Comparison of Long-Term Mortality in Patients Who Underwent Transcatheter Aortic Valve Replacement With or Without Anti-Atherosclerotic Therapy

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Abstract

Background: Atherosclerosis is a risk factor for both aortic stenosis (AS) and coronary artery disease. This study aimed to investigate whether anti-atherosclerotic therapy (AT), defined as the simultaneous use of antiplatelet agents, statins, and renin aldosterone system inhibitors, had long-term clinical benefits for patients who underwent transcatheter aortic valve replacement (TAVR).

Methods: Between October 2013 and May 2017, 2,518 patients (31% men; median age, 85 years) who underwent TAVR in 14 Japanese centers were divided into two groups: patients who were prescribed anti-atherosclerotic therapy (AT, n = 567) and patients who were not (no AT, n = 1,951). The median follow-up period for this cohort was 693 days (interquartile range, 389–870 days).

Results: Compared to no AT group, AT group was associated with significantly lower 2-year all-cause mortality (11.7% vs. 16.5%; log-rank p = 0.002) and 2-year cardiovascular mortality rates (3.5% vs. 6.0%; log-rank p = 0.017). In a propensity-matched cohort (n = 495 each; median follow-up, 710 days [IQR, 394−896 days]), patients in AT group had a lower prevalence of 2-year cardiovascular mortality (3.8% vs. 6.2%, log-rank p = 0.024) than that in the no AT group. In the multivariate stepwise regression analysis, AT was a significant predictor of cardiovascular mortality

(hazard ratio 0.45; 95% confidence interval 0.25-0.80; $p = 0.007$).

Conclusion: AT may improve survival in post-TAVR patients. Future studies are necessary to identify an optimal treatment regimen to improve long-term outcomes after TAVR.

Introduction

Transcatheter aortic valve replacement (TAVR) is an approved treatment for low-risk patients with severe aortic stenosis (AS) [1,2]. As TAVR is indicated for low-risk patients, development of an optimal postoperative therapy that reduces mortality and prolongs the durability of the transcatheter heart valve is essential. Although several medical therapies offer improved outcomes following TAVR, adjunct medical treatment is not indicated for post-TAVR patients [3–7]. AS has been shown to share risk factors with atherosclerosis [8–14]. Therefore, patients, especially elderly patients, undergoing TAVR are at risk for life-threatening cardiovascular diseases. Consequently, cardiovascular events account for more than one-third of deaths in post-TAVR patients [15]. Anti-atherosclerotic therapy (AT), which involves a combination of antiplatelet agents, renin-angiotensin system (RAS) inhibitors, and statins, is a pivotal medical therapy for coronary artery disease (CAD) [16–18]. Given that patients undergoing TAVR are at cardiovascular risk, it is hypothesized that AT could also provide benefits for post-TAVR patients. This study aimed to investigate whether AT has long-term clinical benefits in patients undergoing TAVR.

Methods

All patients with severe AS who underwent TAVR at 14 Japanese centers (Teikyo University Hospital, Kokura Memorial Hospital, Sendai Kosei Hospital, Yokohama City Eastern Hospital, New Tokyo Hospital, Shonan Kamakura General Hospital, Toyama University Hospital, Tokyo Bay Urayasu Ichikawa Medical Center, Osaka City University Hospital, Ogaki Municipal Hospital, Kishiwada Tokushukai Hospital, Toyohashi Heart Center, Nagoya Heart Center, and Keio University Hospital) between 2013 and 2017 were prospectively included in our transcatheter aortic valve implantation (TAVI) registry (Optimized CathEter vAlvular iNtervention [OCEAN-TAVI] registry) [4,19,20]. The registry was established to document the intraoperative and postoperative outcomes of patients who underwent TAVR using the Edwards Sapien XT/Sapien 3 prosthesis (Edwards Lifesciences, Irvine, CA) or the Medtronic Corevalve/Evolut R prosthesis (Medtronic, Minneapolis, MN).

The study protocol was approved by the local institutional review board and registered with the University Hospital Medical Information Network (no.: UMIN000020423). Written informed consent was obtained from all the patients before they underwent TAVR. Between October 2013 and May 2017, a total of 2,588 patients with severe AS who underwent TAVR were enrolled in the OCEAN-TAVI registry. Of these, 2,518 patients survived to discharge and were included in this study. The

inclusion criteria were described previously [19,20]. The prosthesis size, type, and approach site were determined based on findings from pre-procedural echocardiography and multi-slice computed tomography (CT). The success and complications of TAVR were evaluated according to the Valve Academic Research Consortium 2 criteria [21]. To evaluate prosthetic valve dysfunction, structural valve deterioration (SVD) was determined based on hemodynamic and morphologic changes of the prosthetic valve according to a previously described standardized definition [22].

The survival-to-discharge cohort constituted the study population and was divided into two groups according to AT usage (Figure 1). AT was defined as the simultaneous use of antiplatelet therapy, RAS inhibitors, and statins. Antiplatelet agents included aspirin 81 or 100 mg, clopidogrel 75 mg, and prasugrel 3.75 mg. Both single antiplatelet therapy and dual antiplatelet therapy were accounting for usage of antiplatelet drug. RAS inhibitors included angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers. The degree of perivalvular leakage after TAVR was measured in accordance with current guidelines and translated into semiquantitative grades: none, trace, mild, moderate, or severe [23]. Statins comprised all brands of lipid-lowering medications that are available in Japan. Dyslipidemia was defined as presence of high low-density lipoprotein, low high-density lipoprotein, and

high triglyceride levels and use of drugs for lipid disorders. The cut-off values of each disease were higher than 140mg/dl for high low-density lipoprotein, less than 40mg/dl for low high-density lipoprotein and higher than 150mg/dl for high triglycerides respectively.

The primary endpoint was cardiovascular mortality 2 years post-TAVR. Follow-up data were recorded during outpatient visits or by telephone interviews annually post-TAVR. The secondary endpoint was all-cause mortality 2 years post-TAVR and readmission for heart failure or stroke. SVD assessed 2 years after TAVR was also evaluated as a secondary endpoint.

Quantitative variables are expressed as mean ± standard deviation or as median and interquartile range (IQR, 25-75%), as appropriate. Qualitative variables are expressed as numeric values and percentages. Quantitative variables were compared using a Wilcoxon rank-sum test, depending on the variable distribution. The X^2 test or Fisher's exact test was used to compare the qualitative variables. Kaplan-Meier analysis was performed using log-rank tests to compare survival rates between the AT and no AT groups. As patients were not prescribed AT during the procedure and there was potential selection bias in those who had been prescribed AT, propensity score matching was performed to create a cohort of patients with similar characteristics in the AT and

control groups. The propensity score was developed using a logistic regression model based on a non-parsimonious approach, and the following clinical variables were included in the analysis: age, sex, body mass index (BMI), New York Heart Association [NHYA] functional class III/IV, clinical frailty scale, prior CAD, prior cerebrovascular disease, diabetes mellitus, hypertension, dyslipidemia, chronic obstructive pulmonary disease, atrial fibrillation, chronic kidney disease, peripheral artery disease, beta blockers, left ventricular (LV) ejection fraction, and annulus area calculated by multidetector multi-slice CT. Matching was performed in a 1:1 ratio by greedy matching using a caliper width of 0.1 SD. A log-rank test was also performed to evaluate the association between AT and 2-year all-cause mortality and 2-year cardiovascular mortality in the matched cohort. Cox multivariable regression analysis was performed to identify the independent predictors of cardiovascular mortality. Covariates were selected based on their clinical importance and their potential to confound the relationship between AT and cardiovascular mortality. Candidate variables were included if they satisfied the entry criterion of $p < 0.10$ in the univariate analysis. The Cox multivariable model was built using stepwise selection. A p-value < 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 19.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of the study population are presented in Table 1. Significant differences were observed between the AT and no AT groups in terms of BMI (22.8 kg/m^2 IQR [20.5-25.0] vs 21.8 kg/m^2 IQR [19.5-24.2], $p < 0.001$), body surface area (1.42 m^2 IQR [1.3-1.6] vs 1.40 m^2 IQR [1.3-1.5], $p = 0.009$), history of hypertension (88.1% vs 73.5%, $p < 0.001$), dyslipidemia (71.6% vs. 34.3%, $p < 0.001$), diabetes mellitus (26.2% vs 19.9%, $p = 0.002$), atrial fibrillation (12.0% vs 23.3%, $p = 0.002$) and aortic annulus area calculated by CT (384.1 mm^2 IQR [341.0–432.2] vs. 390.2 mm^2 IQR [349.0-441.0], $p = 0.035$).

The median follow-up duration for this cohort was 693 days (IQR, 389–870 days). The overall mortality rate 2 years post-TAVR in the unadjusted cohort was 13.2%. Among all patients, the AT group had significantly lower rates of 2-year cardiovascular mortality (3.5% vs. 6.0%; log-rank $p = 0.017$) and 2-year all-cause mortality (11.7% vs. 16.5%; log-rank $p = 0.002$) than those of the no AT group (Figure 2).

In the propensity-matched cohort, 495 patients in the AT and no AT groups were analyzed. There were no differences in baseline characteristics between the AT and no AT groups in the adjusted cohort except for prosthetic valve regurgitation (0.8% vs 3.2%, $p = 0.007$) (Table 2). The overall mortality rate 2 years post-TAVR in the matched cohort was 10.9%. Patients treated with adjunct AT had a significantly lower rate of

2-year cardiovascular mortality (3.8% vs. 6.2%, log-rank $p = 0.024$) than that of patients not prescribed AT (Figure 3b). Univariate analysis revealed that AT was associated with a low mortality rate (hazard ratio [HR] 0.45, 95% confidence interval [CI] 0.25-0.81, $p = 0.008$, Table 3). The multivariate Cox regression model demonstrated that AT (HR 0.45, 95% CI 0.25-0.80; $p = 0.007$), male sex (HR 2.02, 95% CI 1.16-3.54; $p = 0.013$), and NYHA heart failure functional class III/IV (HR 2.81, 95% CI 1.53-5.15 $p = 0.001$) were the only independent predictors of cardiovascular mortality (Table 3). Regarding secondary outcome analysis, there were trend for lower 2-year all-cause mortality rate (11.8% vs. 14.7%, log-rank $p = 0.091$) and readmission for heart failure (9.7% vs. 21.3%, log-rank $p = 0.074$) in the AT group than those in the no AT group, although these differences were not statistically significant. (Figure 3a, 4a) In contrast, there were no significant differences in stroke (8.6% vs. 9.1%, log-rank $p = 0.398$) and SVD between the two groups (4.6% vs. 5.3%, $p = 0.770$) in the adjusted cohort. (Figure 4b) Likewise, the progression of mean transcatheter heart valve pressure gradients and the indexed effective orifice area in the 2-year echocardiographic follow-up images were comparable between the two groups (Figure 5).

Discussion

This study demonstrated that patients receiving AT, which consisted of antiplatelet agents, RAS inhibitors, and statins, were associated with a lower incidence of 2-year all-cause mortality and cardiovascular mortality than those of patients who did not receive AT. To the best of our knowledge, this is the first study to evaluate the influence of AT on long-term mortality in post-TAVR patients.

Previous studies have demonstrated that several pharmaceutical treatments post-TAVR are associated with reduced mortality and cardiovascular events. Inohara et al. revealed that RAS inhibitor therapy post-TAVR reduced 1-year all-cause mortality rate and readmission due to heart failure in an adjusted cohort [3]. In addition, Ochiai et al. reported a greater 2-year survival rate and LV mass regression index in patients treated with RAS inhibitor therapy post-TAVR than in patients treated without RAS inhibitor therapy [4]. Even with a longer follow-up period of 3 years, Rodriguez-Gabella et al. reported lower cardiovascular mortality rate and fewer cardiovascular events for patients with an RAS inhibitor prescription at discharge than those seen for patients without an RAS inhibitor prescription in a matched cohort [5]. Prescriptions of ACE inhibitors and angiotensin II receptor blockers for high-risk patients with atherosclerosis was associated with a lower incidence of cardiovascular events [24,25]. Given that the use of RAS inhibitors is helpful for prophylaxis among

high-risk patients, it is conceivable that patients undergoing TAVR may benefit from the use of RAS inhibitors as well.

As in CAD, statin treatment diminishes all-cause and cardiovascular mortality post-TAVR. Poghni et al. and Chetan et al. reported that statin therapy following TAVR was associated with a low 2-year all-cause mortality rate [6,7]. Previous studies reported that statin therapy did not delay the progress of degenerative AS or bioprosthetic degeneration [26–28].

Therefore, the influence of statin therapy in patients undergoing TAVR has been attributed to other mechanisms. In patients at high risk of ischemic heart disease, statins were associated with low rates of mortality and cardiovascular events [29]. Considering that AS is a common complication of CAD, statins appear to contribute to lowering of incidence of mortality and cardiovascular events post-TAVR in the same manner.

Although the effect of antiplatelet therapy in patients undergoing TAVR remains uncertain, guidelines recommend the prescription of antiplatelet agents, as is the case with surgical bioprosthetic valves [30,31]. Aspirin is beneficial for the reduction of future cardiovascular events in patients with CAD [32]. However, given that patients undergoing TAVR are at high risk for bleeding, whether antiplatelet therapy

reduces the risk of long-term cardiovascular events is unknown. An ideal antiplatelet therapy post-TAVR has not been sufficiently investigated. Hence, the optimal type and dose of antiplatelet agents and adequate duration of antiplatelet therapy must be clarified.

Optimal medical therapy is a widely accepted strategy for CAD [16–18]. Antiplatelet agents, RAS inhibitors, and statins are pivotal medications for optimal medical therapy. The disease process of AS is like that of atherosclerosis, and severe AS is frequently accompanied by CAD [8–13]. This suggests that risk factors related to AS progression may also affect the progression of atherosclerosis. Therefore, it is plausible that AT also benefits post-TAVR patients. Usage of AT was associated with lower all-cause death and cardiovascular death in the same way. Accordingly, reduction of all-cause mortality in the patients prescribed AT would be mostly result from decreased cardiovascular mortality. As there were no significant differences in prosthetic valve deterioration between the AT and no AT groups in this study period, the advantages of AT did not stem from SVD prevention. AT might affect SVD in a long-term follow-up period; hence, further studies are required.

As TAVR has become a common procedure, and TAVR devices have become safer than before, TAVR is more frequently indicated for patients at low risk from AS

and CAD than before [1,2,33,34]. Since long-term mortality rate following TAVR remains high, assessment of factors that affect long-term outcomes following TAVR is mandatory [15]. Further investigation of treatment strategies that may provide long-term beneficial outcomes post-TAVR is essential. In this retrospective cohort study, AT post-TAVR was independently associated with a low risk of all-cause and cardiovascular mortality. Although the mechanisms of reduced mortality in patients with AT were not clarified in this study, AT might improve the long-term outcomes of post-TAVR patients. To confirm the effect of AT post-TAVR, further investigations of adjunctive medical therapies that provide improved outcomes for the post-TAVR population are necessary.

This study has several limitations. First, this was a retrospective, nonrandomized, observational study conducted with a TAVR cohort. Despite the propensity score-matched cohort analysis for diminishing the baseline differences and the influence of potential confounders, the possibility of residual confounding or undetected bias could not be eliminated. It is plausible that prognosis of patients with AT may differ from those of patients without AT. Further investigations which confirm the impact of AT itself would be required. Second, beta-blockade therapy is also a component of optimal medical therapy for CAD. However, beta-blockade therapy for

symptomatic severe AS patients is traditionally avoided as it induces LV dysfunction and bradycardia and increases fall risk in older populations. Beta-blockade therapy would also be ill advised for post-TAVR patients since beta blockers might induce conduction disturbances. The effect of beta-blockade therapy among post-TAVR patients was observed only in specific patient populations [35]. Therefore, we did not add beta-blockers to AT in this cohort. Finally, although statins and RAS inhibitors are generally medications of choice for chronic conditions, and guidelines recommend continuing antiplatelet agents permanently, the accurate duration, dose, and use of AT both prior to and post-TAVR could not be clarified.

Conclusion

AT was associated with favorable outcomes in post-TAVR patients and might be considered as an adjunctive therapy in this population. AT may improve the survival of post-TAVR patients. Future studies are necessary to identify an optimal treatment regimen to improve long-term outcomes post-TAVR.

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Disclosures

Conflict of Interest: The authors declare that they have no conflict of interest.

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Figure Legends

Figure 1. Study flow diagram

AT, patients treated with anti-atherosclerotic therapy; no AT, patients not treated with anti-atherosclerotic therapy; TAVR, transcatheter aortic valve replacement

Figure 2. Kaplan-Meier curves of 2-year all-cause mortality and cardiovascular mortality in the overall cohort.

(a) 2-year all-cause mortality and (b) cardiovascular mortality of patients treated with AT (n = 567) compared with those of patients treated without AT (n = 1,951).

Abbreviations: AT, patients treated with anti-atherosclerotic therapy; no AT, patients treated without anti-atherosclerotic therapy.

Figure 3. Kaplan-Meier curves of 2-year all-cause mortality and cardiovascular mortality in the adjusted cohort.

(a) 2-year all-cause mortality and (b) cardiovascular mortality of patients treated with AT (n = 495) compared with those of patients treated without AT (n = 495).

Abbreviations: AT, patients treated with anti-atherosclerotic therapy; no AT, patients not treated with anti-atherosclerotic therapy.

Figure 4. Kaplan-Meier curves of readmission for heart failure and stroke in the adjusted cohort.

(a) readmission for heart failure and (b) stroke of patients treated with AT (n = 495) compared with those of patients treated without AT (n = 495).

Abbreviations: AT, patients treated with anti-atherosclerotic therapy; no AT, patients not treated with anti-atherosclerotic therapy.

Figure 5. Comparison between the AT group and no AT group: (a) pressure gradient of aortic valve or transcatheter heart valve and (b) indexed aortic valve area or effective orifice area during the procedure, at discharge, and at 1 year and 2 years post-TAVR in the adjusted cohort.

Abbreviations: AT, patients treated with anti-atherosclerotic therapy; no AT, patients not treated with anti-atherosclerotic therapy; AV, aortic valve; iAVA, indexed aortic valve area; iEOA, indexed effective orifice area; PG, pressure gradient; THV, transcatheter heart valve.

Table 1. Baseline Characteristics

Characteristics	Overall (n = 2518)	AT (n = 567)	no AT (n = 1971)	p value
Sex (male)	769 (30.5%)	171 (30.1%)	598 (30.3%)	0.823
Age	85 (81-88)	84 (81-88)	85 (81-88)	0.475
BMI (kg/m^2)	22.0 (19.6-24.3)	22.8 (20.5-25.0)	21.8 (19.5-24.2)	<0.001
BSA (m^2)	1.4 (1.3-1.5)	1.42 (1.3-1.6)	1.40 (1.3-1.5)	0.009
NYHA class 3-4 Heart Failure	1272 (50.5%)	282 (49.7%)	990 (50.2%)	0.673
CFS ≧ 7	89 (3.5%)	13 (2.3%)	76 (3.9%)	0.069
CAD	915 (36.3%)	284 (50.0%)	631 (32.0%)	0.142
PAD	353 (14.0%)	81 (14.2%)	272 (13.8%)	0.835
COPD	366 (14.5%)	82 (14.5%)	284 (14.6%)	0.955
Prior stroke	285 (11.3%)	61 (10.7%)	224 (11.3%)	0.632
AF	529 (21.0%)	68 (12.0%)	461 (23.3%)	<0.001
Hypertension	1934 (76.8%)	500 (88.1%)	1434 (73.5%)	<0.001
Dyslipidemia	1083 (43.0%)	406 (71.6%)	677 (34.3%)	<0.001
CKD	1749 (69.5%)	408 (72.0%)	1341 (68.0%)	0.142
Diabetes Mellitus,	542 (21.5%)	149 (26.2%)	393 (19.9%)	0.002

Beta blocker	859 (34.1%)	210 (37.0%)	649 (33.0%)	0.095
Statin	1038 (41.2%)	567 (100%)	471 (24.0%)	<0.001
RAS-I	1344 (53.4%)	567 (100%)	777 (39.4%)	<0.001
Aspirin	330 (13.1%)	78 (13.8%)	252 (12.8%)	0.602
P2Y12 inhibitor	109 (4.3%)	24 (4.2%)	85 (4.3%)	0.898
DOAC	110 (4.4%)	0 (0%)	110 (5.6%)	<0.001
Vitamin K antagonists	82 (3.3%)	0 (0%)	82 (4.2%)	<0.001
DAPT	1361 (54.1%)	383 (67.5%)	978 (49.6%)	<0.001
DAPT with anticoagulant therapy	35 (1.4%)	9 (1.6%)	26 (1.3%)	0.648
SAPT with anticoagulant therapy	385 (15.3%)	73 (12.9%)	312 (15.8%)	0.069
eGFR	50.6 (38.0-63.1)	50.0 (38.6-62.1)	50.8 (37.8-63.6)	0.572
Euro II score (%)	6.2 (2.3-5.9)	3.6 (2.4-5.7)	3.7 (2.3-6.0)	0.664
Euro score (%)	12.8 (8.4-20.7)	12.8 (8.4-20.9)	12.8 (8.4-20.6)	0.904

STS score (%)	6.5 (4.5-9.4)	6.25 (4.5-9.1)	6.6 (4.5-9.5)	0.222
CT-aortic annulus area	389.2 (346.8-440.0)	384.1 (341.0-432.2)	390.2 (349.0-441.0)	0.035
Transthoracic echocardiography parameter				
LVEF, median	62.0 (52.6-68.0)	62.0 (53.0-67.0)	62.0 (52.0-68.0)	0.879
Mean pressure gradient	47.0 (37.0-61.0)	47.0 (38.0-62.0)	47.0 (37.0-61.0)	0.475
Indexed AVA, median	0.43 (0.36-0.50)	0.44 (0.36-0.50)	0.43 (0.36-0.50)	0.147
Procedural characteristics				
TF approach	2125 (84.4%)	468 (82.5%)	1657 (84.1%)	0.167
TA approach	331 (13.1%)	80 (14.1%)	251 (12.7%)	0.440
TI approach	30 (11.9%)	10 (1.8%)	20 (1.0%)	0.154
TSC approach	18 (0.7%)	5 (0.8%)	13 (0.6%)	0.592
DA approach	13 (0.5%)	4 (0.7%)	9 (0.4%)	0.475
Valve Size	23 (23-26)	23 (23-26)	23 (23-26)	0.160
Self-expanding valve	331 (13.1%)	78 (13.8%)	253 (12.8%)	0.625

Balloon-expanding valve	2187 (86.9%)	489 (86.2%)	1698 (86.1%)	0.922
Postprocedural echocardiography				
Indexed EOA	1.15 (0.98-1.35)	1.11 (0.94-1.32)	1.16 (0.99-1.36)	0.209
Mean PG	10 (8.0-13.0)	11 (8.0-13.0)	10 (7.0-13.0)	0.319
MR≥moderate	152 (6.0%)	23 (4.0%)	129 (6.5%)	0.024
AR≥moderate	45 (1.8%)	6 (1.0%)	39 (2.0%)	0.135

The study population was stratified by patients with or without anti-atherosclerotic therapy. Values are expressed as total number (percentage) or median (interquartile range).

Abbreviations: AF = atrial fibrillation; AVA = aortic valve area; AR = aortic regurgitation; AT = patients with anti-atherosclerotic therapy; no AT = patients without anti-atherosclerotic therapy; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; CFS = clinical frailty scale; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DA = direct aortic approach; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MR = mitral regurgitation, NYHA = New York Heart Association; PAD = peripheral artery disease; PG = pressure gradients; RAS-I = renin-angiotensin system inhibitors; STS = Society of Thoracic Surgeons; TA = transfemoral; TF = transfemoral; THV =

transcatheter heart valve; TI = transiliac; TSC = transsubclavian

Table 2 Baseline characteristics in matched cohort

Characteristics	Overall (n = 990)	AT (n = 495)	no AT (n= 495)	p value
Sex (male)	295 (29.8%)	145 (29.2%)	150 (30.3%)	0.728
Age	85 (81-85)	85 (81-88)	85 (81-88)	0.954
BMI (kg/m^2)	22.7 (20.2-25.1)	22.8 (20.3-24.8)	22.7 (20.2-25.3)	0.983
BSA (m^2)	1.4 (1.3-1.6)	1.4 (1.3-1.6)	1.4 (1.3-1.6)	0.783
NYHA3-4	475 (48.0%)	238 (48.0%)	237 (47.9%)	0.949
CFS ≧ 7	25 (2.5%)	12 (2.4%)	13 (2.6%)	0.839
CAD	469 (47.4%)	234 (47.3%)	235 (47.5%)	0.949
PAD	136 (13.7%)	73 (14.7%)	63 (12.7%)	0.356
COPD	148 (14.9%)	72 (14.5%)	76 (15.4%)	0.721
Stroke	105 (10.6%)	54 (10.9%)	51 (10.3%)	0.757
AF	135 (13.6%)	64 (12.9%)	71 (14.3%)	0.517
Hypertension	855 (86.3%)	433 (87.4%)	422 (85.2%)	0.308
Dyslipidemia	678 (68.4%)	337 (68.1%)	341 (68.9%)	0.784
Chronic kidney disease	718 (72.5%)	351 (70.9%)	367 (74.1%)	0.255
Diabetes Mellitus	249 (25.1%)	129 (26.1%)	120 (24.2%)	0.510
Beta blocker	370 (37.3%)	181 (36.6%)	189 (38.2%)	0.599
Statin	671 (67.8%)	495 (100%)	176 (35.6%)	<0.001
RAS-I	691 (69.8%)	495 (100%)	196 (39.6%)	<0.001

Aspirin	123 (12.4%)	69 (13.9%)	54 (10.9%)	0.148
P2Y12 inhibitor	49 (4.9%)	23 (4.6%)	26 (5.3%)	0.660
DOAC	28 (2.8%)	0 (0%)	28 (5.7%)	<0.001
Vitamin K antagonists	15 (1.5%)	0 (0%)	15 (3.0%)	<0.001
DAPT	611 (61.7%)	327 (66.1%)	284 (57.4%)	0.005
DAPT with anticoagulant therapy	14 (1.4%)	8 (1.6%)	6 (1.2%)	0.590
SAPT with anticoagulant therapy	124 (12.5%)	68 (13.7%)	56 (11.3%)	0.249
eGFR	49.6 (38.5-61.8)	50.0 (39.0-62.7)	49.4 (38.0-61.0)	0.405
EuroII score (%)	3.6 (2.3-5.8)	3.6 (2.4-5.6)	3.8 (2.1-6.0)	0.543
Euro score (%)	12.8 (8.0-20.4)	12.7 (8.2-20.5)	12.8 (7.9-20.2)	0.981
STS score (%)	6.3 (4.5-9.2)	6.2 (4.5-9.0)	6.5 (4.5-9.4)	0.488
CT-aortic annulus area	384.1 (343.6-429.0)	385.6 (341.2-432.0)	383.5 (345.1-423.5)	0.830
Transthoracic echocardiography parameter				
LVEF	62.0 (52.9-67.3)	62.0 (53.0-67.0)	62.0 (52.0-67.4)	0.925
Mean pressure gradient	47 (37.8-60.0)	47 (38.0-60.0)	47 (37.0-60.0)	0.904
Indexed AVA	0.43 (0.37-0.50)	0.44 (0.36-0.51)	0.43 (0.38-0.50)	0.463
Postprocedural echocardiography				
Indexed EOA	1.13 (0.96-1.34)	1.12 (0.95-1.32)	1.14 (0.96-1.35)	0.473
Mean PG	10 (8-13)	11 (8-13)	10 (8-13)	0.023

MR≥moderate	48 (4.8%)	30 (6.1%)	18 (3.6%)	0.075
AR≥moderate	20 (2.0%)	4 (0.8%)	16 (3.2%)	0.007

Study population was stratified by patients with or without anti-atherosclerotic therapy. Values are expressed as total number (percentage) or median (interquartile range).

AF = atrial fibrillation; AVA = aortic valve area; AR = aortic regurgitation, AT = patients with anti-atherosclerotic therapy; no AT = patients without anti-atherosclerotic therapy; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; CFS = clinical frailty scale; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EOA = effective orifice area, LVEF = left ventricular ejection fraction; MR = mitral regurgitation, NYHA = New York Heart Association; PAD = peripheral artery disease; PG = pressure gradients; RAS-I = renin-angiotensin system inhibitors; STS = Society of Thoracic Surgeons

Table 3 Multivariate Cox proportional hazard regression analyses for cardiovascular mortality in matched cohort

	Univariate		**Multivariate**	
Variable	HR (95% CI)	p value	HR (95% CI)	p value

Age	1.03 (0.97-1.09)	0.342		
Male sex	1.98 (1.13-3.46)	0.017	2.02 (1.16-3.54)	0.013
BMI	0.98 (0.90-1.06)	0.571		
CFS ≧ 7	2.69 (0.84-8.68)	0.097		
NYHA 3-4	2.71 (1.48-4.96)	0.001	2.81 (1.53-5.15)	0.001
Diabetes Mellitus	1.63 (0.92-2.91)	0.096		
Hypertension	1.16 (0.49-2.71)	0.740		
COPD	0.91 (0.41-2.02)	0.809		
AF	0.99 (0.45-2.11)	0.989		
Dyslipidemia	0.76 (0.43-1.34)	0.758		
CAD	1.40 (0.80-2.45)	0.239		
Chronic kidney disease	1.25 (0.66-2.34)	0.495		
AT	0.45 (0.25-0.81)	0.008	0.45 (0.25-0.80)	0.007
PAD	0.972 (0.44-2.16)	0.945		
Prior Stroke	0.97 (0.39-2.45)	0.949		
LVEF	0.99 (0.97-1.01)	0.343		
CT-aortic annulus area	1.00 (0.99-1.00)	0.207		

Abbreviations: AF = atrial fibrillation; AT = anti-atherosclerotic therapy; BMI = body mass index; CAD = coronary artery disease; CFS = clinical frailty scale; CKD = chronic

kidney disease; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CT = computed tomography; HR = hazard ratio; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PAD = peripheral artery disease

Figure 1.

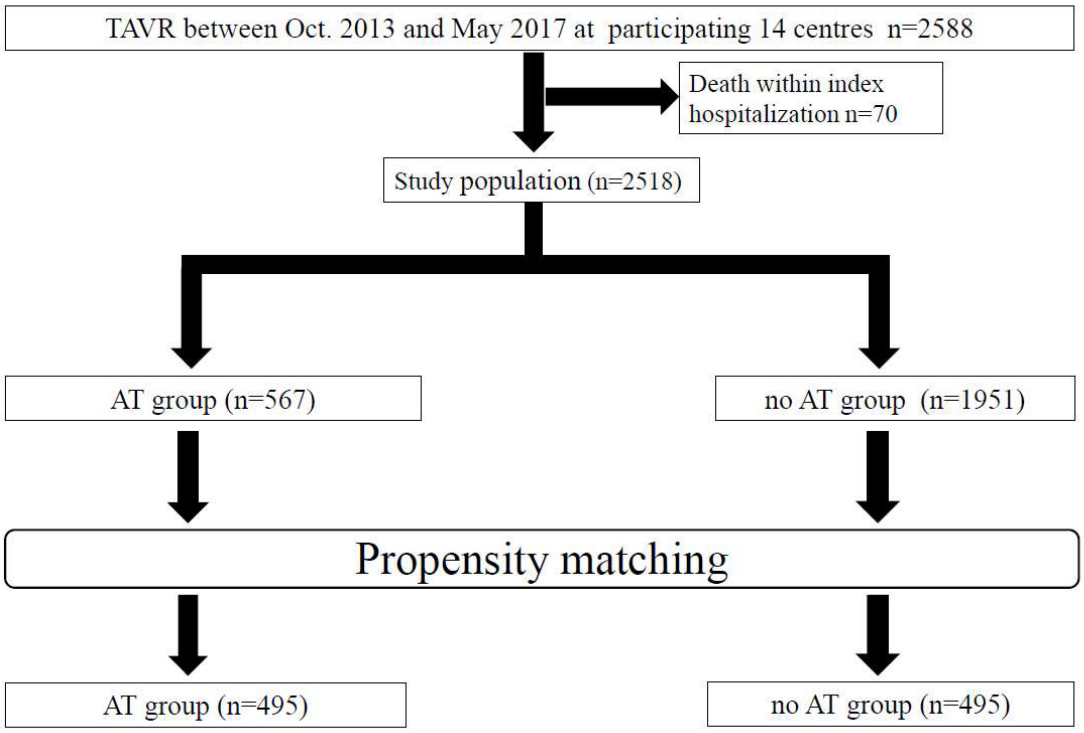


Figure 2.

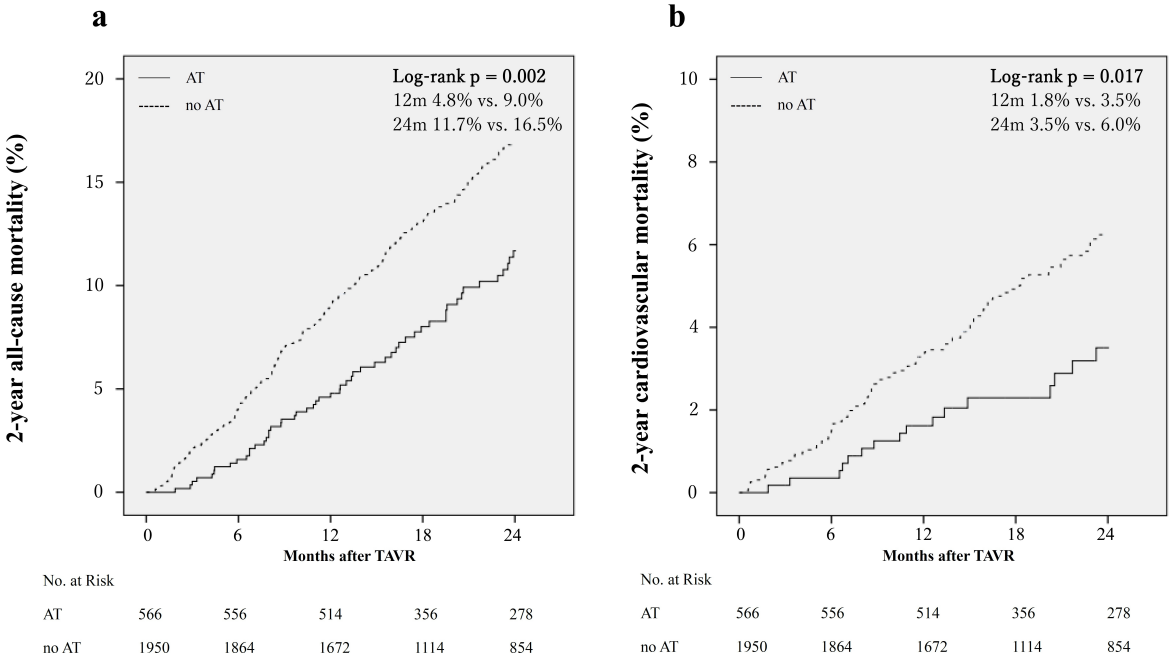

a
AT
no AT
Log-rank p = 0.002
12m 4.8% vs. 9.0%
24m 11.7% vs. 16.5%
2-year all-cause mortality (%)
20
15
10
5
0
0
6
12
18
24
Months after TAVR
No. at Risk
AT 566 556 514 356 278
no AT 1950 1864 1672 1114 854
b
AT
no AT
Log-rank p = 0.017
12m 1.8% vs. 3.5%
24m 3.5% vs. 6.0%
2-year cardiovascular mortality (%)
10
8
6
4
2
0
0
6
12
18
24
Months after TAVR
No. at Risk
AT 566 556 514 356 278
no AT 1950 1864 1672 1114 854

Figure 3.

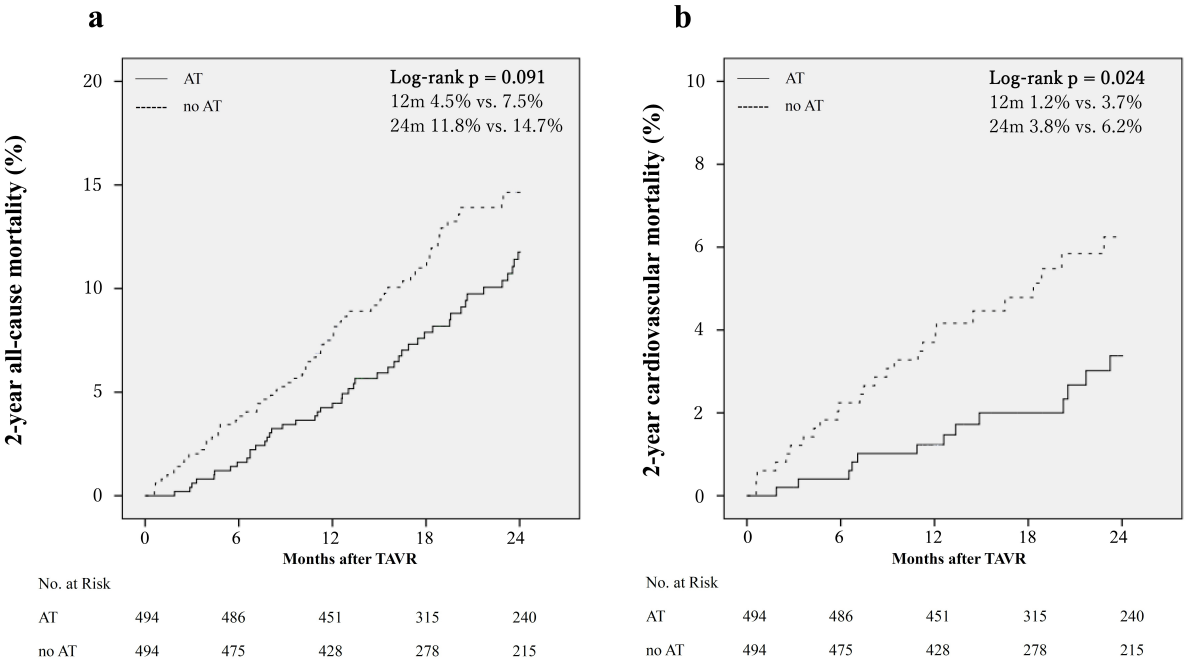

a
AT
no AT
Log-rank p = 0.091
12m 4.5% vs. 7.5%
24m 11.8% vs. 14.7%
2-year all-cause mortality (%)
20
15
10
5
0
0
6
12
18
24
Months after TAVR
No. at Risk
AT 494 486 451 315 240
no AT 494 475 428 278 215
b
AT
no AT
Log-rank p = 0.024
12m 1.2% vs. 3.7%
24m 3.8% vs. 6.2%
2-year cardiovascular mortality (%)
10
8
6
4
2
0
0
6
12
18
24
Months after TAVR
No. at Risk
AT 494 486 451 315 240
no AT 494 475 428 278 215

Figure 4.

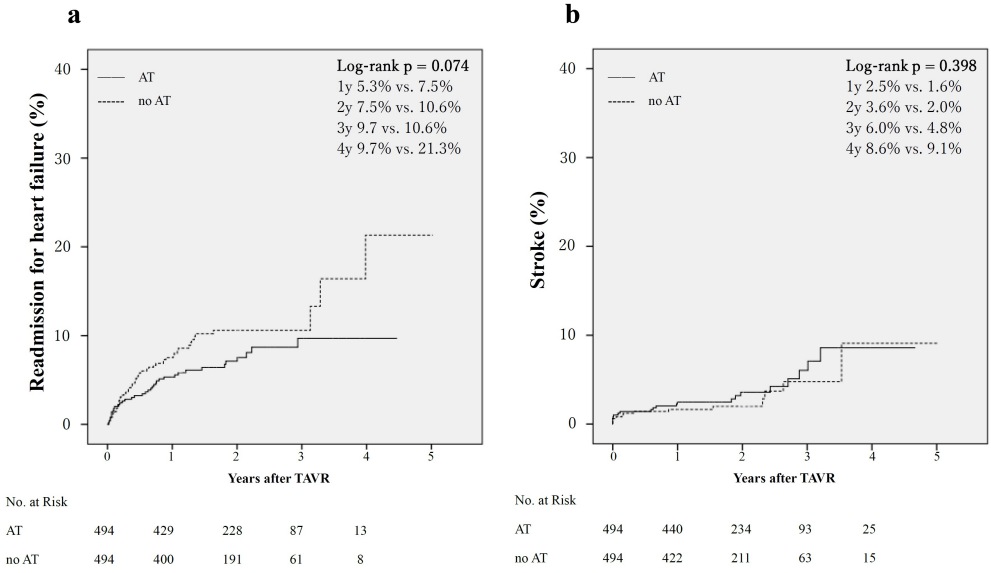
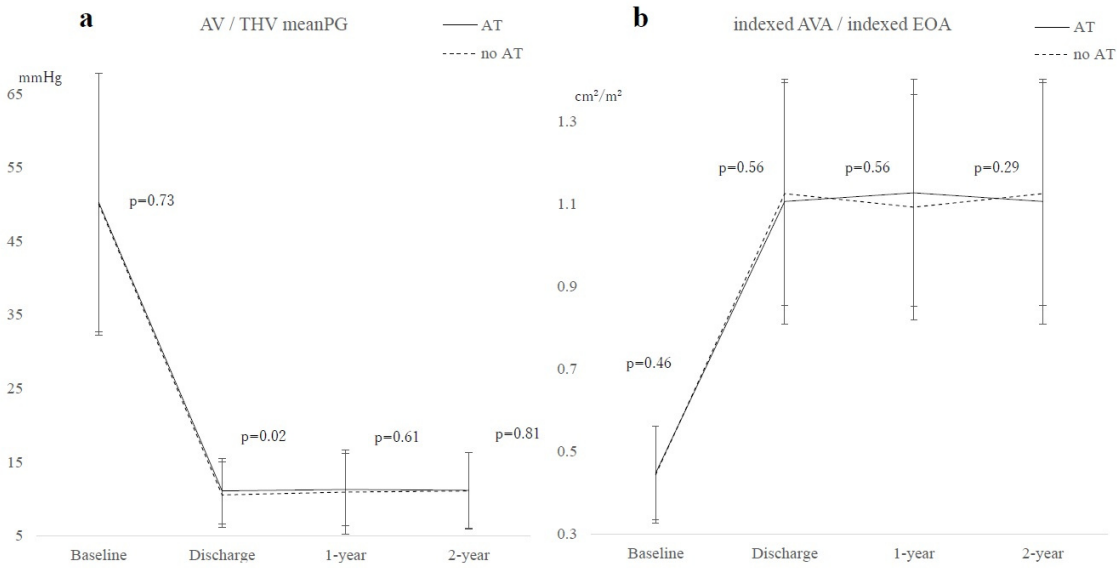

a
Readmission for heart failure (%)
AT
no AT
Log-rank p = 0.074
1y 5.3% vs. 7.5%
2y 7.5% vs. 10.6%
3y 9.7 vs. 10.6%
4y 9.7% vs. 21.3%
Years after TAVR
No. at Risk
AT 494 429 228 87 13
no AT 494 400 191 61 8
b
Stroke (%)
AT
no AT
Log-rank p = 0.398
1y 2.5% vs. 1.6%
2y 3.6% vs. 2.0%
3y 6.0% vs. 4.8%
4y 8.6% vs. 9.1%
Years after TAVR
No. at Risk
AT 494 440 234 93 25
no AT 494 422 211 63 15

Figure 5.



MeanPG AV/THV	Baseline	Discharge	1-year	2-year
AT (mmHg)	50.2±17.8	11.1±4.4	11.2±5.7	11.1±5.2
no AT (mmHg)	50.0±17.6	10.5±4.4	10.9±4.9	11.1±5.2

iAVA iEOA	Baseline	Discharge	1-year	2-year
AT (cm^2/m^2)	0.45±0.12	1.10±0.29	1.12±0.27	1.10±0.27
no AT (cm^2/m^2)	0.44±0.12	1.12±0.31	1.09±0.31	1.12±0.29

「本論文中の内容の一部については、著者の発表論文「Comparison of Long-Term Mortality in Patients Who Underwent Transcatheter Aortic Valve Replacement With or Without Anti-Atherosclerotic Therapy Heart and Vessels 2021 Dec;36(12):1892-1902. doi: 10.1007/s00380-021-01873-4. Epub 2021 Jun 8」より 、
Heart and Vessels 誌に使用許可を確認し一部改変して掲載しています。