Aus dem Deutschen Herzzentrum Berlin

DISSERTATION

Introducing transapical aortic valve implantation: effect of a structured training program on clinical outcome

zur Erlangung des akademischen Grades
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von

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ABSTRAKT

Einführung: Das Ziel der vorliegenden Studie war es zu analysieren, ob das kumulative Wissen auf dem Gebiet der transapikalen kathetergestützten Aortenklappenimplantation - eingebettet in ein strukturiertes Ausbildungsprogramm - die negativen Einflüsse einer Lernkurve auf das klinische Ergebnis bei der Einführung der Methodik eliminieren kann.

Methodik: Bei der vorliegenden Studie handelt es sich um eine retrospektive Einzelzentrums-, Beobachtungs- und Kohortenstudie, basierend auf prospektiv gesammelten Daten aller konsekutiven 500 Hochrisikopatienten, die beginnend im April 2008 bis Dezember 2011 in unserer Einrichtung eine kathetergestützte Aortenklappenimplantation über einen transapikalen Zugang erhalten haben. Unter den 500 Patienten befanden sich 28 Patienten im manifesten kardiogenen Schock. Veränderungen von Ausgangscharakteristika, der prozeduralen und postprozeduralen Variablen sowie im Überleben über den Studienzentraum hinweg wurden mit verschiedenen statistischen Methoden, einschließlich Darstellung der kumulativen Summe, analysiert.

Ergebnisse: Die Gesamtletalität im 30-Tage-Zeitraum betrug 4,6% (95%-Konfidenzintervall, 3,1% - 6,8%) sowie 4,0% (95%-Konfidenzintervall, 2,6% - 6,2%) für Patienten, die sich nicht im kardiogenen Schock befanden. Über den Studienzeitraum hinweg waren keine signifikanten Änderung in der 30-Tage-Letalität erkennbar (U-Test nach Mann-Whitney, p = 0,23; logistische Regressionsanalyse, Odds Ratio 0,83 pro 100 Patienten; 95%-Konfidenzintervall, 0,62 - 1,12; p = 0,23). Ebenso fanden sich keine Unterschiede im Überleben, wenn dies hinsichtlich des ausführenden Chirurgen analysiert wurde (30-Tage-Letalität, p = 0,92). Es war ein nichtsignifikanter Trend hin zu einem besseren Gesamtüberleben sichtbar (Hazard Ratio, 0,83 pro 100 Patienten; 95%-Konfidenzintervall, 0,77 – 1,04; p = 0,15).

Schlussfolgerungen: Das strukturierte Ausbildungsprogramm kann angewandt werden, um die Methodik der transapikalen kathetergestützten Aortenklappenimplantation einzuführen und dann unter schrittweiser interner Anleitung auf weitere Mitglieder des implantierenden Teams zu übertragen, ohne dass dabei für den Patienten nachteilige Begleitfolgen zu beobachten sind.

ABSTRACT

Introduction: The purpose of the study was to test whether the cumulative knowledge from the field of transapical transcatheter aortic valve implantation, when incorporated into a structured training and then gradually dispersed by internal proctoring, might eliminate the negative effect of the learning curve on the clinical outcomes.

Methodology: The present study was a retrospective, single-center, observational cohort study of prospectively collected data from all 500 consecutive high-risk patients undergoing transapical transcatheter aortic valve implantation at our institution from April 2008 to December 2011. Of the 500 patients, 28 were in cardiogenic shock. Differences during the study period in baseline characteristics, procedural and postprocedural variables, and survival were analyzed using different statistical methods, including cumulative sum charts.

Results: The overall 30-day mortality was 4.6% (95% confidence interval, 3.1% - 6.8%) and was 4.0% (95% confidence interval, 2.6% - 6.2%) for patients without cardiogenic shock. Throughout the study period, no significant change was seen in the 30-day mortality (Mann-Whitney U test, $p = 0.23$; logistic regression analysis, odds ratio, 0.83 per 100 patients; 95% confidence interval, 0.62 - 1.12; $p = 0.23$). Also, no difference was seen in survival when stratified by surgeon (30-day mortality, $p = 0.92$). An insignificant change was seen toward improved overall survival (hazard ratio, 0.90 per 100 patients; 95% confidence interval, 0.77 - 1.04; $p = 0.15$).

Conclusions: The structured training program can be used to introduce transapical transcatheter aortic valve implantation and then gradually dispersed by internal proctoring to other members of the team with no concomitant detriment to patients.

AFFIDAVIT

I, Miralem, Pasic certify under penalty of perjury by my own signature that I have submitted the thesis on the topic “Introducing transapical aortic valve implantation: effect of a structured training program on clinical outcome” I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The section on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) corresponds to the URM (s.o) and are answered by me. My contribution in the selected publication for this dissertation corresponds to those that are specified in the following joint declaration with the responsible person and supervisor.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

Date 11 August 2013 Signature

Detailed Declaration of Contribution

Miralem Pasic had the following share in the following publication:

Publication : Pasic M, Unbehaun A, Dreysse S, Buz S, Drews T, Kukucka M, Mladenow A, D'Ancona G, Hetzer R, Seifert B, Introducing transapical aortic valve implantation (part 1): Effect of a structured training program on clinical outcome in a series of 500 procedures, The Journal of Cardiothoracic Surgery, 2013

Contribution in detail: The doctoral candidate introduced and established transcatheter aortic valve implantation (TAVI) at our institution. He organized, built and trained our institutional TAVI team and supervised the clinical and scientific work of the team. He designed the study, developed the methodology, organized the institutional data bank and collection of data for the study, performed analysis and interpretation of data, and wrote the manuscript.

Signature, date and stamp of the supervising University teacher

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☑	9	ANN SURG ONCOL	1068-9265	14447	4.120	4.308	0.731	599	4.6	0.05221	1.367
☑	10	ARCH SURG-CHICAGO	0004-0010	14207	4.100	4.750	1.375	136	>10.0	0.02420	1.772
☑	11	LIVER TRANSPLANT	1527-6465	8889	3.944	3.852	1.229	170	6.2	0.02146	1.158
☑	12	TRANSPLANTATION	0041-1337	25429	3.781	3.548	0.760	358	8.6	0.04600	1.113
☑	13	PLAST RECONSTR SURG	0032-1052	28240	3.535	3.591	0.669	435	10.0	0.03615	0.904
☑	14	J THORAC CARDIOV SUR	0022-5223	20004	3.526	3.539	0.859	419	8.0	0.04895	1.358
☑	15	ANN THORAC SURG	0003-4975	28097	3.454	3.664	0.963	510	8.2	0.06227	1.350
☑	16	SURG ENDOSC	0930-2794	14664	3.427	3.299	0.573	506	5.4	0.03604	0.875
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☑	18	DIS COLON RECTUM	0012-3706	12462	3.336	3.273	0.515	171	9.0	0.02016	0.976
☑	19	J BONE JOINT SURG AM	0021-9355	34843	3.234	4.176	0.382	272	>10.0	0.02104	0.631
☑	20	TRANSPL INT	0934-0874	3526	3.155	2.943	0.547	159	4.9	0.01129	0.964

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Introducing transapical aortic valve implantation (part 1): Effect of a structured training program on clinical outcome in a series of 500 procedures

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Objectives: The purpose of the present study was to test whether the cumulative knowledge from the field of transapical transcatheter aortic valve implantation, when incorporated into a structured training and then gradually dispersed by internal proctoring, might eliminate the negative effect of the learning curve on the clinical outcomes.

Methods: The present study was a retrospective, single-center, observational cohort study of prospectively collected data from all 500 consecutive high-risk patients undergoing transapical transcatheter aortic valve implantation at our institution from April 2008 to December 2011. Of the 500 patients, 28 were in cardiogenic shock. Differences during the study period in baseline characteristics, procedural and postprocedural variables, and survival were analyzed using different statistical methods, including cumulative sum charts.

Results: The overall 30-day mortality was 4.6% (95% confidence interval, 3.1%-6.8%) and was 4.0% (95% confidence interval, 2.6%-6.2%) for patients without cardiogenic shock. Throughout the study period, no significant change was seen in the 30-day mortality (Mann-Whitney U test, $P = .23$; logistic regression analysis, odds ratio, 0.83 per 100 patients; 95% confidence interval, 0.62-1.12; $P = .23$). Also, no difference was seen in survival when stratified by surgeon (30-day mortality, $P = .92$). An insignificant change was seen toward improved overall survival (hazard ratio, 0.90 per 100 patients; 95% confidence interval, 0.77-1.04; $P = .15$).

Conclusions: The structured training program can be used to introduce transapical transcatheter aortic valve implantation and then gradually dispersed by internal proctoring to other members of the team with no concomitant detriment to patients. (J Thorac Cardiovasc Surg 2013;145:911-8)

The pioneering centers of transcatheter aortic valve implantation (TAVI) reported an important initial negative effect of the learning curve on the clinical outcomes.[1-7] Centers that introduced a TAVI program later on, such as our institution,[8] have had the opportunity to benefit from the cumulative knowledge of the "first wave" centers. Therefore, "second wave" centers might have a different learning curve, with a lower negative effect on outcome (ie, survival).

To test this hypothesis, we conducted a single-center study of the first 500 consecutive patients undergoing transapical TAVI. We examined the factors relevant to an institutional learning curve. Subsequently, we assessed ("aim of the study") whether the cumulative knowledge from the field incorporated into a structured training program could be used for introduction of a novel procedure (transapical TAVI) into clinical practice and then dispersed by internal proctoring to other members of the TAVI team without detriment to the clinical outcomes.

METHODS

Study Design

The present study was a retrospective, observational, single-center, cohort study of prospectively collected data from all patients who had undergone transapical TAVI at the Deutsches Herzzentrum Berlin (Berlin, Germany) from the beginning of the clinical introduction of transapical TAVI in April 2008 to December 2011. The study is reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement and the standardized endpoint definitions for TAVI clinical trials.[9] Our institutional review board approved the present study.

Patients

All 500 consecutive high-risk patients with aortic valve stenosis who underwent transapical TAVI at our institution were operated on by the same heart team and were included in the study ("study cohort"). All procedures were performed according to our structured training program and our TAVI checklist[10] (see Part 2, Table 1). All patients or their representatives gave informed consent.

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Disclosures: Drs Pasic, Unbehaun, Drews, Buz, and Dreysse have been proctors to Edwards Lifesciences since July 2009. All other authors have nothing to disclose with regard to commercial support.

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Abbreviations and Acronyms

CPB = cardiopulmonary bypass
CUSUM = cumulative sum analysis
IQR = interquartile range
PCI = percutaneous coronary intervention
TAVI = transcatheter aortic valve implantation

Patient Selection and Procedural Criteria

The patient selection, preoperative evaluation, assessment of the diameter of the aortic annulus, valve size selection, and procedural technique have been previously described in detail[8,11] and summarized as the institutional clinical policies.[10]

Procedure and Device

Transapical TAVI was performed in the hybrid operating room by the same TAVI team[8] using a principal surgical technique,[12] with some modifications,[13] according to the institutional policies.[10] The attendance of each member of the team in the hybrid operating room and his or her particular function during every procedure were precisely recorded in our database. Balloon-expandable transcatheter stent-prosthetic xenograft valves with their delivering systems (both Edwards Lifesciences LLC, Irvine, Calif) were used in all patients. The Edwards Sapien THV valves (size 23 or 26 mm) were used from April 2008 to August 2011 and the Edwards Sapien XT valves (size 23, 26 or 29 mm) from March 2011 until the end of the study period (December 2011).

Structured Educational Training Program

The program[10] regulates the introduction of TAVI at our institution and the building and training of the team. It includes a stepwise acquisition of the tools necessary for preoperative strategic planning, perioperative team communication, technical aspects of the procedure, and postoperative management. The program consists of 4 main parts: general principles, team building, team education and training, and the institutional clinical and procedural policies.[10]

Proctoring

Proctoring was divided into external and internal proctoring. Internal proctoring ("self-proctoring") was established on a basis of interaction between the members of the team ("be proctor and proctored"), with the aim of achieving a complete understanding of the fine details of the TAVI process.[10] It was performed in 4 segments: patient evaluation (segment 1); measurement of the aortic annulus and valve sizing (segment 2); valve preparation, technical procedural part, and guiding of the team (segment 3); and postprocedural patient management (segment 4).[10]

Definition of Outcomes

The primary endpoint was 30-day mortality. It was defined as death from any cause and irrespective of whether the death occurred from day 0 to day 30 (30th day included) after the index procedure.

The secondary endpoints included survival at follow-up and the intraprocedural, procedural, and postprocedural variables. Postimplantation aortic regurgitation, estimated by echocardiography and angiography, was divided (grade 0-IV) into absent (0), trace (<I), mild (I), moderate (II), and severe (>II, III, IV).[14] Technical procedural complications were considered surgical complications if they necessitated revision and were directly caused by surgical technical failure, including pseudoaneurysm of the apex, revision for bleeding, iatrogenic aortic dissection, valve migration, and annular rupture.

Follow-up and Data Collection

Follow-up was 100% complete. The most recent patients had at least 30 days of follow-up. The last update was performed in January 2012. All data concerning patient comorbidities, morbidity, and mortality were prospectively collected in an electronic database and analyzed. Information about the deaths of German patients was obtained from the official state administrative office and/or by direct contact with the patients' families and by telephone for the patients from outside Germany.

Assessment of Institutional Learning Curve

The effect of the learning curve was assessed by the procedural outcome (the incidence of complications and survival) and by the time effectiveness of the procedure (operating time duration, amount of contrast medium, irradiation parameters, intensive care unit stay, and hospitalization period).

Cumulative Sum Analysis

Data are also presented graphically as a plot of the outcome (cumulative sum analysis [CUSUM]). A cumulative failure chart[15,16] was used to evaluate the learning curve. The cumulative sum S_n of deaths until procedure n was plotted against n.

Statistical Analysis

Continuous variables are presented as the mean ± standard deviation or medians and interquartile range (IQR). Categorical variables are described as numbers and percentages. The 30-day rates during the study period are presented as percentages with 95% Wilson confidence intervals (CIs). Changes during the study period were analyzed, with the consecutive number of the procedure as an independent variable. Trends of the binary variables during the study period were compared between groups using the Mann-Whitney *U* test. The strength of the change was assessed by logistic regression analysis, checked by the Hosmer-Lemeshow test, and presented with the odds ratio and 95% CI. To improve readability, the odds ratios are presented for changes within 100 procedures. The trends of continuous variables were tested by nonparametric Spearman rank correlation (rho) with the number of the procedure. The Kruskal-Wallis test was used to assess the difference in the procedure time between different operators. Fisher's exact test was used to test for differences in mortality between groups and to assess the binary risk factors for mortality. The Mann-Whitney *U* test was used to analyze the continuous risk factors for mortality. Bivariate logistic regression analysis was applied to analyze the influence of risk factors on the learning curves of mortality. Overall survival is presented using Kaplan-Meier curves and was compared between groups using the log-rank test. A change in overall survival during the study period was analyzed using Cox regression analysis and is presented as the hazard ratio per 100 procedures with the 95% CI. The data were evaluated using the IBM SPSS Statistics software, version 19 (SPSS Inc, Armonk, NY).

RESULTS

Baseline Characteristics

Patient characteristics. The study cohort consisted of 311 women (62.2%) and 189 men (37.8%). The mean patient age was 79.5 ± 8.1 years (median, 80.6 years; range, 28.9-98.9 years; IQR, 75.3-84.6 years). The median logistic European System for Cardiac Operative Risk Evaluation of the study cohort was 30.4% (IQR 21.0%-48.5%) and the median Society of Thoracic Surgeons predicted operative mortality was 12.2% (IQR, 6.7%-21.6%). Of the 500 patients, 28 (5.6%) were in cardiogenic shock. The mean follow-up period was 458 ± 368 days, with a range of 0 (in the case of death during the procedural day) to 1363

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TABLE 1. Procedural and postprocedural characteristics

Parameter	Value	*P* value*
XT valve	94 (18.8)	<.001
23-mm valve	153 (30.6)	<.001
26-mm valve	306 (61.2)	<.001
29-mm valve	41 (8.2)	<.001
Contrast agent (mL)	100 (80-130)	.053
Radiation time (min)	6.7 (4.8-10.3)	<.001
DAP (μGy m^2)	7.0 (5.1-9.6)	.007
dP_{mean} (mm Hg)	4 (3-5.8)	.002
Aortic valve area (cm^2)	2.2 (1.9-2.4)	.13
No regurgitation	270 (54.0)	.16
Valve redilation	28 (5.6)	.38
Second valve	14 (2.8)	.006
Procedural time (min)	90 (75-115)	<.001
Intraprocedural packed RBCs (U)	0.6 (1.5)	.21
Elective PCI	57 (11.4)	.95
Elective CPB	25 (5.0)	.48
Emergency PCI	4 (0.8)	.79
Emergency CPB	10 (2.0)	.62
Conversion	4 (0.8)	.17
Follow-up (d)	458 ± 368	<.001
ICU time (h)	25.0 (19.8-53.5)	.15
In-hospital stay (d)	6.9 (5.0-10.8)	<.001
Drainage volume (24 h)	400 (238-625)	.91
Total invasive ventilation time (h)	15.1 (2.1-38.4)	<.001
Postoperative packed RBCs (U)	1 (0-2)	.06
Annulus rupture	6 (1.2)	
Aortic dissection	1 (0.2)	
Valve migration	1 (0.2)	
Revision for bleeding	7 (1.4)	
Revision for apical pseudoaneurysm	2 (0.4)	
Coronary obstruction†	2 (0.4)	
Endocarditis (late)	5 (1.0)	
Later aortic valve replacement/second TAVI	5 (1.0)	
Later cardiac surgery (other)	4 (0.8)	

Data presented as n (%), median (interquartile range), or mean ± standard deviation. *DAP,* Dose area product; *dP_{mean},* mean transvalvular gradient; *RBCs,* red blood cells; *PCI,* percutaneous coronary intervention; *CPB,* cardiopulmonary bypass; *ICU,* intensive care unit; *TAVI,* transcatheter aortic valve implantation. *For changes during study period (Spearman rank correlation or Mann-Whitney *U* test, as appropriate). †All treated successfully with PCI.

days (median 399 days; IQR, 126-711 days), with a total of 628 patient-years. At the last data collection, 374 patients (74.8%) were alive and 126 (25.2%) had died during the follow-up period. The patient characteristics are summarized in Appendix Table 1.

Procedures and proctoring. A total of 500 transapical TAVI procedures were performed within 43.8 months. For each subgroup of 100 patients, the duration was 12.4, 9.8, 8.0, 7.7, and 5.6 months, respectively. Of the 5 surgeons, the oldest and first operator performed 221 (44.2%) procedures (Figure 1). Three other operators started after 100 procedures and performed 116 (23.2%), 71 (14.2%), and 84 (16.8%) procedures, respectively. The fifth operator started after 441 procedures and operated on 8 patients (1.6%;

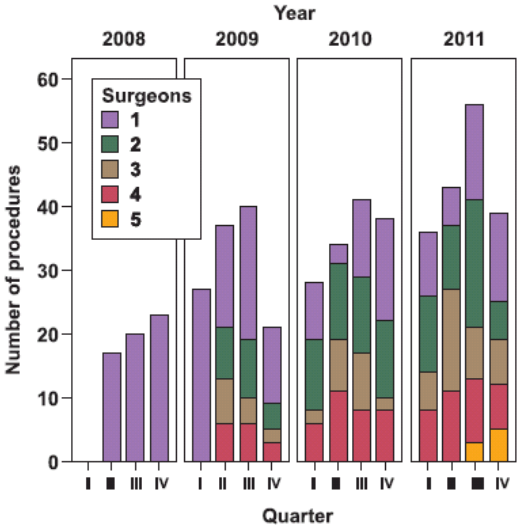

FIGURE 1. Procedures versus calendar time according to surgeon. Of 5 surgeons, the first and most experienced performed first 100 procedures.

Kruskal-Wallis test, $P < .001$ for the different periods of operators; Figure 1). Surgeon 1 participated in 30% (119/400), 7.5% (30/400), and 4% (10/400) of the procedures as the first, second, and third assistant, respectively. Of the 472 patients without cardiogenic shock, 203 (43%), 107 (22.7%), 70 (14.8%), 84 (17.8%), and 8 (1.7%) underwent surgery by surgeons 1 to 5, respectively. Of the 28 patients with cardiogenic shock, 18 (64.3%), 9 (32.1%), and 1 (3.8%) underwent surgery by surgeons 1 to 3, respectively. Segment 1 of the internal proctoring was performed for the first 100 indexed procedures and subsequently only by request. Segment 2 was applied for 300 cases and later only occasionally, according to the CUSUM charts or by request. Segment 3 was performed in the phases according to the CUSUM charts. Segment 4 was performed for 400 procedures and then occasionally.

Procedural characteristics. The intraprocedural and postprocedural data are listed in Table 1. Edwards Sapien THV valves were used in 406 study patients (81.2%) and Edwards Sapien XT valves in 94 (18.8%). Combined planned percutaneous coronary intervention (PCI) was used in 57 patients (11.4%), and cardiopulmonary bypass (CPB) was electively used in 25 (5%). Of the 500 patients, 11 (2.2%) underwent additional combined conventional cardiac surgery. Four conversions (0.8%) were required to conventional aortic surgery (three for annular rupture). The final paravalvular or transvalvular regurgitation grade was 0.4 ± 0.5 (range, 0-2).

Thirty-day mortality. The overall 30-day mortality rate for the whole study cohort of 500 patients was 4.6% (95% CI, 3.1%-6.8%), with 23 deaths among the 500

patients (Appendix Table 2). The 30-day mortality for patients without cardiogenic shock was 4.0% (95% CI, 2.6%-6.2%; 19 deaths among 472 patients). Among the 28 patients who underwent TAVI in cardiogenic shock, 4 died during the first 30 days (14.3%; 95% CI, 5.7%-31.5%; Fisher's exact test, $P = .03$ vs patients without shock). Throughout the study period, no significant change was seen in 30-day mortality (Mann-Whitney U test, $P = .23$; logistic regression odds ratio, 0.83 per 100 patients; 95% CI, 0.62-1.12; $P = .23$). No difference was seen in 30-day mortality when stratified by surgeon (Fisher's exact test, $P = .92$).

The series of 100 patients with the greatest 30-day mortality rate during the study period was between indexed procedures 258 and 357, with mortality of 8.0% (8 of these 100 consecutive patients died). The series of 100 patients with the lowest 30-day mortality rate per 100 consecutive patients (1.0%) was found between indexed procedures 358 and 463. (In this series between indexed procedures 358 and 463, when all 105 consecutive patients were included, the mortality was 0.9%, with 1 death.) One series of 75 consecutive patients (between indexed procedure 358 and 432) had no deaths within 30 days after the index procedure (30-day mortality, 0%). No mortality occurred among the first 11 patients. The last death (indexed procedure 499) occurred intraoperatively. A total of 8 patients (1.6%) died intraoperatively. The 30-day mortality in the 5 subgroups of each 100 consecutive patients was 6%, 6%, 3%, 5%, and 3%.

Changes in patient characteristics during study period. Differences in the demographic characteristics of the treated patients were seen in the percentages of men and women and the risk profile of the patients, as mirrored by the risk scores. During the study period, a significant increase occurred in the percentage of male patients (Mann-Whitney U test, $P = .002$) and a reduction in the risk scores (logistic European System for Cardiac Operative Risk Evaluation, Society of Thoracic Surgeons predicted risk of mortality, Society of Thoracic Surgeons morbidity or mortality risk; Spearman rank correlation for each variable, $P < .001$). However, bivariate logistic regression analysis demonstrated that these changes in patient characteristics did not influence the learning curves of 30-day mortality.

Procedural characteristics with no changes through study period. No significant changes were seen in the mean rates of elective PCI ($P = .95$), elective use of CPB ($P = .48$), and emergency use of CPB ($P = .62$). Also, no significant changes were seen in the mean duration of the induction of anesthesia (Spearman's rho, 0.05; $P = .25$), amount of contrast volume used per procedure (rho, 0.09; $P = .053$), number of repeat ballooning procedures for paravalvular leakage (Mann-Whitney U test, $P = .38$), final regurgitation grade (rho, −0.06; $P = .16$), intensive care unit stay (rho, −0.06; $P = .15$), intermediate care stay (rho, −0.005; $P = .91$), postoperative blood drainage (rho, −0.005; $P = .91$), or mean numbers of units of blood, fresh frozen plasma, or thrombocytes given.

Procedural characteristics with changes during study period. The procedure duration, radiation time, postoperative ventilation time, and hospital stay at our institution decreased during the study period ($P < .001$ for all variables). Also, a significant reduction was seen in the use of a second Edwards Sapien valve during the same procedure ($P = .006$).

Technical procedural complications during study period. The incidence of surgical complications occurring during the technical part of the procedure was very low (Table 1) and included revision for bleeding in 7 (1.4%; indexed procedure 17, 20, 53, 104, 282, 333, and 389), surgical revision of apical pseudoaneurysm in 2 (0.4%; indexed procedure 109 and 261), iatrogenic aortic dissection in 1 (0.2%; indexed procedure 413; treated by transapical placement of an uncovered aortic endostent; patient survived[16]), and valve migration in 1 patient (0.2%; indexed procedure 499; patient died intraoperatively). Annular rupture occurred in 6 patients (1.2%; indexed procedure 60, 169, 259, 305, 422, and 423), with 3 deaths.[11] Because few events occurred per risk factor, the number of events was not sufficient to enable accurate statistical analysis.[18]

Late survival. The overall 6-month, 1-year, and 2-year survival rate was 83.9% ± 1.7%, 80.1% ± 1.9%, and 68.4% ± 2.7%, respectively, for the whole group (Figure 2). An insignificant change was seen toward improved overall survival during the study period, with a 10.3% reduction in mortality per 100 procedures (hazard ratio, 0.90; 95% CI, 0.77-1.04; $P = .15$). No differences were seen in survival when stratified by surgeon (log-rank test, $P = .22$; Figure 2).

Association of baseline and procedural characteristics with survival. The patients had increased 30-day mortality if they were in cardiogenic shock at surgery ($P = .03$), if conversion to conventional valve surgery was performed ($P = .01$), and if emergency CPB was used ($P < .001$). No difference was seen in overall survival between the male and female patients ($P = .52$; Figure 2), if elective PCI ($P = .73$) or emergency PCI ($P = .17$) was performed, if a different valve was used (THV vs XT, $P = .59$), or if valve repeat ballooning was performed ($P = .13$). Univariate analysis revealed that the variables age ($P = .13$), logistic European System for Cardiac Operative Risk Evaluation score ($P = .12$), and Society of Thoracic Surgeons predicted operative mortality score ($P = .14$) were not conjunct with the 30-day mortality. An increased procedure duration ($P < .001$), radiation time ($P = .05$), intraoperative blood and blood products given ($P < .001$ for packed red blood cell units and $P = .02$ for thrombocyte units given), and postoperative fresh frozen plasma application ($P < .001$) were related to increased 30-day mortality. However, the

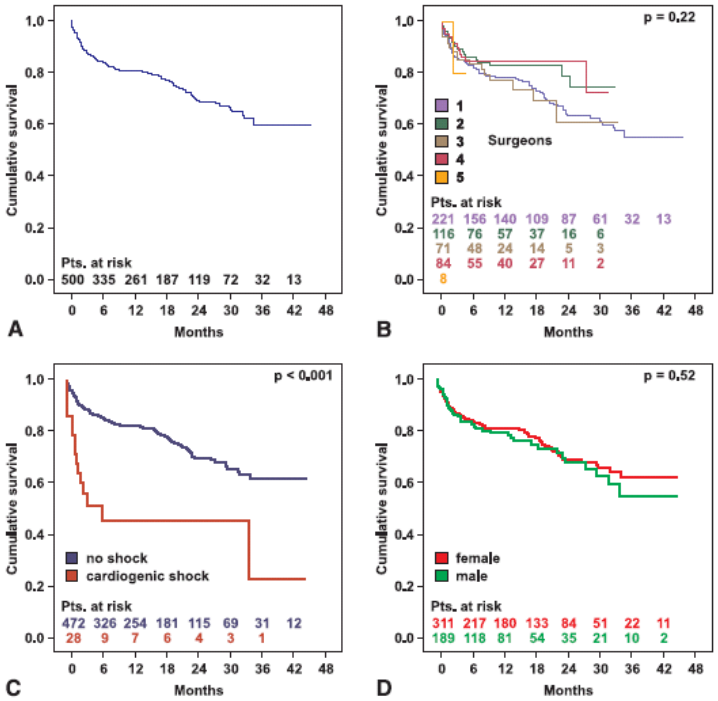

FIGURE 2. Kaplan-Meier survival functions of A, whole cohort of 500 patients and subgroups of patients *(Pts.)* B, according to surgeon, C, patients with and without cardiogenic shock, and D, according to gender.

significant variables showed the consequence of difficulties occurring during the procedure rather than the cause of death. Owing to the small number of deaths, no multiple statistical evaluation was performed.

CUSUM evaluation. The CUSUM failure graph (Figure 3) showed no increase in 30-day mortality at the beginning that could be expected in a classic learning curve.[16] The chart demonstrated a cluster of deaths after indexed procedure 100, after 175, and after 300 (Figure 3) that correlated with the point of a reduction in the level of internal proctoring and forced reintroduction of a greater level of internal proctoring. The Hosmer-Lemeshow test did not detect any violation of a constant odds ratio ($P = .60$), demonstrating an adequate immediate reaction.

Assessment of learning curve. The logistic learning curve (Figure 4) demonstrated the absence of the typical greater values (ie, absence of increased mortality) at the beginning that could be expected in a classic learning curve.[16]

DISCUSSION

The main result of the present study was the evidence that the cumulative knowledge from the field incorporated into a structured training program can be used for initial introduction of a novel technique—transapical TAVI—into clinical institutional practice and can be gradually dispersed by internal proctoring to other members of the team without negative effects on the clinical outcome. This program resulted in lower-than-expected 30-day mortality and a low technical complication rate from the beginning, remaining consistent throughout a series of 500 procedures. The negative effect of the learning curve was absent both for the whole team and individually for each surgeon. Therefore, the study results strongly recommend that a prospective TAVI team should undergo a structured and intensive training program before starting clinical application of TAVI.

An additional and important negative observation of the present study was that early mortality is increased if an intraprocedural complication occurs, requiring conversion to conventional surgery or even only institution of emergency CPB.

Cumulative Knowledge From the Field and the Learning Curve

A typical learning curve shows the "learning phase" at the beginning, with increased mortality or complication rate, the "intermediate phase," with decreasing overall complication and mortality rates, and, finally, the "expert phase," characterized by low rates.[16] In terms of mortality,

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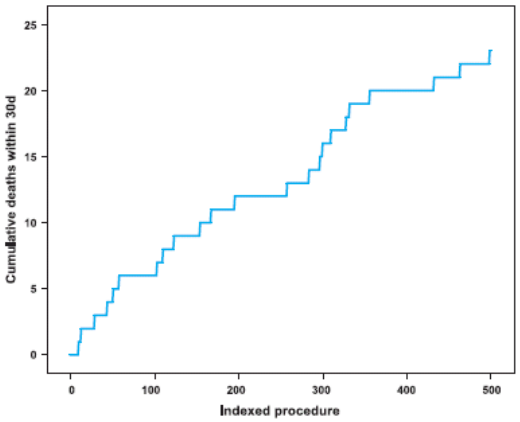

FIGURE 3. Unadjusted cumulative failure chart with 30-day mortality of study cohort showing clusters of failure (deaths) during short period after indexed procedure 100, 175, and 300 correlating with point of reduction of internal proctoring (and forcing a return to a greater level of internal proctoring).

our learning curve missed out the first phase, which we believe to be mostly because of the structured training program that encompassed the cumulative knowledge and experience of the "first-wave" centers. The "first-wave" centers had elevated mortality during their early experience compared with their recent experience,[1-5,7] and their results fit into the classic learning curve. The initial mortality during the learning curve might be double that during the expert phase. The Leipzig group[4] showed a reduction in 30-day mortality from 11.3% to 6%, comparing their first

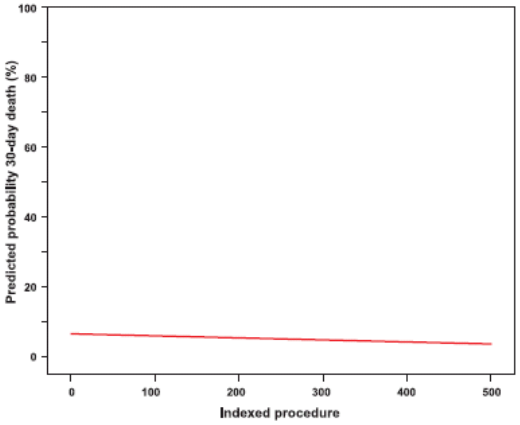

FIGURE 4. Learning curve of 30-day mortality (logistic regression analysis) showing absence of typical greater values (ie, absence of mortality increase) at beginning. No significant change seen in 30-day mortality throughout study period.

150 patients with their subsequent 149 patients and with progressive improvement in outcomes despite an unchanged patient risk profile. It seems that each member (operator) of the team needs—in general—at least 50 to 100 procedures to reach the expert phase. Thus, the more operators/members, the longer the learning curve. However, only a few reports have been published about the "learning curve for TAVI."[1-8,19] Most of them have studied, logically, only a small number of patients. The largest reported experience was of 299 patients.[4] Among the "first-wave" centers with extensive experience with the novel procedure (>100 procedures), the Leipzig group[4] also had the lowest 30-day mortality rate during their recent experience (6%).

Length of Our TAVI Learning Curve

The results from the present study failed to find a complete answer to this question. In terms of the primary endpoint (30-day mortality), the present study has clearly demonstrated the absence of increased mortality throughout the study period. However, in terms of the secondary endpoints, our results only gave a partially positive answer. Although the observed technical procedural complication rate was already low from the beginning of the TAVI program, the study results confirmed that a small, but certain, number of patients would—throughout the study period—have a possibly detrimental intraprocedural complication (eg, annular rupture) that is difficult to manage. This is the main disadvantage of TAVI compared with conventional aortic valve surgery. Therefore, the main problem of TAVI remains—the uncertainty about the definitive result at the end of the procedure. Similarly, it is still not possible to predict clearly whether a patient undergoing TAVI will have relevant paravalvular leakage (with known negative consequences for late survival and a reason for preferring conventional aortic valve surgery). Additionally, the effect on cognitive function of cerebral microembolization and the ischemic microlesions that always occur during all phases of valve implantation[20] remains to be defined. Therefore, we believe we are still in the learning curve. All these factors should be considered critically before the procedural indication is broadened to younger or lower risk patients.

Importance of Heart Team for Prospective Cardiovascular Training

The present study has emphasized the importance of the combined work of surgeons and cardiologists in a team. Our team was able to perform all types of TAVI procedures and conventional aortic valve surgery[21] and to treat its own procedural complications using surgical or catheter-based methods.[11,17,22,23] Thus, 1 team was able to perform the procedure assessed to be the best for each patient. This attitude should have important consequences for the education and training of prospective cardiologists and surgeons. Therefore, in the future, cardiovascular training

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should include the knowledge, skills, and experience of both a cardiologist and a conventional cardiovascular surgeon. A prospective cardiovascular specialist should be able to perform all types of catheter-based and conventional surgery, including managing all complications using both procedures. Complications will be managed mostly using a catheter-based technique,[17,22] with surgical revision needed only if the interventional method is not possible or fails to treat the complication.[11,23]

Study Limitations

The study possessed several limitations. The main limitations were the retrospective study design and the lack of a comparable study group. However, the data were prospectively collected and timely analyzed with immediate clinical consequences. Despite this, a prospective study with a control group would make possible the comparison between proctored and nonproctored cases. Therefore, a prospective study is needed. An additional important limitation was that the device-related factors (using a modified type of valve during the experience) could have some influence (negative or positive) on the results.

CONCLUSIONS

Transapical TAVI could be a valid step toward the ultimate goal of replacing the aortic valve without surgery, but the procedure itself still needs its own learning curve. Thus, the study results strongly recommend a structured and intensive training program before starting clinical application of TAVI.

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APPENDIX TABLE 1. Preoperative characteristics of study cohort (n = 500)

Parameter	Value	*P* value*
Male	189 (37.8)	.002
Female	311 (62.2)	.002
Height (cm)	165 (160-171)	.03
Weight (kg)	72.5 (62-82)	.01
Body mass index (kg/m^2)	26.6 (23.6-29.7)	.28
NYHA class IV	169 (33.8)	.10
Age (y)	80.6 (75.3-84.6)	.97
FEV_1 (L)	1.5 (1.2-1.9)	.01
FEV_1 (%)	74 (59-90)	.05
Creatinine (mg/dL)	1.1 (0.85-1.3)	.04
Creatinine clearance (mL/min)	50.9 (36.9-65.9)	.001
Dialysis	15 (3)	1.0
NT-proBNP (pg/mL)	2146 (1031-5118)	.01
Troponin I (μg/mL)	0.02 (0.01-0.05)	<.001
Cardiogenic shock	28 (5.6)	.34
Logistic EuroSCORE (%)	30.4 (21.1-48.5)	<.001
STS PROM score (%)	12.2 (6.7-21.5)	<.001
STS MoM score (%)	40.9 (30.0-58.3)	<.001
Atrial fibrillation	14.5 ± 29.0	.03
Pacemaker/ICD	57 (11.4)	.50
Previous aortic valve replacement	27 (5.4)	.58
Previous coronary bypass surgery	87 (17.4)	.24
Previous mitral valve replacement	12 (2.4)	.54
Stroke/cerebral lesion	113 (22.6)	<.001
Peripheral arterial disease	342 (68.4)	.22
Chronic pulmonary obstructive disease	240 (48.0)	.10
Systolic PAP > 50 mm Hg	179 (35.8)	.26
Diabetes mellitus	140 (28.0)	<.001
Renal failure	121 (24.2)	.03
Coronary artery disease	301 (60.2)	.09
Previous PCI	93 (18.6)	<.001
Left ventricular ejection fraction (%)	55 (40-60)	.77
LVEDD (mm)	48 (44-54)	.30
dP_{max} (mm Hg)	73 (60-85)	.45
dP_{mean} (mm Hg)	50 (40-56)	.55
Aortic valve area (cm^2)	0.6 (0.6-0.8)	.24
Annulus/TEE (mm)	22.4 (21.1-23.3)	<.001
Annulus/CT (mm)	23.0 (21.9-24.3)	.37
Bicuspid aortic valve	13 (2.6)	.003
Severe calcified ascending aorta	69 (13.8)	<.001

Data are presented as mean ± standard deviation, n (%), or median (interquartile range). *NYHA*, New York Heart Association; *FEV_1*, forced expiratory volume in 1 second; *NT-proBNP*, N-terminal probrain natriuretic peptide; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *STS*, Society of Thoracic Surgeons; *PROM*, predicted operative mortality; *MoM*, mortality or morbidity; *ICD*, implantable cardiodefibrillator; *PAP*, pulmonary artery pressure; *PCI*, percutaneous coronary intervention; *LVEDD*, left ventricular end-diastolic diameter; *dP_{max}*, maximal transvalvular gradient, *dP_{mean}*, mean transvalvular gradient; *TEE*, transesophageal echocardiography; *CT*, computed tomography. *For changes during study period (Spearman rank correlation or Mann-Whitney *U* test, as appropriate).

APPENDIX TABLE 2. Thirty-day outcomes according to standardized endpoint definitions for TAVI clinical trials of Valve Academic Research Consortium

Parameter	n (%)
All-cause mortality	23 (4.6)
Cardiovascular mortality	21 (4.2)
Periprocedural myocardial infarction	3 (0.6)
Spontaneous myocardial infarction	2 (0.4)
Major stroke	5 (1.0)
Minor stroke	5 (1.0)
Life-threatening bleeding	18 (3.6)
Minor vascular complication	4 (0.8)
Major vascular complication	18 (3.6)
Renal dialysis	18 (3.6)
Combined safety endpoint	85 (17.0)
Permanent pacemaker	28 (5.6)

TAVI, Transcatheter aortic valve implantation.

CURRICULUM VITAE

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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Pasic M, Unbehaun A, Dreysse S, Buz S, Drews T, Kukucka M, Mladenow A, D'Ancona G, Hetzer R, Seifert B. Introducing transapical aortic valve implantation (part 1): effect of a structured training program on clinical outcome in a series of 500 procedures. J Thorac Cardiovasc Surg 2013;145:911-8.

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