Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Early and Late Leaflet Thrombosis After Transcatheter Aortic Valve Replacement

A Multicenter Initiative From the OCEAN-TAVI Registry

Ryo Yanagisawa, MD
Makoto Tanaka, MD
Fumiaki Yashima, MD
Takahide Arai, MD
Masahiro Jinzaki, MD
Hideyuki Shimizu, MD
Keiichi Fukuda, MD
Yusuke Watanabe, MD
Toru Naganuma, MD
Akihiro Higashimori, MD
Kazuki Mizutani, MD
Motoharu Araki, MD
Norio Tada, MD
Futoshi Yamanaka, MD
Toshiaki Otsuka, MD
Masanori Yamamoto, MD
Kentaro Hayashida, MD

BACKGROUND: The occurrence and clinical impact of untreated subclinical leaflet thrombosis beyond 1 year after transcatheter aortic valve replacement still remain unclear.

METHODS AND RESULTS: In a multicenter transcatheter aortic valve replacement registry, we analyzed data from 485 patients who underwent 4-dimensional multidetector computed tomography posttranscatheter aortic valve replacement performed to survey hypoattenuated leaflet thickening with reduced leaflet motion compatible with thrombus at a median of 3 days, 6 months, 1 year, 2 years, and 3 years. Incidence, predictors, and clinical outcomes of early (median 3 days) and late (>30 days) leaflet thrombosis were assessed. Additional anticoagulation was not administered because of subclinical findings at the time of computed tomography in all patients. Early leaflet thrombosis occurred in 45 (9.3%) of 485 patients. Mean pressure gradient at discharge was higher in patients with early leaflet thrombosis than in those without. Independent predictors of early leaflet thrombosis in balloon-expandable prostheses were low-flow, low-gradient aortic stenosis, severe prosthesis-patient mismatch, and 29-mm prostheses. No predictors could be identified for self-expanding prosthesis. Cumulative event rates of death, stroke, or rehospitalization for heart failure over 2 years were 10.7% and 16.9% in patients with and without early leaflet thrombosis, respectively (P=0.63). Late leaflet thrombosis occurred late up to 3 years, and male sex and paravalvular leak less than mild were independent predictors.

CONCLUSIONS: Untreated early leaflet thrombosis did not affect the cumulative event rates of death, stroke, and rehospitalization for heart failure. Late leaflet thrombosis was newly detected during 3-year follow-up.

VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: aortic valve stenosis ■ heart failure ■ multidetector computed tomography ■ thrombosis ■ transcatheter aortic valve replacement

https://www.ahajournals.org/journal/circinterventions

WHAT IS KNOWN

- Subclinical leaflet thrombosis is not a rare finding and is a safety concern after transcatheter aortic valve replacement.
- Therapeutic anticoagulation could effectively prevent and treat leaflet thrombosis and reduced leaflet motion.

WHAT THE STUDY ADDS

- Untreated early (median 3 days) leaflet thrombosis did not affect hard end points, and late leaflet thrombosis occurred late up to 3 years.
- Independent predictors of leaflet thrombosis may be related to local hemodynamic stasis on the leaflets.
- Follow-up assessment of transcatheter bioprostheses in patients with predictors of leaflet thrombosis is particularly necessary.

The midterm outcome of transcatheter aortic valve replacement (TAVR) is well established in intermediate-risk patients.[1,2] The clinical relevance of leaflet thrombosis of prostheses after TAVR remains an important unresolved issue. Symptomatic leaflet thrombosis of prostheses after TAVR is rare (0.6%–2.8%).[3,4] Subclinical thrombosis can be observed with much higher incidence based on multidetector computed tomography (MDCT) and can be clinically not apparent in most cases.[5–7] Leaflet thrombosis should not be considered unique to transcatheter bioprostheses and is common even in surgical bioprostheses.[8–10] Leaflet thrombosis may be exacerbated, and long-term effects should be verified.[11] Although previous studies reported the incidence of possible leaflet thrombosis after TAVR,[5,7,12] little is known about the clinical impact and occurrence of leaflet thrombosis beyond 1 year after TAVR.

Anticoagulation therapy could effectively prevent and treat obstructive leaflet thrombosis,[6,13,14] but management of subclinical thrombosis has not yet been established.[9] Moreover, the impact of untreated subclinical thrombosis remains unclear. In this study, we aimed to evaluate the incidence, predictors, and clinical impact of untreated subclinical leaflet thrombosis in patients undergoing TAVR in a multicenter registry.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population and Design

This was an ongoing multicenter prospective registry, which enrolled patients with transcatheter bioprosthesis. This observational study included 485 patients who were enrolled in the OCEAN-TAVI (optimized transcatheter valvular intervention-transcatheter aortic valve implantation; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000023585; UMIN000020423) registry and underwent post-TAVR MDCT at a median of 3 days post-TAVR between October 2013 and July 2016. The baseline and procedural characteristics and clinical outcomes were compared between patients with leaflet thrombosis and those without leaflet thrombosis. The ethics review board approved this study protocol in each treating site, and informed consent was obtained from all the patients.

Baseline characteristics, as well as in-hospital and follow-up data, have been prospectively collected in a dedicated database. We obtained clinical follow-up data at 30 days, 6 months, 1 year, and annually thereafter. Additional follow-up data were collected via phone calls. Clinical, echocardiographic, and adverse events were evaluated according to the Valve Academic Research Consortium-2 criteria.[15] The primary composite end point was all-cause mortality, stroke (ischemic and hemorrhagic stroke excluding periprocedural stroke), or rehospitalization for heart failure.

Echocardiography

Aortic valve stenosis severity, left ventricular ejection fraction, and prosthetic valve function were evaluated by experienced echocardiographers who were unaware of the procedural information. A low-flow, low-gradient (LFLG) aortic stenosis (AS) at baseline was defined based on both a stroke volume index <35 mL/m^2 and a mean aortic gradient <40 mm Hg. Severe prosthesis-patient mismatch (PPM) at postprocedure was defined as an indexed effective orifice area of <0.65 cm^2/m^2.[16]

Prosthesis Size Selection and Procedure

We selected prosthesis size based on an integration of preprocedural MDCT area assessment. The prostheses available during the study period were the Edwards Sapien XT/Sapien 3 (Edwards Lifesciences, Irvine, CA) and the Medtronic CoreValve (Medtronic, Minneapolis, MN). Heparin was administered during the procedure. Dual antiplatelet therapy was basically continued for 3 to 6 months, and aspirin or clopidogrel was continued thereafter.

MDCT Imaging and Evaluation

Postprocedural 4-dimensional MDCT scanning with electrocardiography-gated reconstructions was systematically performed to detect subclinical valvular complications[17] and hypoattenuated leaflet thickening (HALT) that indicated leaflet thrombosis at a median of 3 days, 6 months, 1 year, 2 years, and 3 years post-TAVR at each treatment center. Figure I in the Data Supplement shows a flowchart of this study. All patients included in the present study underwent MDCT at a median of 3 days post-TAVR. All MDCT examinations were evaluated by 2 experienced MDCT readers (Drs Yanagisawa and Tanaka). The data sets were based on a dedicated 4-dimensional MDCT data acquisition protocol, and each phase of the 10-phase datasets was processed, as mandated at each center. Thrombosis analysis was performed in the diastolic phase of the cardiac cycle at 75% of the R-R interval, followed by confirming reduced motion of the corresponding leaflets using 4-dimensional

MDCT scanning on the Ziostation2 PhyZiodynamics software (Ziosoft, Inc, Tokyo, Japan), as previously described.[11] Computed tomography (CT) scans that were not fully interpretable were excluded at each time point. With regard to radiation exposure at each CT evaluation, the median volume-weighted CT dose index was 21.6 mGy (range, 19.2–22.5 mGy), and the median dose-length product was 665 mGy–cm (range, 574–744 mGy–cm). In all patients with subclinical thrombosis, additional anticoagulant was not administered at the timing of HALT detection. Leaflet thrombosis was categorized on the interval from the procedure to detection of HALT on MDCT into early (at a median of 3 days) and late (>30 days). The depth of prosthesis implantation was measured as maximum distance from the bottom of the stent to the native annulus.[18]

Statistical Analysis

Continuous variables were expressed as mean and SD or as medians and interquartile ranges, as appropriate. For comparison of continuous variables between data at each follow-up time, the unpaired Student *t* test or Wilcoxon rank-sum test was used depending on variable distribution. Categorical variables (presented as numbers and percentages) were compared using the χ^2 test or Fisher exact test. Mixed-effect linear model was used to evaluate the interaction in serial measurements of echocardiographic parameters. Kaplan-Meier method was used to estimate cumulative incidence of leaflet thrombosis and time to the primary composite end point. Survival curves were compared using the log-rank test, and hazard ratio estimates corresponded to Cox proportional hazards model. Univariable and multivariable generalized linear models for interval-censored survival data were used to evaluate the predictors of early and late leaflet thrombosis. The model adjustment included variables with $P<0.10$ in the univariable analysis. Results are presented as odds ratios with 95% CIs.

All tests were 2-sided, and a P value <0.05 was considered statistically significant. All data analyses were performed with SPSS statistical software (version 24.0; SPSS, Inc, Chicago, IL).

RESULTS

The baseline and procedural characteristics of the study population are summarized in Table 1. Forty-five (9.3%) of the 485 patients had HALT at a median of 3 days post-TAVR (early leaflet thrombosis; Figure 1, Movies I–III in the Data Supplement). The median age of the entire cohort was 85 (interquartile range, 81–87) years, and 30% of the patients were men. No significant differences were found in clinical variables between the groups. Both anticoagulation and antiplatelet therapies were not associated with the incidence of early leaflet thrombosis. Patients with warfarin had similar risk of thrombosis with those without warfarin (7.9% versus 9.5%, P=0.82). Patients with early leaflet thrombosis showed a higher rate of LFLG-AS on preprocedural transthoracic echocardiography than those without thrombosis (20.0% versus 8.0%, P=0.01). No significant differences were observed in procedural variables. After a 1-year follow-up, 324 patients were censored (termination of follow-up), and 2 dropped out (Figure I in the Data Supplement).

Table 1. Baseline and Procedural Characteristics of the Study Population

	Early Leaflet Thrombosis (n=45)	No Thrombosis (n=440)	*P* Value
Clinical variables			
Age, y	85 (82–88)	85 (81–88)	0.59
Male	12 (26.7)	135 (30.7)	0.74
Body surface area, m^2	1.4 (1.3–1.6)	1.4 (1.3–1.5)	0.81
Diabetes mellitus	16 (35.6)	114 (25.9)	0.16
Chronic kidney disease	26 (57.8)	272 (61.8)	0.63
Atrial fibrillation	6 (13.3)	103 (23.4)	0.14
Previous percutaneous coronary intervention	8 (17.8)	105 (23.9)	0.46
History of stroke	3 (6.7)	38 (8.6)	>0.99
Anticoagulation therapy (postprocedure)			
Warfarin	5 (11.1)	57 (13.0)	>0.99
New oral anticoagulant	4 (8.9)	49 (11.1)	0.81
Antiplatelet therapy (postprocedure)			
Dual antiplatelet therapy	23 (51.1)	244 (55.5)	0.38
Single antiplatelet therapy	21 (46.7)	169 (38.4)	0.38
None	1 (2.2)	27 (6.1)	0.38
Echocardiographic variables			
Mean aortic gradient, mm Hg	47.1±16.5	49.5±17.3	0.39
Left ventricular ejection fraction, %	63.0±10.9	63.9±11.6	0.64
AR more than mild	2 (4.4)	38 (8.6)	0.57
Low-flow, low-gradient AS	9 (20.0)	35 (8.0)	0.01
Procedure variables			
Access			
Transfemoral	43 (95.6)	401 (90.3)	0.41
Nontransfemoral	2 (4.4)	39 (8.9)	0.41
Prosthesis design			
Edwards Sapien XT	11 (24.4)	257 (58.4)	<0.001
Edwards Sapien 3	30 (66.7)	138 (31.4)	<0.001
Medtronic CoreValve	4 (8.9)	45 (10.2)	<0.001

Values are medians (25th–75th percentiles), mean±SD, or n (%). AR indicates aortic regurgitation; and AS, aortic stenosis.

All patients were subclinical at the time of CT scanning. The median interval from the procedure to the follow-up MDCT was 3 days (range 2–11 days) and was similar between the groups (3 days [3–12] versus 5 days [2–9], P=0.73). Of the 45 patients, subclinical thrombi were detected on 1 leaflet of the prostheses in 33 patients (73.3%), 2 leaflets in 8 patients (17.8%), and 3 leaflets in 4 patients (8.9%). The prevalence of early leaflet thrombosis was similar between patients with balloon-expandable prostheses (Sapien XT and Sapien 3) and those with self-expandable prostheses

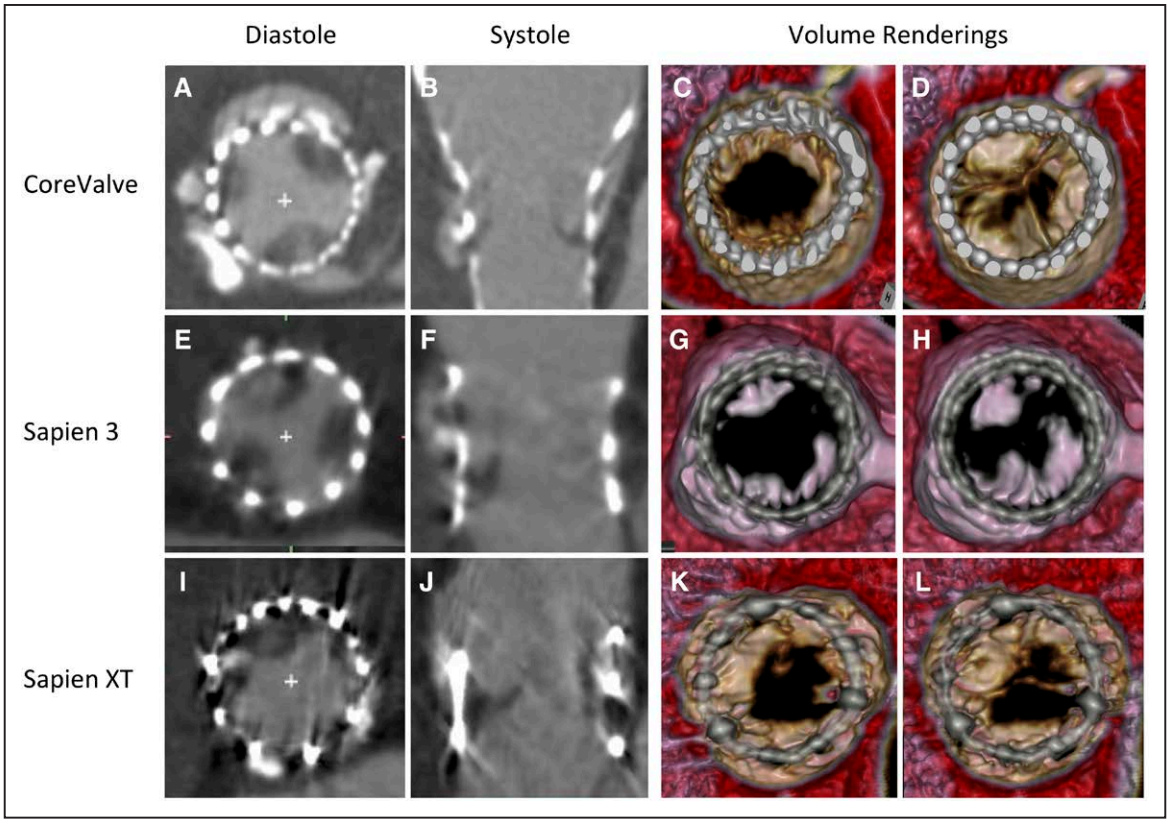

Figure 1. Possible leaflet thrombosis and reduced leaflet motion detected using multidetector computed tomography (MDCT).
MDCT revealed possible leaflet thrombosis (white arrow) with reduced leaflet motion (white arrowhead) in patients with Medtronic CoreValve (**A**–**D**), Edwards Sapien 3 (**E**–**H**), and Sapien XT (**I**–**L**). Movies are provided in the Data Supplement.

(CoreValve; 9.4% versus 8.2%, *P*=0.51). However, Sapien 3 was significantly associated with higher rate of early leaflet thrombosis than Sapien XT (17.9% versus 4.1%, *P*<0.001). The rate in patients with Sapien 3 was approximately double that of patients with CoreValve, but the difference was not significant (17.9% versus 8.2%, *P*=0.07). In depth of implantation, Sapien 3 was implanted in a lower position in patients with early leaflet thrombosis than in those without thrombosis, but the difference was not significant (5.8±1.2 versus 5.2±1.5 mm, *P*=0.05). The depth of implantation was also similar between the groups in Sapien XT (3.9±0.8 versus 3.9±1.0 mm, *P*=0.83) and CoreValve (5.3±1.2 versus 6.0±1.4 mm, *P*=0.36).

In-Hospital Outcomes

Major adverse events, including major bleeding, stroke, and vascular complications, were not associated with the presence of early leaflet thrombosis (Table 2). The frequency of paravalvular leak (PVL) more than mild was also similar between the groups (0% versus 1.1%, *P*>0.99). Patients with early leaflet thrombosis exhibited slightly higher mean transvalvular gradient than those without thrombosis (12.9±5.6 versus 11.0±4.7 mm Hg, *P*=0.03). Moreover, severe PPM was detected in 7 patients (1 with Sapien XT 23 mm, 1 with Sapien 3 20 mm, 4 with Sapien 3 23 mm, and 2 with CoreValve 26 mm) and was associated with higher probability of early leaflet thrombosis (6.7% versus 0.9%, *P*=0.02).

Table 2. In-Hospital Clinical Outcomes for Patients With and Without Early Leaflet Thrombosis

Variables	Early Leaflet Thrombosis (n=45)	No Thrombosis (n=440)	*P* Value
Major bleeding	2 (4.4)	17 (3.9)	0.69
Ischemic stroke	1 (2.2)	5 (1.1)	0.53
Hemorrhagic stroke	0	1 (0.2)	0.75
Acute kidney injury stage 2 or 3	1 (2.2)	16 (3.6)	>0.99
Major vascular complication	1 (2.2)	20 (4.6)	0.71
New pacemaker	2 (4.4)	19 (4.3)	>0.99
New onset atrial fibrillation	1 (2.2)	13 (3.0)	>0.99
PVL more than mild	0	5 (1.1)	>0.99
PVL none or trivial	29 (64.4)	221 (50.2)	0.08
Mean transvalvular gradient, mm Hg	12.9±5.6	11.0±4.7	0.03
Indexed effective orifice area, cm^2	1.10±0.42	1.15±0.30	0.33
Severe prosthesis-patient mismatch	3 (6.7)	4 (0.9)	0.02

Values are mean±SD or n (%). PVL indicates paravalvular leak.

Table 3. Logistic Regression Analysis for Predicting Early Leaflet Thrombosis in Balloon- and Self-Expandable Transcatheter Bioprostheses

	Univariable Analysis			Multivariable Analysis		
Predictors	**Odds Ratio**	**95% CI**	***P* Value**	**Odds Ratio**	**95% CI**	***P* Value**
Balloon-expandable (N=436)						
Age (per 1 y increase)	1.08	0.89–1.16	0.42			
Male (for female)	0.94	0.77–1.15	0.72			
Atrial fibrillation	0.57	0.23–1.38	0.24			
Low-flow, low-gradient AS	2.75	1.17–6.45	0.02	2.71	1.11–6.62	0.03
Warfarin	0.86	0.32–2.28	0.76			
New oral anticoagulant	0.65	0.19–2.18	0.48			
No antiplatelet therapy	0.40	0.05–3.07	0.37			
PVL less than mild	1.82	0.93–3.58	0.08	1.79	0.89–3.60	0.11
Severe prosthesis-patient mismatch	15.5	2.5–95.7	<0.001	16.9	2.56–111	0.003
29-mm prostheses	5.35	1.73–16.5	0.001	6.33	2.00–20.0	0.002
Self-expandable (N=49)						
Age (per 1 y increase)	1.02	0.79–1.31	0.57			
Male (for female)	0.98	0.54–1.77	0.94			
Atrial fibrillation	0.76	0.64–0.89	0.26			
Low-flow, low-gradient AS	1.24	0.70–2.20	0.20			
Warfarin	0.96	0.90–1.02	0.67			
New oral anticoagulant	1.16	0.65–2.06	0.52			
No antiplatelet therapy	0.91	0.83–1.00	0.53			
PVL less than mild	1.20	0.44–3.29	0.70			
Severe prosthesis-patient mismatch	0.96	0.90–1.02	0.67			

AS indicates aortic stenosis; and PVL, paravalvular leak.

Echocardiographic Data

Echocardiographic data were available in 485 (100%) patients at baseline, 483 (99.6%) patients at discharge, 362 (78.8%) patients at 1 year, and 208 (42.9%) patients at a follow-up of 2 years. The comparison between the groups on mean pressure gradient, indexed effective orifice area, stroke volume, and left ventricular ejection fraction is shown in Figure II in the Data Supplement. All the echocardiographic parameters were similar at baseline between the groups. During the follow-up period, patients with early leaflet thrombosis showed higher mean pressure gradient at discharge than those without early leaflet thrombosis (12.9±5.6 versus 11.0±4.7 mm Hg, *P*=0.03). However, no significant differences were found after a 1-year follow-up. Indexed effective orifice area and stroke volume were also similar between the groups over time. In addition, patients with early leaflet thrombosis had a significant decrease in left ventricular ejection fraction compared with those without early leaflet thrombosis. In both groups, all the parameters did not significantly change over time from discharge to 1-year follow-up and from 1-year to 2-year follow-up. In serial measurements, no significant interaction between the groups was observed in mean pressure gradient (*P*=0.62), stroke volume (*P*=0.12), and left ventricular ejection fraction (*P*=0.46), but the interaction was observed in indexed effective orifice area (*P*=0.01).

Predictors of Early Leaflet Thrombosis

Independent predictors of early leaflet thrombosis are shown in Table 3. In multivariable analysis, the incidence of early leaflet thrombosis was independently associated with LFLG-AS, severe PPM, and 29-mm prostheses in balloon-expandable prostheses, but not with the absence of anticoagulant in this study. No predictors were detected in self-expandable prostheses.

End Points

With regard to the composite end point of death, stroke, or rehospitalization for heart failure, the cumulative event rates during the follow-up period (mean, 1.8 years; SD, 0.9) were 10.7% and 16.9% in patients with and without early leaflet thrombosis (hazard ratio, 0.78; 95% CI, 0.28–2.14; *P*=0.63), respectively (Figure 2A). No significant between-group

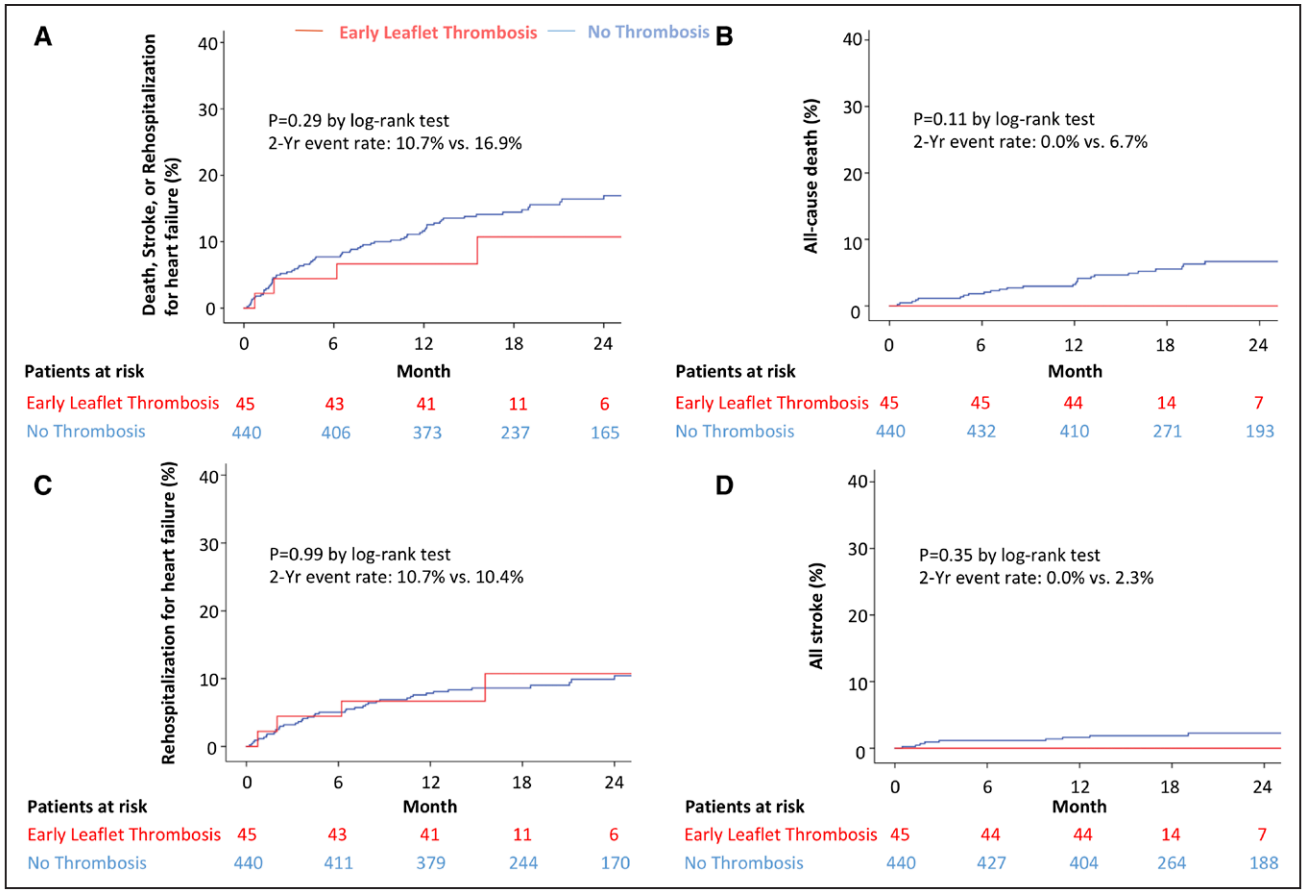

Figure 2. Time-to-event curves for the primary end point.
The cumulative event rates for the composite end point of death, stroke, or rehospitalization for heart failure up to 2 y were similar between patients with and without early leaflet thrombosis (**A**), despite the fact that additional anticoagulation was not administered at the detection of subclinical thrombosis. Kaplan-Meier curves for all-cause death (**B**), rehospitalization for heart failure (**C**), and all stroke (**D**), with cumulative event rates.

difference was found in all-cause mortality (Figure 2B), rehospitalization for heart failure (Figure 2C), and all stroke (ischemic and hemorrhagic stroke excluding periprocedural stroke; Figure 2D). During follow-up, 4 patients had ischemic stroke, and 5 had hemorrhagic stroke. The rates of ischemic and hemorrhagic stroke were similar between the groups (0% versus 0.6%, *P*=0.57; 0% versus 0.7%, *P*=0.52, respectively). All patients with stroke event did not have thrombosis based on MDCT. One of the 45 patients in the thrombosis group who had severe PPM immediately after TAVR required new anticoagulation because of significant increase in transvalvular pressure gradient at 6 months.

Late Leaflet Thrombosis

Among the patients available at each time point, 310 (63.9%) of the 485 patients had follow-up CT at 6 months, 203 (48.1%) of the 422 patients at 1 year, 142 (74.3%) of the 191 patients at 2 years, and 65 (69.1%) of the 94 patients at 3 years. During follow-up, a total of 23 patients had late onset leaflet thrombosis. Male sex and PVL less than mild at discharge were independent predictors of late leaflet thrombosis (Table 4). Spontaneous resolution of leaflet thrombosis was observed in 3 patients (1 at 1 year, 2 at 3 years) during follow-up without change of antithrombotic therapy. At each time point, leaflet thrombosis occurred late in 22 (7.1%) of the 310 patients who had follow-up CT at 6 months, 23 (11.3%) of the 203 patients at 1 year, 18 (12.7%) of the 142 patients at 2 years, and 11 (16.9%) of the 65 patients at 3 years. Compared with patients with CT dataset only at a median of 3 days, patients with CT dataset at a median of 3 days and at least 1 other time point were more likely male and had a lower rate of dual antiplatelet therapy (Table I in the Data Supplement). Other preprocedural variables were similar between the groups. The characteristics of patients with and without CT dataset at each time point are provided in Tables II–IV in the Data Supplement.

Sixty-five patients had complete CT evaluation at all time points up to 3 years. Among them, late leaflet thrombosis occurred in 8 (12.3%), whereas early thrombosis occurred in 3 (4.6%). Of the 8 cases, 2 were newly observed at 6 months, 2 at 1 year, 4 at 2 years, and none at 3 years.

Table 4. Generalized Linear Models Analysis for Predicting Late Leaflet Thrombosis

	Univariable Analysis			Multivariable Analysis		
Predictors	**Odds Ratio**	**95% CI**	***P* Value**	**Odds Ratio**	**95% CI**	***P* Value**
Age (per 1 y increase)	1.03	0.95–1.11	0.55			
Male (for female)	2.46	1.15–5.25	0.02	3.12	1.42–6.83	0.004
Atrial fibrillation	1.22	0.51–2.87	0.66			
Low-flow, low-gradient AS	0.56	0.08–4.11	0.57			
Warfarin	0.21	0.03–1.57	0.13			
New oral anticoagulant	2.08	0.79–5.53	0.14			
No antiplatelet therapy	1.97	0.45–8.50	0.37			
PVL less than mild	2.16	1.00–4.66	0.05	2.77	1.25–6.13	0.01

AS indicates aortic stenosis; and PVL, paravalvular leak.

DISCUSSION

The main findings in this real-world multicenter study were as follows. First, 45 (9.3%) of 485 patients had early leaflet thrombosis on MDCT at a median of 3 days after TAVR, and all were subclinical. Second, early leaflet thrombosis did not affect the cumulative event rates for the composite end point of death, stroke, or rehospitalization for heart failure during the follow-up period (mean, 1.8 years; SD, 0.9). Third, LFLG-AS, severe PPM, and 29-mm prostheses were identified as predictors for early leaflet thrombosis in balloon-expandable prostheses. Fourth, late leaflet thrombosis occurred late up to 3 years, and the independent predictors were male sex and PVL less than mild.

The strengths of the current study were as follows. First, all types of bioprostheses used in the clinical setting were included in a prospective multicenter registry. Second, this cohort eventually represents the natural history of leaflet thrombosis because additional anticoagulation was not administered at the detection of subclinical thrombosis. Third, systematic follow-up MDCT was performed up to 3 years.

Understanding the predictors of thrombosis contributes to the verification of the appropriate design of prostheses in the future. Although recent studies have reported the treated course, the course without additional anticoagulation remains unexplored.[6,7,12] Given the elderly TAVR cohort with high-bleeding risk, the natural history of untreated thrombosis is particularly important.[10]

The 9.3% rate of early leaflet thrombosis was similar to previous studies.[7,12,19] The frequency of subclinical thrombosis in balloon- and self-expandable prostheses was similar. The difference in intra or supraannular position might have a slight effect on static local environment. In the present study, patients with early leaflet thrombosis had a similar dosing rate of warfarin compared with those without early leaflet thrombosis. Moreover, the rates of death, stroke, or rehospitalization for heart failure were not different between those with or without early leaflet thrombosis during the follow-up period. Warfarin is recommended for treatment to resolve obstructive leaflet thrombosis,[6,7,9,12] but the benefit of the routine use for preventive effect in elderly TAVR cohort remains controversial. Although our result did not indicate the preventive effect as reported in a previous study,[7] follow-up CTs were performed in both studies at a median of 3 days, which might be early for anticoagulation to take effect. Hansson et al[12] reported the protective potential of warfarin in a large single-center study. In addition, a recently published multicenter study has reported that a lack of anticoagulation therapy seems to be associated with a higher rate of valve degeneration.[20] The limited evidence supports that discontinuation of warfarin therapy within 6 months after bioprosthetic aortic valve replacement surgery can increase the risk of cardiovascular death and thromboembolism.[21]

We newly found that LFLG-AS and severe PPM are independent predictors of early leaflet thrombosis. As previously described,[12] 29-mm balloon-expandable prostheses can increase the risk of thrombosis. In contrast to large prosthesis, LFLG-AS and severe PPM can also potentially contribute to local static environment. Notably, only one patient who required additional anticoagulation because of increased gradient during follow-up had severe PPM at discharge. However, the relationship between leaflet thrombosis and PPM cannot be concluded in this study. Given that the presence of thrombosis can influence gradient, it is important to note that the presence of thrombosis itself may affect PPM. Although the mean pressure gradient was significantly increased in patients with early leaflet thrombosis only at discharge, the differences might cease to exist at 1 year and 2 years because of missing echocardiographies. Moreover, male sex and PVL less than mild were independent predictors of late leaflet thrombosis. The hemodynamic stasis on the leaflets because of less PVL potentially might have contributed to thrombus formation.[22]

Late leaflet thrombosis was detected up to 3 years. Notably, no leaflet thrombosis was newly observed at 3 years, but the occurrence continued during the first 2 years. This finding may indicate the duration of careful patient monitoring considering the risk of leaflet thrombosis.

Limitations

This study included patients who underwent the procedure until July 2016, and the mean follow-up period was 1.8 years. Therefore, the time from inclusion to the end of the study was not beyond 2 years in more than half of the cohort (311 [64.1%] of 485 patients). With regard to CT analysis of the late phase, data on HALT were verified in a cohort excluding patients who did not undergo follow-up CT considering missing CT scans. However, there is a possibility that bias may exist because of incomplete data acquisition on the entire cohort. It is limited by selection bias because patients with impaired renal function were not included. Lack of core laboratory may influence inter-observer variability in the echocardiographic assessment of prosthetic valves. The direct association between stroke and valve thrombosis is difficult to conclude because simultaneous assessment of valve thrombosis has not been performed at the time of stroke, and the impact of transient ischemic attack was not evaluated. We did not obtain histopathologic data; therefore, the diagnosis of thrombosis is based only on the MDCT imaging. Nonetheless, HALT was verified in combination with reduced motion of the corresponding leaflets on 4-dimensional MDCT imaging. This real-world registry includes all types of bioprosthesis, and the baseline anatomy of aortic valve complex might affect the outcome. A large randomized controlled trial is warranted to elucidate this point.

In conclusion, our data demonstrated that untreated early leaflet thrombosis did not affect the rates of death, stroke, and rehospitalization for heart failure. The independent predictors of early leaflet thrombosis after TAVR with balloon-expandable prostheses were LFLG-AS, severe PPM, and 29-mm prostheses. Late leaflet thrombosis occurred late up to 3 years, and the independent predictors were male sex and PVL less than mild. Longer follow-up of this observation is needed to determine its occurrence and evaluate its clinical impact.

ARTICLE INFORMATION

Received August 24, 2018; accepted December 19, 2018.

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCINTERVENTIONS.118.007349.

Correspondence

Kentaro Hayashida, MD, PhD, FESC, Department of Cardiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160–8582, Japan. Email k-hayashida@umin.ac.jp

Affiliations

Department of Cardiology (R.Y., M.T., F. Yashima, T.A., K.F., K.H.), Department of Diagnostic Radiology (M.J.), and Department of Cardiovascular Surgery (H.S.), Keio University School of Medicine, Tokyo, Japan. Teikyo University School of Medicine, Tokyo, Japan (Y.W.). New Tokyo Hospital, Matsudo, Japan (T.N.). Kishiwada Tokushukai Hospital, Osaka, Japan (A.H.). Osaka City General Hospital, Japan (K.M.). Saiseikai Yokohama-City Eastern Hospital, Tsurumi, Japan (M.A.). Sendai Kousei Hospital, Japan (N.T.). Shonan Kamakura General Hospital, Japan (F. Yamanaka). Department of Hygiene and Public Health and Center for Clinical Research, Nippon Medical School, Tokyo, Japan (T.O.). Toyohashi Heart Center, Japan (M.Y.). Nagoya Heart Center, Japan (M.Y.).

Sources of Funding

This study was funded in part by Edwards Lifesciences and Daiichi Sankyo.

Disclosures

Drs Shimizu, Watanabe, Naganuma, Shirai, Araki, Tada, Yamamoto, and Hayashida are clinical proctors for Edwards Lifesciences. Drs Watanabe, Naganuma, and Yamamoto are proctors for Medtronic. The other authors report no conflicts.

REFERENCES

1. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG; PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609–1620. doi: 10.1056/NEJMoa1514616
2. Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, Smalling R, Lim S, Malaisrie SC, Kapadia S, Szeto WY, Greason KL, Kereiakes D, Ailawadi G, Whisenant BK, Devireddy C, Leipsic J, Hahn RT, Pibarot P, Weissman NJ, Jaber WA, Cohen DJ, Suri R, Tuzcu EM, Svensson LG, Webb JG, Moses JW, Mack MJ, Miller DC, Smith CR, Alu MC, Parvataneni R, D'Agostino RB Jr, Leon MB. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet*. 2016;387:2218–2225. doi: 10.1016/S0140-6736(16)30073-3
3. Latib A, Naganuma T, Abdel-Wahab M, Danenberg H, Cota L, Barbanti M, Baumgartner H, Finkelstein A, Legrand V, de Lezo JS, Kefer J, Messika-Zeitoun D, Richardt G, Stabile E, Kaleschke G, Vahanian A, Laborde JC, Leon MB, Webb JG, Panoulas VF, Maisano F, Alfieri O, Colombo A. Treatment and clinical outcomes of transcatheter heart valve thrombosis. *Circ Cardiovasc Interv*. 2015;8:e001779. doi: 10.1161/CIRCINTERVENTIONS.114.001779
4. Jose J, Sulimov DS, El-Mawardy M, Sato T, Allali A, Holy EW, Becker B, Landt M, Kebernik J, Schwarz B, Richardt G, Abdel-Wahab M. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. *JACC Cardiovasc Interv*. 2017;10:686–697. doi: 10.1016/j.jcin.2017.01.045
5. Leetmaa T, Hansson NC, Leipsic J, Jensen K, Poulsen SH, Andersen HR, Jensen JM, Webb J, Blanke P, Tang M, Norgaard BL. Early aortic transcatheter heart valve thrombosis: diagnostic value of contrast-enhanced multidetector computed tomography. *Circ Cardiovasc Interv*. 2015;8:e001596. doi: 10.1161/CIRCINTERVENTIONS.114.001596
6. Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, De Backer O, Asch FM, Ruiz CE, Olsen NT, Trento A, Friedman J, Berman D, Cheng W, Kashif M, Jelnin V, Kliger CA, Guo H, Pichard AD, Weissman NJ, Kapadia S, Manasse E, Bhatt DL, Leon MB, Søndergaard L. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med*. 2015;373:2015–2024. doi: 10.1056/NEJMoa1509233
7. Pache G, Schoechlin S, Blanke P, Dorfs S, Jander N, Arepalli CD, Gick M, Buettner HJ, Leipsic J, Langer M, Neumann FJ, Ruile P. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. *Eur Heart J*. 2016;37:2263–2271. doi: 10.1093/eurheartj/ehv526
8. Egbe AC, Pislaru SV, Pellikka PA, Poterucha JT, Schaff HV, Maleszewski JJ, Connolly HM. Bioprosthetic valve thrombosis versus structural failure: clinical and echocardiographic predictors. *J Am Coll Cardiol*. 2015;66:2285–2294. doi: 10.1016/j.jacc.2015.09.022

9. Chakravarty T, Søndergaard L, Friedman J, De Backer O, Berman D, Kofoed KF, Jilaihawi H, Shiota T, Abramowitz Y, Jørgensen TH, Rami T, Israr S, Fontana G, de Knegt M, Fuchs A, Lyden P, Trento A, Bhatt DL, Leon MB, Makkar RR; RESOLVE; SAVORY Investigators. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389:2383–2392. doi: 10.1016/S0140-6736(17)30757-2
10. Sondergaard L, De Backer O, Kofoed KF, Jilaihawi H, Fuchs A, Chakravarty T, Kashif M, Kazuno Y, Kawamori H, Maeno Y, Bieliauskas G, Guo H, Stone GW, Makkar R. Natural history of subclinical leaflet thrombosis affecting motion in bioprosthetic aortic valves. *Eur Heart J*. 2017;38:2201–2207. doi: 10.1093/eurheartj/ehx369
11. Yanagisawa R, Hayashida K, Yamada Y, Tanaka M, Yashima F, Inohara T, Arai T, Kawakami T, Maekawa Y, Tsuruta H, Itabashi Y, Murata M, Sano M, Okamoto K, Yoshitake A, Shimizu H, Jinzaki M, Fukuda K. Incidence, predictors, and mid-term outcomes of possible leaflet thrombosis after TAVR. *JACC Cardiovasc Imaging*. 2017;10:1–11. doi: 10.1016/j.jcmg.2016.11.005
12. Hansson NC, Grove EL, Andersen HR, Leipsic J, Mathiassen ON, Jensen JM, Jensen KT, Blanke P, Leetmaa T, Tang M, Krusell LR, Klaaborg KE, Christiansen EH, Terp K, Terkelsen CJ, Poulsen SH, Webb J, Bøtker HE, Nørgaard BL. Transcatheter aortic valve thrombosis: incidence, predisposing factors, and clinical implications. *J Am Coll Cardiol*. 2016;68:2059–2069. doi: 10.1016/j.jacc.2016.08.010
13. De Marchena E, Mesa J, Pomenti S, Marin Y Kall C, Marincic X, Yahagi K, Ladich E, Kutz R, Aga Y, Ragosta M, Chawla A, Ring ME, Virmani R. Thrombus formation following transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2015;8:728–739. doi: 10.1016/j.jcin.2015.03.005
14. Mylotte D, Andalib A, Thériault-Lauzier P, Dorfmeister M, Girgis M, Alharbi W, Chetrit M, Galatas C, Mamane S, Sebag I, Buithieu J, Bilodeau L, de Varennes B, Lachapelle K, Lange R, Martucci G, Virmani R, Piazza N. Transcatheter heart valve failure: a systematic review. *Eur Heart J*. 2015;36:1306–1327. doi: 10.1093/eurheartj/ehu388
15. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol*. 2012;60:1438–1454. doi: 10.1016/j.jacc.2012.09.001
16. Pibarot P, Dumesnil JG. Valve prosthesis-patient mismatch, 1978 to 2011: from original concept to compelling evidence. *J Am Coll Cardiol*. 2012;60:1136–1139. doi: 10.1016/j.jacc.2012.07.005
17. Kakefuda Y, Hayashida K, Yamada Y, Yashima F, Inohara T, Yanagisawa R, Tanaka M, Arai T, Kawakami T, Maekawa Y, Tsuruta H, Itabashi Y, Murata M, Sano M, Okamoto K, Yoshitake A, Shimizu H, Jinzaki M, Fukuda K. Impact of subclinical vascular complications detected by systematic postprocedural multidetector computed tomography after transcatheter aortic valve implantation using balloon-expandable Edwards SAPIEN XT heart valve. *Am J Cardiol*. 2017;119:1100–1105. doi: 10.1016/j.amjcard.2016.12.013
18. Midha PA, Raghav V, Sharma R, Condado JF, Okafor IU, Rami T, Kumar G, Thourani VH, Jilaihawi H, Babaliaros V, Makkar RR, Yoganathan AP. The fluid mechanics of transcatheter heart valve leaflet thrombosis in the neosinus. *Circulation*. 2017;136:1598–1609. doi: 10.1161/CIRCULATIONAHA.117.029479
19. Vollema EM, Kong WKF, Katsanos S, Kamperidis V, van Rosendael PJ, van der Kley F, de Weger A, Ajmone Marsan N, Delgado V, Bax JJ. Transcatheter aortic valve thrombosis: the relation between hypo-attenuated leaflet thickening, abnormal valve haemodynamics, and stroke. *Eur Heart J*. 2017;38:1207–1217. doi: 10.1093/eurheartj/ehx031
20. Del Trigo M, Muñoz-Garcia AJ, Wijeysundera HC, Nombela-Franco L, Cheema AN, Gutierrez E, Serra V, Kefer J, Amat-Santos IJ, Benitez LM, Mewa J, Jiménez-Quevedo P, Alnasser S, Garcia Del Blanco B, Dager A, Abdul-Jawad Altisent O, Puri R, Campelo-Parada F, Dahou A, Paradis JM, Dumont E, Pibarot P, Rodés-Cabau J. Incidence, timing, and predictors of valve hemodynamic deterioration after transcatheter aortic valve replacement: multicenter registry. *J Am Coll Cardiol*. 2016;67:644–655. doi: 10.1016/j.jacc.2015.10.097
21. Mérie C, Køber L, Skov Olsen P, Andersson C, Gislason G, Skov Jensen J, Torp-Pedersen C. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. *JAMA*. 2012;308:2118–2125. doi: 10.1001/jama.2012.54506
22. Scotten LN, Siegel R. Thrombogenic potential of transcatheter aortic valve implantation with trivial paravalvular leakage. *Ann Transl Med*. 2014;2:43. doi: 10.3978/j.issn.2305-5839.2014.05.04