

BACKGROUND

No medical therapy is available for successfully treating calcific aortic stenosis. Treatments that have been used to slow the progression of coronary artery disease have failed to prevent the progression of aortic stenosis or to reverse the damage. The primary treatment for severe aortic stenosis is aortic valve replacement surgery. The survival rate at 3 years in patients with symptomatic aortic stenosis who undergo surgery is 87%; in those who do not have surgery it is 21% ($P < 0.001$). The operative mortality rate in the surgical treatment of aortic stenosis is less than 5%, but at least 30% to 40% of patients with severe aortic stenosis go untreated.^{1,2}

Surgical treatment of severe aortic stenosis has been underused for many reasons. Patients are thought to be too old, or they have left ventricular dysfunction or comorbidities that affect the surgical scores. Alternatively, patients are not referred for surgery because they are misdiagnosed (that is, the severity of the aortic stenosis is underestimated) or are considered “asymptomatic” when they are actually very limited in functional class. In addition, patients can perceive temporary improvement in symptoms after medical therapy.³ All of the above reasons emphasize the major issue in the underuse of surgical treatment: an incomplete understanding of the true surgical risk.

Balloon aortic valvuloplasty is not an alternative to

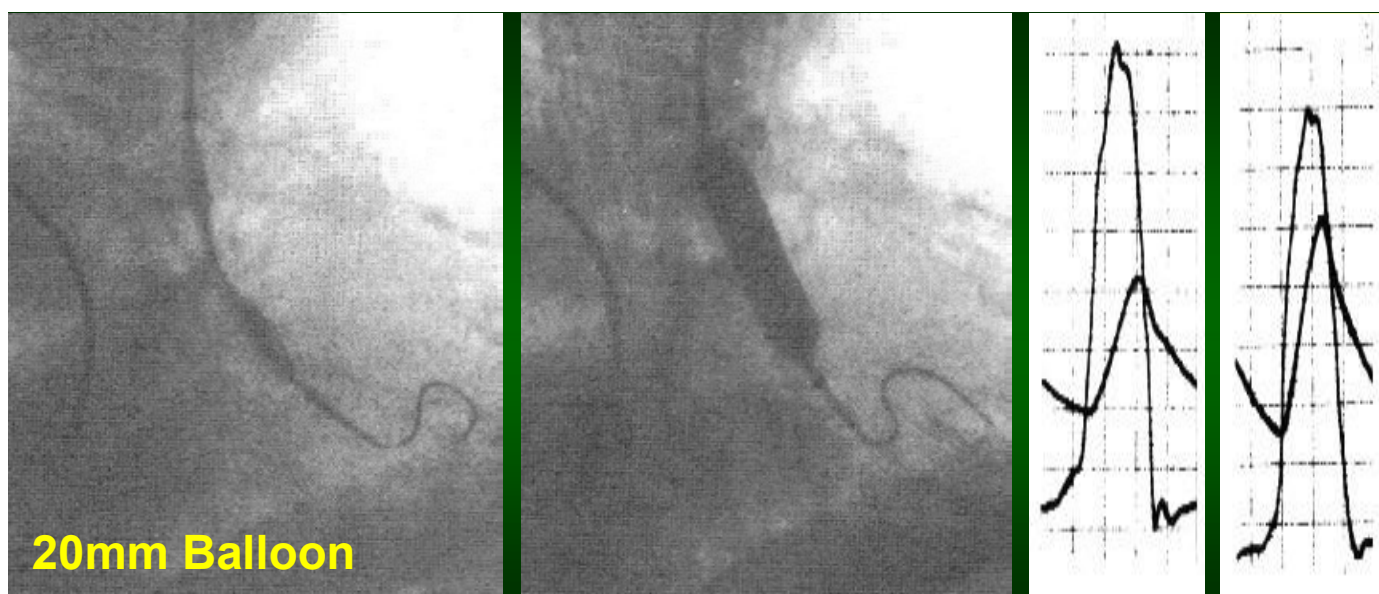
surgical aortic valve replacement. The first procedure was performed by Prof Alain Cribier in 1985 in severe Aortic stenosis in a sick patient with cardiogenic shock. Later on with time it became clear It provides symptomatic benefits for only a limited time (a few months) because of restenosis. When the hemodynamic effects of balloon aortic valvuloplasty and bioprosthetic aortic valve replacement are compared at 1 year, the latter affects a larger orifice area ($2.07\text{--}2.1\text{ cm}^2$ vs $0.78\text{--}0.09\text{ cm}^2$) and has a more favorable mean gradient effect ($5.8\text{--}6.5\text{ mmHg}$ vs $28.2\text{--}30\text{ mmHg}$).⁴

Although surgical aortic valve replacement has been the mainstay of therapy for severe aortic stenosis, transcatheter aortic valve implantation (TAVI) is now an acceptable standard of care for patients with symptomatic aortic stenosis who are not eligible for surgery or who are at very high risk for surgical treatment. The development of transcatheter devices has progressed rapidly during the last decade, and this approach challenges surgical repair as the preferred or only option for treating severe symptomatic aortic stenosis.

DEVELOPMENT OF NON SURGICAL AORTIC VALVE AND FIM

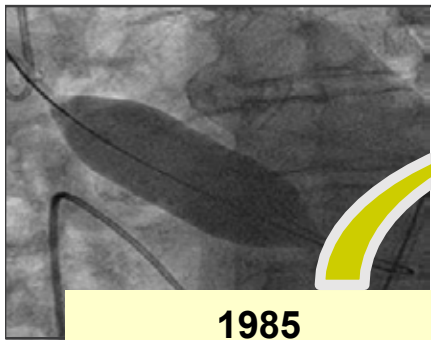
Dr. Cribier followed the saying of Edwin Land Don't undertake a project unless it is manifestly important and nearly impossible »

The challenge was Implanting a valve prosthesis within

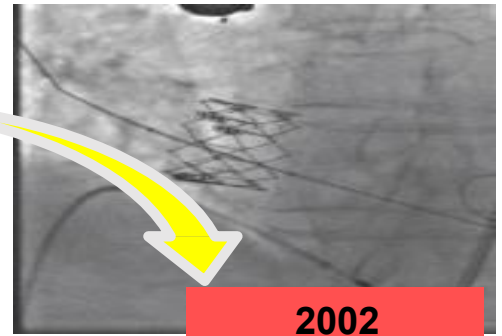


20mm Balloon

First case of BAV 1985



1985
Balloon Aortic Valvuloplasty



2002
Transcatheter Aortic Valve

the diseased calcific aortic valve, on the beating heart, using percutaneous catheter based techniques”

Highly challenging because of Valvular calcification Surrounding structures: Coronary arteries, Mitral valve, IV septum (His bundle) and major clinical issues were Coronary occlusion Mitral valve injury, Permanent AV block, Stroke, Aortic regurgitation, Prosthesis migration, Non lasting results

Birth of the concept of stented valve in Aortic Stenosis: It

was observed that a balloon expandable stent with high radial force might keep the valve open and a valvular structure would have to be attached within the stent.

A challenging combination of balloon expandable frame and valve structure was to be innovated in order to keep the stenosed valve open.

Company PVT in year 1999 took undertook the task of animal experimentation which validated the concept of stented valve as shown in figures (Figures 1-4).

FIRST IN MAN CASE

In 2002, Alan Cribier led the team that performed the first percutaneous transcatheter implantation of an aortic valve prosthesis in a patient with calcific aortic stenosis. They used an antegrade transseptal approach with a 23-mm balloon-expandable valve.⁵ In performing the first clinical retrograde transcatheter implantation of an aortic

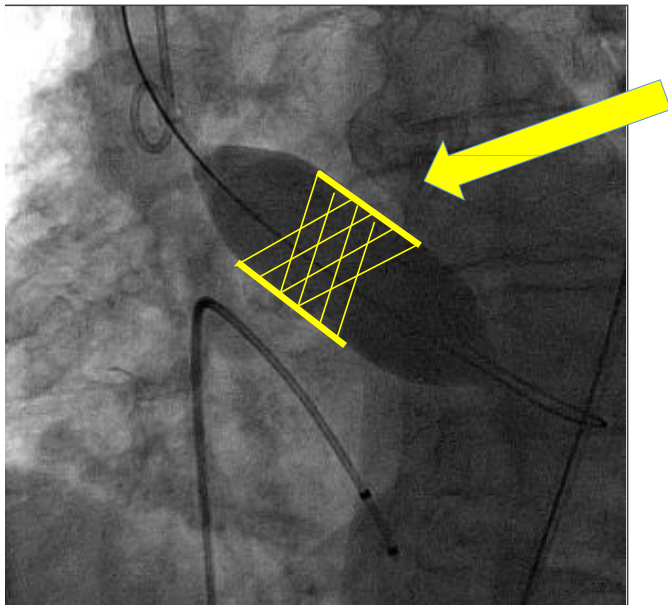
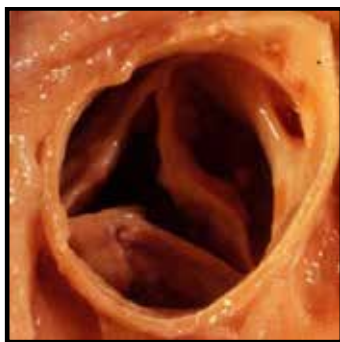


Fig. 1



**Extensive laboratory testing
Animal program (sheep model)
Acute and chronic studies**

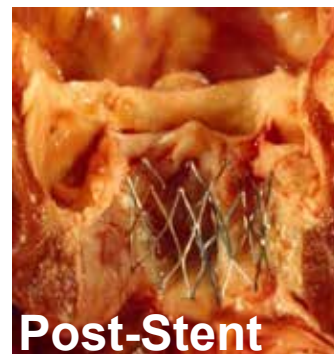
Fig. 3: PVT Valve Design Concepts



Post-BAV 23mm



Post-Stent 23mm



Post-Stent

Fig. 2: Rouen France-1994, Autopsy Study

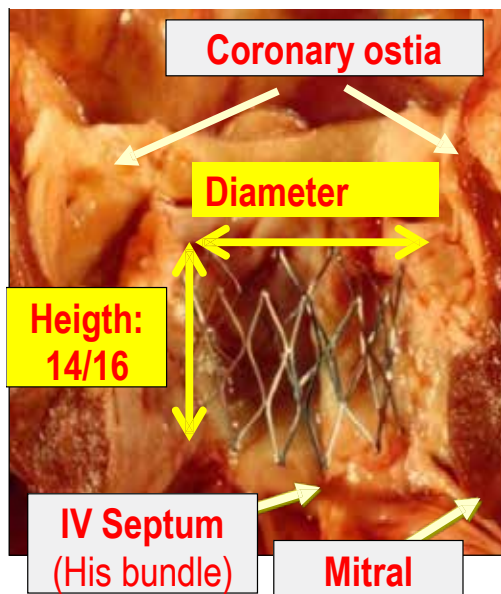


Fig. 4: Optimal dimensions of the frame

valve prosthesis.



THE EDWARDS SAPIEN® VALVE

The Edwards SAPIEN® valve (Edwards Lifesciences, LLC; Irvine, Calif) that is used in the United States is made of bovine pericardium in a trileaflet configuration and is mounted on a 14mm × 23- or 26-mm stainless-steel, balloon-expandable stent (Figure 1A) that is highly resistant to radial stress. The internal diameter of the delivery system is 24F to 26F. In Europe, the XT system has smaller delivery catheters (a 16F eSheath for the 23mm valve, up to a 20F eSheath for the 29-mm valve) (Figure 1B). In addition, the newer SAPIEN 3 valve is being tested in clinical trials.

The Edwards SAPIEN® valve is made of bovine pericardium in a trileaflet configuration. The valve is mounted on a highly resistant, stainless-steel, balloon-expandable ...

Strong evidence supporting the use of TAVI comes from the investigation of the Edwards SAPIEN valve in the landmark Placement of Aortic Transcatheter Valves (PARTNER) trial, in which patients with severe, symptomatic aortic stenosis who were not candidates for surgery were randomized to medical therapy or percutaneous aortic valve implantation (PARTNER 1B

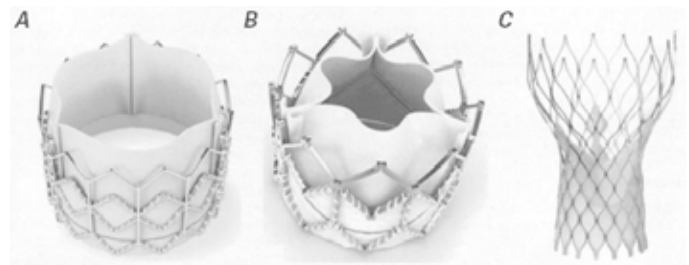


Fig. 1: Valves used in transcatheter aortic valve implantation procedures.

study). At the 1-year follow-up, there was an absolute reduction in mortality rate of 20% and an 18.3% reduction in the combined endpoint of death or stroke in patients who underwent TAVI. Of TAVI patients, the number needed to treat (NNT) in order to prevent a death was 5 and the NNT to prevent a death or a major stroke was 5.5. In comparison with patients who received only medical therapy, TAVI patients experienced a significant reduction in all-cause mortality at 2 years (43.3% vs 68%; hazard ratio=0.56; 95% confidence interval [CI], 0.43–0.73; $P < 0.001$).⁷ Furthermore, TAVI significantly improved quality-of-life measures over 1 year.

The incremental cost-effectiveness for TAVI—computed on the basis of the cost per quality-adjusted life-year (QALY), compared with standard therapy—was \$61,889. The calculated QALYs were 1.4 for TAVI versus 0.4 for medical therapy.⁸ Because of this strong evidence, TAVI is now considered the standard of care for patients with severe symptomatic aortic stenosis who have a life expectancy of more than 1 year and who are ineligible for surgical aortic valve replacement.

Transcatheter aortic valve implantation has also been studied in high-risk surgical patients. Results of the PARTNER trial (cohort A) showed that the all-cause mortality rate at 2 years was similar in TAVI patients and surgical patients (33.9% vs 35%, respectively; $P=0.78$),⁹ indicating that TAVI might be an appropriate strategy in this group.

On the basis of information gleaned from the Kansas City Cardiomyopathy Questionnaire, patients treated with transfemoral TAVI had a greater improvement in health status at 1 month than did patients treated surgically (difference of 9.9 points; 95% CI, 4.9%–14.9%; $P < 0.001$); similar findings were seen at 6 and 12 months. The QALY data suggested that TAVI was less expensive and more effective than surgical treatment. The same was not true for the transapical approach, which resulted in worse quality-of-life scores than did surgery, and cost more.¹⁰

CASE REPORT

84 year old diabetic, hypertensive follow up case of Coronary artery bypass surgery 10 years back with severe aortic valve stenosis (PG of 70 and mean gradient of 55 mm of Hg) was treated with implantation of Edwards XT valve in association with Dr Alain Cribier in the cath lab of Hospital Charles Nicolle, Rouen France in Nov 2011.

Because of co morbid condition of Bypass Surgery, mild

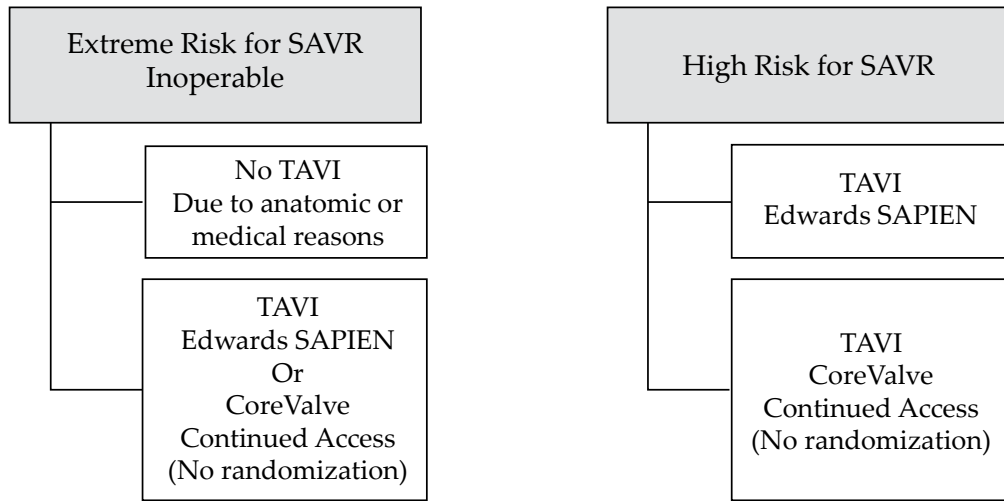


Fig. 2: Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic valve stenosis. Flow chart shows how patients are allocated for TAVI at the Texas Heart Institute, Heart Valve Center

Nephropathy and respiratory disease patient was refused by cardiac surgeons in Delhi for surgical Aortic Valve replacement. Patient was evaluated with us in Delhi with MR / angio to know the size of annulus and also to assess the size of femorals and external iliac arteries.

Patient was flown to France and treated with TAVI under conscious sedation. The procedure time was 40 minutes with minimalist environment. The peak gradient was reduced to 25 and mean gradient of 10 mm of Hg. The patient had trivial AR. The patient was discharged on day third. It has been 5 years now and the patient is doing well. Recent 2 D echo had similar findings 5 years follow up of First Edwards valve treatment in France done in Nov 2011.



THE MEDTRONIC COREVALVE® SYSTEM

The CoreValve® (Medtronic, Inc.; Minneapolis, Minn) is a porcine pericardial tissue valve that is sutured into a self-expanding nitinol frame, which is designed for supra-annular positioning to optimize hemodynamics (Figure 1C). The system uses an 18F catheter delivery system and has 3 valve sizes (26, 29, and 31 mm). In the United States, the CoreValve system is limited to investigational use. The CoreValve PIVOTAL study is currently examining its use in patients who are at high risk or ineligible for

surgical repair (randomized vs TAVI). Enrollment has been completed, and event-driven follow-up is ongoing. Nevertheless, the CoreValve Continued Access and Expanded Use trials have also been launched and are evaluating TAVI in patients whose conditions would have excluded them from randomized trials.

The Medtronic CoreValve ADVANCE Study is one of the largest multicenter transcatheter valve trials to date¹¹; the study group comprises 1,015 patients (mean age, 81 yr) who were consecutively treated at 44 experienced TAVI centers in 12 countries. Clinical endpoints in the trial were calculated according to definitions standardized by the Valve Academic Research Consortium.¹² In the ADVANCE trial, the survival rates were high at both 30 days (95.5%) and 6 months (87.2%). The procedural success rate was 97.8%, and overall complication rates were low: stroke rates of 2.9% and major adverse cardiac and cerebrovascular events (MACCE) rates of 8.3% at 30 days. Valve function improved significantly in the study patients; the mean gradient decreased from 45.6 mmHg at baseline to 9.3 mmHg at 30 days.

The 1-year mortality rates seen in ADVANCE¹³ compare favorably with the 24.2% 1-year all-cause mortality rate in TAVI patients in the PARTNER trial (cohort A). They are also similar to the 1-year results of the SAPIEN valve from the SOURCE registry, in which the 1-year survival rate was 76.1% in the overall cohort (although the survival rate was higher in the transfemoral subgroup, at 81.1%).¹³

Since 2012, a successful TAVI program has been in effect at the Texas Heart Institute at St. Luke's Episcopal Hospital. In a collaborative effort between cardiologists and cardiovascular surgeons, both the SAPIEN and CoreValve protocols are available for patients, in accordance with their anatomy, annular size, and best routes of access (for example, transfemoral, transapical, and direct aortic) (Figure 2).

Table 1: The Hype and the Hope

Hype for TAVI	Hope for TAVI
Used for all patients	Better risk stratification
Used in moderate-to low-risk patients	Expanded access
As safe as or safer than surgical replacement	New, smaller, safer devices
Improves outcomes for all	Cost-effective

TAVI=transcatheter aortic valve implantation

FUNDAMENTAL MESSAGES, SUMMARY, AND UNSOLVED ISSUES

Currently, the only proven, long-term effective treatment for patients with severe symptomatic aortic stenosis is surgical valve replacement. However, many patients with severe symptomatic aortic stenosis remain untreated, often because of the operative and perioperative risks associated with surgical repair. This group of 30% to 60% of patients with untreated aortic stenosis has a high mortality rate and needs to be served by the medical community. The use of a multidisciplinary team of cardiologists, cardiovascular surgeons, and supporting groups (for example, imaging specialists, neurologists, geriatricians, social workers, and rehabilitation specialists) benefits patients and has enabled TAVI to become the standard of care for inoperable patients with severe aortic stenosis. The available results indicate that TAVI is an acceptable alternative to surgery in selected high-risk patients. Future randomized studies should focus on lower-risk patients who are candidates for operation.

Vascular-access complications associated with TAVI are expected to decrease as the design and performance of new devices improve. A major complication of the TAVI procedure is stroke; common causes include balloon valvuloplasty, the passage of stiff catheters through an often-calcified aortic arch, the positioning and implantation of the valve itself, and postdilation (if used). In more recent studies,¹⁴ the incidence of stroke is lower than it was in previous reports, probably because of the use of more flexible and smaller delivery systems. The CoreValve can be implanted without prior valvuloplasty, and that alone might reduce the rate of embolization. Embolization-protection devices and deflectors that can redirect emboli from the arch downstream are being developed and evaluated, but no data support the clinical benefit of these devices.

The clinical durability of the valves used for TAVI is unknown. In preclinical fatigue tests, the transcatheter valves have shown the same excellent performance as standard biological valves; this applies both to the leaflets and to the stents. The structural failure rate of the current generation of transcatheter valves in clinical trials is very low. Long-term follow-up data are of course lacking.

Finally, another controversial issue is the use of TAVI in a younger, lower-risk population. In many centers, TAVI has become a routine procedure, and the results

of recent trials show improved outcomes and safety of the approach.¹⁵ However, the incidence of paravalvular leak and stroke, and the unknown durability factor are lingering concerns. On the basis of the data from the studies described above, trials in younger, lower-risk patients are justified. For now, the 2012 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines for Heart Valve Disease clearly restrict the indication for TAVI to a high-risk population, as do the U.S. Food and Drug Administration-approved guidelines.

As we learn more about the issues and challenges of TAVI, we hope to have available a better risk stratification for TAVI procedures and to identify the populations that benefit (Table 1). We also hope that access to TAVI will improve as smaller and safer devices become available, but TAVI must continue to be cost-effective. We should be cautious in our hype regarding the use of TAVI and not apply it prematurely to other patient groups; and we should be realistic about the risks associated with the procedure (Table 1).

REFERENCES

1. Charlson E, Legedza AT, Hamel MB. Decision-making and outcomes in severe symptomatic aortic stenosis. *J Heart Valve Dis* 2006; 15:312–21 [PubMed].
2. Schwarz F, Baumann P, Manthey J, Hoffmann M, Schuler G, Mehmel HC, et al. The effect of aortic valve replacement on survival. *Circulation* 1982; 66:1105–10 [PubMed].
3. Varadarajan P, Kapoor N, Bansal RC, Pai RG. Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: results from a cohort of 277 patients aged > or =80 years. *Eur J Cardiothorac Surg* 2006; 30:722–7 [PubMed].
4. Jin HK, Yang RH, Chen YF, Thornton RM, Jackson RM, Oparil S. Hemodynamic effects of arginine vasopressin in rats adapted to chronic hypoxia. *J Appl Physiol* 1989; 66:151–60 [PubMed].
5. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation* 2002; 106:3006–8 [PubMed].
6. Paniagua D, Condado JA, Besso J, Velez M, Burger B, Bibbo S, et al. First human case of retrograde transcatheter implantation of an aortic valve prosthesis. *Tex Heart Inst J* 2005; 32: 393–8 [PMC free article] [PubMed].
7. Makkar RR, Fontana GP, Jilalawi H, Kapadia S, Pichard AD, Douglas PS, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med* 2012; 366:1696–704 [PubMed].
8. Reynolds MR, Magnuson EA, Wang K, Lei Y, Vilain K, Walczak J, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the placement of aortic transcatheter valves (PARTNER) trial (Cohort B). *Circulation* 2012; 125:1102–9 [PubMed].
9. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012; 366:1686–95 [PubMed].

10. Reynolds MR, Magnuson EA, Wang K, Thourani VH, Williams M, Zajarias A, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial (Cohort A). *J Am Coll Cardiol* 2012; 60:548–58 [PubMed].
11. Bosmans J, Gerckens U, Wenaweser P, Tamburino C, Brecker S, Bauernschmitt R, Linke A. TCT-814 Health related quality of life following transcatheter aortic valve implantation: results from the CoreValve ADVANCE study. *J Am Coll Cardiol* 2012; 60(17_S):B236.
12. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *J Am Coll Cardiol* 2011; 57:253–69 [PubMed].
13. Linke A. The ADVANCE TAVR registry. In: Proceedings of the TCT 2012; Miami, Florida: 2012.
14. Humphries KH, Toggweiler S, Rodes-Cabau J, Nombela-Franco L, Dumont E, Wood DA, et al. Sex differences in mortality after transcatheter aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol* 2012; 60:882–6. [PubMed].
15. Chieffo A, Buchanan GL, Van Mieghem NM, Tchetché D, Dumonteil N, Latib A, et al. Transcatheter aortic valve implantation with the Edwards SAPIEN versus the Medtronic CoreValve Revalving system devices: a multicenter collaborative study: the PRAGMATIC Plus Initiative (Pooled-Rotterdam-Milano-Toulouse In Collaboration). *J Am Coll Cardiol* 2013; 61:830–6. [PubMed].