

## **Response to the reviewer's comments**

We thank the reviewer for the insightful and constructive comments. We have tried to address all the issues and suggestions raised by the reviewer, and a point-by-point response letter has been provided below. Our manuscript has significantly improved and hope that the revised version meets the requirements by the reviewer.

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### ***Reviewer #1:***

***In this single center retrospective study (n=421), the authors evaluated the the impact of low molecular weight dextran (LMWD) on decline in kidney function in patients undergoing per-cutaneous coronary intervention. LMWD was used during optical coherence tomography (OCT). In multivariate analysis, volume of LMWD used and baseline GFR were independent predictors of GFR decline. The authors conclude that "OCT using LMWD may not be protective against worsening renal function in patients with advanced renal insufficiency". The article is written well. I have the following comments/critiques:***

- 1. Even though LMWD is used during OCT in an attempt to reduce the volume of the contrast used, in fact the average volume of contrast used in the LMWD group was 142 ml compared to 130 ml in control group.***

We thank the reviewer for the insightful comments. As was exactly pointed out by the reviewer, total contrast volume tended to be greater in the LMWD group after propensity-score matching. Because we collected data from our institutional registry, some patients with acute coronary syndrome (ACS) underwent pre- and post-percutaneous coronary intervention (PCI) OCT examinations for the culprit lesion, and some underwent OCT examination for the non-culprit lesion before or after culprit lesion

assessment/treatment for the clinical research. This nature of the study cohort might have led to an increase in contrast medium and/or LMWD volume despite efforts to reduce the total volume. We applied propensity score-matched subgroup analysis adjusted for total contrast volume to reduce the effect of bias regarding exposure to LMWD in this observational study. In the matched cohort, total contrast volume was not statistically different between the 2 groups. Moreover, total contrast volume was not significantly associated with worsening renal function in univariable logistic regression analysis (odds ratio [OR] 0.99 [0.99, 1.01],  $P=0.776$ ) in the range of contrast volume used in this study cohort.

We revised the following sentence in the Limitation section (Page 20, line 6).

“Second, because we collected data from our institutional OCT registry, some patients with ACS underwent pre- and post-PCI OCT examinations for the culprit lesion, and some underwent OCT examination for the non-culprit lesion before or after culprit lesion assessment/treatment for the clinical research. This nature of the study cohort might have led to an increase in contrast medium and/or LMWD volume.”

**2. *The term renal insufficiency should be replaced by chronic kidney disease (CKD) and the authors should divide patients in both groups by CKD stages.***

We thank the reviewer for the insightful comments. The current definition of CKD includes decreased kidney function shown by glomerular filtration rate (GFR)  $<60$  ml/min/1.73 m<sup>2</sup>, or markers of kidney injury, or both, of at least 3 months duration (*Kidney Int Suppl* 2013;1-150). Because renal function was assessed at the time of admission before angiography, the term renal insufficiency instead of CKD was used in this study. In the presence study, advanced renal insufficiency was defined as eGFR  $<45$  ml/min/1.73m<sup>2</sup> at the time of admission. When patients are classified according to the baseline eGFR level in the entire study cohort, the prevalence of GFR category 3b ( $30 \leq$  eGFR  $<45$  ml/min/1.73 m<sup>2</sup>),

category 4 ( $15 \leq \text{eGFR} < 30 \text{ ml/min/1.73 m}^2$ ) and category 5 ( $\text{eGFR} < 15 \text{ ml/min/1.73 m}^2$ ) were 86.1%, 12.6% and 1.3% in the LMWD group vs. 83.0%, 15.8% and 1.2% in the Control group, respectively. There was no significant difference between the 2 groups with respect to the prevalence and distribution of GFR categories. Moreover, in the matched cohort, no patients had GFR category 5 and there was no significant difference in the prevalence and distribution of GFR categories. We added the description of the proportion of GFR categories in both the entire study cohort and the matched cohort, according to the suggestion by the reviewer.

We added the following sentences in the Results section (Page 13, line 4 and Page 14, line 6) and Tables 1 and 2.

Results (Page 13, line 4)

“The baseline eGFR level and the distribution of GFR categories were not different between the two groups.”

Results (Page 14, line 6)

“The baseline eGFR level and the distribution of GFR categories were not different between the two groups. Moreover, no patients had GFR category 5 in the matched cohort.”

Table 1. Patients' characteristics and renal function (entire study cohort)

|                                    | Total (n=421)     | Control (n=342)   | LMWD (n=79)       | P-value |
|------------------------------------|-------------------|-------------------|-------------------|---------|
| Sex                                |                   |                   |                   |         |
| Male                               | 281 (66.7)        | 219 (64.0)        | 62 (78.5)         | 0.017   |
| Female                             | 140 (33.3)        | 123 (36.0)        | 17 (21.5)         |         |
| Age, years                         | 75.0 [69.0, 80.0] | 76.0 [69.0, 80.0] | 74.0 [68.0, 79.0] | 0.178   |
| Body mass index, kg/m <sup>2</sup> | 24.0 [21.1, 26.2] | 23.9 [21.1, 26.0] | 24.4 [21.3, 26.6] | 0.273   |
| Procedure                          |                   |                   |                   |         |
| Coronary angiography               | 279 (66.3)        | 238 (69.6)        | 41 (51.9)         | 0.004   |
| PCI                                | 142 (33.7)        | 104 (30.4)        | 38 (48.1)         |         |
| Diagnosis                          |                   |                   |                   |         |
| Stable CAD                         | 350 (83.1)        | 288 (84.2)        | 62 (78.5)         | 0.243   |

|  |                       |                       |                       |        |
|--|-----------------------|-----------------------|-----------------------|--------|
| Acute coronary syndrome                      | 71 (16.9)             | 54 (15.8)             | 17 (21.5)             |        |
| Prior myocardial infarction                  | 155 (36.8)            | 106 (31.0)            | 49 (62.0)             | <0.001 |
| Prior PCI                                    | 209 (49.6)            | 148 (43.3)            | 61 (77.2)             | <0.001 |
| Prior CABG                                   | 22 (5.2)              | 20 (5.8)              | 2 (2.5)               | 0.397  |
| Hypertension                                 | 266 (63.2)            | 210 (61.4)            | 56 (70.9)             | 0.122  |
| Dyslipidemia                                 | 178 (42.3)            | 140 (40.9)            | 38 (48.1)             | 0.257  |
| Diabetes mellitus                            | 218 (51.8)            | 172 (50.3)            | 46 (58.2)             | 0.214  |
| Stroke                                       | 21 (5.0)              | 20 (5.8)              | 1 (1.3)               | 0.147  |
| Current smoking                              | 56 (13.3)             | 35 (10.2)             | 21 (26.6)             | <0.001 |
| Serum creatinine, mg/dl                      | 1.33 [1.22, 1.56]     | 1.33 [1.20, 1.52]     | 1.36 [1.27, 1.62]     | 0.057  |
| eGFR, ml/min/1.73 m <sup>2</sup>             | 38.4 [32.9, 42.3]     | 38.5 [32.6, 42.4]     | 36.9 [33.1, 41.8]     | 0.368  |
| GFR category                                 |                       |                       |                       |        |
| 3b (30≤eGFR<45), %                           | 352 (83.6)            | 284 (83.0)            | 68 (86.1)             |        |
| 4 (15≤eGFR<30), %                            | 64 (15.2)             | 54 (15.8)             | 10 (12.6)             | 0.783  |
| 5 (eGFR<15), %                               | 5 (1.2)               | 4 (1.2)               | 1 (1.3)               |        |
| Hemoglobin A1c, %                            | 6.3 [5.8, 6.9]        | 6.3 [5.7, 7.0]        | 6.4 [6.0, 6.9]        | 0.109  |
| Low-density lipoprotein cholesterol, mg/dl   | 86 [71, 107]          | 87 [72, 108]          | 82 [70, 103]          | 0.301  |
| Hemoglobin, g/dl                             | 11.8 [10.5, 13.4]     | 11.8 [10.5, 13.4]     | 12.1 [10.9, 13.5]     | 0.375  |
| C-reactive protein, mg/dl                    | 0.14 [0.05, 0.42]     | 0.13 [0.05, 0.40]     | 0.15 [0.06, 0.53]     | 0.180  |
| NT-proBNP, pg/ml                             | 864.5 [279.8, 3471.3] | 991.0 [288.3, 3700.0] | 633.0 [177.3, 1775.5] | 0.099  |
| LVEF, %                                      | 57 [44, 66]           | 58 [44, 66]           | 52 [43, 63]           | 0.140  |
| Mehran risk score                            | 8 [6, 11]             | 8 [6, 11]             | 8 [7, 11]             | 0.710  |
| Catheterization procedure                    |                       |                       |                       |        |
| Total agent volume, ml                       | 150.0 [103.0, 226.0]  | 133.0 [92.0, 192.3]   | 207.0 [167.5, 271.8]  | <0.001 |
| Total contrast volume, ml                    | 135.0 [95.0, 193.0]   | 133.0 [92.0, 192.3]   | 140.0 [102.0, 195.0]  | 0.618  |
| LMWD volume, ml                              | 0.0 [0.0, 0.0]        | 0.0 [0.0, 0.0]        | 67.6 [43.3, 86.0]     | <0.001 |
| OCT, n (%)                                   | 79 (40.6)             | 92 (26.9)             | 79 (100.0)            | <0.001 |
| Renal function post-procedure                |                       |                       |                       |        |
| ΔCre within 5 days, mg/dl                    | −0.01 [−0.11, 0.13]   | 0.00 [−0.10, 0.14]    | −0.03 [−0.14, 0.12]   | 0.414  |
| ΔCre at 1-month, mg/dl                       | −0.01 [−0.15, 0.11]   | −0.01 [−0.16, 0.11]   | −0.01 [−0.13, 0.09]   | 0.686  |
| ΔCre at 1-year, mg/dl                        | 0.01 [−0.13, 0.18]    | 0.00 [−0.14, 0.16]    | 0.07 [−0.04, 0.34]    | 0.004  |
| Acute kidney injury                          | 51 (12.1)             | 42 (12.3)             | 9 (11.4)              | 1.000  |
| Worsening renal function (≥0.3 mg/dl/1 year) | 80 (19.0)             | 58 (17.0)             | 22 (27.8)             | 0.039  |

Data are presented as number (%) or median (25th–75th percentile).

CABG, coronary artery bypass graft surgery; CAD, coronary artery disease;  $\Delta$ Cre, delta creatinine; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; LMWD, low-molecular-weight dextran; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

Table 2. Patients' characteristics and renal function (matched cohort)

|  | Total (n=150)         | Control (n=75)         | LMWD (n=75)           | P-value |
|--|-----------------------|------------------------|-----------------------|---------|
| Sex  |                       |                        |                       |         |
| Male                                       | 119 (79.3)            | 61 (81.3)              | 58 (77.3)             | 0.687   |
| Female                                     | 31 (20.7)             | 14 (18.7)              | 17 (22.7)             |         |
| Age, years                                 | 75.0 [67.5, 80.0]     | 75.0 [69.0, 80.0]      | 74.0 [67.0, 79.5]     | 0.643   |
| Body mass index, kg/m <sup>2</sup>         | 23.7 [21.0, 25.9]     | 23.0 [20.8, 25.4]      | 24.5 [21.3, 26.8]     | 0.030   |
| Procedure                                  |                       |                        |                       |         |
| Coronary angiography                       | 84 (56.0)             | 43 (57.3)              | 41 (54.7)             | 0.869   |
| PCI  | 66 (44.0)             | 32 (42.7)              | 34 (45.3)             |         |
| Diagnosis                                  |                       |                        |                       |         |
| Stable CAD                                 | 121 (80.7)            | 61 (81.3)              | 60 (80.0)             | 1.000   |
| Acute coronary syndrome                    | 29 (19.3)             | 14 (18.7)              | 15 (20.0)             |         |
| Prior myocardial infarction                | 77 (51.3)             | 30 (40.0)              | 47 (62.7)             | 0.009   |
| Prior PCI                                  | 93 (62.0)             | 34 (45.3)              | 59 (78.7)             | <0.001  |
| Prior CABG                                 | 4 (2.7)               | 2 (2.7)                | 2 (2.7)               | 1.000   |
| Hypertension                               | 98 (65.3)             | 45 (60.0)              | 53 (70.7)             | 0.230   |
| Dyslipidemia                               | 63 (42.0)             | 28 (37.3)              | 35 (46.7)             | 0.321   |
| Diabetes mellitus                          | 81 (54.0)             | 37 (49.3)              | 44 (58.7)             | 0.326   |
| Stroke                                     | 5 (3.3)               | 4 (5.3)                | 1 (1.3)               | 0.367   |
| Current smoking                            | 29 (19.3)             | 9 (12.0)               | 20 (26.7)             | 0.037   |
| Serum creatinine, mg/dl                    | 1.36 [1.25, 1.63]     | 1.37 [1.26, 1.71]      | 1.35 [1.25, 1.61]     | 0.612   |
| eGFR, ml/min/1.73 m <sup>2</sup>           | 37.6 [32.8, 42.0]     | 38.0 [31.0, 42.2]      | 37.0 [33.2, 41.8]     | 0.949   |
| GFR category                               |                       |                        |                       |         |
| 3b (30≤eGFR<45), %                         | 125 (83.3)            | 59 (78.7)              | 66 (88.0)             |         |
| 4 (15≤eGFR<30), %                          | 25 (16.7)             | 16 (21.3)              | 9 (12.0)              | 0.189   |
| 5 (eGFR<15), %                             | 0 (0.0)               | 0 (0.0)                | 0 (0.0)               |         |
| Hemoglobin A1c, %                          | 6.3 [5.9, 6.9]        | 6.1 [5.7, 6.9]         | 6.5 [6.0, 7.0]        | 0.058   |
| Low-density lipoprotein cholesterol, mg/dl | 87 [70, 108]          | 88 [72, 114]           | 81 [70, 103]          | 0.155   |
| Hemoglobin, g/dl                           | 11.8 [10.5, 13.4]     | 11.5 [10.3, 13.5]      | 12.1 [10.9, 13.3]     | 0.230   |
| C-reactive protein, mg/dl                  | 0.14 [0.05, 0.46]     | 0.12 [0.05, 0.35]      | 0.15 [0.06, 0.53]     | 0.320   |
| NT-proBNP, pg/ml                           | 835.5 [244.8, 3265.3] | 1560.0 [270.0, 4268.5] | 632.0 [175.0, 1679.5] | 0.076   |
| LVEF, %                                    | 53 [43, 64]           | 56 [44, 64]            | 52 [43, 63]           | 0.697   |
| Mehran risk score                          | 8 [7, 11]             | 8 [7, 11]              | 8 [7, 11]             | 0.548   |
| Catheterization procedure                  |                       |                        |                       |         |
| Total agent volume, ml                     | 174.1 [120.0, 244.8]  | 130.0 [88.0, 196.5]    | 209.7 [170.1, 271.8]  | <0.001  |

|  |                     |                     |                      |        |
|--|---------------------|---------------------|----------------------|--------|
| Total contrast volume, ml                    | 138.0 [97.5, 200.0] | 130.0 [88.0, 196.5] | 142.0 [104.5, 200.0] | 0.408  |
| LMWD volume, ml                              | 7.6 [0.0, 68.2]     | 0.0 [0.0, 0.0]      | 68.5 [43.9, 86.0]    | <0.001 |
| OCT, n (%)                                   | 95 (63.3)           | 20 (26.7)           | 75 (100.0)           | <0.001 |
| Renal function post-procedure                |                     |                     |                      |        |
| ΔCre within 5 days, mg/dl                    | −0.03 [−0.15, 0.13] | −0.04 [−0.15, 0.14] | −0.03 [−0.14, 0.10]  | 0.848  |
| ΔCre at 1-month, mg/dl                       | −0.03 [−0.17, 0.09] | −0.06 [−0.23, 0.10] | −0.02 [−0.14, 0.08]  | 0.276  |
| ΔCre at 1-year, mg/dl                        | 0.01 [−0.14, 0.19]  | −0.04 [−0.23, 0.08] | 0.06 [−0.06, 0.29]   | 0.001  |
| Acute kidney injury                          | 14 (9.3)            | 7 (9.3)             | 7 (9.3)              | 1.000  |
| Worsening renal function (≥0.3 mg/dl/1 year) | 28 (18.7)           | 9 (12.0)            | 19 (25.3)            | 0.059  |

Data are presented as number (%) or median (25th–75th percentile).

CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CKD, chronic kidney disease; ΔCre, delta creatinine; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; LMWD, low-molecular-weight dextran; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

**3. *There were no differences in kidney function at 5 days or 1 month following the procedure. How would the authors explain the differences observed only at 1 year after procedure when no differences were observed earlier. So many factors can impact long term kidney function which could be totally unrelated to the initial procedure. This is a big limitation of the study.***

We thank the reviewer for raising the important issue. We agree with the reviewer that many factors can impact the long-term kidney function. We did not evaluate the influence of medical therapy and clinical status post-procedure on the incidence of contrast-induced AKI and worsening renal function, which could have affected our results. As described in the Study limitations in the original version of the manuscript, the present study was a retrospective observational study from a single center. Previous studies demonstrated that approximately 30% of LMWD was excreted over several days (*Neth J Med* 1989; **35**(5-6): 321-326, *Crit Care Clin* 1991; **7**(3): 713-723). Excretion of LMWD by the kidneys could be reduced particularly in the presence of advanced renal insufficiency. Therefore,

administration of LMWD accompanied by a certain amount of contrast medium could potentially cause prolonged renal insufficiency in the long-term, even if the LMWD does not fully affect renal function in the early phase. Furthermore, univariable logistic regression analysis revealed the acute kidney injury was tended to be associated with worsening renal function in the propensity score-matched cohort (OR 2.73 [0.84, 8.90],  $P=0.096$ ), although the trend did not reach statistical significance.

Since our study reporting the possibility of LMWD-related long-term renal dysfunction is of hypothesis generating nature, further studies are needed to test this hypothesis.

Furthermore, as the reviewer specified, this study evaluated the renal function only at the acute phase (5 days), one month after the procedure, and one year. The mid-term effect of LMWD on renal function should be studied.

We revised the following sentence in the Limitation section (Page 20, line 10).

“Third, we did not evaluate the influence of medical therapy and clinical status post-procedure on the incidence of contrast-induced AKI and worsening renal function, which could have affected our results. Although this study evaluated the renal function only within 5 days, and at 1-month and 1-year post-procedure, the mid-term effect of LMWD on renal function was not fully studied.”

4. *There was no mention of the level of proteinuria between the groups which is a strong risk factor for kidney disease progression. The authors should discuss this limitation*

We thank the reviewer for the important suggestion. As pointed out by the reviewer, the severity of proteinuria was not quantitatively assessed. Positive dipstick proteinuria at baseline was observed in 32.3% (136/421) of the patients in the entire study cohort.

However, post-procedural proteinuria was qualitatively evaluated in only 9.3% (39/421) of the entire cohort. This is an important limitation of this study, as specified by the reviewer.

In the entire study cohort, the prevalence of positive dipstick proteinuria was not statistically different between the 2 groups (25.3% [LMWD group] vs. 51.3% [Control group],  $P=0.180$ ). However, the prevalence of positive dipstick proteinuria was significantly lower in the LMWD group than in the Control group (22.7% vs. 40.0%,  $P=0.035$ ). Therefore, additional LMWD administration might have had a different impact on CKD progression regardless of the presence of baseline proteinuria.

We revised the following sentence in the Limitation section (Page 20, line 15).

“Fourth, the prevalence and severity of proteinuria and the cause of renal insufficiency were not assessed, and both could be closely related to the progression of renal dysfunction.”