JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 69, NO. 21, 2017
ISSN 0735-1097
http://dx.doi.org/10.1016/j.jacc.2017.03.017

ORIGINAL INVESTIGATIONS

Outcomes in Transcatheter Aortic Valve Replacement for Bicuspid Versus Tricuspid Aortic Valve Stenosis

Sung-Han Yoon, MD,[a] Sabine Bleiziffer, MD,[b] Ole De Backer, MD,[c] Victoria Delgado, MD,[d] Takahide Arai, MD,[e] Johannes Ziegelmueller, MD,[b] Marco Barbanti, MD,[f] Rahul Sharma, MD,[a] Gidon Y. Perlman, MD,[g] Omar K. Khalique, MD,[h] Erik W. Holy, MD,[i] Smriti Saraf, MD,[j] Florian Deuschl, MD,[k] Buntaro Fujita, MD,[l] Philipp Ruile, MD,[m] Franz-Josef Neumann, MD,[n] Gregor Pache, MD,[n] Masao Takahashi, MD,[o] Hidehiro Kaneko, MD,[p] Tobias Schmidt, MD,[q] Yohei Ohno, MD,[g] Niklas Schofer, MD,[k] William K.F. Kong, MD,[d,r] Edgar Tay, MD,[r] Daisuke Sugiyama, MD,[s] Hiroyuki Kawamori, MD,[a] Yoshio Maeno, MD,[a] Yigal Abramowitz, MD,[a] Tarun Chakravarty, MD,[a] Mamoo Nakamura, MD,[a] Shingo Kuwata, MD,[t] Gerald Yong, MD,[u] Hsien-Li Kao, MD,[v] Michael Lee, MD,[w] Hyo-Soo Kim, MD,[x] Thomas Modine, MD,[y] S. Chiu Wong, MD,[z] Francesco Bedgoni, MD,[aa] Luca Testa, MD,[aa] Emmanuel Teiger, MD,[o] Christian Butter, MD,[p] Stephan M. Ensminger, MD,[l] Ulrich Schaefer, MD,[k] Danny Dvir, MD,[g] Philipp Blanke, MD,[g] Jonathon Leipsic, MD,[g] Fabian Nietlispach, MD,[t] Mohamed Abdel-Wahab, MD,[i] Bernard Chevalier, MD,[e] Corrado Tamburino, MD,[f] David Hildick-Smith, MD,[j] Brian K. Whisenant, MD,[bb] Seung-Jung Park, MD,[cc] Antonio Colombo, MD,[dd] Azeem Latib, MD,[dd] Susheel K. Kodali, MD,[h] Jeroen J. Bax, MD,[d] Lars Søndergaard, MD,[c] John G. Webb, MD,[e] Thierry Lefèvre, MD,[e] Martin B. Leon, MD,[h] Raj Makkar, MD[a]

ABSTRACT

BACKGROUND Transcatheter aortic valve replacement (TAVR) is being increasingly performed in patients with bicuspid aortic valve stenosis (AS).

OBJECTIVES This study sought to compare the procedural and clinical outcomes in patients with bicuspid versus tricuspid AS from the Bicuspid AS TAVR multicenter registry.

METHODS Outcomes of 561 patients with bicuspid AS and 4,546 patients with tricuspid AS were compared after propensity score matching, assembling 546 pairs of patients with similar baseline characteristics. Procedural and clinical outcomes were recorded according to Valve Academic Research Consortium-2 criteria.

RESULTS Compared with patients with tricuspid AS, patients with bicuspid AS had more frequent conversion to surgery (2.0% vs. 0.2%; $p = 0.006$) and a significantly lower device success rate (85.3% vs. 91.4%; $p = 0.002$). Early-generation devices were implanted in 320 patients with bicuspid and 321 patients with tricuspid AS, whereas new-generation devices were implanted in 226 and 225 patients with bicuspid and tricuspid AS, respectively. Within the group receiving early-generation devices, bicuspid AS had more frequent aortic root injury (4.5% vs. 0.0%; $p = 0.015$) when receiving the balloon-expanding device, and moderate-to-severe paravalvular leak (19.4% vs. 10.5%; $p = 0.02$) when receiving the self-expanding device. Among patients with new-generation devices, however, procedural results were comparable across different prostheses. The cumulative all-cause mortality rates at 2 years were comparable between bicuspid and tricuspid AS (17.2% vs. 19.4%; $p = 0.28$).

CONCLUSIONS Compared with tricuspid AS, TAVR in bicuspid AS was associated with a similar prognosis, but lower device success rate. Procedural differences were observed in patients treated with the early-generation devices, whereas no differences were observed with the new-generation devices. (J Am Coll Cardiol 2017;69:2579–89) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

ABBREVIATIONS AND ACRONYMS

AS = aortic valve stenosis

CI = confidence interval

OR = odds ratio

TAVR = transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) has evolved from a novel technology to an established therapy for high-risk patients with symptomatic severe aortic valve stenosis (AS). Numerous studies have demonstrated the safety and efficacy of TAVR, and more than 250,000 patients have been treated with this technology (1-6). Although randomized trials have established TAVR as the standard treatment in inoperable patients and a reasonable option in high surgical-risk patients, these trials excluded congenital bicuspid AS due to its unique morphological features (1,2,5-7).

SEE PAGE 2590

The experience of TAVR in bicuspid AS is limited to small series (8-12). Based on data from previous registries, the proportion of patients with bicuspid AS may reach 2% to 6% (13,14). Previous studies were limited by the clear baseline differences in age and comorbidities favoring the bicuspid AS study group

From the [a]Department of Interventional Cardiology, Cedars-Sinai Heart Institute, Los Angeles, California; [b]Clinic for Cardiovascular Surgery, German Heart Center Munich, Germany; [c]The Heart Centre, Rigshospitalet University Hospital, Copenhagen, Denmark; [d]Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; [e]Générale de Santé, Institut Cardiovasculaire Paris Sud, Hopital Privé Jacques Cartier, Massy, France; [f]Division of Cardiology, Ferrarotto Hospital, University of Catania, Catania, Italy; [g]Department of Cardiology, St Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; [h]Columbia University Medical Center/New York Presbyterian Hospital, New York, New York; [i]Heart Center, Segeberger Kliniken GmbH, Academic Teaching Hospital of the Universities of Kiel, Hamburg, and Lübeck, Bad Segeberg, Germany; [j]Sussex Cardiac Centre, Brighton and Sussex University Hospitals NHS Trust, Brighton, United Kingdom; [k]Department of General and Interventional Cardiology, University Heart Center, Hamburg, Germany; [l]Department of Thoracic and Cardiovascular Surgery, Heart and Diabetes Center NRW, Ruhr-University Bochum, Bad Oeynhausen, Germany; [m]Department of Cardiology & Angiology II, University Heart Center Freiburg-Bad Krozingen, Bad Krozingen, Germany; [n]Department of Radiology, Section of Cardiovascular Radiology, University of Freiburg, Bad Krozingen, Germany; [o]Department of Cardiology, Henri Mondor University Hospital, Créteil, France; [p]Heart Center Brandenburg in Bernau, Bernau, Germany; [q]Department of Cardiology, Asklepios Klink St. Georg, Hamburg, Germany; [r]Department of Cardiology, National University Heart Centre, Singapore; [s]Department of Preventive Medicine and Public Health, Keio University, Tokyo, Japan; [t]University Heart Center, University Hospital Zurich, Zurich, Switzerland; [u]Division of Cardiology, Royal Perth Hospital, Perth, Western Australia, Australia; [v]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [w]Division of Cardiology, Queen Elizabeth Hospital, Kowloon, Hong Kong; [x]Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Korea; [y]Department of Cardiovascular Surgery, Hospital Cardiologique, Lille, France; [z]Greenberg Division of Cardiology, New York-Presbyterian Hospital, Weil Cornell Medicine, New York, New York; [aa]Department of Cardiology, IRCCS Pol San Donato, San Donato Milanese, Milan, Italy; [bb]Division of Cardiovascular Diseases, Intermountain Heart Institute, Salt Lake City, Utah; [cc]Division of Cardiology, University of Ulsan, Asan Medical Center, Seoul, Korea; and the [dd]Interventional Cardiology Unit, EMO-GVM Centro Cuore Columbus & San Raffaele Scientific Institute, Milan, Italy San Raffaele Hospital, Milan, Italy. The Department of Cardiology at the Leiden University Medical Center received research grants from Edwards Lifesciences, Biotronik, Medtronic, and Boston Scientific. Dr. Bleiziffer has served as a consultant to Medtronic; has served as a proctor for Medtronic and JenaValve; has received travel compensation from Edwards Lifesciences, Medtronic, and Johnson & Johnson; and has served as a proctor for Boston Scientific. Dr. De Backer has served as a consultant for St. Jude Medical and Abbott Medical. Dr. Delgado has received speaking fees from Abbott Vascular. Drs. Barbanti, Pache, Nakamura, and Webb have served as consultants for Edwards Lifesciences. Drs. Khalique and Whisenant have served as consultants for Edwards Lifesciences and Boston Scientific. Drs. Dvir, Modine, and Kodali have served as consultants for Edwards Lifesciences and Medtronic. Dr. Holy has been awarded a training grant sponsored by Edwards Lifesciences. Dr. Schmidt has received lecture honoraria from Medtronic. Drs. Ohno and Teiger have served as proctors for Medtronic. Dr. Neumann has received grant support from Medtronic, Boston Scientific, and Edwards Lifesciences. Drs. Sharma, Tay, Yong, and Lefèvre have served as proctors for Edwards Lifesciences. Dr. Ensminger has served as a proctor for JenaValve and Edwards Lifesciences; has served as a consultant for Edwards Lifesciences; has served on the Scientific Advisory Board of JenaValve; and has received speaker honoraria and travel compensation from Edwards Lifesciences, JenaValve, and Symetis. Dr. Blanke has served as a consultant to Edwards Lifesciences, Tendyne, Neovasc, and Circle Cardiovascular Imaging. Dr. Leipsic's institution (UBC Institutional Core Laboratory) has received support from Edwards Lifesciences, Medtronic, Neovasc, and Tendyne. Dr. Schofer has received travel support from Edwards Lifesciences and Boston Scientific. Dr. Nietlispach has served as a consultant for Edwards Lifesciences, St. Jude Medical, Direct Flow Medical, and Medtronic. Dr. Abdel-Wahab has received institutional research grants from Biotronik and St. Jude Medical; and is a proctor for Boston Scientific. Dr. Chevalier is consultant for Medtronic. Dr. Tamburino has served as a consultant for Medtronic and St. Jude Medical. Dr. Hildick-Smith is a proctor for and serves on the advisory board of Boston Scientific, Edwards Lifesciences, and Medtronic. Dr. Whisenant has received honoraria for consulting and proctoring for Boston Scientific and Edwards Lifesciences. Dr. Latib has served on the advisory board of Medtronic; and has served as a consultant for Direct Flow Medical. Dr. Kodali has served as a consultant (unpaid) for Edwards Lifesciences and Medtronic; and has served on the Scientific Advisory Boards of and holds equity in Thubrikar Aortic Valve and Dura Biotech. Dr. Søndergaard is a proctor for, has received research contracts from, and served on the advisory boards of Medtronic, St. Jude Medical, and Boston Scientific. Dr. Leon is a nonpaid member of the Scientific Advisory Board of Edwards Lifesciences. Dr. Makkar has received grants from Edwards Lifesciences; and has received personal fees from St. Jude Medical and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 21, 2017; revised manuscript received March 6, 2017, accepted March 11, 2017.

compared with the tricuspid AS study group. However, there is a paucity of data comparing the clinical outcomes of TAVR in bicuspid and tricuspid AS. Given the increasing frequency of bicuspid AS in younger patients, coupled with the worldwide shift toward treating younger and lower surgical-risk patients with TAVR, the clinical outcomes of TAVR in bicuspid AS warrant special attention (6,15,16). Furthermore, current TAVR practice is largely based on evidence on TAVR for tricuspid AS, and thus, understanding the differences in clinical outcomes of TAVR in bicuspid and tricuspid AS is meaningful. Therefore, we aim to evaluate the clinical outcomes of TAVR in bicuspid AS and compare them to tricuspid AS. In addition, the differences in outcomes between bicuspid versus tricuspid AS will be analyzed, taking into consideration the technological developments in transcatheter valves.

METHODS

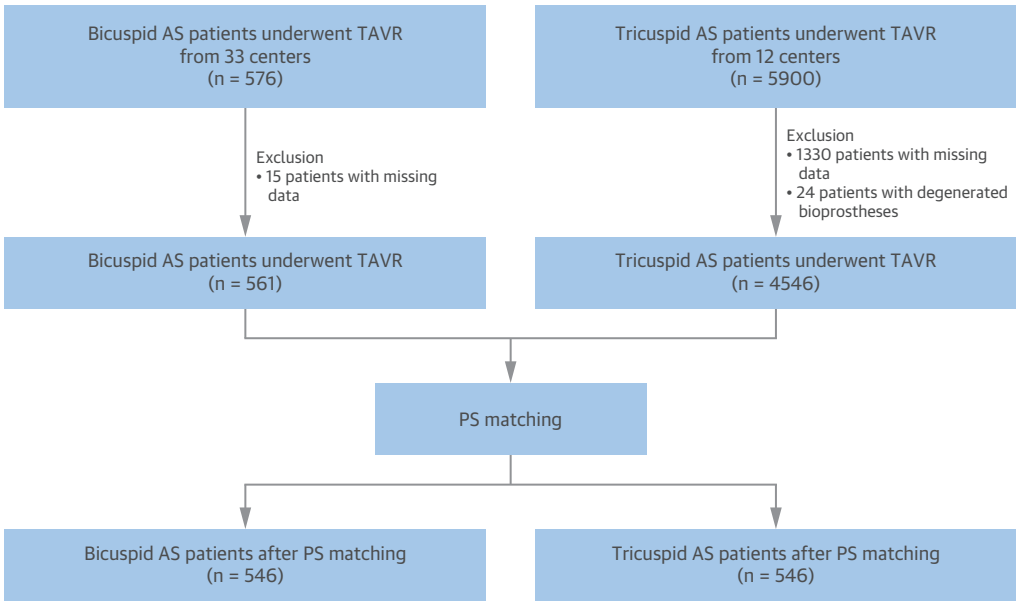
STUDY DESIGN AND PATIENT POPULATION. The Bicuspid AS TAVR registry is an international, multicenter, observational study that enrolled all consecutive patients with bicuspid AS undergoing TAVR. The registry was initiated in December 2013, and a total of 33 centers from Europe, North America, and the Asia-Pacific region contributed to the registry. We collected data retrospectively for cases performed before initiation, and prospectively thereafter. All inconsistencies were resolved directly with local investigators and on-site data monitoring. For the purpose of this study, data for all consecutive patients with tricuspid AS treated with TAVR during the same period were collected from 12 participating centers, and procedural and clinical outcomes of patients with bicuspid and tricuspid AS were compared. As a secondary analysis, the outcomes of TAVR in bicuspid AS were compared with those with tricuspid AS according to device type. This study was approved by the institutional review board of each institution, and all patients provided written informed consent for TAVR and the use of anonymous clinical, procedural, and follow-up data for research. For a retrospective analysis of clinically acquired and anonymized data, the institutional review boards of some institutions waived the need for written patient informed consent.

BICUSPID AORTIC VALVE. Bicuspid aortic valve morphology was classified as previously described by Sievers and Schmidtke (15) according to the number of cusps and the presence of raphes, as well as spatial position and symmetry of raphes and cusps. Type 0 was assigned to morphologies characterized by the presence of 2 symmetric cusps and 1 commissure without evidence of a raphe. Type 1 was assigned to valve morphologies with 1 raphe, and type 2 when 2 raphes were present. All participating centers reviewed and subsequently confirmed the diagnosis and classification of bicuspid AS. When both transesophageal echocardiography and preprocedural computed tomography were performed, patients were excluded if the diagnosis of bicuspid aortic valve was not consistent or remained speculative.

STUDY DEVICES AND PROCEDURE. Patients were selected for TAVR at the institutional level after discussions by the multidisciplinary heart team. The access site was determined by the multidisciplinary heart team. All centers adopted a transfemoral-first approach policy, with criteria for performing a nontransfemoral approach based on the heart team's consideration of the size, calcification, and atheroma of the aorto-iliofemoral artery. Device sizes were selected based on 3-dimensional, multidetector-row computed tomography–based annular measurements or transesophageal echocardiogram assessment. All TAVR procedures were conducted in accordance with local guidelines using standard techniques via transfemoral, transapical, trans-subclavian, or transaortic access, and the early-generation devices (the Sapien XT [Edwards Lifesciences, Irvine, California] and CoreValve [Medtronic, Minneapolis, Minnesota]) or new-generation devices (the Sapien 3 [Edwards Lifesciences], Lotus [Boston Scientific, Natick, Massachusetts] and Evolut R [Medtronic]) were implanted (17–22).

ENDPOINTS AND DEFINITIONS. The primary endpoint of the present study was all-cause mortality at 1 and 2 years. Secondary endpoints were 30-day major clinical endpoints using the Valve Academic Research Consortium (VARC)-2 criteria (23). Device success was defined as a composite endpoint including: 1) absence of procedure-related death; 2) correct positioning of a single prosthetic heart valve into the proper anatomic location; and 3) intended performance of the prosthetic heart valve (no prosthesis-patient mismatch, mean aortic gradient <20 mm Hg or peak velocity <3 m/s, and no moderate or severe paravalvular leak). Other endpoints included new permanent pacemaker insertion, procedure- and device-related complications, and echocardiographic assessment of the valve and cardiac function at discharge. No echocardiographic core laboratory was used, and all echocardiographic data were site-reported. The severity of regurgitation was qualitatively assessed and graded using

FIGURE 1 Study Flow Chart



A total of 576 patients with bicuspid AS consecutively treated with TAVR were enrolled from 33 centers. For the purpose of this study, data from 4,546 patients with tricuspid AS consecutively undergoing TAVR were collected from 12 participating centers. After propensity score matching, 546 patients with bicuspid and tricuspid AS were compared. AS = aortic valve stenosis; PS = propensity score; TAVR = transcatheter aortic valve replacement.

transthoracic echocardiography at each institution, according to established guidelines (23).

DATA COLLECTION. Data collection by a dedicated case report form included baseline clinical, laboratory, echocardiographic, and computed tomographic data, as well as procedural data and clinical follow-up data at pre-specified time points (1, 6, and 12 months, and yearly thereafter). Follow-up was obtained by clinical visits and/or through telephone contacts. Referring cardiologists, general practitioners, and patients were contacted whenever necessary for further information. All data provided by each institution were anonymized, centrally collected, and assessed for quality.

STATISTICAL ANALYSIS. Given the differences in baseline clinical, echocardiographic, and procedural characteristics between patients with bicuspid and tricuspid AS, propensity score matching was applied to identify a cohort of patients with similar baseline characteristics, and thus, clinical outcomes of propensity score–matched cohorts were compared. The propensity score is a conditional probability of having a particular exposure (bicuspid AS or tricuspid AS), given a set of covariates measured at baseline. The propensity score has been developed using a logistic regression model according to a nonparsimonious approach, and all clinical variables (age, sex, New York Heart Association functional class III or IV, hypertension, diabetes mellitus, creatinine, peripheral vascular disease, prior cerebrovascular accident, chronic lung disease, prior percutaneous coronary intervention, prior coronary artery bypass graft, mean gradient, and left ventricular ejection fraction) as well as procedural data (transfemoral access and device type were included in the analysis. Additionally, we created propensity score–matched cohorts for subgroups (early- and new-generation devices), and outcomes were compared. The details of the propensity score method are described in the Online Appendix.

After matching, continuous variables following a normal distribution were compared using the paired-sample Student *t* test; otherwise, the Wilcoxon rank sum test was used. Differences for matched categorical variables were analyzed with McNemar's test. For the VARC-2 major endpoints and other complications, frequencies and relative numbers were given including the odds ratio (OR) with 95% confidence intervals (CIs) and p values of

McNemar's test for the propensity score-matched cohorts or the chi-square test for the subgroup analysis. Cumulative survival rates were analyzed using the Kaplan-Meier method, and were compared using win ratio tests for the propensity score-matched cohort and log-rank test for the subgroup analysis (24). All statistical analyses were performed using SPSS software version 21.0 (SPSS, Inc., Chicago, Illinois) and R software version 2.12.2 (25). A 2-sided p value <0.05 was considered to indicate statistical significance.

RESULTS

BASELINE CHARACTERISTICS. A total of 576 patients with bicuspid AS were treated with TAVR across 33 participating centers between April 2005 and May 2016. During the same period, a total of 5,900 patients with tricuspid AS were treated with TAVR across 12 participating centers. Patients with missing data or those who received TAVR for degenerated bioprostheses were excluded from the analysis. Consequently, 561 patients with bicuspid AS and 4,546 patients with tricuspid AS were included in the present analysis (**Figure 1**). The type of bicuspid AS was diagnosed in 497 patients (88.6%): type 0 was diagnosed in 63 patients (12.7%), type 1 in 426 (85.7%), and type 2 in 8 (1.6%).

In the unadjusted cohort, patients with bicuspid AS were younger and more likely to be male, whereas patients with tricuspid AS were more likely to have multiple comorbidities (Online Table 1). In terms of surgical risk, patients with bicuspid AS had a lower Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) (14.8 ± 12.3% vs. 16.7 ± 11.8%; $p = 0.003$) and Society of Thoracic Surgeons (STS) score (5.0 ± 5.1% vs. 6.5 ± 8.8%; $p < 0.001$). Furthermore, large prostheses were used more often in the bicuspid AS group (34.5% vs. 14.5%; $p < 0.001$), whereas the transfemoral approach was equally frequent in both groups. After performing propensity score matching, both groups were well matched, with no significant differences in baseline characteristics, except more frequent use of the largest prostheses in the bicuspid AS group (**Table 1**).

TABLE 1 Baseline Characteristics

	Propensity Score Matched Cohort		
	Bicuspid AS (n = 546)	Tricuspid AS (n = 546)	p Value
Age, yrs	77.2 ± 8.2	77.2 ± 8.8	0.91
Male	343 (62.8)	331 (60.6)	0.48
NYHA functional class III or IV	439 (80.4)	428 (82.1)	0.48
Logistic EuroSCORE, %	16.1 ± 12.0	16.9 ± 13.9	0.58
STS score, %	4.6 ± 4.6	4.3 ± 3.0	0.29
Hypertension	382 (70.0)	385 (70.5)	0.89
Diabetes mellitus	128 (23.4)	127 (23.3)	>0.99
Creatinine, mg/dl	1.2 ± 0.9	1.2 ± 0.7	0.81
Peripheral vascular disease	83 (15.2)	85 (15.6)	0.93
Prior cerebrovascular accident	77 (14.1)	69 (12.6)	0.53
Chronic lung disease	98 (17.9)	82 (15.0)	0.23
Prior PCI	121 (22.2)	128 (23.4)	0.66
Prior CABG	62 (11.4)	67 (12.3)	0.70
Echocardiographic findings			
Mean gradient, mm Hg	49.7 ± 17.7	48.5 ± 17.1	0.25
Aortic valve area, cm^2	0.7 ± 0.2	0.7 ± 0.2	0.86
LVEF, %	51.6 ± 15.0	51.6 ± 15.2	0.99
Procedural data			
Transfemoral access	432 (85.9)	430 (86.2)	0.93
Device			
Early-generation devices	320 (58.6)	321 (58.8)	>0.99
Sapien XT	155 (28.4)	150 (27.5)	0.77
CoreValve	165 (30.2)	171 (31.3)	0.73
New-generation devices	226 (41.4)	225 (41.2)	>0.99
Sapien 3	160 (29.3)	162 (29.7)	0.94
Lotus	43 (7.9)	47 (8.6)	0.73
Evolut R	23 (4.2)	16 (2.9)	0.32
Size*			
Small	105/503 (20.9)	152/499 (30.5)	0.001
Medium	226/503 (44.9)	238/499 (47.7)	0.38
Large	172/503 (34.2)	109/499 (21.8)	<0.001
Type of bicuspid			
Determined	478 (87.5)	–	
Type 0	61 (12.8)	–	
Type 1	409 (85.6)	–	
Type 2	8 (1.7)	–	
Undetermined/ unavailable	68 (12.5)	–	

Values are mean ± SD, n (%), or n/N (%). *Small = 23 mm for Sapien XT/Sapien 3 and ≤26 mm for CoreValve/Evolut R; medium = 26 mm for Sapien XT/Sapien 3 and 29 mm for CoreValve/Evolut R; large = 29 mm for Sapien XT/Sapien 3, 31 mm for CoreValve, and 34 mm for Evolut R.

AS = aortic valve stenosis; CABG = coronary artery bypass graft; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons.

PROCEDURAL AND CLINICAL OUTCOMES. Table 2 summarizes the procedural and clinical outcomes of the propensity score-matched cohort. Compared with patients with tricuspid AS, patients with bicuspid AS had more frequent conversion to surgery, implantation of second valve, and moderate or severe paravalvular leak, as well as a lower device success rate. There was no significant difference in new permanent pacemaker insertion between the bicuspid and tricuspid AS groups.

In terms of 30-day clinical outcomes, there were no significant differences between the bicuspid

TABLE 2 Procedural and Clinical Outcomes

	Propensity Score Matched Cohort			
	Bicuspid AS (n = 546)	Tricuspid AS (n = 546)	p Value	OR (95% CI)
Procedural outcomes				
Procedure-related death	7 (1.3)	6 (1.1)	>0.99	1.17 (0.39–3.47)
Conversion to surgery	11 (2.0)	1 (0.2)	0.006	11.00 (1.42–85.20)
Coronary obstruction	5 (0.9)	3 (0.5)	0.73	1.67 (0.40–6.97)
Aortic root injury	9 (1.6)	0 (0.0)	0.004	–
Implantation of 2 valves	26 (4.8)	8 (1.5)	0.002	3.71 (1.61–8.56)
New permanent pacemaker	84 (15.4)	84 (15.4)	>0.99	1.00 (0.72–1.39)
Echocardiographic findings				
Mean gradient, mm Hg	10.8 ± 6.7	10.2 ± 4.4	0.18	
LVEF, %	54.2 ± 13.6	54.7 ± 13.9	0.79	
Moderate or severe paravalvular leak	57 (10.4)	37 (6.8)	0.04	1.61 (1.04–2.48)
Device success	466 (85.3)	499 (91.4)	0.002	0.54 (0.37–0.80)
30-day outcomes				
All-cause mortality	20 (3.7)	18 (3.3)	0.87	1.11 (0.59–2.10)
Stroke	16 (2.9)	10 (1.8)	0.33	1.60 (0.73–3.53)
Nondisabling	7 (1.3)	6 (1.1)	>0.99	1.17 (0.39–3.47)
Disabling	9 (1.6)	4 (0.7)	0.27	2.25 (0.69–7.31)
Bleeding				
Major	20 (3.7)	22 (4.0)	0.88	0.91 (0.50–1.67)
Life-threatening	11 (2.0)	19 (3.5)	0.20	0.58 (0.28–1.22)
Major vascular complication	16 (2.9)	16 (2.9)	>0.99	1.00 (0.50–2.00)
Acute kidney injury (stage 2 or 3)	11 (2.0)	5 (0.9)	0.21	2.20 (0.77–6.33)

Values are n (%) or mean ± SD, unless otherwise indicated.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

and tricuspid AS groups in 30-day all-cause mortality, stroke, life-threatening bleeding, major vascular complications, and stage 2 or 3 acute kidney injury.

Outcomes according to device type. When stratified according to whether they received early- versus new-generation devices, patients with bicuspid AS had more frequent procedural complications than those with tricuspid AS when receiving the early-generation devices (conversion to surgery: 2.5% vs. 0.3%; p = 0.02; second valve implantation: 7.2% vs. 2.2%; p = 0.003; moderate or severe paravalvular leak: 15.9% vs. 10.3%; p = 0.03) (**Figure 2A**). However, there were no significant differences in procedural complications between the bicuspid and tricuspid AS groups when receiving the new-generation devices (**Figure 2B**). These findings were consistently observed in propensity score matched cohorts for early- and new-generation devices (Online Figure 1).

Procedural and clinical outcomes according to device type are shown in Online Figure 2. Compared with patients with tricuspid AS, patients with bicuspid AS had more frequent aortic root injury (4.5% vs. 0.0%; p = 0.015) when receiving the Sapien XT. In addition, patients with bicuspid AS had more frequent second valve implantation (11.6% vs. 2.9%; p = 0.002), moderate or severe paravalvular leak (19.4% vs. 10.5%; p = 0.02), and subsequent lower device success rate (72.1% vs. 86.0%; p = 0.002) than those with tricuspid AS when receiving the CoreValve. However, there were no significant differences in these adverse procedural events between groups when receiving the Sapien 3 and Lotus.

There were no significant differences in 30-day mortality and other major clinical endpoints between groups, except that patients with bicuspid AS had a higher rate of major vascular complications compared with patients with tricuspid AS when receiving the Sapien XT (5.8% vs. 0.7%; p = 0.01) (Online Figures 3 to 5).

In terms of outcomes across bicuspid phenotype, there were no significant differences in procedural and clinical outcomes between type 0 and type 1 bicuspid AS (Online Table 2). Of note, moderate or severe paravalvular leak occurred in 5 patients (8.2%) for type 0 bicuspid AS and 44 patients (10.8%) for type 1 bicuspid AS (p = 0.54), whereas all aortic root injury occurred only in patients with type 1 bicuspid AS.

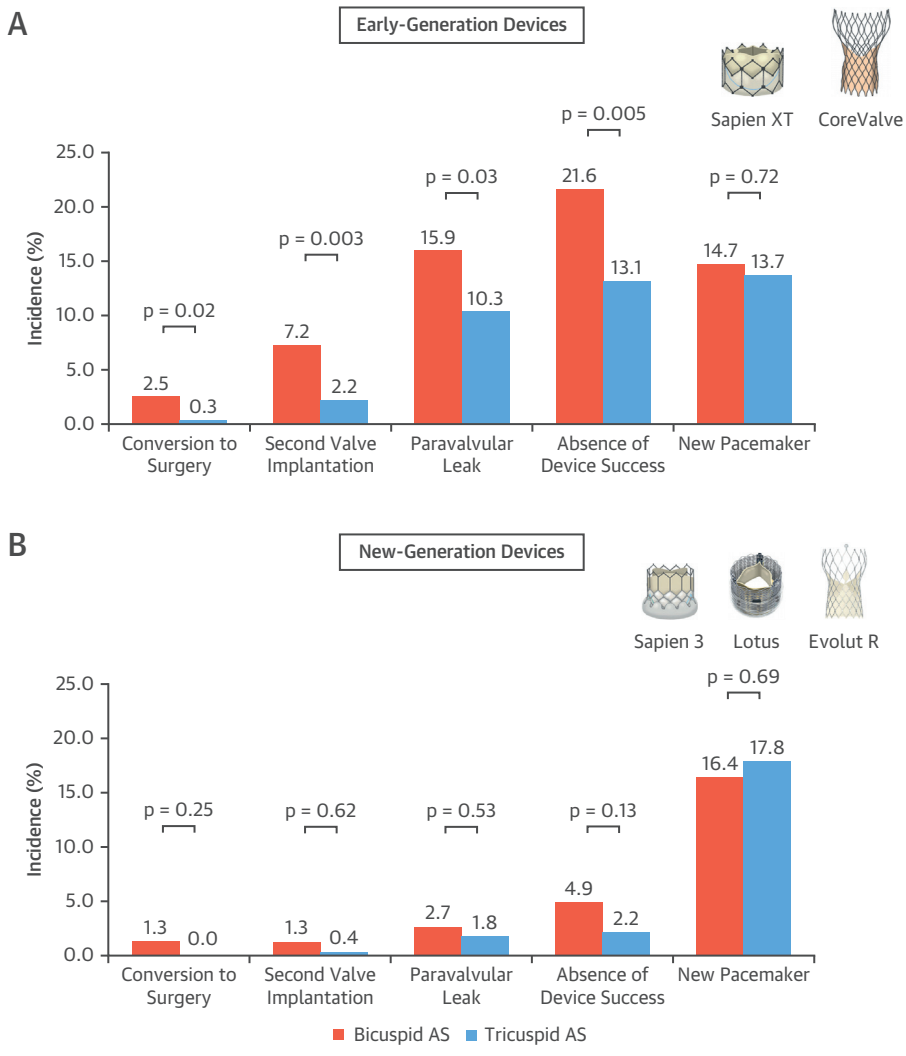
Midterm mortality. Over a median follow-up period of 460 days (IQR: 90 to 710 days), 66 patients died in the bicuspid AS group and 73 patients died in the tricuspid AS group. There were no differences between the 2 groups in cumulative event rates for all-cause mortality at the 2-year follow-up (17.2% vs. 19.4%; p = 0.28) (**Central Illustration**). Furthermore, there were no significant differences in 1-year all-cause mortality rates between groups with stratification according to early- and new-generation devices (early-generation devices: 14.5% vs. 13.7%; log-rank p = 0.80; new-generation devices: 4.5% vs. 7.4%; log-rank p = 0.64) (**Figures 3A and 3B**). These findings were consistently observed in propensity score-matched cohorts for early- and new-generation devices (Online Figures 6A and 6B).

DISCUSSION

The present study is the first large-scale study to compare the safety, efficacy, and clinical outcomes of TAVR in patients with bicuspid and tricuspid AS. The major findings of the present study are as follows:

1. In the propensity score-matched cohort, TAVR in patients with bicuspid AS was associated with more frequent adverse procedural events compared with those with tricuspid AS. These differences were observed among patients treated with the early-generation devices.

FIGURE 2 **Procedural Outcomes in Bicuspid and Tricuspid AS With Early- and New-Generation Devices**

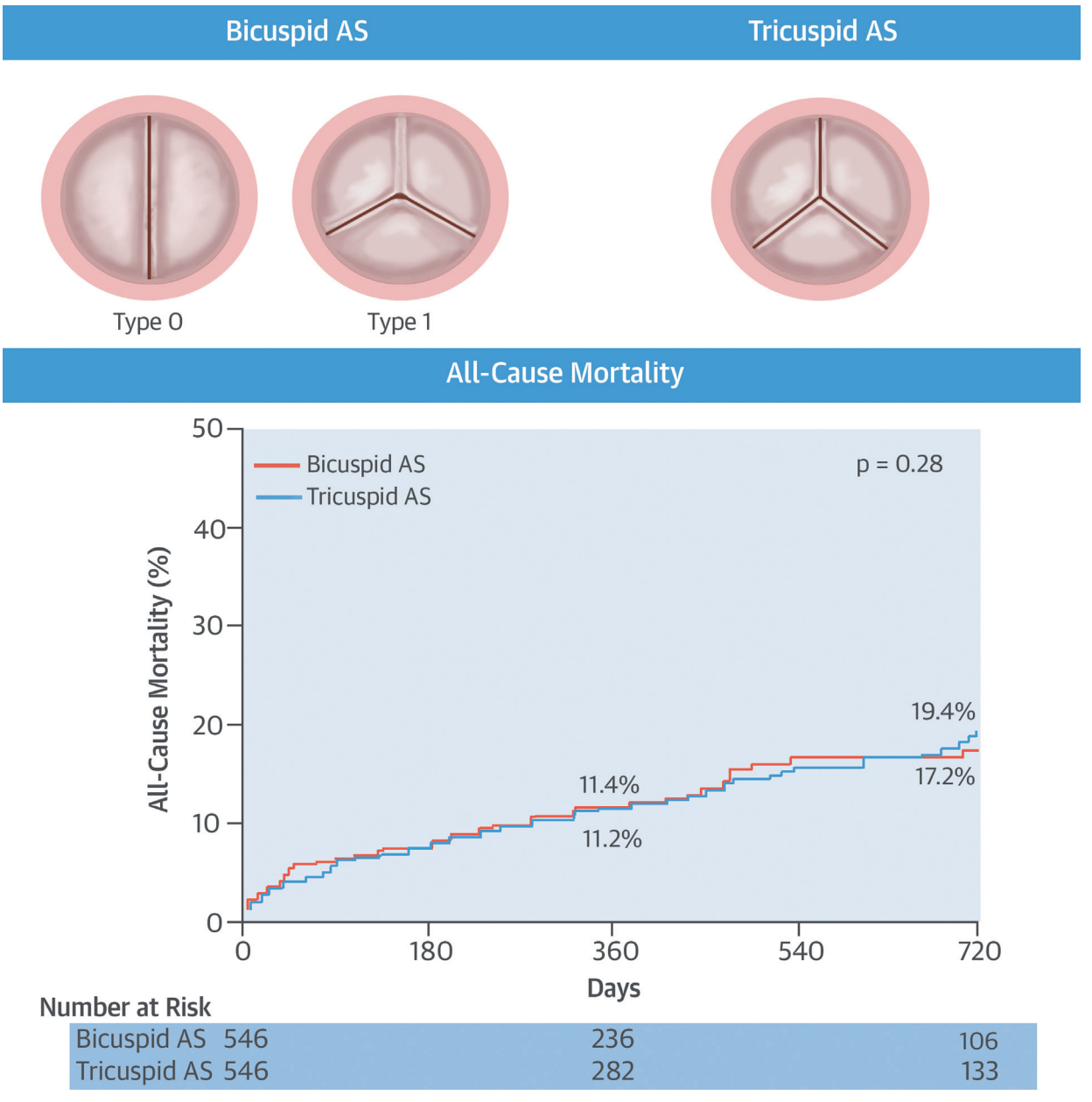


Rates of conversion to surgery, second valve implantation, moderate or severe paravalvular leak, absence of device success, and new permanent pacemaker insertion after TAVR using **(A)** early-generation devices (Sapien XT/CoreValve) and **(B)** new-generation devices (Sapien 3/Lotus/Evolut R). Abbreviations as in Figure 1.

2. However, there were no significant differences in procedural complications between groups when using the new-generation devices.
3. The cumulative event rates for all-cause mortality at 2-year follow-up were comparable between the bicuspid and tricuspid groups.

Recently, 2 multicenter studies demonstrated the acceptable clinical outcomes of TAVR for bicuspid AS (8,10). However, patients included in those studies were younger and had less comorbidities compared with most published trials and observational studies including patients with tricuspid AS. Given that patients with bicuspid AS have less coexisting comorbidities compared with patients with tricuspid AS, there is a potential risk that clinical outcomes of TAVR for bicuspid AS could differ from those for tricuspid AS with equivalent surgical risk. In the present study, patients with bicuspid AS in the crude cohort were younger and had less comorbidity than those with tricuspid AS. Both the bicuspid and tricuspid AS groups had an intermediate-risk profile, with mean logistic EuroSCOREs of 14.8% and 16.7%, and mean STS scores of 5.0% and 6.5%, respectively. In the present study, compared with tricuspid AS, TAVR in bicuspid AS was associated with similar

CENTRAL ILLUSTRATION **TAVR for Bicuspid Versus Tricuspid Aortic Valve Stenosis**



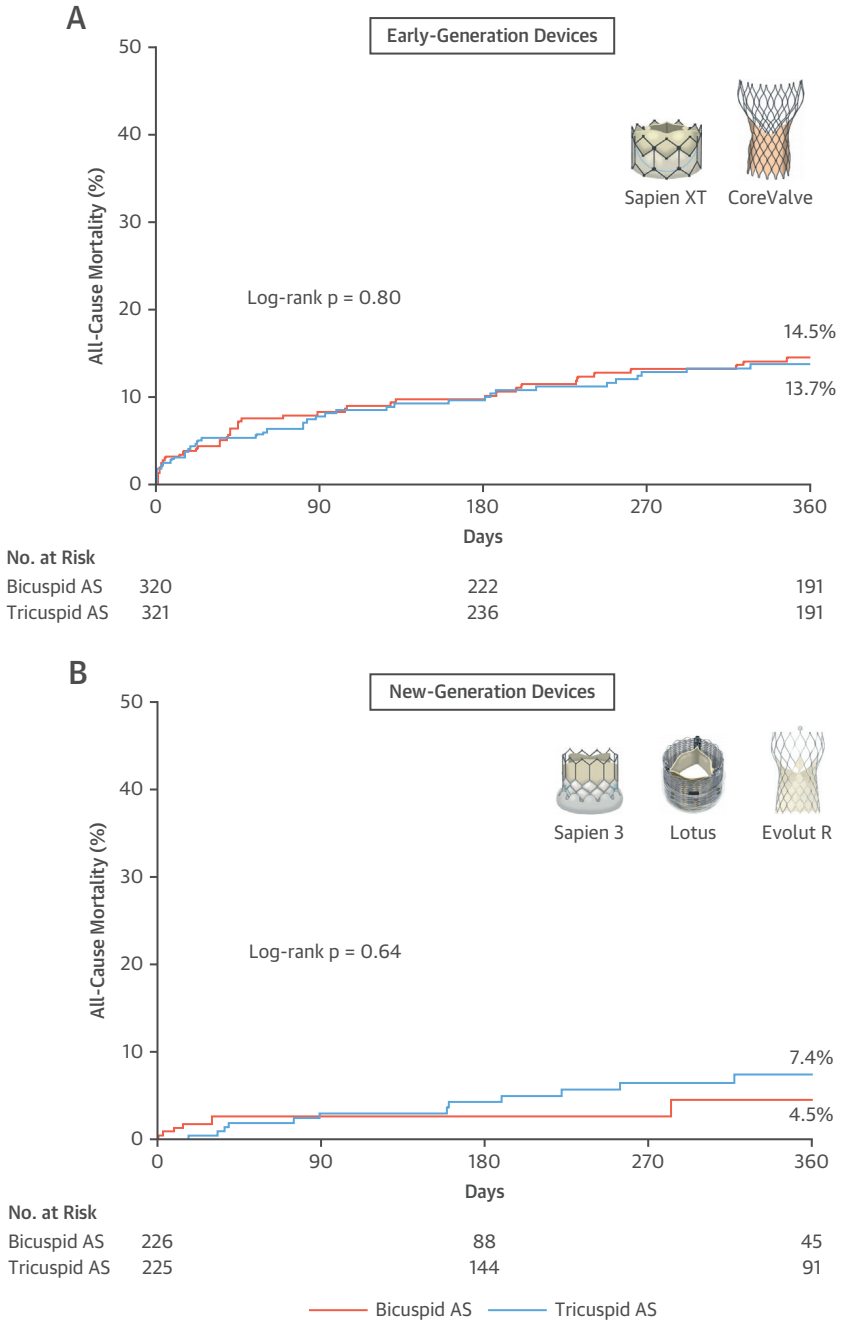
Yoon, S.-H. et al. J Am Coll Cardiol. 2017;69(21):2579-89.

(Top) Schematic presentations of bicuspid and tricuspid aortic valves. Type 0 and 1 indicate bicuspid aortic valve with no raphe, and 1 raphe, respectively. **(Bottom)** Cumulative all-cause mortality rates in patients with bicuspid AS **(orange)** and tricuspid AS **(blue)** in a propensity score matched cohort. Event rates were compared using the win ratio test. AS = aortic valve stenosis.

prognosis, although the device success was lower. The accumulation of a large multicenter database has, for the first time, allowed comparisons of matched cohorts, as well as the potential effect of differences in device type.

The present study also showed that procedural challenges of TAVR in bicuspid AS and related outcomes differed according to early- and new-generation devices. Within the group receiving the early-generation devices, patients with bicuspid

FIGURE 3 **Kaplan-Meier Curves for All-Cause Mortality According to Early- and New-Generation Devices**



Cumulative all-cause mortality rates in patients with bicuspid AS **(orange)** and tricuspid AS **(blue)** treated with **(A)** early- and **(B)** new-generation devices, respectively. Event rates were compared using the log-rank test.

AS had more frequent aortic root injury, mainly related to Sapien XT implantation, and second valve implantation and moderate or severe paravalvular leak, mainly related to CoreValve implantation. Among those treated with the new-generation devices, however, there were no significant differences in procedural outcomes between the bicuspid and tricuspid groups. The new-generation devices were

developed to mitigate the critical limitations of the early-generation devices: significant paravalvular leak, difficulty with optimal positioning, and vascular complications. All of these adverse events were reported to be associated with worse outcomes (26-29). The new-generation balloon-expandable Sapien 3, with an external sealing cuff allowing for effective sealing, eliminates the extreme oversizing and mitigates the morphological challenges of bicuspid AS. Similarly, the mechanical expanding Lotus valve, with an outer adaptive seal, as well as retrievability and repositioning capacity, may ameliorate the difficulties in optimal positioning and prevent paravalvular leak. The present study showed that the initial attempt of device advancement succeeded in overcoming the procedural limitations in tricuspid AS, and now goes beyond the challenges of treating bicuspid AS.

Given that a recent randomized trial demonstrated similar survival rates between TAVR and surgery in intermediate-risk patients (6), the extension of TAVR may be considered for younger and lower-risk patients with a possibly increased proportion of bicuspid AS. Despite procedural challenges of TAVR in bicuspid AS, the present study showed similar overall mortality rates between the bicuspid and tricuspid AS groups. This suggests that long-term mortality of patients with bicuspid AS is determined by multiple factors that also affect the prognosis of the tricuspid AS population.

Several essential factors should be considered in treating patients with bicuspid AS. Sievers et al. (30) showed a similar late survival and freedom from reoperation after surgery between the different types of bicuspid aortic valves. However, given the nature of transcatheter heart valves, future studies should evaluate the association between the types of bicuspid aortic valves and outcomes after TAVR. Furthermore, management of concomitant aortopathy in treating patients with bicuspid aortic valve should be taken into account. The risk of aortic rupture or dissection is greater in patients with a bicuspid aortic valve than in the general population (31), and also increases owing to aging-related progressive aortic dilation and degeneration (32). Given the expanding indication of TAVR for younger and lower-risk patients, physicians will face this dilemma in treating relatively younger patients with bicuspid AS and concomitant aortopathy. Several factors, including age, comorbidities, and additional risk factors for aortic complications, must be considered during the decision-making process to treat patients with bicuspid aortic valve and concomitant aortopathy (33). Nevertheless, longer life expectancy in those patient populations mandates future studies to evaluate the effect of concomitant aortopathy, as well as valve durability for long-term follow-up.

STUDY LIMITATIONS. First, this study had the inherent limitations of an observational study without center-independent adjunction of adverse events and an independent core laboratory to diagnose bicuspid AS and assess paravalvular leak. Moreover, although propensity score matching is a well-accepted approach in observational research to address differences in baseline characteristics, it cannot account for unmeasured bias. Last, device selection was not randomized, but was at the operator's discretion, and patient selection as well as operator experience may have affected the observed outcomes.

CONCLUSIONS

Compared with tricuspid AS, TAVR in bicuspid AS was associated with a similar prognosis, but a lower device success rate. Procedural differences were observed in patients treated with the early-generation devices, whereas no differences were observed with the new-generation devices.

ADDRESS FOR CORRESPONDENCE: Dr. Sung-Han Yoon, Cedars-Sinai Heart Institute, 8700 Beverly Boulevard, Los Angeles, California 90048. E-mail: yunsonhan@gmail.com.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Compared with those with tricuspid AS, patients with bicuspid valves undergoing TAVR with early-generation devices more often developed adverse procedural events, but there were no significant differences between groups in procedural complications with newer-generation devices. Cumulative all-cause mortality at 2-year follow-up was comparable between the bicuspid and tricuspid groups.

TRANSLATIONAL OUTLOOK: Larger studies are needed to evaluate the long-term outcomes and durability of TAVR in patients with bicuspid AS.

REFERENCES

1. Leon MB, Smith CR, Mack M, et al., for the PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.

2. Smith CR, Leon MB, Mack MJ, et al., for the PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.

3. Gilard M, Eltchaninoff H, Iung B, et al., for the FRANCE 2 Investigators. Registry of transcatheter aortic-valve implantation in high-risk patients. N Engl J Med 2012;366:1705–15.

4. Reinöhl J, Kaier K, Reinecke H, et al. Effect of availability of transcatheter aortic-valve replacement on clinical practice. N Engl J Med 2015;373:2438–47.

5. Adams DH, Popma JJ, Reardon MJ, et al., for the U.S. CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790–8.

6. Leon MB, Smith CR, Mack MJ, et al., for the PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374:1609–20.

7. Thyregod HG, Steinbrüchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. J Am Coll Cardiol 2015;65:2184–94.

8. Mylotte D, Lefevre T, Søndergaard L, et al. Transcatheter aortic valve replacement in bicuspid aortic valve disease. J Am Coll Cardiol 2014;64:2330–9.

9. Perlman GY, Blanke P, Dvir D, et al. Bicuspid aortic valve stenosis: favorable early outcomes with a next-generation transcatheter heart valve in a multicenter study. J Am Coll Cardiol Intv 2016;9:817–24.

10. Yoon SH, Lefèvre T, Ahn JM, et al. Transcatheter aortic valve replacement with early- and new-generation devices in bicuspid aortic valve stenosis. J Am Coll Cardiol 2016;68:1195–205.

11. Yousef A, Simard T, Webb J, et al. Transcatheter aortic valve implantation in patients with bicuspid aortic valve: a patient level multi-center analysis. Int J Cardiol 2015;189:282–8.

12. Jilaihawi H, Chen M, Webb J, et al. A bicuspid aortic valve imaging classification for the TAVR era. J Am Coll Cardiol Img 2016;9:1145–58.

13. Mack MJ, Brennan JM, Brindis R, et al., for the STS/ACC TVT Registry. Outcomes following transcatheter aortic valve replacement in the United States. JAMA 2013;310:2069–77.

14. Yoon SH, Ahn JM, Hayashida K, et al., for the Asian TAVR Investigators. Clinical outcomes following transcatheter aortic valve replacement in Asian population. J Am Coll Cardiol Intv 2016;9:926–33.

15. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. J Thorac Cardiovasc Surg 2007;133:1226–33.

16. Sabet HY, Edwards WD, Tazelaar HD, Daly RC. Congenitally bicuspid aortic valves: a surgical pathology study of 542 cases (1991 through 1996) and a literature review of 2,715 additional cases. Mayo Clin Proc 1999;74:14–26.

17. Cribier A, Eltchaninoff H, Tron C, et al. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. J Am Coll Cardiol 2006;47:1214–23.

18. Webb JG, Pasupati S, Humphries K, et al. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. Circulation 2007;116:755–63.

19. Ye J, Cheung A, Lichtenstein SV, et al. Transapical transcatheter aortic valve implantation: 1-year outcome in 26 patients. J Thorac Cardiovasc Surg 2009;137:167–73.

20. Grube E, Laborde JC, Gerckens U, et al. Percutaneous implantation of the CoreValve self-expanding valve prosthesis in high-risk patients with aortic valve disease: the Siegburg first-in-man study. Circulation 2006;114:1616–24.

21. Etienne PY, Papadatos S, El Khoury E, Pieters D, Price J, Glineur D. Transaortic transcatheter aortic valve implantation with the Edwards SAPIEN valve: feasibility, technical considerations, and clinical advantages. Ann Thorac Surg 2011;92:746–8.

22. Bruschi G, de Marco F, Botta L, et al. Direct aortic access for transcatheter self-expanding aortic bioprosthetic valves implantation. Ann Thorac Surg 2012;94:497–503.

23. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438–54.

24. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J 2012;33:176–82.

25. The R Project for Statistical Computing. R version 2.12.2. Available at: https://www.r-project.org. Accessed March 28, 2017.

26. Kodali S, Pibarot P, Douglas PS, et al. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards Sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. Eur Heart J 2015;36:449–56.

27. Abdel-Wahab M, Comberg T, Buttner HJ, et al., for the Segeberg-Krozingen TAVI Registry. Aortic regurgitation after transcatheter aortic valve implantation with balloon- and self-expandable prostheses: a pooled analysis from a 2-center experience. J Am Coll Cardiol Intv 2014;7:284–92.

28. Généreux P, Webb JG, Svensson LG, et al., for the PARTNER Trial Investigators. Vascular complications after transcatheter aortic valve replacement: insights from the PARTNER (Placement of AoRTic TraNscathetER Valve) trial. J Am Coll Cardiol 2012;60:1043–52.

29. Athappan G, Patvardhan E, Tuzcu EM, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. J Am Coll Cardiol 2013;61:1585–95.

30. Sievers HH, Stierle U, Mohamed SA, et al. Toward individualized management of the ascending aorta in bicuspid aortic valve surgery: the role of valve phenotype in 1362 patients. J Thorac Cardiovasc Surg 2014;148:2072–80.

31. Michelena HI, Khanna AD, Mahoney D, et al. Incidence of aortic complications in patients with bicuspid aortic valves. JAMA 2011;306:1104–12.

32. Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. Am J Cardiol 1989;64:507–12.

33. Hiratzka LF, Creager MA, Isselbacher EM, et al. Surgery for aortic dilatation in patients with bicuspid aortic valves: a statement of clarification from the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;67:724–31.

KEY WORDS aortic stenosis, bicuspid aortic valve, transcatheter aortic valve implantation

APPENDIX For a supplemental table and figures, please see the online version of this article.