Learning curves for transapical transcatheter aortic valve replacement in the PARTNER-I trial: Technical performance, success, and safety

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ABSTRACT

Objectives: Introduction of hybrid techniques, such as transapical transcatheter aortic valve replacement (TA-TAVR), requires skills that a heart team must master to achieve technical efficiency: the technical performance learning curve. To date, the learning curve for TA-TAVR remains unknown. We therefore evaluated the rate at which technical performance improved, assessed change in occurrence of adverse events in relation to technical performance, and determined whether adverse events after TA-TAVR were linked to acquiring technical performance efficiency (the learning curve).

Methods: From April 2007 to February 2012, 1100 patients, average age 85.0 ± 6.4 years, underwent TA-TAVR in the PARTNER-I trial. Learning curves were defined by institution-specific patient sequence number using nonlinear mixed modeling.

Results: Mean procedure time decreased from 131 to 116 minutes within 30 cases ($P = .06$) and device success increased to 90% by case 45 ($P = .0007$). Within 30 days, 354 patients experienced a major adverse event (stroke in 29, death in 96), with possibly decreased complications over time ($P \sim .08$). Although longer procedure time was associated with more adverse events ($P < .0001$), these events were associated with change in patient risk profile, not the technical performance learning curve ($P = .8$).

Conclusions: The learning curve for TA-TAVR was 30 to 45 procedures performed, and technical efficiency was achieved without compromising patient safety. Although fewer patients are now undergoing TAVR via nontransfemoral access, understanding TA-TAVR learning curves and their relationship with outcomes is important as the field moves toward next-generation devices, such as those to replace the mitral valve, delivered via the left ventricular apex. (J Thorac Cardiovasc Surg 2016;152:773-80)

Device success increased and procedure time decreased within 30 to 45 cases.

Central Message

The learning curve for TA-TAVR did not compromise patient safety.

Perspective

The learning curve for TA-TAVR was 30 to 45 cases and technical competence was achieved without compromising patient safety. Although fewer patients are undergoing TAVR via non-TF access, understanding TA-TAVR learning curves and their relationship with outcomes is important as the field moves toward next-generation devices delivered via the left ventricular apex.

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Data used for this study were from a December 20, 2012, locked data extract provided to the PARTNER Publications Office by Edwards Lifesciences. These data have been approved for use in research by institutional review boards at each institution. All patients provided written informed consent. Data analysis was performed by

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Abbreviations and Acronyms

AR	= aortic regurgitation
PARTNER	= Placement of Aortic Transcatheter Valves
TA	= transapical
TAVR	= transcatheter aortic valve replacement
TF	= transfemoral

Scanning this QR code will take you to the appendices, supplemental figures, tables, and video for this article.

Transcatheter aortic valve replacement (TAVR) has revolutionized treatment of patients with severe senile calcific aortic valve stenosis. As with introduction of any complex procedure, particularly one requiring a team approach, a set of skills must be mastered to achieve technical competence: the learning curve.^{1,2} To date, the time necessary to traverse this learning phase for transapical (TA) TAVR remains unknown, and it is uncertain whether this learning curve compromises successful valve replacement and patient safety.

International TAVR trials have been designed to mandate a “transfemoral (TF) first” access strategy, with alternative access, such as the TA approach, reserved for patients with severe peripheral vasculopathy.^{3,4} Because clinical risk factors associated with peripheral vascular disease may preclude TF access, understanding learning curves associated with TA-TAVR is necessary to ensure this procedure is performed successfully and safely. In this study, we sought to answer the following questions: (1) Was there a technical performance learning curve for TA-TAVR in the Placement of Aortic Transcatheter Valves (PARTNER) I trial? (2) Were there associated consequences during this period, such as occurrence of adverse events early after TA-TAVR? (3) Did the technical performance learning curve compromise successful valve replacement and patient safety?

METHODS**Patients**

From April 2007 to February 2012, 1100 patients from 24 PARTNER-I trial institutions underwent TA-TAVR. Average age was 85.0 ± 6.4 years and mean transaortic gradient was 44 mm Hg, with a mean aortic valve area of 0.64 cm^2 , consistent with severe senile calcific aortic stenosis. Nearly all patients had peripheral vascular disease (98%), hypertension (96%), and hyperlipidemia (87%), and 51% had undergone previous coronary artery bypass grafting and 46% previous percutaneous coronary intervention; 43% had cerebral vascular disease, 45% chronic pulmonary

disease, and 36% diabetes (Table E1). Median number of cases performed per institution was 48, with 2 the lowest and 112 the highest (Figure E1). Because prevalence of TA-TAVR steadily increased during the PARTNER-I trial (Figure E2) and the interval between TA-TAVR cases decreased at nearly all institutions, that is, institution volume increased (Figure E3), we included all as-treated TA-TAVR patients who were part of both randomized and nonrandomized cohorts (Table E2).

Study Device and Procedure

The Edwards SAPIEN transcatheter heart valve system (Edwards Lifesciences, Irvine, Calif) used in the PARTNER-I trial consisted of a trileaflet bovine pericardial valve (model 9000TFX) and a balloon-expandable, stainless steel support frame. Technical details of TA-TAVR have been previously described.⁵ The procedures themselves were performed by the institution's own team. An experienced industry technical representative was also in attendance for each case, along with qualified interventional cardiologists. Cardiac surgery proctors observed, on average, the first 3 procedures.

Study Design

This is an as-treated analysis. Before start of the PARTNER-I trial, 40 patients underwent TA-TAVR with the SAPIEN device at 3 institutions: Columbia University ($n = 13$), Cleveland Clinic ($n = 12$), and Baylor Health Care System ($n = 15$). For purposes of learning curve analyses, sequential numbering of patients for these 3 institutions was adjusted to reflect the number of procedures that had been performed before the PARTNER-I trial; however, patient-level data were unavailable for these 40 patients. To illustrate, 12 patients underwent TA-TAVR at Cleveland Clinic before the trial, so patient sequence number for analysis started at 13.

Data

Data used for this study were from a December 20, 2012, locked data extract provided to the PARTNER Publications Office by Edwards Lifesciences. These data have been approved for use in research by institutional review boards at each institution. All patients provided written informed consent.

Endpoints

Technical performance. Among the many technical performance measures for which learning curves were assessed, we selected those that would illustrate technical efficiency and the influence on the learning curve of accumulating external experience: procedure time, fluoroscopy time, contrast volume used, and number of postdeployment dilatations. Procedure time was the time from surgical incision until incision closure. Influence of external experience on technical performance was assessed by the institution's date of entry into the trial.

Outcomes. Intra- and postprocedure events assessed included device success, adverse events occurring during the procedure, length of postprocedure hospital stay, and major adverse events occurring within 30 days. All were adjudicated by a clinical events committee and defined as follows:

1. Device success: Delivery and deployment of the prosthesis and retrieval of the delivery catheter, resulting in an aortic valve area larger than 0.9 cm^2 , with less than 3+ aortic regurgitation (AR) in the earliest evaluable echocardiogram and only a single valve deployed and implanted in the correct anatomical position. Even if another valve was required that successfully treated, for example, severe paravalvular leak, this was classified as device failure. This definition closely parallels that of the Valve Academic Research Consortium.⁶
2. Adverse events during procedure: Intraprocedural events included vascular hemorrhage, bleeding, arrhythmia, hypotension, conduction defects, abnormal laboratory values, and paravalvular leak (Table E3). Definitions of these adverse events followed PARTNER-I trial protocol definitions.⁷

3. Length of postprocedure hospital stay: Interval in days between index procedure date and hospital discharge date after the procedure.
4. Major adverse events occurring within 30 days: A composite endpoint that included adverse events during the procedure, all-cause mortality, stroke, major bleeding, and major vascular complications (Appendix E1).

Data Analysis

Analyses were performed using SAS statistical software (SAS v9.2; SAS, Inc, Cary, NC) and R software version 3.0.2 (<http://www.R-project.org>).

Learning curves were explored using 3 general strategies, and a fourth special strategy for procedure time (Appendix E2). First, a learning curve profile for all technical and outcomes endpoints was constructed for each institution according to institution-specific patient sequence number. These were summarized for continuous data using locally weighted scatterplot smoothing (loess).⁸ Second, an overall learning curve profile across all institutions was constructed using mixed-effects modeling to account for correlation of patients within an institution. This methodology permitted us to derive a confidence band around the point estimates and to generate numerical estimates at selected sequence numbers. To obtain tests of statistical significance, this analysis was supplemented by focused modeling of each learning curve variable with patient sequence number. Third, because institutions entered the trial at different times, which confounds date-of-procedure effects, we investigated the effect of entry date of each institution into the PARTNER-I trial on learning curves using a combination of data exploration and estimation of trends according to broad categories of trial entry date.

For procedure time, a more intense modeling approach was used to estimate the number of cases required to reach a steady value. For this, we applied a commonly used hyperbolic model for learning curves that assumes that procedure time would decrease with experience at an institution-specific rate, but eventually would reach an institution-specific average minimum time (mathematically, an asymptote; see Appendix E2). A nonlinear mixed-effects method was used for this. By definition, an asymptote is reached only with an infinite number of cases, so we chose 15 seconds as the difference between successive procedure times to indicate that the curve had become essentially flat. This model permitted us to perform a multivariable analysis that included institution-specific patient sequence number, interval between procedures (an instantaneous measure of the institution's case volume), and trial entry date.

Association of outcomes learning curves with patient variables and technical performance metrics. We investigated the association of major adverse events occurring within 30 days of TA-TAVR and post-TAVR length of stay with patient variables (Appendix E3) and technical performance metrics (procedure time, fluoroscopy time, contrast volume, pacing count during balloon aortic valvotomy and prosthesis deployment, and number of postdeployment dilations). Although procedure time demonstrated a clear learning curve, patient factors and events occurring during the procedure may prolong it. Therefore, to explore the possible link between this learning curve and 30-day major adverse events, we decomposed procedure time into 3 components:

1. Procedure time learning curve: For each patient, we predicted procedure time by a hyperbolic mixed-effects model of patient sequence number as described in Appendix E2. This analysis accounted for institution trial entry date, interval between cases, and patient sequence number.
2. Patient factors influencing procedure time: For each patient, we predicted procedure time by a linear mixed-effects parsimonious model of patient factors. This analysis accounted for institutional variability as a random effect.

3. Unmeasured factors prolonging procedure time: The difference between observed procedure time and that accounted for by the technical learning curve and patient factors was assumed to represent patient selection factors, events during the procedure prolonging its duration, and other unmeasured variables.

Three variables representing each of these 3 components were then forced into models of 30-day major adverse events, along with patient variables.

Missing values. We used fivefold multiple imputation for missing values of variables used in multivariable analyses, as described in Appendix E2.⁹

Presentation. Continuous variables are summarized as mean $\pm$ standard deviation or as equivalent 15th, 50th (median), and 85th percentiles when distribution of values is skewed. Categorical variables are summarized by frequencies and percentages. Confidence limits or bands are 68%, which is consistent with 1 standard error of the point estimate, but may be asymmetric.

RESULTS

Technical Performance

Mean procedure time was 120 ± 67 minutes (Table 1), decreasing from 131 to 116 minutes by case 30 (Table E4), and remaining constant at approximately 117 minutes thereafter (Figures 1 and 2, A, Table E4; $P = .06$). On average, it took 1.7 ± 0.46 years for institutions to perform 30 cases. Institutional values of non-risk-adjusted average minimum (asymptotic) procedure time ranged from 77 to 222 minutes (Figure E4, A). This minimum was reached after 5 to 52 cases, but typically 15 (Figure E4, B). Among the last 5 institutions entering the trial, 9 cases were needed to reach a minimum procedure time (Figure E4, C), although these institutions tended to have a longer asymptotic procedure time than those entering the trial near its beginning (Figure E4, D). The average calendar time it took institutions to reach their asymptote was 14.0 ± 6.9 months. We were unable to demonstrate that higher institutional volume, assessed as lower interval between sequential cases, was associated with procedure time after accounting for sequence number and trial entry date ($P = .5$).

Fluoroscopy time averaged 14 ± 10 minutes (Figure 2, B, Table 1) and decreased only slightly from 14 to 12 minutes by case 60 (Table E4; $P = .01$). Median contrast volume was 90 mL (15th and 85th percentiles 45 and 150 mL), decreasing from 114 to 90 mL by case 60 (Figure 2, C, Table E4; $P < .0001$). Frequency of postdeployment dilations remained low (none in 89% of patients) and constant across the experience (Figure 2, D, Table E4; $P = .5$).

Outcomes

Device success increased from 72% to 80% by 4 cases and to 90% within 45 cases (Figures 1 and 3, Table E4; $P = .0007$). On average, it took 2.20 ± 0.48 years for institutions to perform 45 cases. Intraprocedural adverse events fell from 31% to 25% by 15 cases, but with wide confidence limits, and remained constant thereafter

TABLE 1. Technical performance and outcomes endpoints after transapical transcatheter aortic valve replacement

Endpoint	n*	n (%)
Technical performance		
Procedure time, min	1092	120.0 ± 66.7 [†]
Fluoroscopy time, min	1048	13.5 ± 10.5 [‡]
Contrast medium, mL	1057	45/90/150 [‡]
Postdilations	1096	
0		980 (89)
1		103 (9.4)
2		12 (1.1)
3		1 (0.09)
Outcomes		
Device success	1061	930 (88)
Aortic regurgitation grade at discharge		
Total	1021	
None/trace		587 (57)
Mild		366 (36)
Moderate		64 (6.3)
Severe		4 (0.39)
Transvalvular	1020	
None/trace		907 (89)
Mild		109 (11)
Moderate		4 (0.39)
Severe		0 (0)
Paravalvular	1018	
None/trace		657 (65)
Mild		305 (30)
Moderate		53 (5.2)
Severe		3 (0.29)
Adverse events during procedure	1100	257 (23)
Myocardial perforation	1100	11 (1.0)
Ventricular injury	1100	4 (0.36)
Adverse events within 30 d	1100	
Stroke		29 (2.6)
Mortality		96 (8.7)
Major bleeding		97 (8.8)
Major vascular complication		39 (3.5)
Composite 30-d major adverse event	1100	354 (32)
Postprocedure length of stay, d	1081	5/8/15 [‡]

*Patients with data available. [†]Mean ± standard deviation. [‡]15th/50th/85th percentiles.

(Figure 4, A, Table E4; $P = .3$). Specifically, 15 patients experienced intraprocedural myocardial perforation or ventricular injury (Table 1), with no significant trend over patient sequence number (Figure E5, A, $P = .4$) or years from institution trial entry date (Figure E5, B, $P = .8$). Median postprocedure length of hospital stay was 8 days (15th and 85th percentiles 5 and 15 days) and became slightly shorter with increasing experience (Figure 5, Table E4; $P = .13$); after risk adjustment, postprocedure hospital stay was found to be statistically significantly shorter with increasing sequence number ($P = .04$).

A total of 46% of patients had none/trace paravalvular AR initially, improving to 66% within the first 30 cases, whereas moderate paravalvular AR fell from 11% to

FIGURE 1. Overall profile of procedure time and device success for transapical transcatheter aortic valve replacement, ordered by institution-specific patient sequence number. Solid red line represents average procedure time adjusted for institution and solid blue line represents average percent of patients who experienced successful device deployment.

5.1% (Figure 6, Table E4; $P = .10$). Transvalvular AR was minimal across experience, with 84% of patients having none/trace transvalvular AR and 15% mild initially; prevalence of none/trace transvalvular AR increased to 89% and mild decreased to 10% within 30 cases (Figure E6, A, Table E4; $P = .2$). Initially, 41% of patients had none/trace total AR, which improved to 58% by case 30, whereas moderate total AR fell from 12% to 6.3% (Figure E6, B, Table E4; $P = .13$).

Within 30 days, 354 patients (32%) experienced at least 1 major adverse event: 29 (2.6%) had a stroke, 97 (8.8%) a major bleeding episode, and 39 (3.5%) a major vascular complication; 96 patients (8.7%) died (Table 1, Figure E7). Occurrence of a composite event (adverse event or death) within 30 days fell from 51% initially to 29% by case 30, then rose slightly to 36% by case 90 (Figure 4, B, Table E4; $P = .01$).

Influence of Technical Performance on Outcomes

Total procedure time was strongly associated with outcomes, with a nearly linear increase in risk of 30-day major adverse events (Figure 7). The most significant risk factors for 30-day major adverse events were longer procedure time, baseline antiplatelet drug therapy, higher international normalized ratio, and lower hemoglobin, but only possibly patient sequence number (Table E5; $P = .09$). On further analysis (Table E6), when procedure time was deconstructed into technical performance, patient characteristics, and unknown factors, there was no evidence ($P = .8$) of an effect of technical performance, as reflected by procedure time, on the composite endpoint; rather, patient profile ($P = .05$) and unknown variables ($P < .0001$) were associated, although a possible effect of sequence number persisted ($P = .06$).

FIGURE 2. Overall profile of mean technical performance for transcatheter aortic valve replacement, ordered by institution-specific patient sequence number. *Solid line* represents average profiles adjusted for institution, enclosed within a dashed 68% confidence band equivalent to 1 standard error. For crude verification of model fit, *symbols* in (A) through (C) are mean responses of data unadjusted for institution grouped into deciles by patient sequence number, and *dotted curves* in (D) are profiles for each institution. A, Procedure time (minutes). B, Total fluoroscopy time (minutes). C, Contrast volume (mL). D, Number of postdilations.

DISCUSSION

Principal Findings

Following the introduction of TA-TAVR across PARTNER-I institutions, procedure time, fluoroscopy time, and volume of contrast medium sharply decreased as patient sequence number increased, indicating a short technical performance learning curve from the perspective of number of cases; however, because of a TF-first policy, it took more than a year on average to traverse this learning curve. This trend appeared to be accounted for largely by patient characteristics associated with prolonged

procedures. In conjunction, device success increased while intraprocedural complications and postprocedure AR all decreased within the first 30 to 45 cases; again, however, performing 45 cases extended over a 2-year period. The composite endpoint of intraprocedural adverse events, death, stroke, and major bleeding within 30 days initially fell, then slightly rose, perhaps due to changing patient profile and unmeasured variables. Importantly, extended procedure times typically encountered at the beginning of an institution's experience, and associated with a greater likelihood of adverse events, were found in multivariable

FIGURE 3. Profile of percentage of patients who experienced successful device deployment during transcatheter aortic valve replacement, ordered by institution-specific patient sequence number. Format is as in Figure 2.

analysis not to be an independent risk factor for these adverse events. These findings and those of others¹⁰ have important implications for forthcoming novel structural heart devices deployed via the left ventricular apex.

Findings in Context

The concept of a learning curve associated with TA-TAVR is not new. Aguirre and colleagues¹¹ from Cleveland Clinic recently reported on their early experience with TA-TAVR in 150 patients from 2007 to 2013. They divided patients into 2 groups roughly corresponding to early and mature phases, and found that the need for rescue maneuvers decreased with experience. Although 30-day mortality, bleeding from the left ventricular apex, and deployment of more than 1 valve were similar, 1-year survival improved during the more recent era, perhaps reflecting better patient selection. The authors concluded that despite an elderly, high-risk population, increasing experience was associated with decreasing mortality and complications after TA-TAVR, and that TA-TAVR is as safe and effective as TF-TAVR when performed by skilled teams.

Our finding that occurrence of intraoperative adverse events and 30-day mortality, stroke, and major bleeding initially fell, then slightly rose may have reflected an increased willingness to enroll more complex patients, and evidence supporting this was found in our multivariable analysis. D'Ancona and colleagues¹² detailed their similar experience with 500 consecutive high-risk patients undergoing TA-TAVR between 2008 and 2011. They discovered a significant relationship among procedure time, fluoroscopy time, and institutional experience, concluding that a structured training program was necessary to minimize operating room and radiation times, and approximately 100 cases were necessary to traverse the learning curve. They posited that TA-TAVR may be a more difficult procedure than TF-TAVR, but that risk of neurologic

FIGURE 4. Patients who experienced an adverse event during or after transcatheter aortic valve replacement, ordered by institution-specific patient sequence number. Format is as in Figure 2. A, Adverse events during procedure. B, Major adverse events within 30 days.

complications should be lower due to avoidance of atheromatous debris in the aorta.

In their experience with 299 patients who underwent TA-TAVR between 2006 and 2010, Kempfert and colleagues¹³ found a low occurrence of stroke and a clear trend toward declining 30-day mortality with increasing experience. They further proposed the existence of a technical learning curve associated with shorter fluoroscopy time, lower contrast dye load, fewer postballoon dilations, and shorter cardiopulmonary bypass time, which translated into shorter procedure times during the second half of their experience. The authors suggested that increased technical facility with wire handling and adjuncts, such as multiple imaging snapshots during stepwise implantation, increased the technical precision of deployment, thereby improving early outcomes.

An important task in assessing learning curves is distinguishing between individual and global experience. In our study of 24 institutions participating in the PARTNER-I trial, we found that institution trial entry date was not significantly associated with adverse outcomes. Importantly, the SAPIEN device itself evolved over time and certain technical efficiencies are likely associated with more

FIGURE 5. Length of hospital stay after transapical transcatheter aortic valve replacement, ordered by institution-specific patient sequence number. Format is as in Figure 2.

sophisticated iterations of both the valve and implantation systems. Enhanced imaging also may be associated with valve deployment accuracy and improved early outcomes.

Clinical Implications

What does this large TA-TAVR experience from the PARTNER-I trial tell us? First, the learning curve for TA-TAVR is relatively short in terms of number of cases; these data demonstrate that approximately 30 to 45 cases were required to attain technical proficiency for TA-TAVR. This may relate to the heart teams' previous experience with minimally invasive procedures. Avoiding intraoperative difficulties and complications that increase procedure time may improve early postoperative outcomes. It is unclear whether evolution of the TA-TAVR platform played more of a role than operator proficiency in improving outcomes.

FIGURE 6. Percentage of patients in each paravalvular aortic regurgitation (AR) grade at discharge, ordered by institution-specific patient sequence number. Format is as in Figure 2.

FIGURE 7. Association between procedure time and major adverse events within 30 days after transapical transcatheter aortic valve replacement. Solid line represents average profiles adjusted for institution, enclosed within a dashed 68% confidence band equivalent to 1 standard error.

It is uncertain how these TA-TAVR advances relate to contemporaneous, but admittedly different, technical advances in TF-TAVR. TF-TAVR is rapidly becoming the procedure of choice in patients undergoing transcatheter aortic valve therapy, particularly as device and sheath sizes decrease. Svensson and colleagues¹⁴ recently reported the causes of death in PARTNER-I cohorts A and B. They found that TF-TAVR was associated with an increased risk of cardiovascular death, whereas in high-risk patients, both TA-TAVR and AVR had higher early noncardiovascular risk. They concluded that TF-TAVR is preferred for inoperable patients at high risk of noncardiovascular mortality. Unlike TF-TAVR, however,^{15,16} we found little evidence of a technical performance learning curve, and no suggestion that a technical learning curve is associated with adverse outcomes or prolonged postprocedure hospitalization after adjusting for patient factors.

TA-TAVR may benefit certain patients, including those with severe peripheral vascular disease, although other access routes, including transaortic,^{17,18} are currently being evaluated in ongoing clinical trials. Although, subsequent to PARTNER-I, fewer patients are undergoing TAVR via non-TF access, understanding TA-TAVR learning curves and their effect on outcomes is important as the field moves toward structural devices delivered via the left ventricular apex, such as mitral valve replacement.

Limitations

This is a large study of patients who underwent TA-TAVR with operator teams at 24 institutions. Thus, we were unable to account for variations in team members and whether individual operator experience was more important than a team's accrued experience. Intraoperative risk factors for prolonged procedure time were not recorded and we cannot account for intangible selection factors that may have been at play during the trial.^{19,20} Specific techniques developed and used by

Transapical Transcatheter Aortic Valve Replacement Edwards-Sapien S3 Valve

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VIDEO 1. Transapical transcatheter aortic valve replacement procedure using an Edwards SAPIEN S3 valve. Video available at [http://www.jtcvsonline.org/article/S0022-5223\(16\)30099-X/addons](http://www.jtcvsonline.org/article/S0022-5223(16)30099-X/addons).

successful teams could not be ascertained from registry data. Finally, this analysis cannot account for differences in learning that existed before the PARTNER-I trial and does not account for learning from larger TF-TAVR experiences that may affect the contemporary learning curve.

CONCLUSIONS

The learning curve for TA-TAVR was short in terms of number of cases, but long in calendar time due to a TF-first trial preference. Importantly, technical competence was achieved without compromising patient safety. Although fewer patients are undergoing TAVR via non-TF access, understanding TA-TAVR learning curves and their effect on outcomes is important for structural heart teams as they adopt, learn, and master next-generation therapies delivered via the left ventricular apex.

Conflict of Interest Statement

R.M.S. is a member of the Clinical Steering Committee at Abbott and S.J.M., consults with Sorin and Abbott, has a patent application with Sorin, and does research with Sorin, Edwards Lifesciences, Abbott, and St Jude; A.D.P. is a proctor for Edwards Lifesciences; M.M. is a member of the executive committee for Edwards Lifesciences' PARTNER trial; L.G.S. is on executive committees for Edwards Lifesciences' PARTNER and COMMENCE trials; V.H.T. consults with Edwards Lifesciences; R.M. has research support from Edwards Lifesciences and St Jude Medical, consults with Abbott Vascular, Cordis, and Medtronic, and has equity in Entourage Medical; E.H.B. is on executive committees for Edwards Lifesciences' PARTNER and COMMENCE trials and leads the Cleveland Clinic PARTNER Publications Office, which carries out and publishes independent analyses of PARTNER data. All other authors have nothing to disclose with regard to commercial support.

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Key Words: transapical transcatheter aortic valve replacement, learning curve, technical performance, success, safety

APPENDIX E1. COMPOSITE VARIABLE: MAJOR ADVERSE EVENTS WITHIN 30 DAYS*

Adverse Events During Procedure

See [Table E3](#).

Bleeding

Any episode of major internal or external bleeding that causes death, hospitalization, return to the operating room, or permanent injury, or requires transfusion of more than 3 units of packed red blood cells within 24 hours, pericardiocentesis, or an open or endovascular procedure for repair or hemostasis.

Mortality

Deaths were evaluated to determine if the death was related to the valve or procedure, and subcategorized as cardiovascular, noncardiovascular, or uncategorizable.

Stroke

Focal neurologic deficit lasting 24 hours or longer, or focal neurologic deficit lasting less than 24 hours with imaging findings of acute infarction or hemorrhage. Stroke was further classified as ischemic, hemorrhagic (epidural, subdural, subarachnoid), or ischemic with hemorrhagic conversion. Both major and minor strokes were considered in this analysis.

Vascular Complications

Thoracic aortic dissection; access-site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, or compartment syndrome) leading to death, significant blood transfusions (more than 3 units), unplanned percutaneous or surgical intervention, or irreversible end-organ damage (eg, hypogastric artery occlusion causing visceral ischemia or spinal artery injury causing neurologic impairment); distal embolization (noncerebral) from a vascular source resulting in surgery, amputation, or irreversible end-organ damage; or ventricular perforation.

*PARTNER endpoint definitions were originally published in the [Supplementary Appendix](#) to Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187-98.

APPENDIX E2. LEARNING CURVE ANALYSES

Overall Learning Curve Profiles

The continuous variable. We explored shapes of the learning curve for procedure time using a semiparametric mixed-effects model.^{E1} To identify and depict the

relationship between patient sequence number (sequentially ordered by date of procedure within each institution) and procedure time among institutions, we modeled patient sequence number as a nonparametric function using flexible penalized spline smoothing in a semiparametric mixed-effects model in which the institution effect was treated as a random effect. This semiparametric mixed-effects model was implemented using the SemiPar package in R (<http://www.R-project.org>).^{E2,E3}

The mixed-model representation of penalized spline smoothers allows for automatic fitting. Smoothing parameter selection was accomplished via restricted maximum likelihood, and the class of penalized spline smoothers was obtained by estimated best linear unbiased prediction.^{E3}

Binary (yes/no) variables. We used a fully parametric logistic nonlinear mixed-effects model to explore the shape of the learning curve for binary outcomes with respect to patient sequence number. Institution was treated as a random effect. The model was implemented using PROC NLMIXED in SAS statistical software (SAS v9.2; SAS, Inc, Cary, NC).^{E4,E5} The overall trend of the prevalence of the binary response was estimated by averaging the institution-specific trends across patient sequence number.

Ordinal variables. We used a nonlinear cumulative logit mixed-effects model to explore the shape of the learning curve^{E5} for probability of each aortic regurgitation (AR) grade with respect to patient sequence number. Institution was treated as a random effect. The model was implemented using PROC NLMIXED in SAS statistical software (SAS v9.2; SAS, Inc).^{E4,E5} Because few patients experienced 3+ (moderately severe) AR, these patients were combined with 2+ (moderate) patients for purposes of modeling.

Statistical significance of effects. In all 3 approaches described in the preceding text, our aim was to estimate the trend with respect to patient sequence number, but not the *P* value for the effect. To produce *P* values, we performed a focused analysis using each outcome as the response. The only variable considered in the model was a suitable, but simple, transformation of patient sequence number. For continuous variables, we used a linear mixed-effects model (PROC MIXED) to adjust for the institution-specific effect, with institution as a random effect. For binary and ordinal variables, we used a generalized linear mixed-effects model (PROC NLMIXED), with institution as a random effect.

A model adjusting for patient characteristics (fully adjusted model) used variables selected from those in [Appendix E3](#). Due to the limited capability for variable selection in PROC NLMIXED and PROC MIXED, we used PROC LOGISTIC, PROC REG, and bootstrap bagging

for preliminary variable screening, as described in subsequent text under “Multivariable Analysis.”

Estimates based on fully parametric and semiparametric regression trend models. Estimates based on trend models have been included for specific patient sequence numbers. These include numerical estimates for the 1st, 5th, 15th, and every 15th procedure thereafter. Estimates go up to 90 patients. These estimates encompass approximately 95% of patients in each group.

Effect of Trial Entry Date on Learning Curve

We investigated the relationship between institution-specific trial entry date and the learning curve by data exploration methods. We used conditional and stratification plots to summarize trends for continuous variables. Temporal trends stratified by trial entry date are summarized across patient sequence number using a locally weighted scatterplot smoothing (loess) curve.

Learning Curve for Procedure Time

A detailed study of asymptotic procedure time and number of cases needed to attain the asymptote used an inverse polynomial mixed-effects model. To begin the analysis, we modeled the relation of procedure time to patient sequence number. We explored 4 models: an exponential Type III mixed-effects model, a first-degree hyperbolic mixed-effects model, a hyperbolic mixed-effects model using the square root of sequence number, and a hyperbolic mixed-effects model using an estimated power of sequence number.

Results of these approaches were concordant. However, allowing the data to determine the power for the hyperbolic model provided the closest fit of the parametric model to the data. We therefore have illustrated the findings for this model.

Consider the inverse polynomial (specifically hyperbola) to model procedure time:

$$\frac{1}{Y} = \frac{1}{A} + \frac{B}{X^C},$$

where A is the horizontal asymptote; B is the shaping parameter such that when $B < 0$, it is a decreasing function, and when $B > 0$, it is an increasing function; Y is procedure time; X is sequence number; and C transforms the scale of X . Note that for $C > 0$, as sequence number X gets larger, the second term approaches 0, and thus $1/Y = 1/A$, and $Y = A$. That is, A is procedure time when the learning curve has become flat (asymptotic).

The smaller the absolute value of B , the faster the rate at which the institution-specific learning curve reaches asymptotic procedure time, as depicted in the following figure:

Mixed-Effects Model

We used this nonlinear equation and defined the following nonlinear mixed-effects model, with institution number as the clustering unit:

$$Y_i = \frac{A_i X_i^C}{X_i^C + A_i B_i} + \epsilon_i, i = 1, \dots, 26,$$

where $A_i = a_0 + a_i$ is the institution-specific horizontal asymptote of procedure time, $B_i = b_0 + b_i$ is the institution-specific shape, with random effects $[a_i, b_i]^T = \beta_i \sim N_2(0, \mathbf{G})$, and $\epsilon_i | \beta_i \sim N_{ni}(0, \sigma^2 I)$. The conditional model can be written as:

$$\frac{1}{E(Y_i | \beta_i)} = \frac{1}{A_i} + \frac{B_i}{X_i^C}$$

In the case of procedure time, Y_i , A_i is the procedure time at which the i^{th} institution-specific learning curve reaches an asymptote (becomes flat), and C is a scale-stretching exponent on procedure time to account for more protracted learning curves than a strict hyperbolic function. The smaller the absolute value of B_i the higher the rate at

which the institution-specific learning curve reaches asymptotic procedure time. We implemented and estimated the institution-specific asymptotic procedure times, institution-specific shapes, and profiles using PROC NLMIXED. To then estimate the institution-specific patient number at which the institution-specific curve asymptotes, we must set a convergence criterion, which should be related to having near zero difference in predicted procedure time as sequence number increases. We arbitrarily set the convergence to a difference of 15 seconds between consecutive procedure times.

Multivariable Analysis

We extended the mixed-effects model to perform multivariable analyses to identify the patient and procedure variables associated with procedure time.

We constructed a multivariable model using procedure time as the response. The nonlinear mixed-effect model was augmented as follows:

$$A = A_0 + A_I \text{Trial entry date} + a_i \text{ and}$$

$$B = B_0 + B_I \text{Trial entry date} + b_i$$

and

$$Y_i = \frac{A_i X_i^C}{X_i^C + A_i B_i} + Z_i \beta + \epsilon_i, i = 1, \dots, 26,$$

where Z is a vector of covariables.

For better mathematical tractability, procedure time was scaled as “(procedure time/120).”

SAS PROC NLMIXED has limited capability to explore multivariable relations; thus, we initially screened variables in [Appendix E3](#) using ordinary multivariable linear regression (PROC REG in SAS) with an assumption of independence of observations, entry criteria of $P = .10$, and stay criteria of $P = .05$.

We used bootstrap bagging (bootstrap aggregation)^{E6,E7} for variable selection. This was a 4-step process. First, a patient was randomly selected from the original dataset to begin a new dataset. The original dataset continued to be sampled until the new dataset was 100% the size of the original. Second, risk factors were identified using automated forward stepwise selection. Third, results of variable selection were stored. These 3 steps were repeated 1000 times. Finally, the frequency of occurrence of variables in these 1000 models was ascertained, and this indicated the reliability of each variable (aggregation step). All variables, or 1 variable within a cluster, with bootstrap reliability of 50% or greater were retained in the final analysis.

This analysis was performed simply to identify possible candidates for our model. These candidates and their transformations, if any, were entered into our mixed model and eliminated one-by-one until all variables remaining had $P \leq .05$.

Association of Technical Performance With Clinical Outcomes

We assessed the association of the following technical performance variables with 30-day major adverse events and postprocedure length of stay: total procedure time (minutes), fluoroscopy time (minutes), contrast volume used during procedure (milliliters), pacing count during balloon aortic valvotomy, pacing count during valve deployment, number of postdeployment dilatations, frequency of percutaneous closure device usage, and 23-mm or 26-mm valve.

Multivariable analysis of 30-day major adverse events.

We used a logistic mixed-effects model with institution as the random effect to explore the association of technical performance with the probability of a 30-day major adverse event. The model was implemented using PROC NLMIXED in SAS.

We used bootstrap variable selection to identify patient and procedure variables (see [Appendix E3](#)) associated with a 30-day major adverse event. We then incorporated continuous and binary technical performance variables into the multivariable model, along with the selected patient and procedure variables. Due to the limited capability for variable selection in PROC NLMIXED, we used PROC LOGISTIC and performed variable screening as described in the preceding text.

Multivariable analysis of postprocedure length of stay.

We used a linear mixed-effects model with institution as the random effect to explore the association of technical performance variables with postprocedure length of stay. The parametric mixed-effects model was implemented using PROC MIXED in SAS. The natural logarithmic transformation (LN [length of stay]) was used to normalize the data. Due to the limited capability for variable selection in PROC MIXED, we used PROC REG and performed variable screening as described in the preceding text.

Missing Value Imputation

A number of variables examined in multivariable analyses had missing values. We used fivefold multiple imputation^{E8} using a Markov Chain Monte Carlo technique to impute missing values (SAS PROC MI). In multivariable modeling, for each imputed complete dataset, we estimated the regression coefficients and their variance-covariance matrix. Then, following Rubin,^{E8} we combined estimates from the 5 models (SAS PROC MIANALYZE) to yield final regression coefficient estimates, the variance-covariance matrix, and P values.

APPENDIX E3. VARIABLES USED IN ANALYSES

Baseline Patient Characteristics

Demographics. Age (years), sex, race or ethnicity (white), height (cm), weight (kg), weight-height ratio, body mass index (kg/m²), body surface area (m²).

Functional health status. Syncope not related to atrioventricular block, exertional syncope, New York Heart Association functional class, Society of Thoracic Surgeons (STS) predicted operative mortality, STS >10, frailty.

Aortic valve pathophysiology (including echocardiographic studies). Previous balloon aortic valvotomy, native valve calcified, calcified anulus, native valve leaflet fusion, aortic valve (AV) peak velocity (cm/s), AV time-velocity integral (cm), AV area (effective orifice area) (cm²), AV mean gradient (mm Hg), AV peak gradient (mm Hg), AV regurgitation severity.

Aortic vasculopathy. Pathology: calcified aorta.

Cerebrovascular disease. Cerebrovascular disease, including carotid disease, carotid disease, previous carotid endarterectomy or carotid stent, previous stroke.

Coronary artery disease. Coronary artery disease, angina, coronary artery stenosis (none >50%, any >50%, left main trunk [LMT] >50%, left anterior descending [LAD] >50%, left circumflex [LCX] >50%, right coronary artery [RCA] >50%, left internal thoracic artery >50%, preprocedure stenosis in a saphenous vein graft >50%, coronary artery stenosis: other >50%, grafts >50%), prior percutaneous coronary intervention, prior number of coronary artery bypass graftings (0, 1, 2), number of systems diseased ≥50% (0-system disease ≥50%, 1-system disease ≥50%, 0- or 1-system disease ≥50%, 2-system disease ≥50%, 3-system disease ≥50%, 2- or 3-system disease ≥50%), LMT disease >0%, LAD disease >0%, LCX disease >0%, RCA disease >0%.

Ventricular function. Myocardial infarction.

Other cardiac comorbidity. Mitral valve (MV) disease, baseline MV regurgitation severity, tricuspid valve disease, arrhythmia, atrial fibrillation, pacemaker implant, cardiomyopathy, previous cardiovascular intervention, other previous cardiovascular interventions or surgery.

Left ventricular outflow tract, including proximal aorta. Aortic root diameter (cm).

Preprocedure echocardiogram: left ventricular morphology and function. Left ventricular (LV) end-diastolic dimension (cm), LV end-systolic dimension (cm), visual ejection fraction (%), LV diastolic posterior wall thickness (cm), LV systolic posterior wall thickness (cm), interventricular septal diastolic dimension (cm), interventricular septal systolic dimension (cm), LV mass (g), LV mass index (g/m²), cardiac output (L/min), cardiac index (L·min⁻¹·m⁻²), heart rate (beats per minute), calculated stroke volume from Doppler at baseline (mL), stroke volume index (mL/m²).

Pre-balloon aortic valvotomy catheterization hemodynamics. Systolic pulmonary artery (PA) pressure (mm Hg),

diastolic PA pressure (mm Hg), mean PA pressure (mm Hg), systolic aortic pressure (mm Hg), diastolic aortic pressure (mm Hg), mean aortic pressure (mm Hg), mean right atrial pressure (mm Hg).

Noncardiac comorbidity. Diabetes mellitus (yes/no, type 2, baseline drug treatment: insulin), smoking, pulmonary disease, oxygen-dependent pulmonary disease, history of chronic pulmonary disease, history of oxygen-dependent chronic pulmonary disease, hyperlipidemia, renal disease, gastrointestinal condition, cancer, bilirubin (mg/dL), creatinine (mg/dL), creatinine clearance (Cockcroft-Gault, mL/min), glomerular filtration rate (mL · min⁻¹ · 1.73 m⁻²), blood urea nitrogen (mg/dL), hemoglobin (g/dL), hematocrit (%), international normalized ratio, platelet count (k/μL), white blood cell count (k/μL), albumin (g/dL).

Baseline drug treatment. Angiotensin-converting enzyme inhibitor, antiarrhythmic, anticoagulant, antiplatelet, beta blocker, calcium channel blocker, diuretic, nitrate, statin.

Procedure Characteristics*

Procedure time (min), fluoroscopy time (min), contrast volume (mL), number of post dilatations, number of rapid cardiac pacing attempts during balloon aortic valvotomy, number of rapid cardiac pacing attempts during valve deployment.

Prosthetic valve. Small valve (23 mm) implanted.

Experience

Patient sequence number by institution, intensity: interval between procedures by institution, trial entry date by institution, institution.

*Variables considered when assessing the influence of technical performance on outcomes.

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FIGURE E1. Number of transapical transcatheter aortic valve replacements performed per institution.

FIGURE E2. Percentage of transapical procedures over the course of the PARTNER-I trial. Each *dot* represents the percentage of transapical procedures for each yearly quarter. The randomized trial ended in September 2009, illustrated by *vertical dashed line*. TA-TAVR, Transapical transcatheter aortic valve replacement.

ACQ

FIGURE E3. Interval between sequential transcatheter aortic valve replacements at each of the 18 institutions that performed at least 22 procedures. Each *dot* is an interval; *solid line* is a loess estimate of trend. Notice that values tended to be elevated early in the institutions' experience. Interval between procedures is inversely proportional to institution volume (the lower the volume, the longer the interval).

FIGURE E4. Model parameter estimates of non-risk-adjusted institution-specific learning curves for procedure time. “Asymptote” refers to the minimum procedure time when the learning curve is over; “efficiency sequence number” refers to when this asymptote has been reached. A, Frequency distribution of institution-specific asymptotes, expressed in minutes. B, Frequency distributions of institution-specific sequence numbers at which asymptotes were reached. C, Relationship of sequence number at which asymptote was reached to institution trial entry date. D, Model-based procedure time by institution trial entry date.

FIGURE E5. Occurrence of 4 ventricular injuries and 11 myocardial perforations during the study period. *Light blue bars* represent number of cases performed, and *dark blue areas* are cases in which intraprocedural myocardial perforation or ventricular injury occurred. A, Events as a function of institution-specific patient sequence number. B, Events as a function of institution-specific years from trial entry date.

FIGURE E6. Percentage of patients in each aortic regurgitation (AR) grade at discharge, ordered by institution-specific patient sequence number. Format is as in Figure 1. A, AR. B, Total AR.

ACQ

FIGURE E7. Thirty-day major adverse events after transcatheter aortic valve replacement, ordered by institution-specific patient sequence number. Format is as in Figure 1. A, Stroke. B, Mortality. C, Bleeding. D, Vascular complications.

TABLE E1. Baseline patient characteristics

Characteristic	n*	n (%) or mean $\pm$ SD
Demographics		
Female	1100	574 (52)
Age, y	1100	85 $\pm$ 6.4
Race		
Black	1100	12 (1.1)
White	1100	1049 (95)
Weight, kg	1099	71 $\pm$ 18
Height, cm	1096	164 $\pm$ 11
Aortic valve pathology		
AV peak velocity, cm/s	1066	414 $\pm$ 63
AV area, cm ²	1056	0.64 $\pm$ 0.19
AV mean gradient, mm Hg	1073	44 $\pm$ 14
Cardiac comorbidity		
Stroke volume, mL	1057	64 $\pm$ 18
Heart rate, beats per min	1081	71 $\pm$ 24
MV disease	1099	852 (78)
Heart failure	1097	1079 (98)
Ejection fraction, %	1079	52 $\pm$ 13
Cardiomyopathy	1099	154 (14)
Coronary artery disease	1099	906 (82)
Myocardial infarction	1097	320 (29)
Atrial fibrillation	1098	236 (21)
Porcelain aorta	1092	19 (1.7)
Noncardiac comorbidity		
Hypertension	1100	1051 (96)
Diabetes	1100	392 (36)
Chronic pulmonary disease	1100	499 (45)
Hyperlipidemia	1100	956 (87)
Renal disease	1100	193 (18)
Peripheral arterial disease	1100	1073 (98)
Cerebral vascular disease, including carotid disease	1099	473 (43)
Smoking	1100	601 (55)
Risk profile		
STS risk score	1098	12 $\pm$ 4.1
Frailty		
6-min walk, m	743	166 $\pm$ 105
Previous procedures		
Cardiovascular intervention	1100	927 (84)
Percutaneous coronary intervention	1099	502 (46)
Coronary artery bypass grafting	1100	557 (51)
Balloon aortic valvotomy	1096	289 (26)
Carotid endarterectomy/carotid stent	1098	178 (16)
Peripheral arterial intervention	1098	114 (10)
Peripheral bypass graft	1098	55 (5)
Pacemaker	1099	231 (21)
Other previous cardiovascular interventions/surgery	1100	73 (6.6)
Medications		
ACE inhibitor	1100	447 (41)
Anticoagulant	1100	204 (19)
Antiplatelet	1100	336 (31)
Beta blocker	1100	734 (67)
Diuretic	1100	750 (68)
Nitrate	1100	201 (18)
Statin	1100	743 (68)

SD, Standard deviation; AV, aortic valve; MV, mitral valve; STS, Society of Thoracic Surgeons; ACE, angiotensin-converting enzyme. *Patients with data available.

TABLE E2. Study population overall and by transapical transcatheter aortic valve replacement

Group	Overall	TA-TAVR
Roll-in	62	19
Cohort 1A	344	104
Cohort 1B	175	0
RCA	40	0
NRCA	2000	977
Total	2621	1100

TA-TAVR, Transapical transcatheter aortic valve replacement; RCA, randomized continued access; NRCA, nonrandomized continued access.

TABLE E3. Adverse events during transapical transcatheter aortic valve replacement

Adverse event	n = 346 n (%)
Arrhythmia	47 (14)
Hypotension	44 (13)
Bleeding	42 (12)
Vascular hemorrhage	32 (9.2)
Conduction defect	31 (9)
Abnormal laboratory value	23 (6.6)
Perivalvular leak	20 (5.8)
Aortic regurgitation without paravalvular leak	11 (3.2)
Perforation or damage to myocardium	11 (3.2)
Respiratory	7 (2.0)
Ischemia	5 (1.4)
Ventricular injury	4 (1.2)
Device embolization	3 (0.87)
Transient ischemic attack, stroke, or psychomotor deficit	3 (0.87)
Infection	3 (0.87)
Hypertension	3 (0.87)
Hematoma	2 (0.58)
Heart failure	2 (0.58)
Mitral valve injury	2 (0.58)
Access site nerve injury	1 (0.29)
Thromboembolism	1 (0.29)
Mitral regurgitation	1 (0.29)
Pericardial effusion	1 (0.29)
Pleural effusion	1 (0.29)
Myocardial infarction	1 (0.29)
Systemic peripheral nerve injury	1 (0.29)
Device migration	0 (0)
Electrolyte imbalance	0 (0)
Anular dissection	0 (0)
Gastrointestinal	0 (0)
Nonstructural valve dysfunction	0 (0)
Valvular stenosis	0 (0)
Other	44 (13)

TABLE E4. Mean estimates of technical and outcomes endpoints by patient sequence number

Endpoints	Patient sequence number							
	1	5	15	30	45	60	75	90
Technical								
Procedure time, min	131	127	121	116	117	118	117	117
Fluoroscopy time, min	14.5	14.3	13.9	13.3	12.7	12.2	11.8	11.4
Contrast volume, mL	114	110	102	96	92	90	86	83
Postdeployment dilatation, n	0.089	0.095	0.108	0.122	0.134	0.146	0.149	0.134
Outcomes								
Device success, %	72	81	86	89	90	91	91	92
Adverse events during procedure, %	31	29	25	24	23	23	23	23
Aortic regurgitation grade at discharge, %								
Paravalvular								
None/trace	46	61	65	66	66	66	65	65
Mild	43	33	30	29	29	29	30	30
Moderate or severe	11	6.3	5.3	5.1	5.1	5.2	5.3	5.3
Transvalvular								
None/trace	84	87	88	89	90	90	90	90
Mild	15	13	11	10	10	10	9.4	9.2
Moderate or severe	0.58	0.48	0.42	0.38	0.36	0.35	0.34	0.33
Total								
None/trace	41	53	58	58	59	58	58	58
Mild	47	39	36	35	35	35	36	36
Moderate or severe	12	7.6	6.5	6.3	6.3	6.3	6.4	6.5
Postprocedure length of stay, d	10	10	10	10	9.4	9.2	9.0	8.8
Adverse events within 30 d, %								
Stroke	3.3	3.0	2.8	2.6	2.4	2.3	2.1	2.0
Mortality	14	12	5.9	7.9	9.0	9.3	9.4	9.4
Major bleeding	8.8	8.8	8.8	8.8	8.8	8.8	8.8	8.8
Major vascular complication	5.2	6.0	3.1	3.0	3.0	3.0	3.0	3.0
Composite major adverse events	51	38	31	29	29	31	33	36

TABLE E5. Patient and procedure characteristics associated with major adverse events occurring within 30 days after transapical transcatheter aortic valve replacement

Characteristic	Coefficient ± SE	P	Reliability, %*
Patient			
No coronary artery disease	−0.45 ± 0.19	.02	86
Syncope not related to atrioventricular block	0.44 ± 0.22	.04	69
Higher international normalized ratio†	−1.7 ± 0.53	.002	72
Antiplatelet therapy	0.69 ± 0.15	<.0001	94
Lower hemoglobin	−0.14 ± 0.044	.002	54
Trending			
Lower patient sequence number‡	0.017 ± 0.0099	.09	62
Trial entry date (years from 01/01/2007)	0.086 ± 0.14	.6	15
Interval between procedures	0.25 ± 1.1	.8	16
Technical Performance			
Longer procedure time	0.0075 ± 0.0013	<.0001	100
Longer fluoroscopy time§	0.38 ± 0.18	.04	63
Larger contrast volume	0.00013 ± 0.0011	.9	22
Fewer postdilatations	−0.25 ± 0.20	.2	14
Fewer rapid cardiac pacings during BAV	−0.083 ± 0.11	.4	11
More rapid cardiac pacings during valve deployment	0.064 ± 0.079	.4	11
23-mm valve	0.059 ± 0.15	.7	4.9

SE, Standard error; BAV, balloon aortic valvotomy. *Percentage of times variable appeared in 1000 bootstrap models. †Inverse transformation: (1/International Normalized Ratio)². ‡Inverse transformation: 1/(patient sequence number/45). §Natural log transformation: LN (fluoroscopy time).

TABLE E6. Patient and procedure characteristics associated with major adverse events occurring within 30 days, with procedure time the only technical performance variable

Characteristic	Coefficient ± SE	P	Reliability (%)*
Patient			
No coronary artery disease	−0.46 ± 0.18	.01	86
Syncope not related to atrioventricular block	0.46 ± 0.21	.03	69
Higher international normalized ratio†	−1.5 ± 0.51	.003	72
Antiplatelet therapy	0.66 ± 0.15	<.0001	94
Lower hemoglobin	−0.14 ± 0.044	.001	54
Learning curve			
Lower patient sequence number‡	0.019 ± 0.010	.06	62
Trial entry date (years from 01/01/2007)	0.086 ± 0.14	.5	15
Interval between procedures	0.61 ± 1.1	.6	16
Technical performance			
Predicted learning curve effect on procedure time	−0.0014 ± 0.0068	.8	—§
Predicted covariate effect on procedure time	0.014 ± 0.0073	.05	—§
Contribution of events during procedure, unobserved factors, and random variability	0.0093 ± 0.0014	<.0001	—§

SE, Standard error. *Percentage of times variable appeared in 1000 bootstrap models. †Inverse transformation: (1/International Normalized Ratio)². ‡Inverse transformation: 1/(sequence number/45). §No reliability because component was forced into model.