Contrast volume and in-hospital outcomes of dialysis patients undergoing percutaneous coronary intervention

Toshiki Kuno1*, Yohei Numasawa2, Satoshi Shoji3, Ikuko Ueda1, Masahiro Suzuki4, Shigetaka Noma5, Keiichi Fukuda3 & Shun Kohsaka3

Toxicity resulting from retained contrast media may cause adverse cardiovascular outcomes (e.g., heart failure and cardiogenic shock) for dialysis patients. However, the association between the administered contrast volume and outcomes of dialysis patients after percutaneous coronary intervention (PCI) has not been sufficiently investigated. We evaluated 953 consecutive dialysis patients (age, 67.9 ± 9.9 years; 30.1% with acute coronary syndrome) who underwent PCI between September 2008 and March 2019. Patients were divided into two groups: those with a contrast volume ≥ 200 ml and those with a contrast volume < 200 ml. The cutoff was 200 ml because 100 ml increment of contrast volume is known to raise the risk of acute kidney injury, and 200 ml is more than the average volume used at most PCI centers. The primary endpoint was a composite of in-hospital death, post-PCI cardiogenic shock and post-PCI heart failure. A multivariable logistic regression model and smooth spline curve were constructed to assess the association between contrast volume and the primary endpoint. The median contrast volume was 157 ml (interquartile range, 115–210 ml). The overall primary endpoint incidence was 6.8% (N = 65). A contrast volume ≥ 200 ml was associated with a higher risk of the primary endpoint (odds ratio 2.91; 95% confidence interval 1.42–6.05; P = 0.004). The smooth spline curve demonstrated a linear relationship between the contrast volume and primary endpoint. In conclusions, the contrast volume was associated with adverse in-hospital outcomes of dialysis patients undergoing PCI. Attention should be focused on the contrast volume used for dialysis patients undergoing PCI.

Abbreviations
ACS  Acute coronary syndrome
AKI  Acute kidney injury
JCD-KiCS  Japan Cardiovascular Database-Keio Interhospital Cardiovascular Studies
PCI  Percutaneous coronary intervention
STEMI  ST-segment elevation myocardial infarction

The contrast volume administered to patients undergoing percutaneous coronary intervention (PCI) is strongly associated with the risk of acute kidney injury (AKI)1-4. Clinical practice guidelines recommend minimizing the contrast volume to the lowest feasible level, especially for patients who are at high risk for AKI1. However, these recommendations are largely limited to non-dialysis patients. Several studies of dialysis patients have demonstrated that PCI operators focus little attention on the contrast volume because the contrast medium is cleared by subsequent dialysis5,6.

The association between the contrast volume and adverse outcomes other than AKI (e.g., heart failure and cardiogenic shock) for dialysis patients has been insufficiently investigated. A higher contrast volume is typically needed for PCI procedures performed for dialysis patients because of the higher incidence of complex coronary
lesions; therefore, cardiac toxicity caused by higher concentrations of contrast media reaching the coronary arteries is a concern. Additionally, acute expansion of plasma volume caused by osmotic effects may lead to heart failure.

We hypothesized that cardiovascular toxicity caused by the retained contrast media could result in adverse events, including new-onset cardiogenic shock and heart failure after PCI. Using the contemporary multicenter all-comer PCI registry, we investigated the association between contrast volume and the risk of adverse inhospital outcomes of dialysis patients undergoing PCI.

Methods

Database. This study was conducted as part of the Japan Cardiovascular Database-Keio Interhospital Cardiovascular Studies (JCD-KiCS) PCI registry, which is a multicenter, prospective registry including data of consecutive patients who underwent PCI between 2009 and 2017 at 15 institutions within the Tokyo metropolitan area. It primarily includes large tertiary care referral centers (≥ 200 beds; n = 13) and a few medium-sized satellite hospitals (< 200 beds; n = 2). The details of this registry have been published previously. Participating hospitals were instructed to document and register patient data of consecutive hospital visits for PCI using an internet-based data collection system. Registered data were reviewed for completeness and internal consistency.

Quality assurance of the data was achieved through automatic system validation, reporting of data completeness, and education and training of clinical research coordinators who were specifically trained to use the present PCI registry. The senior study coordinator (I.U.) and exclusive on-site auditing by the investigator (S.K.) ensured appropriate registration of each patient. All participants provided written informed consent. Before the launch of the JCD-KiCS registry, information regarding the objective of this registry was provided for clinical trial registration in the University Hospital Medical Information Network of Japan (UMIN000004736). The present study was approved by the institutional review board Committee of Keio University (Reference Number: 20080073), and was conducted in accordance with the principles of the Declaration of Helsinki. We also confirmed that all methods were performed in accordance with relevant guidelines and regulations.

Definition of outcomes and variables. The clinical variables and outcomes of the JCD-KiCS were aligned with the data of the National Cardiovascular Data Registry CathPCI Registry version 4.1. Acute coronary syndrome (ACS) was defined as ST-segment elevation myocardial infarction (STEMI), non-STEMI, unstable angina. Stable coronary artery disease was defined as stable angina, previous myocardial infarction, and silent ischemia. The presence of heart failure was defined as documentation of heart failure by the attending physician, regardless of left ventricular ejection fraction. Multivessel disease was defined as two or more major coronary arteries with ≥ 75% stenosis. The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease Equation for Japanese Patients proposed by the Japanese Society of Nephrology.

All major procedural complications (e.g., death, bleeding complications, and cardiac and cerebrovascular events) were defined by the clinical research coordinator. Initially, the procedural complications were reviewed by a trained clinical research coordinator under the supervision of the project coordinator and categorized as those in need of adjudication and those exempt from it. A separate member of the event committee reviewed the abstracted record. A second or third adjudicator was asked for assistance in the event of disagreement between the opinions of the project coordinator and the first adjudicator.

Studied patients. Of the 24,162 consecutive PCI patients registered between September 2008 and March 2019, we selected 953 long-term dialysis patients and evaluated their in-hospital outcomes. Patients were divided into two groups: those who received a contrast volume ≥ 200 ml and those who received a contrast volume < 200 ml. The cutoff was set as 200 ml because 100 ml increment of contrast volume is known to be associated with the risk of AKI, and 200 ml is more than the average volume administered at most PCI centers; furthermore, a previous study showed that ≥ 200 ml of contrast volume was the precipitating factor for AKI. Angiographical stenosis was defined as ≥ 50% stenosis for left anterior descending artery, left circumflex artery and right coronary artery; therefore, cardiac toxicity caused by higher concentrations of contrast media reaching the coronary arteries is a concern. Additionally, acute expansion of plasma volume caused by osmotic effects may lead to heart failure.

The primary endpoint was defined as a composite of in-hospital death, post-PCI cardiogenic shock, and post-PCI heart failure. Post-PCI cardiogenic shock was defined as new-onset or acute recurrence of cardiogenic shock, a sustained (> 30 min) episode of systolic blood pressure < 90 mmHg and/or cardiac index < 2.2 L/min/m² determined to be secondary to cardiac dysfunction, and/or the requirement for parenteral inotropic or vasopressor agents or mechanical support (e.g., intra-aortic balloon pump, extracorporeal circulation, ventricular assist device) to maintain the blood pressure and cardiac index above the specified levels. Post-PCI heart failure was defined as new-onset or acute recurrence of heart failure that necessitated new or increased pharmacological therapy. A low ejection fraction without clinical evidence of heart failure was not considered heart failure.

The secondary endpoints were in-hospital mortality and PCI-related complications. PCI-related complications were defined as a composite endpoint that included severe flow-limiting coronary dissection/coronary perforation, myocardial infarction after PCI, post-PCI cardiogenic shock/heart failure, cerebral bleeding/stroke, and other bleeding complications defined as those requiring transfusion, prolonging the hospital stay, and/or reducing the hemoglobin level to < 3.0 g/dL. When present, bleeding complications were classified as follows: puncture site bleeding, including external bleeding, or a hematoma > 10 cm for femoral sites, > 5 cm for brachial sites, or > 2 cm for radial access sites, retroperitoneal bleeding, gastrointestinal bleeding, genitourinary bleeding, or other bleeding types. This definition of bleeding-related complications was consistent with the Bleeding Academic Research Consortium definitions of grade 3A to grade 3C bleeds.
The χ² or Fisher’s exact t-test was used to analyze categorical variables. A multivariate logistic regression model was constructed to predict contrast volume ≥ 200 ml. Covariates were age, previous coronary bypass, culprit left main, culprit LAD, bifurcation, CTO, type C and use of rotational atherectomy. A multivariate logistic regression model was also constructed to predict the incidence of the primary endpoint. Covariates were initially selected as the followings; age, baseline hemoglobin, heart failure at admission, cardiogenic shock, ACS, use of an intra-aortic balloon pump, three vessels disease, left main stenosis, contrast volume ≥ 200 ml. However, given the limited number of the primary endpoint, we generated a stepwise logistic regression model, which included age, baseline hemoglobin, cardiogenic shock, ACS, use of an intra-aortic balloon pump, three vessels disease, contrast volume ≥ 200 ml. Additionally, we checked the association between contrast volume and the risk-adjusted primary endpoint. The contrast volume was analyzed as a continuous variable using a smooth spline curve. During the subgroup analysis of patients who presented with ACS, we also performed a multivariable logistic regression analysis of the primary endpoint. Covariates were age, baseline hemoglobin, cardiogenic shock, STEMI, use of an intra-aortic balloon pump, three vessels disease and contrast volume ≥ 200 ml. All statistical calculations and analyses were performed using R 3.6.2 R Foundation for Statistical Computing (Vienna, Austria); p < 0.05 was considered statistically significant.

Results

In this cohort, the mean age of the patients was 67.9 ± 9.9 years, and the baseline characteristics and in-hospital outcomes of patients administered a contrast volume ≥ 200 ml (N = 293; 30.7%) versus those who administered a contrast volume < 200 ml (N = 660; 69.3%) are shown in Tables 1 and 2. Patients administered a contrast volume ≥ 200 ml were younger and had significantly higher proportions of complex PCI, including bifurcation, chronic total occlusion, and type C lesions, and more frequently underwent rotational atherectomy and intravascular ultrasound (Table 1).

The overall incidence of the primary endpoint was 6.8% (N = 65). The crude primary endpoints were similar for patients who did and did not receive a contrast volume ≥ 200 ml (Table 2). Additionally, we did a multivariable logistic regression model for the predictor of a contrast volume ≥ 200 ml, showing younger age, culprit of left descending artery, culprit of left main, bifurcation lesion, chronic total occlusion, type C lesion and use of rotational atherectomy were the predictors of a contrast volume ≥ 200 ml (Table 3).

Table 4 shows the patients’ characteristics of those with the primary endpoint and those without. The multivariable logistic regression model demonstrated that the use of a contrast volume ≥ 200 ml was an independent predictor of the incidence of the primary endpoint (odds ratio [OR] 2.91; 95% confidence interval [CI] 1.42–6.05; P = 0.004), as well as for in-hospital death (OR 2.78; 95% CI 1.16–6.81; P = 0.022). Other predictors of the primary endpoint are shown in Table 5. The adjusted smooth spline curve demonstrated a linear relationship between the contrast volume and the primary endpoint (Fig. 1).

The subgroup analysis of patients with ACS (N = 287) demonstrated similar findings. The use of ≥ 200 ml of contrast media was also an independent predictor of the incidence of the primary endpoint (OR 4.32; 95% CI 1.71–11.4; P = 0.002), as well as in-hospital death (OR 3.71; 95% CI 1.29–11.1; P = 0.016).

Discussion

During this study, we found that the administration of ≥ 200 ml of contrast media was an independent predictor of the incidence of the primary endpoint (the composite in-hospital death, post-PCI cardiogenic shock, and post-PCI heart failure). Furthermore, the smooth spline curve revealed a linear relationship between the contrast volume and primary endpoint.

AKI is common in patients undergoing PCI and is associated with increased risks of short-term and long-term mortality. Therefore, PCI operators focus attention on the contrast volume administered to non-dialysis patients who undergo PCI. However, in current practice, they do not focus attention on the contrast volume administered to dialysis patients because they are already on dialysis and there is no perceived risk of AKI. Nevertheless, our data demonstrated that the contrast volume was associated with adverse in-hospital outcomes; therefore, PCI operators should focus attention on the amount of contrast media administered.

Contrast media reaching the coronary arteries in high concentrations can affect cardiac output, and acute expansion of the plasma volume by osmotic effects is considered to affect hemodynamics, resulting in acute pulmonary edema with an increase in systemic blood pressure because dialysis patients have impaired excretion of contrast media. Therefore, toxic cardiovascular effects caused by retained contrast media can result in cardiogenic shock, heart failure, and in-hospital death after PCI. This is a novel finding because no studies have investigated the association of contrast volume and in-hospital outcomes of dialysis patients. Although contrast media can be dialyzable, our study could not investigate the effect of dialysis after PCI because we did not have sufficient information, which was a limitation of our study. Further studies are needed to investigate the utility of dialysis immediately after PCI for dialysis patients.

We constructed a fully adjusted smooth spline curve that illustrated that the contrast volume was linearly associated with in-hospital outcomes of dialysis patients who underwent PCI. We set the cutoff of the contrast volume to 200 ml in the multivariable logistic regression model. Our findings that PCI operators should minimize the contrast volume to decrease the risk of adverse in-hospital outcomes for these patients could be applied in clinical practice.
Our study had several limitations. First, we selected our patient cohort from a prospective observational study that was not designed to enable a focused investigation of the association between contrast volume and in-hospital outcomes of dialysis patients. Second, we excluded dialysis patients who did not have any contrast volume data.

### Table 1. Baseline characteristics of all patients; contrast volume < 200 ml versus contrast volume ≥ 200 ml.

| Characteristic                                      | Contrast volume < 200 ml (N = 660) | Contrast volume ≥ 200 ml (N = 293) | P value |
|-----------------------------------------------------|-----------------------------------|------------------------------------|---------|
| Age                                                 | 68.5 ± 9.8                        | 66.5 ± 10.2                        | 0.003   |
| Male                                                | 515 (78.0)                        | 228 (77.8)                         | 1.00    |
| Baseline hemoglobin (g/dl)                          | 10.7 [9.7, 11.7]                  | 10.7 [9.8, 11.7]                   | 0.70    |
| Previous myocardial infarction                      | 171 (25.9)                        | 86 (29.4)                          | 0.31    |
| Previous heart failure                              | 187 (28.3)                        | 65 (22.2)                          | 0.057   |
| Diabetes mellitus                                   | 445 (67.8)                        | 194 (67.1)                         | 0.89    |
| Cerebrovascular disease                             | 104 (15.8)                        | 55 (18.8)                          | 0.29    |
| Peripheral artery disease                           | 164 (24.8)                        | 72 (24.7)                          | 1.00    |
| Chronic lung disease                                | 13 (2.0)                          | 7 (2.4)                            | 0.86    |
| Hypertension                                        | 501 (75.9)                        | 236 (80.5)                         | 0.14    |
| Dyslipidemia                                        | 317 (48.1)                        | 144 (49.1)                         | 0.82    |
| Atrial fibrillation                                 | 71 (12.5)                         | 19 (8.3)                           | 0.12    |
| Previous PCI                                        | 368 (55.8)                        | 149 (50.9)                         | 0.18    |
| Previous coronary bypass                            | 59 (8.9)                          | 41 (14.0)                          | 0.025   |
| Heart failure on admission                          | 92 (13.9)                         | 42 (14.3)                          | 0.95    |
| Cardiogenic shock on admission                      | 21 (3.2)                          | 5 (1.7)                            | 0.28    |
| Cardiopulmonary arrest on admission                 | 14 (2.1)                          | 6 (2.0)                            | 1.00    |
| **Puncture site**                                   |                                   |                                    | 0.002   |
| Femoral artery approach                             | 579 (87.7)                        | 269 (91.8)                         |         |
| Radial artery approach                               | 60 (9.1)                          | 9 (3.1)                            |         |
| Brachial artery approach                             | 21 (3.2)                          | 15 (5.1)                           |         |
| Use of intra-aortic balloon pump                    | 37 (5.6)                          | 22 (7.5)                           | 0.33    |
| ST-elevation myocardial infarction                  | 42 (6.5)                          | 15 (5.2)                           | 0.53    |
| UA/NSTEMI                                           | 158 (24.6)                        | 72 (25.1)                          | 0.94    |
| Acute coronary syndrome                             | 200 (30.3)                        | 87 (29.7)                          | 0.91    |
| Three vessels disease                               | 153 (24.7)                        | 71 (26.0)                          | 0.745   |
| **Angiographical stenosis**                         |                                   |                                    |         |
| Left main                                           | 81 (12.6)                         | 37 (13.0)                          | 0.954   |
| Left descending artery                              | 453 (70.7)                        | 202 (71.1)                         | 0.95    |
| Left circumflex                                     | 348 (54.3)                        | 169 (59.7)                         | 0.144   |
| Right coronary artery                               | 370 (58.2)                        | 157 (56.3)                         | 0.643   |
| **Culprit vessel**                                  |                                   |                                    |         |
| Left main                                           | 29 (4.4)                          | 25 (8.5)                           | 0.016   |
| Left descending artery                              | 272 (41.2)                        | 151 (51.5)                         | 0.004   |
| Left circumflex                                     | 165 (25.0)                        | 82 (28.0)                          | 0.373   |
| Right coronary artery                               | 238 (36.1)                        | 82 (28.0)                          | 0.018   |
| Fluoroscopy time (min)                              | 26.8 [16.5, 42.6]                 | 45.1 [29.7, 72.4]                  | <0.001  |
| Contrast volume (ml)                                | 130 [105, 160]                    | 246 [218, 290]                     | <0.001  |
| Bifurcation lesion                                  | 163 (26.3)                        | 114 (40.4)                         | <0.001  |
| Chronic total occlusion                             | 42 (6.4)                          | 36 (12.3)                          | 0.003   |
| Type C lesion                                       | 257 (41.1)                        | 165 (58.9)                         | <0.001  |
| Use of intravascular ultrasound                     | 521 (78.9)                        | 256 (87.4)                         | 0.003   |
| Use of rotational atherectomy                       | 59 (8.9)                          | 71 (24.2)                          | <0.001  |
volume information. Third, we did not have information about the timing of dialysis before and after PCI, which may have affected the events of cardiogenic shock or heart failure after PCI. However, we demonstrated that the amount of contrast media was associated with worse in-hospital outcomes for ACS patients who relatively did not have time to undergo dialysis before PCI because of the urgency to undergo PCI compared to patients who underwent elective PCI. This finding also demonstrates the robustness of the data. Fourth, we did not have information about the types of contrast media, which would have affected the outcomes because lower-osmolarity contrast media may not require immediate dialysis to avoid hemodynamic effects. Nonetheless, the data were mainly derived from the use of less than 100 ml of contrast media, suggesting that our data showing the risk of using more than 200 ml of contrast media is meaningful. Fifth, we did not have information of time course of events to assess the association of the contrast volume and the primary endpoint. Finally, we showed the association of the contrast volume and adverse outcomes after PCI. However, we could not conclude whether the contrast volume affected outcomes or whether patients who needed more contrast volume had worse outcomes. Further studies investigating liberal versus restrictive contrast use are needed to confirm our findings.

In conclusion, contrast volume was associated with the risk of adverse in-hospital outcomes among dialysis patients undergoing PCI. Attention should be focused on the contrast volume used for dialysis patients undergoing PCI.

### Table 2. In-hospital mortality and complications.

|                      | Contrast volume < 200 ml (N = 660), n (%) | Contrast volume ≥ 200 (N = 293), n (%) | P value |
|----------------------|------------------------------------------|---------------------------------------|---------|
| Primary endpoint     | 40 (6.1)                                 | 25 (8.5)                              | 0.21    |
| In-hospital mortality| 28 (4.3)                                 | 15 (5.1)                              | 0.67    |
| All complications    | 49 (7.5)                                 | 41 (14.3)                             | 0.002   |
| Coronary dissection  | 1 (0.2)                                  | 4 (1.4)                               | 0.056   |
| Coronary perforation | 4 (0.6)                                  | 5 (1.7)                               | 0.21    |
| Myocardial infarction| 4 (0.6)                                  | 7 (2.4)                               | 0.04    |
| Cardiogenic shock    | 18 (2.7)                                 | 12 (4.1)                              | 0.56    |
| Heart failure        | 8 (1.2)                                  | 7 (2.4)                               | 0.29    |
| Cerebral infarction  | 2 (0.3)                                  | 2 (0.7)                               | 0.77    |
| Intracranial hemorrhage| 0 (0.0)                                | 1 (0.3)                               | 0.68    |
| Cardiac tamponade    | 1 (0.2)                                  | 0 (0.0)                               | 1.00    |
| Transfusion          | 26 (3.9)                                 | 20 (6.8)                              | 0.079   |
| Bleeding (all types) | 22 (3.3)                                 | 16 (5.5)                              | 0.17    |
| Puncture site bleeding| 9 (1.4)                                | 2 (0.7)                               | 0.56    |
| Puncture site hematoma| 4 (0.6)                                | 4 (1.4)                               | 0.42    |
| Peritoneal bleeding  | 0 (0.0)                                  | 1 (0.3)                               | 0.68    |
| Gastrointestinal bleeding | 3 (0.5)                            | 3 (1.0)                               | 0.56    |
| Genitourinary bleeding| 1 (0.2)                                | 0 (0.0)                               | 1.00    |
| Other bleeding       | 8 (1.2)                                  | 8 (2.7)                               | 0.16    |

### Table 3. Multivariable logistic regression model of the factor for contrast ≥ 200 ml.

|                        | Odds ratio | Confidential interval | P value |
|------------------------|------------|-----------------------|---------|
| Age                    | 0.98       | 0.96–0.99             | 0.004   |
| Previous coronary bypass| 1.51       | 0.93–2.45             | 0.093   |
| Culprit left main      | 1.55       | 0.82–2.91             | 0.176   |
| Culprit left descending artery | 1.37     | 1.01–1.87             | 0.046   |
| Bifurcation lesion     | 1.56       | 1.11–2.18             | 0.009   |
| Chronic total occlusion| 2.08       | 1.21–3.56             | 0.008   |
| Type C lesion          | 1.39       | 1.001–1.92            | 0.048   |
| Use of rotational atherectomy | 2.92   | 1.95–4.40             | < 0.001 |

In conclusion, contrast volume was associated with the risk of adverse in-hospital outcomes among dialysis patients undergoing PCI. Attention should be focused on the contrast volume used for dialysis patients undergoing PCI.
Table 4. Baseline characteristics of all patients; patients with primary endpoint versus those without. PCI percutaneous coronary intervention, UA/NSTEMI unstable angina/non-ST-elevation myocardial infarction. Data are presented as the mean ± standard deviation, number (%), and number [interquartile range].
Data availability

The data that support the findings of this study are available from JCD-KiCS but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of JCD-KiCS to the corresponding author.

Received: 3 September 2022; Accepted: 4 October 2022
Published online: 21 October 2022

References

1. Mehran, R. et al. A contemporary simple risk score for prediction of contrast-associated acute kidney injury after percutaneous coronary intervention: Derivation and validation from an observational registry. Lancet 398, 1974–1983 (2021).
2. Kuno, T. et al. Effects of body habitus on contrast-induced acute kidney injury after percutaneous coronary intervention. PLoS ONE 13, e0203352 (2018).
3. Chandiramani, R., Cao, D., Nicolas, J. & Mehran, R. Contrast-induced acute kidney injury. Cardiovasc. Interv. Ther. 35, 209–217 (2020).
4. Mehran, R. et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: Development and initial validation. J. Am. Coll. Cardiol. 44, 1393–1399 (2004).
5. Laskey, W. K. et al. Volume-to-creatinine clearance ratio: a pharmacokinetically based risk factor for prediction of early creatinine increase after percutaneous coronary intervention. J Am Coll Cardiol 50, 584–590 (2007).
6. Mohebi, R. et al. Long-term clinical impact of contrast-associated acute kidney injury following PCI: An ADAPT-DES substudy. JACC Cardiovasc. Interv. 15, 753–766 (2022).

Table 5. Multivariable logistic regression model of the primary endpoint.

|                        | Odds ratio | Confidential interval | P value |
|------------------------|------------|-----------------------|---------|
| Age                    | 1.05       | 1.01–1.09             | 0.007   |
| Baseline hemoglobin    | 0.52       | 0.40–0.66             | <0.001  |
| Cardiogenic shock at presentation | 3.95   | 1.17–13.3             | 0.026   |
| Acute coronary syndrome| 1.90       | 0.96–3.85             | 0.069   |
| Use of intra-aortic balloon pump | 18.4  | 7.76–45.1             | <0.001  |
| Three vessels disease  | 1.79       | 0.85–3.71             | 0.116   |
| Contrast volume ≥ 200 ml | 2.91      | 1.42–6.05             | 0.004   |

Figure 1. Smooth spline showing the association between contrast volume and the primary endpoint. The y axis shows the log odds ratio of the adjusted incidence of the primary endpoint. The x axis shows the contrast volume. The gray area shows the confidence interval.
Acknowledgements
The authors appreciate the contribution of all of the investigators, clinical coordinators, and institutions involved in the JCD-KiCS study.

Author contributions
T.K., S.K. had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: T.K., Y.N., S.K. Data Curation: S.K. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: T.K. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: T.K. Administrative, technical, or material support: S.K. Study supervision: Y.N., S.K.

Funding
This research study was supported by a grant from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (KAKENHI No. 20H03915).

Competing interests
Dr. Kohsaka received a research grant from the Department of Cardiology, Keio University School of Medicine, Daiichi Sankyo Co. Ltd. The funder did not play any role in the study design, data collection, data analysis, decision to publish, or manuscript preparation. The authors declare that they have no conflicts of interest.

Additional information
Correspondence and requests for materials should be addressed to T.K.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/

© The Author(s) 2022