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Transcatheter Aortic Valve Replacement With Early- and New-Generation Devices in Bicuspid Aortic Valve Stenosis

Sung-Han Yoon, MD,[a] Thierry Lefèvre, MD,[b] Jung-Ming Ahn, MD,[a] Gidon Y. Perlman, MD,[c] Danny Dvir, MD,[c] Azeem Latib, MD,[d] Marco Barbanti, MD,[e] Florian Deuschl, MD,[f] Ole De Backer, MD,[g] Philipp Blanke, MD,[c] Thomas Modine, MD,[h] Gregor Pache, MD,[i] Franz-Josef Neumann, MD,[j] Philipp Ruile, MD,[j] Takahide Arai, MD,[b] Yohei Ohno, MD,[e] Hidehiro Kaneko, MD,[k] Edgar Tay, MD,[l] Niklas Schofer, MD,[f] Erik W. Holy, MD,[m] Ngai H.V. Luk, MD,[g] Gerald Yong, MD,[n] Qingsheng Lu, MD,[o] William K.F. Kong, MD,[l,p] Jimmy Hon, MD,[l] Hsien-Li Kao, MD,[q] Michael Lee, MD,[r] Wei-Hsian Yin, MD,[s] Duk-Woo Park, MD,[a] Soo-Jin Kang, MD,[a] Seung-Whan Lee, MD,[a] Young-Hak Kim, MD,[a] Cheol Whan Lee, MD,[a] Seong-Wook Park, MD,[a] Hyo-Soo Kim, MD,[t] Christian Butter, MD,[k] Omar K. Khalique, MD,[u] Ulrich Schaefer, MD,[f] Fabian Nietlispach, MD,[m] Susheel K. Kodali, MD,[u] Martin B. Leon, MD,[u] Jian Ye, MD,[c] Bernard Chevalier, MD,[b] Jonathon Leipsic, MD,[c] Victoria Delgado, MD,[q] Jeroen J. Bax, MD,[q] Corrado Tamburino, MD,[e] Antonio Colombo, MD,[d] Lars Søndergaard, MD,[g] John G. Webb, MD,[c] Seung-Jung Park, MD[a]

ABSTRACT

BACKGROUND Few studies have evaluated the clinical outcomes of transcatheter aortic valve replacement (TAVR) in patients with bicuspid aortic valve stenosis (AS). Particularly, limited data exist comparing the results of TAVR with new-generation devices versus early-generation devices.

OBJECTIVES This study sought to evaluate the clinical outcomes of TAVR for bicuspid AS with early- and new-generation devices.

METHODS The Bicuspid TAVR Registry is an international multicenter study enrolling consecutive patients with bicuspid AS undergoing TAVR between April 2005 and May 2015.

RESULTS Of 301 patients, 199 patients (71.1%) were treated with early-generation devices (Sapien XT [Edwards Lifesciences Corporation, Irvine, California]: n = 87; CoreValve [Medtronic, Minneapolis, Minnesota]: n = 112) and 102 with new-generation devices (Sapien 3 [Edwards Lifesciences Corporation]: n = 91; Lotus [Boston Scientific Corporation, Marlborough, Massachusetts]: n = 11). The mean Society of Thoracic Surgeons score was 4.7 ± 5.2 without significant differences between groups (4.6 ± 5.1 vs. 4.9 ± 5.4; p = 0.57). Overall, all-cause mortality rates were 4.3% at 30 days and 14.4% at 1 year. Moderate or severe paravalvular leak was absent and significantly less frequent with new-generation compared to early-generation devices (0.0% vs. 8.5%; p = 0.002), which resulted in a higher device success rate (92.2% vs. 80.9%; p = 0.01). There were no differences between early- and new-generation devices in stroke (2.5% vs. 2.0%; p > 0.99), life-threatening bleeding (3.5% vs. 2.9%; p > 0.99), major vascular complication (4.5% vs. 2.9%; p = 0.76), stage 2 to 3 acute kidney injury (2.5% vs. 2.9%; p > 0.99), early safety endpoints (15.1% vs. 10.8%; p = 0.30), and 30-day all-cause mortality (4.5% vs. 3.9%; p > 0.99).

CONCLUSIONS The clinical outcomes of TAVR in patients with bicuspid AS were favorable. New-generation devices were associated with less paravalvular leak and, hence, a higher device success rate than early-generation devices. (The Bicuspid Aortic Stenosis Following Transcatheter Aortic Valve Replacement Registry [Bicuspid TAVR]; NCT02394184) (J Am Coll Cardiol 2016;68:1195–205) © 2016 by the American College of Cardiology Foundation.

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From the [a]Division of Cardiology, University of Ulsan, Asan Medical Center, Seoul, Korea; [b]Générale de Santé, Institut Cardiovasculaire Paris Sud, Hôpital Privé Jacques Cartier, Massy, France; [c]Department of Cardiology, St Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; [d]Interventional Cardiology Unit, EMO-GVM Centro Cuore Columbus & San Raffaele Scientific Institute, Milan, Italy San Raffaele Hospital, Milan, Italy; [e]Division of Cardiology, Ferrarotto Hospital, University of Catania, Catania, Italy; [f]Department for General and Interventional Cardiology, University Heart Center, University

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ABBREVIATIONS AND ACRONYMS

AS = aortic valve stenosis

CI = confidence interval

CT = computed tomography

EuroSCORE = European System for Cardiac Operative Risk Evaluation

HR = hazard ratio

PVL = paravalvular leak

STS = Society of Thoracic Surgeons

TAVR = transcatheter aortic valve replacement

VARC = Valve Academic Research Consortium

Transcatheter aortic valve replacement (TAVR) has evolved from a novel technology to an established therapy for high-risk patients with severe symptomatic aortic valve stenosis (AS) (1–6). However, patients with congenital bicuspid AS were not enrolled in initial pivotal randomized trials. Moreover, real-world experience of TAVR for bicuspid AS has been limited, given the anatomical challenges of bicuspid AS—namely, a larger aortic annulus, severe and asymmetric leaflet calcification, presence of calcified raphe, or a dilated ascending aorta—raised concerns about procedure-related complications and worse long-term clinical outcomes (7–9).

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Newer transcatheter heart valves have shown favorable outcomes with less frequent paravalvular leak (PVL) and fewer vascular complications than earlier devices (10–14). Several reports have suggested that TAVR is feasible for bicuspid AS with these new-generation devices (15–17). However, previous reports evaluating TAVR using these newer devices in bicuspid AS have included only a small number of cases with no comparison between different devices.

The Bicuspid TAVR Registry assessed the efficacy and safety of TAVR for bicuspid AS in a large group of patients. In particular, we sought to: 1) examine the clinical outcomes, including long-term analysis; 2) supply data on possible rare complications; and 3) compare the procedural and clinical results of TAVR in bicuspid AS with the use of early- and new-generation devices.

METHODS

The Bicuspid 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 20 centers from Europe, North America, and the Asia-Pacific 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, patients with bicuspid aortic valves who were treated with early-generation devices (Sapien XT, Edwards Lifesciences Corporation, Irvine, California; and CoreValve, Medtronic, Minneapolis, Minnesota) and new-generation devices (Sapien 3, Edwards Lifesciences; and Lotus, Boston Scientific Corporation, Marlborough, Massachusetts) were compared. This study was approved by the

Hospital Hamburg-Eppendorf (UKE), Hamburg, Germany; [g]The Heart Centre, Rigshospitalet University Hospital, Copenhagen, Denmark; [h]Department of Cardiovascular Surgery, Hospital Cardiologique, Lille, France; [i]Department of Radiology, Section of Cardiovascular Radiology, University of Freiburg, Bad Krozingen, Germany; [j]Department of Cardiology & Angiology II, University Heart Center Freiburg-Bad Krozingen, Bad Krozingen, Germany; [k]Heart Center Brandenburg in Bernau, Bernau, Germany; [l]Department of Cardiology, National University Heart Centre, Singapore; [m]University Heart Center, Cardiology and Cardiovascular Surgery, University Hospital Zürich, Zurich, Switzerland; [n]Division of Cardiology, Royal Perth Hospital, Perth, Western Australia, Australia; [o]Division of Vascular Surgery, Changhai Hospital, Shanghai, China; [p]Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; [q]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [r]Division of Cardiology, Queen Elizabeth Hospital, Kowloon, Hong Kong; [s]Division of Cardiology, Heart Center, Cheng Hsin General Hospital, Taipei, Taiwan; [t]Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Korea; and the [u]Columbia University Medical Center/New York Presbyterian Hospital, New York, New York. This study was supported by a grant from the CardioVascular Research Foundation, Seoul, Republic of Korea. The Department of Cardiology at the Leiden University Medical Center received research grants from Edwards Lifesciences, Biotronik, Medtronic, and Boston Scientific. Drs. Lefèvre, Tay, and Yong have served as proctors for Edwards Lifesciences. Drs. Dvir, Modine, and Kodali have served as consultants for Edwards Lifesciences and Medtronic. Dr. Latib has served on the Medtronic advisory board; and has served as a consultant for Direct Flow Medical. Dr. De Backer has served as a proctor for St. Jude Medical. Drs. Barbanti, Blanke, Pache, Ye, and Webb have served as consultants for Edwards Lifesciences. Dr. Neumann has received grant support from Medtronic, Boston Scientific, and Edwards Lifesciences. Dr. Ohno has served as a proctor for Medtronic. Dr. Schofer has received travel support from Edwards Lifesciences and Boston Scientific. Dr. Holy has been awarded a training grant sponsored by Edwards Lifesciences. Dr. Khalique has served as a consultant for Edwards Lifesciences and Boston Scientific. Dr. Nietlispach has served as a consultant for Edwards Lifesciences, St. Jude Medical, Direct Flow Medical, and Medtronic. Dr. Leon has served as a nonpaid member of the Scientific Advisory Board of Edwards Lifesciences. Dr. Chevalier has served as a consultant for Medtronic. Dr. Leipsic has served as a consultant and provides the core laboratory for Edwards Lifesciences. Dr. Delgado has received speaking fees from Abbott Vascular. Dr. Søndergaard has served as a proctor for, received research contracts from, and served on the advisory board for Medtronic, St. Jude Medical, and Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Yoon and Lefèvre contributed equally to this work.

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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 retrospective analysis of clinically acquired and anonymized data, the institutional review board of some institutions waived the need for written patient informed consent.

Bicuspid aortic valve morphology was classified as previously described by Sievers and Schmidtke (18) 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 leaflets or 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 pre-procedural computed tomography (CT) were performed, patients were excluded if the diagnosis of bicuspid aortic valve was not consistent or remained speculative.

DEVICES, PROCEDURES, AND DATA COLLECTION. Patients were selected for TAVR at the institutional level after discussion within a multidisciplinary heart team, which also determined the access site. All centers adopted a transfemoral-first approach policy with the criteria for a nontransfemoral approach based on the heart team's consideration of the size, level of calcification, and tortuosity of the aortoiliofemoral artery. Device sizes were selected based on CT or transesophageal echocardiography assessment. All TAVR procedures were conducted in accordance with local guidelines using standard techniques via transfemoral, transapical, transsubclavian, or transaortic access (19–24).

Data were collected using a dedicated case report form that included baseline clinical, laboratory, pre-procedural CT, and echocardiographic data, as well as procedural data and clinical follow-up data at pre-specified time points (1, 6, and 12 months). Follow-up was obtained by clinical visits 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.

ENDPOINTS AND DEFINITIONS. All study endpoints were defined according to the Valve Academic Research Consortium (VARC)-2 criteria (25). The primary outcome measures in the present study were all-cause death at 1 month and 1 year. Secondary outcomes were cardiac death, stroke, bleeding, vascular complications, acute kidney injury, and device success. Other endpoints included permanent pacemaker insertion, procedure- and device-related complications, and echocardiographic assessment of the valve and left ventricular function at discharge. With respect to CT data, aortic annulus maximal or minimal diameter, area, and perimeter were collected. The aortic annulus ellipticity index was calculated according to the formula (maximal diameter)/(minimal diameter). Degree of area oversizing of the device was calculated as: [(device area - annulus area)/annulus area] $\times$ 100. All echocardiographic data were site reported. The severity of regurgitation was qualitatively assessed and graded using transthoracic echocardiography at each institution according to established guidelines (25).

STATISTICAL ANALYSIS. Continuous variables are presented as mean $\pm$ SD and compared using the Student *t* test or Mann-Whitney *U* test. Categorical variables are presented as counts or percentages and compared using the chi-square or Fisher exact test. Cumulative rates of death were calculated using Kaplan-Meier survival analysis, and the log-rank test was used for comparisons across the group. The entire follow-up was used to analyze time-to-event outcomes and patients were censored at the time of

TABLE 1 Baseline and Procedural Characteristics

	Overall (N = 301)	Early-Generation Devices (n = 199)	New-Generation Devices (n = 102)	p Value
Age, yrs	77.0 ± 9.2	77.0 ± 8.9	77.0 ± 9.8	0.97
Male	173 (57.5)	129 (64.8)	44 (43.1)	<0.001
NYHA functional class III or IV	223 (74.1)	148 (74.4)	75 (73.5)	0.88
Logistic EuroSCORE, %	14.9 ± 11.7	15.0 ± 11.2	14.7 ± 12.8	0.88
STS score, %	4.7 ± 5.2	4.6 ± 5.1	4.9 ± 5.4	0.57
Diabetes mellitus	66 (21.9)	41 (20.6)	25 (24.5)	0.44
Creatinine, mg/dl	1.1 ± 0.5	1.1 ± 0.6	1.1 ± 0.3	0.47
Hypertension	188 (62.5)	120 (60.3)	68 (66.7)	0.28
Peripheral vascular disease	38 (12.6)	22 (11.1)	16 (15.7)	0.25
Prior cerebrovascular accident	49 (16.3)	30 (15.7)	19 (18.6)	0.43
Chronic lung disease	52 (17.3)	36 (18.1)	16 (15.7)	0.60
Prior PCI	63 (20.9)	38 (19.1)	25 (24.5)	0.27
Prior CABG	28 (9.3)	15 (7.5)	13 (12.7)	0.14
Echocardiographic findings				
Mean gradient, mm Hg	52.1 ± 18.5	53.6 ± 19.6	49.3 ± 15.8	0.06
Aortic valve area, cm^2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.86
LVEF, %	51.1 ± 15.1	52.9 ± 14.6	47.5 ± 15.6	0.004
Mitral regurgitation, moderate or worse	29 (9.6)	17 (8.5)	12 (11.8)	0.37
Pulmonary hypertension*	42 (14.0)	29 (14.6)	13 (12.7)	0.67

Values are mean ± SD or n (%). *Pulmonary hypertension indicates pulmonary artery pressure ≥60 mm Hg.

CABG = coronary artery bypass graft surgery; 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.

TABLE 2 CT and Procedural Data

	Overall (N = 301)	Early-Generation Devices (n = 199)	New-Generation Devices (n = 102)	p Value
CT data				
Pre-procedural CT assessment*	259 (86.0)	157 (78.9)	102 (100.0)	<0.001
Aortic annulus minimal diameter, mm	22.3 ± 2.5	22.4 ± 2.5	22.2 ± 2.5	0.19
Aortic annulus maximal diameter, mm	27.9 ± 2.9	27.9 ± 2.8	27.7 ± 3.0	0.66
Aortic annulus area, mm^2	491 ± 95	492 ± 92	488 ± 103	0.77
Aortic annulus perimeter, mm	79.3 ± 7.7	79.9 ± 7.7	78.5 ± 7.7	0.31
Annular ellipticity index†	1.25 ± 0.12	1.25 ± 0.13	1.25 ± 0.09	0.92
Area oversizing, %	21.2 ± 17.9	26.4 ± 17.5	9.3 ± 12.4	<0.001
Sapien XT	–	19.6 ± 13.7	–	
CoreValve	–	33.1 ± 18.2	–	
Sapien 3	–	–	12.9 ± 1.8	
Lotus	–	–	8.4 ± 2.5	
Type of bicuspid				
Determined	260 (86.4)	161 (80.9)	99 (97.1)	<0.001
Type 0	31 (11.9)	21 (13.0)	10 (10.1)	0.53
Type 1	224 (86.2)	136 (84.5)	88 (88.9)	
Type 2	5 (1.9)	4 (2.5)	1 (1.0)	
Undetermined/unavailable	41 (13.6)	38 (19.1)	3 (2.9)	
Procedural data				
Transfemoral access	253 (84.1)	156 (78.4)	97 (95.1)	<0.001
Nontransfemoral access	48 (15.9)	43 (21.6)	5 (4.9)	<0.001
Transapical	19 (39.6)	18 (9.0)	1 (20.0)	
Transsubclavian	10 (20.8)	8 (4.0)	2 (40.0)	
Transaortic	17 (35.4)	17 (8.5)	0 (0.0)	
Transcarotid	2 (4.2)	0 (0.0)	2 (40.0)	
Device type				
Sapien XT	–	87 (43.7)	–	<0.001
CoreValve	–	112 (56.3)	–	
Sapien 3	–	–	91 (89.2)	
Lotus	–	–	11 (10.8)	

Values are n (%) or mean ± SD. *Annulus dimension data were obtained from 199 patients (early-generation devices: 139 patients; new-generation devices: 60 patients). †Annular ellipticity index was calculated using the formula (maximal diameter)/(minimal diameter).

CT = computed tomography.

death or last available follow-up. Univariate Cox regression models were used to evaluate potential predictors of all-cause mortality. Statistically significant variables with a p value <0.10 by univariate analysis were included in the multivariate model. The final model was determined by backward elimination procedures with a threshold p value <0.10. The proportional hazards assumption was confirmed by examination of log (-log [survival]) curves and by testing of partial (Schoenfeld) residuals, and no relevant violations were found. The estimated hazard ratio (HR) with 95% confidence interval (CI) was provided by the Cox model. All statistical analyses were performed using SPSS Version 21.0 (IBM Corporation, Armonk, New York). A p value <0.05 was considered statistically significant.

RESULTS

Between April 2005 and May 2015, a total of 301 patients with bicuspid AS undergoing TAVR were enrolled from 20 heart centers in Europe, North America, and Asia-Pacific. The baseline characteristics of the study population for early- and new-generation devices and each device type are shown in **Table 1** and Online Table 1, respectively. Of the total study population, 199 patients were treated with older devices (Sapien XT: n = 87; CoreValve: n = 112), and 102 patients received newer devices (Sapien 3: n = 91; Lotus: n = 11). Most patients were men (57.5%) and the overall cohort had a mean age of 77 years, a logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) of 14.9 ± 11.7, and a Society of Thoracic Surgeons (STS) score of 4.7 ± 5.2%. Both early- and new-generation devices showed similar surgical risk in terms of EuroSCORE and STS score. Male sex was more predominant in the older devices (64.8% vs. 43.1%; p < 0.001). The pre-procedural left ventricular ejection fraction was significantly lower in the group receiving the newer devices with a tendency toward a lower mean gradient.

The CT and procedural findings are presented in **Table 2**. Pre-procedural CT assessment was conducted for 157 patients with early-generation devices compared to all patients with new-generation devices. Among 199 patients with available CT data (139 patients treated with older devices vs. 60 patients with new devices), there were no significant differences in aortic annulus dimensions between the 2 groups, whereas area oversizing was significantly smaller in the new-generation device group (9.3 ± 12.4% vs. 26.4 ± 17.5%; p < 0.001). The type of bicuspid AS was determined in 260 patients: type 0 in 31 patients, type 1 in 224 patients, and type 2 in 5 patients. The transfemoral approach was more commonly used for the newer devices (95.1% vs. 78.4%; p < 0.001).

OUTCOMES. For procedural and clinical outcomes (**Table 3**), in the overall group, procedure-related death, conversion to conventional surgery, coronary obstruction, and annulus rupture were observed in 4 (1.3%), 8 (2.9%), 3 (1.0%), and 5 patients (1.7%), respectively. Second valve implantation occurred more frequently with older devices (6.5% vs. 1.0%; p = 0.04). In terms of PVL, 17 patients (8.5%) had moderate or severe PVL with earlier devices, whereas there was no moderate or severe PVL with the newer devices (p = 0.002). Consequently, device success was higher with the more recent transcatheter heart valves (92.2% vs. 80.9%; p = 0.01). In contrast, new

permanent pacemaker insertion rates were similar between groups (13.1% vs. 16.7%; p = 0.40). There were no significant differences between groups for 30-day mortality and VARC 2-defined endpoints, including stroke, bleeding, vascular complications, acute kidney injury, and early safety endpoint (**Central Illustration**).

DEVICE AND BICUSPID TYPE. Procedural and clinical outcomes according to device type are shown in Online Table 2. Of note, moderate or severe PVL occurred in 5 patients (5.7%) with the Sapien XT and 12 (10.7%) with the CoreValve. However, there was no moderate or severe PVL with the either of the newer transcatheter valves (**Figure 1**). Annulus rupture occurred in 4 patients with the Sapien XT (4.6%) and 1 patient with the Sapien 3 (1.1%), whereas no rupture was observed with the other devices (**Figure 2A**). Use of CT assessment tended to reduce moderate or severe PVL when using the Sapien XT (3.9% vs. 18.2%; p = 0.12), which resulted in higher device success rate (88.2% vs. 63.6%; p = 0.056) (Online Figure 1). Unexpectedly, CT assessment was performed for all annulus rupture cases, and thus, the rate of annulus rupture after Sapien XT implantation remained high (5.3%) even with pre-procedural CT.

Second valve implantation was significantly more frequent with the CoreValve (10.7%) than the other valves (**Figure 2B**), whereas new pacemaker insertion occurred more often in patients with the Sapien 3 (**Figure 2C**). In general, there were no significant differences in VARC 2-defined endpoints between devices, except for higher rates of major vascular complications and the early safety endpoint with the Sapien XT compared with the CoreValve (Online Figure 2).

The clinical outcomes according to bicuspid type are indicated in Online Table 3. In general, there were no significant differences in procedural outcomes and VARC 2-defined endpoints between the types of bicuspid morphology. Moderate or severe PVL occurred only in patients with type 1 bicuspid AS (6.7%). Furthermore, all annulus rupture cases occurred in type 1 bicuspid AS with calcified raphe. Similar to the entire cohort, patients with type 1 bicuspid AS had moderate or severe PVL most frequently with the CoreValve (15.9%) and annulus rupture with the Sapien XT (6.0%) (Online Figure 3).

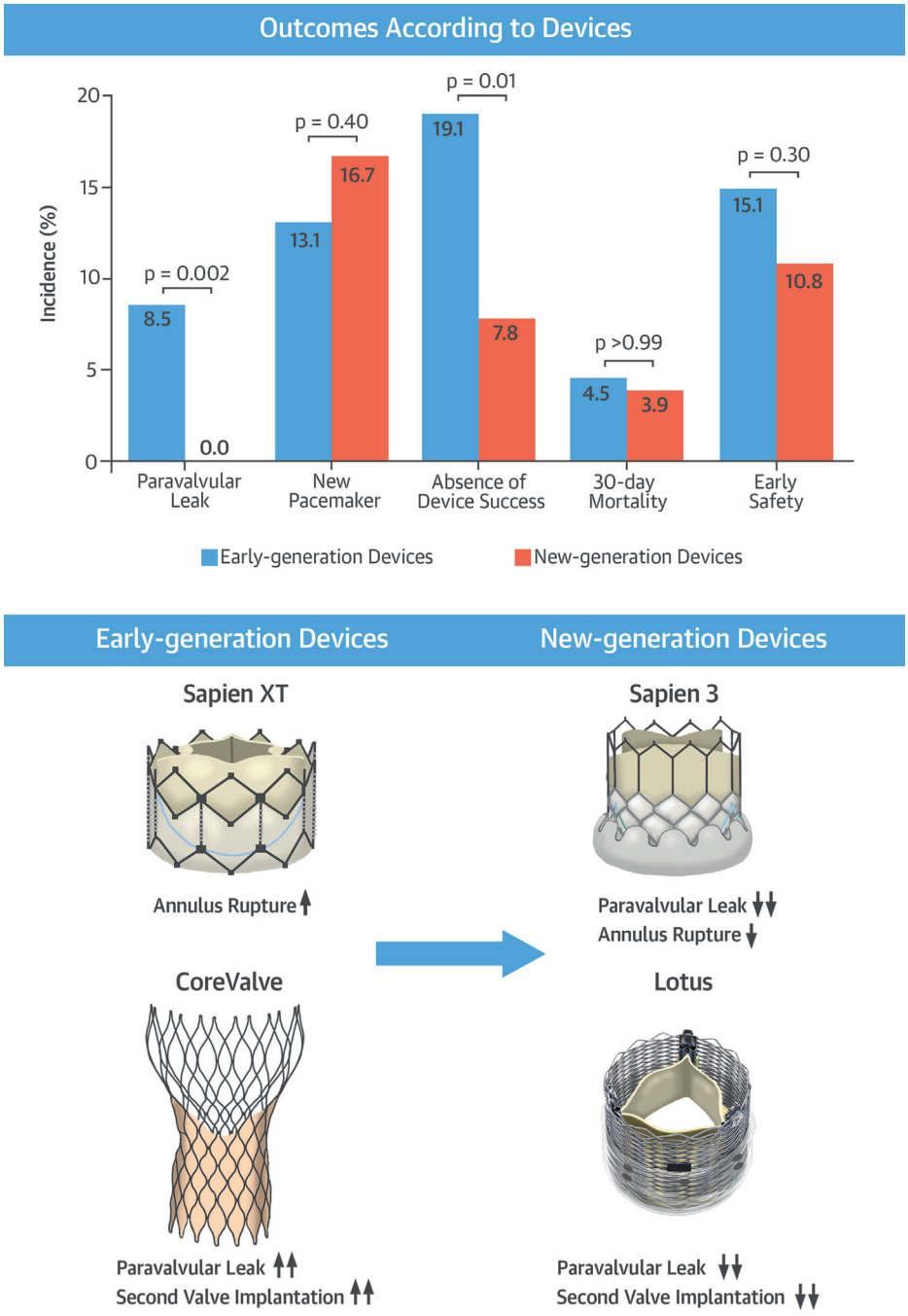
MORTALITY. During a median follow-up of 360 days (range: 90 to 700 days), 39 patients died. Cumulative all-cause and cardiovascular mortality rates were 4.3% and 3.7% at 30 days and 14.4% and 8.9% at 1 year (**Figure 3A**). There were no differences in cumulative all-cause mortality between the older transcatheter valves (1-year mortality: 17.6% vs. 14.8%; log-rank p = 0.49) (**Figure 3B**). Landmark analysis showed that a higher EuroSCORE was not associated with increased early mortality (0 to 30 days) (EuroSCORE <20 vs. ≥20: 4.8% vs. 2.9%; p = 0.74) but was significantly associated with a higher rate of late mortality (30 to 360 days) (8.7% vs. 16.1%; log-rank p = 0.03) (**Figure 3C**). By multivariate analysis, the factors significantly associated with overall mortality were logistic EuroSCORE (HR: 1.03; 95% CI: 1.01 to 1.05; p = 0.03), life-threatening or major bleeding (HR: 2.76; 95% CI: 1.24 to 6.11; p = 0.01), and stage 2 or 3 acute kidney injury (HR: 5.48; 95% CI: 1.66 to 18.12; p = 0.005) (**Table 4**).

TABLE 3 Procedural and Clinical Outcomes

	Overall (N = 301)	Early-Generation Devices (n = 199)	New-Generation Devices (n = 102)	p Value
Procedural outcomes				
Procedure-related death	4 (1.3)	3 (1.5)	1 (1.0)	>0.99
Conversion to conventional surgery	8 (2.9)	7 (4.0)	1 (1.0)	0.27
Coronary obstruction	3 (1.0)	3 (1.5)	0 (0.0)	0.55
Annulus rupture	5 (1.7)	4 (2.0)	1 (1.0)	0.67
Second valve implantation	14 (4.7)	13 (6.5)	1 (1.0)	0.04
New permanent pacemaker	43 (14.3)	26 (13.1)	17 (16.7)	0.40
Post-procedural echocardiographic findings				
Mean gradient, mm Hg	10.8 ± 5.5	10.9 ± 5.7	10.8 ± 5.0	0.86
Mean gradient ≥20 mm Hg	14 (4.7)	8 (4.0)	6 (5.9)	0.57
LVEF, %	54.6 ± 12.7	56.5 ± 12.0	51.1 ± 13.1	0.001
Paravalvular leak moderate or worse	17 (5.6)	17 (8.5)	0 (0.0)	0.002
Device success	255 (84.7)	161 (80.9)	94 (92.2)	0.01
Clinical outcomes				
Stroke	7 (2.3)	5 (2.5)	2 (2.0)	>0.99
Disabling	3 (1.0)	3 (1.5)	0 (0.0)	0.55
Nondisabling	4 (1.3)	2 (1.0)	2 (2.0)	0.61
Bleeding				
Life threatening	10 (3.3)	7 (3.5)	3 (2.9)	>0.99
Major	14 (4.7)	11 (5.5)	3 (2.9)	0.40
Minor	27 (9.0)	17 (8.5)	10 (9.8)	0.72
Major vascular complication	12 (4.0)	9 (4.5)	3 (2.9)	0.76
Acute kidney injury				
Stage 2	5 (1.7)	3 (1.3)	2 (2.0)	>0.99
Stage 3	3 (1.0)	2 (1.0)	1 (1.0)	>0.99
Stage 2 or 3	8 (2.7)	5 (2.5)	3 (2.9)	>0.99
Early safety endpoints	41 (13.6)	30 (15.1)	11 (10.8)	0.30
Death at 30 days				
From any cause	13 (4.3)	9 (4.5)	4 (3.9)	>0.99
From cardiovascular cause	11 (3.7)	8 (4.0)	3 (2.9)	0.76

Values are n (%) or mean ± SD.
LVEF = left ventricular ejection fraction.

CENTRAL ILLUSTRATION **Transcatheter Aortic Valve Replacement With Early- and New-Generation Devices in Bicuspid Aortic Valve Stenosis**



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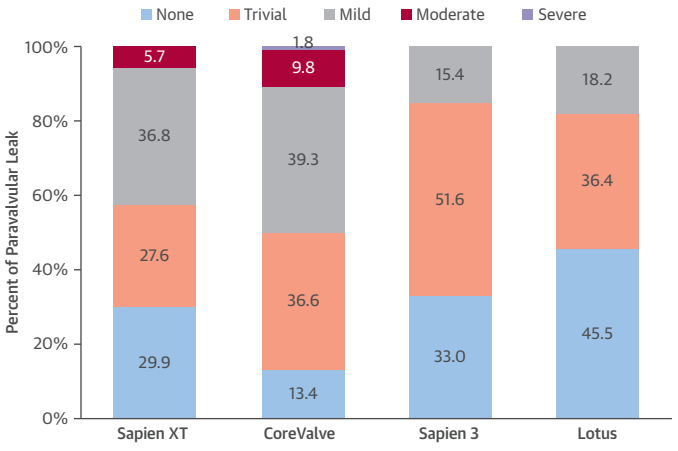
In comparing clinical outcomes of the early- and new-generation devices **(Top)**, paravalvular leak moderate or greater was less frequent and device success rate was higher with new-generation devices; however, there were no significant differences in new permanent pacemaker implantation, 30-day mortality, and early safety endpoint between groups. **(Bottom)** The procedural outcomes improved with device advancement. Compared to the early-generation devices, both of the new-generation devices were associated with less frequent paravalvular leak; specific new-generation devices improved on rates of annulus rupture and second valve implantation as shown.

DISCUSSION

To the best of our knowledge, this is the largest study evaluating the safety, efficacy, and clinical outcomes of TAVR comparing early- and new-generation devices in patients with bicuspid AS. Our major findings were as follows: 1) overall clinical outcomes of TAVR in bicuspid AS are comparable to those of reported studies; 2) new-generation devices are associated with less PVL, and consequently a higher device success rate than early-generation devices; and 3) these improved procedural outcomes did not translate into a significant reduction in 30-day mortality or other major clinical endpoints.

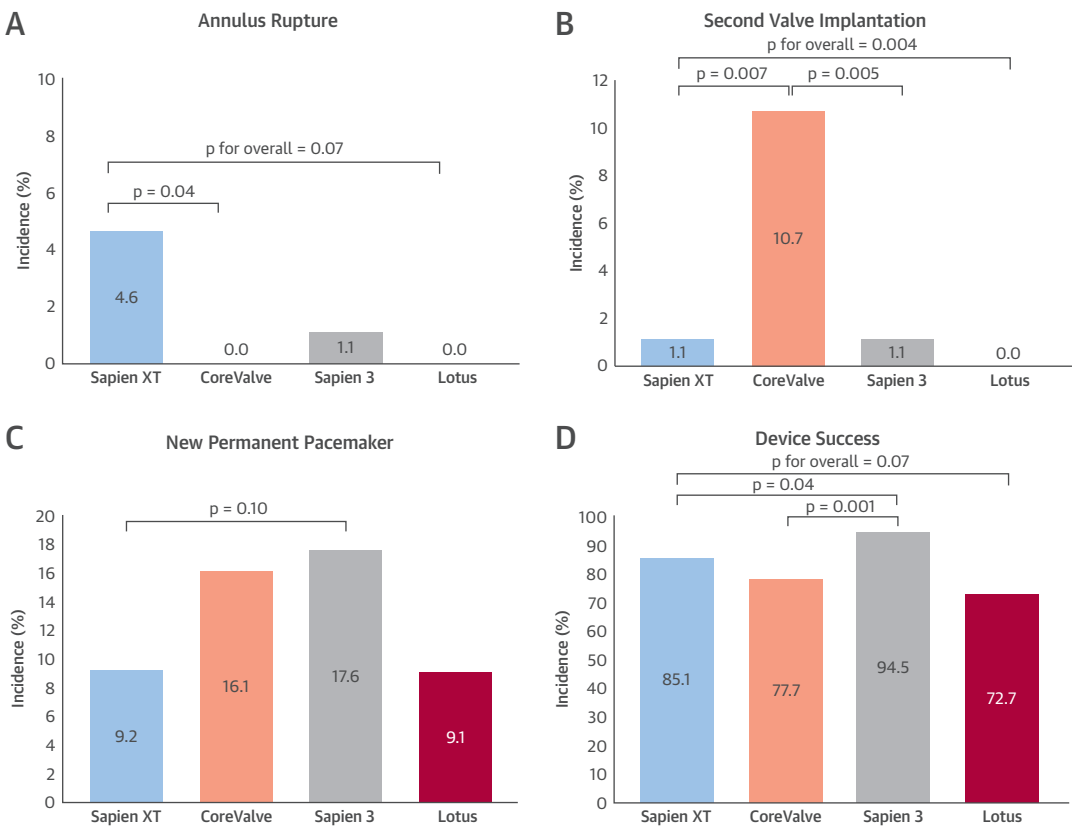
Recently, 2 large-scale studies reported the clinical outcomes of patients with bicuspid AS undergoing TAVR using earlier transcatheter heart valves (26,27). The all-cause mortality rates were 5.0% and 8.3% at 30 days and 17.5% and 16.9% at 1 year, respectively. Both studies showed the

FIGURE 1 Paravalvular Leak



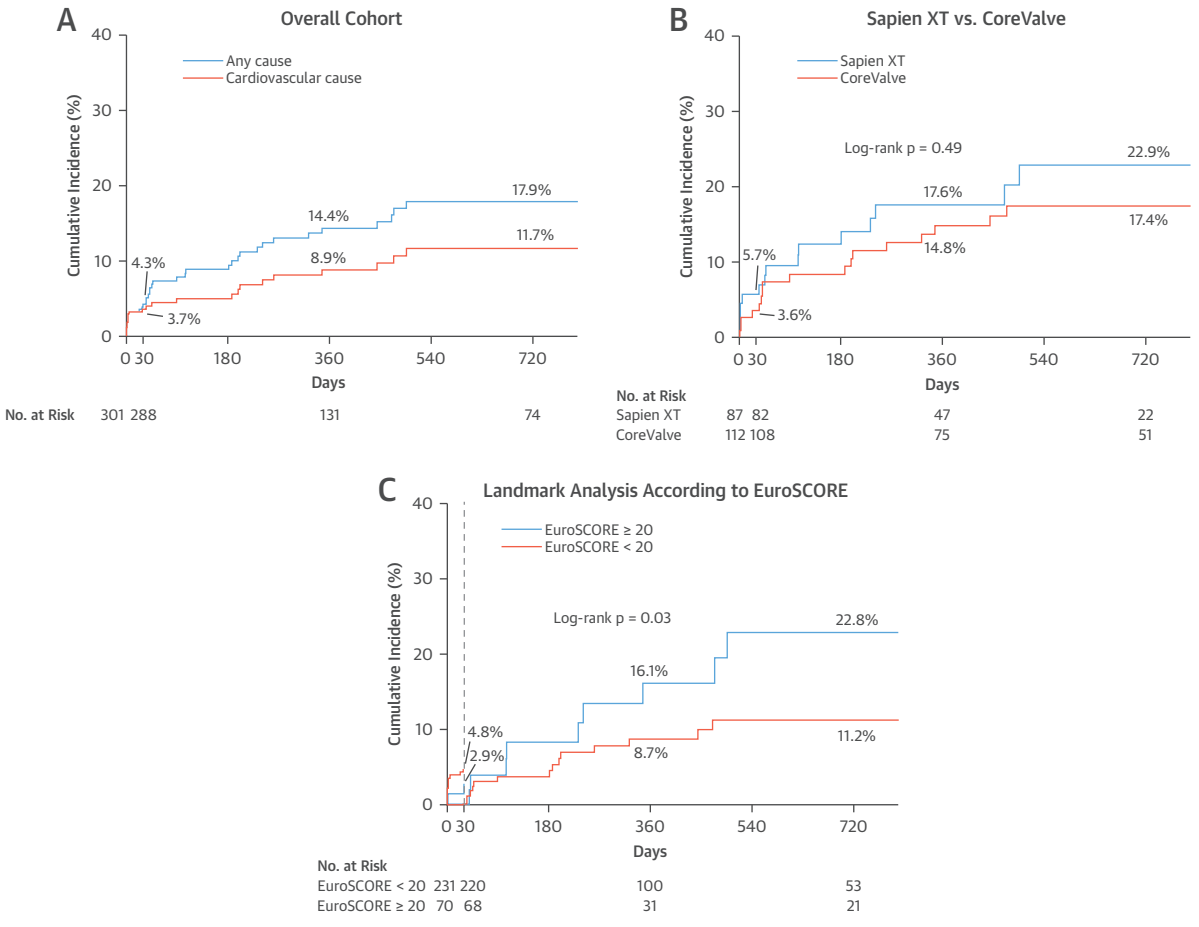
Percent of severity of paravalvular leak at discharge was reduced with new-generation devices.

FIGURE 2 Procedural Outcomes



Incidences of **(A)** annulus rupture, **(B)** second valve implantation, **(C)** new permanent pacemaker insertion, and **(D)** device success varied among the individual devices studied.

FIGURE 3 Cumulative Mortality



(A) Overall, death from any cause and cardiovascular cause both increased over time. **(B)** There was no significant difference in all-cause mortality between the early-generation devices. **(C)** The cumulative incidence curves for death from any cause with landmark analyses (0 to 30 days and 30 to 360 days) with a higher European System for Cardiac Operative Risk Evaluation (EuroSCORE) (≥20) did not increase early mortality (0 to 30 days), but was significantly associated with a higher rate of all-cause late mortality (30 to 360 days).

feasibility of TAVR for bicuspid AS with encouraging short- and intermediate-term clinical outcomes. However, high incidences of moderate or severe PVL (6.0% and 9.6%) were reported and showed the limitation of TAVR to treat bicuspid AS with the early devices. More recent reports have shown promising results with newer devices; for example, moderate or severe PVL has been reported in only 0% to 3.8% of cases using the Sapien 3 in tricuspid AS (10,11,28,29). This improvement can most likely be attributed to specific features of this newer transcatheter heart valve, including an outer polyethylene terephthalate-sealing skirt at its lower portion and a more accurate positioning mechanism. Similarly, the incidence of moderate or severe PVL in tricuspid AS has been reported to be very low with the Lotus (2.0%), which has an outer adaptive seal as well as retrievability and repositioning capacity (12).

The present study with an intermediate-risk profile showed acceptable outcomes with 30-day and 1-year mortality rates of 4.3% and 14.4% in bicuspid AS patients treated with TAVR, respectively; these data are in line with the mortality rates reported in 2 previous TAVR-bicuspid studies (26,27). As shown by landmark analysis, the patient risk profile was not associated with early mortality, but was significantly associated with late mortality. This might be explained in that

the anatomical features of bicuspid AS—such as abnormal cusp fusion, heavily calcified leaflets, calcified raphe, asymmetric annulus, and dilated horizontal aorta—could adversely affect procedure success and subsequent complications, or, after a successful TAVR procedure, patient comorbidities rather than anatomical factors might affect long-term survival. In line with previous studies of tricuspid AS populations, vital complications such as life-threatening or major bleeding and acute kidney injury were associated with increased mortality in the bicuspid AS population. Therefore, effort should be concentrated on mitigating these vital complications.

Significant PVL has been shown to correlate with increased mortality (3,30–32). The better outcome regarding PVL reported for newer-generation devices in tricuspid AS patients was also observed in our large bicuspid AS populations. Moderate or severe PVL occurred in 5.7% with the Sapien XT and 10.7% with the CoreValve, whereas no moderate or severe PVL was observed with either of the newer devices. Similar to previous multicenter studies, the present study did not show an association of PVL with increased mortality in the bicuspid AS population, although our cohort was admittedly underpowered to assess the impact of PVL. Nevertheless, minimizing PVL is mandatory for further application of TAVR, particularly in an intermediate-to-low risk population.

Three-dimensional CT assessment for annulus measurement has been a gold standard for device sizing (33–37). When using the Sapien XT, CT assessment reduced moderate or severe PVL (3.9% vs. 18.2%; p = 0.12), whereas rate of annulus rupture remained high (5.3%). This might be attributable to the nature of the balloon-expandable Sapien XT: a relatively high degree of oversizing is required for anchoring and preventing significant PVL. In contrast, the newer-generation balloon-expandable device provides sufficient anchoring with less oversizing, leading to improved outcomes regarding PVL and annulus rupture (38,39).

There was a numerically but not significantly higher rate of new permanent pacemaker insertion after implantation of the newer transcatheter heart valves, mainly driven by the Sapien 3 (17.6%). Recent studies reported relatively higher rates of new pacemaker insertion after TAVR with this newer device (13% to 25.5%) as well as the Lotus (28.6% to 31.8%) (10–12,14,29,40). Implantation depth and extreme oversizing have already been associated with an increased risk of pacemaker implantation after TAVR with the Sapien 3 (41).

Vascular complications after TAVR occur frequently and are reported to cause bleeding and increased mortality (42,43). The incidence of major vascular complications was 4.5% after TAVR with early-generation devices. In contrast, the Sapien 3 device, which has a low profile (14- to 16-F inner diameter), showed a numerically but nonsignificantly lower major vascular complication rate (2.9%). Nevertheless, there were no significant differences in 30-day mortality and other major clinical endpoints between early- and new-generation devices. To evaluate the impact of these favorable outcomes on mortality, future studies with longer-term follow-up and larger numbers of patients will be required.

Historically, interventional device-related outcomes have improved with increased experience. It should be noted that increased experience combined with dedicated imaging modalities and improved patient selection might favorably affect the outcomes of new-generation devices. Additionally, bicuspid AS patients undergoing TAVR might be selected based on the morphology of the bicuspid valve. Therefore, the findings of this study require cautious interpretation and the generalization of TAVR to all high-risk patients with bicuspid AS should be recommended only after further investigation.

STUDY LIMITATIONS. First, this study had the inherent limitations of an observational study without

TABLE 4 Predictors of All-Cause Mortality

	Univariate Model		Multivariate Model	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, yrs	1.02 (0.99–1.06)	0.23		
Male	0.84 (0.45–1.56)	0.58		
NYHA functional class III or IV	1.43 (0.66–3.11)	0.36		
Logistic EuroSCORE	1.02 (0.99–1.04)	0.06	1.03 (1.01–1.05)	0.03
Diabetes mellitus	0.79 (0.35–1.78)	0.57		
Prior cerebrovascular accident	1.31 (0.62–2.74)	0.48		
Peripheral vascular disease	0.98 (0.39–2.51)	0.97		
LVEF	1.00 (0.98–1.02)	0.99		
Nontransfemoral access	1.62 (0.79–3.31)	0.19		
Second valve implantation	1.53 (0.47–5.01)	0.48		
Paravalvular leak moderate or worse	1.26 (0.45–3.56)	0.66		
Life-threatening or major bleeding	2.44 (1.11–5.33)	0.026	2.76 (1.24–6.11)	0.01
Major vascular complication	2.78 (0.85–9.07)	0.09		
Acute kidney injury (stage 2 or 3)	5.29 (1.61–17.45)	0.006	5.48 (1.66–18.12)	0.005

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

center-independent adjunction of adverse events and an independent core laboratory to diagnose bicuspid AS and assess PVL. Second, device selection was not randomized but at the operator's discretion. Third, unmeasured change in patient selection, and increased experience may favorably affect outcomes of new-generation devices. Finally, a relatively small number of new-generation devices were included.

CONCLUSIONS

The clinical outcomes of TAVR in patients with bicuspid AS were favorable. New-generation transcatheter heart valves were associated with less PVL and, hence, a higher device success rate than early-generation devices.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Jung-Ming Ahn, Heart Institute, Asan Medical Center, 388-1 Poongap-dong, Songpa-gu, Seoul 138-736, South Korea. E-mail: drjmahn@gmail.com.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with bicuspid valves undergoing TAVR, the use of newer-generation devices has reduced the incidence of PVL.

TRANSLATIONAL OUTLOOK: Future studies should evaluate long-term outcomes of TAVR in patients with stenotic bicuspid valves.

REFERENCES

1. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686–95.

2. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med 2012;366:1696–704.

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

4. Hamm CW, Mollmann H, Holzhey D, et al. The German Aortic Valve Registry (GARY): in-hospital outcome. Eur Heart J 2014;35:1588–98.

5. Moat NE, Ludman P, de Belder MA, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. J Am Coll Cardiol 2011;58:2130–8.

6. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790–8.

7. Siu SC, Silversides CK. Bicuspid aortic valve disease. J Am Coll Cardiol 2010;55:2789–800.

8. Himbert D, Pontnau F, Messika-Zeitoun D, et al. Feasibility and outcomes of transcatheter aortic valve implantation in high-risk patients with stenotic bicuspid aortic valves. Am J Cardiol 2012;110:877–83.

9. Zhao ZG, Jilaihawi H, Feng Y, Chen M. Transcatheter aortic valve implantation in bicuspid anatomy. Nat Rev Cardiol 2015;12:123–8.

10. Webb J, Gerosa G, Lefevre T, et al. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. J Am Coll Cardiol 2014;64:2235–43.

11. Husser O, Pellegrini C, Kessler T, et al. Outcomes after transcatheter aortic valve replacement using a novel balloon-expandable transcatheter heart valve: a single-center experience. J Am Coll Cardiol Intv 2015;8:1809–16.

12. Meredith Am IT, Walters DL, Dumonteil N, et al. Transcatheter aortic valve replacement for severe symptomatic aortic stenosis using a repositionable valve system: 30-day primary endpoint results from the REPRISE II study. J Am Coll Cardiol 2014;64:1339–48.

13. Meredith IT, Walters DL, Dumonteil N, et al. 1-Year outcomes with the fully repositionable and retrievable Lotus transcatheter aortic replacement valve in 120 high-risk surgical patients with severe aortic stenosis. J Am Coll Cardiol Intv 2016;9:376–84.

14. Rampat R, Khawaja MZ, Byrne J, et al. Transcatheter aortic valve replacement using the repositionable LOTUS valve. J Am Coll Cardiol Intv 2016;9:367–72.

15. Thilo C, Shivaraju A, von Scheidt W, Kasel AM. Bicuspid aortic valve stenosis with successful transfemoral transcatheter aortic valve replacement (TAVI) using the Sapien 3 valve. Eur Heart J 2014;35:2662.

16. Seeger J, Gonska B, Rodewald C, Rottbauer W, Wohrle J. Bicuspid aortic stenosis treated with the repositionable and retrievable Lotus Valve. Can J Cardiol 2016;32:135.e17–9.

17. 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.

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

19. 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.

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

25. Kappetein AP, Head SJ, Genereux 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.

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

27. 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.

28. Amat-Santos IJ, Dahou A, Webb J, et al. Comparison of hemodynamic performance of the

balloon-expandable SAPIEN 3 versus SAPIEN XT transcatheter valve. Am J Cardiol 2014;114:1075–82.

29. Murray MI, Geis N, Pleger ST, et al. First experience with the new generation Edwards Sapien 3 aortic bioprosthesis: procedural results and short term outcome. J Interv Cardiol 2015;28:109–16.

30. Abdel-Wahab M, Zahn R, Horack M, et al. Aortic regurgitation after transcatheter aortic valve implantation: incidence and early outcome. Results from the German transcatheter aortic valve interventions registry. Heart 2011;97:899–906.

31. 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.

32. Abdel-Wahab M, Comberg T, Buttner HJ, et al. 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.

33. Jilaihawi H, Kashif M, Fontana G, et al. Cross-sectional computed tomographic assessment improves accuracy of aortic annular sizing for transcatheter aortic valve replacement and reduces the incidence of paravalvular aortic regurgitation. J Am Coll Cardiol 2012;59:1275–86.

34. Willson AB, Webb JG, Labounty TM, et al. 3-dimensional aortic annular assessment by multidetector computed tomography predicts moderate or severe paravalvular regurgitation after transcatheter aortic valve replacement: a multicenter retrospective analysis. J Am Coll Cardiol 2012;59:1287–94.

35. Binder RK, Webb JG, Willson AB, et al. The impact of integration of a multidetector computed tomography annulus area sizing algorithm on outcomes of transcatheter aortic valve replacement: a prospective, multicenter, controlled trial. J Am Coll Cardiol 2013;62:431–8.

36. Mylotte D, Dorfmeister M, Elhmidi Y, et al. Erroneous measurement of the aortic annular diameter using 2-dimensional echocardiography resulting in inappropriate CoreValve size selection: a retrospective comparison with multislice computed tomography. J Am Coll Cardiol Intv 2014;7:652–61.

37. Yoon SH, Ahn JM, Ohno Y, et al. Predictors for paravalvular regurgitation after TAVR with the self-expanding prosthesis: quantitative measurement of MDCT analysis. J Am Coll Cardiol Img 2015 Dec 30 [E-pub ahead of print].

38. Tan JS, Leipsic J, Perlman G, et al. A strategy of underexpansion and ad hoc post-dilation of balloon-expandable transcatheter aortic valves in patients at risk of annular injury: favorable mid-term outcomes. J Am Coll Cardiol Intv 2015;8:1727–32.

39. Yang TH, Webb JG, Blanke P, et al. Incidence and severity of paravalvular aortic regurgitation with multidetector computed tomography nominal area oversizing or undersizing after transcatheter heart valve replacement with the Sapien 3: a comparison with the Sapien XT. J Am Coll Cardiol Intv 2015;8:462–71.

40. Tarantini G, Mojoli M, Purita P, et al. Unravelling the (arte)fact of increased pacemaker rate with the Edwards SAPIEN 3 valve. EuroIntervention 2015;11:343–50.

41. Husser O, Pellegrini C, Kessler T, et al. Predictors of permanent pacemaker implantations and new-onset conduction abnormalities with the SAPIEN 3 balloon-expandable transcatheter heart valve. J Am Coll Cardiol Intv 2016;9:244–54.

42. Steinvil A, Leshem-Rubinow E, Halkin A, et al. Vascular complications after transcatheter aortic valve implantation and their association with mortality reevaluated by the valve academic research consortium definitions. Am J Cardiol 2015;115:100–6.

43. Genereux P, Webb JG, Svensson LG, et al. 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.

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