Transcatheter Aortic Valve Replacement in Low-Risk Patients with Symptomatic Severe Bicuspid Aortic Valve Stenosis

Ron Waksman, MD, Paige E. Craig, MPH, Rebecca Torguson, MPH, Federico M. Asch, MD, Gaby Weissman, MD, Daniel Ruiz, MD, Paul Gordon, MD, Afshin Ehsan, MD, Puja Parikh, MD, Thomas Bilfinger, MD, Robert Levitt, MD, Chiwon Hahn, MD, David Roberts, MD, Michael Ingram, MD, Nicholas Hanna, MD, George Comas, MD, Cheng Zhang, PhD, Itsik Ben-Dor, MD, Lowell Satler, MD, Hector M. Garcia-Garcia, MD, PhD, Christian Shults, MD, Toby Rogers, MD, PhD

PII: S1936-8798(20)30498-2

DOI: https://doi.org/10.1016/j.jcin.2020.02.008

Reference: JCIN 4961

To appear in: *JACC: Cardiovascular Interventions*

Received Date: 4 February 2020

Accepted Date: 4 February 2020

Please cite this article as: Waksman R, Craig PE, Torguson R, Asch FM, Weissman G, Ruiz D, Gordon P, Ehsan A, Parikh P, Bilfinger T, Levitt R, Hahn C, Roberts D, Ingram M, Hanna N, Comas G, Zhang C, Ben-Dor I, Satler L, Garcia-Garcia HM, Shults C, Rogers T, Transcatheter Aortic Valve Replacement in Low-Risk Patients with Symptomatic Severe Bicuspid Aortic Valve Stenosis, *JACC: Cardiovascular Interventions* (2020), doi: https://doi.org/10.1016/j.jcin.2020.02.008.

Transcatheter Aortic Valve Replacement in Low-Risk Patients with Symptomatic Severe Bicuspid Aortic Valve Stenosis

Ron Waksman, MD[a]; Paige E. Craig, MPH[a]; Rebecca Torguson, MPH[a]; Federico M. Asch, MD[b]; Gaby Weissman, MD[c]; Daniel Ruiz, MD[a]; Paul Gordon, MD[d]; Afshin Ehsan, MD[e]; Puja Parikh, MD[f]; Thomas Bilfinger, MD[g]; Robert Levitt, MD[h]; Chiwon Hahn, MD[i]; David Roberts, MD[j]; Michael Ingram, MD[j]; Nicholas Hanna, MD[k]; George Comas, MD[l]; Cheng Zhang, PhD[a]; Itsik Ben-Dor, MD[a]; Lowell Satler, MD[a]; Hector M Garcia-Garcia, MD, PhD[a]; Christian Shults, MD[m]; Toby Rogers, MD, PhD[a,n]

Affiliations:
[a] Section of Interventional Cardiology, MedStar Washington Hospital Center, Washington, District of Columbia.
[b] MedStar Health Research Institute, MedStar Washington Hospital Center, Washington, District of Columbia
[c] Department of Cardiology, MedStar Washington Hospital Center, Washington, District of Columbia
[d] Division of Cardiology, The Miriam Hospital, Providence, RI
[e] Division of Cardiothoracic Surgery, Lifespan Cardiovascular Institute, Providence, RI
[f] Department of Medicine, Stony Brook Hospital, Stony Brook, NY
[g] Department of Surgery, Stony Brook Hospital, Stony Brook, NY
[h] Department of Cardiology, Henrico Doctors' HospitalRichmond, VA
[i] Department of Cardiothoracic Surgery, Henrico Doctors' Hospital, Richmond, VA
[j] Sutter Medical Center, Sacramento, Sutter Heart and Vascular Institute, Research, Sacramento, CA
[k] St. John Heart Institute Cardiovascular Consultants, St. John Health System, Tulsa, OK
[l] St. John Clinic Cardiovascular Surgery, St. John Heart Institute Cardiovascular Consultants, St. John Health System, Tulsa, OK
[m] Department of Cardiac Surgery, MedStar Washington Hospital Center, Washington, DC
[n] Cardiovascular Branch, Division of Intramural Research, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Running Title: TAVR in Low-Risk Patients with Bicuspid Valves

Address for Correspondence:
Ron Waksman, MD
MedStar Washington Hospital Center
110 Irving St., NW, Suite 4B-1
Washington, DC 20010
Phone: 202-877-2812
Fax: 202-877-2715
Email: ron.waksman@medstar.net

Word Count: 3225

Funding:
The Low Risk TAVR (LRT) trial, NCT02628899, was funded by MedStar Health Research Institute, Washington, DC.

Relationships with Industry
Ron Waksman: Consultant: Abbott Vascular, Biosensors International, Biotronik, Boston Scientific, Medtronic Vascular, Symetis, Lifetech; Speakers Bureau: AstraZeneca, Boston Scientific, Biotronik, Abbott Vascular; Grant Support: Biosensors International, Biotronik, Boston Scientific, Edwards Lifesciences, Abbott Vascular.
Federico Asch – Director of an academic cardiovascular imaging core lab with institutional contracts with Edwards, Medtronic, Boston Scientific, Biotronik and Abbott.
Gaby Weissman – Director of an academic cardiovascular imaging core lab with institutional contracts with Boston Scientific, Ancora Heart. LivaNova, and HDL Therapeutics.
Nicholas Hanna – Speaker: Edwards.
Lowell Satler: Speakers Bureau: AstraZeneca.
Toby Rogers: Consultant and Proctor: Edwards Lifesciences, Medtronic
All other authors have no conflicts to disclose.

Tweet/handle: @ron_waksman; LRT trial shows TAVR is safe in low-risk bicuspid patients with symptomatic severe AS, with zero mortality and zero disabling stroke at 30 days

ABSTRACT

Background: Transcatheter aortic valve replacement (TAVR) is approved for low-risk patients in the US. However, patients with bicuspid aortic stenosis (AS) were excluded from the randomized cohorts of the pivotal low-risk trials.

Objectives: We aimed to evaluate clinical outcomes and transcatheter heart valve hemodynamics after TAVR in low-risk bicuspid AS patients.

Methods: The Low Risk TAVR (LRT) trial was an investigator-initiated, prospective, multicenter study and was the first and only Food and Drug Administration-approved Investigational Device Exemption trial to evaluate feasibility of TAVR with either balloon-expandable or self-expanding valve in low-risk bicuspid AS patients. The primary endpoint was all-cause mortality at 30 days. Baseline and follow-up echocardiography and computed tomography to detect leaflet thickening were analyzed in an independent Core Laboratory.

Results: Sixty-one low-risk patients with symptomatic, severe AS and bicuspid aortic valves (78.3% Sievers type 1 morphology) underwent TAVR at 7 centers from 2016 to 2019. Mean age was 68.6 years and 42.6% were male. At 30 days, there was zero mortality and zero disabling stroke. New permanent pacemaker implantation rate was 13.1%; just one patient had moderate paravalvular leak at 30 days. Hypoattenuated leaflet thickening was observed in 10% of patients at 30 days.

Conclusions: TAVR appears to be safe in bicuspid AS patients, with short hospital length of stay, zero mortality, and zero disabling stroke at 30 days. Subclinical leaflet thrombosis was observed in a minority of patients at 30 days but did not appear to be associated with clinical events.

KEY WORDS: BICUSPID AORTIC VALVE, AORTIC STENOSIS, TRANSCATHETER AORTIC VALVE REPLACEMENT, LOW RISK

CONDENSED ABSTRACT

The Low Risk TAVR (LRT) trial was the first investigator-initiated, prospective, multicenter study to evaluate feasibility of TAVR in low-risk bicuspid patients with symptomatic severe aortic stenosis. Sixty-one patients (78.3% Sievers type 1 morphology) underwent TAVR at 7 centers from 2016 to 2019. Mean age was 68.6 years and 42.6% were male. At 30 days, there was zero mortality and zero disabling stroke. New permanent pacemaker implantation rate was 13.1%; just one patient had moderate paravalvular leak at 30 days. Hypoattenuated leaflet thickening was observed in 10% of patients at 30 days but did not appear to be associated with clinical events.

ABBREVIATIONS AND ACRONYMS

AS	Aortic stenosis
CT	Computed tomography
HALT	Hypoattenuated leaflet thickening
LRT	Low Risk TAVR
PPM	Permanent pacemaker
PVL	Paravalvular leak
SAVR	Surgical aortic valve replacement
STS	Society of Thoracic Surgeons
TAVR	Transcatheter aortic valve replacement

THV	Transcatheter heart valve

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has never been compared to surgical aortic valve replacement (SAVR) in a randomized clinical trial in symptomatic patients with severe bicuspid aortic stenosis (AS). Retrospective registry-based studies from select centers in predominantly high-risk patients have reported acceptable outcomes using contemporary transcatheter heart valves (THV)(1-3). More recently, data from the Society of Thoracic Surgeons (STS)/American College of Cardiology Transcatheter Valve Therapy (TVT) registry comparing outcomes between propensity-matched cohorts of mostly intermediate-risk patients with bicuspid versus tricuspid AS revealed no significant difference in 30-day or 1-year mortality, but the data did show increased 30-day stroke(4). This is important because in 2019, the US Food and Drug Administration (FDA) approved TAVR for low-surgical-risk patients with symptomatic severe AS regardless of aortic valve morphology (bicuspid vs. tricuspid)(5), even though the patients with bicuspid valves were excluded from the randomized cohorts of the industry-sponsored pivotal low-risk trials(6,7). Consequently, one can expect many younger low-risk patients with bicuspid AS to undergo TAVR, even though safety and efficacy in this population has never been tested. Herein, we report the results from the bicuspid arm of the Low Risk TAVR (LRT) trial(8,9), the first FDA-approved Investigational Device Exemption (IDE) trial in the US to enroll low-risk patients with bicuspid valves.

METHODS

The LRT trial (NCT02628899) was a prospective, investigator-initiated, multicenter feasibility trial to test the safety of transfemoral TAVR in low-risk patients with symptomatic severe AS. The trial design has been described previously(10). The research protocol was approved by the relevant institutional review boards. All patients gave written informed consent

and were evaluated before enrollment by an independent Clinical Review Committee to ensure low-risk status and clinical and anatomical eligibility for transfemoral TAVR, which was performed using commercially available THVs, the choice of which was at operator discretion. Patients were enrolled into two separate arms depending on the morphology of the aortic valve: tricuspid or bicuspid. Patients with dilated ascending aorta were excluded from the LRT trial. All preprocedural and postprocedural echocardiograms and computed tomography (CT) studies were analyzed by an independent Core Laboratory, including determination of bicuspid valve morphology using the Sievers classification (Figure 1)(11). All patients underwent contrast-enhanced CT at 30 days to evaluate for THV leaflet thrombosis(12). The primary endpoint of the study was all-cause mortality at 30 days. All clinical endpoints were adjudicated by an independent Clinical Events Adjudication Committee comprising an interventional cardiologist, a cardiothoracic surgeon, and a neurologist using Valve Academic Research Consortium (VARC) 2 definitions(13). The 30-day and 1-year results for the tricuspid cohort of the LRT trial have been reported previously(8,9).

All patients who underwent isolated SAVR for bicuspid valve (as defined by STS) at the LRT enrolling centers between January 1, 2013, and December 31, 2017, and whose data were recorded in the STS Adult Cardiac Surgery database were included in a SAVR cohort for comparison. Patients were excluded from the SAVR cohort if they were not low risk according to the STS Predicted Risk of Mortality (PROM) score or due to significant co-morbidities (Supplemental Table 2), or if they underwent a concomitant procedure (e.g., coronary artery bypass, another valve repair/replacement, or aortic root repair/replacement). Supplemental Figure 1 summarizes the most common exclusion criteria.

Continuous variables are presented as means and standard deviations, categorical variables as percentages. All analyses were performed with SAS software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 61 patients with bicuspid aortic valves were enrolled in the bicuspid arm of the LRT trial and underwent TAVR with a commercially available THV between August 2016 and September 2019. Table 1 summarizes baseline characteristics of these 61 patients who were low risk (STS 30-day PROM score 1.5±0.6%), with mean age of 68.6 years, and with a typical profile of cardiovascular risk factors and co-morbidities for a TAVR population. To place this cohort in context with surgery, demographics and characteristics of an unadjusted cohort of patients with bicuspid AS who underwent SAVR at the same enrolling centers are also summarized in Table 1. The mean age in the SAVR cohort was 5 years younger than the TAVR cohort, and most patients were male, with similar comorbidities to patients in the TAVR cohort.

Table 2 summarizes important findings of the baseline CT analysis for the TAVR cohort. Ascending aorta dimensions were below guideline criteria for surgery, as patients with dilated aorta were excluded from the LRT trial. The vast majority of patients had Sievers type 1 bicuspid morphology (78.3%), and the minority (13.3%) had Sievers type 0 and (3.3%) Sievers type 2 morphology (Figure 1 and Central Illustration). The STS data collection form started collecting Sievers classification for bicuspid valves in version 2.9 (implemented in February 2017). Prior versions only collected “bicuspid valve” without Sievers type. Only 31 patients in our SAVR cohort underwent surgery after implementation of version 2.9; therefore, Sievers classification is unknown for 86% of the cohort and comparisons between the SAVR and TAVR cohorts could not be made.

TAVR procedural details are summarized in Table 3. Most patients (74%) received a balloon-expandable THV (Sapien 3, Edwards Lifesciences, Irvine, California) and the minority (26%) received a self-expanding THV (Evolut R/Pro, Medtronic, Minneapolis, Minnesota) (Central Illustration). The majority of patients (79%) received a 26-mm or larger THV. All procedures were performed via transfemoral access, and most under moderate sedation. No patient required implantation of a second valve. Mean aortic valve gradients decreased significantly, and aortic valve area increased significantly, after TAVR (Figure 2). Mean hospital length of stay was 2 days. The rates of procedure-related complications were low and are summarized in Table 4. One patient complained of diplopia shortly after recovery from the TAVR procedure. Brain magnetic resonance imaging revealed a recent ischemic infarct in the right paramedian pons. The patient's symptoms resolved after two days, and this event was determined to be a non-disabling stroke. This patient did not have leaflet thrombosis on 30-day CT.

There was zero mortality and zero disabling stroke at 30 days (Table 4 and Central Illustration). The overall rate of new permanent pacemaker (PPM) implantation at 30 days was 13.1%. In patients who received a balloon-expandable THV, the rate of new PPM implantation was 6.7%, and in patients who received a self-expanding THV, the rate was 31.3%. Two patients had pre-existing RBBB, but neither required PPM implantation within 30 days. Only one patient had moderate paravalvular leak (PVL) at 30 days, and no patients had severe PVL (Figure 3). Ninety-five percent of patients were in New York Heart Association (NYHA) functional class II or higher before TAVR, and all were in NYHA class I or II at 30 days (Supplemental Figure 2). At 30 days, 60 of 61 subjects underwent contrast-enhanced CT scans, which were analyzed for subclinical leaflet thrombosis(12). Important findings are summarized in Figure 4.

Hypoattenuated leaflet thickening (HALT) was present in 6 patients (1 self-expanding and 5 balloon-expandable THVs).

DISCUSSION

LRT was the first prospective trial to test feasibility and safety of TAVR in low-risk symptomatic patients with severe bicuspid AS. The key findings can be summarized as follows: First, TAVR in low-risk bicuspid patients was safe, with zero mortality and zero disabling stroke at 30 days. Second, the rates of procedural complications, including clinically significant PVL, life-threatening and major bleeding, and vascular complications, were low and comparable to those of tricuspid AS patients, albeit with a numerically higher new PPM implantation rate. Finally, leaflet thrombosis was observed in a minority of patients at 30 days but did not appear to be associated with thromboembolic events.

The mean age of the bicuspid cohort of the LRT trial was 5 years younger than the previously published tricuspid cohort(8). This is expected because symptomatic severe AS is more likely to develop at a younger age in patients with bicuspid morphology. The mean age of the bicuspid SAVR cohort was 5 years younger again, possibly reflecting a higher proportion of patients with type 0 morphology, although this could not be confirmed because the STS database did not collect Sievers classification before 2017.

Procedural details were similar between the bicuspid and tricuspid arms of the LRT trial, including total procedure time (91.4 vs. 88.2 mins), transfemoral access (100% in both cohorts) and utilization of general anesthesia (19.7% vs. 24.5%)(8). Similar to the tricuspid arm, the majority of patients in the LRT trial's bicuspid arm received a balloon-expandable THV. A recent report from the TVT registry compared outcomes after TAVR with a balloon-expandable THV in mostly intermediate-risk patients (mean STS-PROM score 4.9%) with bicuspid versus

tricuspid AS(4). Compared with the TVT report, which predates FDA approval of low-risk TAVR(5), patients in the bicuspid arm of the LRT trial were younger (mean age 68 years), likely reflecting their low-surgical-risk profile. Unfortunately, the TVT registry does not collect information regarding bicuspid valve morphology. The vast majority of patients in LRT had Sievers type 1 morphology. This is to be expected because patients with Sievers Type 0 aortic valve are more likely to develop symptoms at a younger age and, in accordance with current guidelines, undergo SAVR with a mechanical valve. Another reason why few Sievers Type 0 patients were enrolled in LRT is because aortopathy is more common in patients with Type 0 bicuspid valve. Patients with dilated ascending aorta were excluded from the LRT trial.

A key finding of the TVT report was significantly higher 30-day stroke rate in bicuspid vs. tricuspid patients (2.5% vs 1.6%). The overall stroke rate at 30 days in the bicuspid arm of the LRT trial was numerically lower (1.6%). This is higher than for tricuspid patients in the LRT (0.5%) and PARTNER 3 trials (0.6%) but lower than for tricuspid patients in the Evolut Low Risk trial (2.1%)(6-8). The rate of new PPM implantation was 13.1%, which is numerically higher than for tricuspid patients in the LRT (6.5%) and PARTNER 3 trials (6.5%), and similar to the TVT registry's bicuspid cohort (9.1%), but lower than for tricuspid patients in the Evolut Low Risk trial (17.4%). This is an important consideration in younger low-risk patients because long-term PPM dependency is not benign. The rate of moderate and higher PVL at 30 days was 2%, which is numerically higher than for tricuspid patients in the LRT (0.5%) and PARTNER 3 trials (0.8%), and similar to the TVT registry bicuspid cohort (2%), but lower than for tricuspid patients in the Evolut Low Risk trial (3.5%). Furthermore, the rate of mild PVL at 30 days was similar between bicuspid and tricuspid arms of the LRT trial (35.3% vs. 31.1%). This is important because residual PVL was a common problem after TAVR with early generation

THVs(1). Choice of THV was at operator discretion in the LRT trial. Only 16 patients in the LRT bicuspid arm received a self-expanding THV, and therefore, it is not appropriate to compare outcomes between balloon-expandable and self-expanding THVs in this cohort. Further data are needed to determine whether a particular THV is preferable for bicuspid anatomy.

HALT was observed in 10% of bicuspid TAVR patients at 30 days, which is similar to the previously published tricuspid LRT cohort (14%)(8), the PARTNER 3 trial (13%)(14), and the larger Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed with Four-Dimensional Computed Tomography (SAVORY) and Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and its Treatment with Anticoagulation (RESOLVE) observational registries (13%)(15). The stroke rate in the bicuspid arm of the LRT trial was extremely low (only one non-disabling stroke at 30 days), so it was not possible to correlate THV leaflet thrombosis with clinical events. In the tricuspid arm of the LRT trial, patients with HALT had inferior THV hemodynamics compared to those without HALT at 30 days, but hemodynamic differences disappeared at 1 year(16). Longer follow-up of larger cohorts with serial echocardiography will be needed to determine whether THV leaflet thrombosis impacts long-term THV hemodynamics, durability, and rate of late thromboembolic events.

The FDA approved TAVR for low-risk AS patients regardless of valve morphology, even though patients with bicuspid valves were excluded from the randomized cohorts of both industry-sponsored trials(6,7). The results herein showing short-term outcomes comparable to published outcomes in tricuspid AS patients provide the first prospective data supporting the use of TAVR in low-risk bicuspid AS patients. It is all but inevitable that more and more bicuspid patients will choose TAVR because it is less invasive than surgery, and it will be very challenging to perform a randomized clinical trial comparing TAVR and SAVR in bicuspid

patients. Nonetheless, it is important to recognize that the mean age of patients in the bicuspid arm of the LRT trial was 68 years, and few patients had Sievers type 0 morphology. Thus, these findings should be extrapolated to younger patients with type 0 valves with caution and would be better assessed within a randomized clinical trial with a focus on younger patients with Sievers type 0 bicuspid valves. Bioprosthetic valve durability is of utmost importance in these younger patients, and ideally, they should be followed up for their entire life span. Also, these findings should not be extrapolated to patients with concomitant aortopathy, as they were excluded from the LRT trial.

Limitations

The LRT trial was not a randomized study. A cohort of tricuspid TAVR patients from the LRT trial and a cohort of bicuspid SAVR patients from the STS database are presented to place the bicuspid TAVR cohort in context. Baseline characteristics and clinical outcomes for these three cohorts are presented unadjusted because it is not appropriate to adjust for the presence of a congenital bicuspid aortic valve. As the bicuspid TAVR cohort was relatively small, further subgroup analysis, for example, comparing outcomes between different Sievers morphologies, is not appropriate. THV sizing strategy (e.g., annular versus supra-annular) was not captured in the LRT trial. TAVR is already approved for low-risk patients regardless of aortic valve morphology (tricuspid vs. bicuspid). To the best of our knowledge, no large-scale randomized trials comparing TAVR vs. SAVR in low-risk patients with bicuspid aortic valves are ongoing or forthcoming. Larger prospective registries of TAVR in low-risk bicuspid patients with longer follow-up will be useful. Data from the STS/American College of Cardiology TVT registry will also be useful, but are limited because the TVT registry does not currently collect Sievers classification. In contrast, Core Laboratory verification of bicuspid aortic valve morphology is a

unique strength of the LRT trial. The extremely low rate of cerebrovascular events in the LRT trial prevents comparison of clinical outcomes between patients with or without THV leaflet thrombosis.

CONCLUSIONS

Low-risk patients with symptomatic severe bicuspid AS are younger than patients with tricuspid AS. TAVR in bicuspid AS patients appears to be safe, with short hospital length of stay, zero mortality, and zero disabling stroke at 30 days. Subclinical leaflet thrombosis was observed in a minority of patients at 30 days but did not appear to be associated with clinical events. A randomized clinical trial comparing TAVR and SAVR in low-risk patients with bicuspid AS is warranted to determine optimal treatment strategy in this population.

PERSPECTIVES

WHAT IS KNOWN?

Transcatheter aortic valve replacement (TAVR) is approved in the United States for patients with symptomatic severe aortic stenosis regardless of surgical risk and regardless of aortic valve morphology. Safety and effectiveness of TAVR has never been studied in low-risk patients with bicuspid aortic valves.

WHAT IS NEW?

In low-risk bicuspid valve patients, TAVR using commercially available transcatheter heart valves (THVs) is safe, with low rates of procedure-related complications, excellent hemodynamics, and short-term clinical outcomes.

WHAT IS NEXT?

Further data are needed to determine whether a particular THV design (balloon-expandable, self-expanding, or mechanically expandable) is superior in patients with bicuspid aortic valves.

REFERENCES

1. Yoon SH, Lefevre 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.
2. 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. JACC Cardiovascular interventions 2016;9:817-24.
3. Yoon SH, Bleiziffer S, De Backer O, et al. Outcomes in Transcatheter Aortic Valve Replacement for Bicuspid Versus Tricuspid Aortic Valve Stenosis. J Am Coll Cardiol 2017;69:2579-89.
4. Makkar RR, Yoon S-H, Leon MB, et al. Association Between Transcatheter Aortic Valve Replacement for Bicuspid vs Tricuspid Aortic Stenosis and Mortality or Stroke. Jama 2019;321:2193-202.
5. FDA expands indication for several transcatheter heart valves to patients at low risk for death or major complications associated with open-heart surgery. https://www.fda.gov/news-events/press-announcements/fda-expands-indication-several-transcatheter-heart-valves-patients-low-risk-death-or-major. Accessed December 9, 2019.
6. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. The New England journal of medicine 2019 2019/03/19 [E-pub ahead of print]. 10.1056/NEJMoa1814052.
7. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. The New England journal of medicine 2019 2019/03/19 [E-pub ahead of print]. 10.1056/NEJMoa1816885.

8. Waksman R, Rogers T, Torguson R, et al. Transcatheter Aortic Valve Replacement in Low-Risk Patients With Symptomatic Severe Aortic Stenosis. J Am Coll Cardiol 2018;72:2095-105.

9. Waksman R, Corso PJ, Torguson R, et al. Transcatheter Aortic Valve Replacement in Low-Risk Patients: One-Year Results from the LRT Trial. JACC Cardiovascular interventions 2019 2019/03/13 [E-pub ahead of print]. 10.1016/j.jcin.2019.03.002.

10. Rogers T, Torguson R, Bastian R, Corso P, Waksman R. Feasibility of transcatheter aortic valve replacement in low-risk patients with symptomatic severe aortic stenosis: Rationale and design of the Low Risk TAVR (LRT) study. Am Heart J 2017;189:103-9.

11. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. The Journal of thoracic and cardiovascular surgery 2007;133:1226-33.

12. Jilaihawi H, Asch FM, Manasse E, et al. Systematic CT Methodology for the Evaluation of Subclinical Leaflet Thrombosis. JACC Cardiovasc Imaging 2017;10:461-70.

13. 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 (VARC-2). Eur J Cardiothorac Surg 2012;42:S45-60.

14. Makkar R. Makkar, R. on behalf of the PARTNER 3 Trial Investigators. PARTNER 3 Low-Risk Computed Tomography (CT) Sub-study: Subclinical Leaflet Thrombosis in Transcatheter and Surgical Bioprosthetic Valves. Oral presentation, Transcatheter Cardiovascular Therapeutics (TCT). 2019 [E-pub ahead of print].

15. Chakravarty T, Sondergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet 2017;389:2383-92.

16. Khan JM, Rogers T, Waksman R, et al. Hemodynamics and Subclinical Leaflet Thrombosis in Low-Risk Patients Undergoing Transcatheter Aortic Valve Replacement. Circ Cardiovasc Imaging 2019;12:e009608.

17. Jilaihawi H, Chen M, Webb J, et al. A Bicuspid Aortic Valve Imaging Classification for the TAVR Era. JACC Cardiovasc Imaging 2016;9:1145-58.

FIGURE LEGENDS

Figure 1 – Bicuspid aortic valve Sievers classification

Red arrows indicate fused raphes in Sievers type 1 and 2 bicuspid morphologies(11).

Figure 2 – Aortic valve hemodynamics

Echocardiography was performed at baseline, before hospital discharge, and at 30-day follow up (aortic valve area [AVA] (cm^2) blue and mean gradient (mmHg) mustard].

Figure 3 – Aortic regurgitation

Echocardiography was performed at baseline, before hospital discharge, and at 30-day follow-up. No patient had transvalvular aortic regurgitation. All regurgitation was paravalvular.

Figure 4 – Subclinical leaflet thrombosis in the bicuspid TAVR cohort

Contrast-enhanced CT or TEE was performed at 30-day follow up. THV leaflet findings were defined according to Jilaihawi(12). All imaging studies were analyzed in an independent Core Laboratory. CT: computed tomography; TEE: transesophageal echocardiography; THV: transcatheter heart valve.

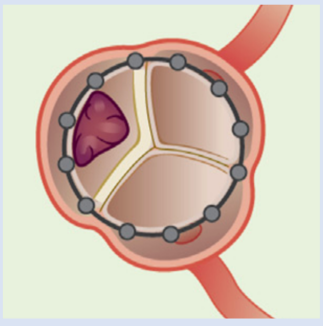
Central Illustration – Summary of the Bicuspid Low-Risk TAVR trial

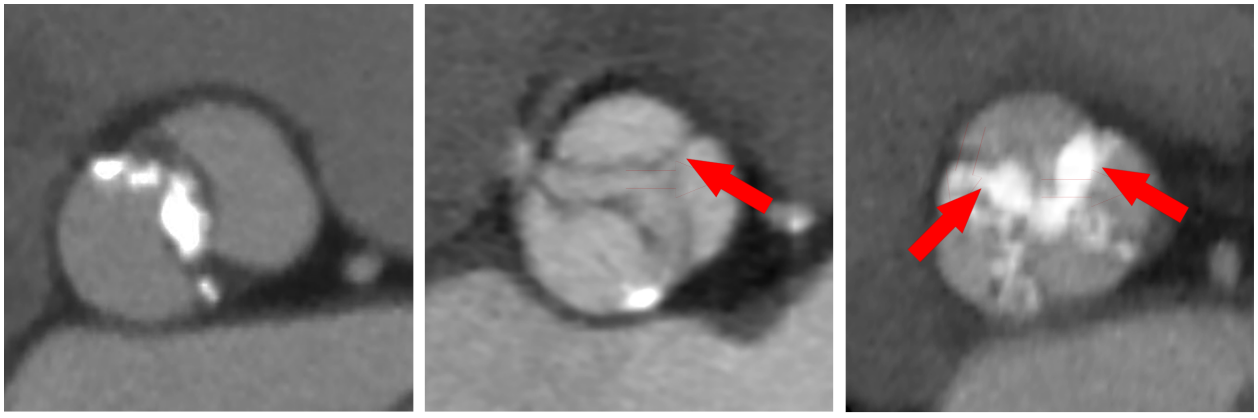
61 Bicuspid Low-Risk Patients
13.3% Sievers type 0
78.3% Sievers type 1
3.3% Sievers type 2

TAVR
100% transfemoral
74% balloon-expandable valve
26% self-expanding valve

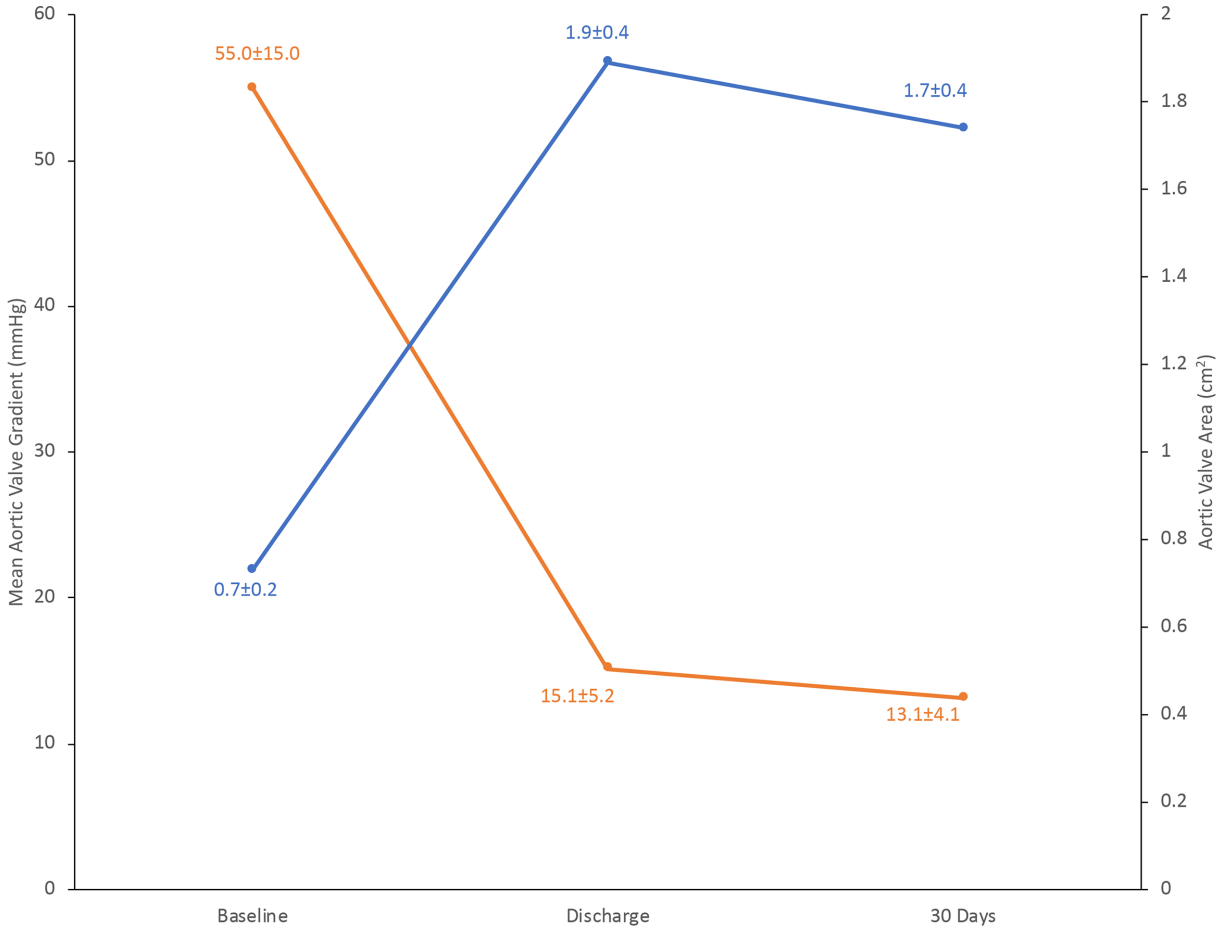
30-day Clinical Outcomes
0.0% mortality
0.0% disabling stroke
13.1% permanent pacemaker implantation
1.6% >mild paravalvular leak

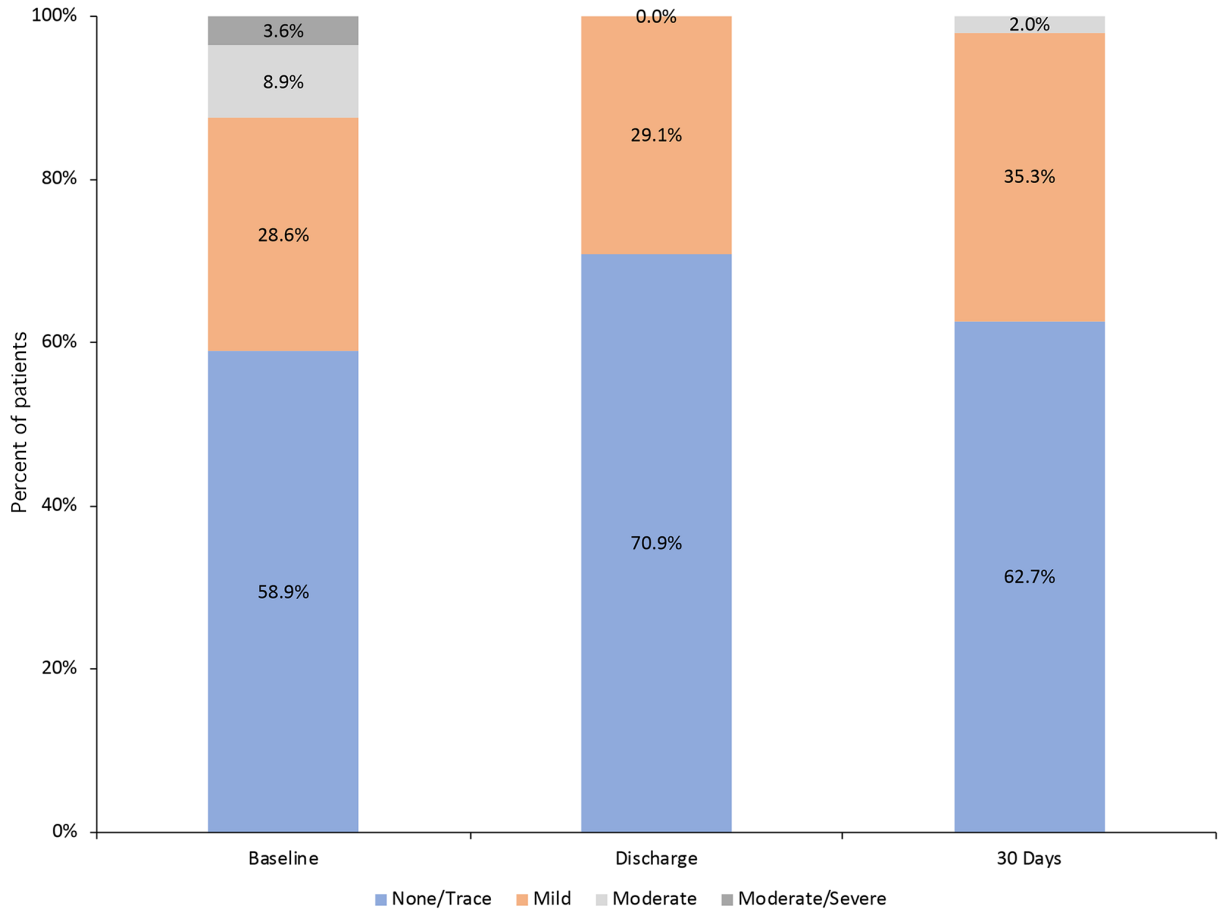
30-day CT
10.2% Hypo-Attenuating Leaflet Thickening (HALT)

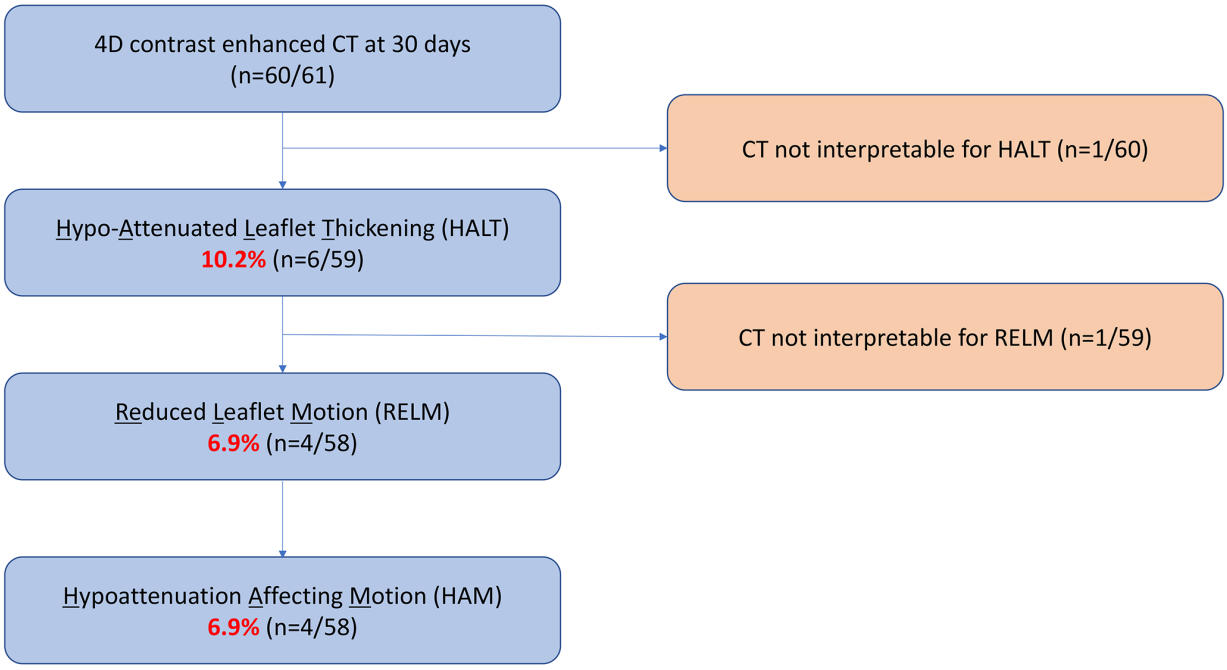




Sievers Type 0 (14.0%) | **Sievers Type 1 (82.5%)** | **Sievers Type 2 (3.5%)**


60
50
40
30
20
10
0
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Mean Aortic Valve Gradient (mmHg)
Aortic Valve Area (cm²)
55.0±15.0
1.9±0.4
1.7±0.4
0.7±0.2
15.1±5.2
13.1±4.1
Baseline
Discharge
30 Days


100%
80%
60%
40%
20%
0%
Percent of patients
3.6%
8.9%
28.6%
58.9%
0.0%
29.1%
70.9%
2.0%
35.3%
62.7%
Baseline
Discharge
30 Days
None/Trace
Mild
Moderate
Moderate/Severe


4D contrast enhanced CT at 30 days
(n=60/61)
CT not interpretable for HALT (n=1/60)
Hypo-Attenuated Leaflet Thickening (HALT)
10.2% (n=6/59)
CT not interpretable for RELM (n=1/59)
Reduced Leaflet Motion (RELM)
6.9% (n=4/58)
Hypoattenuation Affecting Motion (HAM)
6.9% (n=4/58)

SUPPLEMENTAL MATERIALS

Supplemental Table 1 – Complete list of LRT investigators

	Name	Role
Sponsor	Ron Waksman, MD	National Co-Principal Investigator
	Christian Shults, MD	National Co-Principal Investigator
	Rebecca Torguson, MPH	Director Clinical Research Operations
Clinical Review Committee	Itsik Ben-Dor, MD	Member, Interventional Cardiologist
	Christian Shults, MD	Member, Cardiac Surgeon
	Toby Rogers, MD, PhD	Coordinator, Facilitator
	Anees Musallam, MD	Coordinator, Facilitator
Data Management	Alan Monath	Director Data Management
	Paige Craig, MPH	Manager Data Management
Echocardiography Core Lab	Federico Asch, MD	Director Echo Core Lab
	Amir Zohdi	Echo Core Lab tech
CT Core Lab	Gaby Weissman, MD	Director CT Core Lab
	Fernando Rodriguez-Weisson, MD	CT Core Lab tech
Clinical Events Committee	Hector Garcia-Garcia, MD, PhD	Chairman
	Richard Benson, MD	Adjudicator, Neurologist
	Prerna Malla, MD	Adjudicator, Neurologist
	Eugene McFadden, MD	Adjudicator, Interventional Cardiologist
	Ezequiel Molina, MD	Adjudicator, Cardiac Surgeon
	Hiroto Kitahara, MD	Adjudicator, Cardiac Surgeon
	Syed Ali, MBBS	Coordinator, Facilitator
DSMB	William S. Weintraub, MD	Chairman
	Daniel H. Steinberg, MD	Member, Interventional Cardiologist
	Marc Katz, MD	Member, Cardiac Surgeon

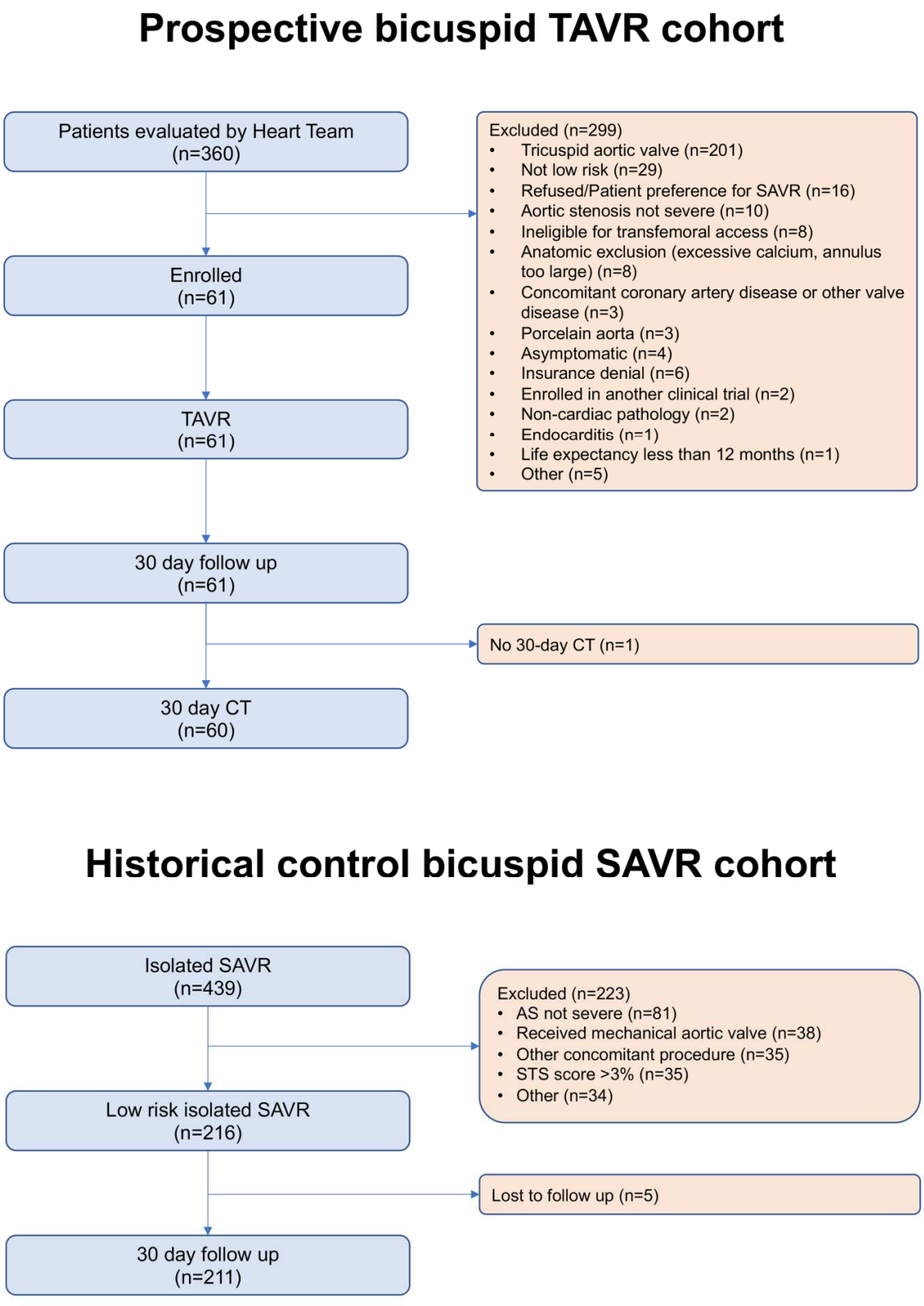
Site	Site Name	Principal Investigators	Site Address
001	MedStar Washington Hospital Center	Ron Waksman, MD (IC) Christian Shults, MD (CS)	110 Irving St, NW Suite 4B-1 Washington, DC 20010
007	Miriam Hospital	Paul Gordon, MD (IC) Afshin Ehsan, MD (CS)	The Miriam Hospital Cardiovascular Research 164 Summit Avenue Providence, RI 02906
009	Stony Brook Hospital	Puja Parikh, MD (IC) Thomas Bilfinger, MD (CS)	Stony Brook University Hospital HSC L16 Rm 080 Stony Brook, NY 11794
011	Henrico Doctors' Hospital	Robert Levitt, MD (IC) Chiwon Hahn, MD (CS)	Henrico Doctors' Hospital/ Cardiothoracic Surgical Associates 7605 Forest Avenue Suite 302 Richmond, VA 23229
014	Sutter Health System	David Roberts, MD (IC) Michael Ingram, MD (CS)	Sutter Medical Center, Sacramento Sutter Heart and Vascular Institute, Research 2800 L Street, Suite #250 Sacramento, CA 95816
016	St. John Heart Institute	Nicholas Hanna, MD (IC) George Comas, MD (CS)	St. John Health System Clinical Research Institute 1725 S. 19th, Suite 701 Tulsa, OK 74104

IC- Interventional Cardiologist; CS- Cardiac Surgeon

Supplemental Table 2 – Exclusion criteria for the historical SAVR cohort from the STS database

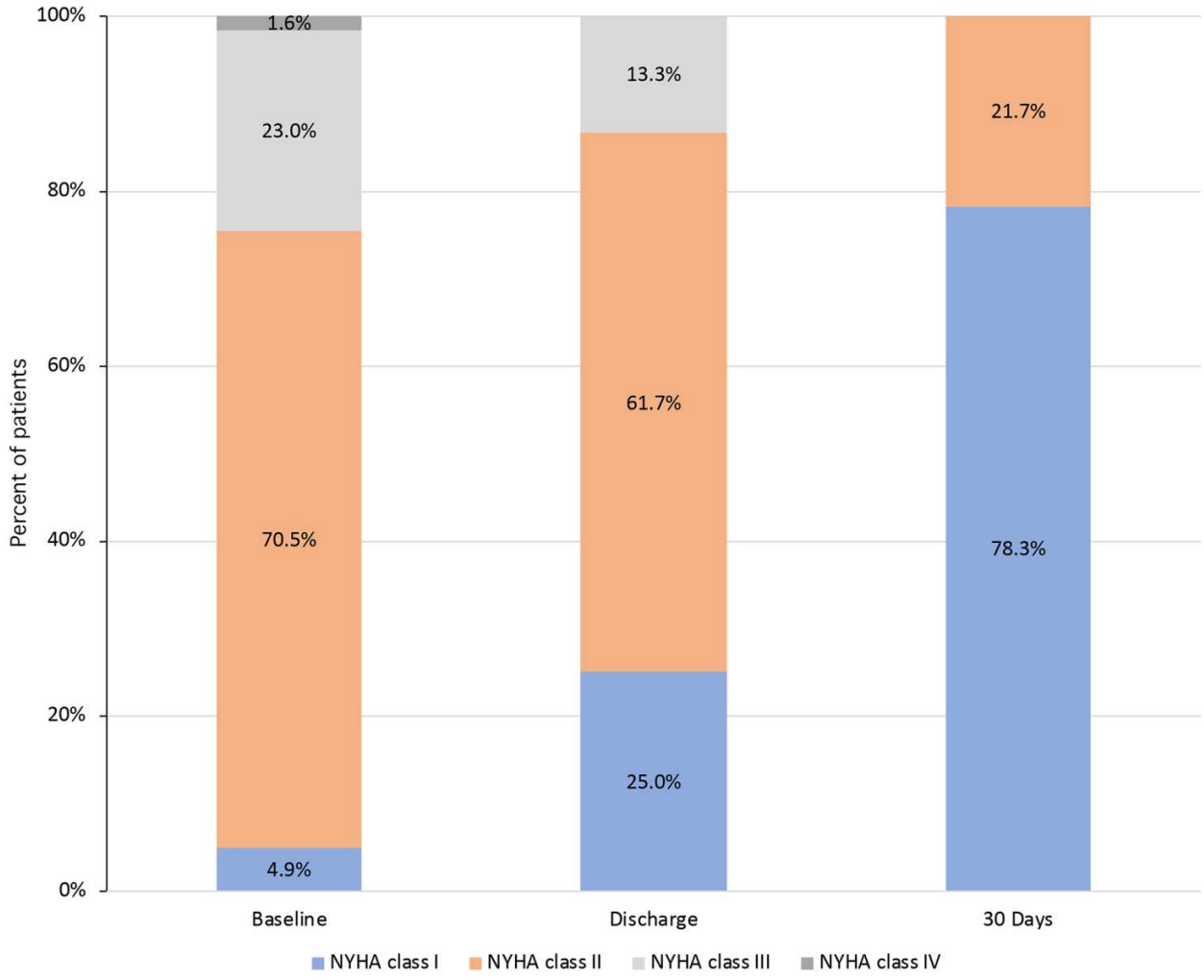
Exclusion criteria
Not low risk (STS-PROM score >3)
Neither severe nor symptomatic aortic stenosis
Bicuspid aortic valve
Concomitant cardiac procedure
Received mechanical prosthesis
Inotropes within 24 hours
Symptomatic carotid disease
Re-do surgical aortic valve replacement
Severe chronic lung disease
Recent acute myocardial infarction (within 21 days)
Left ventricular ejection fraction <20%
Ongoing infective endocarditis
Aortic root procedure
Antiplatelet contraindication
Thrombolytics within 48 hours
Liver failure
Concomitant non-cardiac procedure
End stage renal disease
Planned PCI
Glycoprotein IIb/IIIa within 24 hours
Ventricular Assist Device from prior procedure
No aortic valve implanted
Recent stroke (within 30 days)

Supplemental Figure 1 – Study design



The SAVR cohort comprised of patients who underwent isolated SAVR for bicuspid valve at the enrolling centers.

Supplemental Figure 2 –New York Heart Association (NYHA) functional class



NYHA functional class was recorded in bicuspid TAVR patients at baseline, prior to hospital discharge and at 30-day follow up.

TABLES

	Bicuspid TAVR	**Bicuspid SAVR**
Age, years	68.6±7.4	63.4±8.2
Male	26/61 (42.6%)	142/216 (65.7%)
Body mass index *	29.5±6.7	29.4±5.5
NYHA class III or IV	15/61 (24.6%)	34/215 (15.8%)
STS-PROM score †, %	1.5±0.6	1.1±0.5
Diabetes mellitus	8/61 (13.1%)	41/216 (19%)
Renal insufficiency§	2/61 (3.3%)	4/213 (1.9%)

Table 1 – Unadjusted baseline characteristics

Hypertension	38/61 (62.3%)	150/216 (69.4%)
Peripheral vascular disease	2/60 (3.3%)	9/216 (4.2%)
Cerebrovascular disease	2/61 (3.3%)	18/216 (8.3%)
Prior CVA/TIA	4/61 (6.6%)	17/216 (7.9%)
Chronic lung disease	6/61 (9.8%)	37/216 (17.1%)
LVEF	63.9±9.1	57.7±9.1
Prior PCI	2/61 (3.3%)	11/216 (5.1%)
Prior CABG	0/61 (0%)	3/216 (1.4%)
Pre-existing PPM	1/61 (1.6%)	2/212 (0.9%)
Prior myocardial infarction	2/61 (3.3%)	7/214 (3.3%)
Pre-existing arrhythmia	10/61 (16.4%)	8/216 (3.7%)

Plus-minus variables are mean±standard deviation. All other variables are n/N (%). CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PPM: permanent pacemaker; PVD: peripheral vascular disease; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement; TIA: transient ischemic attack. * Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. † The Society of Thoracic Surgeons – Predicted Risk of Mortality (STS-PROM) score estimates the rate of death at 30 days among patients undergoing SAVR based on a predefined number of baseline demographic and clinical characteristics, and procedural variables. § Renal insufficiency defined as either GFR <60mL/min/1.73m^2 or dialysis dependent.

Table 2 – TAVR cohort pre-procedural imaging analysis

CT	
Sievers classification	
Sievers type 0	8/60 (13.3%)
Sievers type 1 (fused raphe)	47/60 (78.3%)
Right-Left	40/47 (85.1%)
Non-Right	7/47 (14.9%)
Left-Non	0/47 (0%)
Sievers type 2 (two fused raphes)	2/60 (3.3%)
Right-Left and Non-Right	2/2 (100%)
Right-Left and Left-Non	0/2 (0%)
Non-Right and Left-Non	0/2 (0%)
Sievers type uncertain	3/60 (5.0%)
TAVR-specific bicuspid aortic valve classification*	
Tri-commissural	11/60 (18.3%)
Bi-commissural raphe-type	36/60 (60.0%)
Bi-commissural non raphe-type	8/60 (13.3%)
Uncertain	5/60 (8.3%)
Ascending aorta dimensions	
Ascending aorta max, mm	36.9±4.5
Ascending aorta min, mm	36.0±4.7
Aortic annulus	
Perimeter (mm)	80.6±8.2
Area (mm^2)	524.0±107.6
Sinus of Valsalva	
Right (mm)	32.3±4.2
Left (mm)	34.1±4.4
Non (mm)	34.3±4.4
Sinotubular junction	
Minimum diameter (mm)	28.9±4.3
Maximum diameter (mm)	32.1±4.9

Left main coronary height (mm)	13.6±3.7
Right coronary artery height (mm)	16.1±3.9
Echocardiography	
Aortic valve calcification	
Severe	56/60 (93.3%)
Moderate	1/60 (1.7%)
Mild	0/60 (0%)
None	0/60 (0%)
Not evaluable	3/60 (5%)

Plus-minus variables are mean±standard deviation. All other variables are n/N (%).

*TAVR-specific bicuspid aortic valve classification according to Jilaihawi et al(17).

Table 3 – Procedural details

	Bicuspid TAVR
Total procedure time, min	91.4±33.6
General anesthesia	12/61 (19.7%)
Transfemoral access	61/61 (100%)
Transcatheter heart valve type	
Balloon-expandable valve	45/61 (74%)
Self-expanding valve	16/61 (26%)
Implantation of >1 valve	0/61 (0%)
Conversion to surgery	0/61 (0%)
Valve size implanted	
20mm	0/61 (0%)
23mm	13/61 (21%)
26mm	26/61 (43%)
29mm	17/61 (28%)
31/34mm	5/61 (8%)
	Bicuspid SAVR
Valve size implanted	
≤19mm	7/216 (3%)
21mm	50/216 (23%)
23mm	92/216 (43%)
25mm	51/216 (24%)
27mm	12/216 (6%)
29mm	4/216 (1%)

Plus-minus variables are mean±standard deviation. All other variables are n/N (%).

Table 4 – Unadjusted clinical outcomes

In-hospital outcomes	**Bicuspid TAVR**	**Bicuspid SAVR**	**Tricuspid TAVR***
All-cause death	0/61 (0%)	1/216 (0.5%)	0/200 (0%)
Length of stay post-procedure, days	2.0±1.0	5.8±2.2	2.0±1.1
VARC 2 life-threatening or major bleeding†	1/61 (1.6%)	—	5/200 (2.5%)
VARC 2 major vascular complications	1/61 (1.6%)	—	5/200 (2.5%)
Acute kidney injury‡	0/61 (0%)	—	0/200 (0%)
All stroke	1/61 (1.6%)	2/216 (0.9%)	0/200 (0%)
MI	0/61 (0%)	—	0/200 (0%)
Endocarditis	0/61 (0%)	—	0/200 (0%)
New-onset atrial fibrillation	1/61 (1.6%)	92/216 (42.6%)	6/200 (3%)
New PPM implantation	7/61 (11.5%)	12/216 (5.6%)	10/200 (5%)
Coronary artery obstruction	0/61 (0%)	—	1/200 (0.5%)
30-day outcomes	**Bicuspid TAVR**	**Bicuspid SAVR**	**Tricuspid TAVR**
All-cause death	0/61 (0%)	1/211 (0.5%)	0/200 (0%)
VARC 2 life-threatening or major bleeding†	1/61 (1.6%)	—	6/200 (3%)
VARC 2 major vascular complications	2/61 (3.3%)	—	6/200 (3%)
Acute kidney injury‡	0/61 (0%)	—	0/200 (0%)
All stroke	1/61 (1.6%)	—	1/200 (0.5%)
MI	0/61 (0%)	—	1/200 (0.5%)
Endocarditis	0/61 (0%)	—	0/200 (0%)
New-onset atrial fibrillation	2/61 (3.3%)	—	9/200 (4.5%)
New PPM implantation	8/61	—	13/200 (6.5%)

	(13.1%)		
Coronary artery obstruction	0/61 (0%)	—	1/200 (0.5%)

* Previously published data(8). All TAVR patients were followed through 30 days, and 5 SAVR patients were lost to follow-up prior to 30 days. Plus-minus variables are mean ± standard deviation. All other variables are n/N (%). Abbreviations as in Table 1. † VARC 2 major bleeding for SAVR assumed if ≥3 units red blood cell transfusion given during procedure. ‡ Stage 3 acute kidney injury defined as increase in serum creatinine to ≥300% (>3x increase compared to baseline) OR serum creatinine ≥4.0 mg/dL with an acute increase ≥0.5 mg/dL OR new requirement for dialysis.