

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



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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.

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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

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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.⁴⁶ 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

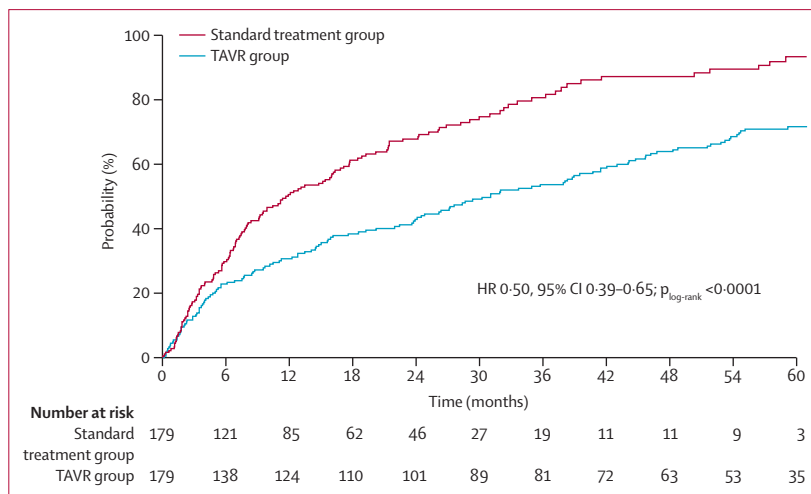


Figure 1: Kaplan-Meier analysis of all-cause mortality for the intention-to-treat population. TAVR=transcatheter aortic valve replacement. HR=hazard ratio.

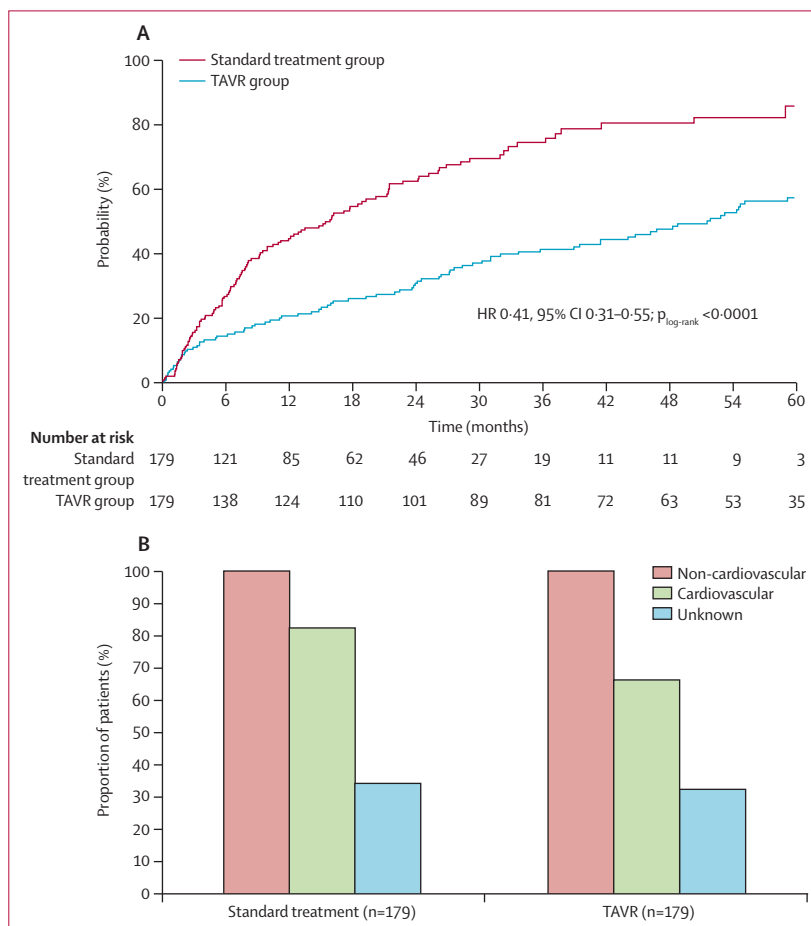


Figure 2: Cardiovascular mortality (A) and causes of death (B). TAVR=transcatheter aortic valve replacement. HR=hazard ratio.

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.

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 ($\geq 5\%$) 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

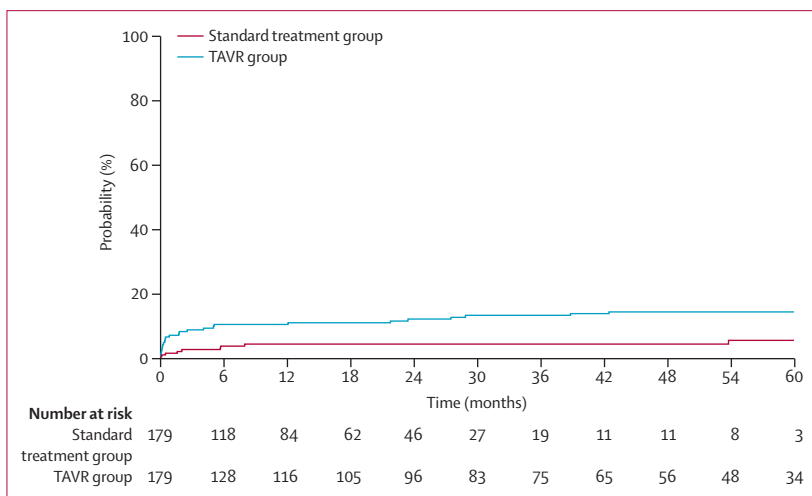


Figure 3: Risk of stroke as determined by competing risk analysis of stroke and mortality
TAVR=transcatheter aortic valve replacement.

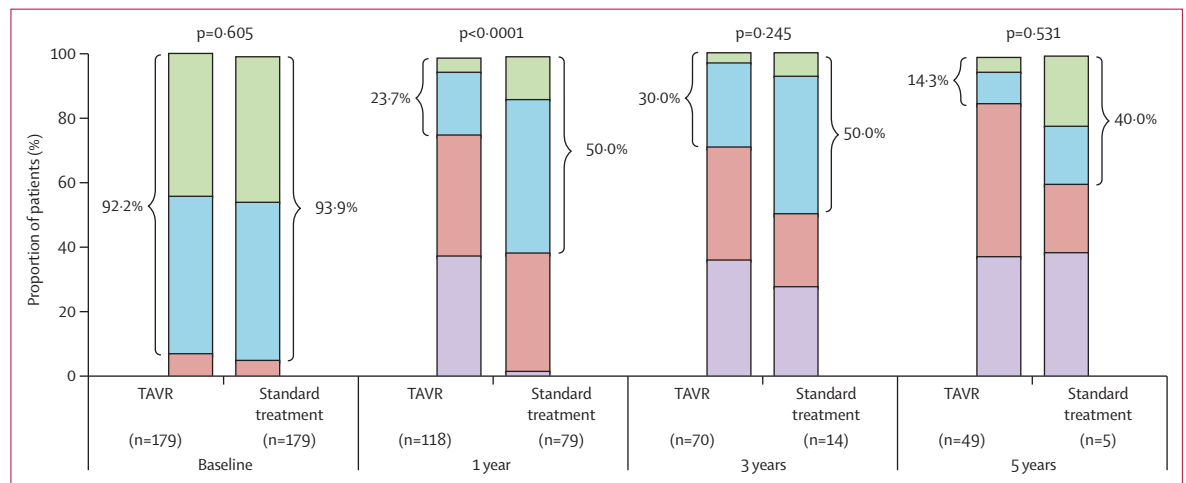


Figure 4: New York Heart Association functional class of the survivors
p values are for TAVR versus standard treatment for the full range of functional classes. TAVR=transcatheter aortic valve replacement.

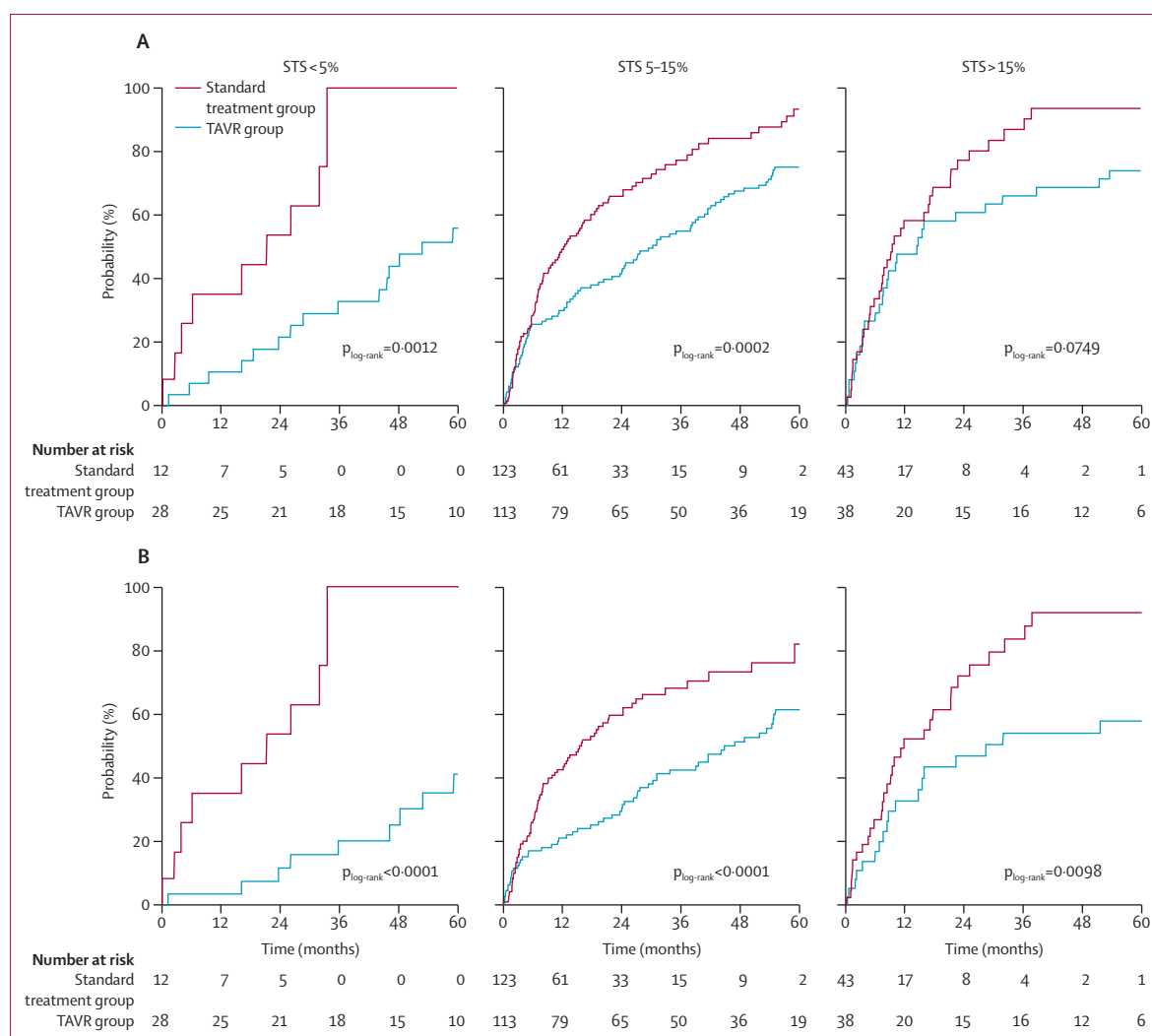


Figure 5: Mortality outcomes stratified by STS score

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 Administration 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. Reassuringly, 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 Posthox, 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

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