Chapter 7: The Evidence Base for TAVR: Landmark Trials

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Introduction

As recently as a decade ago, the only definitive treatment for aortic stenosis was surgical aortic valve replacement (SAVR). The first landmark clinical trial evidence for transcatheter aortic valve replacement (TAVR) was introduced to the medical community in 2010 [1], and successive clinical trials have led to TAVR's expeditious adoption across an ever-expanding population of patients (Table 1). Increasing operator experience and improvements in device design have further enhanced the success of TAVR over time [2-7]. In this chapter, landmark trials for TAVR are explored in chronological order of the publication of initial trial results.

PARTNER I (COHORT B)

The initial results of the Placement of AoRtic TraNscathetER Valves (PARTNER) trial cohort B were published in the *New England Journal of Medicine* (NEJM) in 2010. This trial is unique in cardiovascular medicine in that it is one of the few randomized trials where a novel device or drug is tested in a sicker population first, rather than the traditional paradigm of drug and device development, where therapeutics are first studied in healthier populations. PARTNER B was a prospective, randomized trial designed to study patients with severe, symptomatic aortic stenosis considered poor (or "inoperable") surgical candidates. Patients were randomized 1:1 either to TAVR using the balloon-expandable SAPIEN (Edwards Lifesciences Corporation, Irvine, CA) valve system vs. medical therapy, which included balloon aortic valvuloplasty (BAV) as a means of symptom relief. The study included 358 patients with 179 TAVR and 179 medical therapy patients. The trial had a superiority design with co-primary endpoints of all-cause mortality and the composite endpoint of all-cause mortality or repeat hospitalization for valve or procedure-related deterioration at 1 year.

Remarkably, TAVR was associated with a significantly lower rate of all-cause mortality compared with medical therapy at 1 year (30.7% vs. 49.7%, NNT 5). The use of TAVR was also associated with lower rates of all-cause mortality or repeat hospitalization at 1 year (42.5% vs. 70.4%, NNT 4). This 20% absolute survival advantage of TAVR over medical therapy was the basis for FDA approval of the SAPIEN valve system in inoperable patients.

Despite the observed mortality advantage, TAVR was associated with an increased rate of stroke at 30 days as compared to medical therapy (6.7% vs. 1.7%, p=0.03). Major bleeding (16.8% vs. 3.9%, p<0.001) and major vascular complications (16.2% vs. 1.1%) at 30 days were also increased with TAVR (Table 2) [1]. However, the incidence of bleeding and vascular complications represented some of the earliest TAVR devices (requiring 22 and 24 French sheaths at that time) and some of the earliest operator experience and techniques (not specifically designed to mitigate vascular complications). While the trial was somewhat criticized for a high use of BAV in the medical therapy arm, most patients were highly

symptomatic, and the use of palliative BAV in these patients was not associated with an increase in early adverse outcomes.

PARTNER I (COHORT A)

On the heels of the PARTNER Cohort B trial, the first published results of the overall PARTNER trial, cohort A was published in NEJM in 2011. PARTNER A was a prospective, randomized trial designed to study patients with severe, symptomatic aortic stenosis classified as high-risk surgical candidates. Patients were randomized 1:1 to either TAVR using the SAPIEN (Edwards Lifesciences Corporation, Irvine, CA) valve vs. SAVR. TAVR patients were also stratified by access approach (transfemoral vs. transapical). The trial included 699 patients with 348 TAVR and 351 SAVR patients. The trial used a non-inferiority design, and the primary endpoint was all-cause mortality at 1 year.

The rates of one-year mortality were 24.2% for TAVR vs. 26.8% for SAVR, meeting non-inferiority criteria and leading to FDA approval of the SAPIEN valve as an alternative to SAVR for high-risk surgical patients. Regarding outcomes at 30 days, the rate of major stroke for TAVR was numerically greater with TAVR than for SAVR (3.8% vs. 2.1%; p=0.20). Major vascular complications were 11.0% vs. 3.2% for TAVR compared with SAVR; conversely, SAVR had an absolute 10.2% higher rate of major bleeding compared with TAVR. The need for permanent pacemaker (PPM) implantation was equivalent between groups; however, there was less paravalvular leak (PVL) with SAVR (Table 2).

TAVR patients had a 2-day shorter ICU stay and a 4-day shorter overall hospital length of stay as compared with SAVR. More patients in the TAVR group had improvement of their symptoms to NYHA class II or lower as compared to SAVR at 30 days; but among subjects assessed at one year, the groups were equivalent. Additionally, outcomes for TAVR vs. SAVR, when stratified by a transfemoral vs. transapical approach, were similar; although, the transapical subgroup was notably underpowered (2).

CoreValve® US Pivotal Trial Extreme Risk Study

The initial results of the US CoreValve® Extreme Risk Study were published in the *Journal of American Cardiology* (JACC) in 2014. Of note, this was a non-randomized trial because after the presentation and publication of the PARTNER I Cohort B study, randomization to medical therapy was no longer considered ethical. This trial was designed to study patients with severe, symptomatic aortic stenosis deemed prohibitive risk for surgery ("inoperable"). This trial used a non-inferiority design with a composite primary endpoint of all-cause mortality or major stroke at 1 year. TAVR outcomes using the self-expanding CoreValve® transcatheter heart valve (THV) (Medtronic, Inc., Minneapolis, MN) were compared to a pre-specified objective performance goal (43%) extracted primarily from the medical therapy arm of PARTNER I Cohort B.

A total of 489 patients underwent TAVR with the CoreValve® device. The primary outcome was observed in 26.0% of patients; all-cause mortality was 23.7%, meeting non-inferiority. This trial resulted in FDA approval of the CoreValve® THV self-expanding system for inoperable patients (3). At 30 days, all-cause mortality was 8.4%, and the rate of major stroke was 2.3%. Major bleeding was seen in 12.7%

of TAVR patients with major vascular complications occurring in 8.2%. PPM was required in 21.6% of TAVR patients (3) (Table 2).

CoreValve® US Pivotal Trial High Risk Study

The initial results of the US CoreValve® High Risk Study were published in NEJM in 2014. This trial was a prospective, randomized multicenter trial designed to study patients with severe, symptomatic aortic stenosis classified as high-risk surgical candidates. This trial compared TAVR vs. SAVR patients. Patients were randomized 1:1 to TAVR using the self-expanding CoreValve® bioprosthesis vs. SAVR. TAVR patients were stratified into transfemoral access vs. alternate access (subclavian or direct aortic) based on pre-procedural imaging. The trial included a total of 795 patients with 394 TAVR and 401 SAVR patients as the intention-to-treat population. The trial used a non-inferiority design with a primary endpoint of all-cause mortality at 1 year; it was also powered for a pre-specified hierarchical superiority test if non-inferiority was met. Of note, the pre-specified primary analysis was based on the as-treated population.

All-cause mortality at 1 year was 14.2% for TAVR and 19.1% in the SAVR group, meeting non-inferiority criteria ($p<0.001$ for non-inferiority, one-sided $p=0.04$ for superiority). This trial led to FDA approval for the CoreValve® THV as an alternative to SAVR in high-risk patients. The rate of any stroke was 4.9% in TAVR and 6.2% in SAVR at 30 days ($p=0.46$). At 30 days, major bleeding and new or worsened atrial fibrillation was significantly more frequent in the SAVR group; however, the frequency of major vascular complications, need for PPM, and post-procedure PVL was higher in the TAVR group (4) (Table 2).

PARTNER 2A

The initial results of PARTNER 2A were published in NEJM in 2016. The trial was a prospective, randomized trial designed to study patients with severe, symptomatic aortic stenosis categorized as intermediate surgical risk (i.e. no longer high-risk for SAVR) by a multi-disciplinary heart team. Patients were randomized 1:1 to TAVR using a 2nd generation SAPIEN XT (Edwards Lifesciences Corporation, Irvine, CA) valve system vs. SAVR. TAVR patients were further stratified into transfemoral vs. alternate access (transapical or trans-aortic) based on pre-procedural evaluation. The trial included a total of 2032 patients with 1,011 TAVR and 1,021 SAVR patients. A non-inferiority design was used with a primary composite endpoint of all-cause mortality or disabling stroke at 2 years.

The primary composite endpoint occurred in 19.3% of TAVR vs. 21.1% of SAVR ($p=0.33$), meeting pre-specified non-inferiority criteria. PARTNER 2A resulted in FDA approval of SAPIEN XT for use as an alternative to SAVR in intermediate-risk patients. All-cause mortality at 30 days (3.9% vs. 4.1%; $p=0.78$) was similar between groups. Major stroke at 30 days was lower in the TAVR group 3.2 vs. 4.3 ($p=0.20$), but this did not reach statistical significance. TAVR showed lower rates of major bleeding as compared to SAVR. However, TAVR had 3% more major vascular complications, an increased incidence of PPM implantation, and increased rates of PVL as compared to SAVR (Table 2). Of note, there was a 4% absolute decrease in the primary endpoint with transfemoral TAVR and a 4% absolute increase in the primary endpoint with transthoracic TAVR (5).

PARTNER 2 S3i

The results of the PARTNER 2 S3i trial were published in *The Lancet* in 2016. This trial included intermediate-risk TAVR patients with severe, symptomatic aortic stenosis undergoing TAVR with the 3rd generation balloon-expandable SAPIEN 3 valve (Edwards Lifesciences Corporation, Irvine, CA). Of note, this was not a randomized trial, but a propensity-score analysis trial. The SAPIEN 3 valve system was introduced after PARTNER 2A had begun and was not included in the PARTNER 2A trial. This newer valve system was designed for more accurate positioning and for reduction of PVL.

The SAPIEN 3 TAVR cohort was initially observed prospectively for 1 year and subsequently compared against a propensity-matched cohort of patients from the SAVR group of PARTNER 2A. There were 1,077 SAPIEN 3 TAVR patients included in the cohort.
A pre-specified propensity-based analysis to control for differences in patient baseline characteristics was used with a primary composite endpoint of mortality, stroke, or moderate-severe PVL at 1 year. The aforementioned TAVR observational data was compared to 944 SAVR patients from PARTNER 2A. Non-inferiority and superiority were both met for the primary composite endpoint. In superiority analysis, both all-cause mortality and stroke were lower with the SAPIEN 3 valve, although the incidence of ≥ moderate PVL remained slightly higher in TAVR when compared with SAVR. Specifically, the all-cause mortality rate in TAVR was 7.4% vs. 13% in SAVR (weighted difference of proportions -5.2%; p-value for superiority < 0.001), any stroke rate in TAVR was 4.6% vs. 8.2% in SAVR (weighted difference of proportions -3.5%; p-value for superiority = 0.004), and a moderate-severe PVL rate in TAVR of 1.5% (1.4% moderate; 0.1% severe) vs. 0.4% (0.2% moderate; 0.2% severe) in the SAVR group (weighted difference of proportions +1.2%; p-value for superiority = 0.015) (6). The results of this trial resulted in FDA approval of the SAPIEN 3 valve system as an alternative to SAVR for intermediate-risk patients.

SURTAVI

The initial results of the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial were published in NEJM in early 2017. The trial was a prospective, randomized trial conducted across 87 centers in the United States, Canada, and Europe. It was designed to study patients with severe, symptomatic aortic stenosis classified as intermediate surgical risk.

Patients enrolled in the study were randomized 1:1 to either TAVR with the self-expandable CoreValve® system (16% received the newer Evolut R® system) vs. SAVR. Transfemoral access was preferred for TAVR; however, subclavian or direct aortic approach was used if patients had anatomy unsuitable for a transfemoral approach. The trial included 1746 patients with 864 undergoing TAVR and 796 undergoing SAVR. A non-inferiority design employing Bayesian analytical methods was used. The primary composite endpoint was all-cause mortality or disabling stroke at 2 years – the same composite endpoint as PARTNER 2A.

The primary endpoint occurred in 12.6% of TAVR and 14.0% in SAVR patients with Bayesian analyses showing a 95% credible interval for difference of -5.2 to 2.3 with a posterior probability of non-inferiority of >0.999 (non-inferiority was met). The results of this trial led to FDA approval of the

CoreValve® device as an alternative to SAVR in intermediate-risk patients. All-cause mortality was similar between groups at 2 years (11.4% in the TAVR group vs. 11.6% in the SAVR group (-3.8 to 3.3)). Any stroke at 30 days was lower in TAVR compared with SAVR (3.4% vs. 5.6; -4.0 to -0.2). Major bleeding and major vascular complications at 30 days occurred more frequently with TAVR. The incidence of PPM implantation at 30 days was significantly higher in TAVR vs. SAVR (25.6% vs. 6.6%; 15.9 to 22.7). This did not seem to improve in the subset of patients who received the newer Evolut R® valve, although the population receiving the Evolut R® valve was relatively small. Additionally, moderate to severe PVL at 1 year was higher in TAVR as compared to SAVR (5.3% vs 0.6%; 2.8 to 6.8) (7).

Future Trials

With improving results and accelerating interest in TAVR, trials studying outcomes with newer valve designs in low surgical risk patients are currently underway. The PARTNER 3 trial (balloon-expandable valve system) and the CoreValve® Low-Risk trial (self-expanding valve system) are currently enrolling patients. In addition, trials studying TAVR in asymptomatic patients with severe aortic stenosis (EARLY-TAVR) as well as in patients with moderate aortic stenosis and impaired left ventricular function (TAVI-UNLOAD) seek to examine broader clinical indications for TAVR and challenge the treatment paradigm for patients with aortic valve disease.

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Table 1. TAVR Trial Characteristics

Table 1. Major TAVR Trial Characteristics

Trial	Year	Population	Groups	TAVR Valve(s) Used	Primary Outcome(s)	Primary Outcome Result	Mean STS (%)†
PARTNER 1, Cohort B	2010	Inoperable	TAVR vs. OMT*	SAPIEN	Death from any cause at 1 year	TAVR met superiority	11.6
PARTNER 1, Cohort A	2011	High risk	TAVR vs. SAVR	SAPIEN	Death from any cause at 1 year	TAVR met non-inferiority	11.8 vs. 11.7
CoreValve Extreme Risk*	2014	Inoperable	TAVR vs. BMT	CoreValve®	Death from any cause or major stroke at 1 year	TAVR met non-inferiority	10.3
CoreValve High Risk	2014	High risk	TAVR vs. SAVR	CoreValve®	Death from any cause at 1 year	TAVR met non-inferiority & superiority	7.3 vs. 7.5
PARTNER 2 A	2016	Intermediate risk	TAVR vs. SAVR	SAPIEN XT	Death from any cause or major stroke at 2 years	TAVR met non-inferiority	5.8 vs. 5.8
PARTNER 2 S3i*	2016	Intermediate risk	TAVR vs. SAVR	SAPIEN 3	Death from any cause, stroke, or ≥ moderate PVL at 1 year	TAVR met non-inferiority & superiority	5.2 vs. 4.4
SURTAVI	2017	Intermediate risk	TAVR vs. SAVR	CoreValve®, Evolut R®	Death from any cause or major stroke at 2 years	TAVR met non-inferiority	4.4 vs. 4.5

*OMT: Optimal medical therapy

**Non-randomized studies

† TAVR versus control

Table 2. Outcomes of Randomized Trials

Table 2. Outcomes of randomized trials*

Trial	Follow-up	All-cause mortality (%)	Cardiac mortality (%)	Major stroke (%)	Major bleeding (%)	Major vascular (%)	Atrial fibrillation (%)	PPM† (%)	PVL‡ (≥ moderate) (%)
PARTNER B	**30 days**	5.0 vs. 2.8 (p=0.41)	4.5 vs. 1.7 (p=0.22)	5.0 vs. 1.1 (p=0.06)	16.8 vs. 3.9 (p<0.001)	16.2 vs. 1.1 (p<0.001)	0.6 vs. 1.1 (p=1.00)	3.4 vs. 5.0 (p=0.60)	12 vs. 0 (p<0.001)
	1 year	30.7 vs. 49.7 (p<0.001)	19.6 vs. 41.9 (p<0.001)	7.8 vs. 3.9 (p=0.18)	22.3 vs. 11.2 (p=0.007)	16.8 vs. 2.2 (p<0.001)	0.6 vs. 1.7 (p=0.62)	4.5 vs. 7.8 (p=0.27)	11 vs. 0 (p<0.001)
PARTNER A	**30 days**	3.4 vs. 6.5 (p=0.07)	3.2 vs. 3.0 (p=0.90)	3.8 vs. 2.1 (p=0.20)	9.3 vs. 19.5 (p<0.001)	17.0 vs. 3.8 (p<0.001)	8.6 vs. 16.0 (p=0.006)	3.8 vs. 3.6 (p=0.89)	12.2 vs. 0.9 (p<0.001)
	1 year	24.2 vs. 26.8 (p=0.44)	14.3 vs. 13.0 (p=0.63)	5.1 vs. 2.4 (p=0.07)	14.7 vs. 25.7 (p<0.001)	18.0 vs. 4.8 (p<0.001)	12.1 vs. 17.1 (p=0.07)	5.7 vs. 5.0 (p=0.68)	6.8 vs. 1.9 (p<0.001)
CoreValve® High-Risk	**30 days**	3.3 vs. 4.5 (p=0.46)	3.1 vs. 4.5 (p=0.32)	3.9 vs. 3.1 (p=0.55)	13.6 vs. 35.0 (p<0.001)	5.6 vs. 1.7 (p=0.003)	11.7 vs. 40.5 (p<0.001)	19.8 vs. 7.1 (p<0.001)	9.0 vs. 1.0 (p<0.001)
	1 year	14.2 vs. 19.1 (p=0.04)	10.4 vs. 12.8 (=0.31)	5.8 vs. 7.0 (p=0.59)	16.6 vs. 38.4 (p<0.001)	6.2 vs. 2.0 (p=0.004)	15.9 vs. 32.7 (p<0.001)	22.3 vs. 11.3 (p<0.001)	6.1 vs 0.5 (p<0.001)
PARTNER 2A	**30 days**	3.9 vs. 4.1 (p=0.78)	3.3 vs. 3.2 (p=0.92)	3.2 vs. 4.3 (p=0.20)	10.4 vs. 43.4 (p<0.001)	7.9 vs. 5.0 (p=0.008)	9.1 vs. 26.4 (p<0.001)	8.5 vs. 6.9 (p=0.17)	3.7 vs. 0.53 (p<0.001)
	1 year	12.3 vs. 12.9 (p=0.69)	7.1 vs. 8.1 (p=0.40)	5.0 vs. 5.8 (p=0.46)	15.2 vs. 45.5 (p<0.001)	8.4 vs. 5.3 (p=0.007)	10.1 vs. 27.2 (p<0.001)	9.9 vs. 8.9 (p=0.43)	3.4 vs. 0.33 (p<0.001)
	2 years	16.7 vs. 18.0 (p=0.45)	10.1 vs. 11.3 (p=0.38)	6.2 vs. 6.4 (p=0.83)	17.3 vs. 47.0 (p<0.001)	8.6 vs. 5.5 (p=0.006)	11.3 vs. 27.3 (p<0.001)	11.8 vs. 10.3 (p=0.29)	8.0 vs. 0.6 (p<0.001)
SURTAVI**									
	30 days	2.2 vs. 1.7 (-2.8 , 0.7)	2.0 vs. 1.7 (-1.0, 1.6)	1.2 vs. 2.5 (-2.6, 0.1)	12.2 vs 9.3 (-0.1, 5.9)	6.0 vs 1.1 (3.2, 6.7)	12.9 vs. 43.4 (-34.7, -26.4)	25.9 vs 6.6 (15.9, 22.7)	3.4 vs. 0.3^
	1 year	6.7 vs. 6.8 (-2.7, 2.4)	4.8 vs. 5.5 (-2.9, 1.5)	2.2 vs. 3.6 (-3.1. 0.4)	-	-	-	-	5.3 vs. 0.6 (2.8, 6.8)
	2 years	11.4 vs. 11.6 (-3.8, 3.3)	7.7 vs. 8.0 (-3.3, 2.6)	2.6 vs. 4.5 (-4.0, 0.1)	-	-	-	-	-

*All results reported as TAVR vs. comparison group

**Values are posterior median rates and 95% credible interval for the difference between groups, all results reported as modified intention-to-treat analysis unless otherwise indicated

^ Intention-to-treat analysis

†PPM: permanent pacemaker (PPM) placement required

‡PVL: paravalvular leak