Supplementary Online Content

Feldman TE, Reardon MJ, Rajagopal V, et al. Effect of mechanically expanded vs self-expanding transcatheter aortic valve replacement on mortality and major adverse clinical events in high-risk patients with aortic stenosis: the REPRISE III randomized clinical trial. *JAMA*. doi:10.1001/jama.2017.19132

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplemental Methods and Results

Study Design

The REPRISE III trial also included a non-randomized roll-in phase for centers without previous experience implanting the Lotus Valve, a concurrent non-randomized nested registry of patients receiving the 21 mm Lotus Valve, and a subsequent non-randomized continued access study of US patients receiving a Lotus Valve after completion of RCT enrollment. The results from the randomized controlled trial are reported here.

The sponsor (Boston Scientific) performed the statistical analysis; the powered endpoints and all VARC safety endpoints were validated by an external statistician (John Gregson, PhD; London School of Hygiene & Tropical Medicine).

Randomization

REPRISE III Endpoints

Additional measurements based on the VARC endpoints and definitions available at the time of trial start were collected peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, and 1 year and will be collected annually for 5 years post index procedure, unless otherwise specified below.

- Safety endpoints adjudicated by an independent Clinical Events Committee (CEC):
  - Mortality: all-cause, cardiovascular, and non-cardiovascular
  - Stroke: disabling and non-disabling
  - Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure)
  - Bleeding: life-threatening (or disabling) and major
  - Acute kidney injury (≤7 days post index procedure): based on the AKIN System Stage 3 (including renal replacement therapy) or Stage 2
  - Major vascular complication
  - Repeat procedure for valve-related dysfunction (surgical or interventional therapy)
  - Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)
  - New permanent pacemaker implantation resulting from new or worsened conduction disturbances
  - New onset of atrial fibrillation or atrial flutter
  - Coronary obstruction: periprocedural (≤72 hours post index procedure)
  - Ventricular septal perforation: periprocedural (≤72 hours post index procedure)
  - Mitral apparatus damage: periprocedural (≤72 hours post index procedure)
  - Cardiac tamponade: periprocedural (≤72 hours post index procedure)
  - Prosthetic aortic valve malpositioning, including valve migration, valve embolization, or ectopic valve deployment
  - Transcatheter aortic valve (TAV)-in-TAV deployment

  - Prosthetic aortic valve thrombosis
  - Prosthetic aortic valve endocarditis

- Device performance endpoints peri- and post-procedure.

- Clinical procedural success at 30 days was defined as implantation of the study device in the absence of death, disabling stroke, major vascular complications, and life-threatening or major bleeding.

- Procedural success (30 days), defined as absence of procedural mortality, correct positioning of a single transcatheter valve into the proper anatomical location, intended performance of the study device (effective orifice area [EOA] >0.9 cm2 for BSA <1.6 m2 and EOA >1.1 cm2 for BSA ≥1.6 m2 plus either a mean aortic valve gradient <20 mm Hg or a peak velocity <3m/sec, and no moderate or severe prosthetic valve aortic regurgitation) plus no serious adverse events at 30 days

- Additional indications of prosthetic aortic valve performance as measured by transthoracic echocardiography and assessed by an independent core laboratory, including effective orifice area, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation.

- Modified device success at 30 days was reported for patients randomized and implanted with an assigned study device and defined as follows: absence of mortality with the originally implanted transcatheter valve in the proper anatomical location, no additional aortic valve procedures, and with the intended performance of the prosthetic valve (either a mean aortic valve gradient <20 mmHg or a peak velocity <3m/sec with no moderate or severe prosthetic valve aortic regurgitation).

- Functional status as evaluated by the following:
  - 5-m gait speed test[1]
  - New York Heart Association (NYHA) classification

- Neurological status as determined by the following:
  - Neurological physical exam by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner at discharge and 1 year
  - National Institutes of Health Stroke Scale (NIHSS) at discharge and 1 year
  - Modified Rankin Scale (mRS) at all time points

The following additional measurements will be reported separately:
- Health status as evaluated by Kansas City Cardiomyopathy[2] and SF-12[3] Quality of Life questionnaires at baseline; 1 and 6 months; and 1, 3, and 5 years
- Resource utilization associated with the procedure and/or follow-up.

Statistical Analyses

Patient Analysis Sets

Intent-to-Treat (ITT): all patients who sign an Informed Consent Form, are enrolled in the trial, and are randomized, whether or not an assigned study device is implanted. Event rates are calculated post randomization.

Implanted: all subjects who sign an Informed Consent Form, are enrolled in the trial, and are implanted with the assigned, randomized study device (excludes cross-over subjects). Event rates are calculated post index procedure.

Hierarchical Analysis of Primary and Secondary Endpoints

Testing of endpoints was carried out in a hierarchal manner in order to ensure the experiment-wise type I error rate was controlled. Testing was done in 3 steps with each step needing to reject the null hypothesis in order to proceed to the next step:

1. Test the primary safety endpoint and the primary hypothesis of the primary effectiveness endpoint. If non-inferiority is met for both, then step 2 was performed.
2. Test the secondary endpoint; if superiority is met, then step 3 was performed.
3. Test the secondary hypothesis of the primary effectiveness endpoint.

To test for superiority of the primary effectiveness endpoint, a chi-square test was used (in the ITT population) and superiority was concluded if $P<.025$ which corresponded to the 2-sided upper 95% confidence bound on the difference between treatment groups (MEV – SEV) being less than 0. For this test, given enrollment of 912 patients (2:1 MEV:SEV) and 10% attrition, there is approximately 86% power to show superiority with the given expected rates.

For the primary and secondary endpoint analyses, site poolability and potential interactions between site and treatment were evaluated. Sites with 6 or fewer randomized patients were combined based on geographic location. There were no treatment by site interactions and no site effects for any of the three powered endpoints.

Online Results

Procedural outcomes

Repositioning (n=197) and retrieval (n=40) were successful in all MEV patients attempted. Repositioning could be performed in patients receiving EvolutR and was successful in all 35 patients attempted; retrieval was successful in 13 of 14 EvolutR patients.

Tipping Point Analysis

The missing data sensitivity analyses using the tipping point approach were performed for the powered primary endpoints by imputing missing data in both treatment groups with all possible combinations of failures to identify tipping points that result in a change of statistical conclusion.

For the 30-day primary safety endpoint, 2 patients in the SEV group and 6 patients in the MEV group had missing data. The analysis showed that in the worst-case scenario where no SEV

patient and all MEV patients with missing 30-day primary safety endpoint had an event, the *P* value from the Farrington-Manning test would still be <.025. Thus, the conclusion of non-inferiority would not change.

For the 1-year primary effectiveness endpoint, 43 patients in the SEV group and 87 patients in the MEV group had missing data for the non-inferiority testing. eFigure 2 shows results of imputing the missing values. The white area represents outcomes where the *P* value from the Farrington-Manning test was < .025 and the gray area represents outcomes that produced a *P* value ≥ .025; the lower right corner represents the tipping of non-inferiority statistical significance over to statistical non-significance. The analysis showed that if all SEV patients with missing primary effectiveness endpoint data did not have an event (0/43), then up to 87.4% (76/87) of the MEV patients with missing data could have had an event without changing the conclusion of non-inferiority. If all MEV patients with missing data had an event (100%; 87/87), then the non-inferiority conclusion would not change if 14.0% (6/43) or more of the SEV patients with missing data had an event. This analysis suggests the white area to grey area ratio is .99 to .01, approximately 99:1, implying that it is highly unlikely that the conclusion of the non-inferiority testing would have been different if the missing data were available.

eFigure 3 shows results of imputing the missing values for superiority testing of the 1-year primary effectiveness endpoint (43 patients in the SEV group and 87 patients in the MEV group with missing data). The white area represents outcomes where the *P* value from the Chi-square test was < .05 and the gray area represents outcomes that produced a *P* value ≥ .05. The lower right corner of eFigure 3 represents the tipping of superior statistical significance over to statistical non-significance. The analysis showed that if all SEV patients with missing primary effectiveness endpoint data did not have an event (0/43), then up to 23.0% (20/87) of the MEV patients with missing data could have had an event without changing the conclusion of superiority. If all MEV patients with missing data had an event (100%; 87/87), then the superiority conclusion would not change if 86.0% (37/43) or more of the SEV patients with missing data had an event. This analysis suggests the white area to grey area ratio is 0.68 to 0.32, approximately 2.1:1, implying the conclusion of superiority is unlikely to be changed.

To assess the robustness of the superiority testing of the primary effectiveness endpoint of all-cause mortality, disabling stroke and moderate or greater PVL through 1 year and the secondary endpoint of moderate or greater PVL at 1 year, imputation of missing PVL data was performed using the last available (non-missing) PVL value post-procedure for the missing 1-year PVL data. For the primary effectiveness endpoint, the calculated composite endpoint rate was 24.6% for CoreValve compared to 15.4% for Lotus with a *P* value of .001. For the secondary endpoint, the calculated rate of moderate or greater PVL was 7.9% for CoreValve compared to 0.8% for Lotus with a *P* value <.0001. Thus, the same superiority conclusion could be made for both endpoints.

Additional Measurements – Functional, Neurological, and Health Status

The functional status of patients from baseline to 1 year is shown in eTable 10. There were no significant differences between the two cohorts at any time point.

eTable 1. REPRISE III Investigators and Study Support by Site Name

Site	Study Team
Abbott Northwestern Hospital Minneapolis MN	Principal Investigators: Wesley Pedersen Co-Principal Investigator: Benjamin Sun Sub-investigators: Richard Bae, Frazier Ealesm, Robert Farivar, Thomas Flavin, Mario Goessl, Kevin Harris, Desmond Jay, Vibhu Kshettry, David Lin, Michael Mooney, Karol Mudy, Anil Poulose, Paul Sorajja, Mark Young Research Coordinators: Aisha Ahmed, Brittany Fitzpatrick, Kate Jappe, Karen Meyer, Pamela Morley, Sara Olson, Lauren Ware
Aurora St. Luke's Medical Center	Principal Investigators: Tanvir Bajwa Co-Principal Investigator: Daniel O'Hair Sub-investigators: Suhail Allaqaband, Paul Werner Research Coordinators: Wendy Dunaj, Kathleen Behrens, Lindsay Biddick, Michelle Bennett, Deborah Waller, Anthony Chambers
Baptist Cardiac and Vascular Institute Miami FL	Principal Investigator: Ramon Quesada Sub-investigators: Kathy Ortiz, Rafael Machado, Alvaro Montoya, Niberto Moreno, Bernardo Sanabria, Marcus St. John Research Coordinators: Sarah Alegre, Maria Ardid, Susan Arp, Poliana Ayala, Ivette Cruz, Kimberly Dizon, Claudia Hodgson, Pearlie Kelly, Sylvia Morales Olivares
Baylor Heart & Vascular Hospital Dallas, TX	Principal Investigators: Robert Stoler Co-Principal Investigator: Robert Hebeler Sub-investigators: Paul Grayburn, Carl Henry, Ravi Vallabhan Research Coordinators: Janet Dunkerley, Geoffery Gong, Dion Graybeal, Emily Laible, Vivi St. John, Leslie Willcott
Beth Israel Deaconess Medical Center, Boston MA	Principal Investigators: Donald Cutlip Sub-investigators: James Chang, Kamal Khabbaz, Sandeep Kumar, Roger Laham, Vasileios-Arsenios Lioutas, David Liu, Warren Manning, Senthil Nathan, Duane Pinto, David Searls, Magdy Selim Research Coordinators: Michael Chen, Kimberly Guibone, Felicity Heath, Jenifer Kaufman, Sarah Kennedy, Susan Papazian, Trishna Sadhwani, Nanditha Shivaprakash, Vinessa Tjoa, Patricia Tyler
Cardiac & Vascular Research Center of Northern Michigan – Northern Michigan Hospital Petoskey, MI	Principal Investigators: Louis Cannon Sub-investigators: Chris Akins, David Corteville, Miranda Dalton, Thomas Earl, Jason Ricci, John Talbott Research Coordinators: Jane Fisher, Jennifer LaLonde, Joan Morey, Cindy Witucki
Cedars - Sinai Medical Center Los Angeles CA	Principal Investigators: Raj Makkar Co-Principal Investigator: Wen Cheng Sub-investigators: Hasanian Al-Jilaihawi, Saibal Kar, Mamoo Nakamura Research Coordinators: Zev Allison, David Anderson, Hormoz Babaei, Mitch Gheorghiu, Babak Hariri, Sharjeel Israr, Geeteshwar Mangat, George Matar, Kashif Mohammad, Emil Pais, Jigarkumar Patel, Tejas Rami, Jaideep Sandhu, Nisha Shah, Ripandeep Tiwana, Isil Uzun, Cynthia Valencia, Jonathan Winnick, Paya Zadeh
Centre Hôpital Universitaire Rangueil Toulouse, France	Principal Investigators: Didier Carrie Co-Principal Investigator: Bertrand Marcheix Sub-investigators: Frederic Bouisset, Thibault Lhermusier Research Coordinators: Adeline Hupe, Ludovic Lacassagne
Cleveland Clinic Foundation Cleveland, OH	Principal Investigators: Samir Kapadia Sub-investigators: Amar Krishnaswamy, Mei Lu, Stephanie Mick, Jose Navia, Eric Roselli, Lars Svensson, E. Murat Tuzcu Research Coordinators: Laurie Boehk, Mary Dettmer, Carrie Melgaard, Adrienne Nadvornik, Veronica Peck, Andrea Rohr, Christine Shin, Lydia Sweeney
Clinique Pasteur	Principal Investigators: Didier Tchetche

eTable 1. REPRISE III Investigators and Study Support by Site Name

Site	Study Team
Toulouse, France	Sub-investigators: Nicolas Dumonteil, Bruno Farah Research Coordinators: Brigitte Jacob, Frederic Petit
Columbia University Medical Center New York, NY	Principal Investigators: Tamim Nazif Sub-investigators: Isaac George, Rebecca Hahn, Omar Khalique, Susheel Kodali, Martin Leon, Torsten Vahl Research Coordinators: Sarah Borden, Marian Hawkey, Rosa Lazarte, Cynthia Martinez, Marina Mathews, Dawn Scotto
Delray Medical Center Delray Beach, FL	Principal Investigators: Brian Bethea Co-Principal Investigator: Brijeshwar Maini Research Coordinators: Pamela Beck, Christine Da Costa, Laura Hudson, Joanne Krasnoff, Ricardo Thompson, Wanda Trabal
Duke University Medical Center Durham, NC	Principal Investigators: John Harrison Co-Principal Investigator: G. Chad Hughes Sub-investigators: Jeffrey Gaca, Todd Kiefer, Andres Maldonado, Andrew Wang Research Coordinators: Megan Arthur, Caroline Bishop, Krista Camuglia, Edana Christy, Megan Eure, Dana Henderson, Sara Michael, Stephanie Newbold, Cynthia Pierce, Dana Schrantz, Alexis Sharp, Leanne Stanton
Emory University Hospital, Emory University Hospital Midtown, Emory St. Joseph's Atlanta, GA	Principal Investigators: Vinod Thourani (now at MedStar, Washington DC); Robert Guyton Sub-investigators: Vasilis Babaliaros, Chandan Devireddy, Stamatios Lerakis, Bradley Leshnower, James Stewart, Eric Sarin Research Coordinators: Kim Baio, Elizabeth Charles, Renee Cook, Atira Goodwin, Maria Kaner, Patricia Keegan, Madeline Kohrumel, Kimberly McWhorter, Mary Mungai, Alexis Neill, Maryellen Nelms, Leslie Ogburn, Himaben Patel, Kristy Pitts, Michael Quinn, Heather Sigler, Amy Simone, Lauren Wheeler
Erasmus MC - University Medical Center Rotterdam Rotterdam, Netherlands	Principal Investigators: Nicolas van Mieghem Sub-investigators: Joost Daemen, Peter de Jaegere, Nahid El Faquir, Marcel Geleijnse, A.Pieter Kappetein, Herbert Kroon, Zouhair Rahhab, Ramon Rodriguez-Olivares, Lennart Van Gils Research Coordinators: Elisabeth Huijskens, Arno Ruiter, Nico Van den Berg
Evanston Hospital Evanston, IL	Principal Investigators: Ted Feldman Sub-investigators: Mayra Guerrero, Justin Levisay, Paul Pearson, Hyde Russell, Michael Salinger Research Coordinators: Craig Konwinski, Dale Seifert, Jean Skelskey, Lisa Smalley, Frances Uy
Herzzentrum Universität Leipzig Leipzig, Germany	Principal Investigators: Axel Linke Sub-investigators: Stephan Haussig, Robert Hoellriegel, David Holzhey, Philipp Kiefer, Sergey Leontyev, Norman Mangner, Dominik Michalski, Anne katrin Mueller, Katrin Pomrehn, Maximilian Roeder, Beate Rott, Marcus Sandri, Florian Schlotter, Gerhard Schuler, Georg Stachel, Anika Stockert, Gesa Weise, Ephraim Winzer, Felix Woitek, Marion Zimmer Research Coordinators: Jennifer Adam, Jacqueline Foehlisch, Mandy Ludwig
Hospital of the University of Pennsylvania, Presbyterian University of Pennsylvania Medical Center Philadelphia, PA	Principal Investigators: Howard Herrmann Co-Principal Investigator: Saif Anwaruddin, Wilson Szeto Sub-investigators: Joseph Bavaria, Nimesh Desai, Jay Giri, Prashanth Vallabhajosyula Research Coordinators: Delonjo Barber, Rachel Callahan, Zach Fox, Ashley Hoedt, Marisa Konig, Matt Kramer, Grace Lacorte, Krimi Patel, Laura Schuck, Mary Siki, Madeleine Walsh
Kaleida Health Buffalo, NY	Principal Investigators: Vijay Iyer Co-Principal Investigator: Gary Grosner Sub-investigators: Hashmet Ashraf, Eileen Daetsch, Stanley Fernandez, Saurabh

eTable 1. REPRISE III Investigators and Study Support by Site Name

Site	Study Team
	Malhotra, William Morris, Kishor Phadke, David Zlotnick Research Coordinators: Courtney Bishop, Robin Stein, Adeline Thurston
Lindner Center for Research and Education at Christ Hospital Cincinnati, OH	Principal Investigators: Dean Kereiakes Sub-investigators: Geoffrey Answini, Amit Arora, Mario Castillo-Sang, Joseph Choo, Ian Sarembock Research Coordinators: Kathleen Buszek, Megan Francis, Janet Fricker, Ann Friedmann, Deborah Garza, Karen Ibanez, Laura Joy, Christine Lawrence, Tessa Messinger, Linda Pennington, Roxanne Robertson, Darlene Rock, Jane Schwartz, Terri Sikora, Ngoc Tran, David White, Julie Williams
Mayo Clinic Foundation Rochester, MN	Principal Investigators: Gurpreet Sandhu Sub-investigators: Kevin Greason, Rajiv Gulati, Alberto Pochettino Research Coordinators: Desirae Howe-Clayton, Ramona Johnson, Pamela Mundt, Jackie Reiter
McGill University Health Centre Montreal, QC, Canada	Principal Investigators: Nicolo Piazza Sub-investigators: Jean Buithieu, Benoit De Varennes, Liam Durcan, Kevin Lachapelle, Giuseppe Martucci, Marco Spaziano Research Coordinators: Zuyi Jiang
Medical City Dallas Hospital Dallas, TX	Principal Investigators: Todd Dewey Co-Principal Investigator: Bruce Bowers Sub-investigators: Ambarish Gopal Research Coordinators: Lynn Blair-Anton, Mona Hedra, Brandon Prince, Gina Remington
Methodist DeBakey Heart Center, Methodist Hospital Research Institute Houston, TX	Principal Investigators: Neal Kleiman Co-Principal Investigator: Michael Reardon Sub-investigators: Colin Barker, Gerald Lawrie, Chun Lin, Stephen Little, Mahesh Ramchandani, Basel Ramlawi, Manuel Reyes, Scott Scheinin, Karanbir Singh Research Coordinators: Jeannie Arredondo, Patricia Brinegar, Laura Canter, Lisa Green, LaShawna Green, Meagan Griffith, Pamela Hazen, Chizoba Ifeorah, Chioma Ikoku, Amber Jacobs, Mary Mata, Tammara Moore, Wesley Oglesby, Carol Underwood
Methodist Heart Hospital/South Texas Methodist Hospital San Antonio, TX	Principal Investigators: Jorge Alvarez Sub-investigators: Daniel Donovan, James Garrison Research Coordinators: Gloria Carreon, Johnie Piper, Sherri Shade
Monash Medical Centre Clayton, Australia	Principal Investigators: Robert Gooley Sub-investigators: Adam Brown, David Di Fiore, Abdul Ihdayhid, Siobhan Lockwood, Liam McCormick, Sarah Zaman Research Coordinators: MaryAnne Austin, Brianna Davidson, Adele Manzoney, Wendy Wallace-Mitchell
Morristown Memorial Hospital Morristown, NJ	Principal Investigators: Barry Cohen Sub-investigators: John Brown, Robert Kipperman, Konstantinos Koulogiannis, Christopher Magovern, Leo Marcoff, Marek Polomsky, James Slater, Steve Xydas Research Coordinators: Diane Agar, Autumn Benner, Christine Ciprich, Mary DiNapoli, Elena Lobur, Lucille Polise, Susan Sentman
Morton Plant Mease Healthcare System Clearwater, FL	Principal Investigators: Joshua Rovin Co-Principal Investigator: Douglas Spriggs Sub-investigators: Michael Barry, Todd Kovach, Lang Lin, Jorge Navas, John Ofenloch, Vijay Patel Research Coordinators: Laura Blanchard, Donna Bulmer, Sue Fisher, Delia Johnson, Teresa Jones, Susie Montgomery
NC Heart and Vascular Research, Rex Hospital	Principal Investigators: Robert Jobe Sub-investigators: Curtis Anderson, Christian Gring, James Jollis, Lance Landvater,

eTable 1. REPRISE III Investigators and Study Support by Site Name

Site	Study Team
Raleigh, NC	Willis Wu, James Zidar Research Coordinators: Heather Dionne, Jamal Moss, Nicole Trader
North Shore University Hospital (Manhasset) Manhasset, NY	Principal Investigators: Bruce Rutkin Sub-investigators: Sonia Henry, Rajiv Jauhar, Robert Palazzo, Jacob Scheinerman, Bart Steinberg Research Coordinators: Christina Brennan, Diane Delliliune, Natasha Phrsai, Vadewattie Seeratan
OhioHealth Research and Innovation Institute - Riverside Methodist Hospital Columbus, OH	Principal Investigators: Steven Yakubov Sub-investigators: Arash Arshi, Geoffrey Blossom, Steven Duff, Nathan Kander, Jefferson Lyons, Carlos Sanchez, Daniel Watson Research Coordinators: Christina Belcher, Rose Fischer, Vickie Hatch, Kitra Hunter, Katy Monnin, Lori Popelas, Martha Slyman, Carolann Strausbaugh
Ohio State University Medical Center Columbus, OH	Principal Investigators: Scott Lilly Sub-investigators: Konstantinos Boudoulas, Juan Crestanello, Barry George, Danielle Jones, Ahmet Kilic, Scott Lilly, David Orsinelli, John Sirak, Bryan Whitson Research Coordinators: Denise Fadorsen, Hallie Hank, Annie Kellum, Roderick Liptrot
Piedmont Hospital Atlanta, GA	Principal Investigators: Vivek Rajagopal Co-Principal Investigator: James Kauten Sub-investigators: W. Morris Brown, David Dean, John Gott, Christopher Meduri, Federico Milla Research Coordinators: Elisa Amoroso, Nita Cadic, Kashaine Gray, Shelley Holt
Providence St. Vincent Medical Center Portland, OR	Principal Investigators: Robert Hodson Sub-investigators: Eric Kirker, Jeffrey Swanson, Gary Ott, Geoffrey Wilson, Ethan Korngold Research Coordinators: Ellen Muir, Heather Aiona, Sarah Grant, Angela Redd, Gretchen Sminkey
Scottsdale Healthcare – Shea Scottsdale, AZ	Principal Investigators: David Rizik Sub-investigators: Robert Burke, Bimal Padaliya, Robert Riley, Maulik Shah, Alok Sharma Research Coordinators: Lindsay Arth, Amy Boylan, Donna Duerr, Joanne Saczynski, Regina Valenzuela, Patricia Williams
Scripps Clinic La Jolla, CA	Principal Investigators: Paul Teirstein Sub-investigators: Scot Brewster, Curtiss Stinis, J. Jeffrey Tyner Research Coordinators: Tiffany Buchanan, Chelsea Butler, Sarah Clarke, Harleen Dhaliwal, Matthew Hollen, Ann Jensen, Jennifer Lutes, Kathleen Rees, Andrew Roberts, Pamela Staggs, Connor Wayman
St. John's Hospital Springfield, IL	Principal Investigators: Gregory Mishkel Co-Principal Investigator: William Stevens Sub-investigators: Jennifer Nichelson, Raja Gopaldas, Jeffrey Christy, Robert Woodruff, Nilesh Goswami, Jeffrey Goldstein, John Gill, Charlene Shallow, Vincent Zuck, Roberto Pacheco, Shailesh Nandish, Nasar Nallamothu Research Coordinators: Lauren McNeil, Amy Woolfolk, Lauren Bainter, Jannelle Megginson, Christine Shugart, Michelle Williamson
St. Vincent's Hospital	Principal Investigators: James Hermiller Co-Principal Investigator: David Heimansohn, Sina Moainie Sub-investigators: Gregory Elsner, Douglas Segar, Andrew Sampson, Scott Hanan, Peter Walts, Frank Green, Christopher Salerno, Michael Ball Research Coordinators: Rachel Johnson, Patrice Powell, Barbara Kingma
Stanford University Medical Center	Principal Investigators: Alan Yeung Co-Principal Investigator: Michael Fischbein

eTable 1. REPRISE III Investigators and Study Support by Site Name

Site	Study Team
	Sub-investigators: D. Craig Miller, William Fearon Research Coordinators: Cheryl McWard, Leigh Trautman, Zoe Magee, Martina Speight, Danna Salcaleon-Cua, Sandra Cardoza, Mykl Morrissey
Swedish Medical Center Seattle, WA	Principal Investigators: Robert Hodson Sub-investigators: Eric Kirker, Ethan Korngold, Gary Ott, Jeffrey Swanson, Geoffrey Wilson Research Coordinators: Heather Aiona, Sarah Grant, Ellen Muir, Angela Redd
The Prince Charles Hospital Chermside, Australia	Principal Investigators: Darren Walters Sub-investigators: Julian Chan, Niranjan Gaikwad, Ryan Markham, Dale Murdoch, Karl Poon, Anthony Putrino, Owen Raffel Research Coordinators: Tracy McCulloch, Sandy Phillips, Maria Pietsch, Maricel Roxas, Suzanne Spencer, Chantal Tabrett
UC Davis Medical Center	Principal Investigators: Jeffrey Southard Sub-investigators: Thomas Smith, Reginald Low, Garrett Wong, Jason Rogers, Walter Boyd Research Coordinators: Kimberley Book, Kori Harder, Teresa Facchini, Codi Cole, Lisa Ayer-Rand
Union Memorial Hospital	Principal Investigators: John Wang Sub-investigators: Amish Sura, Michael Fiocco, Antony Kaliyadan, Nauman Siddiqi, Dipin Gupta, Momina Mastoor, Luis Dibos Research Coordinators: Mary Park, Judith Raqueno, Sandeep Kumar, Rachel Campbell
Universitaetsklinik Eppendorf, Universitares Herzzentrum UKE Hamburg, Germany	Principal Investigators: Mahir Karakas, Ulrich Schaefer Sub-investigators: Lenard Conradi, Florian Deuschl, Sarina Schaefer, Moritz Seiffert, Karsten Sydow, Gotz Thomalla, Eike Tigges Research Coordinators: Arthur Behnke, Janine Nebel, Dagmar Ott, Marion Redlefsen, Diana Sprechert
University of Kansas Hospital Kansas City, KS	Principal Investigators: George Zorn Co-Principal Investigator: Peter Tadros Sub-investigators: Greg Muehlebach, Mark Wiley Research Coordinators: Jenny Bush, Alyssa Boyce, Donita Atkins, Tilitha Shawgo, Susie Page
University of Miami Hospital Miami FL	Principal Investigators: Mauricio Cohen Sub-investigators: Carlos Alfonso, Martin Blisker, Roger Carrillo, Eduardo de Marchena, Claudia Martinez, Donald Williams Research Coordinators: Carmen Baez-Garcia, Bonni Lang
University of Michigan Hospitals Ann Arbor, MI	Principal Investigators: Michael Deeb Sub-investigators: David Bach, Nicole Bhave, Stanley Chetcuti, Paul Grossman, Troy LaBounty, Daniel Menees, Himanshu Patel, Richard Prager, Matthew Romano Research Coordinators: Lauren Conlin, Rachel Geml, Jessica Oakley Kimberly Redburn, Sarah Rubin
University of Minnesota Medical Center Minneapolis, MN	Principal Investigators: Gregory Helmer Sub-investigators: Bilal Ali, Timinder Biring, Mustapha Ezzeddine, Ranjit John, Kenneth Liao, Emil Missov, Ganesh Raveendran, Uma Valeti, Demitris Yannopoulos, Alexander Zubkov Research Coordinators: Mary Baker, Barbara Bruhn-Ding, Emily Caldwell, Kassandra Malchow, Gretchen Peichel, Margaret Peterson, Deb Wilder
University of Pittsburgh Medical Center	Principal Investigators: Thomas Gleason Sub-investigators: Joon Lee, Ibrahim Sultan, Dustin Kliner, Matthew Harinstein, Elizabeth Christensen, Forozan Navid, William Katz, Frederick Crock, Joao Cavalcante, Dhaval Trivedi, John Schindler Research Coordinators: Rachel McGargle, Laurie Dennis, Elizabeth Younkin,

eTable 1. REPRISE III Investigators and Study Support by Site Name

Site	Study Team
	Chrissy Butler, Kristin Valchar, Melissa Enlow, Mary Kunkel
University of Washington Medical Center	Principal Investigators: Creighton Don Sub-investigators: James McCabe, Jason Smith, Mark Reisman, Larry Dean, Gabriel Aldea Research Coordinators: Kate Jordan, Devin Baerenwald, Fatemeh Ranjbara, Angela LeClair, Rebecca Letterer, Emily Anderson
Veterans Administration Palo Alto Medical Center Palo Alto, CA	Principal Investigators: John Giacomini Co-Principal Investigator: Thomas Burdon Sub-investigators: Maurice Buchbinder, James Fann, Robert Mitchell, Research Coordinators: Judy Baer, Grace Liang, Son Nguyen, Theresa Peters
Wake Forest University School of Medicine Winston-Salem, NC	Principal Investigators: David Zhao Co-Principal Investigator: Neal Kon Sub-investigators: Robert Applegate, Sanjay Gandhi, Edward Kincaid, Research Coordinators: Sharon McDaniel, Amanda Morgan, Wendi White, Travis Young
Washington Hospital Center Washington, DC	Principal Investigators: Ron Waksman Co-Principal Investigator: Paul Corso Sub-investigators: Itsik Ben-Dor, August Pichard, Lowell Satler, Christian Shults Research Coordinators: M. Chadi Alraies, Elizabeth Bond, Kyle Buchanan, Tina Daovd, Michelle Deville, Sandra Griffin, Prerna Malla, Petros Okubagzi, Farhanaz Panjshiri, Toby Rogers, Arie Steinvil, Donna Whitman
Washington University School of Medicine St. Louis, MO	Principal Investigators: John Lasala Co-Principal Investigator: Hersh Maniar Sub-investigators: Brian Lindman, Spencer Melby, Nishath Quader, Alan Zajarias Research Coordinators: Kelly Koogler, Michelle Myers, Sam Neudecker
William Beaumont Hospital Royal Oak, MI	Principal Investigators: George Hanzel Sub-investigators: Amr Abbas, Abhay Bilolikar, Michael Gallagher, Ivan Hanson, Nathan Kerner, Robert Safian, Marc Sakwa, Francis Shannon Research Coordinators: Diedre Brunk, Ann McHugh, Pat O'Bryan, Katherine Wood

eTable 2. REPRISE III Data Monitoring Committee, Case Review Committee, Steering Committee, and Core Laboratories

Data Monitoring Committee Members	
Name	**Institution**
Stuart Pocock, PhD DMC Chair	Department of Medical Statistics London School of Hygiene & Tropical Medicine
David P. Faxon, MD DMC Member	Brigham & Women's Hospital Cardiovascular Division
Bernard Gersh, MB, ChB, DPhil DMC Member	Mayo Clinic Division of Cardiovascular Diseases
Steven Livesey, MD DMC Member	Department of Cardiothoracic Surgery Southampton General Hospital
Independent Study Statisticians (non-voting)	
Timothy Collier, MSc	Department of Medical Statistics London School of Hygiene & Tropical Medicine
John Gregson, PhD	
Core Laboratories	
Type	**Institution**
Angiography & CT/X-ray	Jeffrey J. Popma, MD (Director) Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center, Boston, MA, USA
Echocardiography	Neil J. Weissman, MD (Director) MedStar Health Research Institute, Washington, DC, USA
Electrocardiography	Peter J. Zimetbaum, MD (Director) Harvard Clinical Research Institute, Boston, MA, USA
Pathology	Renu Virmani, MD (Director) CV Path Institute, Inc., Gaithersburg, MD, USA
Clinical Events Committee (Baim Institute for Clinical Research)	
Name	**Institution**
Sergio Waxman, MD (IC, Chair)	Lahey Clinic, Burlington, MA, USA
Carey Kimmelstiel, MD (IC)	Tufts New England Medical Center, Boston, MA, USA
Gregory Smaroff, MD (CT Surg)	Lahey Clinic, Burlington, MA, USA
Roberto Rodriguez, MD (CT Surg)	Lankenau Hospital, Wynnewood, PA, USA
Viken Babikian, MD (Neurologist)	Boston Medical Center, Boston, MA, USA
Case Review Committee • was responsible for the review of patient screening data to confirm eligibility given the increased surgical risk of the patient population being studied and to ensure consistency of patients enrolled across study centers	
Name	**Institution**
Ted Feldman (CRC Co-Chairmen)	Evanston Hospital Cardiology Division, Evanston, IL
Michael Reardon (CRC Co-Chairmen)	Houston Methodist DeBakey Heart and Vascular Center, Houston, TX, USA
Dan Blackman	Department of Cardiology, Leeds General Infirmary, Leeds, UK
Colin Barker	Methodist DeBakey Heart & Vascular Center, Houston, TX
Henrik Bjursten	Department of Cardiology, Skåne University Hospital, Lund, Sweden
Nicolas Dumonteil	Clinique Pasteur, Toulouse, France
Thomas Gleason	University of Pittsburgh Medical Center, Pittsburgh PA
Matthias Götberg	Department of Cardiology, Clinical Sciences, Lund University,

eTable 2. REPRISE III Data Monitoring Committee, Case Review Committee, Steering Committee, and Core Laboratories	
	Skane University Hospital, Lund, Sweden
David Hildick-Smith	Sussex Cardiac Centre, Brighton and Sussex University Hospitals, UK
Chris Meduri	Piedmont Hospital, Atlanta GA
A. Pieter Kappetein	Erasmus MC - University Medical Center Rotterdam Rotterdam, Netherlands
Paul Pearson	Evanston Hospital Cardiology Division, Evanston, IL
Vivek Rajagopal	Piedmont Hospital, Atlanta GA
David Rizik	HonorHealth and the Scottsdale-Lincoln Health Network, Scottsdale, AZ
Mike Salinger	Evanston Hospital Cardiology Division, Evanston, IL
Mark Spence	NHS, Belfast, United Kingdom
Didier Tchétché	Clinique Pasteur, Toulouse, France
Uday Trivedi	Royal Sussex County Hospital, Brighton, UK
Dominic Allocco (Sponsor Representative)	Boston Scientific, Marlborough, MA
Paul Underwood (Sponsor Representative)	Boston Scientific, Marlborough, MA
REPRISE III Steering Committee	
Name	**Institution**
Ted Feldman (co-PI)	Evanston Hospital Cardiology Division, Evanston, IL
Michael Reardon (co-PI)	Houston Methodist DeBakey Heart and Vascular Center, Houston, TX, USA
Joseph Bavaria	Hospital of the University of Pennsylvania, Philadelphia, PA
Maurice Buchbinder	Foundation for cardiovascular medicine, Professor of clinical medicine, Stanford university, Stanford CA
Anson Cheung	St Paul's Hospital - University of British Columbia, Vancouver, BC
Michael Deeb	University of Michigan Hospitals, Ann Arbor, MI
Todd Dewey	HCA Medical City Dallas Hospital, Dallas
Eberhard Grube	Elisabeth-Krankenhaus Hospital, Essen, Germany
Alan Heldman	University of Miami Miller School of Medicine, Miami, FL,
Samir Kapadia	Cleveland Clinic, Cleveland, OH
A. Pieter Kappetein	Erasmus MC - University Medical Center Rotterdam Rotterdam, Netherlands
Martin Leon	Columbia University Medical Center, Cardiovascular Research Foundation, New York City, NY
Ian Meredith	Boston Scientific, Marlborough, MA
Vinod Thourani	Emory University Hospital, Atlanta GA

eTable 3. REPRISE III Inclusion Criteria

IC1. Patient has documented calcific, severe native aortic stenosis with an initial AVA of ≤1.0 cm^2 (or AVA index of ≤0.6 cm^2/m^2) and a mean pressure gradient ≥40 mm Hg or jet velocity ≥4.0 m/s, as measured by echocardiography and/or invasive hemodynamics.

IC2. Patient has a documented aortic annulus size of ≥20 mm and ≤27 mm based on the center's assessment of pre-procedure diagnostic imaging (and confirmed by the CRC) and, for the randomized cohort, is deemed treatable with an available size of both test and control device.

IC3. Patient has symptomatic aortic valve stenosis with NYHA Functional Class ≥ II

IC4. There is agreement by the heart team (which must include a site investigator interventionalist and a site investigator cardiac surgeon) that patient is at high or extreme operative risk for surgical valve replacement (see **Note 1** below for definitions of extreme and high risk, the required level of surgical assessment, and CRC confirmation) and that TAVR is appropriate. Additionally, patient has at least one of the following.

- Society of Thoracic Surgeons score ≥8% -OR-
- If STS <8, patient has at least one of the following conditions:
  - Hostile chest
  - Porcelain aorta
  - Severe pulmonary hypertension (>60 mmHg)
  - Prior chest radiation therapy
  - Coronary artery bypass graft(s) at risk with re-operation
  - Severe lung disease (need for supplemental oxygen, FEV_1 <50% of predicted, DLCO <60%, other evidence of major pulmonary dysfunction)
  - Neuromuscular disease that creates risk for mechanical ventilation or rehabilitation after surgical aortic valve replacement
  - Orthopedic disease that creates risk for rehabilitation after surgical aortic valve replacement
  - Childs Class A or B liver disease (patients with Childs Class C disease are not eligible for inclusion in this trial)
- Frailty as indicated by at least one of the following: 5-meter walk >6 seconds, Activities of Daily Living Score of 3/6 or less, body mass index <21, wheelchair bound, unable to live independently
  - Age ≥90 years
  - Other evidence that patient is at high or extreme risk for surgical valve replacement (CRC must confirm agreement with site heart team that patient meets high or extreme risk definition)

IC5. Heart team (which must include a cardiac interventionalist and an experienced cardiac surgeon) assessment that the patient is likely to benefit from valve replacement.

IC6. Patient (or legal representative) understands the study requirements and the treatment procedures, and provides written informed consent.

IC7. Patient, family member, and/or legal representative agree(s) and patient is capable of returning to the study hospital for all required scheduled follow up visits.

Note 1: Extreme operative risk and high operative risk were defined as shown below. The risk of operative mortality and morbidity was to be assessed via an in-person evaluation by a center cardiac surgeon and was confirmed by the CRC (which included an experienced cardiac surgeon).

Extreme Operative Risk: Predicted operative mortality or serious, irreversible morbidity risk ≥50% at 30 days.

High Operative Risk: Predicted operative mortality or serious, irreversible morbidity risk ≥15% at 30 days.

Abbreviations: AVA=aortic valve area; CRC=case review committee; DLCO= diffusion capacity of the lung for carbon monoxide; FEV= forced expiratory volume; NYHA=New York Heart Association; TAVR=transcatheter aortic valve replacement

eTable 4. REPRISE III Exclusion Criteria

EC1.	Patient has a congenital unicuspid or bicuspid aortic valve.
EC2.	Patient has had an acute myocardial infarction within 30 days prior to the index procedure (defined as Q-wave MI or non–Q-wave MI with total CK elevation ≥ twice normal in the presence of CK-MB elevation and/or troponin elevation).
EC3.	Patient has had a cerebrovascular accident or transient ischemic attack within the past 6 months prior to study enrollment.
EC4.	Patient has end-stage renal disease or has GFR <20 (based on Cockcroft-Gault formula).
EC5.	Patient has a pre-existing prosthetic heart aortic or mitral valve.
EC6.	Patient has severe (4+) aortic, tricuspid, or mitral regurgitation.
EC7.	Patient has a need for emergency surgery for any reason.
EC8.	Patient has a history of endocarditis within 6 months of index procedure or evidence of an active systemic infection or sepsis.
EC9.	Patient has echocardiographic evidence of new intra-cardiac vegetation or intraventricular or paravalvular thrombus requiring intervention.
EC10.	Patient has Hgb <9 g/dL, platelet count <50,000 cells/mm^3 or >700,000 cells/mm^3, or white blood cell count <1,000 cells/mm^3.
EC11.	Patient requires chronic anticoagulation therapy after the implant procedure and cannot be treated with warfarin (other anticoagulants are not permitted in the first month) for at least 1 month concomitant with either aspirin or clopidogrel[a].
EC12.	Patient has had a gastrointestinal bleed requiring hospitalization or transfusion within the past 3 months, or has other clinically significant bleeding diathesis or coagulopathy that would preclude treatment with required antiplatelet regimen, or will refuse transfusions.
EC13.	Patient has known hypersensitivity to contrast agents that cannot be adequately pre-medicated, or has known hypersensitivity to aspirin, all $P2Y_{12}$ inhibitors, heparin, nickel, tantalum, titanium, or polyurethanes.
EC14.	Patient has a life expectancy of less than 12 months due to non-cardiac, comorbid conditions based on the assessment of the investigator at the time of enrollment.
EC15.	Patient has hypertrophic obstructive cardiomyopathy.
EC16.	Patient has any therapeutic invasive cardiac or vascular procedure within 30 days prior to the index procedure (except for balloon aortic valvuloplasty or pacemaker implantation, which are allowed).
EC17.	Patient has untreated coronary artery disease, which in the opinion of the treating physician is clinically significant and requires revascularization.
EC18.	Patient has severe left ventricular dysfunction with ejection fraction <20%.
EC19.	Patient is in cardiogenic shock or has hemodynamic instability requiring inotropic support or mechanical support devices.
EC20.	Patient has severe vascular disease that would preclude safe access (e.g., aneurysm with thrombus that cannot be crossed safely, marked tortuosity, significant narrowing of the abdominal aorta, severe unfolding of the thoracic aorta, or symptomatic carotid or vertebral disease).
EC21.	Patient has thick (>5 mm) protruding or ulcerated atheroma in the aortic arch
EC22.	Patient has arterial access that is not acceptable for the test and control device delivery systems as defined

eTable 4. REPRISE III Exclusion Criteria	
	in the device Instructions For Use.
EC23.	Patient has current problems with substance abuse (e.g., alcohol, etc.).
EC24.	Patient is participating in another investigational drug or device study that has not reached its primary endpoint.
EC25.	Patient has untreated conduction system disorder (e.g., Type II second degree atrioventricular block) that in the opinion of the treating physician is clinically significant and requires a pacemaker implantation. Enrollment is permissible after permanent pacemaker implantation.
EC26.	Patient has severe incapacitating dementia.

a: An alternative $P2Y_{12}$ inhibitor may be prescribed if patient is allergic to or intolerant of clopidogrel.
Abbreviations: CK=creatine kinase; GFR= Glomerular Filtration Rate; MI=myocardial infarction; PCI=percutaneous coronary intervention; RCT=randomized controlled trial

eTable 5. Additional Measurements

Variable	Mechanically-expanded Valve (N=607)	Self-expanding Valve (N=305)
Procedural Characteristics		
TEE used during implant procedure	353/596 (59.2)	167/300 (55.7)
Final post-deployment aortogram of the ascending aorta performed	577/596 (96.8)	284/300 (94.7)
Successful vascular access, delivery and deployment of the study Valve System, and successful retrieval of the delivery system	583/596 (97.8)	297/300 (99.0)
Conversion to open heart surgery	4/596 (0.7)	2/300 (0.7)
TAV-in-TAV deployment performed[a]	0/596 (0.0)	7/300 (2.3)
Prosthetic aortic valve malpositioning, including valve migration, valve embolization, ectopic valve deployment	0 (0.0)	8 (2.7)
Valve Migration	0 (0.0)	2 (0.7)
Valve Embolization	0 (0.0)	6 (2.0)
Ectopic Valve Deployment	0 (0.0)	1 (0.3)
Periprocedural coronary obstruction (≤72 h after index procedure)	1/587 (0.2)	2/297 (0.7)
Periprocedural cardiac tamponade (≤72 h after index procedure)	15/587 (2.6)	4/297 (1.3)
30 days		
Clinical Procedural Success at 30 days[b]	494/607 (81.4)	258/305 (84.6)
Procedural success at 30 days[c]	186/582 (32.0)	113/288 (39.2)
Modified device success at 30 days[d]	472/532 (88.7)	231/265 (87.2)

Values are mean (SD) (N) or n (%). Implanted patient population. [a]An additional transcatheter aortic valve (TAV) prosthesis implanted within a previously implanted transcatheter valve prosthesis. [b]implantation of the study device in the absence of death, disabling stroke, major vascular complications, and life-threatening or major bleeding; [c]absence of procedural mortality, correct positioning of a single transcatheter valve into the proper anatomical location, intended performance of the study device (effective orifice area [EOA] >0.9 cm^2 for BSA <1.6 m2 and EOA >1.1 cm2 for BSA ≥1.6 m^2 plus either a mean aortic valve gradient <20 mm Hg or a peak velocity <3m/sec, and no moderate or severe prosthetic valve aortic regurgitation) plus no serious adverse events at 30 days; [d]reported for patients randomized and implanted with an assigned study device and defined as follows: absence of mortality with the originally implanted transcatheter valve in the proper anatomical location, no additional aortic valve procedures, and with the intended performance of the prosthetic valve (either a mean aortic valve gradient <20 mmHg or a peak velocity <3m/sec with no moderate or severe prosthetic valve aortic regurgitation).
Abbreviations: TAV=transcatheter aortic valve; TEE= Transesophageal Echocardiography

eTable 6. Antiplatelet/Anticoagulant Medications

Timepoint and Medications	Mechanically-expanded Valve (N=607)	Self-expanding Valve (N=305)
Baseline		
Aspirin and Clopidogrel or Ticlopidine or Ticagrelor or Prasugrel or Other Anti-Platelet Medication	208 (34.3%)	107 (35.1%)
Aspirin	422 (69.5%)	228 (74.8%)
Clopidogrel	237 (39.0%)	122 (40.0%)
Ticlopidine	0 (0.0%)	0 (0.0%)
Ticagrelor	5 (0.8%)	1 (0.3%)
Prasugrel	1 (0.2%)	1 (0.3%)
Other Anti-Platelet Medication	5 (0.8%)	3 (1.0%)
Warfarin	53 (8.7%)	17 (5.6%)
Other Anticoagulant Medication	32 (5.3%)	27 (8.9%)
Discharge or 7 Days		
Aspirin and Clopidogrel or Ticlopidine or Ticagrelor or Prasugrel or Other Anti-Platelet Medication	421 (69.4%)	203 (66.6%)
Aspirin	515 (84.8%)	250 (82.0%)
Clopidogrel	471 (77.6%)	232 (76.1%)
Ticlopidine	0 (0.0%)	0 (0.0%)
Ticagrelor	5 (0.8%)	2 (0.7%)
Prasugrel	0 (0.0%)	1 (0.3%)
Other Anti-Platelet Medication	7 (1.2%)	3 (1.0%)
Warfarin	112 (18.5%)	45 (14.8%)
Other Anticoagulant Medication	65 (10.7%)	34 (11.1%)
30 Days Post Procedure		
Aspirin and Clopidogrel or Ticlopidine or Ticagrelor or Prasugrel or Other Anti-Platelet Medication	358/589 (60.8%)	181/296 (61.1%)
Aspirin	479/589 (81.3%)	239/296 (80.7%)
Clopidogrel	419/589 (71.1%)	212/296 (71.6%)
Ticlopidine	0/589 (0.0%)	0/296 (0.0%)
Ticagrelor	4/589 (0.7%)	2/296 (0.7%)
Prasugrel	0/589 (0.0%)	0/296 (0.0%)
Other Anti-Platelet Medication	2/589 (0.3%)	4/296 (1.4%)
Warfarin	125/589 (21.2%)	47/296 (15.9%)
Other Anticoagulant Medication	45/589 (7.6%)	17/296 (5.7%)
6 Months Post Procedure		
Aspirin and Clopidogrel or Ticlopidine or Ticagrelor or Prasugrel or Other Anti-Platelet Medication	267/551 (48.5%)	142/276 (51.4%)
Aspirin	428/551 (77.7%)	217/276 (78.6%)
Clopidogrel	318/551 (57.7%)	167/276 (60.5%)
Ticlopidine	0/551 (0.0%)	0/276 (0.0%)
Ticagrelor	4/551 (0.7%)	0/276 (0.0%)
Prasugrel	0/551 (0.0%)	0/276 (0.0%)
Other Anti-Platelet Medication	4/551 (0.7%)	4/276 (1.4%)
Warfarin	117/551 (21.2%)	38/276 (13.8%)
Other Anticoagulant Medication	37/551 (6.7%)	7.2% (20/276)
1 Year Post Procedure		
Aspirin and Clopidogrel or Ticlopidine or Ticagrelor or Prasugrel or Other Anti-Platelet Medication	205/512 (40.0%)	99/252 (39.3%)

eTable 6. Antiplatelet/Anticoagulant Medications

Timepoint and Medications	Mechanically-expanded Valve (N=607)	Self-expanding Valve (N=305)
Aspirin	406/513 (79.1%)	199/252 (79.0%)
Clopidogrel	242/512 (47.3%)	114/252 (45.2%)
Ticlopidine	0/511 (0.0%)	0/252 (0.0%)
Ticagrelor	3/511 (0.6%)	1/252 (0.4%)
Prasugrel	0/511 (0.0%)	0/252 (0.0%)
Other Anti-Platelet Medication	4/511 (0.8%)	4/252 (1.6%)
Warfarin	108/511 (21.1%)	38/252 (15.1%)
Other Anticoagulant Medication	43/512 (8.4%)	20/252 (7.9%)
Values are n (%). ITT patient population.		

eTable 7. Hierarchical Testing of the Prespecified Safety and Effectiveness Endpoints in Alternative Patient Populations

	Mechanically-expanded Valve	Self-expanding Valve	Difference (Upper Confidence Interval[a]) [95% CI]	P Value
Noninferiority Testing of Primary Endpoints				
30-day Composite Primary Safety Endpoint[b] (ITT)	114/601 (19.0)	49/303 (16.2)	2.8 [7.75] -2.4, 8.0	.001
1-year Composite Primary Effectiveness Endpoint[c] (ITT)	82/520 (15.8)	68/262 (26.0)	-10.2 [-4.54] -16.3, -4.0	<.001
Superiority Testing of Secondary Endpoint				
1-year Moderate or Greater PVL[d] (Implanted)	4/443 (0.9)	158/216 (6.9)	-6.0 -9.5, -2.5	<.001
Superiority Testing of Primary Effectiveness Endpoint				
1-year Composite Primary Effectiveness Endpoint[c, e] (Implanted)	78/506 (15.4)	66/259 (25.5)	-10.1 -16.2, -3.9	<.001

Values are n/N (%). Difference is shown as MEV-SEV [1-sided 97.5% Farrington-Manning Upper Confidence Interval]. Abbreviations: CI=confidence interval. Hierarchical testing of the primary and secondary endpoints was prespecified. If the null hypotheses for the primary safety and effectiveness endpoints were both rejected to show noninferiority of MEV to SEV then superiority of the secondary endpoint was tested. If the null hypothesis was rejected to show superiority of MEV to SEV then superiority of MEV to SEV for the primary effectiveness endpoint could be tested. The primary analysis set for noninferiority testing was the implanted patient population (includes all patients who signed an Informed Consent Form, were enrolled in the trial, and were implanted with the assigned, randomized study device (excludes cross-over patients); event rates were calculated post-index procedure. The primary analysis set for superiority testing was the Intention-to-Treat (ITT) patient population (includes all patients who signed an Informed Consent Form, were enrolled in the trial, and were randomized, whether or not an assigned study device was implanted; event rates are calculated post-randomization). [a]1-sided 97.5% Farrington-Manning Upper Confidence Interval; [b]Composite of all-cause mortality, stroke, life-threatening and major bleeding, stage 2 and 3 acute kidney injury and major vascular complications through 30 days. P value is from the Farrington-Manning test and is based on the standard normal distribution; between-arm difference was 2.8% and non-inferiority margin was 10.5%; [c]Composite of all-cause mortality, disabling stroke and moderate or greater paravalvular aortic regurgitation through 1 year. P value is from the Farrington-Manning test and is based on the standard normal distribution for the noninferiority testing; between-arm difference was -4.54% and non-inferiority margin was 9.5%; [d]Moderate or greater paravalvular leak based on core lab assessment; p value is from chi-square test for the superiority testing and echocardiograms with less than moderate total aortic regurgitation and visible PVL that was not gradable were included in the group with less than moderate PVL.[e]chi-square test in the ITT patient population for the superiority testing. Abbreviations: CI=confidence interval; ITT=intention-to-treat; PVL=paravalvular leak.

eTable 8. Grades of aortic regurgitation or paravalvular leak presented over time

Variable	Mechanically-expanded Valve	Self-expanding Valve	Difference [95% CI]
Baseline[a]	**(n=562)**	**(n=290)**	
None	136 (24.2%)	56 (19.3%)	4.9% [-0.9%, 10.6%]
Trace or Trivial	97 (17.3%)	49 (16.9%)	0.4% [-5.0%, 5.7%]
Mild	289 (51.4%)	161 (55.5%)	-4.1% [-11.1%, 3.0%]
Moderate	36 (6.4%)	21 (7.2%)	-0.8% [-4.4%, 2.8%]
Moderate-Severe	0 (0.0%)	1 (0.3%)	-0.3% [-1.0%, 0.3%]
Severe	0 (0.0%)	1 (0.3%)	-0.3% [-1.0%, 0.3%]
AR but Severity Not Evaluable	4 (0.7%)	1 (0.3%)	0.4% [-0.6%, 1.3%]
Discharge or 7 days[b]	**(n=553)**	**(n=277)**	
None	404 (73.1%)	76 (27.4%)	45.6% [39.2%, 52.0%]
Trace or Trivial	58 (10.5%)	50 (18.1%)	-7.6% [-12.8%, -2.4%]
Mild	65 (11.8%)	130 (46.9%)	-35.2% [-41.6%, -28.7%]
Moderate	2 (0.4%)	10 (3.6%)	-3.2% [-5.5%, -1.0%]
Moderate-Severe	0 (0.0%)	0 (0.0%)	0.0% [NA, NA]
Severe	0 (0.0%)	0 (0.0%)	0.0% [NA, NA]
Moderate or Greater	2 (0.4%)	10 (3.6%)	-3.2% [-5.5%, -1.0%]
AR but Severity Not Evaluable	24 (4.3%)	11 (4.0%)	0.4% [-2.5%, 3.2%]
30 Days Post Procedure[b]	**(n=541)**	**(n=265)**	
None	392 (72.5%)	65 (24.5%)	47.9% [41.5%, 54.3%]
Trace or Trivial	58 (10.7%)	39 (14.7%)	-4.0% [-9.0%, 1.0%]
Mild	58 (10.7%)	129 (48.7%)	-38.0% [-44.5%, -31.4%]
Moderate	2 (0.4%)	19 (7.2%)	-6.8% [-9.9%, -3.7%]
Moderate-Severe	1 (0.2%)	0 (0.0%)	0.2% [-0.2%, 0.5%]
Severe	0 (0.0%)	0 (0.0%)	0.0% [NA, NA]
Moderate or Greater	3 (0.6%)	19 (7.2%)	-6.6% [-9.8%, -3.4%]
AR but Severity Not Evaluable	30 (5.5%)	13 (4.9)	0.6% [-2.6%, 3.9%]
6 Months Post-Procedure[b]	**(n=471)**	**(n=236)**	
None	366 (77.7%)	88 (37.3%)	40.4% [33.2%, 47.6%]
Trace or Trivial	20 (4.2%)	16 (6.8%)	-2.5% [-6.2%, 1.2%]
Mild	54 (11.5%)	100 (42.4%)	-30.9% [-37.8%, -24.0%]
Moderate	2 (0.4%)	11 (4.7%)	-4.2% [-7.0%, -1.5%]
Moderate-Severe	1 (0.2%)	0 (0.0%)	0.2% [-0.2%, 0.6%]
Severe	0 (0.0%)	0 (0.0%)	0.0% [NA, NA]
Moderate or Greater	3 (0.6%)	11 (4.7%)	-4.0% [-6.8%, -1.2%]
AR but Severity Not Evaluable	13 (2.8%)	12 (5.1%)	-2.3% [-5.5%, 0.8%]
1 Year Post-Procedure[b]	**(n=453)**	**(n=219)**	
None	362 (79.9%)	81 (37.0%)	42.9% [35.5%, 50.3%]
Trace or Trivial	26 (5.7%)	23 (10.5%)	-4.8% [-9.4%, -0.2%]
Mild	51 (11.3%)	85 (38.8%)	-27.6% [-34.6%, -20.5%]
Moderate	4 (0.9%)	13 (5.9%)	-5.1% [-8.3%, -1.8%]
Moderate-Severe	0 (0.0%)	2 (0.9%)	-0.9% [-2.2%, 0.3%]
Severe	0 (0.0%)	0 (0.0%)	0.0% [NA, NA]
Moderate or Greater	4 (0.9%)	15 (6.8%)	-6.0% [-9.4%, -2.5%]
AR but Severity Not Evaluable	10 (2.2%)	15 (6.8%)	-4.6% [-8.3%, -1.0%]

Values are n (%). ITT patient population.Only echocardiograms with gradable PVL were included.[a] Native valve leakage; [b]Leakage due to a separation of the prosthetic valve from the annulus; any evidence of leakage of blood around the device. Graded based on Pibarot et al 2015.[4] Abbreviations: AR=aortic regurgitation; NA=not applicable; PVL=paravalvular leak.

eTable 9. Clinical Outcomes at 30 Days and 1 Year Post Procedure in the Implanted Patient Population

	30 days			1 year		
	Mechanically-expanded Valve (N=576)	**Self-expanding Valve (N=297)**	**Difference [95% CI]**	**Mechanically-expanded Valve (N=566)**	**Self-expanding Valve (N=291)**	**Difference [95% CI]**
All-cause mortality or disabling stroke	28 (4.9%)	17 (5.7%)	-0.9% [-4.0%, 2.3%]	74 (13.1%)	51 (17.5%)	-4.5% [-9.6%, 0.7%]
Cardiac death or disabling stroke	25 (4.3%)	17 (5.7%)	-1.4% [-4.5%, 1.7%]	53 (9.4%)	42 (14.4%)	-5.1% [-9.8%, -0.4%]
All-cause mortality	18 (3.1%)	8 (2.7%)	0.4% [-1.9%, 2.8%]	65 (11.5%)	38 (13.1%)	-1.6% [-6.3%, 3.1%]
Cardiovascular	15 (2.6%)	7 (2.4%)	0.2% [-1.9%, 2.4%]	41 (7.2%)	27 (9.3%)	-2.0% [-6.0%, 1.9%]
Non-cardiovascular	3 (0.5%)	1 (0.3%)	0.2% [-0.7%, 1.1%]	24 (4.2%)	11 (3.8%)	0.5% [-2.3%, 3.2%]
Stroke	33 (5.7%)	14 (4.7%)	1.0% [-2.1%, 4.1%]	42 (7.4%)	28 (9.6%)	-2.2% [-6.2%, 1.8%]
Disabling	15 (2.6%)	11 (3.7%)	-1.1% [-3.6%, 1.4%]	22 (3.9%)	21 (7.2%)	-3.3% [-6.7%, 0.0%]
Non-disabling	18 (3.1%)	3 (1.0%)	2.1% [0.3%, 3.9%]	21 (3.7%)	7 (2.4%)	1.3% [-1.0%, 3.7%]
Myocardial infarction	5 (0.9%)	4 (1.3%)	-0.5% [-2.0%, 1.0%]	20 (3.5%)	12 (4.1%)	-0.6% [-3.3%, 2.2%]
Peri-procedural MI	3 (0.5%)	4 (1.3%)	-0.8% [-2.3%, 0.6%]	3 (0.5%)	4 (1.4%)	-0.8% [-2.3%, 0.6%]
Spontaneous MI	2 (0.3%)	0 (0.0%)	0.3% [-0.1%, 0.8%]	17 (3.0%)	9 (3.1%)	-0.1% [-2.5%, 2.3%]
Bleeding	74 (12.8%)	34 (11.4%)	1.4% [-3.1%, 5.9%]	100 (17.7%)	50 (17.2%)	0.5% [-4.9%, 5.8%]
Life-threatening or disabling	41 (7.1%)	15 (5.1%)	2.1% [-1.2%, 5.3%]	53 (9.4%)	26 (8.9%)	0.4% [-3.6%, 4.5%]
Major bleeding	33 (5.7%)	19 (6.4%)	-0.7% [-4.0%, 2.7%]	48 (8.5%)	25 (8.6%)	-0.1% [-4.1%, 3.8%]
Acute kidney injury[a]	15 (2.7%)	11 (3.7%)	-1.1% [-3.6%, 1.4%]	15 (2.7%)	11 (3.8%)	-1.1% [-3.7%, 1.4%]
Major vascular complications	39 (6.8%)	14 (4.7%)	2.1% [-1.1%, 5.2%]	40 (7.1%)	15 (5.2%)	1.9% [-1.4%, 5.2%]
Repeat procedure	0 (0.0%)	3 (1.0%)	-1.0% [-2.1%, 0.1%]	1 (0.2%)	6 (2.1%)	-1.9% [-3.6%, -0.2%]
Aortic valve reintervention	0 (0.0%)	2 (0.7%)	-0.7% [-1.6%, 0.3%]	0 (0.0%)	5 (1.7%)	-1.7% [-3.2%, -0.2%]
Hospitalization for valve-related symptoms or worsening congestive heart failure	11 (1.9%)	13 (4.4%)	-2.5% [-5.0%, 0.1%]	62 (11.0%)	41 (14.1%)	-3.1% [-7.9%, 1.6%]
Permanent pacemaker implantation						
All patients	193 (33.5%)	53 (17.8%)	15.7% [9.8%, 21.5%]	199 (35.2%)	55 (18.9%)	16.3% [10.3%, 22.2%]
Pacemaker-naïve patients	193/470 (41.1%)	53/240 (22.1%)	19.0% [12.1%, 25.9%]	199/465 (42.8%)	55/234 (23.5%)	19.3% [12.2%, 26.3%]
New onset of atrial fibrillation	39 (6.8%)	14 (4.7%)	2.1% [-1.1%, 5.2%]	39 (6.9%)	14 (4.8%)	2.1% [-1.1%, 5.3%]
Periprocedural coronary obstruction	0 (0.0%)	2 (0.7%)	-0.7% [-1.6%, 0.3%]	0 (0.0%)	2 (0.7%)	-0.7% [-1.6%, 0.3%]
Periprocedural cardiac tamponade	12 (2.1%)	4 (1.3%)	0.7% [-1.0%, 2.5%]	12 (2.1%)	4 (1.4%)	0.7% [-1.0%, 2.5%]
Prosthetic aortic valve malpositioning[b]	0 (0.0%)	8 (2.7%)	-2.7% [-4.5%, -0.9%]	0 (0.0%)	8 (2.7%)	-2.7% [-4.6%, -0.9%]

eTable 9. Clinical Outcomes at 30 Days and 1 Year Post Procedure in the Implanted Patient Population

	30 days			1 year		
	Mechanically-expanded Valve (N=576)	**Self-expanding Valve (N=297)**	**Difference [95% CI]**	**Mechanically-expanded Valve (N=566)**	**Self-expanding Valve (N=291)**	**Difference [95% CI]**
TAV-in-TAV deployment[c]	0 (0.0%)	9 (3.0%)	-3.0% [-5.0%, -1.1%]	0 (0.0%)	11 (3.8%)	-3.8% [-6.0%, -1.6%]
Prosthetic aortic valve thrombosis	3 (0.5%)	0 (0.0%)	0.5% [-0.1%, 1.1%]	10 (1.8%)	0 (0.0%)	1.8% [0.7%, 2.9%]
Prosthetic aortic valve endocarditis	1 (0.2%)	0 (0.0%)	0.2% [-0.2%, 0.5%]	4 (0.7%)	0 (0.0%)	0.7% [0.0%, 1.4%]
Effective Orifice Area, cm^2	1.59 (0.46) (492)	1.98 (0.51) (238)	-0.39 [-0.47, -0.32]	1.49 (0.45) (411)	1.69 (0.52) (199)	-0.20 [-0.28, -0.12]
Mean Aortic Valve Gradient, mmHg	12.07 (6.12) (531)	7.25 (3.44) (261)	4.82 [4.02, 5.62]	12.34 (5.85) (452)	7.89 (3.48) (219	4.45 [3.61, 5.29]
Peak Aortic Valve Gradient, mmHg	21.60 (10.32) (531)	13.59 (6.21) (261)	8.02 [6.66, 9.38]	22.874 (10.56) (452)	15.22 (6.44) (219)	7.62 [6.10, 9.14]
Peak Aortic Velocity, m/s	2.26 (0.46) (531)	1.80 (0.40) (261)	0.47 [0.40, 0.53]	2.33 (0.51) (452)	1.91 (0.41) (219)	0.42 [0.34, 0.50]

Values are mean (SD) (N) or n (%). All percentages are binary rate estimates at 30 days or one year in Implanted patients with 30-day (>21 days) or 12-month (>335 days) follow-up or a VARC event. Neurologic exams were performed by a neurology professional following any suspected stroke. Neurologic exams were performed by a neurology professional following any suspected stroke. [a]Acute kidney injury is stage 2/3 based on the AKIN System Stage.[5,6]; [b]Prosthetic aortic valve malpositioning included valve migration, valve embolization, and ectopic valve deployment. [c]An additional transcatheter aortic valve (TAV) prosthesis implanted within a previously implanted prosthesis. Abbreviations: MI=myocardial infarction; TAV=transcatheter aortic valve

eTable 10. Functional status over time

Variable	Mechanically-expanded Valve (N=607)	Self-expanding Valve (N=305)	P Value
	Baseline		
Gait speed average to walk 5 meters (seconds)	8.7 (5.2) (565)	8.7 (4.2) (285)	>.99
NYHA Functional Class	**(n=607)**	**(n=305)**	
I	0 (0.0%)	0 (0.0%)	.28
II	174 (28.7%)	98 (32.1%)	
III	386 (63.6%)	186 (61.0%)	
IV	47 (7.7%)	21 (6.9%)	
	30 Days Post-Procedure		
NYHA Functional Class	**(n=556)**	**(n=276)**	
I	270 (48.6%)	139 (50.4%)	.79
II	233 (41.9%)	104 (37.7%)	
III	51 (9.2%)	30 (10.9%)	
IV	2 (0.4%)	3 (1.1%)	
	1 Year Post-Procedure		
Gait speed average to walk 5 meters (seconds)	7.7 (4.2) (408)	7.6 (3.4) (192)	.77
NYHA Functional Class	**(n=477)**	**(n=226)**	
I	251 (52.6%)	121 (53.5%)	.78
II	180 (37.7%)	85 (37.6%)	
III	45 (9.4%)	19 (8.4%)	
IV	1 (0.2%)	1 (0.4%)	

Values are mean (SD) (n) or n (%). Data are for the ITT population. This analysis did not include patients who died. P-value for ordinal data is from Mantel-Haenszel Chi-square test. Abbreviations: NYHA=New York Heart Association

Neurological status was determined by a neurological physical examination at baseline, discharge, and 1 year; National Institutes of Health Stroke Scale (NIHSS) assessment at baseline, discharge, and 1 year; and modified Rankin Scale (mRS) assessment at all time points. The neurological physical examinations were performed by a neurology professional (neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner). The NIHSS and mRS assessments were performed by a neurology professional or certified personnel. There were no significant differences between the cohorts (eTable 11).

eTable 11. Neurological Assessment from Baseline through 1 Year Post-Procedure

Variable	Mechanically-expanded Valve (N=607)	Self-expanding Valve (N=305)	P Value
Baseline			
National Institutes of Health Stroke Scale (NIHSS) Total Score	0.39 (1.00) (593)	0.41 (0.91) (301)	.84
Neurologic Exam			
Cerebellar Function			
Normal	521/584 (89.2%)	265/285 (93.0%)	.08
Abnormal	63/584 (10.8%)	20/285 (7.0%)	
Reflexes			
Normal	390/581 (67.1%)	198/285 (69.5%)	.49
Abnormal	191/581 (32.9%)	87/285 (30.5%)	
Cranial Nerves			
Normal	484/584 (82.9%)	236/285 (82.8%)	.98
Abnormal	100/584 (17.1%)	49/285 (17.2%)	
Sensation			
Normal	481/584 (82.4%)	237/285 (83.2%)	.77
Abnormal	103/584 (17.6%)	48/285 (16.8%)	
Muscle Strength			
Normal	503/584 (86.1%)	249/285 (87.4%)	.62
Abnormal	81/584 (13.9%)	36/285 (12.6%)	
Modified Rankin Scale (mRS)			
0: No Symptoms	334/594 (56.2%)	163/301 (54.2%)	.62
1: No Significant disability	96/594 (16.2%)	59/301 (19.6%)	
2: Slight disability	76/594 (12.8%)	46/301 (15.3%)	
3: Moderate disability	64/594 (10.8%)	24/301 (8.0%)	
4: Moderately severe disability	24/594 (4.0%)	9/301 (3.0%)	
5: Severe disability	0/594 (0.0%)	0/301 (0.0%)	
30 Days Post-Procedure			
Modified Rankin Scale (mRS)			
0: No Symptoms	349/552 (63.2%)	161/275 (58.5%)	.09
1: No Significant disability	85/552 (15.4%)	37/275 (13.5%)	
2: Slight disability	51/552 (9.2%)	33/275 (12.0%)	
3: Moderate disability	46/552 (8.3%)	33/275 (12.0%)	
4: Moderately severe disability	18/552 (3.3%)	10/275 (3.6%)	
5: Severe disability	3/552 (0.5%)	1/275 (0.4%)	
6: Dead	0/552 (0.0%)	0/275 (0.0%)	
Dead without mRS	15/607 (2.5%)	7/305 (2.3%)	.87

eTable 11. Neurological Assessment from Baseline through 1 Year Post-Procedure

Variable	Mechanically-expanded Valve (N=607)	Self-expanding Valve (N=305)	P Value
1 Year Post-Procedure			
National Institutes of Health Stroke Scale (NIHSS) Total Score	0.33 (0.82) (466)	0.32 (0.80) (216)	.97
Neurologic Exam			
Cerebellar Function			
Normal	395/430 (91.9%)	187/204 (91.7%)	.93
Abnormal	35/430 (8.1%)	17/204 (8.3%)	
Reflexes			
Normal	298/428 (69.6%)	137/202 (67.8%)	.65
Abnormal	130/428 (30.4%)	65/202 (32.2%)	
Cranial Nerves			
Normal	382/430 (88.8%)	177/204 (86.8%)	.45
Abnormal	48/430 (11.2%)	27/204 (13.2%)	
Sensation			
Normal	365/430 (84.9%)	180/204 (88.2%)	.26
Abnormal	65/430 (15.1%)	24/204 (11.8%)	
Muscle Strength			
Normal	381/430 (88.6%)	181/204 (88.7%)	.96
Abnormal	49/430 (11.4%)	23/204 (11.3%)	
Modified Rankin Scale (mRS)			
0: No Symptoms	286/475 (60.2%)	136/224 (60.7%)	.74
1: No Significant disability	73/475 (15.4%)	35/224 (15.6%)	
2: Slight disability	59/475 (12.4%)	20/224 (8.9%)	
3: Moderate disability	45/475 (9.5%)	24/224 (10.7%)	
4: Moderately severe disability	11/475 (2.3%)	8/224 (3.6%)	
5: Severe disability	1/475 (0.2%)	1/224 (0.4%)	
6: Dead	0/475 (0.0%)	0/224 (0.0%)	
Dead without mRS	70/607 (11.5%)	39/305 (12.8%)	.58

Values are mean (SD) (n) or n (%). Data are for the ITT population. P value for ordinal data is from Mantel-Haenszel Chi-square test. mRS 0: No Symptoms at all; mRS 1: No Significant disability despite symptoms; able to carry out all usual duties and activities; mRS 2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance; mRS 3: Moderate disability; requiring some help, but able to walk without assistance; mRS 4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; mRS 5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention; mRS 6: Dead

eTable 12. Effectiveness Endpoints SEV-E vs MEV patients

	Mechanically-expanded Valve	Self-expanding Valve	Difference (Upper Confidence Interval[a]) [95% CI]	P Value
1-year Composite Primary Effectiveness Endpoint[b] (Implanted)	78/506 (15.4%)	25/ 123	-4.9% [1.5%] -12.7% , 2.9%	<.001
1-year Secondary Endpoint[c] (ITT)	4/452 (0.9%)	3/105 (2.9%)	-2.0% -5.3% , 1.3%	.13

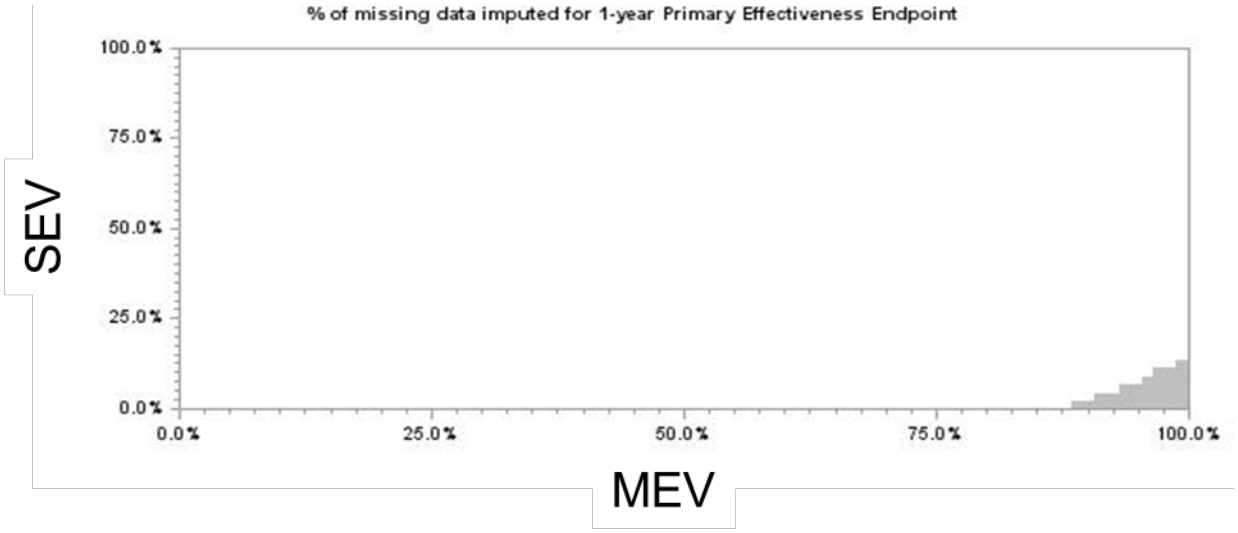
Values are n/N (%). Difference is shown as MEV-SEV [1-sided 97.5% Farrington-Manning Upper Confidence Interval]. Abbreviations: CI=confidence interval; ITT=intention-to-treat. The implanted patient population includes all patients who signed an Informed Consent Form, were enrolled in the trial, and were implanted with the assigned, randomized study device (excludes cross-over patients); event rates were calculated post-index procedure. The Intention-to-Treat (ITT) patient population includes all patients who signed an Informed Consent Form, were enrolled in the trial, and were randomized, whether or not an assigned study device was implanted; event rates are calculated post-randomization. [a]1-sided 97.5% Farrington-Manning Upper Confidence Interval; [b]Composite of all-cause mortality, disabling stroke and moderate or greater paravalvular aortic regurgitation through 1 year. P value is from the Farrington-Manning test and is based on the standard normal distribution for the noninferiority testing; between-arm difference was 1.5% and non-inferiority margin was 9.5%; [c]Moderate or greater paravalvular leak based on core lab assessment; p value is from chi-square test for the superiority testing and echocardiograms with less than moderate total aortic regurgitation and visible PVL that was not gradable were included in the group with less than moderate PVL; chi-square test in the ITT patient population for the superiority testing. Abbreviations: CI=confidence intervals; ITT=intention-to-treat.

eTable 13. Paravalvular Leak in SEV-E vs MEV patients

Outcomes Through 1 Year Post-Procedure	Mechanically-expanded Valve	Self-expanding Valve - EvolutR	Difference [95% CI]
Aortic Regurgitation[a]			
Baseline	**(n=529)**	**(n=135)**	
None	133 (25.1%)	27 (20.0%)	5.1% [-2.6% , 12.8%]
Trace/Trivial	89 (16.8%)	34 (25.2%)	-8.4% [-16.3% , -0.4%]
Mild	274 (51.8%)	68 (50.4%)	1.4% [-8.0% , 10.9%]
Moderate	33 (6.2%)	5 (3.7%)	2.5% [-1.3% , 6.3%]
Moderate-Severe	0 (0.0%)	1 (0.7%)	-0.7% [-2.2% , 0.7%]
Severe	0 (0.0%)	0 (0.0%)	NE
Paravalvular Leak[b]			
Discharge or 7 Days	**(n=517)**	**(n=134)**	
None	402 (77.8%)	33.6% (45/ 134)	44.2% [35.4% , 52.9%]
Trace/Trivial	52 (10.1%)	17.9% (24/ 134)	-7.9% [-14.8% , -0.9%]
Mild	61 (11.8%)	45.5% (61/ 134)	-33.7% [-42.6% ,-24.8%]
Moderate	2 (0.4%)	3.0% (4/ 134)	-2.6% [-5.5% , 0.3%]
Moderate-Severe	0 (0.0%)	0 (0.0%)	NE
Severe	0 (0.0%)	0 (0.0%)	NE
30 Days	**(n=497)**	**(n=124)**	
None	387 (77.9%)	36 (29.0%)	48.8% [40.1% , 57.6%]
Trace/Trivial	54 (10.9%)	17 (13.7%)	-2.8% [-9.5% , 3.8%]
Mild	54 (10.9%)	65 (52.4%)	-41.6% [-50.8% ,-32.3%]
Moderate	1 (0.2%)	6 (4.8%)	-4.6% [-8.4% , -0.8%]
Moderate-Severe	1 (0.2%)	0 (0.0%)	0.2% [-0.2% , 0.6%]
Severe	0 (0.0%)	0 (0.0%)	NE
6 Month	**(n=436)**	**(n=102)**	
None	362 (83.0%)	40 (39.2%)	43.8% [33.7% , 53.9%]
Trace/Trivial	19 (4.4%)	9 (8.8%)	-4.5% [-10.3% , 1.4%]
Mild	52 (11.9%)	50 (49.0%)	-37.1% [-47.3% ,-26.9%]
Moderate	2 (0.5%)	3 (2.9%)	-2.5% [-5.8% , 0.9%]
Moderate-Severe	1 (0.2%)	0 (0.0%)	0.2% [-0.2% , 0.7%]
Severe	0 (0.0%)	0 (0.0%)	NE
12 Month	**(n=434)**	**(n=99)**	
None	357 (82.3%)	44 (44.4%)	37.8% [27.4% , 48.2%]
Trace/Trivial	25 (5.8%)	8 (8.1%)	-2.3% [-8.1% , 3.5%]
Mild	48 (11.1%)	44 (44.4%)	-33.4% [-43.6% ,-23.2%]
Moderate	4 (0.9%)	3 (3.0%)	-2.1% [-5.6% , 1.4%]
Moderate-Severe	0 (0.0%)	0 (0.0%)	NE
Severe	0 (0.0%)	0 (0.0%)	NE

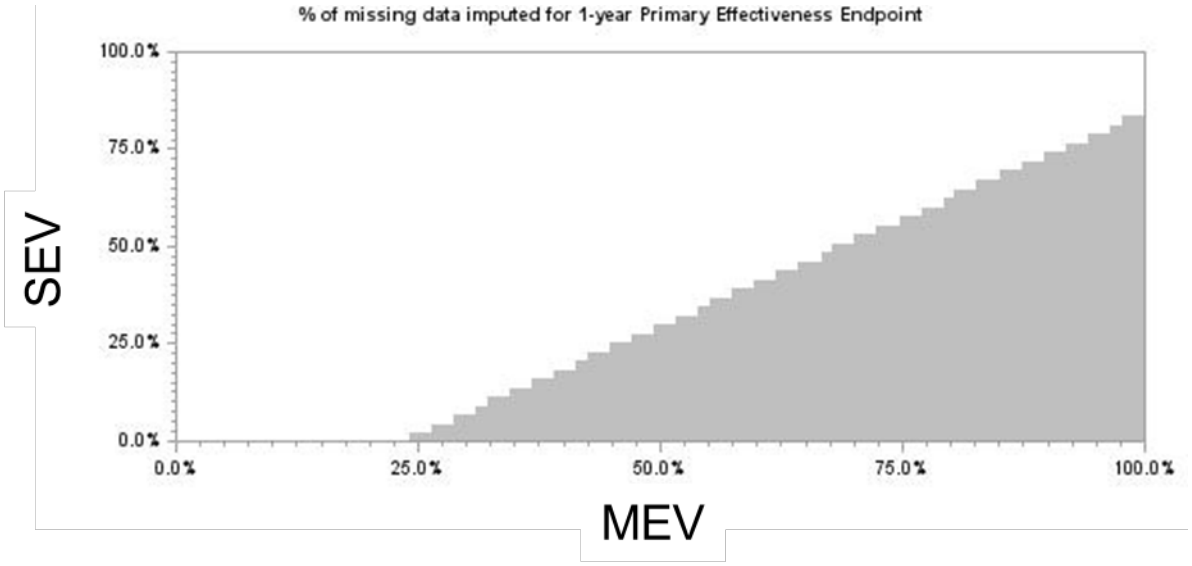
Values are n (%). ITT patient population. The SEV-E group only includes patients treated with EvolutR. NE = non-evaluable; Only echocardiograms with gradable PVL were included. [a]Aortic regurgitation; [b]Leakage due to a separation of the prosthetic valve from the annulus; any evidence of leakage of blood around the device. Graded based on Pibarot et al 2015.[1]

eFigure 1. Missing Data Sensitivity Analysis for the 1-Year Primary Effectiveness Endpoint for Non-inferiority Testing



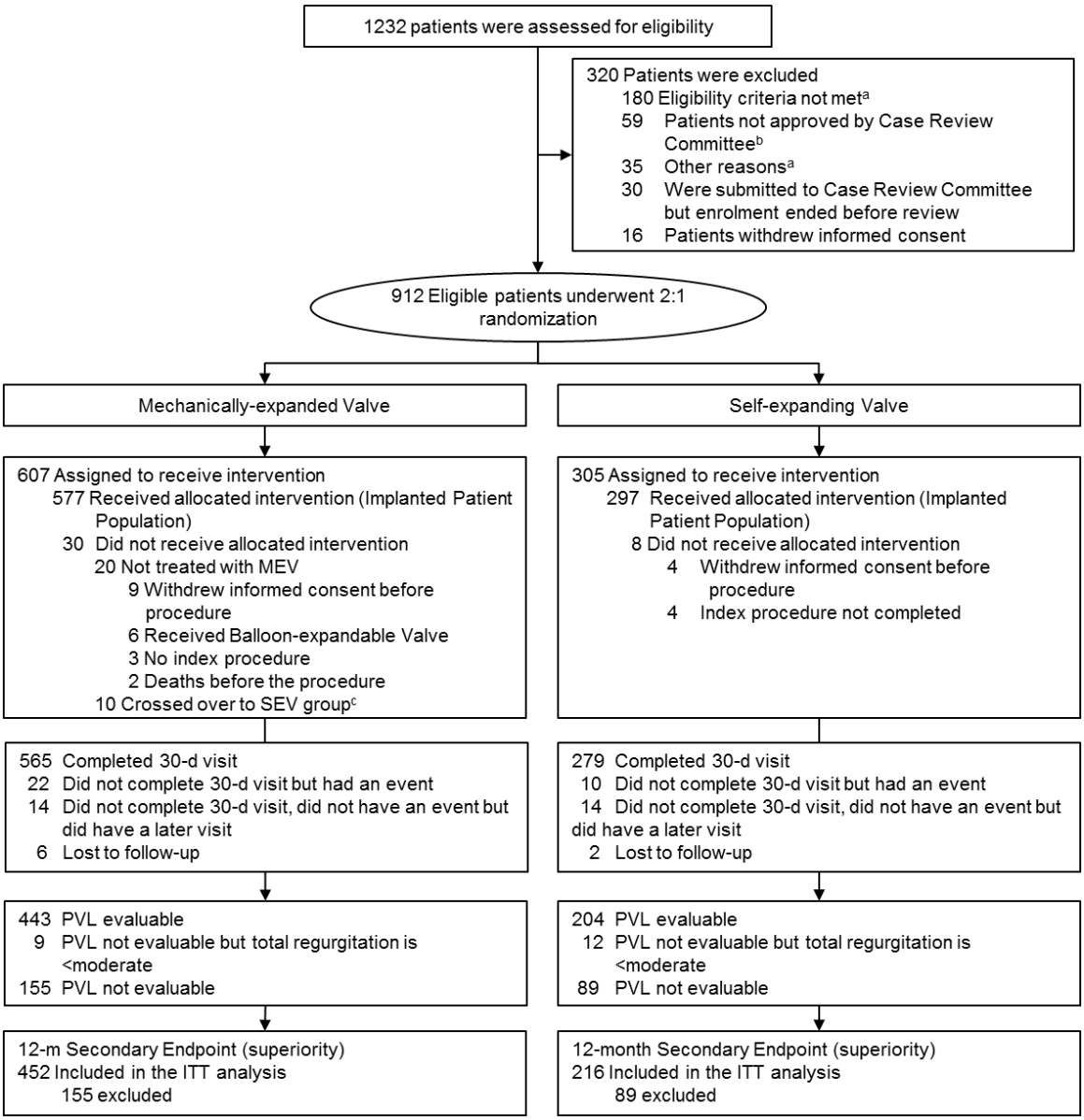
The white area indicates p value >.025; the grey area indicates p≤.025. Abbreviations: MEV=mechanically-expandable valve; SEV=self-expanding valve

eFigure 2. Missing Data Sensitivity Analysis for the 1-Year Primary Effectiveness Endpoint for Superiority Testing



The white area indicates p value >.05; the grey area indicates p≤.05. Abbreviations: MEV=mechanically-expandable valve; SEV=self-expanding valve

eFigure 3. Patient Flow for the Secondary Endpoint Superiority Comparison



a: No additional information is available; b: Clinical Review Committee was responsible for the review of patient screening data to confirm eligibility given the increased surgical risk of the patient population being studied and to ensure consistency of patients enrolled across study centers; 24 had aortic structures that were too large; 12 patients had aortic structures that were too small; 12 had peripheral vessels that were too small, and the rest were a mix of patients who had bicuspid valve, excessive aortic tortuosity or did not meet the risk criteria; c: Patients who crossed over were included in the Intention-to-Treat analysis set but were not included in the Implanted Analysis Set; Intention-to-Treat (ITT): includes all subjects who signed an Informed Consent Form, were enrolled in the trial, and were randomized, whether or not an assigned study device was implanted. Event rates are calculated post-randomization. The ITT patient population was the prespecified analysis population for superiority testing.

eReferences

1. Cesari M, Kritchevsky SB, Penninx BW, et al. Prognostic value of usual gait speed in well-functioning older people--results from the Health, Aging and Body Composition Study. *J Am Geriatr Soc*. 2005;53(10):1675-1680. doi:10.1111/j.1532-5415.2005.53501.x.

2. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol*. 2000;35(5):1245-1255.

3. Ware JE, Kosinski M, Keller SD. A 12-item Short-Form Health Survey: Construction of scales and preliminary test of reliability and validity. *Med Care*. 1996;34:220-226.

4. Pibarot P, Hahn RT, Weissman NJ, Monaghan MJ. Assessment of Paravalvular Regurgitation Following TAVR. *JACC Cardiovasc Imaging*. 2015;8(3):340-360. doi:10.1016/j.jcmg.2015.01.008.

5. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204-R212. doi:10.1186/cc2872.

6. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11(2):R31. doi:10.1186/cc5713.