

# BMJ Open Is elevation of N-terminal pro-B-type natriuretic peptide at discharge associated with 2-year composite endpoint of all-cause mortality and heart failure hospitalisation after transcatheter aortic valve implantation? Insights from a multicentre prospective OCEAN-TAVI registry in Japan

Kazuki Mizutani,<sup>1</sup> Masahiko Hara,<sup>2</sup> Mana Nakao,<sup>1</sup> Tsukasa Okai,<sup>1</sup> Keiko Kajio,<sup>1</sup> Takashi Murakami,<sup>3</sup> Toshihiko Shibata,<sup>3</sup> Minoru Yoshiyama,<sup>1</sup> Toru Naganuma,<sup>4</sup> Futoshi Yamanaka,<sup>5</sup> Akihiro Higashimori,<sup>6</sup> Norio Tada,<sup>7</sup> Kensuke Takagi,<sup>8</sup> Motoharu Araki,<sup>9</sup> Hiroshi Ueno,<sup>10</sup> Minoru Tabata,<sup>11</sup> Shinichi Shirai,<sup>12</sup> Yusuke Watanabe,<sup>13</sup> Masanori Yamamoto,<sup>14</sup> Kentaro Hayashida<sup>15</sup>

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For numbered affiliations see end of article.

## Correspondence to

Dr Kazuki Mizutani; [mizutani.kazuki@med.osaka-cu.ac.jp](mailto:mizutani.kazuki@med.osaka-cu.ac.jp)

## ABSTRACT

**Objectives** The aim of this study was to investigate the 2-year prognostic impact of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels at discharge following transcatheter aortic valve implantation (TAVI).

**Design** Multicentre prospective observational study.

**Settings** Seven institutions from multicentre, observational registry of symptomatic patients with severe aortic stenosis who undergo TAVI.

**Participants** We enrolled 500 consecutive patients who underwent TAVI with measurements of NT-proBNP at discharge between 2013 and 2016. Study patients were stratified into two groups according to survival classification and regression tree (CART) analysis: high versus low NT-proBNP groups.

**Interventions** The impact of high NT-proBNP on a 2-year composite endpoint consisting of all-cause mortality and heart failure hospitalisation was evaluated using a multivariable Cox model.

**Results** Median age was 86 years (quartile 82–89), and 24.2% of the study population were men. Median Society of Thoracic Surgeon score was 7.1 (5.1–9.8), and NT-proBNP at discharge was 1381 (653–3136) pg/mL. The composite endpoint incidence was 13.0% (95% CI 9.5% to 16.3%) at 1 year and 22.3% (95% CI 16.1%–27.9%) at 2 years. The survival CART analysis revealed that the NT-proBNP level required to discern the 2-year composite endpoint was 4288 pg/mL. Elevated NT-proBNP had a statistically significant impact on outcomes, with adjusted HR of 2.21 (95% CI 1.21 to 4.04,  $p=0.010$ ), and with a significant sex difference ( $P$  for interaction=0.003).

## Strengths and limitations of this study

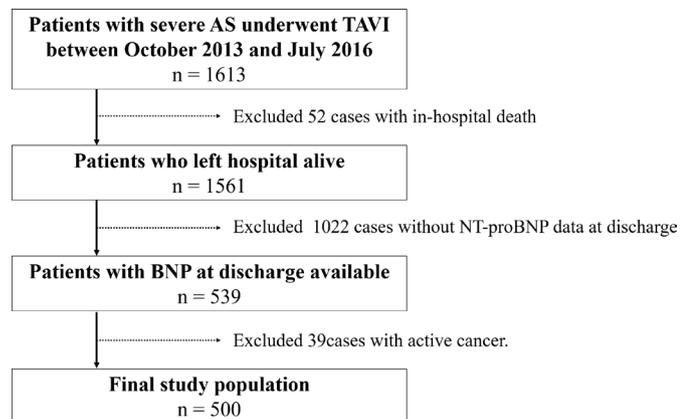
- The study has a multicentre prospective design.
- The size of the study population is the largest ever ( $n=500$ ).
- A survival classification and regression tree analysis was used for a simple risk stratification with a single biomarker.
- The N-terminal pro-B-type natriuretic peptide was not measured at a core laboratory.
- Heart failure hospitalisation was determined by each individual physician's judgement.

**Conclusion** Elevation of NT-proBNP at discharge is associated with higher incidence of the 2-year composite endpoint after TAVI.

**Trial registration number** 000020423

## INTRODUCTION

Severe aortic stenosis (AS) is one of the most prevalent forms of heart valve disease. AS causes left ventricular pressure overload, which leads to acute decompensated heart failure (HF) and high cardiovascular mortality.<sup>1 2</sup> Surgical aortic valve replacement (SAVR) has been the mainstay of treatment for symptomatic severe AS for decades.<sup>2</sup> Transcatheter aortic valve implantation (TAVI) has also recently been recognised as a promising therapeutic option and has been reported to



**Figure 1** Patient selection flow. AS, aortic stenosis; NT-proBNP, N-terminal pro-B-type; TAVI, transcatheter aortic valve implantation.

have non-inferior long-term clinical outcome in patients with intermediate surgical risk who underwent TAVI as compared with a SAVR cohort.<sup>3-5</sup> With the expanding indication and prolongation of life expectancy after TAVI, it is speculated that risk stratification and long-term management of HF may be the next challenge facing physicians.<sup>3-6</sup> For example, a recent meta-analysis that predominantly included intermediate-risk patients with AS demonstrated that transfemoral TAVI is associated with more severe HF symptoms than SAVR during 2-year follow-up.<sup>6</sup>

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a hormone released by the cardiac ventricles as a result of elevated end-diastolic pressure overload.<sup>7</sup> NT-proBNP has been used for stratification of long-term mortality in patients with chronic HF.<sup>1 2 7-9</sup> Although several reports have evaluated the relationship between NT-proBNP levels and the postprocedural prognosis of the TAVI cohort, these reports had some limitations. For example, all reports were derived from a single centre with relatively small numbers of patients, and most studies evaluated NT-proBNP prior to performance of the TAVI procedure.<sup>10-15</sup> Since TAVI could dramatically release the left ventricle from pressure overload and contribute to the decrease in NT-proBNP level, we speculated that it is preferable to use NT-proBNP levels at discharge for risk stratification of long-term prognosis in patients who underwent TAVI.<sup>13 16</sup> Finally, the risk of hospitalisation for HF following TAVI was not investigated in most NT-proBNP studies.<sup>10-15</sup> Consequently, a multicentre TAVI study of the long-term prognostic impact of NT-proBNP levels at discharge warrants consideration. In the present study, we investigated NT-proBNP levels at discharge in terms of their impact on the 2-year composite endpoint of all-cause mortality and hospitalisation for HF, and usefulness for risk stratification in patients with AS who underwent TAVI. This was the largest study population ever enrolled (n=500) from a multicentre, prospective TAVI registry.

## METHODS

### Study population

Figure 1 shows patient selection flow. Study candidates included 500 consecutive patients from 7 of 14 institutions where NT-proBNP was measured at discharge, who were enrolled in the Optimised Transcatheter Valvular Intervention (OCEAN)-TAVI registry. The enrolled patients were discharged alive from the hospital and had a record of NT-proBNP at discharge, without active cancer present, between October 2013 and July 2016 (figure 1).<sup>17</sup> The OCEAN-TAVI is a prospective, multicentre, observational registry of symptomatic patients with severe AS who undergo TAVI using the Edwards Sapien XT/Sapien 3 Transcatheter Heart Valve (Edwards Lifesciences, Irvine, California, USA) or the Medtronic CoreValve Revalving System (Medtronic, Minneapolis, Minnesota, USA) at 14 collaborating hospitals. This trial was registered with the University Hospital Medical Information Network Clinical Trials Registry, as accepted by the International Committee of Medical Journal Editors (UMIN-ID;000020423). Inclusion criteria were: (1) the presence of HF symptoms defined as New York Heart Association (NYHA) functional class  $\geq$ II; (2) the presence of degenerative AS; (3) a mean gradient of  $>40$  mm Hg or a jet velocity of  $>4.0$  m/s; and/or (4) an aortic valve area (AVA)  $<1.0$  cm<sup>2</sup> (or an effective orifice area (EOA) index  $<0.6$  cm<sup>2</sup>/m<sup>2</sup>). Indication for TAVI was determined based on the clinical consensus of a heart team comprised of cardiac surgeons, interventional cardiologists, anaesthesiologists and imaging specialists. Exclusion criteria were: (1) presence of a non-calcified aortic valve; (2) failed surgical bioprosthesis implantation; (3) presence of severe aortic regurgitation (AR); and/or (4) the current use of dialysis. The study protocol was developed in accordance with the Declaration of Helsinki. All patients gave written informed consent prior to participating in this study. All authors had full access to the data and were responsible for its integrity, and have read and authorised the publication of the manuscript in its current form.

### Blood sampling and NT-proBNP measurement

Among 14 participating institutions in the OCEAN-TAVI registry, NT-proBNP at discharge was measured at seven institutions with a daily clinical practice. Blood samples were drawn from the antecubital or other accessible veins such as the dorsal hand vein, and collected in blood sampling tubes at the time of hospital discharge following TAVI procedure. NT-proBNP levels were measured using a chemiluminescence microparticle immunoassay (Elecys NT-proBNP, Roche Diagnostics, Tokyo, Japan) at five of the seven institutions (n=374), or a chemiluminescence enzyme immunoassay (HISCL NT-proBNP, Sysmex Corporation, Kobe, Japan) at two institutions (n=126). All samples were measured at each institutional laboratory and was not measured at a core laboratory. However, these two assays are reported to be highly comparable, with  $r=0.998$ ; the least square formula is  $y=0.94x-38.69$  in the product literature.

## Data collection and statistical analysis

All data shown in tables and figures were collected from the OCEAN-TAVI multicentre prospective registry database.<sup>17 18</sup> We set the primary endpoint as the 2-year composite of all-cause mortality and hospitalisation for HF after hospital discharge. The secondary endpoints were set as 2-year all-cause mortality and 2-year hospitalisation for HF, where the necessity of hospitalisation was determined based on the attending physician's discretion. Although there were no definite prespecified criteria for HF rehospitalisation in the OCEAN-TAVI registry, the consensus indication includes patients with HF symptoms, such as dyspnoea with objective signs of volume overload, such as pulmonary oedema or signs of hypoperfusion, where the administration of intravenous diuresis or inotropic therapy should be considered.

The series of statistical analyses performed in this study was common in our previous report.<sup>17</sup> Continuous variables were summarised using medians and IQR (quartiles 1 to 3), and categorical variables were summarised by means of counts and percentages. To provide a simple risk stratification model, we first classified our study patients into two groups according to survival classification and regression tree (CART) analysis for the primary endpoint.<sup>17 19 20</sup> We performed survival CART analysis using the primary endpoint as an outcome measure, with NT-proBNP levels at discharge as an independent variable. The purpose was to identify the cut-off value of NT-proBNP for the risk stratification of the primary endpoint. After the survival CART revealed the cut-off NT-proBNP value at discharge, we divided the study population into two groups based on this result. Patients with NT-proBNP levels lower than or equal to the cut-off value were defined as the 'low NT-proBNP group,' whereas those with NT-proBNP levels greater than the cut-off value were defined as the 'high NT-proBNP group.' We evaluated the impact of high NT-proBNP on endpoints as compared with that of low NT-proBNP, using univariable and multivariable Cox regression models, with a cross-product term between NT-proBNP groups and sex for the assessment of sex differences, and a *P* for interaction. The following variables were included as possible confounders: Clinical Frailty Scale; Society of Thoracic Surgeons (STS) surgical mortality risk score; apical approach; postprocedural transthoracic echocardiographic indices such as left ventricular ejection fraction (LVEF); EOA; mean aortic valve pressure gradient (mAVPG); the presence of moderate to severe AR; the presence of postprocedural acute kidney injury; and institution as a stratum to minimise institutional selection bias and maintain the validity. These confounders were determined clinically, considering the number of endpoints and multicollinearity. For example, information such as age, sex and arrhythmia data were included in the analysis since they are used in the calculation of the STS score. We also employed Akaike Information Criteria in order to select the best predictive Cox model for use. The incidence of each endpoint was estimated using the Kaplan-Meier method, with a 95% CI,

and the difference between the NT-proBNP groups was evaluated using the log-rank test. Differences in continuous and categorical variables between NT-proBNP groups were compared using the Wilcoxon rank-sum test or the  $\chi^2$  test, respectively. Although NT-proBNP levels on admission were available, we did not perform any analysis regarding the best timing of the measurements and did not evaluate whether a difference in the value between preprocedural and postprocedural NT-proBNP was more informative or not, considering the objective of the present study.<sup>21–23</sup> There were no missing data regarding NT-proBNP at discharge and any additional statistical methods like imputation were not performed to address this. Statistical analyses were performed using R software packages (V.3.3.2; R Development Core Team). The significance level of statistical hypothesis testing was set at 0.05 and the alternative hypothesis was two-sided.

## Patient and public involvement

Patients and the public were not involved in a development of the research question, outcome measures or recruitment to and conduct of the study. The study results will be disseminated to participants by publishing the study manuscript as written on the informed consent form.

## RESULTS

The patients' characteristics are shown in [table 1](#). The median age of the study population was 86 years, and 24.2% of the patients were men. Almost all of the participants presented with NYHA HF functional class II or higher. The median Canadian Study of Health and Ageing Clinical Frailty Scale value was 4. Preoperative transthoracic echocardiography revealed that the median LVEF was 63% and the median AVA with Doppler method was 0.60 cm<sup>2</sup>, with mAVPG of 47.9 mm Hg. The STS was 7.1% and the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) was 13.5% ([table 1](#)). The median NT-proBNP level at discharge in the entire cohort was 1381 pg/mL (quartile; 653–3136), without statistical difference between men and women (*p*=0.065) or between patients with or without moderate to severe AR after TAVI (*p*=0.560); the distribution is presented in [figure 2](#). NT-proBNP levels at discharge were 2382 (1143–3422) pg/mL in patients who underwent a transapical approach versus 1208 (544–2,818) pg/mL in patients who underwent a transfemoral approach (*p*<0.001). The median interval from the time of TAVI to NT-proBNP measurement was 9 (7–15) days, and hospitalisation length was 10 (7–16) days.

[Table 2](#) shows the information related to the TAVI procedure. Most of the patients in this study received the SAPIEN XT valve (Edwards Lifesciences, Irvine, CA, USA) with a median valve size of 23 mm. The percentage of patients who underwent the TAVI procedure with a transapical approach was 21.6%. Echocardiography revealed that postprocedural mAVPG was 10.5 mm Hg and EOA

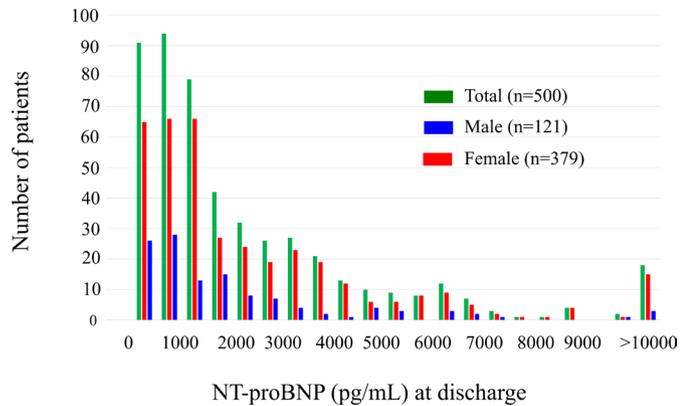
**Table 1** Patient characteristics

Parameters	Total n=500	Low NT-proBNP n=421	High NT-proBNP n=79	P value
NT-proBNP at discharge (pg/mL)				
Total population	1381 (653–3136)	1152 (544–2211)	6396 (5403–9318)	<0.001
Men	1354 (569–2543)	903 (499–1860)	6234 (5315–7147)	<0.001
Women	1388 (706–3297)	1161 (560–2339)	6402 (5485–9564)	<0.001
AR grade ≥ moderate after TAVI	1931 (1104–2107)	1660 (1049–2012)	5659 (5659–5659)*	0.222
AR grade < moderate after TAVI	1371 (645–3145)	1152 (540–2213)	6407 (5419–9659)	<0.001
Time from TAVI (days)	9 (7–15)	9 (7–15)	12 (8–16)	0.003
Age (years)	86 (82–89)	86 (82–89)	86 (84–89)	0.191
Men	121 (24.2)	104 (24.7)	17 (21.5)	0.544
BSA (m <sup>2</sup> )	1.39 (1.29–1.51)	1.40 (1.30–1.52)	1.33 (1.26–1.44)	0.004
Atherosclerotic risks				
Hypertension	391 (78.2)	326 (77.4)	65 (82.3)	0.339
Dyslipidaemia	200 (40.0)	177 (42.0)	23 (29.1)	0.031
Diabetes mellitus	126 (25.2)	104 (24.7)	22 (27.8)	0.555
Current smoking	8 (1.6)	7 (1.7)	1 (1.3)	0.796
Atrial fibrillation	96 (19.2)	74 (17.6)	22 (27.8)	0.033
Prior coronary artery bypass graft	37 (7.4)	33 (7.8)	4 (5.1)	0.387
Previous myocardial infarction	44 (8.8)	31 (7.4)	13 (16.5)	0.009
Previous ischaemic stroke	53 (10.6)	48 (11.4)	5 (6.3)	0.179
NYHA class				0.001
Class II	258 (51.6)	229 (54.4)	29 (36.7)	–
Class III	198 (39.6)	160 (38.0)	38 (48.1)	–
Class IV	27 (5.4)	17 (4.0)	10 (12.7)	–
Clinical Frailty Scale	4 (3–5)	4 (3–4)	4 (3–6)	0.001
Medical treatment on admission				
ACEI or ARB	303 (60.6)	259 (61.5)	44 (55.7)	0.331
Beta-blocker	207 (41.4)	166 (39.4)	41 (51.9)	0.039
Ca blocker	224 (44.8)	193 (45.8)	31 (39.2)	0.279
Diuretics	298 (59.6)	239 (56.8)	59 (74.7)	0.003
Statin	233 (46.6)	209 (49.6)	24 (30.4)	0.002
Laboratory data on admission				
NT-proBNP (pg/mL)	1854 (718–4343)	1473 (598–3298)	5909 (3095–13202)	<0.001
e-GFR (mL/min/1.73 m <sup>2</sup> )	49.7 (37.6–61.3)	51.1 (40.2–64.0)	37.8 (28.6–51.6)	<0.001
TTE data before TAVI				
LV end-diastolic diameter (mm)	43 (39–48)	43 (39–47)	44 (39–49)	0.312
LV end-systolic diameter (mm)	28 (25–33)	28 (25–32)	29 (26–34)	0.067
LVEF (%)	63 (55–67)	63 (55–67)	58 (46–65)	0.001
Mean AVP gradient (mm Hg)	47.9 (37.0–61.7)	48.4 (37.0–62.7)	47.3 (35.8–56.9)	0.243
Peak AVP gradient (mm Hg)	83.4 (65.0–106.0)	84.0 (65.0–108.0)	80.3 (63.0–95.0)	0.257
AVA with Doppler (cm <sup>2</sup> )	0.60 (0.50–0.70)	0.60 (0.50–0.71)	0.60 (0.49–0.70)	0.776
STS score	7.1 (5.1–9.8)	6.9 (4.9–9.2)	9.8 (6.3–15.3)	<0.001
Logistic EuroSCORE	13.5 (9.5–20.7)	12.8 (9.2–20.1)	18.4 (11.2–25.6)	0.001
Euro II score	3.6 (2.3–5.5)	3.5 (2.2–5.2)	4.9 (3.4–8.0)	<0.001

Categorical variables are shown as numbers (percentages) and continuous variables are shown as medians (25–75 percentiles).

\*Only one patient was categorised in this group.

ACE-I, angiotensin converting- enzyme inhibitor; AR, aortic regurgitation; ARB, angiotensin  $\square$  receptor blocker; AVA, aortic valve area; AVP, aortic valve pressure; BSA, body surface area; e-GFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LV, left ventricle; LVEF, left ventricular ejection fraction by modified Simpson or Teichholz methods; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; STS, Society of Thoracic Surgeon; TAVI, transcatheter aortic valve implantation; TTE, transthoracic echocardiography.



**Figure 2** Distribution of N-terminal pro-B-type natriuretic peptide (NT-proBNP) level at discharge after transcatheter aortic valve implantation.

was 1.47 cm<sup>2</sup>. Periprocedural complications defined by Valve Academic Research Consortium-2 consensus, including coronary obstruction, permanent pacemaker implantation, and acute kidney injury, occurred in 1.0%, 6.6%, and 8.8% of the study participants, respectively. Furthermore, the incidences of life-threatening or disabling bleeding and minor bleeding in the high NT-proBNP group were significantly higher than those in the low NT-proBNP group.

During the 2-year follow-up period, there were 37 mortality events and 32 hospitalisation events due to HF. **Figure 3** shows the Kaplan-Meier estimates of each endpoint following discharge. The primary endpoint occurred in 13.0% (95% CI 9.5% to 16.3%) at 1 year and 22.3% (95% CI 16.1%–27.9%) at 2 years. All-cause mortality was 6.7% (4.0%–9.3%) at 1 year and 16.0% (10.2%–21.4%) at 2 years; hospitalisation rates for HF were 7.2% (4.6%–9.8%) at 1 year and 9.2% (5.7%–12.6%) at 2 years. The survival CART analysis revealed that the NT-proBNP level at discharge required to discern the 2-year composite endpoint was 4288 pg/mL; hence, we divided the study population into two NT-proBNP groups, based on this result. Patients in the low NT-proBNP group were defined as having NT-proBNP at discharge  $\leq 4288$  pg/mL, and patients in the high NT-proBNP group were defined as having NT-proBNP at discharge  $>4288$  pg/mL.

Comparisons between the low and high NT-proBNP groups showed a number of significant differences in patient characteristics and procedure-related indices (**tables 1,2**). The high NT-proBNP group had a higher proportion of factors associated with increased procedural risks, such as increased third quartile CFS, decreased estimated glomerular filtration rate, reduced LVEF and higher STS and logistic EuroSCORE, than the low NT-proBNP group. Moreover, the Kaplan-Meier estimates clarified that the 2-year composite endpoint of all-cause mortality and hospitalisation for HF was higher in the high NT-proBNP group than in the low NT-proBNP group, with log-rank  $p < 0.001$  (**figure 3**). Specifically, the composite endpoint of all-cause mortality and hospitalisation for HF was 30.3% (95% CI 17.8% to 40.6%) versus 9.5% (95% CI 6.2% to

12.8%) at 1 year and 41.9% (95% CI 23.9% to 55.7%) versus 18.5% (95% CI 17.8% 12.0%–24.6%) at 2 years in the high NT-proBNP and low NT-proBNP groups, respectively. **Table 3** demonstrates that high NT-proBNP levels had a statistically significant impact on outcomes, with an adjusted HR of 2.21 (95% CI 1.21 to 4.04,  $p=0.010$ ) for the primary endpoint and adjusted HR of 2.66 (1.13–6.25,  $p=0.026$ ) for hospitalisation due to HF in a standard multivariable model, with a statistically significant difference between men and women for the primary endpoint ( $P$  for interaction=0.003) and hospitalisation for HF ( $P$  for interaction  $<0.001$ ).

## DISCUSSION

We demonstrated that elevated NT-proBNP levels at discharge were associated with higher 2-year composite events of all-cause mortality and hospitalisation for HF, and provided risk stratification cut-off values of NT-proBNP after TAVI via enrollment of the largest relevant study population ever ( $n=500$ ), from the multi-centre, prospective OCEAN-TAVI registry. As a result, we revealed that the best risk stratification NT-proBNP level at discharge was 4288 pg/mL. Regarding secondary endpoints, elevation of NT-proBNP was associated with increased risk of HF hospitalisation, but not with all-cause mortality. As none of the previous studies evaluated whether NT-proBNP levels at discharge were relevant to long-term prognosis following TAVI, even in this HF pandemic era, our study could provide physicians with new insights into this field.<sup>10–15 24</sup>

### NT-proBNP at discharge

Previous studies have provided evidence that NT-proBNP is greatly valuable as a risk stratification marker in patients with HF due to a wide spectrum of cardiovascular diseases.<sup>12 7–9</sup> However, previous studies described the relationship between NT-proBNP levels before the TAVI procedure and patient prognosis, and many of these data were derived from single-centre studies that only focused on all-cause mortality, without describing the incidence of HF.<sup>10–15</sup> For example, Ribeiro *et al* reported that a high baseline NT-proBNP was associated with a higher all-cause and cardiovascular mortality, as well as higher incidence of rehospitalisation for HF, in a single-centre study that included 333 patients, where differences in event rates might arise in the very early period after TAVI.<sup>12</sup> In contrast, Köhler *et al* suggested that preprocedural NT-proBNP was in fact not associated with all-cause mortality at a median of 290 days, in a multivariable analysis based on data from 259 patients in a single-centre prospective study.<sup>10</sup> Considering the short half-life of NT-proBNP (approximately 120 min) and the association between high baseline NT-proBNP and high short-term mortality risk, we believe that NT-proBNP level at discharge would be more beneficial than preprocedural NT-proBNP level for risk stratification of long-term prognosis after TAVI because the

**Table 2** Procedural and periprocedural data

Parameters	Total n=500	High NT-proBNP		P values
		Low NT-proBNP n=421	n=79	
<b>Procedural data</b>				
Apical approach	108 (21.6)	81 (19.2)	27 (34.2)	0.003
Valve type				0.284
Edwards SAPIEN XT	425 (85.0)	355 (84.3)	70 (88.6)	
Edwards SAPIEN 3	33 (6.6)	31 (7.4)	2 (2.5)	
Medtronic CoreValve	42 (8.4)	35 (8.3)	7 (8.9)	
Valve size (mm)	23 (23–26)	23 (23–26)	23 (23–26)	0.767
Fluoro time (min)	20 (16–27)	21 (16–27)	19 (15–27)	0.518
Procedure time (min)	86 (66–108)	83 (65–104)	93 (77–118)	0.007
Anaesthesia time (min)	152 (125–180)	150 (124–179)	159 (132–185)	0.115
<b>TTE Data after TAVI</b>				
LV end-diastolic diameter (mm)	44 (40–48)	43 (40–47)	45 (40–50)	0.109
LV end-systolic diameter (mm)	28 (25–32)	28 (25–31)	30 (26–36)	0.005
LVEF (%)	62 (55–67)	63 (57–67)	57 (50–63)	<0.001
Mean AVP gradient (mm Hg)	10.5 (8.0–13.2)	11.0 (8.0–13.7)	9.3 (7.1–12.5)	0.048
Peak AVP gradient (mm Hg)	20.0 (15.4–26.0)	20.2 (15.5–26.2)	18.2 (15.0–23.2)	0.057
Effective orifice area (cm <sup>2</sup> )	1.47 (1.25–1.71)	1.49 (1.28–1.73)	1.40 (1.21–1.62)	0.072
AR grade $\geq$ moderate	9 (1.8)	8 (1.9)	1 (1.3)	0.703
MR grade $\geq$ moderate	42 (8.5)	34 (8.1)	8 (10.3)	0.532
<b>Periprocedural complications by VARC-2 definitions</b>				
Coronary obstruction	5 (1.0)	5 (1.2)	0 (0.0)	0.330
Periprocedural MI	3 (0.6)	3 (0.7)	0 (0.0)	0.452
Stroke	10 (2.0)	10 (2.4)	0 (0.0)	0.166
TIA	2 (0.4)	1 (0.2)	1 (1.3)	0.184
Life-threatening or disabling bleeding	31 (6.2)	21 (5.0)	10 (12.7)	0.009
Major bleeding	53 (10.6)	44 (10.5)	9 (11.4)	0.803
Minor bleeding	102 (20.4)	76 (18.1)	26 (32.9)	0.003
Major vascular complications	19 (3.8)	13 (3.1)	6 (7.6)	0.055
Minor vascular complications	29 (5.8)	26 (6.2)	3 (3.8)	0.407
Conduction disturbances and arrhythmias	59 (11.9)	50 (12.0)	9 (11.4)	0.880
Permanent PM implantation	33 (6.6)	25 (5.9)	8 (10.1)	0.169
Acute kidney injury	44 (8.8)	25 (5.9)	19 (24.1)	<0.001

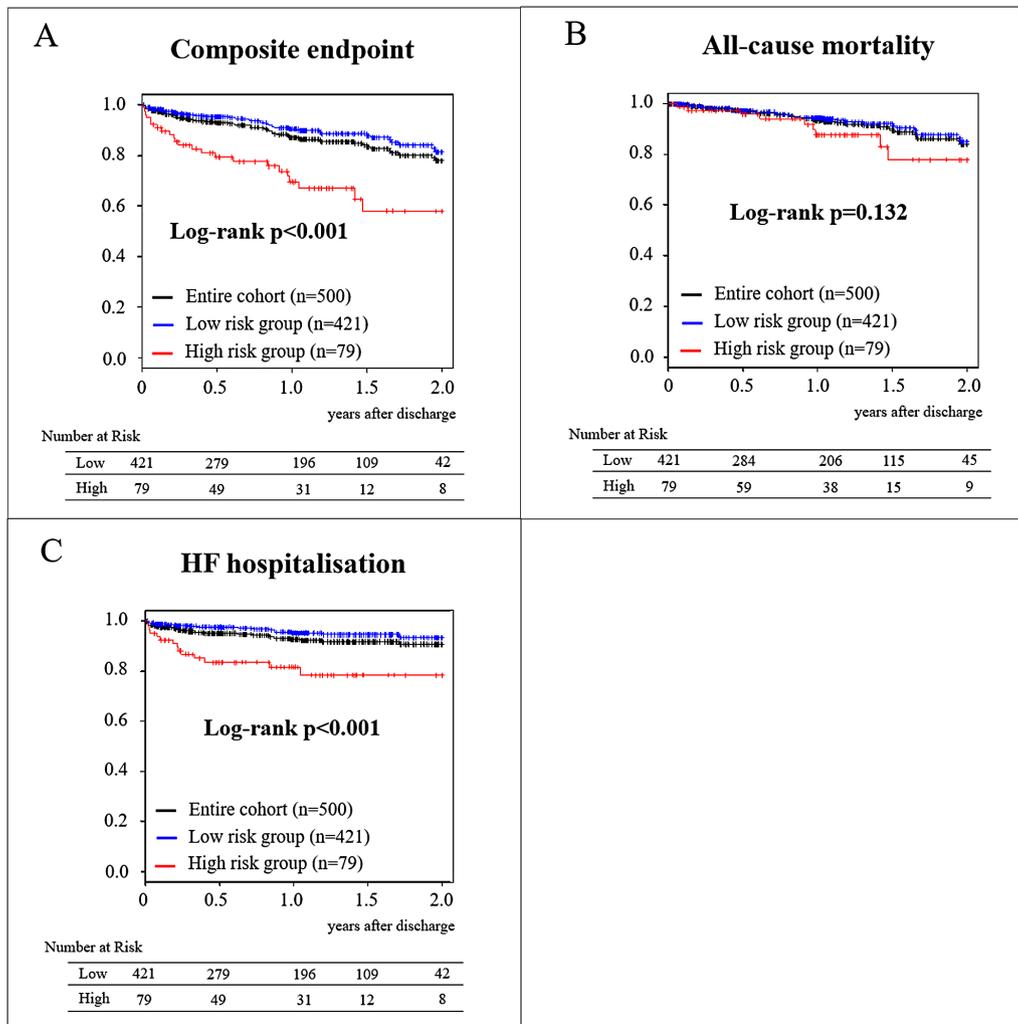
AR, aortic regurgitation; AVP, aortic valve pressure; LV, left ventricle; LVEF, left ventricular ejection fraction by modified Simpson or Teichholz methods; MI, myocardial infarction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PM, pacemaker; TAVI, transcatheter aortic valve implantation; TIA, transient ischaemic attack; TTE, transthoracic echocardiography; VARC-2, Valve Academic Research Consortium-2.

TAVI procedure immediately improves left ventricular pressure overload.<sup>13 16</sup> However, we also must keep in mind that direct comparison of preprocedural and postprocedural NT-proBNP values is needed to reach a conclusion of this issue, as it is controversial with B-type natriuretic peptide (BNP).<sup>17 21–23</sup>

#### Long-term prognosis after TAVI

In this study, we found that elevated NT-proBNP levels at discharge were independently associated

with a higher 2-year composite endpoint consisting of all-cause mortality and hospitalisation for HF. It seemed that differences in the incidence of the primary endpoint were mainly due to differences in the incidence of HF hospitalisation rather than all-cause mortality (figure 3). In fact, the adjusted HR of hospitalisation for HF was higher than that of all-cause mortality (2.66 vs 1.23). Although the management of HF become ever more important with improvements in



**Figure 3** Kaplan-Meier estimates for each endpoint. Kaplan-Meier estimates of (A) the primary endpoint, (B) all-cause mortality and (C) hospitalisation for heart failure (HF).

midterm survival and prolongation of life expectancy following TAVI, most previous studies on NT-proBNP in patients who underwent TAVI procedures did not focus on hospitalisation for HF.<sup>10–15</sup> Thus, to the best of our knowledge, this is the first report to examine the association between NT-proBNP at discharge and hospitalisation for HF following TAVI, using a multicentre prospective large cohort data set. In contrast, we previously reported the significant association between the BNP at discharge and 2-year mortality from the same registry.<sup>17</sup> This discrepancy, regarding the associations with all-cause mortality between NT-proBNP and BNP, may be mainly derived from a relatively small number of patients (n=500 vs 1094), considering an estimated statistical power for the log-rank test of 0.167 with the current number of patients and event rates.

### Sex differences

In the present study, the proportion of male participants was relatively low (24.2%) in comparison with those in studies in Western countries.<sup>3–5 25</sup> Although several previous studies reported higher NT-proBNP levels

in women than in men in the general population,<sup>26</sup> NT-proBNP levels at discharge were not statistically significantly different between the men and the women in our cohort. This sex disparity should be taken into consideration when interpreting our data. The impact of elevated NT-proBNP levels at discharge on the primary endpoint and hospitalisation for HF was statistically greater in the female than in the male patients, with p values for interaction of 0.003 and  $< 0.001$ , respectively. This is consistent with a previous report that demonstrated different predictors of survival between men and women after TAVI.<sup>27</sup>

### Clinical implications

As TAVI cohorts are generally aged and often have complications due to multiple risk factors that can affect their prognoses, we believe that a simple risk stratification model is helpful for physicians to support better patient care, especially those with HF. NT-proBNP has already been used for this purpose in a wide spectrum of cardiovascular diseases.<sup>1 2 7–9</sup> From this viewpoint, we employed survival CART and revealed that patients in the high NT-proBNP group, defined as those with

**Table 3** Impact of NT-proBNP stratification on outcomes

Endpoint	Univariable		Multivariable		AIC based multivariable	
	HR (95% CI)	P values	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P values
Composite	3.44 (2.06 to 5.76)	<0.001	2.21 (1.21 to 4.04)	0.010	2.76 (1.60 to 4.77)	<0.001
Men	1.35 (0.45 to 4.02)	0.588	0.35 (0.05 to 2.31)	0.275	0.68 (0.18 to 2.62)	0.576
Women	5.03 (2.73 to 9.27)	<0.001	3.69 (1.86 to 7.34)	<0.001	4.29 (2.29 to 8.04)	<0.001
			Interaction	0.003	Interaction	0.008
All-cause mortality	1.77 (0.83 to 3.75)	0.137	1.23 (0.51 to 2.97)	0.642	–	–
Men	1.18 (0.25 to 5.46)	0.835	0.22 (0.02 to 3.06)	0.259	–	–
Women	2.03 (0.85 to 4.83)	0.112	2.11 (0.78 to 5.71)	0.142	–	–
			Interaction	0.409	Interaction	–
Hospitalisation for HF	4.44 (2.21 to 8.94)	<0.001	2.66 (1.13 to 6.25)	0.026	2.78 (1.26 to 6.13)	0.011
Men	0.98 (0.22 to 4.40)	0.983	0.08 (0.00 to 3.76)	0.197	0.12 (0.01 to 1.32)	0.084
Women	11.13 (4.18 to 29.67)	<0.001	7.10 (2.31 to 21.83)	<0.001	9.66 (3.36 to 27.79)	<0.001
			Interaction	<0.001	Interaction	<0.001

In a multivariable model, the adjusted HR of high N-terminal pro-B-type natriuretic peptide (NT-proBNP) as compared with that of low NT-proBNP was calculated by adjusting the following variables with a cross-product term between NT-proBNP groups and sex for the assessment of sex differences, with a *P* for interaction: Clinical Frailty Scale, Society of Thoracic Surgeons score, apical approach, left ventricle (LV) ejection fraction, effective orifice area, mean aortic valve pressure gradient (AVPG), moderate to severe aortic regurgitation, acute kidney injury after TAVI and institution as a stratum. The AIC model selected mean AVPG as a covariate for composite endpoint, and mean AVPG and LV ejection fraction as covariates for heart failure hospitalisation. AIC, Akaike Information Criteria.

NT-proBNP at discharge >4288 pg/mL, should be carefully followed up in outpatient care to ensure hospitalisation for HF and/or decrease the composite of all-cause mortality and HF hospitalisation.

### Limitations

This study had several limitations. First, the NT-proBNP values collected were not measured in a core laboratory but at individual OCEAN-TAVI registry institutions using different methods rather than at a single core laboratory; however, the assay methods were highly comparable. To minimise this problem, we performed multivariable Cox regression analysis, with each institution as a stratum. Second, the decision to hospitalise patients was individually judged by each attending physician, without adherence to any pre-specified criteria. However, we had a consensus indication for HF hospitalisation. Third, our clinical data from the OCEAN-TAVI registry had a relatively low proportion of males as compared with previous studies in Western countries.<sup>3–5 17 25</sup> Lastly, we did not evaluate the impact of NT-proBNP level on admission and compare it with that at discharge. This should be evaluated in future research.

### CONCLUSION

Elevation of NT-proBNP at discharge is associated with 2-year all-cause mortality and hospitalisation for HF after TAVI.

### Author affiliations

<sup>1</sup>Department of Cardiovascular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan

<sup>2</sup>Center for Community-based Healthcare Research and Education, Shimane University, Izumo, Japan

<sup>3</sup>Department of Cardiovascular Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan

<sup>4</sup>Department of Cardiology, New Tokyo Hospital, Matsudo, Japan

<sup>5</sup>Department of Cardiology, Shonan Kamakura General Hospital, Kamakura, Japan

<sup>6</sup>Department of Cardiology, Kishiwada Tokusuyukai Hospital, Kishiwada, Japan

<sup>7</sup>Department of Cardiology, Sendai Kousei Hospital, Sendai, Japan

<sup>8</sup>Department of Cardiology, Ogaki Municipal Hospital, Ogaki, Japan

<sup>9</sup>Department of Cardiology, Saiseikai Yokohama City Eastern Hospital, Yokohama, Japan

<sup>10</sup>Second Department of Internal Medicine, University of Toyama, Toyama, Japan

<sup>11</sup>Department of Cardiovascular Surgery, Tokyo Bay Urayasu-Ichikawa Medical Center, Urayasu, Japan

<sup>12</sup>Department of Cardiology, Kokura Memorial Hospital, Kitakyusyu, Japan

<sup>13</sup>Department of Cardiology, Teikyo University School of Medicine, Toyohashi, Japan

<sup>14</sup>Department of Cardiology, Toyohashi Heart Center, Toyohashi, Japan

<sup>15</sup>Department of Cardiology, Keio University School of Medicine, Tokyo, Japan

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