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Disclosure Statement

Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis

Published online in The Lancet on April 3, 2016

This article discusses a clinical study of Edwards Lifesciences' SAPIEN 3 transcatheter heart valve. The PARTNER II S3i study was sponsored by Edwards in support of the FDA approval of the use of the SAPIEN 3 valve for transcatheter aortic valve replacement (TAVR) in intermediate-risk patients.

Some of the authors have a consulting or other financial relationship with Edwards and are compensated in excess of the amount set forth in 21 U.S.C. §54.2, for services including training and proctoring of physicians in the safe and effective use of Edwards' products, speaking engagements, advice on product development, and similar activities. This includes Drs. Herrmann, Lim, Webb, and Whisenant.

Edwards is not aware of publications reaching conclusions different from those described in this article.

Also enclosed is the approved Instructions for Use for the SAPIEN 3 valve.

Edwards Lifesciences v. Boston Scientific Scimed
IPR2017-01293 U.S. Patent 8,992,608
Exhibit 2003

Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis

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Summary

Background Transcatheter aortic valve replacement (TAVR) with the SAPIEN 3 valve demonstrates good 30 day clinical outcomes in patients with severe aortic stenosis who are at intermediate risk of surgical mortality. Here we report longer-term data in intermediate-risk patients given SAPIEN 3 TAVR and compare outcomes to those of intermediate-risk patients given surgical aortic valve replacement.

Methods In the SAPIEN 3 observational study, 1077 intermediate-risk patients at 51 sites in the USA and Canada were assigned to receive TAVR with the SAPIEN 3 valve [952 [88%] via transfemoral access) between Feb 17, 2014, and Sept 3, 2014. In this population we assessed all-cause mortality and incidence of strokes, re-intervention, and aortic valve regurgitation at 1 year after implantation. Then we compared 1 year outcomes in this population with those for intermediate-risk patients treated with surgical valve replacement in the PARTNER 2A trial between Dec 23, 2011, and Nov 6, 2013, using a prespecified propensity score analysis to account for between-trial differences in baseline characteristics. The clinical events committee and echocardiographic core laboratory methods were the same for both studies. The primary endpoint was the composite of death from any cause, all strokes, and incidence of moderate or severe aortic regurgitation. We did non-inferiority (margin 7·5%) and superiority analyses in propensity score quintiles to calculate pooled weighted proportion differences for outcomes.

Findings At 1 year follow-up of the SAPIEN 3 observational study, 79 of 1077 patients who initiated the TAVR procedure had died (all-cause mortality 7·4%; 6·5% in the transfemoral access subgroup), and disabling strokes had occurred in 24 (2%), aortic valve re-intervention in six (1%), and moderate or severe paravalvular regurgitation in 13 (2%). In the propensity-score analysis we included 963 patients treated with SAPIEN 3 TAVR and 747 with surgical valve replacement. For the primary composite endpoint of mortality, strokes, and moderate or severe aortic regurgitation, TAVR was both non-inferior (pooled weighted proportion difference of –9·2%; 90% CI –12·4 to –6; p<0·0001) and superior (–9·2%, 95% CI –13·0 to –5·4; p<0·0001) to surgical valve replacement.

Interpretation TAVR with SAPIEN 3 in intermediate-risk patients with severe aortic stenosis is associated with low mortality, strokes, and regurgitation at 1 year. The propensity score analysis indicates a significant superiority for our composite outcome with TAVR compared with surgery, suggesting that TAVR might be the preferred treatment alternative in intermediate-risk patients.

Funding None.

Published **Online**
April 3, 2016
http://dx.doi.org/10.1016/S0140-6736(16)30073-3

See **Online/Comment**
http://dx.doi.org/10.1016/S0140-6736(16)30122-2

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Introduction

Transcatheter aortic valve replacement (TAVR) is established for treatment of severe symptomatic aortic stenosis in patients deemed to be at high risk of surgical mortality or who are not suitable for surgery.[1,2] The encouraging clinical outcomes with earlier-generation TAVR systems in cohorts of high-risk patients,[3–8] as well as rapid device refinements that led to improved clinical outcomes,[9–11] have generated interest in use of these devices in intermediate-risk patients. A 2015 report from an observational study using the latest-generation SAPIEN 3 TAVR system (Edwards Lifesciences, Irvine, CA, USA) indicated good 30 day outcomes in both high-incidence of disabling strokes in intermediate-risk patients were both about 1% and moderate or severe paravalvular regurgitation was recorded in about 4%. The SAPIEN 3 valve system differs from previous versions through the following factors: improved geometry of the trileaflet bovine pericardial valve; different cobalt alloy frame, which is longer than the early version of the balloon-expandable valve system (SAPIEN XT valve; Edwards Lifesciences) with more open outlet cells and denser inlet cells; a polyethylene terephthalate fabric skirt sewn to the bottom portion of the interior and exterior of the frame (providing an external circumferential seal to reduce paravalvular leak); four valve sizes (20 mm,

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Research in context

Evidence before this study

Before we did the PARTNER 2A and SAPIEN 3 studies, clinical trial evidence comparing transcatheter aortic valve replacement (TAVR) to surgery was mainly limited to patients at high risk of death during surgery. Data from large national registries have now indicated a global trend towards TAVR being used in lower-risk populations despite little rigorous clinical trial evidence for this practice. We searched MEDLINE on Jan 31, 2016, with the terms "transcatheter aortic valve implantation", "transcatheter aortic valve implantation in low risk patients", "transcatheter aortic valve implantation in intermediate risk patients", "transcatheter aortic valve replacement in low risk patients", "transcatheter aortic valve replacement in intermediate risk patients", "surgical aortic valve replacement", and "surgical aortic valve replacement in intermediate risk patients" in English with no date limitations. The published studies include a small randomised trial and several non-adjudicated comparisons between TAVR and surgery in intermediate-risk patients. These studies did not use neurologists for stroke assessment, a clinical events committee to adjudicate outcomes, or core laboratories for analysis of imaging studies.

Added value of this study

We show TAVR with SAPIEN 3 to be superior to surgery at 1 year follow-up with lower rates of all-cause mortality, stroke, and the composite endpoint of mortality, stroke, and moderate or severe aortic regurgitation, but higher rates or moderate or severe regurgitation. Our analysis is the first rigorously designed and carried out clinical study to compare TAVR with the SAPIEN 3 device with surgery in intermediate-risk patients. The prespecified propensity analysis allows for meaningful comparisons between the two groups.

Implications of all the available evidence

TAVR should be considered as the preferred alternative to surgery in intermediate-risk patients and future should consider expanding the indications for TAVR.

delivery catheters with more precise valve positioning inserted through 14 or 16 French expandable sheaths for transfemoral access.

Here we aimed to report 1 year outcomes with SAPIEN 3 TAVR in intermediate-risk patients from this observational study and then use a prespecified propensity score analysis to compare these outcomes with those for similar patients given surgical aortic valve replacement in the PARTNER 2A randomised trial.

Methods

Study design and participants

In this analysis we used populations from the PARTNER 2 SAPIEN 3 intermediate risk observational study[10] and the PARTNER 2A randomised trial (NCT01314313).[12] These two prospective multicentre studies enrolled patients with symptomatic severe aortic stenosis who were considered to be at intermediate risk for 30 day surgical mortality. Risk status was evaluated by a Heart Team that included cardiac surgeons. Patients were deemed intermediate risk via clinical assessment or if their Society of Thoracic Surgeons (STS) score was 4% or higher. In those with an STS score lower than 4%, the Heart Team deemed the patient intermediate risk if they had risk factors not present within the predictive score (eg, liver disease, frailty, and pulmonary hypertension).

In PARTNER 2A, patients were randomly assigned to receive either surgical valve replacement or TAVR using SAPIEN XT; here we analyse only the patients assigned to surgery.[12] In the SAPIEN 3 study, all TAVR patients who were eligible to receive a valve had mandated multidetector computed tomography (MDCT) analysed by the study core laboratory and were presented on a imaging and clinical data and approved patients prior to enrolment.

Inclusion and exclusion criteria for SAPIEN 3[10] and PARTNER 2A[12] were the same. Key exclusion criteria were a congenitally bicuspid aortic valve, severe aortic regurgitation, left ventricular ejection fraction lower than 20%, severe renal insufficiency, and estimated life expectancy of less than 2 years. Patients with non-complex coronary disease requiring revascularisation could be enrolled if a treatment plan for the coronary disease (medical therapy or revascularisation) was agreed on before enrolment. Both trials were approved by the institutional review boards of each participating site and written informed consent was provided by all patients.

Procedures

Preprocedural valve sizing for TAVR was determined through MDCT or 3D transoesophageal echocardiography. Access was via transfemoral, transapical, or transaortic routes, depending on preprocedural peripheral vascular assessments. Postoperative dual antiplatelet therapy with aspirin and clopidogrel was recommended for at least 1 month, at the Heart Team's discretion. Warfarin was also recommended in patients with atrial fibrillation, based on patient tolerance.

The co-principal investigators and other members of the executive committee had access to the data after the database was locked and prepared the manuscript. The same executive committee was used for both trials and attest to the completeness and accuracy of the data and adherence of the studies to the protocol. All echocardiograms in patients given TAVR were analysed independently by a consortium of echocardiography

regurgitation was based on an expanded and more granular classification scheme, which was then reduced to the standard classification scheme.[13] Clinical events were independently adjudicated by a clinical events committee and neurologists examined all patients to ascertain any changes in neurological status after the procedures. The clinical events committee and echocardiographic core laboratory methods were the same for both studies. Clinical outcomes were reported as defined by Valve Academic Research Consortium (VARC)-2 definitions.[14]

Statistical analysis

For our analysis of 1 year clinical outcomes after the SAPIEN 3 TAVR procedure we included only patients who initiated the procedure—ie, the as-treated population. Echocardiography outcomes are based on the valve-implanted cohort (ie, patients who received the valve as assigned and excluding those who did not complete or died during the procedure). For statistical comparisons between baseline, 30 day, and 1 year values we used McNemar's test.

In a prespecified analysis we used propensity score analysis methodology to compare outcomes from the SAPIEN 3 TAVR patient cohort with those of similar intermediate-risk patients in the surgical arm of the PARTNER 2A trial who received surgical valve replacement (appendix).[15,16] This analysis was done in the valve-implanted analysis population. The primary endpoint for the propensity score analysis was the 1 year non-hierarchical composite event of death from any cause, all strokes, and post-treatment aortic regurgitation (moderate or greater [severe]). Secondary endpoints included each of the individual components of the composite primary endpoint.

Propensity score methodology was used to reduce the confounding in the statistical comparison of outcomes of two treatment groups from the two different studies by accounting for differences in baseline patient characteristics. First, a logistic regression model was performed on the prespecified baseline characteristic variables to calculate the propensity score for each patient (appendix). Propensity scores represent the likelihood that the patient was in the TAVR arm. All patients with propensity scores were partitioned into five quintiles (1–5; patients in quintile 1 represent the lowest 20% of propensity scores while patients in quintile 5 represent the highest 20% of scores) based on their propensity scores. The variable balance was then assessed to confirm the adequacy of the propensity model. Within each quintile, patients in both groups had similar degrees of residual bias from randomness. An independent biostatistician blinded to the treatment groups and with no knowledge of the clinical outcome data carried out the propensity score analyses. The issue of missing baseline covariates was addressed using score model was finalised and propensity score and quintiles derived for the outcome analyses adjustments.

The analyses of the primary and secondary endpoints were based on the proportion difference between the two treatment groups, and were done as a non-inferiority analysis with designated non-inferiority margins. To estimate the overall treatment effect and confidence limits adjusted for the propensity score quintiles, we calculated the weighted proportion difference using the average treatment effect on the treated methods with weights derived based on the sample size of the SAPIEN 3 cohort within each quintile. If the upper bound of the two-sided 90% CI was 7·5% or lower (absolute margin), then non-inferiority was fulfilled. Superiority between the groups in this study was established if the upper bound of the two-sided 95% CI for the difference in proportion was lower than 0%.

Time-to-event Kaplan-Meier curves were constructed for mortality, stroke, and a composite of death and stroke at 1 year, using all available follow-up data in the as-treated population for both studies. All-cause mortality up to 1 year was plotted for patients who received TAVR, stratified by paravalvular regurgitation classification and

See Online for appendix

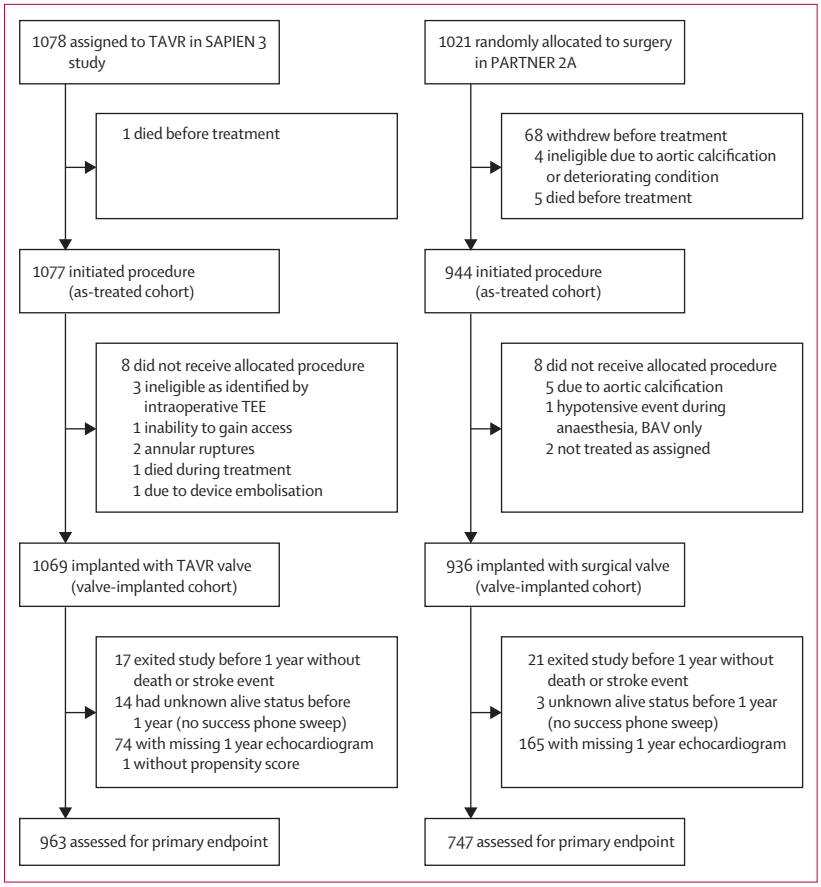

Figure 1: **Study profile**
TAVR=transcatheter aortic valve replacement, BAV=balloon aortic valvuloplasty, TEE=transoesophageal

with a log-rank p value calculated for differences between classes. The SAPIEN 3 observational study was nested within the PARTNER 2 trial, which was registered with ClinicalTrials.gov, number NCT01314313.

Role of the funding source

There was no funding source for this analysis; SAPIEN 3 and PARTNER 2A were sponsored by Edwards Lifesciences. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From Feb 17, 2014, to Sept 3, 2014, 1078 intermediate- risk patients were enrolled in the SAPIEN 3 observational study at 51 sites in the USA and Canada. One patient died before treatment, leaving 1077 patients in the as-treated analysis population (figure 1). From Dec 23, 2011, to Nov 6, 2013, 2032 intermediate-risk patients were enrolled in the PARTNER 2A randomised trial at 57 sites in the USA and Canada. 1021 patients were randomly allocated to surgery and 944 received surgical valve replacement (ie, the as-treated population; figure 1). The main reason for non-treatment in the surgery arm (85 patients) was withdrawal from the study, most commonly due to a decision not to have surgery after randomisation.

	TAVR population (n=1077)	Surgery population (n=944)	p value
Age (years)	81·9 (6·6)	81·6 (6·76)	0·23
Men	665 (62%)	519 (55%)	0·002
Body-mass index (kg/m²)	28·7 (6·1)	28·4 (6·2)	0·32
Society of Thoracic Surgeons score (%)	5·2 (4·3–6·3)	5·4 (4·4–6·7)	0·0002
NYHA class III or IV	781 (73%)	718/943 (76%)	0·07
Coronary artery disease	750 (70%)	628 (67%)	0·14
Previous myocardial infarction	172 (16%)	167 (18%)	0·31
Previous CABG	301 (28%)	243 (26%)	0·27
Previous PCI	344 (32%)	254 (27%)	0·01
Previous BAV	55 (5%)	45 (5%)	0·76
Cerebrovascular disease	97 (9%)	97 (10%)	0·36
Peripheral vascular disease	304 (28%)	304 (32%)	0·052
COPD			
Any	322/1075 (30%)	283/938 (30%)	0·92
Oxygen dependent	54/1070 (5%)	28/931 (3%)	0·02
Creatinine ≥177 μmol/L	81 (8%)	51 (5%)	0·058
Atrial fibrillation	388 (36%)	329 (35%)	0·61
Permanent pacemaker	142 (13%)	113 (12%)	0·42
Frail condition			
15 ft walk time >7 s	434/1050 (41%)	391/855 (46%)	0·057
Albumin <35 g/L	138/1056 (13%)	138/925 (15%)	0·24
Aortic valve area (cm²)	0·7 (0·17)	0·7 (0·20)	0·45
Mean gradient (mm Hg)	46·1 (12·6)	44·7 (12·6)	0·01
Left ventricular ejection fraction (%)	58·5 (13·4)	55·4 (11·8)	<0·0001
Left ventricular mass index (g/m²)	116·27 (33·5)	118·7 (32·2)	0·12
Moderate or severe mitral regurgitation	91/1033 (9%)	153/841 (18%)	<0·0001

Data are mean (SD), median (IQR), n (%), or n/N (%). TAVR=transcatheter aortic valve replacement. NYHA=New York Heart Association. CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention. BAV=balloon aortic valvuloplasty. COPD=chronic obstructive pulmonary disease.

Most baseline characteristics were similar between the SAPIEN 3 and the PARTNER 2A patient populations (table 1). Patients in the SAPIEN 3 group were more frequently male and had more frequent oxygen-dependent chronic obstructive pulmonary disease, whereas PARTNER 2A surgery patients had higher median STS scores, lower mean gradients and left ventricle ejection fractions, and had more frequent moderate or severe mitral regurgitation (table 1). The median postoperative length of hospital stay was shorter in the TAVR cohort than in the surgical cohort (4 days [range 1·0–122·0] *vs* 9 days [1·0–77·0]) and a higher percentage of patients went home after the procedure (912 [85%] *vs* 436 [46%]).

79 of the patients who received TAVR with SAPIEN 3 died within 1 year (all-cause mortality 7·4%; table 2). 61 (7%) patients died in the subset of 925 who had received transfemoral TAVR (appendix). 49 (5%) patients had a stroke, with nearly half having disabling strokes (table 2). At 1 year, 119 (11%) patients were rehospitalised for procedure-related or valve-related reasons, but both endocarditis and aortic valve re-interventions were rare (table 2). 132 (12%) had a new pacemaker permanently implanted. At 1 year after TAVR, cardiac symptoms had significantly improved, with 94% of patients in New York Heart Association function class I or II (appendix).

The improvements in mean aortic valve areas and gradients after TAVR seen at 30 days were maintained at 1 year (valve areas 1·7 cm² and gradient 11·4 mm Hg; appendix). On both a standard grading system and an extended grading system, moderate or greater paravalvular regurgitation at 1 year was noted only in 1·5% of patients after TAVR; 40% of patients had mild regurgitation on standard grading (appendix). In patients with no or trace paravalvular regurgitation at 30 days, mortality at 1 year was 4·5%, which was similar to those patients with mild paravalvular regurgitation (6·4%). However, in patients with moderate or severe paravalvular regurgitation, the 1 year mortality was significantly higher at 13·3% (log-rank p=0·0184; figure 2).

In each of the quintiles, patients undergoing TAVR had a lower incidence of the composite primary endpoint than did the group who received surgery (varying from –14·5% in quintile 1 to –4·3% in quintile 5; table 3). The non-inferiority analysis was based on the pooled weighted proportion difference of –9·2% (90% CI –12·4 to –6) favouring TAVR, which was below the 7·5% non-inferiority margin (p<0·0001).

TAVR was superior to surgery for the composite endpoint (weighted difference of proportions –9·2%, 95% CI –13·0 to –5·4; p<0·0001), and for the individual outcomes of death (–5·2%, –8·0 to –2·4; p= 0·0003) and

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