Transcatheter Aortic Valve Implantation - New Trials, Newer Horizons

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Introduction

More than a decade and several thousands of procedures in over 40 nations, transcatheter aortic valve implantation (TAVI) in patients with severe aortic stenosis (AS) still awaits general acceptance. The reasons for the "guarded" acceptance are simple. While surgical aortic valve replacement (SAVR) confers definite functional and survival benefits proven in numerous trials over decades, similar numerical data in TAVI is lacking. Understandably it is because of ethical issues concerning trial designs and the lack of expertise of the high-risk interventional procedure. While most data have been obtained from registries (FRANCE, SOURCE, UK Tavi registry, etc.) with their inherent limitations, recent trials (PARTNER) prove the feasibility and safety issues in "high-risk" and "inoperable cases" of severe AS.

While experience with the SAPIEN and CORE valve has grown, newer devices (Lotus valve, Acurate, Portico, Jena Clip, direct flow valve) await their turn. It is in this setting, questions regarding patient selection ahead of technical considerations have been raised. While the complications of SAVR and TAVI have been compared and speaks favorably for TAVI (albeit in high-risk and inoperable setting), the expertise is still limited to a few centers. Therefore it is in the interest of scientific community that trials such as PARTNER would have a positive effect in patient randomization for future trials.

PARTNER (Placement of Aortic Transcatheter Valves)

The PARTNER trial was a multicenter, randomized clinical trial comparing TAVI with standard therapy in patients with severe AS considered inoperable (PARTNER 1b); and TAVI with SAVR in surgical high-risk patients of severe AS (PARTNER 1a). Severe AS was defined as aortic valve area of less than 0.8 cm^2, a mean aortic valve gradient of 40 mmHg or more, or a jet velocity of ≥4.0 m/sec. All patients were in NYHA class 2, 3, or 4 symptoms. High surgical risk was defined by a Society of Thoracic Surgeons score (STS) of ≥10% or by the presence of coexisting conditions that would be associated with a predicted risk of death by 30 days after surgery of 15% or higher. Candidates were not considered suitable for surgery if they had coexisting conditions that would be associated with probability of ≥50% of either death by 30 days after surgery or a serious irreversible condition. A candidate was considered not suitable for surgery only when agreed upon by two surgeon investigators. Exclusion criteria are discussed in Table 1.

Table 1.

Exclusion criteria

Bicuspid or noncalcified aortic valve
Acute myocardial infarction
Coronary artery disease requiring revascularization
Left ventricular ejection fraction of <20%
Aortic annulus diameter <18 mm or >25 mm
Severe (>3+) mitral or aortic regurgitation
Transient ischemic attack or stroke within the previous 6 months
Severe renal insufficiency

The Edwards SAPIEN heart valve consists of a trileaflet bovine pericardial valve and a balloon-expandable, stainless steel frame. A balloon aortic valvuloplasty (BAV) was performed followed by transfemoral insertion of either a 22 or 24 F sheath depending on the selected size of the valve (23 or 26 mm). The bioprosthetic heart valve crimped onto a balloon catheter was advanced across the native aortic valve. During rapid right ventricular pacing, the bioprosthetic valve was deployed by balloon inflation. Heparin was administered during

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the procedure and dual antiplatelet therapy (aspirin and clopidogrel) for 6 months after the procedure. The trial was funded by Edwards Lifesciences

(PARTNER 1b).

TAVI for AS in Patients who cannot Undergo Surgery

Leon MB, Smith CR, Mack M, et al; PARTNER Trial Investigators Trascatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. NEJM. 2010; 363:1597–607.

Trial Summary

A total of 358 patients with severe AS who were considered inoperable were enrolled in 21 centers and were randomly assigned to TAVI (n=179) or standard therapy (n=179) (standard therapy included medical therapy and BAV). All patients were followed for at least 1 year (median follow-up 1.6 years; maximum, 2.8 years). The baseline characteristics were well matched and the mean age of patients in both the groups was 83 years.

The primary end point was the rate of death from any cause over the duration of trial (at least 1 year). Crossover from standard therapy to TAVI group was not permitted. The rate of a hierarchical composite of time to death from any cause or the time to first occurrence of repeat hospitalization due to valve-related or procedure-related clinical deterioration was the coprimary end point. Prespecified secondary end points included the rates of cardiovascular deaths, NYHA class, rate of repeat hospitalization due to valve- or procedure-related problems, distance covered during 6-minute walk test, valve performance, myocardial infarction, stroke, acute kidney injury, bleeding and vascular complications.

Results

Rates of death, stroke and repeat hospitalization

At 30 days, the rate of death from any cause was not significantly different between the groups (5% TAVI vs. 2.8% standard therapy). At 1-year follow-up, the rate of death from any cause was 30.7% in the TAVI group as compared to 50.7% in the standard-therapy group (p<0.001). The superiority of TAVI with respect to the coprimary end point was confirmed (p<0.001). The rate of the nonhierarchical composite of death from any cause or repeat hospitalization at 1-year follow-up was significantly less in TAVI as compared to standard therapy (42.5% vs. 71.6%, p<0.001).

Major strokes although not of statistical significance were more frequent with TAVI at 30 days (5.0% vs. 1.1%) and 1 year (7.8% vs. 3.9%). Nevertheless, the rate of the composite of major stroke or death from any cause was significantly lower in the TAVI group than in the standard therapy group at 1 year (33.0% vs. 51.3%, p<0.001).

Procedural outcomes

The details have been discussed in Table 2.

Table 2.

Procedural outcomes

■ Patients assigned to TAVI (n=179)
• TAVI not done (n=6)
◊ 2 died before procedure
◊ 2 large annulus detected during procedure
◊ 2 unsuccessful transfemoral access
• First 24 hours of TAVI
◊ 2 died (1.1%)
◊ 3 major strokes (1.7%)
◊ 1 valve embolism (0.6%)
◊ 2 multiple (≥2) valve implantation (1.1%)
◊ None underwent cardiac surgery to manage complications
■ Patients assigned to standard therapy (n=179)
◊ 114 patients underwent BAV (63.7%) within30 days of randomization
◊ 36 underwent BAV (20.1%) after 30 days of randomization
◊ 12 underwent SAVR (6.7%) (1-year death rate 33%)
◊ 5 underwent placement of a conduit from left ventricular apex to descending aorta plus SAVR (2.8%) (1-year death rate 80%)
◊ 4 underwent TAVI (2.2%) in a nonparticipating center (1-year deaths 0%)

Other clinical outcomes

At 30 days and 1 year, the major vascular complications (16.2% vs. 1.1% and 16.8% vs. 2.2%) and bleeding (16.8% vs. 3.9% and 22.3% vs. 11.2%) were more frequent in the TAVI group than in the standard therapy group. A significant reduction in symptoms was demonstrated at 30 days, 6 months and 1 year in the

TAVI group (p<0.001). At 1 year among survivors, a significant number of patients had become asymptomatic or had mild symptoms (NYHA class 1 or 2). Due to the presence of coexisting conditions, the 6-minute walk test could be performed in only a subgroup of patients.

Echocardiographic findings

A significant increase in aortic valve area along with a significant decrease in mean aortic valve gradient was demonstrated at 30 days in patients who underwent TAVI. The improved valve hemodynamics was maintained at 1 year. In patients who underwent TAVI, moderate or severe paravalvular aortic regurgitation was present in 11.8% at 30 days and 10.5% at 1 year. No substantial change in the severity of paravalvular regurgitation was seen at 1-year follow-up. The incidence of moderate or severe transvalvular regurgitation was 1.3% at 30 days and 4.2% at 1 year among patients in the TAVI group. Three patients in the TAVI group had to undergo a repeat TAVI due to significant paravalvular regurgitation in two and transvalvular regurgitation in one patient.

Limitations

1. The protocol excluded patients requiring treatment of coronary stenosis and patients with severe peripheral vascular disease.
2. The durability and long-term clinical safety of the bioprosthetic valve would require long-term follow-up.
3. At the time of the trial, TAVI was new in the USA. Therefore the experience of the interventionists is questionable. Besides the study used an earlier generation delivery system that was more likely to cause complications.
4. The protocol was violated as a few patients in the standard therapy group (considered inoperable) did undergo aortic valve replacement.

Conclusion

In patients with severe AS who were not suitable for surgery, TAVI significantly reduced the rates of death from any cause, the composite end point of death from any cause or repeat hospitalization and cardiac symptoms despite higher incidence of major strokes and vascular events as compared to standard therapy (PARTNER 1a).

Transcatheter versus SAVR in High-risk Patients

Smith CR, Leon MB, Mack M, et al; PARTNER Trial Investigators. Transcatheter versus surgical aortic – valve replacement in high risk patients. NEJM. 2011; 364:2187–98.

Trial Summary

A total of 699 patients with severe AS and cardiac symptoms (NYHA class 2 or worse) were enrolled at 25 centers (22 USA, 2 Canada, 1 Germany). Only those patients who were at high risk for operative complications and death were selected. The SAPIEN valve was implanted by transfemoral or transapical route in patients assigned to TAVI group. Patients were randomly assigned to undergo either TAVI (348 patients) or SAVR (351 patients). In the TAVI group, 244 were assigned to undergo transfemoral placement and 104 were assigned to undergo transapical placement. The primary end point was the rate of death from any cause at 1 year. The primary hypothesis was that the TAVI was not inferior to SAVR.

Results

The baseline characteristics including the mean age in the TAVI (83.6 years) and SAVR groups (84.5 years) were similar. Among 699 patients who were assigned to a study group, 42 did not undergo the procedure (4 in TAVI group; 38 in SAVR group).

Mortality

In the intention-to-treat analysis, the rates of death from any cause at 30 days were 3.4% in the TAVI and 6.5% in SAVR group (p= 0, NS). In the AS-treated analysis the rates of death were similar at 30 days (5.2% TAVI vs. 8% SAVR, p=NS). At 30 days, higher rates of death were observed among patients who had undergone transapical placement in the TAVI group. At 1 year, the rate of death from any cause in the intention-to-treat population was 24.2% in the TAVI group as compared to 26.8% in the SAVR group (p=NS) (p=0.001 for noninferiority). According to the STS risk model, the expected 30-day rate of death in the SAVR group (11.8%) was higher than the actual rate of death (8%) suggesting good operative results.

Stroke

Although statistically nonsignificant, the rates of all neurological events were higher in the TAVI group than in the SAVR group at 30 days (5.5% vs. 2.4%) and at 1 year (8.3% vs. 4.3%). Rate of major stroke was not significantly different between the groups at 30 days and 1 year.

Other clinical outcomes

Higher rates of major vascular complications were seen in the TAVI group at 30 days (11% vs. 3.2%). The rate of major bleeding (9.3% vs. 19.5%) and new onset atrial fibrillation (8.6% vs. 16%) was lower in the TAVI group as compared to the SAVR group. A significant reduction in symptoms was seen in the TAVI group at 30 days, which failed to show any statistical significance at 1 year. Patients in the TAVI group had a shorter hospital stay.

Procedural outcomes

Four patients died during the procedure (3 in TAVI, 1 in SAVR). In 16 out of 348 patients (4.6%), TAVI was either aborted or converted to SAVR. Among these 16 patients, 9 immediately underwent SAVR (includes 1 death), 2 underwent surgery 30 days later, and 5 did not undergo either of the procedure (includes 3 deaths). Multiple transcatheter valves (≥2) were implanted in 7 patients (valve embolism 2, residual regurgitation 5) of which 3 died.

Echocardiographic findings

A significant improvement in the aortic valve gradients and area were observed in either of the groups at 30 days and 1 year. However, moderate or severe paravalvular regurgitation was more frequent in the TAVI group at 30 days (12.25 vs. 0.9%, $p<0.001$) and at 1 year (6.8% vs. 1.9%, $p<0.001$).

Limitations

1. Frequent withdrawals and decision to forego the procedure in the SAVR group hinders a balanced perspective in the early outcomes of the two procedures.
2. Durability of the bioprosthetic valve in TAVI awaits longer follow-up.
3. An early generation of the transcatheter device was used.
4. The study had insufficient statistical power to reach strong conclusions with respect to specific subgroups.

Conclusion

Patients with severe AS who are at high surgical risk were associated with similar mortality and improvement in cardiac symptoms at 30 days and 1 year by either TAVI or SAVR. Hence TAVI is an alternative to SAVR in a well chosen, high-risk subgroup of patients with severe AS at the cost of a higher risk of neurological events and vascular complications.

Two-year Outcomes after Transcatheter or SAVR

Kodah SK, Williams MR, Smith CR, et al; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. NEJM. 2012; 366:1686–95.

Trial Summary

Methods

All patients in PARTNER trial (high-risk severe AS) were followed for at least 2 years. They were assessed for clinical outcomes and echocardiographic evaluation.

Results

Between 1 and 2 years, there were 32 additional deaths in the TAVI and 25 in the SAVR group. At 2 years, there were no significant differences in mortality from any cause and mortality from cardiovascular cause between the groups. Between 1 and 2 years, 8 strokes (4 in TAVI and 4 in SAVR groups) and 4 transient ischemic attacks (2 in TAVI and 1 SAVR group) occurred. The frequency of all neurological events at 2 years was higher with TAVI than with the SAVR group (11.2% vs. 6.5%, $p=0.005$). There were no significant differences in the number of overall strokes between the groups. The composite of the rate of death from any cause or stroke did not differ significantly between the two groups.

Major vascular complications and bleeding events after 1 year were uncommon and did not differ significantly between the groups. Endocarditis was rare and occurred at a similar rate in the two groups. No patient required surgical replacement of valve due to structural deterioration during follow-up. At 2 years, there was no significant difference in the rate of repeat hospitalization between the groups. The mean NYHA class at 2 years

was similar and the majority had class 1 or 2 status (83.9% in TAVI vs. 85.2% SAVR).

At echocardiography, the significantly improved valvular hemodynamics was unchanged and similar between the groups. However, moderate or severe paravalvular aortic regurgitation was more common after TAVI at 1 and 2 years (7% vs. 1.9% at 1 year and 6.9% vs. 0.9% at 2 years, $p<0.001$). The effect of aortic regurgitation, even if mild, was associated with increased late mortality and proportional to the severity of regurgitation.

Conclusion

The 2-year follow-up of patients in this trial supports the use of TAVI as an alternative to surgery in selected high-risk patients with severe AS. The two treatment arms were similar in mortality, reduction in cardiac symptoms and improved valve dynamics. Initial increase in the risk of stroke with TAVI attenuated over time. The observation that paravalvular aortic regurgitation is associated with late mortality requires technical considerations with respect to valve designs.

Perspective

The PARTNER trial has demonstrated the feasibility of TAVI in highly selected group of patients with severe AS at the cost of increased neurological and vascular events. Its role in specific patient subgroups needs to be evaluated. The incidence of paravalvular aortic regurgitation and its relationship to mortality demands superior valve designs.