JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 12, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.04.085

EDITORIAL COMMENT

Transcatheter Aortic Valve Replacement

Lessons Gained From Extreme-Risk Patients*

Thomas Pilgrim, MD, Stephan Windecker, MD

Percutaneous coronary intervention (PCI) and transcatheter aortic valve replacement (TAVR) have started at the antipodes of the risk spectrum. Although the former was established in low-risk patients and later adopted in higher risk subsets with increasing experience, TAVR was first introduced among inoperable patients before extending experience to patients who were surgical candidates. Despite the prohibitive risk profile of inoperable patients owing to comorbidities and the procedure being in its infancy, TAVR demonstrated a robust survival benefit compared with conservative management, and the procedural risk was offset by the spontaneous course of the disease, underlining the malignant course of patients with severe aortic stenosis if untreated (1,2). Of note, it is critical to differentiate between extreme-risk interventions on the one hand and futile interventions on the other.

SEE PAGE 1327

TAVR is considered futile in patients with an estimated life expectancy of <1 year and in patients in whom comorbidities preclude the expected benefit from correction of aortic stenosis in terms of survival, symptom relief, and quality of life. The encouraging results in patients at highest risk subsequently propelled research to investigate the safety and efficacy of TAVR among patients at high to intermediate surgical risk (**Figure 1**).

In this issue of the *Journal*, Yakubov et al. (3) report the 2-year clinical outcomes after TAVR with the self-expanding valve prosthesis (CoreValve, Medtronic, Minneapolis, Minnesota) among patients with severe aortic stenosis deemed at extreme risk for surgical aortic valve replacement (SAVR). A total of 489 patients from 41 centers considered to have ≥50% mortality or irreversible morbidity at 30 days in case of SAVR as evaluated by an interdisciplinary heart team underwent transfemoral TAVR. Throughout 2 years of follow-up, rates of all-cause mortality, cardiovascular mortality, and major stroke were 36.5%, 26.6%, and 5.1%, respectively. Incremental rates of adverse events between the first and second years of 12.3% for all-cause mortality, 7.9% for cardiovascular mortality, and 0.8% for major stroke reflect the burden of comorbidities and limited life expectancy in this elderly study population, whereas improvement in the aortic valve effective orifice area, reduction in transvalvular gradient, and improvement in functional class was sustained.

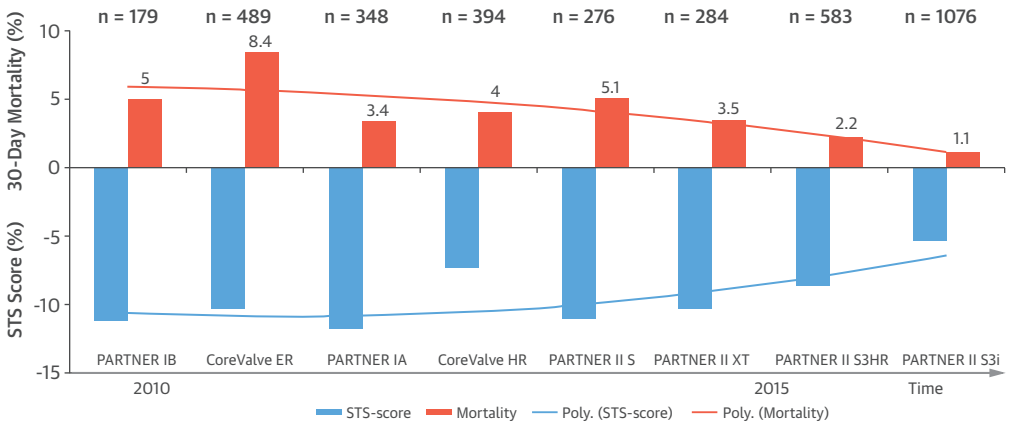
All-cause mortality in the present study was comparable to the 2-year event rates observed in PARTNER (Placement of Aortic Transcatheter Valves) Trial 1B (43%) and PARTNER Trial 1A (34%), and Society of Thoracic Surgeons scores >15% tended to be predictive of 2-year mortality in the present analysis. However, 5-year data from the PARTNER 1B study suggested benefit in favor of TAVR even in the subset of patients with Society of Thoracic Surgeons scores >15% compared with conservative management. Measures of frailty as well as need for assisted living may be clinically more meaningful and predictive than risk scales developed for conventional SAVR to identify patients who may no longer be candidates for an intervention in the patient population under discussion (4,5). The findings of the extreme-risk study with the self-expandable valve, as well as the PARTNER 1B, suggest that conservative management should be limited to patients with palliative

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Department of Cardiology, Swiss Cardiovascular Center Bern, Bern University Hospital, Bern, Switzerland. Dr. Pilgrim has received speaker fees from Biotronik and Medtronic. Dr. Windecker has received institutional research grants from Abbott Vascular, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, The Medicines Company, and St. Jude Medical; and speaker fees from AstraZeneca, Abbott Vascular, Biotronik, Biosensors, Boston Scientific, Bayer, Eli Lilly, Edwards Lifesciences, and Medtronic.

JACC VOL. 66, NO. 12, 2015
SEPTEMBER 22, 2015:1335–8

FIGURE 1 Expected Risk According to Society of Thoracic Surgeons Scores and Observed 30-Day Mortality of Patients Enrolled Into Major TAVR Trials Over Time



Lines represent polynomial (Poly) regression estimates for all-cause mortality **(red)** and Society of Thoracic Surgeons (STS) scores **(blue)**. PARTNER IB = Placement of Aortic Transcatheter Valves (PARTNER) Trial IB; CoreValve ER = CoreValve US Pivotal Trial Extreme Risk Study; PARTNER IA = Placement of Aortic Transcatheter Valves (PARTNER) Trial IA; CoreValve HR = CoreValve US Pivotal Trial High Risk Study; PARTNER II S = Placement of Aortic Transcatheter Valves (PARTNER) II Sapien Trial; PARTNER II XT = Placement of Aortic Transcatheter Valves (PARTNER) II Sapien XT Trial; PARTNER II S3HR = Placement of Aortic Transcatheter Valves (PARTNER) II Sapien 3 High Risk Trial; PARTNER II S3i = Placement of Aortic Transcatheter Valves (PARTNER) II Sapien 3 Intermediate Risk Trial; TAVR = transcatheter aortic valve replacement.

conditions, whereas additional efforts should aim to fully exploit adequate access of extreme- and high-risk patient populations to TAVR.

Among patients deemed inoperable, all-cause mortality as high as 72% has been reported in the PARTNER 1B study at 5 years and 38% in the present study at 2 years, whereas structural valve deterioration is rare in this patient population (<3% in survivors) (1,2,6,7). The discrepancy between rather low rates of prosthesis deterioration and high rates of clinical adverse events highlights the critical impact of patient comorbid conditions in studies evaluating TAVR among extreme- and high-risk populations. Of note, survivorship bias may distort evidence of TAVR outcomes in 2 ways. On the one hand, early death unrelated to aortic stenosis but due to comorbidities may limit the benefits of TAVR in some patients. On the other hand, the adverse clinical course determined by comorbidities may camouflage the clinical detection of valve-related adverse outcomes, which could emerge during longer-term follow-up. In this context, paravalvular regurgitation amounted to 10.7% at discharge, but was unchanged between 1 and 2 years, at 4.3% and 4.4%. respectively, in the present study. Although a paired analysis of echocardiographic findings at discharge and 1-year follow-up in 29 patients suggests remodeling of the annular-bioprosthesis interface as a potential explanation for the lower rate of paravalvular regurgitation during follow-up after self-expandable valve implantation, attrition bias due to premature death cannot be excluded. This is important as moderate and severe paravalvular regurgitation has been consistently reported as a predictor of mortality after TAVR and constitutes the most important barrier to extending the procedure to lower-risk patients (8). Conversely, the stable transvalvular aortic valve gradient and effective orifice area throughout 2 years of follow-up in the present study are notable. These findings are in line with recent data of the PARTNER 1A Trial suggesting similar valve performance for transcatheter and surgical bioprostheses throughout 5 years of follow-up and address concerns regarding valve durability (6). In addition, hemodynamic measurements after TAVR suggest larger effective aortic valve area and lower transvalvular gradient compared with SAVR (9), hence reducing the incidence of patient prosthesis mismatch (10). This finding appears pronounced with use of the self-expandable prosthesis and may be of particular importance in patients with small valve anatomy compared with SAVR (11).

Inevitably, the findings of the present analysis are of somewhat historical value due to recent device iterations. Technical refinements of newer-generation transcatheter bioprostheses successfully minimize the risk of paravalvular aortic regurgitation by means of circumferential skirts at the valvular inflow

site, mitigate the risk of vascular access site and bleeding complications due to lower profile delivery catheters, and reduce the risk of atrioventricular conductance disturbances related to more precise positioning within the annulus. Outcomes based on recent iterations of balloon-expandable and repositional transcatheter valve systems have reported significant improvements, with rates of paravalvular aortic regurgitation mimicking results of SAVR and very low rates of periprocedural mortality (12,13) (**Figure 1**).

Presence of coronary artery disease was predictive of all-cause mortality at 2 years in the present analysis. Available observational data on the impact of coronary artery disease on clinical outcomes among patients undergoing TAVR are equivocal and limited by the small sample size, relatively short duration of follow-up, substantial heterogeneity in terms of anatomic and physiological extent of coronary artery disease, and selection bias introduced by revascularization (14). Of note, patients with previous PCI/coronary artery bypass grafting and those in need for revascularization were excluded from participation in the present study. Notwithstanding, more advanced coronary artery disease (SYNTAX score >22) and extent of ischemia may be associated with adverse clinical outcome after correction of aortic stenosis and requires careful consideration in therapeutic decision making (14,15).

The risk of thromboembolic cerebrovascular accidents is greatest within the first hours after TAVR and is a function of patient age, severity of aortic valve stenosis, extent of aortic arch atheroma, post-valve deployment balloon dilation, and repeated prosthesis placement (16). The optimal type and duration of antithrombotic and antiplatelet treatment after TAVR remain to be defined as well as the role of dedicated cerebral protection devices (17,18). In the present study, the risk of stroke was 8.6% at 2 years and rather stable between 1 and 2 years of follow-up. Moreover, recent data from the CoreValve US Pivotal Trial High Risk Study demonstrate a trend toward a lower risk of stroke after TAVR compared with SAVR (11).

Atrioventricular conductance disturbances with the need for permanent pacemaker (PPM) implantation occur more frequently with self-expandable compared with balloon-expandable prostheses. In the present study, the rate of PPM implantation was 22% at 30 days, 26% at 1 year, and 29% at 2 years. The most important predictors of PPM implantation include intraoperative atrioventricular block, right bundle branch block, implantation of a self-expandable TAVR prosthesis, left anterior hemiblock, first-degree atrioventricular block, and male sex (19). However, PPM implantation has not been associated with adverse clinical outcome after TAVR so far, and device iterations aiming at more precise positioning of the prosthesis within the annulus may further mitigate the frequency of this adverse event (20).

In summary, TAVR in extreme-risk patients not only improves survival but has pronounced effects on quality of life, symptom and functional status as well as cognitive function. With a number needed to treat of <5 to prevent 1 death among inoperable patients, TAVR has resulted in a paradigm shift in the treatment of patients with severe aortic stenosis. In line with recent guidelines on valvular heart disease in Europe and the United States, TAVR has become the standard of care in inoperable patients (Class IB) and a valuable alternative to SAVR among high-risk patients (Class IIaB) (21,22). Challenges to be addressed in the future will be to improve education and timely access to medical care as well as adequate reimbursement. Although evidence from randomized clinical trials suggests similar or superior outcomes of TAVR compared with SAVR among high- and intermediate-risk patients with severe aortic stenosis (6,9,11), the ongoing refinement of the procedure and TAVR prostheses will catalyze research among lower-risk patients. The expansion of TAVR to lower-risk patients further raises the bar in terms of outcomes and shifts the focus beyond patient-related to prosthesis-related outcomes. Although TAVR has started at the extreme end of the risk spectrum, it has the potential to mature into a procedure for all patients with severe aortic stenosis, irrespective of risk, in the future.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Stephan Windecker, Department of Cardiology, Bern University Hospital, Freiburgstrasse 10, 3010 Bern, Switzerland. E-mail: stephan.windecker@insel.ch.

REFERENCES

1. Kapadia SR, Leon MB, Makkar RR, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2485–91.

2. Pilgrim T, Englberger L, Rothenbuhler M, et al. Long-term outcome of elderly patients with severe aortic stenosis as a function of treatment modality. Heart 2015;101:30–6.

3. Yakubov SJ, Adams DH, Watson DR, et al. 2-year outcomes after iliofemoral self-expanding

transcatheter aortic valve replacement in patients with severe aortic stenosis deemed extreme risk for surgery. J Am Coll Cardiol 2015;66:1327–34.

4. Stortecky S, Schoenenberger AW, Moser A, et al. Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. J Am Coll Cardiol Intv 2012;5:489–96.

5. Puls M, Sobisiak B, Bleckmann A, et al. Impact of frailty on short- and long-term morbidity and mortality after transcatheter aortic valve implantation: risk assessment by Katz Index of activities of daily living. EuroIntervention 2014;10:609–19.

6. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2477–84.

7. Toggweiler S, Humphries KH, Lee M, et al. 5-year outcome after transcatheter aortic valve implantation. J Am Coll Cardiol 2013;61:413–9.

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

9. Thyregod HG, Steinbruchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: One-year results from the All-comers Nordic Aortic Valve Intervention (NOTION) randomized clinical trial. J Am Coll Cardiol 2015;65:2184–94.

10. Pibarot P, Weissman NJ, Stewart WJ, et al. Incidence and sequelae of prosthesis-patient mismatch in transcatheter versus surgical valve replacement in high-risk patients with severe aortic stenosis: a PARTNER trial cohort-a analysis. J Am Coll Cardiol 2014;64:1323–34.

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

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

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

14. Goel SS, Ige M, Tuzcu EM, et al. Severe aortic stenosis and coronary artery disease–implications for management in the transcatheter aortic valve replacement era: a comprehensive review. J Am Coll Cardiol 2013;62:1–10.

15. Stefanini GG, Stortecky S, Cao D, et al. Coronary artery disease severity and aortic stenosis: clinical outcomes according to SYNTAX score in patients undergoing transcatheter aortic valve implantation. Eur Heart J 2014;35:2530–40.

16. Stortecky S, Windecker S, Pilgrim T, et al. Cerebrovascular accidents complicating transcatheter aortic valve implantation: frequency, timing and impact on outcomes. EuroIntervention 2012;8:62–70.

17. Lansky AJ. First report of the DEFLECT III trial results: a prospective randomized evaluation of the TriGuard HDH Embolic DEFLECTion device during transcatheter aortic valve replacement. Paper presented at: American College of Cardiology/i2Scientific Session; March 15, 2015; San Diego, CA.

18. Linke A. CLEAN-TAVI study. Presented at Transcatheter Cardiovascular Therapeutics; September 13, 2014; Washington, DC.

19. Siontis GC, Juni P, Pilgrim T, et al. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. J Am Coll Cardiol 2014;64:129–40.

20. Buellesfeld L, Stortecky S, Heg D, et al. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. J Am Coll Cardiol 2012;60:493–501.

21. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185.

22. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012;42:S1–44.

KEY WORDS aortic stenosis, paravalvular regurgitation, self-expandable valve, surgical aortic valve replacement

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 12, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.07.042

2-Year Outcomes After Iliofemoral Self-Expanding Transcatheter Aortic Valve Replacement in Patients With Severe Aortic Stenosis Deemed Extreme Risk for Surgery

Steven J. Yakubov, MD,* David H. Adams, MD,† Daniel R. Watson, MD,* Michael J. Reardon, MD,‡ Neal S. Kleiman, MD,‡ David Heimansohn, MD,§ James Hermiller, Jr, MD,§ G. Chad Hughes, MD,‖ J. Kevin Harrison, MD,‖ Joseph Coselli, MD,¶ Jose Diez, MD,¶ Theodore Schreiber, MD,# Thomas G. Gleason, MD,** John Conte, MD,†† G. Michael Deeb, MD,‡‡ Jian Huang, MD,§§ Jae Oh, MD,‖‖ Timothy Byrne, MD,¶¶ Michael Caskey, MD,¶¶ Jeffrey J. Popma, MD,## for the CoreValve United States Clinical Investigators

ABSTRACT

BACKGROUND We reported favorable 1-year outcomes in patients unsuitable for surgery who underwent self-expanding transcatheter aortic valve replacement (TAVR) compared with an objective performance goal. Longer-term outcomes in these patients are not known.

OBJECTIVES This study sought to evaluate the 2-year safety and efficacy in patients with severe aortic stenosis (AS) at extreme risk of surgery treated with self-expanding TAVR.

METHODS We performed a prospective, multicenter, controlled, nonrandomized investigation of self-expanding TAVR in patients with severe AS and prohibitive surgical risk. We report the 2-year clinical outcomes in these patients.

RESULTS A total of 489 extreme-risk patients were treated transfemorally with a self-expanding aortic bioprosthesis at 41 centers. The rate of all-cause mortality or major stroke was 38.0% at 2 years (all-cause mortality, 36.5%; major stroke, 5.1%). The rates of all-cause mortality, cardiovascular mortality, and major stroke were 36.6%, 26.2%, and 5.1%, respectively, at 2 years. Between 1 and 2 years, the incremental all-cause mortality, cardiovascular mortality, and major stroke rates were 12.3%, 7.9%, and 0.8%, respectively. Multivariable predictors of all-cause mortality at 2 years included the presence of coronary artery disease and admission from an assisted living center. A Society of Thoracic Surgeons score >15% was also predictive of 2-year all-cause mortality. At 2 years, 94% of patients had New York Heart Association functional class I or II symptoms. The frequency of moderate or severe paravalvular regurgitation (4.3% at 1 year; 4.4% at 2 years) was unchanged between the first and second year.

CONCLUSIONS Patients with severe AS at extreme surgical risk treated with self-expanding TAVR continued to show good clinical outcomes and hemodynamic valve performance at 2 years. The presence of comorbid conditions rather than valve performance affected 2-year outcomes in these patients. (Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Symptomatic Severe Aortic Stenosis in High Risk and Very High Risk Subjects Who Need Aortic Valve Replacement; NCT01240902) (J Am Coll Cardiol 2015;66:1327–34) © 2015 by the American College of Cardiology Foundation.

From the *Riverside Methodist Hospital, Columbus, Ohio; †Mount Sinai Health System, New York, New York; ‡Houston-Methodist-DeBakey Heart and Vascular Center, Houston, Texas; §St. Vincent's Heart Center of Indiana, Indianapolis, Indiana; ‖Duke University Medical Center, Durham, North Carolina; ¶Texas Heart Institute at St. Luke's Medical Center, Houston, Texas; #Detroit Medical Center, Detroit, Michigan; **University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; ††Johns Hopkins Medical Center, Baltimore, Maryland; ‡‡University of Michigan Medical Center, Ann Arbor, Michigan; §§Medtronic, Minneapolis, Minnesota; ‖‖Mayo Clinic Foundation, Rochester, Minnesota, ¶¶Banner Good Samaritan Hospital, Phoenix, Arizona; and the ##Beth Israel Deaconess Medical Center, Boston, Massachusetts. Medtronic, Minneapolis, Minnesota, sponsored this study.

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

NYHA = New York Heart Association

STS-PROM = Society for Thoracic Surgery Predicted Risk of Mortality

TAVR = transcatheter aortic valve replacement

Patients with severe symptomatic aortic stenosis (AS) deemed unsuitable for surgery have an estimated 50.0% mortality at 1 year without valve replacement (1). Transcatheter aortic valve replacement (TAVR) using balloon-expandable (1) and self-expanding (2) bioprostheses has become standard of care in these patients, who often have significant comorbidities, frailties, and disabilities that affect their long-term prognosis (3). Late outcomes after TAVR have been reported (4–7), but there is limited information about late survival in patients deemed to be at extreme risk of surgery (8,9).

SEE PAGE 1335

The CoreValve US Extreme Risk Pivotal Trial evaluated patients deemed unsuitable for surgery by 2 cardiac surgeons and 1 interventional cardiologist (2). A total of 489 patients underwent implantation with self-expanding TAVR by means of an iliofemoral access approach (2). Despite significant concomitant morbidities, the rate of 1-year all-cause mortality and major stroke at 1 year was superior to a rigorously defined objective performance goal (2). The self-expanding aortic bioprosthesis provided sustained improvement in the aortic valve effective orifice area, a reduction in the aortic valve gradient, and an overall improvement in New York Heart Association (NYHA) functional class (2). Our objective in this study was to evaluate the 2-year clinical outcomes in these patients.

TABLE 1 Baseline Clinical Characteristics and Comorbidities (N = 489)

Age, yrs	83.2 ± 8.7
Men, %	47.9 (234/489)
Society of Thoracic Surgeons Predicted Risk of Mortality, %	10.3 ± 5.5
<10	55.6 (272/489)
10–15	27.2 (133/489)
>15	17.2 (84/489)
Logistic euroSCORE, %	22.6 ± 17.1
New York Heart Association functional class III/IV	91.8 (449/489)
Diabetes mellitus	41.5 (203/489)
Insulin controlled	18.4 (90/489)
Cardiac history	
Previous stroke	13.7 (67/488)
Coronary artery disease	81.8 (400/489)
Previous coronary artery bypass graft	39.5 (193/489)
Previous percutaneous coronary intervention	37.0 (181/489)
Previous balloon artic valvuloplasty	20.4 (100/489)
Prohibitive anatomy	
Severe aortic calcification	17.2 (84/488)
Hostile mediastinum	11.9 (58/488)
Comorbidities	
Severe chronic lung disease	23.5 (115/489)
Home oxygen	29.9 (146/489)
Charlson Comorbidity Index	5.3 ± 2.3
Frailty	
Anemia with previous transfusion	22.8 (108/473)
Albumin <3.3 g/dl	18.2 (88/484)
5-m gait speed >6 s	84.2 (283/336)
Disabilities	
Assisted living	27.6 (135/489)
≥2 Katz ADL deficits	20.9 (102/489)
Wheelchair bound	16.6 (81/489)

Values are mean ± SD or frequency, % (n/N).
ADL = activities of daily living; euroSCORE = European System for Cardiac Operative Risk Evaluation.

METHODS

PATIENT ENROLLMENT AND STUDY DESIGN. Detailed patient enrollment criteria, inclusion and exclusion criteria, and study methods have been reported elsewhere (2). In brief, patients with severe symptomatic AS defined as having at least NYHA functional class II symptoms, an aortic valve area ≤0.8 cm^2 (or aortic valve index ≤0.5 cm^2/m^2), and a mean aortic valve gradient >40 mm Hg or a peak aortic

Dr. Yakubov has received institutional research grants from Boston Scientific, Direct Flow Medical, and Medtronic; and serves on an Advisory Board for Boston Scientific and Medtronic. Dr. Adams has received institutional grants and institutional royalties for patents from Medtronic; and institutional royalties for patents from Edwards Lifesciences. Dr. Reardon serves on an Advisory Board for Medtronic. Dr. Kleiman provides educational services to Medtronic. Dr. Heimansohn serves as a proctor for Sorin Biomedical. Dr. Hermiller has received institutional research grants from Medtronic. Dr. Hughes serves as a consultant and speaker for Medtronic. Dr. Harrison has received institutional research grants from Boston Scientific, Direct Flow Medical, Edwards Lifesciences, and Medtronic; serves on an Advisory Board for St. Jude Medical; and is on a DSMB for CardiAQ. Dr. Coselli serves as an advisor to Medtronic. Dr. Gleason has received institutional research grants from Medtronic. Dr. Conte serves on the Surgery Advisory Board for Medtronic and Sorin; and has received research support from Boston Scientific, Medtronic, and St. Jude Medical. Dr. Deeb serves as a consultant for Edwards Lifesciences; and as an advisor and consultant for Medtronic. Dr. Huang is an employee of and shareholder in Medtronic. Dr. Oh has received institutional research grants from Medtronic. Dr. Caskey serves as a consultant for Medtronic. Dr. Popma has received institutional research grants from Boston Scientific, Direct Flow Medical, and Medtronic; and serves on a Medical Advisory Board for Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Antonio Colombo, MD, served as Guest Editor for this paper.
Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Manuscript received February 16, 2015; revised manuscript received July 15, 2015, accepted July 16, 2015.

valve velocity >4.0 m/s were eligible. Patients were considered to be at extreme risk if they were determined to have a 50.0% or greater risk for mortality or irreversible morbidity at 30 days with surgical replacement (2). Baseline assessment included calculation of risk using the Society of Thoracic Surgery Predictors of Mortality (STS-PROM) (10) and logistic euroSCORE (European System for Cardiac Operative Risk Evaluation) (11), the Charlson Comorbidity Index (12), and assessments of frailty using 5-m gait speed (13) and disability using the Katz Activities of Daily Living (14).

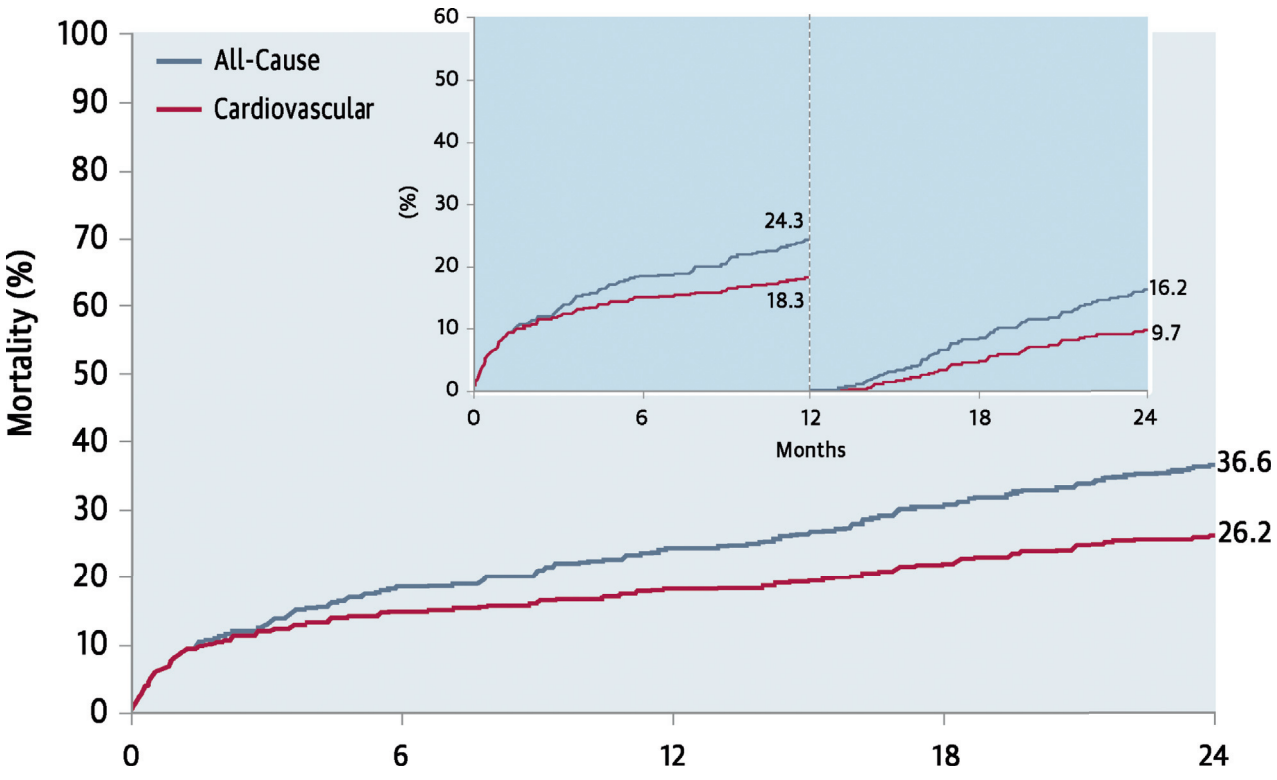
The CoreValve US Extreme Risk Pivotal Trial was a prospective, multicenter, controlled, nonrandomized, single-arm clinical study performed at 41 clinical sites in the United States (2). The responsible institutional review boards approved the study protocol, and written informed consent was obtained from all patients. The sponsor (Medtronic, Minneapolis,

TABLE 2 Clinical Outcomes at 1 and 2 Years After Self-Expanding TAVR

	1 Year	2 Years
Death from any cause or major stroke	127 (26.0)	185 (38.0)
Death		
Any cause	119 (24.3)	178 (36.6)
Cardiovascular	88 (18.3)	122 (26.2)
Stroke	31 (7.0)	37 (8.6)
Major	19 (4.3)	22 (5.1)
Minor	14 (3.2)	17 (4.1)
Myocardial infarction	9 (2.0)	12 (2.8)
Reintervention	8 (1.8)	8 (1.8)
Life-threatening or disabling bleeding	85 (18.0)	96 (21.1)
Major vascular complications	41 (8.4)	41 (8.4)
Valve thrombosis	0.0	0.0
Endocarditis	5 (1.3)	6 (1.6)
Device embolization/migration	1 (0.2)	1 (0.2)
Permanent pacemaker	124 (26.4)	132 (28.8)

Values are number of patients with event (Kaplan-Meier estimated rates).
TAVR = transcatheter aortic valve replacement.

CENTRAL ILLUSTRATION Long-Term Outcomes After TAVR: Kaplan-Meier Estimates of All-Cause and Cardiovascular Mortality Through 2 Years



Yakubov, S.J. et al. J Am Coll Cardiol. 2015; 66(12):1327–34.

(Inset) Landmark survival analysis of all-cause and cardiovascular mortality for the first year after TAVR for all patients **(left)** and during the second year after TAVR for patients alive at 1 year **(right)**. TAVR = transcatheter aortic valve replacement.

Minnesota), funded the study and, along with the study Steering Committee, designed the study. The study sponsor was responsible for selection of the clinical sites, monitoring of the data, and management of the case report forms and statistical analyses. An independent Clinical Events Committee adjudicated all major adverse clinical events. The primary author (S.J.Y.) and Co-Principal Investigators of the CoreValve US Pivotal Trials (J.J.P. and D.H.A.) drafted the initial manuscript. All authors contributed to this manuscript and made the decision to submit it for publication.

STUDY ENDPOINTS. The attempted iliofemoral implant population was the primary analysis group (2). All-cause mortality or stroke was assessed at 2 years. Major and minor strokes were defined using Valve Academic Research Consortium 1 criteria (15). Valve Academic Research Consortium 1 criteria also were used to define major adverse cardiovascular and cerebral events that comprised all-cause death, myocardial infarction, all stroke, and reintervention to alter, adjust, or replace a previously implanted valve (15). Symptom status at 2 years was assessed using the NYHA functional classification system.

ECHOCARDIOGRAPHIC ANALYSIS. Echocardiograms were collected at 1 and 2 years and were interpreted by a central laboratory (Mayo Echocardiography Core Laboratory, Rochester, Minnesota). Prosthetic valve dysfunction and periprocedural aortic regurgitation were determined using Valve Academic Research Consortium 1 criteria (15). Aortic valve orifice area and mean gradient were compared at 1 and 2 years.

STATISTICAL ANALYSIS. Categorical variables were compared using the Fisher exact test. Continuous variables were presented as mean ± SD and compared with the Student *t* test. The Kaplan-Meier estimate and its 95% confidence interval were summarized for each subgroup. The difference between subgroups was compared using Cox regression with subgroup as a factor and the time to event endpoint as the outcome. All testing used a 2-sided alpha level of 0.05. Multivariable predictors of 2-year all-cause mortality were identified from univariable predictors with $p < 0.05$. Stepwise multivariable analyses were performed. The significance-level thresholds for entry and exit of independent variables were set at 0.10. All statistical analyses were performed with SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

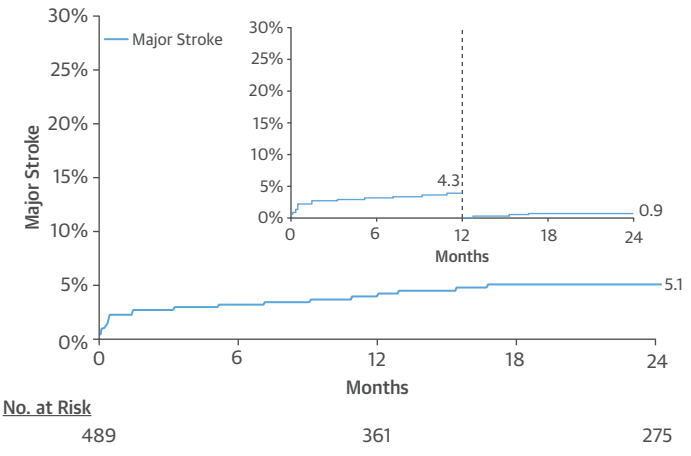
RESULTS

PATIENT FLOW AND DEMOGRAPHICS. A total of 489 patients underwent attempted iliofemoral self-expanding TAVR at 41 U.S. centers between February 2011 and August 2012; 486 patients were implanted with a self-expanding bioprosthesis (2). Between 1 and 2 years, 58 patients died, and 2 patients withdrew from the study. Two-year follow-up was available for 289 of 307 patients (94.1%).

Clinical characteristics for the attempted implant population are shown in Table 1. The mean age was 83.2 ± 8.7 years; 47.9% were men; 81.8% had coronary artery disease, and 27.6% were in an assisted living facility. The mean STS-PROM was 10.3% ± 5.5% and >15% in 17.2% of patients. Nearly 92% of patients experienced NYHA functional class III or IV symptoms.

CLINICAL OUTCOMES. Two-year clinical outcomes are shown in Table 2. The Kaplan-Meier rate of 2-year all-cause mortality or major stroke in the attempted iliofemoral implant population was 38.0% with a 2-sided upper 95% confidence interval of 42.6%. Two-year Kaplan-Meier rates were 36.6% for all-cause mortality and 26.2% for cardiovascular mortality (Central Illustration); the incremental rates between year 1 and year 2 were 12.3% for all-cause mortality and 7.9% for cardiovascular mortality. Causes of death during year 2 are listed in the Online Table 1. The rate of major stroke at 2 years was 5.1% (Figure 1), with a difference in the rates at 1 and 2 years of 0.8%. Univariable predictors for 2-year all-cause mortality are shown in Table 3 (Figures 2A to 2C). Multivariable predictors of all-cause mortality at 2 years included the presence of coronary artery disease ($p = 0.002$), and admission from an assisted living center

FIGURE 1 Kaplan-Meier Estimates of Major Stroke Through 2 Years



(Inset) Landmark analysis for the first year after TAVR for all patients **(left)** and during the second year after TAVR for patients alive at 1 year **(right)**. TAVR = transcatheter aortic valve replacement.

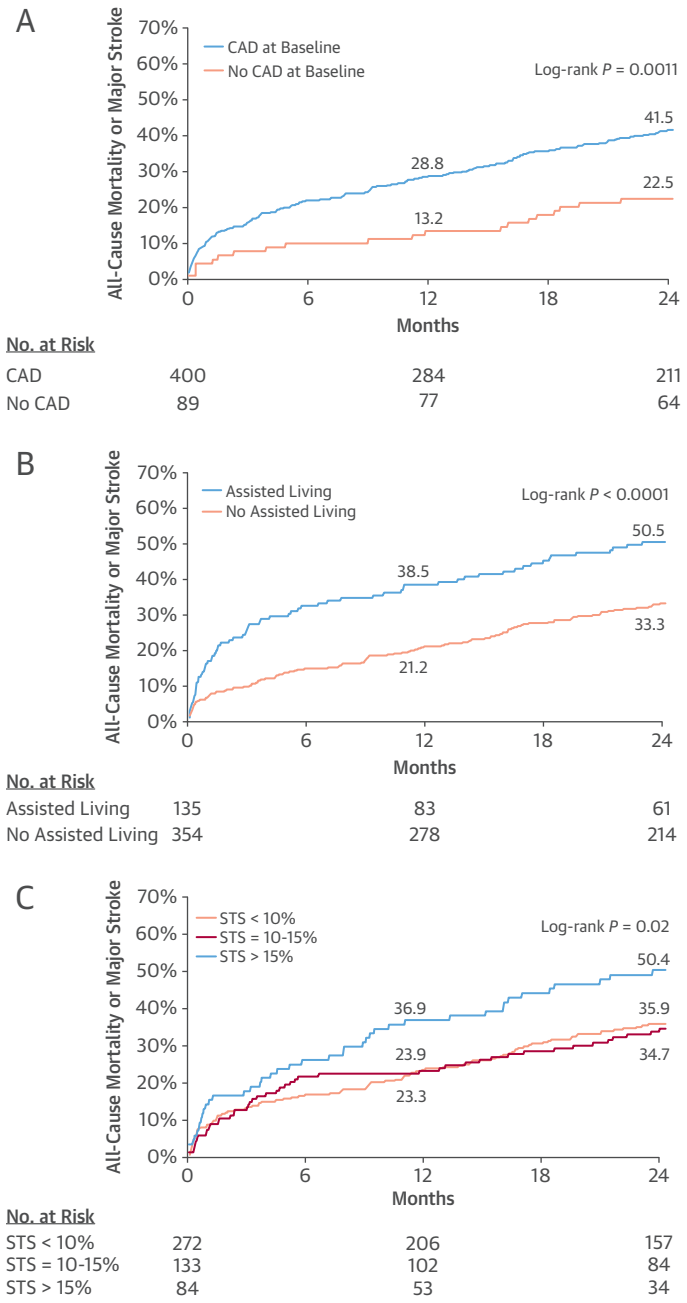
TABLE 3 All-Cause Mortality or Major Stroke for Select Subgroups

	No. of Patients	All-Cause Mortality or Major Stroke	p Value*
Sex			0.16
Male	255	35.1 (29.2-40.9)	
Female	234	41.2 (34.9-47.6)	
Age, yrs			0.41
≤85	263	36.7 (30.9-42.5)	
>85	226	39.6 (33.2-46.0)	
New York Heart Association functional class			
II	40	30.0 (15.8-44.2)	
III	313	38.3 (32.9-43.7)	0.35
IV	136	39.8 (31.6-48.1)	0.31
Left ventricular ejection fraction, %			0.09
≥40	404	36.4 (31.7-41.1)	
<40	83	45.8 (35.1-56.5)	
STS score, %			
<10	272	35.9 (30.1-41.6)	
10-15	133	34.7 (26.6-42.8)	0.84
>15	84	50.4 (39.7-61.2)	0.01
Hypertension			0.25
Yes	441	39.0 (34.4-43.6)	
No	48	29.2 (16.3-42.0)	
Diabetes			0.41
Yes	203	40.0 (33.3-46.8)	
No	286	36.6 (31.0-42.3)	
Chronic lung disease/COPD			0.36
Yes	288	40.1 (34.4-45.8)	
No	201	35.0 (28.4-41.6)	
Peripheral vascular disease			0.17
Yes	171	41.7 (34.3-49.1)	
No	315	35.8 (30.4-41.1)	
Previous stroke			0.57
Yes	67	40.3 (28.6-52.0)	
No	421	37.8 (33.1-42.4)	
Previous myocardial infarction			0.07
Yes	151	43.8 (35.8-51.7)	
No	338	35.4 (30.3-40.6)	
Coronary artery disease			0.0015
Yes	400	41.5 (36.7-46.4)	
No	89	22.5 (13.8-31.1)	
Assisted living			<0.0001
Yes	135	50.5 (42.1-59.0)	
No	315	33.3 (28.3-38.2)	

Values are n or Kaplan-Meier rates (95% confidence interval). *Proportional hazard models.

COPD = chronic obstructive pulmonary disease; STS = Society of Thoracic Surgeons.

FIGURE 2 Kaplan-Meier 2-Year All-Cause Mortality or Major Stroke Estimates for Select Subgroups

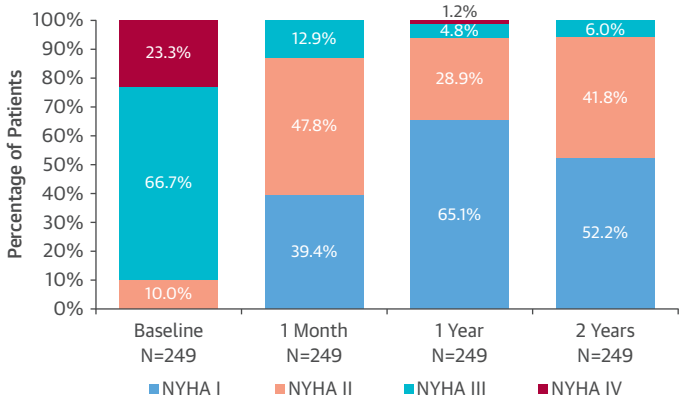


All-cause mortality to 2 years by **(A)** the presence of CAD; **(B)** residing in an assisted living facility before undergoing TAVR; and **(C)** by STS risk severity. CAD = coronary artery disease; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

(p = 0.0001). An STS-PROM score >15% was also predictive of 2-year all-cause mortality (p = 0.07). Coronary artery disease was defined as the presence of at least 1-vessel disease or having previous coronary artery bypass grafting or a previous percutaneous coronary intervention.

Improvement in symptom status was still present at 2 years after self-expanding TAVR. Compared with baseline symptoms, 92.0% of patients improved at 2 years by at least 1 NYHA functional class, and 58.0%

FIGURE 3 NYHA Functional Classification Through 2 Years

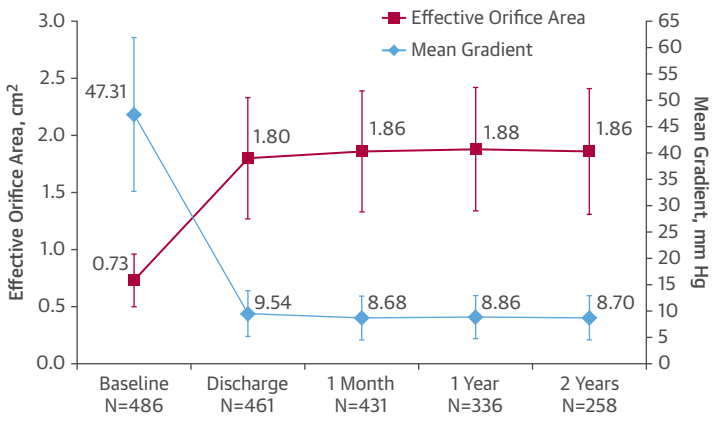


Symptom status for 249 patients with matched datasets at all time points are presented. NYHA = New York Heart Association.

improved by at least 2 classes (Figure 3). An additional 8 patients (2.4%) required a permanent pacemaker between the first and second year after TAVR (Table 2). There was no effect on 2-year survival for patients with or without a pacemaker (38.5% vs. 35.0%; log-rank p = 0.55).

ECHOCARDIOGRAPHIC FINDINGS. Aortic valve orifice area (1.88 cm^2 at 1 year and 1.86 cm^2 at 2 years; p = 0.43) and mean gradient (8.86 mm Hg at 1 year and 8.70 mm Hg at 2 years; p = 0.13) were unchanged at 2 years (Figure 4). The rates of moderate paravalvular aortic regurgitation were similar at 1 and 2 years (Figure 5).

FIGURE 4 Valve Hemodynamics Over Time



Mean aortic valve gradient **(blue)** and effective orifice area **(red)** remain consistent through 2 years. **Error bars** represent SDs.

DISCUSSION

Our study shows that the good survival and low stroke rates at 1 year associated with the self-expanding TAVR in patients deemed unsuitable for surgery were sustained 2 years after the procedure (Central Illustration, Figure 1). Our study also showed that the improvement in aortic valve effective orifice area and reduction in the aortic valve gradient was maintained and that improvement in functional class persisted in patients undergoing self-expanding TAVR. We also found that the degree of paravalvular regurgitation remained unchanged over the second year after the procedure. Longer-term mortality was most influenced by the presence of coronary artery disease and disability requiring assisted living.

MORTALITY AND MAJOR STROKE. Left untreated in patients deemed unsuitable for surgery, severe AS is associated with an all-cause mortality rate of 50.0% at 1 year (1) and 68.0% at 2 years (8). Both balloon-expandable (1) and self-expanding bioprostheses (2) improve survival in these patients. We previously reported a rate of 1-year all-cause mortality and major stroke of 26.0% (95% upper confidence bound: 29.9%) in extreme-risk patients undergoing self-expanding TAVR, which was significantly lower than an objective performance goal of patients with medical therapy alone (43.0%; p < 0.0001) (2). We now report an increase in all-cause mortality from 24.3% at 1 year to 36.6% at 2 years with an incremental increase in all-cause mortality in the second year of 12.3%, similar to the second-year mortality rate in the PARTNER B (Placement of Aortic Transcatheter Valve Trial B) of 18.2% (6). Late deaths in the PARTNER B were attributable to extensive comorbidities, as reflected in a worsened outcome in patients with an STS-PROM >15.0% (8). Our study also found a relationship between STS-PROM >15% and late mortality, and we identified that severe disability, as assessed by admission from an assisted living facility also worsened prognosis with a untoward 2-year mortality rate (50.5% vs. 33.3% in patients admitted from home for TAVR: p < 0.001).

Strokes occur in approximately 3.0% to 4.0% of patients after TAVR (16). With careful neurological examination before and after TAVR, we reported low major stroke rates at 30 days (2.3%) and 1 year (4.3%) (2). The current study also found a low (1.6%) stroke rate in the second year after TAVR, similar to the 2.6% increase in stroke in the second year in PARTNER B (6). Although we did not characterize the type of stroke in our study, hemorrhagic strokes occurred most often after 30 days in the PARTNER B (8). Due to

the occasional occurrence of atrial fibrillation after TAVR and the higher risk of bleeding complications in the elderly population, a careful balance is needed to optimize anticoagulation in this population of patients.

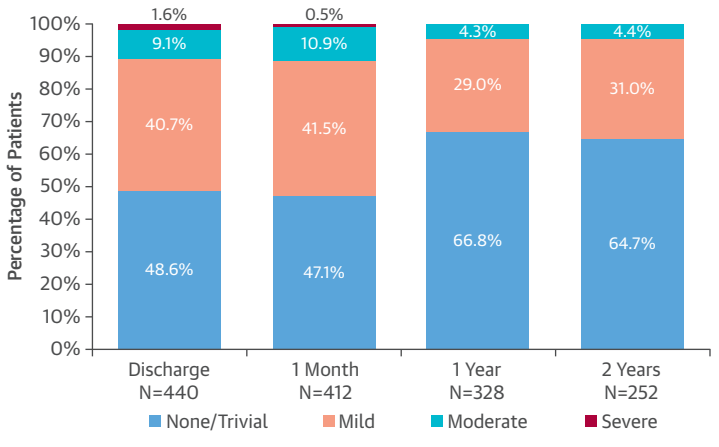
We observed a durable improvement in symptom status associated with self-expanding TAVR in our patients, with 94.0% of patients reporting NYHA functional class I or II symptoms at 2 years. This symptomatic improvement at 2 years in inoperable patients treated with TAVR was also found in the PARTNER B with 83.1% of patients having NYHA functional class I or II symptoms (8).

PARAVALVULAR AORTIC REGURGITATION. Significant residual paravalvular regurgitation is an important prognostic finding after TAVR (17,18). Predictors of paravalvular regurgitation include implantation depth, aortic valve area (17), annular size (17–19), presence of severe calcification (17,20,21), and the use of computed tomography imaging to guide valve sizing (22,23). We previously reported paired analyses that showed a reduction in the frequency of moderate or severe paravalvular regurgitation during the first year after self-expanding TAVR (from 10.7% at discharge to 4.2% at 1 year; p = 0.004) (2). We hypothesized that the mechanism of this improvement resulted from annular remodeling due to appropriate valve sizing on the basis of multidetector computed tomography imaging (19,24). In the current report, we found that the frequency of moderate paravalvular regurgitation remained stable from 1 to 2 years (4.3% to 4.4%, respectively) (**Figure 5**). Longer-term studies in a larger number of patients are needed to understand the complex relationship between moderate paravalvular regurgitation and late mortality.

HEMODYNAMIC FINDINGS. We found no evidence of valve degeneration in the second year after self-expanding TAVR in our study, and there were no cases of valve thrombosis. There was no significant change in the aortic valve effective orifice area or increase in the aortic valve gradients in the second year after self-expanding TAVR. This is similar to hemodynamic reports by others (4,8). Although the 2-year timeframe is short for the identification of structural deterioration of the self-expanding bioprosthesis, it is reassuring that there is no evidence of early failure in this population of patients.

STUDY LIMITATIONS. We did not pre-specify an objective performance goal for the composite of all-cause mortality or major stroke in our study beyond 1 year, and there is no active control group for our extreme-risk patients. Our predictor model for later term mortality was not pre-specified, and identified predictors should be considered exploratory for larger analyses. The presence of coronary artery disease was based on a simple definition and did not include detailed ischemia scoring or specific vessel stenosis.

FIGURE 5 Degree of Paravalvular Regurgitation



The 2-year follow-up of paravalvular regurgitation in surviving patients.

CONCLUSIONS

In patients with AS at extreme risk with surgical aortic valve replacement, iliofemoral placement of a self-expanding transcatheter bioprosthesis was shown to safe and effective through 2 years. Longer-term mortality was most influenced by the presence of coronary artery disease and disability. Hemodynamic improvements in aortic valve area and mean gradients were maintained at 2 years, and the rates of moderate or severe paravalvular regurgitation remained unchanged over the second year after the procedure. We conclude that self-expanding TAVR is beneficial in patients with AS without surgical options.

ACKNOWLEDGMENTS The authors thank Jane Moore, MS, ELS, for help in reviewing the manuscript for technical accuracy, and Gloria Toledo, MBA, and Eric Vang, PhD, for overall trial management. All are employees of Medtronic.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Steven J. Yakubov, OhioHealth, Riverside Methodist Hospital, 3705 Olentangy River Road, Columbus, Ohio 43214. E-mail: steven.yakubov@gmail.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with severe AS facing a high risk of death or major complications with surgical valve replacement who undergo TAVR with self-expanding prostheses exhibit sustained improvement in valve function and clinical outcomes after 2 years.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The main determinants of clinical outcomes during the first 2 years after TAVR in patients with severe, symptomatic AS at high risk of early operative mortality are comorbid medical conditions.

TRANSLATIONAL OUTLOOK: More work is needed to define the specific diseases, conditions, and other factors contributing to frailty and disability as they relate to long-term outcomes after TAVR. These efforts could lead to the development and validation of a clinical risk prediction instrument to guide selection of patients for this procedure.

REFERENCES

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

2. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63:1972–81.

3. Green P, Woglom AE, Genereux P, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. J Am Coll Cardiol Intv 2012;5:974–81.

4. Buellesfeld L, Gerckens U, Schuler G, et al. 2-year follow-up of patients undergoing transcatheter aortic valve implantation using a self-expanding valve prosthesis. J Am Coll Cardiol 2011;57:1650–7.

5. Petronio AS, De Carlo M, Giannini C, et al. 2-year results of the subclavian access for TAVI with the CoreValve bioprosthesis. J Am Coll Cardiol 2011;60:502–7.

6. Kapadia SR, Tuzcu EM, Makkar RR, et al. Long-term outcomes of inoperable patients with aortic stenosis randomly assigned to transcatheter aortic valve replacement or standard therapy. Circulation 2014;130:1483–92.

7. Urena M, Webb JG, Elchaninoff H, et al. Late cardiac death in patients undergoing transcatheter aortic valve replacement: incidence and predictors of advanced heart failure and sudden cardiac death. J Am Coll Cardiol 2015;65:437–48.

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

9. Kapadia SR, Leon MB, Makkar RR, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2485–91.

10. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2–isolated valve surgery. Ann Thorac Surg 2009;88 Suppl:S23–42.

11. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J 2003;24:881–2.

12. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

13. Afilalo J, Eisenberg MJ, Morin JF, et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. J Am Coll Cardiol 2010;56:1668–76.

14. Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged. The Index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963;185:914–9.

15. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. Eur Heart J 2011;32:205–17.

16. Eggebrecht H, Schmermund A, Voigtlander T, et al. Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients. EuroIntervention 2012;8:129–38.

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

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

19. Detaint D, Lepage L, Himbert D, et al. Determinants of significant paravalvular regurgitation after transcatheter aortic valve: implantation impact of device and annulus discongruence. J Am Coll Cardiol Intv 2009;2:821–7.

20. Feuchtner G, Plank F, Bartel T, et al. Prediction of paravalvular regurgitation after transcatheter aortic valve implantation by computed tomography: value of aortic valve and annular calcification. Ann Thorac Surg 2013;96:1574–80.

21. Khalique OK, Hahn RT, Gada H, et al. Quantity and location of aortic valve complex calcification predicts severity and location of paravalvular regurgitation and frequency of post-dilation after balloon-expandable transcatheter aortic valve replacement. J Am Coll Cardiol Interv 2014;7:885–94.

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

23. Hansson NC, Thuesen L, Hjortdal VE, et al. Three-dimensional multidetector computed tomography versus conventional 2-dimensional transesophageal echocardiography for annular sizing in transcatheter aortic valve replacement: influence on postprocedural paravalvular aortic regurgitation. Catheter Cardiovasc Interv 2013;82:977–86.

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

KEY WORDS extreme risk, self-expanding, severe aortic stenosis, transcatheter aortic valve replacement

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

5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial

Samir R Kapadia, Martin B Leon, Raj R Makkar, E Murat Tuzcu, Lars G Svensson, Susheel Kodali, John G Webb, Michael J Mack, Pamela S Douglas, Vinod H Thourani, Vasilis C Babaliaros, Howard C Herrmann, Wilson Y Szeto, Augusto D Pichard, Mathew R Williams, Gregory P Fontana, D Craig Miller, William N Anderson, Jodi J Akin, Michael J Davidson†, Craig R Smith, for the PARTNER trial investigators*

Summary

Background Based on the early results of the Placement of Aortic Transcatheter Valves (PARTNER) trial, transcatheter aortic valve replacement (TAVR) is an accepted treatment for patients with severe aortic stenosis who are not suitable for surgery. However, little information is available about the late clinical outcomes in such patients.

Methods We did this randomised controlled trial at 21 experienced valve centres in Canada, Germany, and the USA. We enrolled patients with severe symptomatic inoperable aortic stenosis and randomly assigned (1:1) them to transfemoral TAVR or to standard treatment, which often included balloon aortic valvuloplasty. Patients and their treating physicians were not masked to treatment allocation. The randomisation was done centrally, and sites learned of the assignment only after a patient had been screened, consented, and entered into the database. The primary outcome of the trial was all-cause mortality at 1 year in the intention-to-treat population, here we present the prespecified findings after 5 years. This study is registered with ClinicalTrials.gov, number NCT00530894.

Findings We screened 3015 patients, of whom 358 were enrolled (mean age 83 years, Society of Thoracic Surgeons Predicted Risk of Mortality 11·7%, 54% female). 179 were assigned to TAVR treatment and 179 were assigned to standard treatment. 20 patients crossed over from the standard treatment group and ten withdrew from study, leaving only six patients at 5 years, of whom five had aortic valve replacement treatment outside of the study. The risk of all-cause mortality at 5 years was 71·8% in the TAVR group versus 93·6% in the standard treatment group (hazard ratio 0·50, 95% CI 0·39–0·65; p<0·0001). At 5 years, 42 (86%) of 49 survivors in the TAVR group had New York Heart Association class 1 or 2 symptoms compared with three (60%) of five in the standard treatment group. Echocardiography after TAVR showed durable haemodynamic benefit (aortic valve area 1·52 cm² at 5 years, mean gradient 10·6 mm Hg at 5 years), with no evidence of structural valve deterioration.

Interpretation TAVR is more beneficial than standard treatment for treatment of inoperable aortic stenosis. TAVR should be strongly considered for patients who are not surgical candidates for aortic valve replacement to improve their survival and functional status. Appropriate selection of patients will help to maximise the benefit of TAVR and reduce mortality from severe comorbidities.

Funding Edwards Lifesciences.

Lancet 2015; 385: 2485–91

Published Online
March 15, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60290-2

See Comment page 2439

See Articles page 2477

*J J Akin MS has no affiliations

†M J Davidson MD died in January, 2015

Cleveland Clinic, Cleveland, OH, USA (Prof S R Kapadia MD, Prof E M Tuzcu MD, Prof L G Svensson MD); **Columbia University Medical Center/New York Presbyterian Hospital, New York, NY, USA** (Prof M B Leon MD, S Kodali MD, Prof C R Smith MD); **Cedars Sinai Medical Center, Los Angeles, CA, USA** (R R Makkar MD); **St Paul's Hospital, Vancouver, BC, Canada** (Prof J G Webb MD); **Baylor Scott & White Health, Plano, TX, USA** (Prof M J Mack MD); **Duke Clinical Research Institute/Duke University Medical Center, Durham, NC, USA** (Prof P S Douglas MD); **Emory University School of Medicine, Atlanta, GA, USA** (Prof V H Thourani MD, V C Babaliaros MD); **University of Pennsylvania, Philadelphia, PA, USA** (Prof H C Herrmann MD, W Y Szeto MD); **Medstar Washington Hospital Center, Washington, DC, USA** (A D Pichard MD); **NYU Langone Medical Center, New York, NY, USA** (M R Williams MD); **Lenox Hill Hospital, New York, NY, USA** (G P Fontana MD); **Stanford University School of Medicine, Department of Cardiovascular Surgery, Falk CV Research Center, Stanford, CA, USA** (Prof D C Miller MD); **and independent consultant, Lake Forest, CA, USA** (W N Anderson PhD)

Introduction

Severe symptomatic aortic stenosis is a common valvular heart disease in elderly people and, if not treated with surgical aortic valve replacement, can be rapidly fatal. This seminal observation on the time course of aortic stenosis was made by Braunwald and Ross almost 50 years ago from a small number of patients with severe aortic stenosis who did not undergo surgery.[1,2] The Placement of Aortic Transcatheter Valves (PARTNER) trial compared clinical and echocardiographic data for high-risk patients treated either with a first-generation transcatheter aortic valve replacement (TAVR) or with standard treatment.[3–5]

1-year follow-up from the PARTNER trial showed mortality and functional benefits of TAVR compared with standard treatment, leading the US Food & Drug Administration to approve TAVR.[4] Data at 2 years and 3 years showed similar results.[3,5] This report presents the prespecified final 5-year follow-up of patients deemed inoperable.

Methods

Study design and participants

We did this randomised controlled trial at 21 experienced valve centres in Canada, Germany, and the USA. We included patients with severe symptomatic aortic stenosis (aortic valve area <0·8 cm²) who were not candidates for surgical aortic valve replacement because of clinical or anatomical factors. The risk status of patients, including Society of Thoracic Surgeons Predicted Risk of Mortality (STS) was assessed by a team of experienced cardiac

Correspondence to:
Prof Samir R Kapadia, Sones Cardiac Catheterization Laboratories, Cleveland Clinic, 9500 Euclid Avenue, J2-3, Cleveland, OH 44195, USA
kapadis@ccf.org

Research in context

Systematic review

We searched Medline on March 7, 2015, with the terms "transcatheter aortic valve replacement" or "transcatheter aortic valve implantation", which returned 3300 results, of which 284 were filtered "clinical trials". We reviewed these citations and found no other randomised study comparing transcatheter aortic valve replacement with treatment without aortic valve replacement. The Placement of Aortic Transcatheter Valves (PARTNER) 1B trial is the only randomised trial published to date comparing outcomes of percutaneous aortic valve replacement with contemporary standard treatment (without aortic valve replacement) in surgically inoperable patients.

Interpretation

Although other technologies (either newer iterations of approved valves or new valve designs) have been and are being tested in extreme risk patients, this study is the only randomised trial with a standard treatment control arm. This report describes the crucial 5-year (end of study) follow-up data from this study. This study shows sustained benefit of TAVR as measured by all-cause mortality, cardiovascular mortality, repeat hospital admission, and functional status compared with standard treatment. By contrast, long-term outcomes of patients with severe symptomatic aortic stenosis treated with standard treatment are dismal. Furthermore, this study confirmed transcatheter valve durability over 5 years of follow-up. This rigorous trial with comparative effectiveness analyses of adjudicated endpoints provides the benchmark for TAVR benefit compared with standard treatment.

surgeons, interventional cardiologists, and others. The definition of an inoperable patient was an estimated probability of death or serious irreversible morbidity after surgical aortic valve replacement of more than 50%. Complete details on inclusion and exclusion criteria have been reported previously.[4] The PARTNER trial included another cohort of high-risk but operable patients, which has been reported separately.[6,7]

The trial was approved by institutional review boards at each site and written informed consent was obtained from all patients.

Randomisation and masking

The randomisation sequence was generated by central computer randomisation. Patients were randomly assigned (1:1) to TAVR or standard treatment (medical management with or without balloon aortic valvuloplasty at the discretion of the treating physician). Patients and their treating physicians were not masked to treatment allocation.

Procedures

We used the first-generation Sapien heart-valve system (Edwards Lifesciences, Irvine, CA, USA) in this study. It consisted of a balloon-expandable, stainless steel stent frame housing a trileaflet bovine pericardial valve within a deflectable delivery catheter. Valve replacement was done under general anaesthesia via common femoral artery access. This study did not include alternative access. Both transoesophageal echocardiography and fluoroscopic guidance were used for deployment of the valve. CT-guided annular sizing was not routinely used to select valve size. Only 23 mm and 26 mm valves were used. Serial echocardiographic assessments of the bioprosthetic aortic valve and left ventricular haemodynamics were analysed in a core echocardiography laboratory.[8] An independent clinical events committee adjudicated cause of death cardiovascular or non-cardiovascular.

Outcomes

The primary endpoint was all-cause mortality at 1 year. Secondary endpoints were cardiovascular mortality, stroke, vascular complications, major bleeding, and functional status. The results presented here are prespecified analyses at 5 years.

Statistical analysis

All clinical outcomes were analysed for the intention-to-treat population, which included all patients who were randomly assigned treatment. Echocardiographic data were analysed according to the treatment received. We compared categorical variables with Fisher's exact test and continuous variables with Student's *t* test; we used paired-sample *t* tests to compare continuous variables between time periods. We used Kaplan-Meier estimates to assess time-to-event variables, which we compared with log-rank test. We calculated hazard ratios (HRs) by Cox regression analysis; the interaction terms result from Cox regression with a trial arm×covariate interaction term. This interaction analysis was not specified in the protocol; it was done in the 1-year analyses and presented in the premarket approval application; the same subgroups are analysed here. We also used Cox regression for multivariable analysis. We did competing risks analyses with Aalen's multistate generalisation of Kaplan-Meier. We did landmark analyses, in which the patient group was all patients alive at the start of the analyses. Neither the competing risk nor the landmark analyses were prespecified in the protocol.

The close date for this analysis was March 16, 2014; 5 years after the last patient was enrolled. We did univariate analyses without imputation for missing values. After all patients completed 1 year of follow-up, those in the standard treatment group could crossover to the TAVR group. Data from patients in the standard treatment group who crossed over to TAVR were censored

at the time of crossover. We assessed long-term freedom from stroke non-parametrically by the Kaplan-Meier estimates. We did the statistical analyses with SAS (version 9.3). We deemed a p value less than 0·05 as statistically significant.

Role of the funding source

The funder designed and monitored the study and participated in the selection and management of study sites and collection of data. The funder had no role in data analysis, data interpretation, or writing of the report. The authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

We screened 3015 patients, of whom 358 patients were enrolled between May 11, 2007, and March 16, 2009. 179 patients were assigned to each treatment group. The appendix shows the trial profile and baseline characteristics.[4,6] Mean age was 83 years, mean STS was 11·7%, and 54% of participants were female. 140 (79%) of 179 patients in the standard treatment group underwent balloon aortic valvuloplasty during the trial.

At 5 years, risk of mortality was 71·8% in the TAVR group and 93·6% in the standard treatment group (HR 0·50, 95% CI 0·39–0·65; p<0·0001; figure 1A). Six patients were alive at 5 years in the standard treatment group, of which two had had TAVR outside of the USA, two had surgical aortic valve replacement, and one had an apical-descending aorta valve-conduit. Only one patient who had not had aortic valve replacement was alive at 5 years and this patient had a balloon aortic valvuloplasty during follow-up (last echocardiography showed aortic valve area of 0·4 cm² and mean gradient 56 mm Hg). Median survival was 31·0 months (IQR 7·7–>60) in the TAVR group compared with 11·7 months (IQR 4·8–30·9) in the standard treatment group (p<0·0001).

Results of landmark analyses showed that the differences in survival remained significant at 3–5 years despite few survivors in the standard treatment group (appendix). For patients alive at 3 years, risk of all-cause mortality at 5 years was 38·9% in the TAVR group and 66·7% in the standard treatment group (p=0·028).

The risk of cardiovascular-related mortality at 5 years was 57·5% in the TAVR group and 85·9% in the standard treatment group (p<0·0001; figure 2A). 43 (34%) of 127 deaths in TAVR group compared with 25 (17%) of 143 in the standard treatment group were judged as non-cardiovascular, suggesting that non-cardiovascular comorbidities were an important cause of death (figure 2B).

Risk of stroke at 5 years was 16·0% in the TAVR group versus 18·2% in the standard treatment group (HR 1·39, 95% CI 0·62–3·11; p=0·555). Because the mortality in the standard treatment group was very high and patients have to be alive to have a stroke, we did a competing risk analysis for mortality and stroke (figure 3), which confirmed that there was no continuous hazard of stroke associated with TAVR after the initial procedural risk.

See Online for appendix

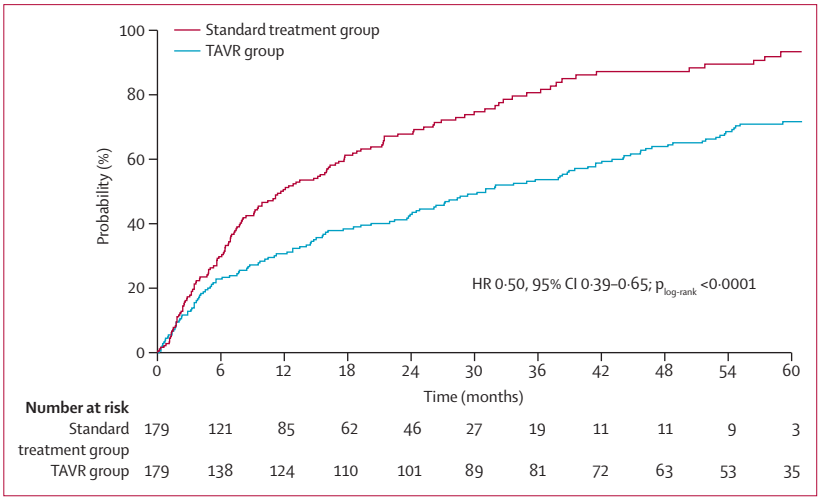


Figure 1: **Kaplan-Meier analysis of all-cause mortality for the intention-to-treat population**
TAVR=transcatheter aortic valve replacement. HR=hazard ratio.

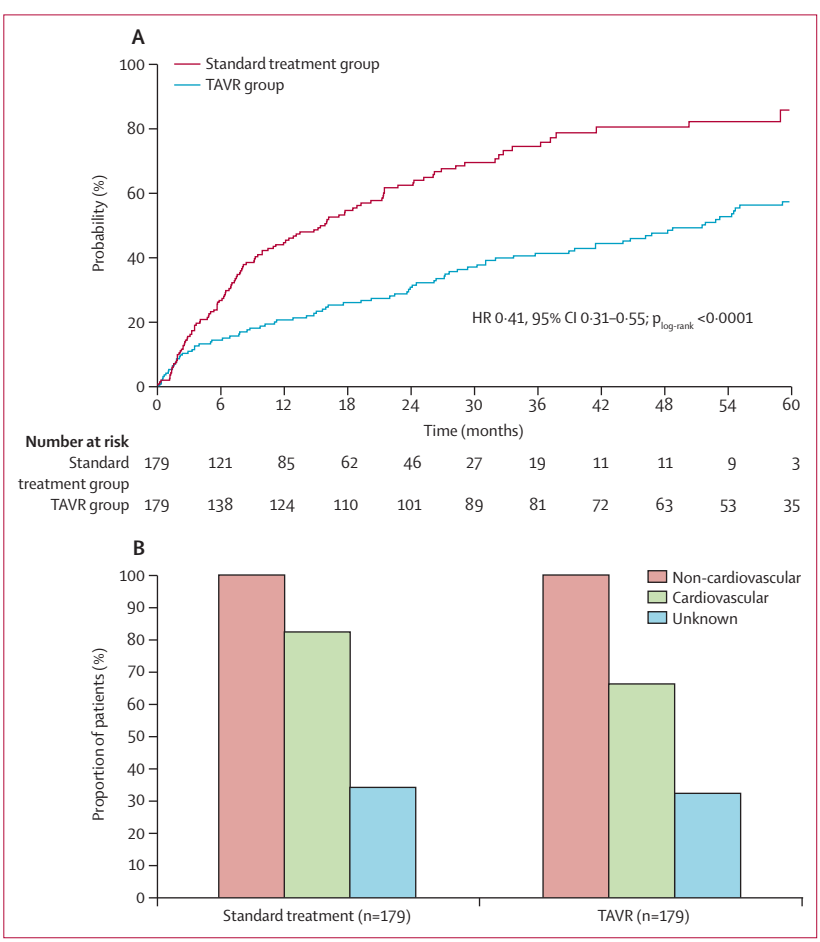


Figure 2: **Cardiovascular mortality (A) and causes of death (B)**
TAVR=transcatheter aortic valve replacement. HR=hazard ratio.

Risk of repeat hospital admission was 47·6% in the TAVR group compared with 87·3% in the standard treatment group (p<0·0001; appendix). At 5 years, 42 (86%) of 49 survivors in the TAVR group had New York Heart Association (NYHA) class 1 or 2 symptoms compared with three (60%) of five in the standard treatment group (figure 4).

Valve area and mean transvalvular gradient across the aortic valve were stable throughout follow-up; mean valve area was 1·52 cm² (SD 0·28) and mean gradient was 10·6 mm Hg (SD 3·9) at 5 years (appendix). The durability of bioprosthetic valve performance was further confirmed by paired analysis at 5 years of patients who had had TAVR (appendix). Moderate or severe paravalvular leak was present in 23 (14%) of 165 patients at the first available measurement after TAVR but none of these patients had an echocardiogram at 5 years, although four patients were alive at 5 years.

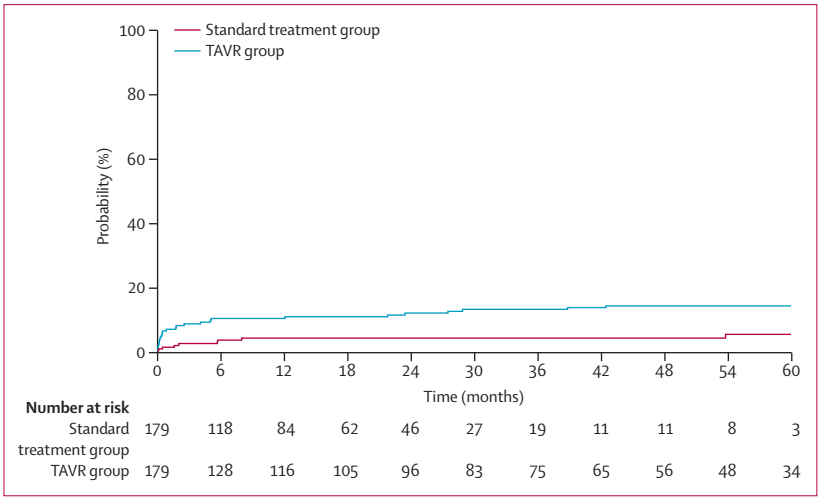


Figure 3: **Risk of stroke as determined by competing risk analysis of stroke and mortality**
TAVR=transcatheter aortic valve replacement.

No patient had structural valve deterioration requiring re-intervention. Only one patient underwent valve replacement for endocarditis after the initial procedure.

Patients who had TAVR and high STS (≥5%) had higher mortality than those with low STS scores (<5%); however, we recorded no mortality difference between patients who had TAVR and STS of 5–14·9% and those who had STS of 15% or more (data not shown). Similarly, all-cause mortality did not differ significantly between STS categories for patients in the standard treatment group (data not shown). At 5 years, for patients with STS of less than 5%, mortality was significantly lower in the TAVR group than in the standard treatment group (p=0·0012). We found a similar trend for patients with STS of 5–14·9% (p=0·0002), but not for those with STS of more than 15% (p=0·075; figure 5A). The mortality curves of TAVR and standard treatment groups separated immediately in patients with STS less than 5%, at around 1 year in patients with STS 5–14·9%, and at around 2 years in patients with STS more than 15%. Cardiovascular mortality was significantly lower with TAVR than with standard treatment across all STS strata (figure 5B).

5-year all-cause mortality of patients with post-procedural moderate to severe paravalvular leak was not significantly different compared with patients with no or mild paravalvular leak (78% *vs* 69%; p=0·510; appendix). However, cardiovascular mortality was significantly higher (75% *vs* 51%; p=0·043; appendix).

Several subgroups showed a mortality benefit with TAVR compared with standard treatment (appendix). The only exception was for patients with oxygen-dependent chronic obstructive pulmonary disease. The p values from the subgroup analyses should be interpreted with caution; no formal analysis was done to assess equivalence or non-inferiority. Multivariate predictors of mortality for patients who had TAVR included body-mass index of 26 kg/m² or more (odds

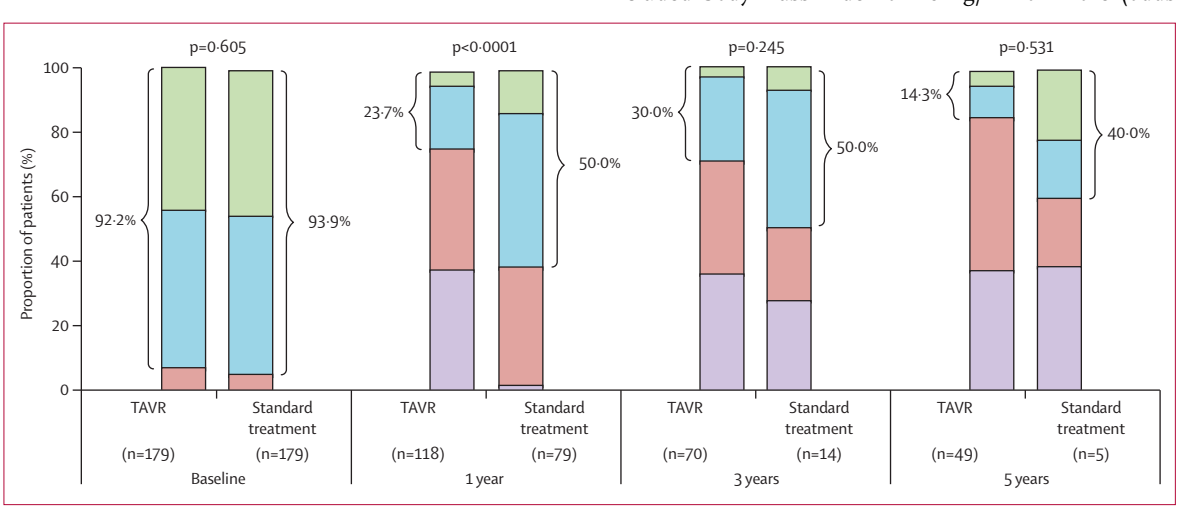


Figure 4: **New York Heart Association functional class of the survivors**
p values are for TAVR versus standard treatment for the full range of functional classes. TAVR=transcatheter aortic valve replacement.

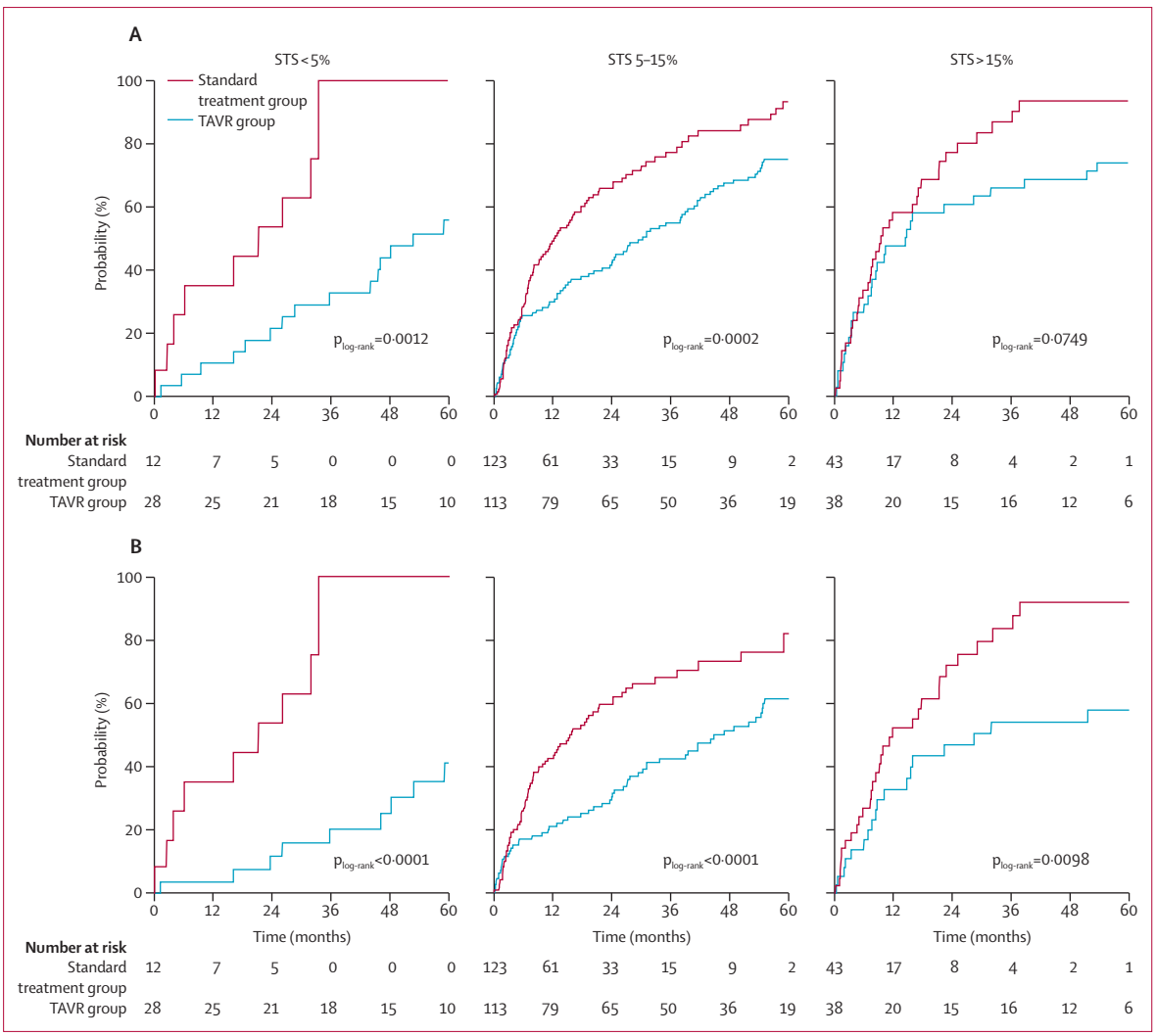


Figure 5: **Mortality outcomes stratified by STS score**
For all-cause mortality (A) and cardiovascular mortality (B). TAVR=transcatheter aortic valve replacement. STS=Society of Thoracic Surgeons Predicted Risk of Mortality.

ratio 0·50, 95% CI 0·34–0·73), oxygen-dependent chronic obstructive pulmonary disease (1·83, 1·22–2·75), and peripheral vascular disease (1·53, 1·04–2·24).

Discussion

Our findings show a sustained benefit of TAVR as measured by all-cause mortality, cardiovascular mortality, repeat hospital admission, and functional status. Valves were durable, with no increase in transvalvular gradient, attrition of valve area, or worsening of aortic regurgitation. Other important findings were: (1) cardiovascular mortality and all-cause mortality benefits occurred even in patients with high STS; (2) patients with oxygen-dependent chronic obstructive pulmonary disease might have less mortality benefit; (3) beyond early procedural risk of stroke, there was no persistent risk over 5 years; and (4) having moderate and severe paravalvular leak was associated with higher cardiovascular mortality but not all-cause mortality, particularly in patients with fewer comorbidities.

The mortality difference between TAVR and standard treatment continued to increase in 3-year survivors, which was surprising considering how very few survivors remained in the standard treatment group. This finding should be interpreted with caution because of the inherent limitations of landmark analyses. Median survival was increased from 1 year to 2·5 years with TAVR, and of the patients who had TAVR who were alive after 5 years, less than 50% needed hospital readmission (appendix), and 86% had NYHA functional class 1 or 2 symptoms. Cardiovascular mortality was decreased even more with TAVR. Because most of the enrolled patients were deemed inoperable primarily because of comorbidities (except for a small proportion with anatomical contraindications to surgery such as porcelain aorta or chest radiation), we expected their non-cardiovascular mortality to be high.

Non-cardiovascular mortality was high in the TAVR group. A third of deaths had an unknown cause and for all analyses these patients were included in the cardiovascular death group to provide a conservative estimate. Despite this presumption, cardiovascular mortality was substantially reduced even in patients with the highest STS. To understand the residual mortality in the TAVR group, we assessed mortality of an age-matched and sex-matched US population without aortic stenosis or comorbidities. Mortality in this population was roughly 8% per year over 5 years. Although all-cause mortality in the TAVR group was 43% in the first 2 years, all-cause mortality dropped to roughly 10% per year thereafter.

Although these clinical outcomes are encouraging, better patient selection and reduction in procedural complications can help to make TAVR even more beneficial. As shown by the mean STS of 7% in the Transcatheter Valve Therapy registry, which includes TAVR done in the USA after the Food & Drug Administation approval, the definition of extreme or high surgical risk is evolving.[9] Investigators in several studies have attempted to identify baseline predictors of poor outcome after TAVR. Post-procedural complications such as aortic regurgitation, stroke, acute kidney injury, and vascular complications have also been associated with poor long-term outcomes.[10–13] At 1 year, 2 years, and 3 years,[3–5] unlike at 5 years, we have not been able to detect a mortality difference in inoperable high-risk TAVR patients with moderate or severe paravalvular leak compared with those with no or mild paravalvular leak. Non-cardiac comorbidities might have increased mortality to a degree which overshadowed, and made difficult to detect, a mortality difference caused by paravalvular leak. In the 5-year analysis, we detected a difference in cardiovascular mortality—a more sensitive endpoint—in patients with moderate or severe paravalvular leak after TAVR, substantiating the earlier explanation. Non-cardiac comorbidities that have been associated with poor outcome include chronic obstructive pulmonary disease, chronic kidney disease, diabetes, previous stroke, liver disease, and frailty,[14–19] whereas cardiac comorbidities associated with poor outcome include low ejection fraction, pulmonary hypertension, severe mitral regurgitation, and coronary artery disease.[15,16,20,21]

In this analysis, mortality was higher in patients with multiple comorbidities, as evidenced by higher STS. Nevertheless, even in patients with the highest STSs, TAVR was beneficial for cardiovascular mortality, although fewer patients survived. Early survival was not different in patients with severe comorbidities underscoring the probable effect of these comorbidities on early survival despite successful TAVR. If patients lived beyond 2 years, they derive survival benefit from TAVR. Taken together, these results show the importance of making every attempt to differentiate patients who will derive survival benefit from those who are unlikely to survive, despite successful TAVR. Quality-of-life data were not collected beyond 1 year, therefore we could not assess the benefit or futility of TAVR based on quality of life at 5 years.

Stroke is an important potential long-term hazard of TAVR. Risk of stroke in the TAVR and standard treatment groups were similar at 5 years. However, few patients survived in the standard treatment group, which gives an artificially high weight to a small number of strokes.

A crucial result relates to the durability of the transcatheter valve over 5 years. Durability of the Sapien heart-valve system has been a concern and needs systematic echocardiographic long-term follow-up. Re-assurringly, we detected no structural valve deterioration or migration, and improvements in valve area and gradient were maintained at 5 years.

This report provides insight into the natural history of severe aortic stenosis without valve replacement treatment. In 1937, when haemodynamic severity of aortic stenosis could not be measured in vivo, Contratto and Levine described the average survival after the onset of symptoms in 180 patients, of whom 53 underwent necropsy.[22] Braunwald and Ross combined data from these patients and another 12 with haemodynamic measurements to conclude that average survival after the onset of heart failure is 2 years in patients with severe aortic stenosis.[1] The PARTNER study confirms this finding in a much larger contemporary cohort of patients (median survival was only 12 months). This trial is the first (and will probably be the only) randomised aortic stenosis trial that includes a standard treatment group. Before denying aortic valve replacement to any patient, one has to keep these data in perspective. A large proportion of patients in the standard treatment group had balloon aortic valvuloplasty, which is considered an acceptable palliative modality for the management of symptomatic severe aortic stenosis. It is difficult to analyse the effect of balloon aortic valvuloplasty in the standard treatment group because it was done at the discretion of investigators and was not part of the study protocol. A detailed analysis of patients given standard treatment and balloon aortic valvuloplasty suggested that the procedure improves survival and quality of life at 3–6 months but identified no long-term survival benefit or risk.[23]

In summary, this study shows that TAVR should be strongly considered for patients who are not surgical candidates for aortic valve replacement to improve their survival and functional status. Appropriate selection of patients will help to maximise the benefit of TAVR and reduce mortality from coexisting severe comorbidities.

Contributors

All authors contributed to study design, data collection, data interpretation, and revising the report. WNA analysed the data and SK wrote the first draft.

Declaration of interests

MBL has received travel reimbursements from Edwards Lifesciences related to the PARTNER trial. RRM has received grant support and consulting fees from Edwards Lifesciences, St Jude Medical, and Medtronic. EMT has received travel reimbursements from Edwards Lifesciences related to the PARTNER trial. LGS holds equity in Cardiosolutions and ValvXchange, intellectual property rights and

royalties from Posthorax, and has received travel reimbursements from Edwards Lifesciences related to the PARTNER trial. SK is a consultant for Edwards Lifesciences and a member of the scientific advisory board of Thubrikar Aortic Valve. JGW is a consultant for Edwards Lifesciences. MJM has received travel reimbursements related to the PARTNER trial. PSD has received grant support from Edwards Lifesciences. VHT is a consultant for Edwards Lifesciences, Sorin Medical, St Jude Medical, and DirectFlow. HCH has received institutional grant support from Edwards Lifesciences, St Jude Medical, Medtronic, and Boston Scientific and has received honoraria from Edwards Lifesciences for fellows training courses. ADP is a consultant for Edwards Lifesciences. MRW is a consultant for Edwards Lifesciences. DCM is supported by a research grant from the NHLBI #HL67025, has received grant funding from Abbott Vascular, Edwards Lifesciences, and Medtronic, and is a consultant for Medtronic. WNA has received consulting fees from Edwards Lifesciences and holds common stock in Edwards Lifesciences. JJA is a former employee of Edwards Lifesciences. CRS has received travel reimbursements from Edwards Lifesciences related to the PARTNER trial. The other authors report no competing interests.

Acknowledgments

The PARTNER trial was funded by Edwards Lifesciences, and the protocol was developed by the sponsor and the trial steering committee. We thank Maria Alu (Columbia University Medical Center) for editorial assistance and administrative support, and Dan Chin (Edwards Lifesciences) for assistance with preparation of figures. This report is dedicated to the memory of Michael J Davidson, MD, a cherished colleague and friend, for his outstanding contributions to the PARTNER trial and for his inspirational leadership. Our team has lost a valuable partner.

References

1 Ross J Jr, Braunwald E. Aortic stenosis. *Circulation* 1968; **38** (1 suppl)**:** 61–67.

2 Braunwald E. On the natural history of severe aortic stenosis. *J Am Coll Cardiol* 1990; **15:** 1018–20.

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

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

5 Kapadia SR, Tuzcu EM, Makkar RR, et al. Long-term outcomes of inoperable patients with aortic stenosis randomly assigned to transcatheter aortic valve replacement or standard therapy. *Circulation* 2014; **130:** 1483–92.

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

7 Reynolds MR, Magnuson EA, Lei Y, et al. Health-related quality of life after transcatheter aortic valve replacement in inoperable patients with severe aortic stenosis. *Circulation* 2011; **124:** 1964–72.

8 Douglas PS, Waugh RA, Bloomfield G, et al. Implementation of echocardiography core laboratory best practices: a case study of the PARTNER I trial. *J Am Soc Echocardiogr* 2013; **26:** 348–58.

9 Mack MJ, Brennan JM, Brindis R, et al. Outcomes following transcatheter aortic valve replacement in the United States. *JAMA* 2013; **310:** 2069–77.

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

11 Miller DC, Blackstone EH, Mack MJ, et al. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. *J Thorac Cardiovasc Surg* 2012; **143:** 832–43.

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

13 Pilgrim T, Stortecky S, Luterbacher F, Windecker S, Wenaweser P. Transcatheter aortic valve implantation and bleeding: incidence, predictors and prognosis. *J Thromb Thrombolysis* 2013; **35:** 456–62.

14 Rodes-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J Am Coll Cardiol* 2010; **55:** 1080–90.

15 Moat NE, Ludman P, de Belder MA, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J Am Coll Cardiol* 2011; **58:** 2130–38.

16 Sarkar K, Sardella G, Romeo F, et al. Transcatheter aortic valve implantation for severe regurgitation in native and degenerated bioprosthetic aortic valves. *Catheter Cardiovasc Interv* 2012; **81:** 864–70.

17 Thomas M, Schymik G, Walther T, et al. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation* 2011; **124:** 425–33.

18 Green P, Woglom AE, Genereux P, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. *JACC Cardiovasc Interv* 2012; **5:** 974–81.

19 Pilgrim T, Kalesan B, Wenaweser P, et al. Predictors of clinical outcomes in patients with severe aortic stenosis undergoing TAVI: a multistate analysis. *Circ Cardiovasc Interv* 2012; **5:** 856–61.

20 Rodes-Cabau J. Transcatheter aortic valve implantation: current and future approaches. *Nat Rev Cardiol* 2012; **9:** 15–29.

21 Dewey TM, Brown DL, Herbert MA, et al. Effect of concomitant coronary artery disease on procedural and late outcomes of transcatheter aortic valve implantation. *Ann Thorac Surg* 2010; **89:** 758–67.

22 Contratto AW, Levine SA. Aortic stenosis with special reference to angina pectoris and syncope. *Ann Intern Med* 1937; **10:** 1636–53.

23 Kapadia SR, Stewart WJ, Anderson WN, et al. Outcomes of inoperable symptomatic aortic stenosis patients not undergoing aortic valve replacement: insight into the impact of balloon aortic valvuloplasty from the PARTNER Trial (Placement of AoRtic TraNscathetER Valve Trial). *JACC Cardiovasc Interv* 2015; **8:** 327–36.