Tricuspid regurgitation after transcatheter mitral valve repair: Clinical course and impact on outcome

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Abstract

Objectives: The aim of this study was to determine the course of tricuspid regurgitation (TR) after transcatheter mitral valve repair (TMVR), identify predictors for severe TR after TMVR and determine the association of severe TR after TMVR with outcome.

Background: TR is often present in patients with symptomatic mitral regurgitation (MR) and is associated with increased morbidity and mortality. The clinical course of TR after TMVR has not been clearly determined.

Methods: Patients that underwent TMVR between 2009 and 2017 were included. Clinical data were compared between patients with and without severe TR at 6 months after TMVR. Multivariate logistic regression analysis was performed to identify predictors for severe TR after TMVR. Survival analysis was done for both groups, using the Kaplan–Meier method.

Results: A total of 146 patients were included (mean age 76 years, 51% male, 79% New York Heart Association class ≥3 and 29% severe TR at baseline). Advanced age, atrial fibrillation (AF), right ventricular (RV) dysfunction, and limited procedural MR reduction were revealed as independent predictors for severe TR after TMVR. Survival of patients with severe TR after TMVR was 58% after 2 years compared to 82% for those with non, mild or moderate TR.

Conclusions: Severe TR after TMVR is common in patients at advanced age, those with AF, RV dysfunction and limited MR reduction during TMVR and is associated with impaired survival. As the associated parameters are indicators of longstanding MR, research investigating the benefits of earlier intervention in MR should be initiated.

Keywords
atrial fibrillation, MitraClip, mitral valve regurgitation, right ventricular dysfunction, tricuspid valve regurgitation

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1 | INTRODUCTION

Mitral regurgitation (MR) is widely present in the general population and its prevalence increases with age. Transcatheter mitral valve repair (TMVR) is indicated in patients with symptomatic MR deemed high risk for mitral valve (MV) surgery. Longstanding chronic MR causes atrial fibrillation (AF), and induces pulmonary hypertension (PH), which leads to right ventricle (RV) pressure overload. Both are key components in the etiology of functional tricuspid regurgitation (TR), which comprises annulus dilatation, RV dilatation and in the end RV dysfunction. Significant TR reduces quality of life and survival in patients after cardiac surgery and in patients with AF. While in the past it was assumed that functional TR would improve after eliminating MR, studies showed that improvement after isolated MV surgery is limited. Guidelines recommend performing concomitant tricuspid valve (TV) surgery in patients undergoing left-sided valve surgery who also have severe TR or mild–moderate TR with dilated annulus (≥ 40 mm) or signs of right-heart failure. Moderate–severe (TR) is highly relevant among patients undergoing TMVR, and prevalence ranges from 25–65%. Earlier studies suggest that if moderate–severe TR is present, survival after TMVR is worse. Improvement of both MR and TR after TMVR might therefore improve outcome and survival. Predictors of the clinical course of TR after TMVR can be an important aid in clinical decision making. The aim of this study was to determine the course of TR after TMVR and identify clinical predictors for severe TR after TMVR and determine the association of severe TR after TMVR with outcome.

2 | MATERIALS AND METHODS

2.1 | Population

This retrospective cohort study was performed using a prospectively maintained database of patients undergoing TMVR with the MitraClip device between 2009 and 2017. All patients with a complete echo dataset were included. All patients had symptomatic severe MR and were denied surgery by the multidisciplinary heart team. Written informed consent was obtained from all patients and the study was conducted in accordance with the Declaration of Helsinki.

2.2 | Procedure

TMVR with the MitraClip device has been described earlier. The procedure is being performed under general anesthesia, using transesophageal echocardiography and fluoroscopy guidance. The team consists of two interventional cardiologists and one imaging cardiologist. One or more clips were implanted according to the treating physician. The procedure was finished when a favorable degree of MR reduction had been achieved, as agreed on by the team.

2.3 | Echocardiographic examination

All patients underwent transthoracic echocardiography (TTE) examination in the work-up for treatment and at follow-up after 6 months. All TTE examinations were performed according to the procedural guidelines of the American Society for Echocardiography (ASE) and European Association for Cardiovascular Imaging (EACVI) and were reviewed by an imaging cardiologist. TR was assessed by color flow Doppler in multiple views and measuring vena contracta and graded according to the ASE/EACVI guidelines as none/trivial (0), mild (1), moderate (2) or severe (3). Left ventricular ejection fraction (LVEF) was calculated in the apical view using the Simpson biplane method. RV function was measured as the Tricuspid Annular Plane Systolic Excursion (TAPSE) in the apical 4-chamber view. Tricuspid annulus dimension (TAD) was measured end-diastolic in the apical 4-chamber view. Systolic pulmonary artery pressure (sPAP) was derived from the...
maximal TR velocity as measured by continuous wave Doppler and inferior vena cava diameter. MR was graded as none/trivial (0), mild (1), moderate (2) or severe (3) according to the ASE/EACVI guidelines.

2.4 | Clinical endpoints

All patients had regular follow-up at our outpatient clinic 6 months after the procedure, including New York Heart Association (NYHA) class assessment and TTE examination. Data regarding mortality were obtained from electronic patient record or the general practitioner was consulted.

2.5 | Statistical analysis

Continuous variables were expressed as mean ± SD or median (interquartile range), as appropriate. Categorical variables were expressed as frequency and percentage. Between group differences for continuous normally distributed variables were calculated with an unpaired t test, for non-parametric continuous data Mann–Whitney U test was used. Chi-squared test and Fischer’s exact test were used for categorical data. Survival analysis was done with the Kaplan–Meier method and between group differences were calculated with the log rank test. Independent predictors for severe TR at 6 months follow-up were identified by fitting multivariate backward stepwise binary logistic regression models. All variables with p ≤ .20 in univariate analysis were included in multivariate analysis. The likelihood ratio test was used for variable entry and removal from the model and was set at .05. Confidence intervals were set at 95%, statistical significance was established at p ≤ .05. IBM SPSS statistics 25.0 (IBM Corporation, Chicago, IL) was used.

3 | RESULTS

3.1 | Clinical baseline characteristics

A total of 194 consecutive patients underwent TMVR, of whom 48 were excluded (see Figure 1 and Supplementary Table A). No relevant differences were found between in- and excluded patients. A complete set of baseline data as well as 6 month echocardiographic follow-up data were available for 146 patients. Mean age was 76.0 ± 10.0 years, 51% were male, median EuroSCORE II was 4.1% (2.7–7.3), 62% had a history of hypertension, 60% had AF, and 79%

| TABLE 1 | Baseline characteristics of patients who underwent TMVR |
|---|---|---|---|---|
| | Total (n = 146) | ≤ Moderate TR at 6 months (n = 94) | Severe TR at 6 months (n = 52) | p-value |
| Age (years) | 76.0 ± 10.0 | 74.6 ± 10.4 | 78.4 ± 8.8 | .03 |
| Gender (male) | 75 (51.4) | 51 (54.3) | 24 (46.2) | .35 |
| EuroSCORE II (%) | 4.1 [2.7–7.3] | 4.1 [2.6–7.3] | 4.1 [2.8–6.9] | .91 |
| STS-score (%) | 3.0 [1.8–4.9] | 2.7 [1.7–4.9] | 3.4 [2.0–5.9] | .18 |
| BMI (kg/m²) | 26.2 ± 4.3 | 26.6 ± 4.6 | 25.5 ± 3.7 | .13 |
| Hypertension | 91 (62.3) | 54 (57.4) | 37 (71.2) | .10 |
| Diabetes mellitus | 36 (24.7) | 22 (23.4) | 14 (26.9) | .64 |
| MI | 66 (45.2) | 46 (48.9) | 20 (38.5) | .22 |
| PCI | 33 (22.6) | 25 (26.6) | 8 (15.4) | .12 |
| CABG | 32 (21.9) | 21 (22.3) | 11 (21.2) | .87 |
| Atrial fibrillation | 88 (60.3) | 48 (51.1) | 40 (76.9) | .002 |
| PM | 7 (4.8) | 4 (4.3) | 3 (5.8) | .70 |
| ICD | 14 (9.6) | 10 (10.6) | 4 (7.7) | .77 |
| CRT | 11 (7.5) | 8 (8.5) | 3 (5.8) | .75 |
| Creatinine (µmol/L) | 104 [83–134] | 101 [82–134] | 110 [85–135] | .43 |
| COPD | 31 (21.2) | 20 (21.3) | 11 (21.2) | .99 |
| NYHA class | II 30 (20.5) | 17 (18.1) | 13 (25.0) | .58 |
| III 90 (61.6) | 59 (62.8) | 31 (59.6) | .12 |
| IV 26 (17.8) | 18 (19.1) | 8 (15.4) | |
| 6-MWT distance (m) | 331 ± 126 | 348 ± 131 | 299 ± 112 | .05 |
| NT-proBNP (pg/ml) | 2,102 [1,062–4,040] | 1872 [896–3,461] | 2,628 [1,581–5,209] | .09 |

Note: Values are expressed as mean ± SD, median [interquartile range] or n (%).
Abbreviations: 6-MWT, six minute walk test; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EuroSCORE, European System for Cardiac Operative Risk Evaluation; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; NYHA, New York Heart Association; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PCI, percutaneous coronary intervention; PM, pacemaker; TMVR, transcatheter mitral valve repair.
were in NYHA functional class III/IV. Baseline characteristics are shown in Table 1. In Tables 1 and 2, comparisons were made between patients who had severe TR at 6 months and those who did not. Patients with severe TR at follow-up were older ($p = .03$), more often had a history of AF ($p = .002$) and walked a shorter distance during the 6 minute walk test (6-MWT) ($p = .05$).

### 3.2 | Echo baseline and procedural characteristics

At baseline 60 patients (41%) had moderate TR and 42 patients (29%) had severe TR. A total of 107 patients (73%) had MR grade 4 and 39 had MR grade 3 (27%), mean LVEF was 38.3 ± 13.4%. Etiology of

| TABLE 2 | Echo characteristics at baseline, during TMVR and at follow-up |
|----------|---------------------------------------------------------------|
|          | Total ($n = 146$) | ≤ Moderate TR at 6 months ($n = 94$) | Severe TR at 6 months ($n = 52$) | $p$-value |
| Baseline |                   |                                       |                               |           |
| MR grade | 3                  | 39 (26.7)                             | 24 (25.5)                      | 15 (28.8) | .67 |
|          | 4                  | 107 (73.3)                            | 70 (74.5)                      | 37 (71.2) |    |
| MR type  | Degenerative      | 48 (32.9)                             | 28 (29.8)                      | 20 (38.5) | .11 |
|          | Functional        | 94 (64.4)                             | 65 (69.1)                      | 29 (55.8) |    |
|          | Mixed             | 4 (2.7)                               | 1 (1.1)                        | 3 (5.8)   |    |
| TR grade | 0                 | 4 (2.7)                               | 4 (4.3)                        | 0 (0)     | <.001 |
|          | 1                 | 40 (27.4)                             | 36 (38.3)                      | 4 (7.7)   |    |
|          | 2                 | 60 (41.1)                             | 46 (48.9)                      | 14 (26.9) |    |
|          | 3                 | 42 (28.8)                             | 8 (8.5)                        | 34 (65.4) |    |
| LVEF (%) | 38.3 ± 13.4       | 37.9 ± 12.4                           | 39.5 ± 15.9                    | .65       |
| Systolic PAP (mmHg) | 42 [35–54] | 41 [33–54]                           | 44 [37–57]                    | .26       |
| TAPSE (mm) | 18 [15–22] | 19 [15–22]                           | 17 [14–20]                    | .05       |
| TAD (mm) | 37 [33–41]       | 37 [33–40]                            | 38 [34–43]                    | .20       |
| During TMVR |                     |                                       |                               |           |
| MR reduction | No               | 16 (11.1)                             | 5 (5.4)                        | 11 (21.2) | .04 |
|          | 1 grade           | 38 (26.4)                             | 25 (27.2)                      | 13 (25.0) |    |
|          | 2 grades          | 62 (43.1)                             | 43 (46.7)                      | 19 (36.5) |    |
|          | 3 grades          | 28 (19.4)                             | 19 (20.7)                      | 9 (17.3)  |    |
| Follow-up |                     |                                       |                               |           |
| Systolic PAP (mmHg) | 42 [35–50] | 39 [33–47]                           | 48 [41–63]                    | <.001     |
| TAPSE (mm) | 19 ± 5            | 20 ± 5                               | 18 ± 5                        | .06       |
| TR grade  | 0                 | 5 (3.4)                               | 5 (5.3)                        | 0 (0)     | <.001 |
|          | 1                 | 54 (37.0)                             | 54 (57.4)                      | 0 (0)     |    |
|          | 2                 | 35 (24.0)                             | 35 (37.2)                      | 0 (0)     |    |
|          | 3                 | 52 (35.6)                             | 0 (0)                          | 52 (100)  |    |
| MR grade  | 1                 | 24 (16.6)                             | 19 (20.4)                      | 5 (9.6)   | .11 |
|          | 2                 | 56 (38.4)                             | 39 (41.9)                      | 17 (32.7) |    |
|          | 3                 | 45 (30.8)                             | 24 (25.8)                      | 21 (40.4) |    |
|          | 4                 | 20 (13.7)                             | 11 (11.8)                      | 9 (17.3)  |    |

Note: Values are expressed as mean ± SD, median [interquartile range] or n (%).

Abbreviations: LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PAP, pulmonary artery pressure; TAD, tricuspid annulus dimension; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TMVR, transcatheter mitral valve repair.

FIGURE 2 Course of tricuspid regurgitation after TMVR. TMVR, transcatheter mitral valve repair.
MR was functional in 94 patients (64%). In patients with severe TR at follow-up, baseline TAPSE was lower ($p = .05$) and MR reduction after TMVR was less ($p = .04$). Echo baseline characteristics are shown in Table 2.

Technical success (implantation of a clip) was achieved in 144 patients (99%), a single clip was implanted in 49%, 2 clips in 45%, $\geq 3$ clips in 5%. Single leaflet detachment was seen in one patient ($< 0.1%$), this needed no further treatment. Pericardial effusion occurred in four patients (3%), for which percutaneous drainage was performed in three patients.

### 3.3 Outcome after TMVR

At 6 months follow-up after TMVR, 34% of patients were in NYHA class III/IV. MR was reduced to grade 1 or 2 in 55% of patients. Figure 2 gives a plain overview of the course of TR. Ninety-four patients (64%) had $\leq$ moderate TR after TMVR. Improvement of TR was most obvious in patients with moderate TR at baseline (42%). Severe TR improved in eight patients (19%). Patients with severe TR at follow-up were more often in NYHA class III/IV (47 vs. 28%, $p = .03$) (Figure 3), had a higher sPAP at follow-up (48 vs. 39 mmHg, $p < .001$), and lower TAPSE at follow-up (18 vs. 20 mm, $p = .06$). Echo outcome parameters are shown in Table 2.

### 3.4 Determinants for severe TR at 6 months

Multivariate logistic regression analysis revealed age (70–79 years: OR 12.0, CI 1.9–74.0, $p = .007$, $\geq$ 80 years: OR 13.9, CI 2.3–85.1, $p = .004$), AF (OR 3.7, CI 1.3–10.3, $p = .01$), TAPSE ($\leq 17$ mm: OR 3.0, CI 1.2–7.7, $p = .02$) and MR reduction (1 grade reduction: OR 0.1, CI 0.0–0.7, $p = .02$, $> 1$ grade reduction: OR 0.2, CI 0.0–0.7, $p = .02$) as independent predictors for severe TR at 6 months (Table 3).

### 3.5 Survival

Overall survival after echocardiographic follow-up (at 6 months) was 83% at 1 year and 73% at 2 years. In patients with severe TR at follow-up, survival rate was 65% at 1 year and 58% at 2 years. In patients with less than severe TR at follow-up survival was 93% at 1 year and 82% at 2 years ($p < .001$ and $p < .001$, respectively for 1 and 2 years) (Figure 4). Median survival from 6 month follow-up echo was 46 months (26 months for patients with severe TR at follow-up vs. 61 months for patients with less than severe TR at follow-up).

### 4 DISCUSSION

The current study demonstrated that severe TR at 6 months after TMVR is common especially in patients at advanced age (> 70 years) and those with AF, RV dysfunction and a limited reduction of MR during the procedure.

Severe TR after TMVR was associated with worse clinical outcome and survival, and it will be highly relevant to investigate whether modifying this risk factor may improve outcomes. The impact on short- and long-term survival has been shown to be tremendous in earlier studies. However, the concern remained why TR failed to improve in some patients after TMVR and which factors were associated with this phenomena. The current study revealed that (1) advanced age (2) presence of AF (3) RV dysfunction and (4) a limited reduction of MR during the procedure were independent predictors for severe TR after TMVR. The association between advanced age and severe TR after TMVR might be explained by longer existence of TR and age-induced histological changes, making atrial reverse remodeling less likely.
The high prevalence of AF, RV dysfunction and TR in patients undergoing TMVR is often the consequence of long existing MR. Once TR is present it maintains itself in a vicious circle, where TR begets further RV dilatation and dysfunction, causing more TR etcetera.\textsuperscript{17} Patients undergoing TMVR are often in an advanced stage of MR, which is reflected by the high prevalence of AF, RV dysfunction and TR (Figure 5).\textsuperscript{7} It appeared that referral for TMVR was often delayed as physicians tend to wait until patients are progressively symptomatic, despite optimal medical therapy. It may be hypothesized that MR treatment by TMVR in an earlier stage of the disease would reduce the prevalence of post-procedural TR and improve long-term survival and outcome.\textsuperscript{18} Otherwise, if severe symptomatic TR is present after TMVR (despite sufficient MR reduction), transcatheter treatment of TR might be considered.

Functional TR in patients with MR was long considered reversible once MR and pulmonary hypertension had been eliminated.\textsuperscript{19,20} However, our understanding of TR pathophysiology has evolved, and current guidelines now recommend performing TV repair in patients undergoing left-sided heart surgery if the tricuspid annulus is dilated or \( \geq \) moderate TR is present.\textsuperscript{2,21} In the current study TR was reduced by \( \geq \) 1 grade in 25\% of patients at 6 months after TMVR. It has been proposed that acute reduction of TR after TMVR is the immediate

| TABLE 3 | Univariate and multivariate logistic regression analyses for severe TR 6 months after TMVR |
|---------|--------------------------------------------------------------------------------------------------|
|         | Univariate analysis                                                                 | Multivariate analysis |
|         | OR (95\% CI)                                  | p-value | OR (95\% CI)                                  | p-value |
| Age     |                                                                                       |          |                                                                 |
| < 70 years | 1.0                                                                                                 |
| 70–79 years | 4.07 (1.34–12.37)                          | .01      | 11.99 (1.94–74.01)                          | .007    |
| \( \geq \) 80 years | 4.67 (1.60–13.58)                          | .005     | 13.88 (2.26–85.08)                          | .004    |
| Gender |                                                                                       |          |                                                                 |
| Male   | 1.0                                                                                                 |
| Female | 1.38 (0.70–2.73)                          | .35      |                                                                 |
| AF     |                                                                                       |          |                                                                 |
| No     | 1.0                                                                                                 |
| Yes    | 3.19 (1.49–6.84)                          | .003     | 3.67 (1.31–10.29)                          | .01     |
| STS score (per \% increase) | 1.08 (0.98–1.19)                             | .12      |                                                                 |
| BMI    |                                                                                       |          |                                                                 |
| < 26 kg/m\(^2\) | 1.0                                                                                                 |
| \( \geq \) 26 kg/m\(^2\) | 0.51 (0.25–1.01)                          | .05      |                                                                 |
| Hypertension |                                                                                       |          |                                                                 |
| No     | 1.0                                                                                                 |
| Yes    | 1.83 (0.88–3.78)                          | .10      |                                                                 |
| Previous PCI |                                                                                       |          |                                                                 |
| No     | 1.0                                                                                                 |
| Yes    | 0.50 (0.21–1.21)                          | .13      |                                                                 |
| 6-MWT distance (per meter increase) | 1.00 (0.99–1.00)                             | .05      |                                                                 |
| TAPSE  |                                                                                       |          |                                                                 |
| \( \geq \) 17 mm | 1.0                                                                                                 |
| \( \leq \) 17 mm | 1.97 (0.98–3.97)                          | .06      | 3.02 (1.19–7.68)                          | .02     |
| TAD    |                                                                                       |          |                                                                 |
| \( \leq \) 40 mm | 1.0                                                                                                 |
| \( > \) 40 mm | 2.61 (1.21–5.64)                          | .02      |                                                                 |
| MR reduction |                                                                                       |          |                                                                 |
| No reduction | 1.0                                                                                                 |
| 1 grade | 0.24 (0.07–0.83)                          | .02      | 0.14 (0.03–0.74)                          | .02     |
| \( > \) 1 grade | 0.21 (0.07–0.65)                          | .007     | 0.15 (0.03–0.69)                          | .02     |

Abbreviations: 6-MWT, six minute walk test; AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; MR, mitral regurgitation; OR, odds ratio; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; TAD, tricuspid annulus dimension; TAPSE, tricuspid annular plane systolic excursion; TMVR, transcatheter mitral valve repair.
Our results show that reduction was most significant in patients with moderate TR. This suggests that moderate TR is more likely to benefit from LA volume and sPAP reduction. We speculate that reduction of TR also compromises the effect of RV reverse remodeling, which is likely to be a process with a duration up to 6 months. Studies with short TTE follow-up
interval (≤ 3 months) could therefore underestimate the benefit of TMVR regarding TR improvement.13,24-26 Our reduction rate of 25% after 6 months potentially reflects the effect of both acute and chronic reduction of TR. The less pronounced reduction of severe TR is likely explained by lack of structural reverse remodeling.27 Longstanding AF and RV dysfunction have caused irreversible structural changes to the RA and tricuspid annulus in these patients.28,29 Our finding that TAPSE improved in patients with ≤ moderate TR after TMVR supports this.

The role of pulmonary hypertension in the emergence of functional TR appears to be important.30 Reduction of sPAP after TMVR was a determinant for TR improvement in earlier studies.24-26 We found that limited reduction of MR was associated with severe TR after TMVR. It can be assumed that less MR reduction has led to less systolic PAP reduction, emphasizing the importance of optimal MR reduction. If recurrent (≥ moderate) MR develops, redo TMVR might be considered.

4.1 | Limitations

This was a retrospective single center study, which has its intrinsic limitations. However, the database was prospectively maintained. Severity of TR was assessed semi-quantitatively by vena contracta and qualitatively by color Doppler flow. RV function was measured by TAPSE, which is influenced by RV loading condition. Optimally this is determined by strain echocardiography or cardiac magnetic resonance assessment, though these images were not available or were of insufficient quality for accurate assessment.

Follow-up assessment of TR was at 6 months after TMVR, which represents a considerable time interval for remodeling to take place. Assessment of TR directly after TMVR might over-estimate TR improvement. Our patient sample represents an all comer real world population, which makes it relevant for daily cardiology practice.

4.2 | Clinical relevance

Our results indicate that intervention for MR is performed in an advanced stage of MR in a considerable part of patients, at least in our center. The current study suggests that earlier treatment of MR may result in a lower prevalence of TR at 6 months after TMVR. Whether such an improvement in TR translates into improved clinical outcome and survival needs to be tested in future studies.18 Severe TR after TMVR should be closely monitored, and if these patients remain symptomatic, additional transcatheter tricuspid valve repair might be considered to improve clinical outcome. Early studies suggest that additional transcatheter treatment of TR is beneficial regarding survival.31,32 Yet preventing severe TR from developing, seems to be important for better symptom relief and prognosis and treating MR at an earlier stage appears to be a promising strategy. Future studies comparing TMVR with watchful waiting (including optimal medical therapy) in patients at an earlier stage of MR could answer this question and potentially extend the indication for TMVR.

5 | Conclusion

Severe TR at 6 months after TMVR is common in patients at advanced age and those with AF, RV dysfunction and only a limited reduction of MR during TMVR and carries a decreased survival. As the associated parameters are indicators of longstanding MR, research investigating the benefits of earlier intervention in MR should be initiated.

Conflicts of interest

Jan Baan receives an unrestricted research grant from Abbott Vascular. Frank Meijerink, Karel T. Koch, Robbert J. de Winter, Danielle Robbers-Visser, S. Matthijs Boekholdt, Marja Holierook, and Berto J. Bouma declare that they have no competing interests.

Data availability statement

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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