

# Meta-Analysis of Impact of Baseline N-Terminal Pro-Brain Natriuretic Peptide Levels on Survival After Transcatheter Aortic Valve Implantation for Aortic Stenosis



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We performed a meta-analysis of currently available studies investigating impact of baseline N-terminal pro-brain natriuretic peptide (NT-proBNP) on mortality after transcatheter aortic valve implantation (TAVI) for aortic stenosis (AS). MEDLINE and EMBASE were searched through August 2018 using PubMed and OVID. Studies considered for inclusion met the following criteria: the design was a study researching impact of baseline NT-proBNP levels on survival; the study population was patients underwent TAVI for AS; outcomes included all-cause mortality. For each study, we directly extracted odds ratio (ORs) or hazard ratios (HRs) of mortality (for high vs low baseline NT-proBNP); and generated ORs using mortality rates in both patients with high and low levels of baseline NT-proBNP. Study-specific estimates were combined using inverse variance-weighted averages of logarithmic ORs/HRs in the random-effects model. We identified 16 eligible studies including a total of 3,679 patients who underwent TAVI for AS. Pooled analyses demonstrated that high levels of baseline NT-proBNP were associated with a statistically nonsignificant increase in early (30-day or 2-month) mortality (pooled OR, 1.60; 95% confidence interval, 0.84 to 3.04;  $p = 0.15$ ) and a statistically significant increase in midterm (6-month to 4-year) mortality (pooled OR/HR, 1.88; 95% confidence interval, 1.54 to 2.28;  $p < 0.00001$ ). Although funnel-plot asymmetry suggesting publication bias was detected, adjusting for funnel-plot asymmetry indicated an association of high levels of baseline NT-proBNP with a still significant increase in midterm mortality. In conclusion, high levels of baseline NT-proBNP predict increased midterm, not early, mortality after TAVI for AS. © 2018 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;123:820–826)

In patients with asymptomatic and symptomatic aortic stenosis (AS), brain natriuretic peptide (BNP), and its N-terminal pro-form (NT-proBNP) are independently associated with outcomes.<sup>1</sup> Preoperative BNP and NT-proBNP also are predictors of outcomes after surgical aortic valve replacement for AS.<sup>2,3</sup> A number of studies have recently investigated associations of BNP and NT-proBNP with outcomes after transcatheter aortic valve implantation (TAVI). A meta-analysis<sup>4</sup> (published in 2014) showed that preprocedural proBNP predicted 30-day and 1-year mortality after TAVI; however, extremely wide confidence intervals (CIs) of pooled odds ratios (ORs) suggest low statistical power of the analysis probably due to inclusion of few studies and events. In the present article, we

performed a meta-analysis of currently available studies researching impact of baseline NT-proBNP on survival after TAVI.

## Methods

We performed a meta-analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline (available from <http://www.prisma-statement.org>). All studies investigating impact of baseline NT-proBNP levels on mortality after TAVI for AS were identified using a 2-level search strategy. First, databases including MEDLINE and EMBASE were searched through August 2018 using Web-based search engines (PubMed and OVID). Search terms included *natriuretic peptide(s)*; *percutaneous*, *transcatheter*, *transluminal*, *transarterial*, *transapical*, *transaortic*, *transcarotid*, *transaxillary*, *trans-subclavian*, *transubclavian*, *transiliac*, *transfemoral*, *transiliofemoral*, or *transcaval*; *aortic valve*; and *implantation(s)* or *replacement(s)*. Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles, reviews, and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analyses.

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See page 825 for disclosure information.

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Table 1  
Baseline characteristics and mortality

Study	Reference	Baseline blood sampling	Cut point of NT-proBNP	Patient number			Age (years)	Men (%)	Predicted operative mortality (%)		
				High NT-proBNP	Low NT-proBNP	Total			LES	LE-II	STS
Baldenhofer 2017	6	≤24 h before TAVI	2354 pg/mL (median)	50	50	100	78 ± 8	45.0	17.3 ± 15.3	N/A	N/A
Borz 2014	7	24 h before TAVI	2222.5 pg/ml (median)	118	118	236	85 (80–88.7)	41.9	20.6 ± 11.5	N/A	N/A
Burke 2018	8	N/A	3000 pg/mL (midpoint between upper quartile and median value)	46	96	142	88	54.9	N/A	N/A	8
Elhmidi 2013	9	The day before TAVI	4691 ng/L (upper tertile)	123	250	373	81 (77–85)	37.3	20.4 ± 13.2	N/A	6.17 ± 4.1
Frank 2013	10	24 h before TAVI	4657.00 pg/mL (upper quartile)	26	81	107	81.63 ± 6.34	38.3	21.4 ± 14.0	N/A	N/A
Krau 2015	11	24 h before TAVI	4970.5 pg/mL (upper quartile)	54	163	217	81.8 ± 6.0	44.2	20.1 (13.6–32.6)	6.1 (3.8–10.3)	5.2 (3.5–7.8)
Pfister 2010	12	N/A	1975 pg/ml (median)	15	16	31	84 (80–85)	41.9	12.27 (8.94–19.18)	N/A	N/A
Ribeiro 2014	13	≤48 h before TAVI	2000 pg/mL (determined by ROC curve analysis)	148	185	333	79.6 ± 7.8	53.2	N/A	N/A	7.3 ± 4.9
Spargias 2011	14	≤24 h before TAVI	3520 pg/mL (upper quartile)	27	54	81	82	75.8	26	N/A	13
Stundl 2017	15	The evening (5 p.m.–8 p.m.) before TAVI	8145 pg/mL (upper quartile)	113	348	461	81.3 ± 6.4	50.8	20.1 (12.1–32.7)	5.9 (3.4–10.8)	6.6 (4.2–10.5)
Stähli 2015	16	N/A	NT-proBNP-ratio (measured NT-proBNP value/maximal normal NT-proBNP), 4.2 (median)	122	122	244	84 ± 7.1	50.0	22.0 ± 13.8	7.2 ± 5.9	6.3 ± 4.7
Vale 2018	17	The week before TAVI	1350 pg/mL (determined by ROC curve analysis)	110	41	151	81.5 ± 7.6	37.7	N/A	5.4 (3.4–8.8)	5.3 (3.6–7.5)

Study	Reference	Baseline blood sampling	Follow-up	Patient number			Age (years)	Men (%)	Predicted operative mortality (%)		
				Nonsurvivors	Survivors	Total			LES	LE-II	STS
Hultkvist 2018	18	<24 h before TAVI	1 year	16	110	126	82 (76–85)	47.6	N/A	5.0 (3.0–7.6)	N/A
Sinning 2015	19	1 day before TAVI	1 year	80	230	310	82.0 (77.0–86.0)	53.2	22.2 (13.2–36.8)	5.9 (3.6–11.0)	6.9 (4.6–11.4)

Study	Reference	Baseline blood sampling	Patient number	NT-proBNP levels			Age (years)	Men (%)	Predicted operative mortality (%)		
				Unit	Median	IQR			LES	LE-II	STS
Elhmidi 2013	9	The day before TAVI	373	ng/L	2710	1177–6332	81 (77–85)	37.3	20.4 ± 13.2	N/A	6.17 ± 4.1
Lange 2012	20	N/A	420	ng/L <sup>§</sup>	2680 <sup>§</sup>	1173–6337 <sup>§</sup>	80.3 ± 7.1	36.9	20.17 ± 13.00	N/A	20.17 ± 13.00
Ribeiro 2014	13	≤48 h before TAVI	333	pg/mL	1692	667–3910	79.6 ± 7.8	53.2	N/A	N/A	7.3 ± 4.9
Seiffert 2014	21	N/A	347	pg/mL	3364	1127–9445	80.9 ± 6.2	51.9	22.5 (14.0–37.8)	7.2 (4.1–11.9)	7.2 (4.6–11.4)

Study	Reference	Follow-up	Mortality					Newcastle-Ottawa scale			
			High NT-proBNP		Low NT-proBNP		Relative risk estimate [95% CI]	Selection	Comparability	Exposure/outcome	
			Number	%	Number	%					
Baldenhofer 2017	6	1 year	3	6.0	13	26.0	HR	4.94 [1.41, 17.33]	**	–	**
Borz 2014	7	30 days	7	5.9	4	3.4	OR	1.80 [0.51, 6.31]	**	**	***
		2 years	Overall mortality, 35.1%				HR <sup>†</sup>	2.95 [1.39, 6.25] <sup>‡</sup>			

Table 1 (Continued)

Study	Reference	Follow-up	Mortality						Newcastle-Ottawa scale		
			High NT-proBNP		Low NT-proBNP		Relative risk estimate [95% CI]	Selection	Comparability	Exposure/outcome	
			Number	%	Number	%					
Burke 2018	8	30 days	1	2.2	2	2.1	OR	1.04 [0.09, 11.82]	**	—	—
Elhmidi 2013	9	30 days	6	4.9	16	6.4	OR	0.75 [0.29, 1.97]	**	**	**
		1 year	35	29.2	42	16.8	OR	1.97 [1.18, 3.29]	**	—	*
Frank 2013	10	600 days	9	34.6	12	14.8	HR	2.37 [1.00, 5.64]	**	—	*
Krau 2015	11	2 years	N/A	N/A	N/A	N/A	HR	1.71 [1.03, 2.83]	**	—	*
Pfister 2010	12	2 months	3	20.0	5	31.3	OR	0.55 [0.11, 2.86]	**	—	—
Ribeiro 2014	13	4 years	N/A	70.5	N/A	54.9	HR	1.69 [1.24, 2.30]	**	**	**
Spargias 2011	14	500 days	8	29.6	8	14.8	OR	2.42 [0.79, 7.39]	**	—	*
Stundl 2017	15	30 days	11	9.7	16	4.6	OR	2.24 [1.01, 4.98]	**	—	***
		1 year	43	38.1	76	21.8	HR	1.405 [1.229, 1.607]	**	**	*
Stähli 2015	16	30 days	17	13.9	4	3.3	OR	4.78 [1.56, 14.65]	**	**	*
		1 year	N/A	32.1	N/A	8.5	HR for 3-year mortality <sup>†</sup>	2.95 [1.41, 6.18]	**	—	*
Vale 2018	17	1 year	18	16.4	1	2.4	OR	7.83 [1.01, 60.65]	**	—	*

Study	Reference	NT-proBNP levels				SMD [95% CI] of NT-proBNP levels	OR [95% CI] of mortality	Newcastle-Ottawa scale			
		Unit	Nonsurvivors		Survivors			Selection	Comparability	Exposure/outcome	
			Median	IQR	Median						IQR
Hultkvist 2018	18	ng/L	2525	1465–4260	1990	920–5120	0.18 [–0.35, 0.70]	1.38 [0.53, 3.57]	**	—	**
Sinning 2015	19	pg/mL	5077	1820–14,670	2699	937–7206	0.38 [0.12, 0.63]	1.99 [1.25, 3.16]	**	—	**

Study	Reference	Follow-up	Mortality				Newcastle-Ottawa Scale				
			Number	%	Relative risk estimate [95% CI]		Selection	Comparability	Exposure/outcome		
Elhmidi 2013	9	1 year	77	18	HR <sup>‡</sup>	—	1.02 [1.01, 1.05]	p = 0.006	**	**	**
Lange 2012	20	30 days	40	9.5	HR	for log NT-proBNP	1.26 [0.62, 2.56]	p = 0.5	**	**	*
		6 months	84	20.0	HR <sup>‡</sup>	for log NT-proBNP	1.07 [0.55, 2.06]	p = 0.84	**	**	**
Ribeiro 2014	13	30 days	29	8.7	OR	per 1000-unit increase	1.04 [1.01, 1.08]	p = 0.043	**	**	**
		4 years	116	34.8	HR <sup>‡</sup>	per 1000-unit increase	1.03 [1.01, 1.08]	p = 0.045	**	**	***
Seiffert 2014	21	1 year	84	24.2	HR <sup>‡</sup>	per 1-SD increase	1.57 [1.26, 1.95]	p < 0.001	**	**	***

CI = confidence interval; ES-II = European system for cardiac operative risk evaluation II; HR = hazard ratio; IQR = interquartile range; LES = logistic European system for cardiac operative risk evaluation; N/A = not available; NT-proBNP = N-terminal pro-brain natriuretic peptide; OR = odds ratio; ROC = receiver operating characteristic; SD = standard deviation; SMD = standardized mean difference; STS = Society of thoracic surgeons predicted risk of mortality; TAVI = transcatheter aortic valve implantation.

Continuous values are expressed as number, percentage, mean, mean  $\pm$  SD, and median (IQR).

<sup>†</sup> Adjusted relative risk estimate.

<sup>‡</sup> Calculated from an adjusted hazard ratio for low versus high NT-proBNP.

<sup>§</sup> Pro-brain natriuretic peptide.

\* Identifying “high” quality choices with a “star.”

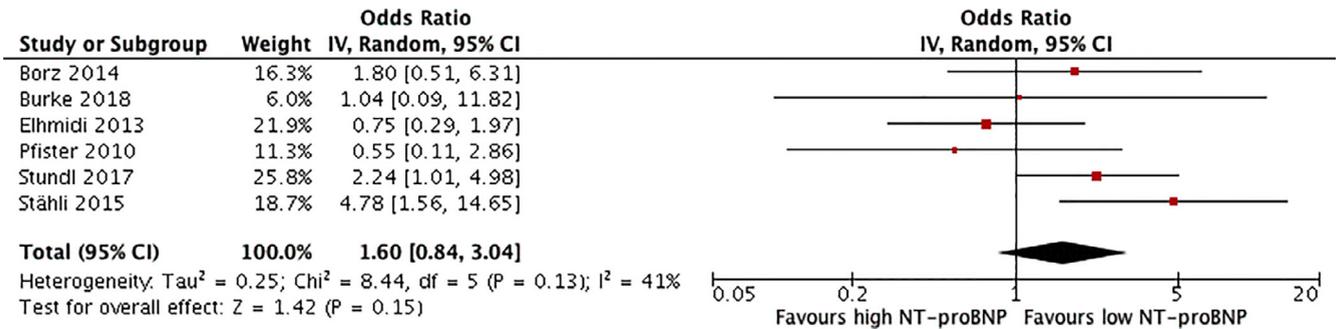


Figure 1. Forest plot of odds ratios of early (30-day or 2-month) mortality after transcatheter aortic valve implantation for high versus low levels of baseline N-terminal pro-brain natriuretic peptide (NT-proBNP). CI = confidence interval; IV = inverse variance.

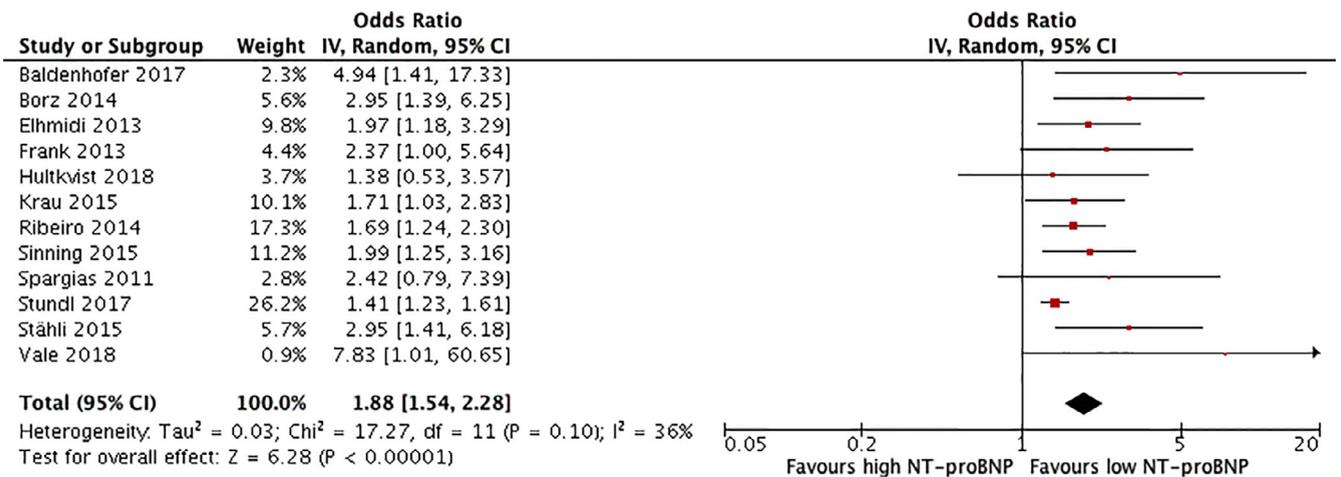


Figure 2. Forest plot of odds and hazard ratios of midterm (6-month to 4-year) mortality after transcatheter aortic valve implantation for high versus low levels of baseline N-terminal pro-brain natriuretic peptide (NT-proBNP). CI = confidence interval; IV = inverse variance.

Studies considered for inclusion met the following criteria: the design was a study researching impact of baseline NT-proBNP levels on survival; the study population was patients underwent TAVI for AS; outcomes included all-cause mortality. Data regarding baseline NT-proBNP levels and mortality rates were abstracted (as available) from each individual study.

For each study, we directly extracted ORs or hazard ratios (HRs) of mortality (for high vs low baseline NT-proBNP); and generated ORs using mortality rates in both patients with high and low levels of baseline NT-proBNP, otherwise using baseline NT-proBNP levels in both nonsurvivors and survivors according to the established formulae<sup>4,5</sup> (Appendix). We examined between-study heterogeneity using the standard chi-square test. Study-specific estimates were combined using inverse variance-weighted averages of logarithmic ORs/HRs in the random-effects model. Sensitivity analyses were performed to evaluate the contribution of each study to the pooled estimate by excluding individual studies one at a time and recalculating the pooled estimates for the remaining studies. Publication bias was assessed graphically using a funnel plot and mathematically using the linear-regression test.

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (available from [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)). All

analyses were conducted using Review Manager version 5.3 (available from <http://tech.cochrane.org/revman>) and Comprehensive Meta-Analysis version 3 (Biostat, Englewood, New Jersey).

## Results

As shown in Supplementary Figure 1, we identified 16 eligible studies<sup>6–21</sup> including a total of 3,679 patients who underwent TAVI for AS (Table 1). Mortality in patients with high and low levels of baseline NT-proBNP was reported in 12 studies,<sup>6–17</sup> and baseline NT-proBNP levels in nonsurvivors and survivors were provided in 2 studies.<sup>18,19</sup> From these 18 studies, ORs and HRs of mortality (for high vs low baseline NT-proBNP) were obtained (Table 1).

Pooled analyses demonstrated that high levels of baseline NT-proBNP were associated with a statistically nonsignificant increase in early (30-day<sup>7–9,15,16</sup> or 2-month<sup>12</sup>) mortality (pooled OR, 1.60; 95% CI, 0.84 to 3.04;  $p = 0.15$ ; Figure 1) and a statistically significant increase in midterm (6-month to 4-year) mortality (pooled OR/HR, 1.88; 95% CI, 1.54 to 2.28;  $p < 0.00001$ ; Figure 2). In cut-point stratified analyses, high levels of baseline NT-proBNP were predictors of a statistically significant increase in midterm mortality in both the subgroups of median cut point<sup>6,7,16</sup> (pooled HR, 3.19;  $p < 0.00001$ ) and upper-quartile cut

### Funnel Plot of Precision by Log hazard ratio

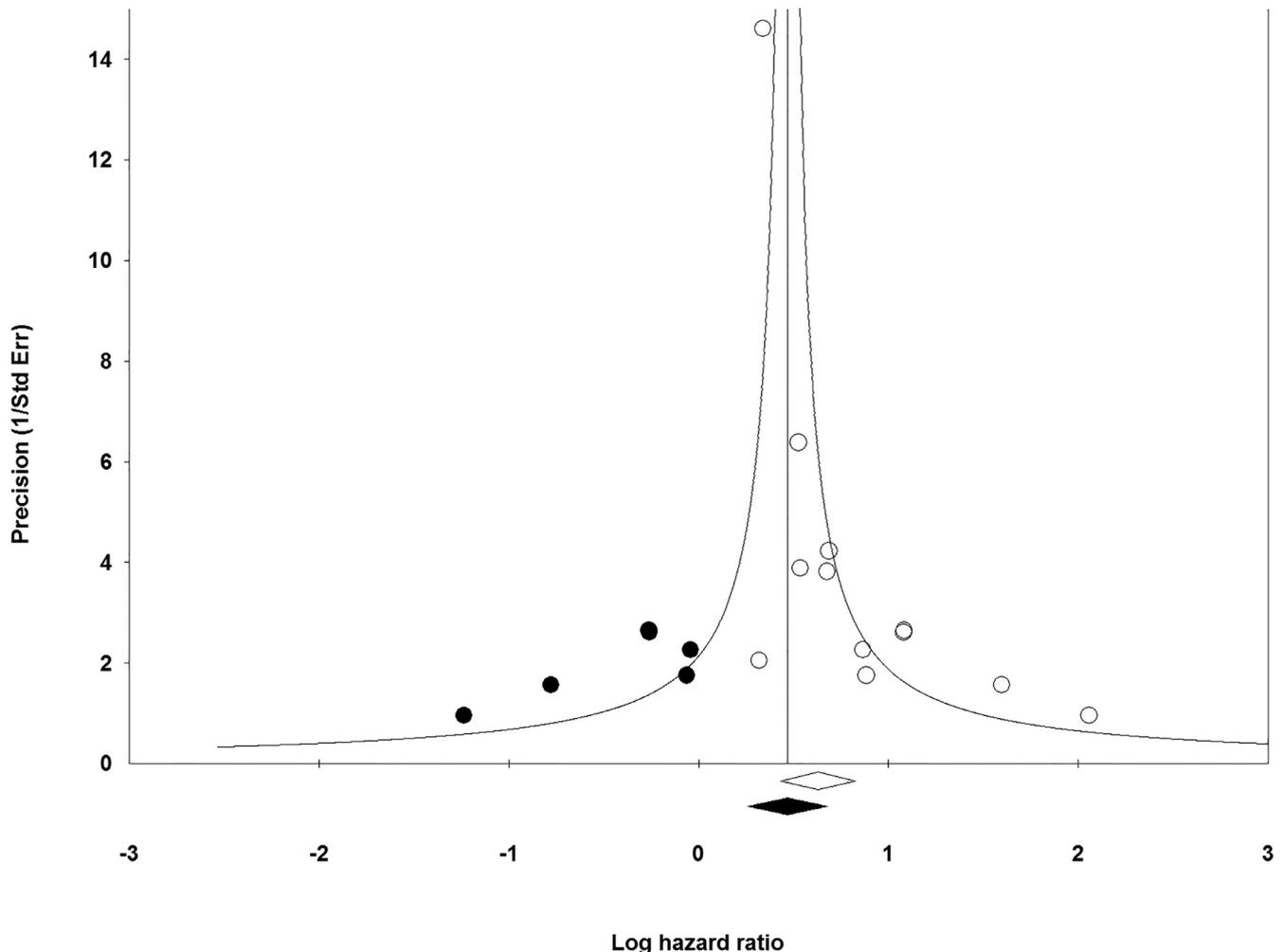


Figure 3. Adjusted funnel plot of odds and hazard ratios of midterm (6-month to 4-year) mortality after transcatheter aortic valve implantation for high versus low levels of baseline N-terminal pro-brain natriuretic peptide, using the trim-and-fill method.<sup>22</sup> Open circles, closed circles, an open lozenge, and a closed lozenge denote identified published studies, hypothetical negative unpublished studies, a summary estimate of identified published studies, and an adjusted summary estimate incorporating hypothetical studies, respectively.

point<sup>10,11,14,15</sup> (pooled OR/HR, 1.45;  $p < 0.00001$ ), with a statistically significant subgroup difference ( $p = 0.002$ ).

To assess the impact of qualitative heterogeneity in study design and patient selection on the pooled effect estimate, we performed several sensitivity analyses for midterm mortality. Excluding any single study from the analysis did not substantially change the result of the primary analysis. To assess publication bias in the analysis of midterm mortality, we generated a funnel plot of the logarithm of effect size (OR/HR) versus the precision (reciprocal of standard error) for each study. There was statistically significant funnel-plot asymmetry (2-tailed  $p = 0.00013$ ; Figure 3), which suggested the potential publication bias. Thus, we undertook a sensitivity analysis using the trim-and-fill method,<sup>22</sup> which conservatively imputes hypothetical negative unpublished studies to mirror the positive studies causing funnel-plot asymmetry. The imputed studies produced a symmetrical funnel plot, and a pooled analysis

incorporating the hypothetical studies continued to indicate a statistically significant association of baseline NT-proBNP with midterm mortality (adjusted pooled OR/HR, 1.60; 95% CI, 1.30 to 1.97;  $p = 0.00001$ ; Figure 3).

Of 4 studies dealing with baseline NT-proBNP levels as continuous (not dichotomous) data (Table 1), a study<sup>13</sup> demonstrated an association of baseline NT-proBNP levels with a statistically significant increase in 30-day mortality, whereas another study<sup>20</sup> indicated no association; 3 studies<sup>9,13,21</sup> demonstrated an association of baseline NT-proBNP levels with a statistically significant increase in midterm (1-year<sup>9,21</sup> and 4-year<sup>13</sup>) mortality, whereas, a study<sup>20</sup> indicated no association with 6-month mortality.

### Discussion

The present analysis identified that high levels of baseline NT-proBNP predicted increased midterm, not

early, mortality after TAVI for AS. To profoundly appreciate risk factors predicting prognosis after TAVI is extremely momentous for clinical practice to precisely select suitable patients and devise a countermeasure to impede complications in high-risk patients. Logistic European System for Cardiac Operative Risk Evaluation, European System for Cardiac Operative Risk Evaluation II, and Society of Thoracic Surgeons Predicted Risk of Mortality can predict merely early mortality, not mid- to long-term mortality. Baseline NT-proBNP may be one of prepotent candidates predicting mid- to long-term mortality after TAVI.

Baseline NT-proBNP combined with other biomarkers may be associated with mortality after TAVI more strongly than NT-proBNP alone. Baldenhofer et al<sup>6</sup> found that the combination of baseline NT-proBNP, midregional pro-adrenomedullin, and midregional pro-atrial natriuretic peptide was a stronger predictor of 1-year mortality (HR, 7.03;  $p = 0.001$ ) than NT-proBNP (HR, 4.94;  $p = 0.013$ ), midregional pro-adrenomedullin (HR, 3.34;  $p = 0.037$ ), and midregional pro-atrial natriuretic peptide alone (HR, 4.94;  $p = 0.013$ ). There may be an association of baseline NT-proBNP with not only mortality (identified in the present meta-analysis) but also cardiovascular events after TAVI. In the study by Baldenhofer et al,<sup>6</sup> baseline NT-proBNP predicted 1-year composite of cardiovascular mortality, nonfatal myocardial infarction, and stroke or transient ischemic attack ( $p = 0.013$ ). Ribeiro et al<sup>13</sup> showed that baseline NT-proBNP was associated with 4-year cardiac mortality ( $p = 0.035$ ), rehospitalization for heart failure ( $p = 0.002$ ), and composite of cardiac mortality and/or rehospitalization for heart failure ( $p = 0.026$ ). Postprocedural, not preprocedural (baseline), NT-proBNP also may be a predictor of mortality after TAVI. In a study by Spargias et al,<sup>14</sup> there was an association of 1- to 3-day NT-proBNP with 500-day mortality ( $p = 0.028$ ). Vale et al<sup>7</sup> found that 1-month NT-proBNP predicted 1-year mortality ( $p = 0.008$ ).

In the study by Ribeiro et al,<sup>13</sup> renal dysfunction ( $p < 0.001$ ), lower left ventricular (LV) ejection fraction ( $p < 0.001$ ), lower stroke volume index ( $p = 0.027$ ), and greater LV mass index ( $p < 0.001$ ) were independently associated with elevated pre-TAVI NT-proBNP levels. A meta-analysis by Eleidet et al<sup>23</sup> showed that lower LV ejection fraction and stroke volume index per se were predictors of 1-year mortality after TAVI. In a study by Gaudino et al,<sup>24</sup> there was an independent association of greater LV mass index per se with 3-year mortality after surgical aortic valve replacement. These findings may strengthen the present results.

A number of potential biomarkers predicting outcomes after TAVI have been investigated, including troponins, C-reactive protein, galectin-3, growth differentiation factor-15, microRNAs, and so on.<sup>25</sup> These biomarkers would be required to play an important role for stratification of procedural risk and prediction of postprocedural outcomes.

The present results should be interpreted with caution in the context of their limitations. First, most of relative risk estimates (ORs/HRs) combined in the present meta-analysis were unadjusted, not adjusted. Thus, the present results are subject to potential measured and unmeasured

confounding. Second, publication bias in favor of low levels of baseline NT-proBNP may militate our results. Although exhaustively searching available literature minimized the risk, the established statistical test detected funnel-plot asymmetry suggesting publication bias. Adjusting for funnel-plot asymmetry, however, demonstrated that high levels of baseline NT-proBNP were still significantly associated with increased midterm mortality. Third, we focused limited outcomes, that is, early/midterm mortality. A future meta-analysis including more original studies and researching other outcomes would be required.

In conclusion, high levels of baseline NT-proBNP are predictors of increased midterm, not early, mortality after TAVI for AS.

## Disclosures

The authors have no conflicts of interest to disclose.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.amjcard.2018.11.030>.

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