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ORIGINAL ARTICLE

Periprocedural changes in natriuretic peptide levels and clinical outcome after transcatheter mitral valve repair

Tetsu Tanaka[1†], Refik Kavsur[1†], Maximilian Spieker[2], Christos Iliadis[3], Clemens Metze[3], Patrick Horn[2], Atsushi Sugiura[1], Malte Kelm[2], Stephan Baldus[3], Georg Nickenig[1], Ralf Westenfeld[2], Roman Pfister[3] and Marc Ulrich Becher[1*]

[1]*Heart Center Bonn, Department of Internal Medicine II, University Hospital Bonn, Venusberg Campus 1, Bonn, 53127, Germany;* [2]*Heart Center, Department of Cardiology, University Hospital Düsseldorf, Düsseldorf, Germany; and* [3]*Heart Center, Department of Cardiology, University Hospital Cologne, Cologne, Germany*

Abstract

Aims This multicentre study investigated the association of periprocedural changes in the levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) with clinical outcomes after transcatheter edge-to-edge mitral valve repair (TMVR).

Methods and results Patients were retrospectively analysed who underwent TMVR with the MitraClip system (Abbott Vascular, Santa Clara, CA, USA) and had available sequential NT-proBNP testing at baseline and 2 months after TMVR. Periprocedural changes in NT-proBNP following TMVR were assessed as the percent change in NT-proBNP between baseline and the 2 month follow-up, and the significant reduction in NT-proBNP was defined as a decrease of >30% in the follow-up NT-proBNP compared with the pre-procedural NT-proBNP level. Primary outcome was defined as a composite outcome consisting of all-cause mortality and hospitalization due to heart failure from 2 months to 2 years after TMVR. Additionally, we identified the cut-off value of pre-procedural NT-proBNP to predict the composite outcome using a receiver operating characteristic analysis (cut-off: 2485 pg/mL). Of 485 patients undergoing TMVR (age: 76.2 ± 9.2 years, female: 42.1%, secondary mitral regurgitation: 67.2%), 150 patients (30.9%) had the significant reduction in NT-proBNP (>30%) following the procedure. Patients with the NT-proBNP reduction had a lower incidence of the composite outcome, compared with those without the reduction in NT-proBNP (31.4% vs. 40.2%; log-rank $P = 0.03$). The significant reduction in NT-proBNP was also associated with a lower risk of the composite outcome [adjusted hazard ratio (HR): 0.67; 95% confidence interval (CI): 0.45–0.97; $P = 0.04$], independently of pre-procedural NT-proBNP levels and other clinical parameters. The percent change in NT-proBNP was associated with a linear trend of the incidence of the composite outcome (adjusted HR per 10% decrease: 0.96; 95% CI: 0.94–0.98; $P < 0.001$). A stratified analysis revealed that the prognostic impact of the significant reduction in NT-proBNP was consistent among clinical subgroups, including aetiology of mitral regurgitation (P for interaction = 0.99). Higher pre-procedural NT-proBNP level (>2485 pg/mL) was associated with the increased risk of the composite outcome (adjusted HR: 1.50; 95% CI: 1.03–2.17; $P = 0.03$); however, patients with a higher pre-procedural NT-proBNP who achieved the significant reduction in NT-proBNP had a similar risk of the composite outcome to those with a lower pre-procedural NT-proBNP.

Conclusions Changes in sequential NT-proBNP measurements were associated with clinical outcomes within 2 years after TMVR. The assessment of NT-proBNP dynamics may be valuable to assess the residual risk for patients undergoing TMVR and could assist with post-procedural management after TMVR.

Keywords Transcatheter mitral valve repair; N-terminal pro-B-type natriuretic peptide; Mitral regurgitation

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**Correspondence to: Marc Ulrich Becher, Heart Center Bonn, Department of Internal Medicine II, University Hospital Bonn, Venusberg Campus 1, 53127 Bonn, Germany. Tel: +49 (228) 287 13619; Fax: +49 (228) 287 14983. Email: ubecher@uni-bonn.de*
†Tetsu Tanaka and Refik Kavsur contributed equally to the study.

Introduction

Transcatheter mitral valve repair (TMVR) is an emerging treatment option for symptomatic severe mitral regurgitation (MR).[1,2] In particular, edge-to-edge TMVR has become a minimally invasive therapeutic alternative to mitral valve surgery in patients with a prohibitive surgical risk that have been diagnosed with primary MR. Furthermore, this procedure is also gaining in importance for patients with secondary MR.[3] However, according to the latest dataset from the Transcatheter Valve Therapy Registry,[4] during a 1 year follow-up after TMVR, 21% of patients were readmitted because of heart failure (HF) and approximately a quarter of the patients died. Therefore, careful monitoring is necessary following the TMVR procedure. Because patients with MR most often have multiple risk factors, which can affect their clinical outcome, it is crucial to identify a simple risk stratification tool to assist the clinical management after TMVR.

Natriuretic peptides, such as B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), are hormones released from the cardiac myocardium in response to pressure and volume overload,[5] which can reflect changes in congestion status or the symptomatic burden of patients with HF. The utility of BNP and NT-proBNP levels to predict long-term mortality and/or cardiovascular events has already been established in patients with chronic HF.[6,7] In addition, decreased levels of NT-proBNP during HF therapy are associated with a better clinical outcome.[8,9] Thus, the measurements of BNP or NT-proBNP can help in making clinical decisions related to the diagnosis and management of HF patients.

For patients with MR, natriuretic peptide levels are related to the severity of MR and cardiac dysfunction.[10] Repeated measurements of NT-proBNP levels have been shown to be effective in predicting cardiovascular events and to determine the best timing for mitral valve intervention in these patients.[11–13] In TMVR patients, a reduction in NT-proBNP after TMVR was previously reported[14]; however, the prognostic impact of post-procedural changes in NT-proBNP levels has not been assessed in patients undergoing TMVR. In the present study, we investigated the association between periprocedural changes in NT-proBNP and the incidence of adverse clinical events after TMVR with the MitraClip system (Abbott Vascular, Santa Clara, CA, USA).

Methods

Study population

This study was designed as a retrospective analysis of data from the Heart Failure Network Rhineland registry, which is a multicentre, prospective, observational registry of symptomatic patients with MR who underwent TMVR at three high-volume heart centres in Germany (University Hospitals of Bonn, Cologne, and Düsseldorf).[15,16] We identified consecutive patients who underwent their first edge-to-edge TMVR with the MitraClip system from October 2011 to September 2018. Only patients with available pre-procedural and post-procedural [2 months ± 1 month after TMVR (henceforth referred to as '2 months')] NT-proBNP results were included in the analysis (Supporting Information, *Figure S1*). The patients all agreed to participate in our registry, which was approved by the ethics committees of the individual centres in accordance with the Declaration of Helsinki.

Procedure

The indication for TMVR was moderate-to-severe or severe MR accompanied by symptomatic HF, according to the New York Heart Association (NYHA) functional classification in patients considered as inoperable or at high surgical risk. After a standardized diagnostic workup, including transoesophageal echocardiography, the decision to perform the intervention was made by the interdisciplinary heart team of each centre. The procedures were performed under general anaesthesia or sedation with three-dimensional transoesophageal echocardiography and fluoroscopic guidance. Details of the device system and procedure have previously been well described.[17] Whether a second or third device was needed was left up to the discretion of the treating physicians. Technical success was defined as the successful deployment of clips and retrieval of the delivery systems without procedural mortality or emergent surgery.[18] Residual MR was assessed by using echocardiography at discharge and at the 2 month follow-up.

Echocardiographic parameters

We assessed the echocardiographic parameters that were collected at baseline and at discharge, according to the current guidelines.[19] The severity of MR was graded as follows: Grade 0, none; Grade 1+, mild; Grade 2+, moderate; Grade 3+, moderate to severe; and Grade 4+, severe, according to the current guidelines.[20] All measurements were reviewed by an independent cardiologist dedicated to echocardiographic evaluation at each centre.

Clinical follow-up

The primary endpoint was a composite outcome, consisting of all-cause mortality and hospitalization due to worsening HF from 2 months to 2 years after TMVR. Patients were excluded from the analysis if they were hospitalized earlier than 2 months after TMVR (n = 23). All suspected adverse events were independently adjudicated by the local heart team,

according to the criteria of the Mitral Valve Academic Research Consortium.[18] The need for hospitalization due to worsening HF was determined based on the attending physicians' discretion, without any prespecified criteria. The occurrence of clinical events was recorded from admission and outpatient medical records. Telephone interviews were also performed with the patients' general practitioners or family. In addition, HF medications, including beta-blockers, renin–angiotensin system inhibitor, and aldosterone antagonist, and a standardized furosemide equivalent were recorded at baseline and at the 2 month follow-up.[21]

N-terminal pro-B-type natriuretic peptide assessments

Patients underwent NT-proBNP measurements at baseline and at 2 months after TMVR at the institutional laboratory of each centre. Periprocedural changes in NT-proBNP levels were evaluated by calculating the percent change in NT-proBNP as follows: 100 × (follow-up NT-proBNP − pre-procedural NT-proBNP)/pre-procedural NT-proBNP. A significant reduction in NT-proBNP was defined as a decrease of >30% in NT-proBNP at the 2 month follow-up compared with pre-procedural NT-proBNP.[14,22,23]

We performed a receiver operating characteristic analysis for 2-year composite outcome using the pre-procedural NT-proBNP value and identified a cut-off value for pre-procedural NT-proBNP.

Statistical analysis

Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. Normally distributed variables are presented as the mean ± standard deviation, whereas non-normally distributed variables were expressed as medians [with an inter-quartile range (IQR)]. Continuous variables were compared using *t*-test and the Mann–Whitney *U* test between two groups. Categorical data were presented as numbers and percentages, and the differences between groups were evaluated using the χ^2 test or Fisher's exact test. A Wilcoxon signed-rank test was used to compare NT-proBNP values and dosage of loop diuretics between baseline and follow-up, and a McNemar test compared the use of medications. Kaplan–Meier cumulative event curves for the composite outcome were generated by using the groups based on NT-proBNP reduction and pre-procedural NT-proBNP level. Differences between the groups were compared using the log-rank test.

Univariate and multivariable Cox proportional hazard models were used to calculate the hazard ratios (HRs) with 95% confidence intervals (CIs) for the composite outcome from 2 months to 2 years after TMVR. In univariate analyses, we analysed the HRs of conventional covariables that were determined according to previous reports. In multivariable analyses, we conducted two models, considering the multicollinearity. In Model 1, pre-procedural covariates that showed significance ($P < 0.05$) in the univariate analysis were included, and the parameters included in Model 1 were replaced with those updated at 2 month follow-up, such as left ventricular ejection fraction (LVEF) and furosemide standardized dose (Model 2). We tested for collinearity in the multivariable models using variance inflation factor, and the variables in the multivariable models had low variance inflation factors (<2). We performed a restricted cubic spline with three knots at the percent change in NT-proBNP to model a relationship between percent change in NT-proBNP and the adjusted HR for the composite outcome.

A stratified analysis was performed to assess the effects on the composite outcome of interactions between a significant reduction in NT-proBNP (>30%) and clinical parameters. The stratified analysis consisted of the following parameters: age (≥75 vs. <75 years), sex (male vs. female), estimated glomerular filtration rate (≥45 vs. <45 mL/min/1.73 m^2), atrial fibrillation (yes or no), aetiology of MR (primary MR vs. secondary MR), MR severity at baseline (moderate to severe vs. severe), LVEF (>30% vs. ≤30%), tricuspid annular plane systolic excursion (≥15 vs. <15 mm), tricuspid regurgitation (TR) severity at baseline (≥moderate vs. <moderate), and residual MR at discharge (≥3+ vs. <3+). Additionally, the *P* value for the interaction between subgroups was examined.

Statistical significance was set as a two-sided $P < 0.05$. All analyses were conducted using Stata 15.1 (StataCorp, College Station, TX, USA) or JMP Version 16.0 for Mac (SAS Institute Inc., Cary, NC, USA).

Results

Clinical characteristics

Of 1010 consecutive patients in our registry, 525 patients were excluded from the analysis, including 53 patients who died within 2 months, 8 patients lost to follow-up within 2 months, 102 patients without available pre-procedural NT-proBNP results, and 362 patients without available post-procedural NT-proBNP results at 2 months. Thus, a total of 485 consecutive patients were analysed (Supporting Information, *Figure S1*). The differences in baseline characteristics between patients included or excluded from the analysis are summarized in Supporting Information, *Table S1*.

Of the 485 included patients, the mean age was 76.8 ± 9.2 years and 42.1% were of female sex (*Table 1*). Eighty-six percent of the patients were classified as NYHA Class III or IV. The expected surgical mortality rate was elevated, as

Table 1 Baseline characteristics

	All $n = 485$	NT-proBNP reduction (+) $n = 150$	NT-proBNP reduction (−) $n = 335$	*P* value
Age (years)	76.8 ± 9.2	78 ± 9	76 ± 9	0.19
Female, *n* (%)	204 (42.1)	68 (45.3)	136 (40.6)	0.37
BMI (kg/m^2)	26.0 ± 4.8	25.8 ± 5.1	26.4 ± 4.6	0.61
Diabetes, *n* (%)	132 (27.2)	37 (24.7)	95 (28.4)	0.44
Hypertension, *n* (%)	389 (80.2)	123 (82.0)	266 (79.4)	0.54
CAD, *n* (%)	295 (60.8)	90 (60.0)	205 (61.2)	0.84
Prior CABG, *n* (%)	136 (28.0)	38 (25.3)	98 (29.3)	0.44
Prior valve intervention, *n* (%)	53 (10.9)	14 (9.3)	39 (11.6)	0.53
Previous MI, *n* (%)	138 (28.5)	39 (26.0)	99 (29.6)	0.45
Previous stroke, *n* (%)	57 (11.8)	18 (12.0)	39 (11.6)	0.88
Atrial fibrillation, *n* (%)	296 (61.2)	76 (50.7)	220 (65.9)	0.002
NYHA Class III/IV, *n* (%)	417 (86.0)	124 (83.2)	293 (87.7)	0.20
Pacemaker, *n* (%)	37 (7.6)	10 (6.7)	27 (8.1)	0.71
ICD, *n* (%)	76 (15.7)	21 (14.0)	55 (16.4)	0.59
CRT, *n* (%)	55 (11.3)	16 (10.7)	39 (11.6)	0.88
COPD, *n* (%)	95 (19.6)	24 (16.0)	71 (21.2)	0.22
eGFR (mL/min/1.73 m^2)	49.1 ± 19.3	49.8 ± 19.2	48.7 ± 19.4	0.58
Logistic EuroSCORE (%)	17.3 [9.2–28.2]	16.1 [9.0–28.7]	17.4 [9.3–27.8]	0.85
Medication at baseline				
Beta-blocker, *n* (%)	419 (86.4)	132 (88.0)	287 (85.7)	0.57
RAS inhibitor, *n* (%)	389 (80.2)	115 (76.7)	274 (81.8)	0.22
Aldosterone antagonist, *n* (%)	217 (44.7)	73 (48.7)	144 (43.0)	0.28
Loop diuretic, *n* (%)	399 (82.3)	124 (82.7)	275 (82.1)	1.00
Standardized furosemide equivalent (mg/day)	30 [10–60]	30 [10–60]	30 [10–60]	0.48
Echocardiographic findings				
Secondary MR, *n* (%)	326 (67.2)	102 (68.0)	224 (66.9)	0.83
MR severity				0.77
3+, *n* (%)	62 (12.8)	18 (12.2)	44 (13.3)	
4+, *n* (%)	423 (87.2)	132 (87.8)	291 (86.7)	
EROA (mm^2)	28 [20–35]	28 [20–38]	28 [20–35]	0.53
VC (mm)	6.5 [5.0–8.0]	6.0 [5.0–9.0]	6.5 [5.0–8.0]	0.98
RVol (mL)	45 [32–64]	43 [33–58]	46 [30–64]	0.77
PISA (mm)	7.1 [6.0–9.0]	7.0 [6.2–9.0]	7.4 [6.0–9.0]	0.65
LVEF (%)	43.1 ± 15.3	42.9 ± 14.8	43.3 ± 15.5	0.82
LVEF ≤ 30%, *n* (%)	105 (21.6)	34 (22.8)	71 (21.2)	0.72
LVEDV (mL)	140 [102–183]	124 [101–173]	143 [102–187]	0.15
LVESV (mL)	75 [45–123]	75 [45–119]	77 [45–127]	0.53
LA diameter (mm)	47.4 ± 8.2	47.2 ± 8.1	47.5 ± 8.3	0.75
TR ≥ moderate, *n* (%)	252 (52.0)	81 (56.6)	171 (51.5)	0.32
TAPSE (mm)	18.5 ± 4.9	18.1 ± 4.8	18.7 ± 4.9	0.26
SPAP (mmHg)	51.4 ± 17.1	55.6 ± 16.7	49.5 ± 17.0	0.001

BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; EuroSCORE, European System for Cardiac Operative Risk Evaluation; ICD, implantable cardioverter defibrillator; LA, left atrial; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PISA, proximal isovelocity surface area; RAS, renin–angiotensin system; RVol, regurgitant volume; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VC, vena contracta width.
Values shown are *n* (%), mean ± SD, or median [inter-quartile range].

evidenced by the median logistic European System for Cardiac Operative Risk Evaluation of 17.3% [IQR: 9.2–28.2%]. The mean LVEF was 43.1 ± 15.3%, and secondary MR was 67% of the patients. Technical success was achieved in 99.2% of the patients, and the mean number of implanted clips was 1.5 ± 0.6 (*Table 2*).

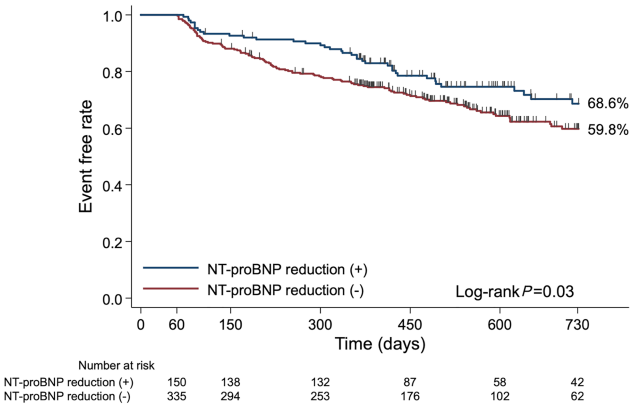
The median NT-proBNP levels decreased from 2614 pg/mL [IQR: 1445–5536 pg/mL] to 2488 pg/mL [IQR: 1360–4605 pg/mL] after TMVR ($P = 0.005$) (*Table 2*, Supporting Information, *Figure S2*). The median percent change in NT-proBNP was −7.2% [IQR: −37.4% to +34.3%]. Of the 485 patients, 150 patients (30.9%) had a significant reduction in NT-proBNP (>30%). Patients with NT-proBNP reduction had a lower rate of atrial fibrillation and higher systolic pulmonary artery pressure (SPAP) compared with those without NT-proBNP reduction (50.7% vs. 65.9%; $P = 0.002$, and 55.6 ± 16.7 vs. 49.5 ± 17.0 mmHg; $P = 0.001$, respectively) (*Table 1*). In contrast, the severity of MR and the procedural findings showed no significant differences between the two groups (*Tables 1* and *2*). Moreover, residual MR at 2 month follow-up was comparable between the two groups (Supporting Information, *Table S2*).

Table 2 Periprocedural NT-proBNP assessments and procedural findings

	All n = 485	NT-proBNP reduction (+) n = 150	NT-proBNP reduction (−) n = 335	P value
NT-proBNP measurements				
NT-proBNP at baseline (pg/mL)	2614 [1445–5536]	4306 [2169–9058]	2271 [1348–4248]	<0.001
NT-proBNP at follow-up (pg/mL)	2488 [1360–4605]	1810 [696–3379]	2805 [1624–5037]	<0.001
Percent change in NT-proBNP (%)	−7.2 [−37.4 to 34.3]	−51.6 [−67.7 to −40.6]	11.8 [−9.9 to 55.6]	<0.001
Periprocedural findings				
Mean number of clips	1.5 ± 0.6	1.6 ± 0.6	1.5 ± 0.6	0.43
Post-procedural mean MVG (mmHg)	4.0 [3.0–5.0]	4.0 [3.0–5.0]	4.0 [3.0–5.0]	0.51
Residual MR ≥ 3+, n (%)	22 (4.6)	9 (6.1)	13 (4.0)	0.35
Length of stay (days)	8 [6–11]	8 [6–11]	8 [6–11]	0.73
Major or life-threating bleeding, n (%)	21 (4.3)	9 (6.0)	12 (3.6)	0.24

MR, mitral regurgitation; MVG, mitral valve gradient; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Values shown are n (%), mean ± SD, or median [inter-quartile range].

Figure 1 A Kaplan–Meier curve demonstrating the composite outcome, consisting of all-cause mortality and heart failure hospitalization, from 2 months to 2 years after transcatheter mitral valve repair (TMVR), according to a reduction in NT-proBNP at 2 months after TMVR (>30% or ≤30% compared with the pre-procedural NT-proBNP level). Tick marks indicate censoring. NT-proBNP, N-terminal pro-B-type natriuretic peptide.



Association between significant reduction in N-terminal pro-B-type natriuretic peptide and clinical outcome after transcatheter mitral valve repair

The median follow-up period was 559 days [IQR: 383–730 days]. From 2 months to 2 years after TMVR, 70 patients (14.4%) died, including 52 patients (10.7%) due to cardiovascular causes; 101 patients (20.8%) were rehospitalized due to worsening HF; and 150 patients (30.9%) experienced the composite outcome. Patients with NT-proBNP reduction had a lower incidence of the composite outcome, compared with those without NT-proBNP reduction (31.4% vs. 40.2%; log-rank P = 0.03; *Figure 1*).

Results from the univariate Cox proportional hazard analysis are shown in Supporting Information, *Table S3*. The multivariable analysis showed that NT-proBNP reduction was associated with a lower risk of the composite outcome within 2 years after TMVR (adjusted HR in model 1: 0.67; 95% CI:

Table 3 Association of changes in NT-proBNP with an incidence of the composite outcome from 2 months to 2 years after TMVR

	Multivariable analysis					
	Model 1			Model 2		
	HR	95% CI	P value	HR	95% CI	P value
NT-proBNP reduction[a]	0.67	0.45–0.97	0.04	0.60	0.36–0.96	0.03
Percent change in NT-proBNP (per 10% reduction)[a]	0.96	0.94–0.98	<0.001	0.96	0.94–0.99	0.006
Female	0.73	0.50–1.06	0.101	0.90	0.55–1.44	0.67
COPD	1.62	1.10–2.35	0.02	1.77	1.06–2.87	0.03
Previous MI	1.06	0.73–1.52	0.76	1.05	0.66–1.65	0.85
NYHA Class III/IV	1.33	0.79–2.44	0.31	1.74	0.93–3.64	0.09
eGFR (per 10 mL/min/1.73 m^2 increase)	0.88	0.80–0.97	0.008	0.89	0.78–1.01	0.08
MR severity: 4+	2.00	1.27–3.03	0.004	1.75	1.00–2.92	0.049
LVEF ≤ 30% at baseline	1.43	0.98–2.08	0.07			
LVEF ≤ 30% at follow-up				1.39	0.84–2.28	0.20
Standardized furosemide equivalent at baseline (per 10 mg/day increase)	1.03	1.01–1.05	0.01			
Standardized furosemide equivalent at follow-up (per 10 mg/day increase)				1.06	1.04–1.09	<0.001

CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection function; MI, myocardial infarction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TMVR, transcatheter mitral valve repair.
[a]Included separately in the multivariable analysis.

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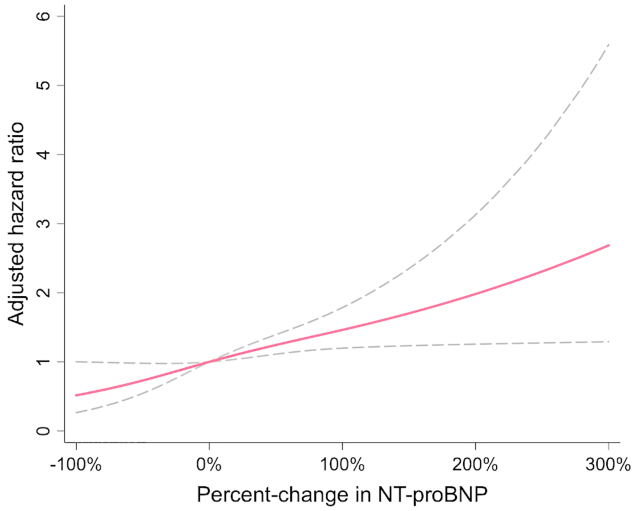
Figure 2 A restricted cubic spline curve showing the association between percent change in NT-proBNP at the 2-month follow-up compared with baseline and the incidence of the composite outcome after transcatheter mitral valve repair. The red solid line indicates the adjusted hazard ratio in the multivariable model 1, and the dashed lines indicate the 95% confidence interval. NT-proBNP, N-terminal pro-B-type natriuretic peptide.



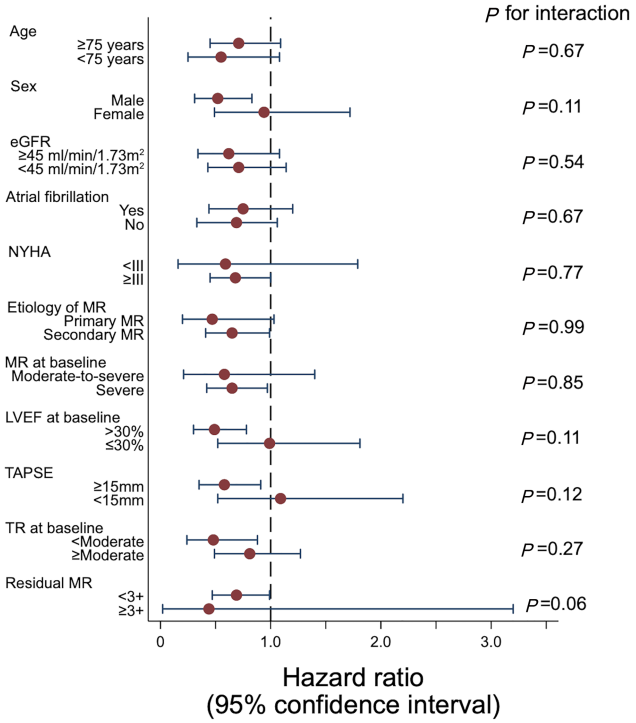
0.45–0.97; P = 0.04, and adjusted HR in model 2: 0.60; 95% CI: 0.36–0.96; P = 0.03), independently of pre-procedural NT-proBNP level (*Table 3*). Similarly, a decreasing percent change in NT-proBNP was associated with a lower risk of the composite outcome (adjusted HR per 10% reduction in model 1: 0.96; 95% CI: 0.94–0.98; $P < 0.001$, and adjusted HR per 10% reduction in model 2: 0.96; 95% CI: 0.94–0.99; P = 0.006).

The restricted cubic spline demonstrated the association between the percent change in NT-proBNP and adjusted HR of the composite outcome (*Figure 2*). Percent change in NT-proBNP was associated with a linear trend of the risk of the composite outcome after TMVR. The association of percent change in NT-proBNP with adjusted HR was consistent in patients with secondary MR (Supporting Information, *Figure S3*).

The association between the NT-proBNP reduction and the composite outcome in subgroups is shown in *Figure 3*. In the stratified analysis for the composite outcome, there were no significant interactions across the subgroups, including aetiology of MR (P for interaction = 0.99).

Among patients without NT-proBNP reduction, use of loop diuretics and its dosage increased at the 2 month follow-up

Figure 3 A forest plot illustrates the hazard ratios for 2-year composite outcome after transcatheter mitral valve repair in patients with a reduction in N-terminal pro-B-type natriuretic peptide values. In each subgroup, the adjusted hazard ratios by pre-procedural NT-proBNP and 95% confidence intervals are presented. eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.



(from 82.1% to 91.3%; *P* = 0.02, and from 30 mg [IQR: 10–60 mg] to 40 mg [IQR: 20–60 mg]; *P* = 0.01, respectively; Supporting Information, *Table S4*), while the use and dosage of loop diuretics were stable in patients with NT-proBNP reduction.

Prognostic impacts of significant reduction in N-terminal pro-B-type natriuretic peptide according to pre-procedural N-terminal pro-B-type natriuretic peptide levels

The receiver operating characteristic analysis revealed that the discriminating pre-procedural NT-proBNP value to discern a 2 year composite outcome was 2485 pg/mL (area under the curve: 0.61; *P* = 0.02; Supporting Information, *Figure S4*). According to the cut-off value, 251 (51.8%) of 485 patients had high NT-proBNP at baseline, which was associated with a higher risk to reach the composite endpoint (adjusted HR: 1.50; 95% CI: 1.03–2.17; *P* = 0.03; *Figure 4A* and Supporting Information, *Table S5*).

When patients were stratified based on the cut-off value of pre-procedural NT-proBNP (high or low) and the significant reduction in NT-proBNP (>30% or ≤30%), patients with a high pre-procedural NT-proBNP and the reduction in NT-proBNP had a lower risk of the composite outcome compared with those with a high NT-proBNP and without the reduction in NT-proBNP (adjusted HR: 0.63; 95% CI: 0.40–0.98; *P* = 0.04; *Figure 4B* and Supporting Information, *Table S5*). Furthermore, patients with a high pre-procedural NT-proBNP who achieved the significant reduction in NT-proBNP had a similar risk of the composite outcome to those with a lower pre-procedural NT-proBNP.

Also, we separately assessed cut-off values of pre-procedural NT-proBNP according to the aetiology of MR. The cut-off values were 2420 pg/mL for primary MR and 3410 pg/mL for secondary MR (Supporting Information, *Figure S4*). Among patients with high pre-procedural NT-proBNP, a significant reduction of NT-proBNP was associated with a lower risk of the composite outcome in either primary or secondary MR (*Figure 5*).

Discussion

In the current multicentre study of patients undergoing TMVR, the main findings can be summarized as follows: (i) in total, NT-proBNP values declined statistically significantly after edge-to-edge TMVR; (ii) the percent change in NT-proBNP and significant reduction in NT-proBNP (>30%) in relation to pre-procedural NT-proBNP were associated with a lower risk of the composite outcome, consisting of mortality and first HF hospitalization, within 2 years after TMVR, independent of pre-procedural NT-proBNP levels; and (iii) the association between the significant reduction in NT-proBNP and the composite outcome was consistent among the clinical subgroups, including aetiology of MR.

While pre-procedural natriuretic peptide levels have attracted attention as a predictor of adverse events after TMVR,[24,25] less emphasis has been placed on the changes in natriuretic peptide levels following TMVR. In this multicentre study, we revealed the association of a reduction in

Figure 4 Kaplan–Meier curves demonstrating the composite outcome from 2 months to 2 years after transcatheter mitral valve repair, according to pre-procedural NT-proBNP levels (cut-off value: 2485 pg/mL) (A) and periprocedural changes in NT-proBNP levels based on the pre-procedural NT-proBNP (high or low) and the reduction in NT-proBNP (>30% or ≤30%) (B). Tick marks indicate censoring. NT-proBNP, N-terminal pro-B-type natriuretic peptide.

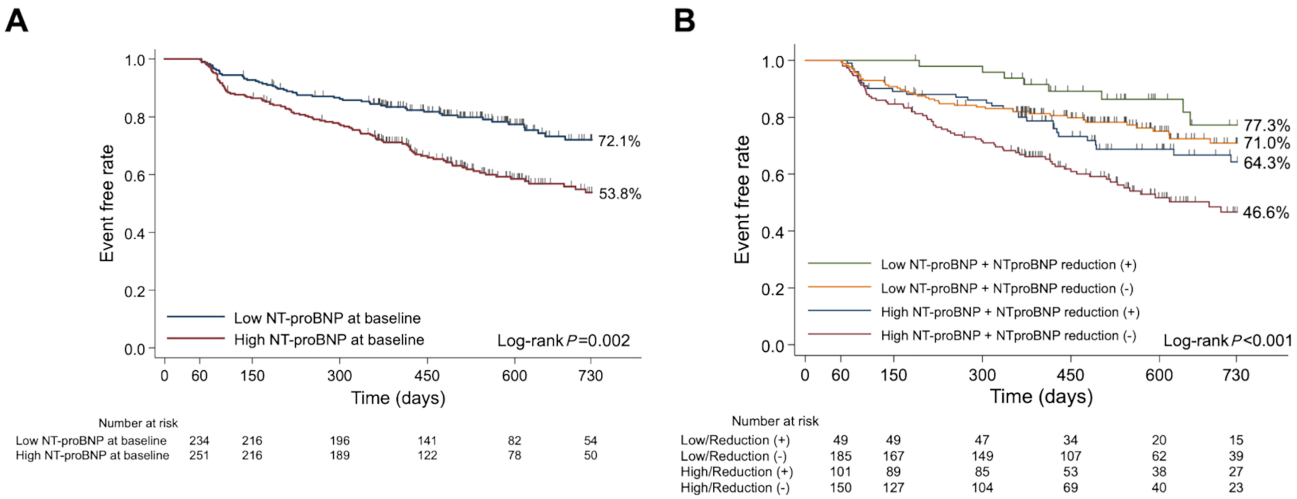
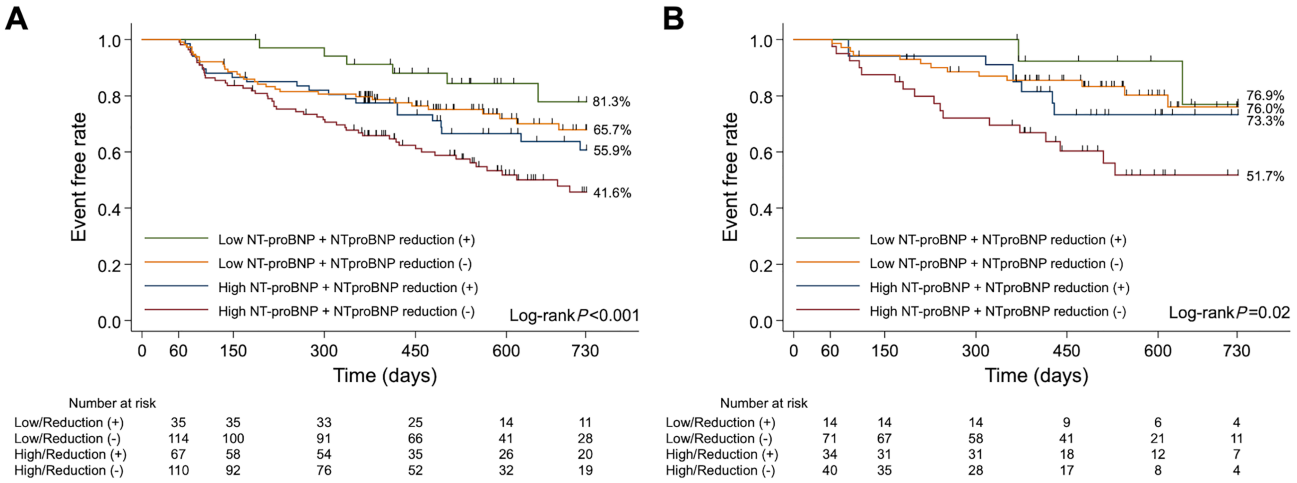


Figure 5 Kaplan–Meier curves demonstrating the composite outcome from 2 months to 2 years after transcatheter mitral valve repair, according to changes in NT-proBNP levels in secondary MR (A) and primary MR (B). The cut-off values of pre-procedural NT-proBNP were 3410 pg/mL for secondary MR and 2420 pg/mL for primary MR. Tick marks indicate censoring. NT-proBNP, N-terminal pro-B-type natriuretic peptide; MR, mitral regurgitation.



NT-proBNP (>30%) following TMVR with a lower risk of the 2 year composite outcome, which remained robust after being adjusted by pre-procedural NT-proBNP levels and cardiac parameters. Furthermore, the assessment of consecutive changes in NT-proBNP had an incremental value on periprocedural assessments of NT-proBNP levels in patients undergoing TMVR. In previous studies with a relatively small population, the clinical impact of changes in NT-proBNP after TMVR was unclear.[14,26] Thus, this is the first study revealing the association of consecutive changes in NT-proBNP with clinical outcome after TMVR, and our findings imply that the sequential changes in NT-proBNP might be as important as the absolute values to predict clinical outcomes after TMVR.

A decrease in NT-proBNP levels, during treatment for HF, is associated with cardiac reverse remodelling in response to the treatment. Daubert *et al*. showed that a greater reduction in NT-proBNP was associated with a more extensive improvement in left ventricular (LV) structure and function in patients with HF.[27] In patients with MR, the changes in NT-proBNP can reflect the haemodynamic benefit of mitral valve repair. Kainuma *et al*. showed that a decrease in BNP levels after surgical mitral valve repair in patients with secondary MR was correlated with a reduction in LV myocardial wall stress and, consequently, led to an increase in LVEF or a reduction in LV volume.[28] In addition, low post-procedural NT-proBNP levels are associated with an improvement of left atrial volume and strain after a MitraClip procedure.[29] Previous reports that outline the association between changes in NT-proBNP with beneficial alterations in cardiac geometry could also support our results. On the other hand, a post-procedural increase in NT-proBNP was related to the risk of the composite outcome, irrespective of other important HF markers such as LVEF. Theoretically, elevated NT-proBNP might reflect adverse haemodynamic effects that are induced by TMVR, such as iatrogenic mitral stenosis or progressive LV remodelling, even after the intervention. In the present study, the percent change in NT-proBNP correlated negatively with the pre-procedural NT-proBNP level (standardized β: −0.10; P = 0.02) and SPAP (standardized β: −0.16; P = 0.002; Supporting Information, *Table S6*). Given that high pre-procedural NT-proBNP and SPAP values could indicate the presence of cardiac congestion due to MR, a greater congestion due to MR might be associated with a greater reduction in NT-proBNP after correction of MR. However, we could not fully clarify the triggers of periprocedural changes in NT-proBNP, and further investigation is therefore needed to evaluate the pathogenesis of NT-proBNP changes following TMVR.

Patients in the present study had a higher frequency of use of HF medications at baseline, including beta-blockers and renin–angiotensin system inhibitors, compared with previous registry data for TMVR.[4] Moreover, this frequency remained stable at the 2 month follow-up. In the present study, there was no significant association of HF medication with clinical outcome. On the other hand, the dosage of loop diuretics at the follow-up was higher in patients without an NT-proBNP reduction than in those with a reduction, which indicates that patients without an NT-proBNP reduction needed more aggressive diuretic treatment. Ultimately, the use of a lower dose of diuretics in patients with NT-proBNP reduction might be caused by a lower burden of post-procedural volume overload and HF symptoms. Our analysis confirmed that the association between a reduction in NT-proBNP and the clinical outcome was independent from the use and dosage of HF medications and diuretics.

Our findings may provide a novel way of evaluating the residual risk associated with adverse events after TMVR. For patients with secondary MR, the beneficial impact of TMVR remains controversial owing to the seemingly conflicting results of two previous randomized control trials,[2,30] which most likely are caused by multiple parameters, rather than just one variable such as proportionate/disproportionate MR.[31] Consequently, the patient selection of TMVR has been complex in secondary MR, and several scoring systems for patient selection and risk have been reported.[25] On the other hand, post-procedural assessments of residual risk after TMVR may also be important to improve the clinical prognosis of patients undergoing TMVR, and periprocedural assessments of NT-proBNP could be useful for the assessment of the residual risk. Longitudinal NT-proBNP assessments could help to identify patients that are in need of more intensive post-procedural monitoring or a more aggressive approach for treating HF after TMVR. If patients have an insufficient reduction in NT-proBNP after TMVR, more careful follow-up or up-titration of medications may be necessary. Furthermore, in the present study, the prognostic impact of changes in NT-proBNP was consistent across the aetiology of MR. Given the complexity of patient selection for TMVR in secondary MR, the periprocedural assessments of NT-proBNP may be one of the several tools that are needed for risk assessment, especially in patients with secondary MR. Longitudinal assessments of NT-proBNP following TMVR could refine the post-procedural strategies in TMVR.

Limitations

Several limitations to this study should be acknowledged. First, this was a retrospective study. Therefore, a certain patient selection bias might have impacted our results. Second, ~50% of patients in the registry were excluded from the analysis owing to a lack of post-procedural assessment of NT-proBNP values. There were some differences in the baseline characteristics between patients included and excluded from the analysis (Supporting Information, *Table S1*); however, the characteristics of the patients included in the analysis were comparable with those in previous reports.[4] Third, the cut-off value for pre-procedural NT-proBNP identified in the present study is relatively higher than that of a previous study,[24] and we did not test this cut-off value in validation cohorts. Fourth, we did not have prespecified criteria to determine the need for hospitalization due to worsening HF, and the decision was based on the attending physicians' discretion, which might lead to a misclassification bias. Finally, the data from echocardiographic assessments and medications at follow-up were not fully available in the present study. Moreover, echocardiographic changes in LV geometry, which may have led to changes in NT-proBNP values, could not be analysed.

Conclusions

Changes in consecutive NT-proBNP measurements after edge-to-edge TMVR were associated with clinical outcome, irrespective of the aetiology of MR. Patients with a significant reduction of NT-proBNP (>30%) at the 2 month follow-up had a lower incidence of the composite outcome, consisting of all-cause mortality and HF hospitalization, within 2 years after TMVR, compared with those without a significant reduction of NT-proBNP. Assessment of NT-proBNP dynamics may be valuable to help determine the residual risk following TMVR and could assist post-procedural management in patients undergoing TMVR.

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Conflict of interest

G.N. has received speaker honoraria and research grants from Abbott, Abiomed, Medtronic, Boston Scientific, and Edwards Lifesciences, outside the submitted work. S.B. has received lecture honoraria from Edwards Lifesciences, Bayer Vital, CVRx, MSD Sharp & Dohme GmbH, JenaValve Technology, and Abbott and research grants from IcoVifor, Symetis SA, Pfizer, JenaValve Technology, Valtech, OptumInsight, Biotronik, and Abbott, outside the submitted work. R.P. has received speaker and consultant honoraria from Abbott and Edwards Lifesciences, outside the submitted work. C.I. has received travel support by Abbott and speaker and consultant honoraria from Abbott and Edwards Lifesciences, outside the submitted work. T.T. is financially supported in part by a fellowship from the Japanese College of Cardiology. The other authors report no conflicts of interest.

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Supporting information

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

Figure S1. Study flowchart.
Figure S2. Distribution of NT-proBNP at baseline and two-month follow-up.
Figure S3. Association between percent change in NT-proBNP and the composite outcome in patients with FMR.
Figure S4. The ROC curves for 2-year composite outcome.
Table S1. Comparison of characteristics between patients included or excluded in the analysis.
Table S2. Echocardiographic findings at two-month follow-up.
Table S3. Univariate Cox-proportional hazard analysis for the composite outcome after TMVR.
Table S4. Comparison of medications between baseline and two-month follow-up.
Table S5. Univariate and multivariable Cox-proportional hazard analysis for the composite outcome according to periprocedural changes in NT-proBNP.
Table S6. Association of clinical parameters with percent change in NT-proBNP.

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