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

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Summary

Background **The Placement of Aortic Transcatheter Valves (PARTNER) trial showed that mortality at 1 year, 2 years, and 3 years is much the same with transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) for high-risk patients with aortic stenosis. We report here the 5-year outcomes.**

Methods **We did this randomised controlled trial at 25 hospitals, in Canada (two), Germany (one), and the USA (23). We used a computer-generated randomisation sequence to randomly assign high-risk patients with severe aortic stenosis to either SAVR or TAVR with a balloon-expandable bovine pericardial tissue valve by either a transfemoral or transapical approach. Patients and their treating physicians were not masked to treatment allocation. The primary outcome of the trial was all-cause mortality in the intention-to-treat population at 1 year, we present here predefined outcomes at 5 years. The study is registered with ClinicalTrials.gov, number NCT00530894.**

Findings **We screened 3105 patients, of whom 699 were enrolled (348 assigned to TAVR, 351 assigned to SAVR). Overall mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 11·7%. At 5 years, risk of death was 67·8% in the TAVR group compared with 62·4% in the SAVR group (hazard ratio 1·04, 95% CI 0·86–1·24; p=0·76). We recorded no structural valve deterioration requiring surgical valve replacement in either group. Moderate or severe aortic regurgitation occurred in 40 (14%) of 280 patients in the TAVR group and two (1%) of 228 in the SAVR group (p<0·0001), and was associated with increased 5-year risk of mortality in the TAVR group (72·4% for moderate or severe aortic regurgitation *vs* 56·6% for those with mild aortic regurgitation or less; p=0·003).**

Interpretation **Our findings show that TAVR as an alternative to surgery for patients with high surgical risk results in similar clinical outcomes.**

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Introduction

Transcatheter aortic valve replacement (TAVR) is an alternative to surgical valve replacement in high-risk patients with aortic stenosis.[1,2] The Placement of Aortic Transcatheter Valves (PARTNER) study is a randomised trial comparing TAVR with standard-of-care treatments in both inoperable and high surgical risk patients with aortic stenosis. 1-year mortality after TAVR was superior to standard non-operative treatment in patients who could not have surgery and was non-inferior to surgical aortic valve replacement (SAVR) in high-risk patients who could have surgery.[3,4] These findings were maintained at 2 years and 3 years.[5–7] This report describes the final 5-year clinical and valve performance outcomes for high-risk patients in the PARTNER-1 trial.

Methods

Study design and participants

Details of the trial have been previously published.[4] We did this randomised controlled trial at 25 hospitals: two in Canada, one in Germany, and 22 in the USA. Inclusion criteria were severe symptomatic aortic stenosis (aortic valve area ≤0·8 cm², and resting or inducible peak velocity ≥4 m/s or a mean valve gradient ≥40 mm Hg) and high-risk status for SAVR, as assessed by a heart team, which included experienced surgeons. Patients were considered to be at high surgical risk if they had coexisting conditions that were associated with a predicted risk of death of more than 15% at 30 days after the procedure. 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 computer. Patients were randomly assigned centrally to TAVR or SAVR and sites were informed of assignment after patients were enrolled. Those assigned to TAVR were treated by a transfemoral approach unless precluded by vascular access, in which case a transapical approach was used. Patients assigned to SAVR were stratified according to whether a transfemoral or transapical approach would have been used had they been assigned to TAVR

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Research in context

Systematic review

We searched Medline on Feb 25, 2015 with the terms "transcatheter aortic valve replacement", "transcatheter aortic valve implantation", and "surgical aortic valve replacement". The only multicentre, randomised trials published are the 1-year, 2-year, and 3-year outcomes of the PARTNER study as well as the 1-year outcomes of the CoreValve trial of transcatheter aortic valve replacement (TAVR) versus surgery. Multiple registries have published TAVR outcomes including the UK National Registry, the GARY Registry in Germany, the FRANCE II Registry, the SOURCE Registry of the Sapien valve, and the national STS ACC TVT Registry in the USA. All registries have reported early, or 1-year and 2-year outcomes. The only long-term data are from a single centre series over 6 years from Paris and a single centre series over 5 years from Vancouver.

Interpretation

The PARTNER I trial, with two parallel randomised cohorts of (1) TAVR versus surgical aortic valve replacement in high-risk operable patients with aortic stenosis and (2) TAVR versus medical treatment in inoperable patients, is the first and largest randomised trial of a first-of-a-kind medical device. This report is also the longest follow-up of any randomised trial and therefore adds substantially to the evidence about TAVR. The study shows that death and stroke are much the same for each treatment at 5 years. However, the higher incidence of paravalvular leak associated with TAVR, even when only mild, is associated with higher mortality. This trial was the first study of this first generation device in most clinical study centres. Present devices are second and third generation, with smaller delivery systems and designed to prevent paravalvular leak. Thus, outcomes of TAVR are likely to be better in current clinical practice. In addition, many more years of clinical experience leading to better patient selection and surmounting early learning curves probably further contributes to better outcomes. A subsequent trial, the PARTNER II trial, has randomly assigned 2000 intermediate risk patients with a second-generation version of this valve to surgery.

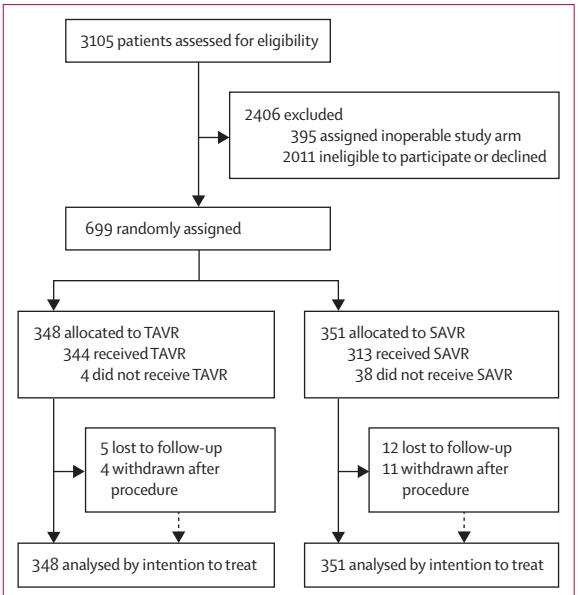

Figure 1: **Trial profile**
Eligibility was based on whether the patient would benefit equally from either treatment. If the heart team judged that the patient was not equally served by either treatment, then they were not enrolled. Lost to follow-up was declared only after contact efforts by the sites; patients had the right to withdraw at any time without giving reasons. TAVR=transcatheter aortic valve replacement. SAVR=surgical aortic valve replacement.

treatment. Patients and their treating physicians were not masked to treatment allocation.

Procedures

The Sapien balloon-expandable heart-valve system (Edwards Lifesciences, Irvine, CA, USA) and the TAVR procedure have been described previously.[4] Crossover between the treatment groups was not permitted. A clinical events committee adjudicated all endpoints. Echocardiographic data were analysed by a central core laboratory as previously described.[8] Patients were followed up yearly and this report, and a companion report by Kapadia[9] for inoperable patients, presents the final 5-year outcomes.

Outcomes

The prespecified primary endpoint of the trial was all-cause mortality at 1 year for the pooled cohort in the intention-to-treat population. Prespecified secondary endpoints included cardiovascular mortality, stroke, repeat hospital admission, acute kidney injury, vascular complications, bleeding events, and New York Heart Association (NYHA) functional class, all in the intention-to-treat population. Definitions of the endpoints are identical to those in the original trial and have been reported elsewhere.[3,4] In this report we present these outcomes at 5 years, all of which were prespecified.

Statistical analysis

The intention-to-treat analysis started at the time of randomisation, and the as-treated analysis started at the time of induction of anaesthesia in the procedure room. All composite analyses were prespecified.

Echocardiographic analyses were done for the as-treated population. We compared categorical variables with Fisher's exact test. We compared continuous variables, presented as means (SDs) with Student's *t* test; for comparisons of continuous variables between periods, we used a paired-sample *t* test. We assessed time-to-event variables with Kaplan-Meier estimates based on all available data and compared with the log-rank test. To study the

effect of risk factors on mortality, we did Cox proportional hazards regression. Interaction analysis from the Cox regression was not specified in the protocol; it was done in the 1-year analyses and presented in the pre-market approval submission; the same subgroups are considered here. We also used Cox regression for multivariable analysis, in which we used multiple imputations to accommodate missing baseline variables. The multivariable models included covariates with a p value of less than 0·20 in univariate analyses. We did an additional time-dependent covariate analysis to test the association of complications during TAVR or SAVR with subsequent mortality. The primary and key secondary endpoint analyses in the protocol were for non-inferiority at 1 year; no such analyses were specified for 5 years, and no such analyses are presented in this report. We did landmark analyses including all patients alive at the start point of the analyses; the landmark analyses were not prespecified. We did all statistical analyses with SAS (version 9.3).

This study is registered with ClinicalTrials.gov, NCT00530894.

Role of the funding source

The funder designed and monitored the study and participated in the selection and management of the study sites and data collection. The funder had no role in data analysis or interpretation, or the writing of the report. MJM and the executive committee had unrestricted access to the data after the database was locked and had full responsibility for the decision to submit for publication.

Results

We screened 3105 patients, of whom 699 were enrolled: 348 assigned to TAVR and 351 assigned to SAVR (figure 1).

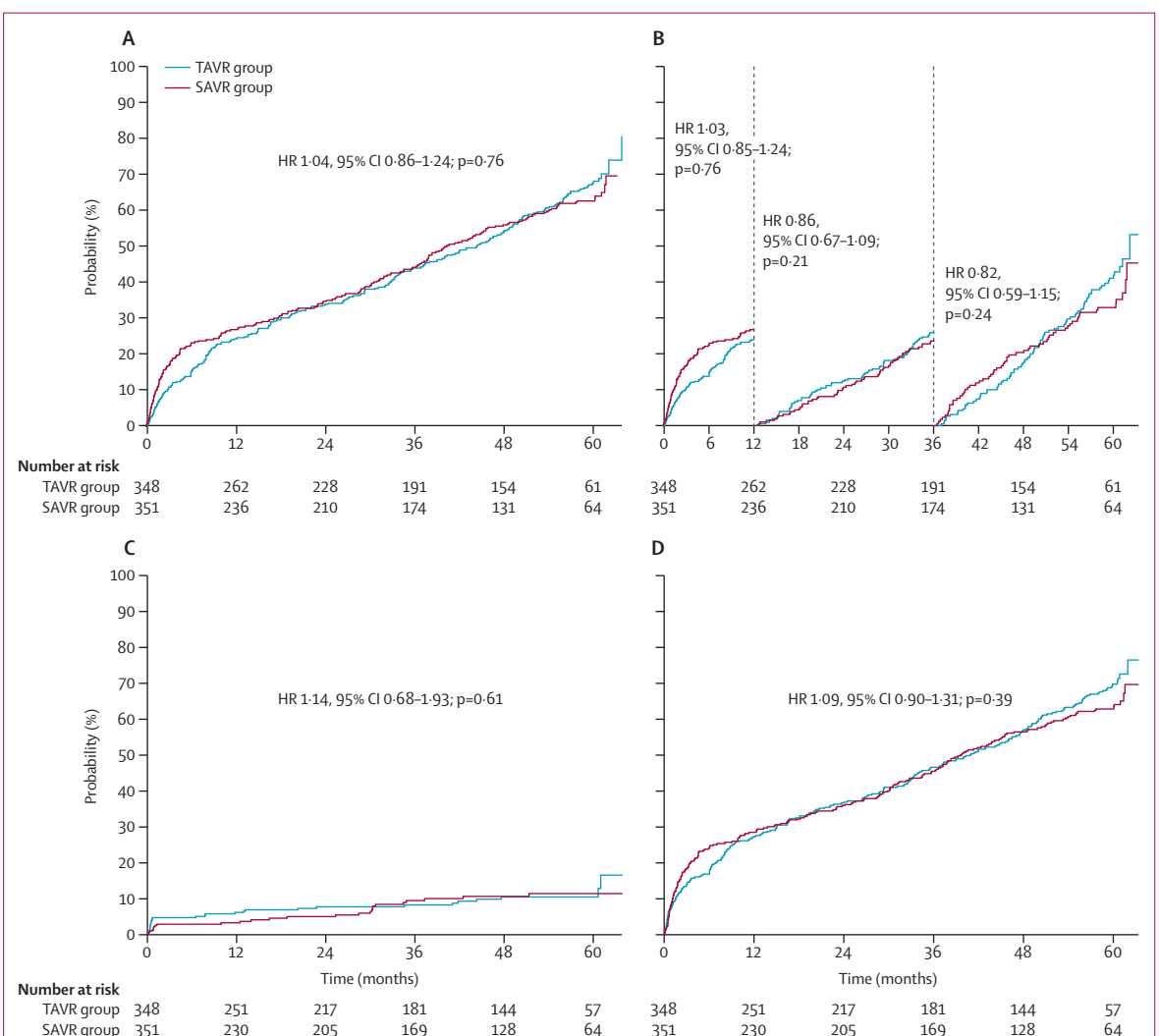

Figure 2: **Mortality and cardiovascular outcomes**
Kaplan-Meier analysis of all-cause death in the intention-to-treat population (A) and by landmark analysis (B); stroke or transient ischaemic attack (C); and stroke, transient ischaemic attack, or death from any cause (D). HR=hazard ratio. TAVR=transcatheter aortic valve replacement. SAVR=surgical aortic valve replacement.

	At 1 year		At 5 years		
	TAVR group (n=348)	SAVR group (n=351)	TAVR group (n=348)	SAVR group (n=351)	Log-rank p value
Death					
From any cause	84 (24·2%)	89 (26·8%)	229 (67·8%)	198 (62·4%)	0·76
From cardiovascular causes	46 (14·0%)	40 (13·0%)	147 (53·1%)	123 (47·6%)	0·67
Repeat hospital admission	59 (18·5%)	51 (17·7%)	108 (42·3%)	81 (34·2%)	0·17
Death from any cause or repeat hospital admission	121 (34·9%)	125 (37·7%)	265 (77·8%)	228 (71·3%)	0·49
Stroke or transient ischaemic attack					
All	28 (8·6%)	13 (4·3%)	42 (15·9%)	33 (14·7%)	0·35
Stroke	20 (6·0%)	10 (3·2%)	29 (10·4%)	26 (11·3%)	0·61
Transient ischaemic attack	8 (2·6%)	4 (1·5%)	14 (6·3%)	8 (3·8%)	0·30
Stroke or death from any cause	95 (27·4%)	95 (28·6%)	236 (69·8%)	200 (62·9%)	0·39
Stroke or transient ischaemic attack, or death from any cause	102 (29·4%)	98 (29·5%)	242 (71·6%)	205 (64·4%)	0·35
Myocardial infarction	0 (0·0%)	2 (0·6%)	5 (2·9%)	11 (5·9%)	0·15
Major vascular complication	40 (11·6%)	13 (3·8%)	41 (11·9%)	14 (4·7%)	0·0002
Major bleeding	52 (15·7%)	88 (26·7%)	75 (26·6%)	103 (34·4%)	0·003
Endocarditis	2 (0·6%)	3 (1·0%)	5 (2·0%)	6 (2·5%)	0·65
Renal failure	18 (5·4%)	20 (6·5%)	24 (8·6%)	24 (8·5%)	0·69
New pacemaker	21 (6·4%)	17 (5·3%)	28 (9·7%)	23 (9·1%)	0·64

Data are number of patients (Kaplan-Meier probability [%]). TAVR=transcatheter aortic valve replacement. SAVR=surgical aortic valve replacement.

Table 1: **Clinical outcomes at 1 year and 5 years for the intention-to-treat population**

See Online for appendix

The appendix shows baseline characteristics. Four patients in the TAVR group did not receive it, five patients were lost to follow-up and four withdrew after receiving the procedure. In the SAVR group, 38 patients did not receive the allocated procedure, mainly because of patient decision not to undergo surgery; 19 of these withdrew immediately. 12 patients assigned to SAVR were lost to follow-up and 11 withdrew after receiving the procedure.

In the TAVR group, 244 patients were assigned to undergo the procedure by a transfemoral approach and 104 by a transapical approach. Surviving patients were followed up for at least 5 years (median follow-up 3·14 years, IQR 0·68–4·92). Mean age was 84·1 years (SD 6·6), and 656 (94%) of 697 were NYHA functional class 3 or 4. Mean Society of Thoracic Surgeons Predicted Risk of Mortality (STS) at 30 days was 11·8% (SD 3·3) in the TAVR group and 11·7% (3·5%) in the SAVR group, with both groups well matched except for a slightly higher incidence of renal dysfunction in the TAVR group.[4]

At 5 years, risk of death from any cause in the intention-to-treat population was 67·8% in the TAVR group and 62·4% in the SAVR group (hazard ratio [HR] 1·04, 95% CI 0·86–1·24; p=0·76; figure 2A, table 1). The outcomes were much the same for the as-treated population (appendix). Likewise, risk of cardiovascular causes of death did not differ significantly between groups (table 1, appendix). Landmark analysis of all-cause mortality in the intention-to-treat population showed that the outcomes were similar at any timeframe assessed: 0–1 years, 1–3 years, and 3–5 years (figure 2B). Median survival of patients in the TAVR group was 44·5 months (IQR 13·7–63·7) compared with 40·6 months (IQR 10·1–not assessable) in the SAVR group (p=0·76).

For patients suitable for a transfemoral approach, risk of all-cause mortality at 5 years was 63% in the TAVR group versus 64% in the SAVR group (p=0·41); for those suitable for a transapical approach, the risk was 79% versus 60% (p=0·067; appendix).

Multivariable baseline predictors of overall all-cause mortality included body-mass index, serum creatinine concentration, presence of liver disease, lower mean aortic valve gradient, and presence of preoperative atrial fibrillation (table 2). These variables were also associated with mortality in the TAVR group, as was peripheral vascular disease. For patients in the SAVR group, presence of liver disease, STS risk score, peripheral vascular disease, moderate or severe mitral regurgitation, and body-mass index were all predictors of all-cause mortality. Subgroup analyses showed that patients with peripheral vascular disease and those without pulmonary hypertension fared better with SAVR than with TAVR (figure 3).

The risk of stroke or transient ischaemic attack was much the same in each treatment group at 5 years (14·7% in the TAVR group *vs* 15·9% in the SAVR group; figure 2C), as was the composite endpoint of stroke or transient ischaemic attack or death from any cause (71·6% *vs* 64·4%; figure 2D).

At 5 years, the incidence of myocardial infarction, endocarditis, renal failure, or need for new pacemaker were similar in each group; however, vascular complications were more common in patients in the TAVR group than those in the SAVR group, and the incidence of

	Hazard ratio (95% CI)	p value
Overall (n=699)		
Assignment to TAVR group	1·09 (0·90–1·31)	0·39
Body-mass index	0·96 (0·94–0·98)	<0·0001
Creatinine concentration	1·41 (1·17–1·71)	0·0004
Liver disease	2·31 (1·41–3·78)	0·0008
Mean gradient per increase of 10 mm Hg	0·91 (0·85–0·97)	0·004
Atrial fibrillation	1·37 (1·10–1·69)	0·004
TAVR group (n=348)		
Body-mass index	0·96 (0·93–0·98)	0·0001
Creatinine concentration	1·61 (1·24–2·09)	0·0004
Liver disease	2·68 (1·31–5·49)	0·007
Mean gradient per increase of 10 mm Hg	0·84 (0·77–0·92)	0·0003
Atrial fibrillation	1·40 (1·04–1·88)	0·03
Peripheral vascular disease	1·36 (1·05–1·77)	0·02
SAVR group (n=351)		
Body-mass index	0·97 (0·95–1·00)	0·04
Liver disease	2·24 (1·14–4·40)	0·02
Peripheral vascular disease	0·73 (0·55–0·98)	0·03
Moderate or severe mitral regurgitation	1·46 (1·03–2·07)	0·04
STS risk score	1·05 (1·01–1·09)	0·02

STS=Society of Thoracic Surgeons Predicted Risk of Mortality. TAVR=transcatheter aortic valve replacement. SAVR=surgical aortic valve replacement.

Table 2: **Multivariable baseline predictors of all-cause mortality**

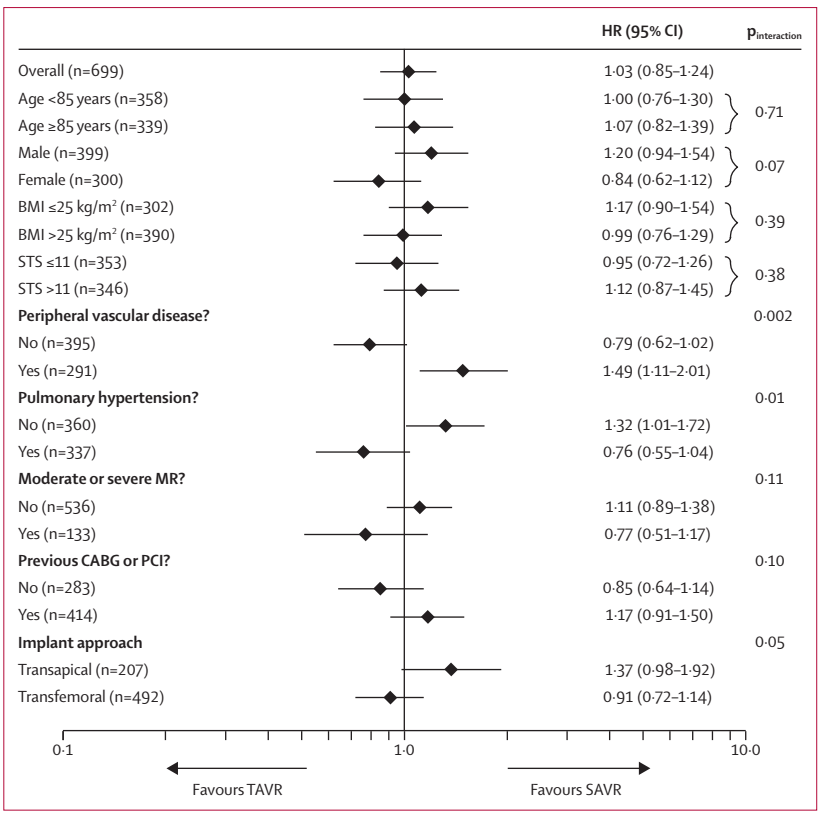

Figure 3: **Subgroup analyses**

The interaction terms result from using Cox regression with a trial arm × covariate interaction term. HR=hazard ratio. TAVR=transcatheter aortic valve replacement. SAVR=surgical aortic valve replacement. STS=Society of Thoracic Surgeons Predicted Risk of Mortality. BMI=body-mass index. MR=mitral regurgitation. CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention.

bleeding complications was lower in the TAVR group than in the SAVR group (table 1). Most vascular and bleeding complications occurred soon after treatment.

The need for repeat hospital admission was not significantly different between treatment groups (appendix). Readmission to hospital was more common in patients deemed suitable for a transapical approach than in those who would have a transfemoral approach, for both treatment groups (data not shown). Patients treated with transapical TAVR were readmitted to hospital 8·8% more often than were those treated with transfemoral TAVR (48·9% *vs* 40·1%). However, patients in the SAVR group in the transapical stratification were admitted to hospital 6·4% more often than those in the transfemoral stratification, probably a result of different patient-related comorbidities (38·6% *vs* 32·2%). Functional outcomes were much the same in each group, with 85 (85%) of 100 surviving patients in the TAVR group and 79 (81%) of 97 surviving patients in the SAVR being in NYHA class 1 or 2 (p=0·57; appendix).

Valve haemodynamics at 5 years were much the same in each treatment group. According to echocardiography, mean aortic valve areas were 1·6 cm² with TAVR versus 1·5 cm² with SAVR (p=0·29; figure 4A) and mean valve gradients were 10·7 mm Hg versus 10·6 mm Hg (p=0·92; figure 4B). Left ventricular mass regression was also similar in each group (figure 4C). No structural valve deterioration requiring surgical valve replacement occurred in either group. Moderate or severe aortic regurgitation was present at 30 days in 40 (14%) of 280 patients in the TAVR group and two (1%) of 228 in the SAVR group (p<0·0001) and was largely caused by paravalvular regurgitation; central transvalvular regurgitation occurred in similar proportions of patients in each treatment group (2/280 TAVR *vs* 1/228 SAVR). Total aortic regurgitation was associated with increased 5-year mortality risk in the TAVR group (72·4% for moderate or severe aortic regurgitation *vs* 56·6% for those with mild aortic regurgitation or less; p=0·003; appendix). As reported at for earlier timepoints, even the presence of mild aortic regurgitation was associated with lower survival at 5 years. The appendix shows 5-year mortality in patients treated by a transfemoral approach with no or trace paravalvular leak compared with surgery.

Discussion

The final 5-year follow-up of high risk surgical patients shows equivalent outcomes after TAVR and SAVR. We detected no significant differences in all-cause mortality, cardiovascular mortality, stroke, or need for repeat hospital admission. Functional outcomes were also

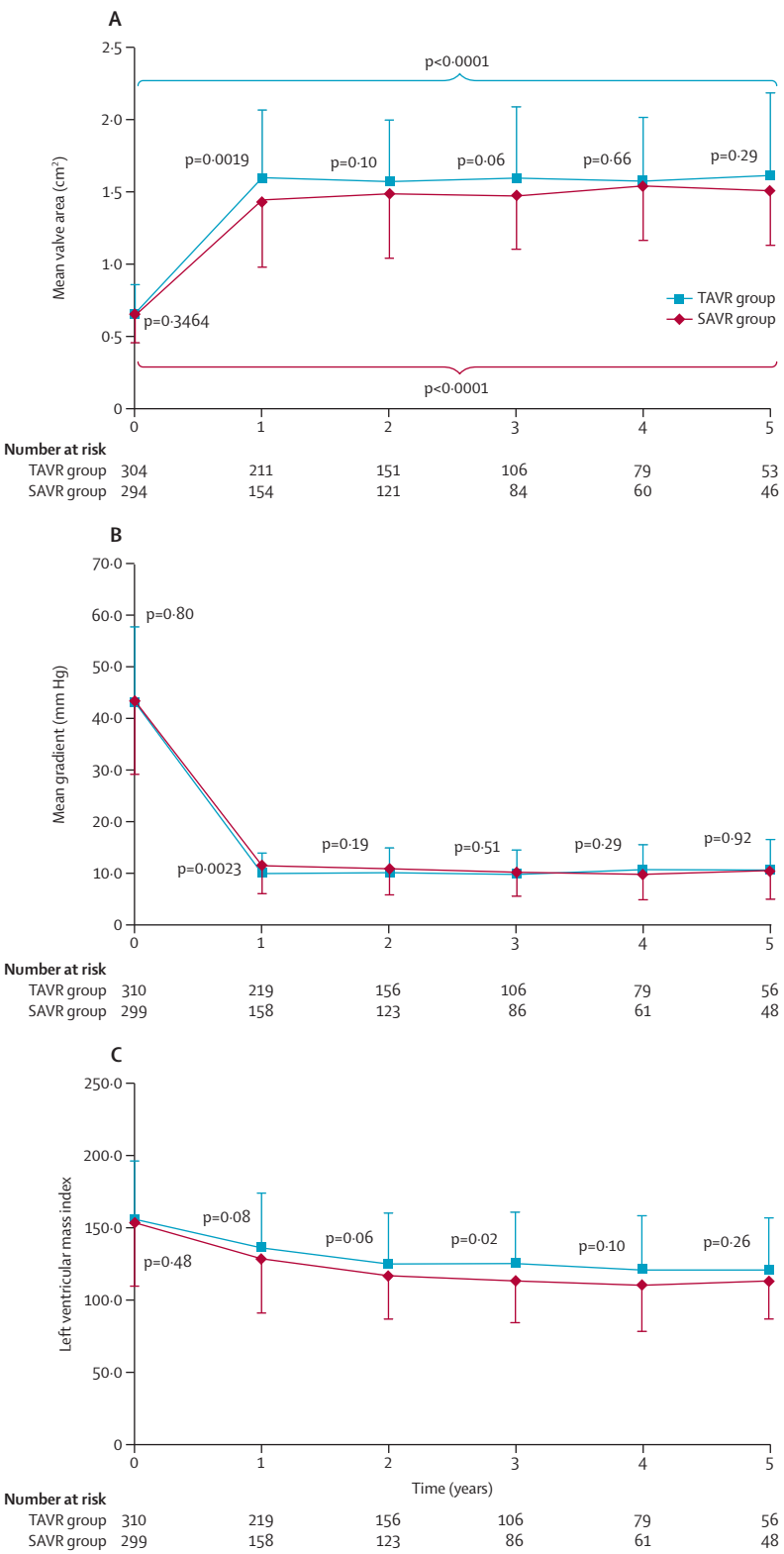

Figure 4: **Echocardiographic findings**
Aortic valve area (A), mean gradient (B), and left ventricular mass regression (C). Points are means, bars are SDs. TAVR=transcatheter aortic valve replacement. SAVR=surgical aortic valve replacement.

similar and preservation of valve haemodynamics was equivalent in both groups. Although we recorded no evidence of structural valve deterioration in either group, moderate or severe aortic regurgitation caused by paravalvular regurgitation was more common in the TAVR group and was associated with lower survival.

When reviewing the results of this trial, including mortality, several factors should be considered. First, TAVR was done with a first-generation device requiring a large sheath-delivery system in a very high surgical risk population; major advances in devices have since occurred, and the Sapien device used in the trial is no longer being implanted. The Sapien device underwent new iterations even during the study. A second generation balloon-expandable valve (Sapien XT; Edwards Lifesciences, Irvine, CA, USA) is now the only balloon-expandable valve commercially available in the USA, and pivotal trials of a third generation valve, Sapien 3 (Edwards Lifesciences, Irvine, CA) have now completed enrolment in USA with regulatory approval already received in Europe.[9] One self-expanding valve (CoreValve; Medtronic Vascular, Minneapolis, MN, USA) has also been approved for use in high-risk and extreme-risk patients in the USA. Although not definitively proven, it is a reasonable expectation that newer generation devices might lead to better long term outcomes in terms of vascular complications and paravalvular leak.[10,11]

Second, this trial is the first TAVR experience of most sites in the USA.[12] A learning curve was undoubtedly present, which affected TAVR outcomes early in the trial, especially with the transapical approach.[12–14] For most trial sites, this study was their first experience with the transapical approach, which was introduced into the trial well after the transfemoral approach; therefore contemporary outcomes might be different.[12] The same is probably true for the transfemoral approach, as evidenced by the fact that vascular and bleeding complications were less common in the continued access patients when the trial centres had more experience.[15] Furthermore, from a surgical standpoint, this high surgical risk population consisted of very old, very ill patients not often seen and offered surgical valve replacement in many centres; the challenging surgical management of these patients has also evolved since the start of the trial. Outcomes of surgical aortic valve replacement have improved substantially, with lower observed:expected ratios of outcomes in surgical programmes at TAVR centres.[16]

Third, this trial includes an extremely high-risk cohort, with a mean STS of 12%. Other trials have had lower mean STS scores and the initial clinical experience of commercial TAVR with the Sapien and Sapien XT valves in the USA for high-risk and inoperable patients showed a mean STS of 7%.[17] Many explanations for the lower STS risk scores are possible, including not offering TAVR to the highest risk patients who are unlikely to benefit because of their underlying medical problems and advanced age. Additionally, the STS was updated

during the PARTNER trial, so the comparison with other studies is difficult. Another reason might be risk thresholds for treatment changing, with low-risk patients being offered TAVR because of advanced age and patient preference.

When the outcomes were analysed by access approach, we detected no differences between patients receiving TAVR by a transfemoral approach and SAVR patients who were in the transfemoral stratum; however, we did record a mortality difference at 12 months between transapical TAVR and transapical SAVR patients, which continued to diverge until 5 years. The explanation for this effect is unclear; any treatment effect should have long-since dissipated. However, the difference was not statistically significant.

Concerns have been raised about a possible higher risk of stroke associated with TAVR.[18] Although periprocedural stroke or transient ischaemic attack were more common with TAVR than with SAVR at 30 days (5·5% *vs* 2·4%; p=0·04 [intention-to-treat population]), by 5 years this difference had dissipated. A neurologist was not involved in the neurological assessment of patients in this trial, raising concerns of under-reporting of neurologic events; however, if neurologic events were under-diagnosed, it would probably occur equally in each treatment group.

Concerns were raised about the possibility of early structural valve deterioration in the TAVR group as a result of the potential for leaflet damage during the crimping process and the asymmetric expansion with suboptimum leaflet coaptation or incomplete expansion with leaflet frame interaction.[19,20] Although 5 years is still too short a time to expect differences in durability between transcatheter and surgical prostheses, especially in this very elderly patient population, it is reassuring that structural valve deterioration in the TAVR groups have not been reported—even with few patients remaining at risk at 4 and 5 years.

One concern with TAVR is the incidence of paravalvular leak and its effect on mortality and long-term outcomes.[21,22] As shown by the 2-year analysis of this trial, even mild paravalvular leak was associated with poorer survival,[6] which was further substantiated in this 5-year follow-up. Since enrolments started, much has been learned about the predictors and causes of paravalvular leak and methods for proper sizing of the valve prosthesis relative to the aortic annulus.[23–28] Use of 3D multislice CT scan reconstruction and 3D transoesophageal echo, which were not used in this trial, has refined valve sizing. Additionally, the availability of a wider range of valve sizes has helped to address this shortcoming. For this trial, only 23 mm and 26 mm valves were available. Subsequently, a 29 mm Sapien XT valve has become available and has further helped to prevent paravalvular leak.[29] Furthermore, newer valves with different sealing mechanisms, including an external fabric skirt, seem to also help minimise paravalvular leak.[11]

The clinical outcomes and valve performance in this trial might not reflect that of subsequent generations of balloon-expandable transcatheter valves, present operator expertise and experience, and more rigorous patient selection for TAVR. The patients selected for treatment in this trial, which started in 2007, are also representative of clinical practice at that time; clinicians have since refined patient selection, at least partly on the basis of early outcomes from this trial. Because the patients in this trial were at such a high risk, only roughly a third of patients were still alive for analysis and comparison at 5 years.

In summary, the 5-year data comparing outcomes of high-risk surgical patients with severe aortic stenosis undergoing TAVR or SAVR show no significant difference between the two treatments. Based on these results, TAVR is an alternative to surgery for the treatment of aortic stenosis in high surgical risk patients.

Contributors

All authors contributed to study design, data collection, data interpretation, and editing of the report. WNA analysed data. MJM wrote the first draft.

Declaration of interests

MJM, MBL, CRS, DCM, JWM, and EMT have received travel reimbursements from Edwards Lifesciences relating to their positions as unpaid members of the PARTNER trial executive committee. Additionally, 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. JGW is a consultant for Edwards Lifesciences and a member of the PARTNER trial executive committee. PSD has received research grant support from Edwards Lifesciences. WNA has received consulting fees from Edwards Lifesciences and holds common stock in Edwards Lifesciences. SKK is a consultant for Edwards Lifesciences and a member of the scientific advisory board of Thubrikar Aortic Valve. RRM has received grant support and consulting fees from Edwards Lifesciences, St Jude Medical, and Medtronic. RTH has received research grant support from Philips Healthcare, and is a consultant for Edwards Lifesciences and St Jude Medical. VHT is a consultant for Edwards Lifesciences, Sorin Medical, St Jude Medical, and DirectFlow. AP is a consultant for Edwards Lifesciences. 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. MW is a consultant for Edwards Lifesciences. JA is a former employee of Edwards Lifesciences. LGS holds equity in Cardiosolutions and ValvXchange, intellectual property rights and royalties from Posthorax, and has received travel reimbursements from Edwards Lifesciences related to his role as an unpaid member of the PARTNER trial executive committee. The other authors declare no competing interests.

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