hemoglobin A1c; hs-TnT, high-sensitivity troponin T; LAD, left anterior descending artery; LCX, left circumflex coronary artery; LVEF, left ventricular ejection fraction; OMI, old myocardial infarction; OR, odds ratio; RCA, right coronary artery.

elevation; 3) hs-TnT elevation was independently associated with the presence of any significant coronary stenosis; 4) the best cut-off values of hs-TnT level at follow-up to predict any significant coronary stenosis was 0.016 ng/ml.

hs-TnT is a known biomarker of cardiac ischemia and has been reported to be an independent predictor of mortality in patients with unstable angina.[4] More-

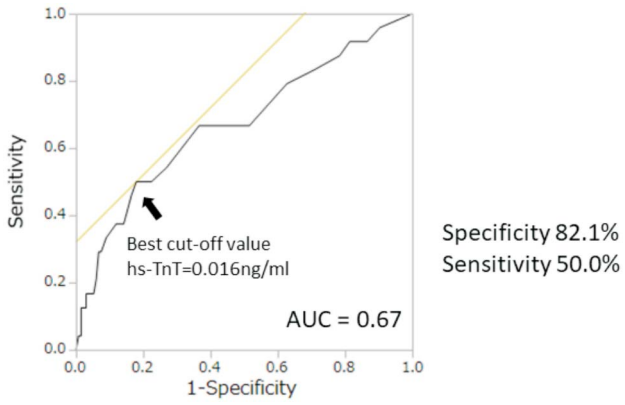


***Figure 4.*** *Receiver operating characteristic curve for hs-TnT level at 9 months after a successful PCI to predict an any significant coronary stenosis. The best cut-off value of the hs-TnT level at 9 months after a successful PCI to predict the presence of significant coronary stenosis was 0.016 ng/ml (Specificity: 82.1%; Sensitivity: 50.0%). AUC, area under the curve. hs-TnT, high-sensitivity troponin T; PCI, percutaneous coronary intervention.*

over, the hs-TnT level immediately after PCI has been reported to be elevated in 80% of patients with SAP.[5] However, the clinical significance of hs-TnT level in the chronic phase of a successful initial PCI in patients with SAP remains unclear, and to the best of our knowledge, this is the first report to reveal the clinical impact of hs-TnT in such cases.

Elevated hs-TnT has been reported to be related not only to coronary artery disease but also to heart failure,[6-8] anemia,[9] and renal dysfunction.[10] In the current study, patients with elevated hs-TnT had a significantly higher BNP level and lower levels of Hb and eGFR compared to the patients without elevated hs-TnT. These results are consistent with those of previous reports. The mechanism for the increase in hs-TnT in patients with heart failure is thought to be due to ongoing cardiac myocyte death.[11,12] As for the relationship between low eGFR and high hs-TnT, chronic kidney disease may lead to myocardial injury via endothelial dysfunction and microvascular disease, which is caused by elevated levels of asymmetric dimethylarginine or mediators of oxidative stress.[13,14]

Our data showed that hs-TnT elevation was significantly associated with restenosis, but not progression in non-target lesions. The pathophysiology of restenosis may be different from that of progression in non-target lesions, and the progression of restenosis is known to be mainly characterized by smooth muscle cell and neointimal tissue proliferation. Buchanan et al.[15] reported that the incidence of cardiovascular events after treatment for restenosis was worse compared to treatment for de novo lesions based on atherosclerotic plaques. Furthermore, Magalhaes et al.[16] demonstrated that restenosis had a tendency to present clinically in the form of unstable angina and myocardial infarction. The neointimal proliferation that leads to near-total obstruction of the lumen and compromises flow will ultimately lead to a thrombotic event. In overall clinical outcomes, hs-TnT elevation in the chronic phase after PCI was independently associated with the presence of any significant coronary stenosis, defined as both restenosis of the target lesion and de novo development of angiographic stenosis in non-target lesions. A previous study reported a significant relationship between hs-TnT elevation and severity of coronary stenosis in patients with SAP before PCI.[15] Therefore, this result suggests that even SAP patients with hs-TnT elevation in the chronic phase after successful PCI may be associated with recurrent significant coronary stenosis. In the current study, the diagnostic efficiency (area under the ROC curve) of hs-TnT to predict the presence of significant coronary stenosis in the chronic phase after PCI was 0.67. Yamazaki et al.[17] reported that the diagnostic efficiency of hs-TnT to predict the presence of SAP prior to first coronary angiography was 0.66. These findings suggest that regardless of when hs-TnT is measured, the association between hs-TnT and coronary stenosis has certain clinical implications.

Since the advent of balloon angioplasty and bare-metal stent era, routine follow-up coronary angiography after PCI has been performed due to the high degree of restenosis.[18,19] Even though the incidence of restenosis in the chronic phase with DES is significantly lower, angiography is commonly performed as usual care in Japan. A recent study in Japan showed that checkups did not improve clinical outcomes,[20] and the current clinical guidelines in the United States have already disregarded routine follow-up coronary angiography.[21] Therefore, follow-up CAG after PCI is not routinely performed in Japan. However, we regularly performed follow-up CAG 9 months after PCI in this study, and found that the SAP patients with an elevated level of hs-TnT on follow-up after a successful PCI were associated with a significantly higher incidence of any significant coronary ste-

nosis compared to those without hs-TnT elevation. Accordingly, it seems to be reasonable to measure hs-TnT first in the chronic phase. When this value is positive, coronary angiography or coronary computed tomographic angiography should be added to check significant epicardial coronary stenosis. Risk stratification is important before performing invasive angiography.[20] Further large-scale studies with long-term follow-up are necessary to reveal the clinical impact of hs-TnT in the chronic phase in SAP patients who undergo a successful PCI.

There are several limitations to the present study. First, the study was cross-sectional in design so that possible prognostic evaluations could not be performed. Second, this study excluded patients with renal dysfunction and prior CABG, which are conditions associated with a high risk of troponin elevation. Therefore, the number of patients with hs-TnT elevation in this study could be much higher than that in real-world clinical practice.

## CONCLUSIONS

Elevated plasma levels of hs-TnT at 9 months of follow-up were independently associated with the presence of angiographic coronary stenosis in SAP patients after a successful PCI with second-generation DES. Routine measurement of hs-TnT in the chronic phase may be useful to refine the risk of patients after PCI.

## CONFLICT OF INTEREST

Department of cardiology obtained funding as an encouragement of study donation from Abbott Japan Co., Ltd. S. Uemura obtain personal fees from Daiichi Sankyo Company, and Astellas Amgen biopharma. The other authors report no financial relationships to disclose.

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