



The Edwards SAPIEN® THV Transcatheter Heart Valve System for High Risk Surgical Patients with Severe Aortic Stenosis

Briefing Document for the Circulatory Systems Device Panel Advisory Committee

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List of Abbreviations

| | |
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| 6MWD | 6 Minute Walk Distance |
| 6MWT | 6Minutte Walk Test |
| ACC | American College of Cardiology |
| ACT | Activated Clotting Time |
| AE | Adverse Event |
| AHA | American Heart Association |
| ANCOVA | Analysis of Covariance |
| AS | Aortic Stenosis |
| AT | As Treated |
| AVA | Aortic Valve Area |
| AVR | Aortic Valve Replacement |
| BAV | Balloon Aortic Valvuloplasty |
| BVC | Balloon Valvuloplasty Catheter |
| CABG | Coronary Artery Bypass Grafting |
| CAD | Coronary Artery Disease |
| CEC | Clinical Events Committee |
| CI | Confidence Interval |
| CMS | Center for Medicare Services |
| CNS | Central Nervous System |
| coPI | co Principal Investigator |
| COPD | Chronic Obstructive Pulmonary Disease |
| CTA | Computed Tomographic Angiography |
| CVA | Cerebrovascular Accident |
| CVVHD | Continuous Venovenous Hemodialysis |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| EO | Ethylene Oxide |
| EOA | Effective Orifice Area |
| EuroSCORE | European system for cardiac operative risk evaluation |
| FDA | Food and Drug Administration |
| GEE | Generalized Estimation Equation |
| GI | Gastrointestinal |
| Hb | Hemoglobin |
| HITS | High Intensity Transient Signals |
| HR | Hazard Ratio |
| IFU | Instructions for Use |
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat |
| KCCQ | Kansas City Cardiomyopathy Questionnaire |
| KM | Kaplan Meier |
| LV | Left Ventricle |
| LVEF | Left Ventricular Ejection Fraction |
| LVOT | Left Ventricular Outflow Tract |



| | |
|---------|--|
| MACCE | Major Adverse Cardiac and Cerebrovascular Events |
| MEM | Medium Eluate Method |
| MES | Micro Embolic Signals |
| MI | Myocardial Infarction |
| MRI | Magnetic Resonance Imaging |
| MSC | Medical Simulation Corporation |
| NRCA | Non Randomized Continued Access |
| NYHA | New York Heart Association |
| OD | Odds Ratio |
| OPC | Objective Performance Criterion |
| OR | Odds Ratio |
| PARTNER | Placement of AoRTic TraNscathetER Valves |
| PAS | Post-Approval Study |
| PCI | Percutaneous Coronary Intervention |
| PET | Polyethylene Terephthalate |
| PHR | Proportional Hazards Regression |
| PMA | Premarket Approval Application |
| PTFE | Polytetrafluoroethylene |
| PVL | Perivalvular Leak |
| QoL | Quality of Life |
| RR | Relative Risk |
| RV | Right Ventricle |
| SAL | Sterility Assurance Levels |
| SAR | Specific Absorption Rate |
| SD | Standard Deviation |
| SF-12 | Short Form-12 |
| STEMI | ST-elevation myocardial infarction |
| STS | Society of Thoracic Surgeons |
| TA | Transapical |
| TAVR | Transcatheter Aortic Valve Replacement |
| TCD | Transcranial Doppler |
| TEE | Transesophageal Echocardiography |
| TF | Transfemoral |
| THV | Transcatheter Heart Valve |
| TIA | Transient Ischemic Attack |
| TLS | Terminal Liquid Sterilization |
| TTE | Transthoracic Echocardiography |
| TVR | Transcatheter Valve Registry |
| ULN | Upper Limit of Normal |
| US | United States |
| VARC | Valve Academic Research Consortium |
| WBC | White Blood Cells |
| WHO | World Health Organization |



1.0 Executive Summary

Following the July 20th, 2010 the FDA Advisory Council Panel vote of 9-0-1 recommending approval of the Edwards SAPIEN™ Transcatheter Heart Valve with transfemoral delivery in patients with symptomatic, severe aortic stenosis who are not candidates for aortic valve replacement surgery, Edwards Lifesciences is seeking an expanded indication for use for patients who are high risk for surgery using either the transfemoral or transapical approach. The currently marketed product was approved based upon a totality of preclinical, feasibility and randomized controlled evidence from the seminal PARTNER Trial (IDE G030069) which is publically available (**Section 4.1**).

The PARTNER Trial is a prospective, randomized controlled multicenter clinical trial which was designed in collaboration with the FDA and multidisciplinary opinion leaders to evaluate the efficacy and safety of Transcatheter Aortic Valve Replacement (TAVR).

The PARTNER Trial design included 2 study cohorts, each separately powered and randomized to appropriate prospective controls. Patients were screened for symptoms and echo criteria of severe aortic stenosis and were subsequently stratified by cohort:

- Cohort A: patients at high risk for aortic valve replacement surgery (AVR)
- Cohort B: patients who cannot undergo AVR (inoperable patients)

In accordance with the FDA approval order issued on November 2, 2011, Edwards is responsibly marketing the devices approved under Cohort B with the following indication:

The Edwards SAPIEN™ Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm, is indicated for transfemoral delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis.

Additional data from Cohort B have been published in NEJM (March, 2012), which demonstrate 2 year or longer safety and efficacy of valve performance. The Panel recommended post approval studies are underway, including a groundbreaking collaborative national registry for transcatheter valve replacement developed through sponsor collaboration with FDA, the Center for Medicare Services (CMS), the Society of



Thoracic Surgery (STS) and the American College of Cardiology (ACC). There is ongoing reporting and publication of worldwide experience with Edwards SAPIEN THV in published literature [22-30]. This Briefing Document focuses on the safety and efficacy in the high risk cohort (Cohort A). Based upon the results of the PARTNER trial randomized Cohort A, as well as from an expanded dataset enrolled during the continued access phase following completion of randomization, the following expanded indication is proposed:

The Edwards SAPIEN™ Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm, is indicated for transfemoral delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by two cardiac surgeons to be inoperable, or at high risk for surgical aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis.

The Edwards SAPIEN™ Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm, is indicated for transapical delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by two cardiac surgeons to be at high risk for surgical aortic valve replacement, not suitable for transfemoral delivery per heart team decision, and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis.

High Risk Surgical Cohort

A total of 699 patients were enrolled in the randomized PMA cohort in the intent-to-treat (ITT) population. A total 492/699 (70.4%) were eligible for the transfemoral approach; the remaining 207/699 (29.6%) patients did not qualify for the transfemoral approach and were eligible for transapical access. Following determination of the implant approach, patients were randomized in 1:1 ratio to TAVR or AVR within each implant approach; 348 patients were randomized to TAVR and 351 patients were randomized to AVR. September 21, 2011 was the analysis close date in order to capture the last patient enrolled with 2 year follow-up.

Patients who did not undergo the randomly assigned study procedure were excluded from the as-treated (AT) population. Four patients did not undergo TAVR; two patients died prior to the procedure, one patient refused TAVR and one patient deteriorated prior to the procedure and was deemed too sick to undergo TAVR, resulting in a pooled AT TAVR



cohort of 344 patients. A total of 38 control patients did not undergo AVR; five patients died prior to AVR, five patients deteriorated prior to the procedure and were deemed too sick to undergo AVR, and 28 patients either refused AVR or withdrew from the study, resulting in a pooled AT AVR cohort of 313 patients.

The mean age at screening was 83.6 years \pm 6.8 years for TAVR patients and 84.5 years \pm 6.4 years for AVR patients. Overall, more patients were male (399/697 or 57.2%), and the vast majority was Caucasian (652/697 or 93.5%). The high proportions of patients, > 99% in each group, reporting cardiovascular conditions (other than AS) underscore the poor cardiac health of the study population. Most (92%) patients reported additional non-cardiovascular conditions at screening. In the TAVR cohort, the mean STS risk score was 11.8 (SD 3.3), and the mean logistic EuroSCORE was 29.3 (SD 16.5). In control AVR patients, the mean STS risk score was 11.7 (SD 3.5) and the mean logistic EuroSCORE was 29.2 (SD 15.6).

The mean follow-up time was 1.8 \pm 1.0 years for pooled TAVR cohort and 1.6 \pm 1.0 years for pooled AVR cohort. Visit compliance was high in both group, i.e., visit compliance for the TAVR arm was 98.5% at 30 days, 99.3% at 6 months, 99.2% at 1 year, and 93.8% at 2 years. Visit compliance for the AVR arm was 97.6% at 30 days and 6 months, 100% at 1 year and 95.7% at 2 years.

Five TAVR patients experienced device malfunction. Four of the 5 malfunctions involved the delivery system. Two TAVR patients underwent valve-in-valve procedures, and in 5 TAVR patients more than one SAPIEN valve was used. Eleven patients randomized to TAVR underwent AVR, including 2 late AVRs (i.e., 3 months after the index procedure). In all these patients, the TAVR procedure was started but aborted; therefore, these patients were included in the TAVR ITT and AT population.

None of the patients randomized to AVR underwent TAVR.

Endpoints

The primary endpoint in the high risk cohort was all cause mortality at 1 year in the intent-to-treat (ITT) population. The one-sided definition of inferiority for this non-inferiority null hypothesis was $\Delta \geq 7.5$ percentage points. The primary analysis met the pre-defined non-inferiority success criterion.



Table 1 summarizes the details of the primary analysis and secondary analyses.

All four secondary non-inferiority endpoints analyzed under type I error probability-control were met:

- 1) Time from randomization to the first occurrence of a major adverse cardiac and cardiovascular event (MACCE) at one year. MACCE consisted of death, myocardial infarction (MI), stroke, and renal failure using per protocol definitions of each adverse event (definition of inferiority: $\Delta \geq +7.5$ %-points);
- 2) Median total hospital days through one year (definition of inferiority: $\Delta \geq +10$ days);
- 3) New York Heart Association (NYHA) functional classification at one year (definition of inferiority: $\Delta \geq +0.25$);
- 4) Six minute walk test (6MWT) at one year (definition of inferiority: $\Delta \leq -70$ meters).



Table 1. Endpoints - High Risk Cohort in the PARTNER Randomized Study (ITT Population)

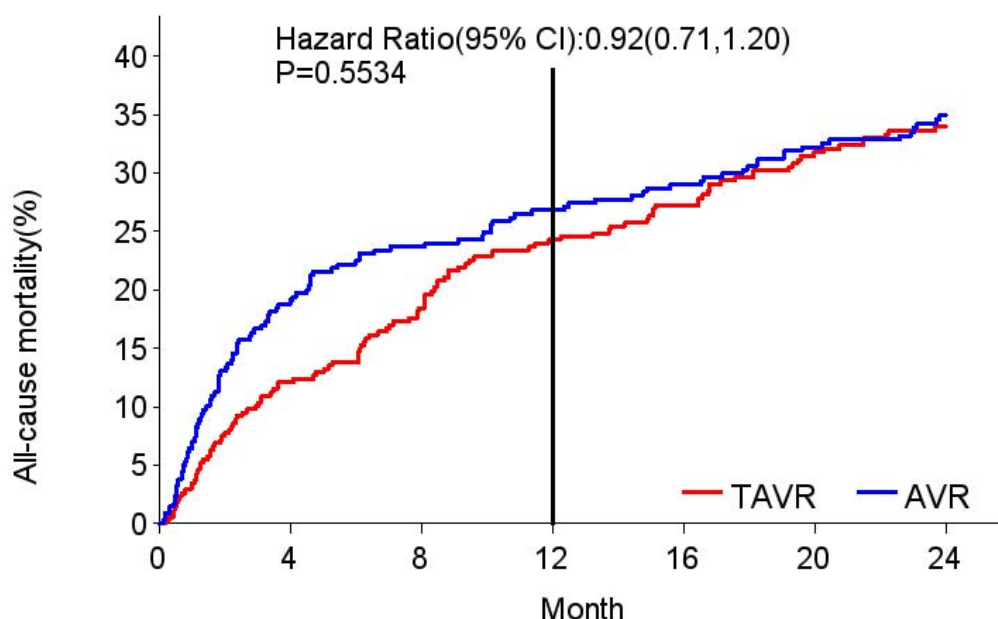
| Analysis | Endpoint | Inferiority Definition | AVR Arm Estimate | TAVR Arm Estimate | Absolute Difference (TAVR-AVR) | One-sided 95% Confidence Limit on Difference | P-value | Success |
|-----------|---|---------------------------|------------------|-------------------|--------------------------------|--|----------|---------|
| Primary | One-year all-cause mortality (Kaplan-Meier estimate) based on ITT | TAVR ≥7.5 %-points more | 26.8% | 24.3% | -2.5% | ≤ 2.99 | 0.0014 | Yes |
| Secondary | One-year MACCE (Kaplan-Meier estimate; no imputation – ITT) | TAVR ≥7.5 %-points more | 29.1% | 27.4% | -1.7% | ≤ 4.0 | 0.0040 | Yes |
| Secondary | Median Hospital Days through one-year (no imputation – ITT) | TAVR ≥10 days more | 18.8 | 16.3 | -3.0 | ≤ -2.00 | 0.0001 | Yes |
| Secondary | NYHA at one year (Completers analyses) | TAVR mean ≥0.25 higher | 1.70 | 1.70 | -0.01 | ≤ 0.11 | 0.0001 | Yes |
| Secondary | 6MWD at one year (Completers analyses) | TAVR mean ≤70 meters less | 169.8 | 165.0 | 4.88 | ≥ -18.51 | < 0.0001 | Yes |

6MWD=6 minute walk distance; AVR=aortic valve replacement; ITT=intent-to-treat; MACCE= major adverse cardiac and cerebrovascular events; NYHA=New York Heart Association; TAVR= transcatheter aortic valve replacement.
Per-protocol definitions - MACCE: Death; Myocardial Infarction = acute MI at autopsy, emergent PCI or thrombolitics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI; Renal Failure = Patient required chronic dialysis for greater than 30 days; Stroke = a neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction.



Kaplan-Meier estimates of all-cause mortality in each randomized group are shown in Figure 1. The vertical line marks the 12 month timepoint when the primary analysis was conducted. The upper one-sided 95% confidence interval limit of the one-year mortality difference in the ITT analysis set, i.e., 2.99 is less than 7.5 % points meeting the statistical criterion set for success ($p=0.0014$).

Figure 1. Kaplan Meier Estimates of All Cause Mortality - High Risk Cohort in the PARTNER Randomized Study (ITT Population)



Number at risk:

| | | | | | | |
|----------|-----|-----|-----|-----|-----|-----|
| TAVR:348 | 305 | 281 | 260 | 243 | 224 | 172 |
| AVR:351 | 266 | 246 | 236 | 224 | 210 | 165 |

Hazard ratio at 2 years; p-value from log-rank test up to 24 months

Sensitivity analyses of the primary endpoint analysis were performed with various assumptions as to the treatment of patients who were censored prior to 1 year, or who did not receive the procedure. All these assumptions are unfavorable to the TAVR arm. Using the worst case scenario analysis, the primary endpoint still met statistical criterion for success and there was no tipping point where an analysis failed to meet statistical criteria.



Finally, in the as-treated (AT) population all cause mortality at 1 year in the TAVR arm was not inferior to all cause mortality in the AVR arm (upper one-sided 95% confidence interval limit of the one-year mortality difference was 4.02%, $p=0.0037$).

Quality of Life (QoL)

Among high surgical risk patients, both AVR and TAVR resulted in substantial improvement in disease-specific and generic QoL over 1 year follow-up. Although the extent of improvement at 1 year was similar with TAVR and AVR, there were important differences in the rate and extent of recovery at the earlier time points:

- For patients eligible for the TF approach, TAVR resulted in substantial QoL benefits compared with AVR at 1 month (mean difference [TAVR-AVR] in the KCCQ summary score was 7.6, $p=0.0018$; mean difference in SF-12 physical was 1.9, $p=0.0414$; mean difference in SF-12 mental was 4.8, $p=0.0000$)
- For patients eligible only for the TA approach, QoL tended to be better with AVR at 1 month (mean difference [TAVR-AVR] in KCCQ summary score was -8.0, $p=0.0382$, mean difference in SF-12 physical was -0.7, $p=0.6053$; mean difference in SF-12 mental was -4.8, $p=0.0077$).

Both groups (TF-TAVR and TA-TAVR) become comparable to AVR but TF-TAVR tends to achieve most of its QoL improvement earlier than TA-TAVR.

NYHA

At 30 days, TAVR was more likely to reduce symptoms to NYHA class I or II than AVR (i.e., at 30 days 72.8% of TAVR patients were in NYHA I or II vs. 59.10% of AVR patients). The difference was not observed at 1 year.

6 Minute Walk Test

At baseline, mean 6MWD was similar for both groups (around 108 meters). Although the extent of improvement in 6MWD at 1 year was similar with TAVR and AVR, at 30 days the mean 6MWD was 143.1 meters in the TAVR group and 104.8 meters in the AVR group demonstrating an important difference in the rate and extent of recovery.

ICU Stay and Total Length of Hospitalization at the Index Procedure



At the time of the index procedure, mean days in the ICU was 4.1 days for TAVR vs. 6.3 days for AVR, and mean duration of entire hospitalization (including ICU stay) was 8.8 days for TAVR vs. 14.1 days for AVR.

Echocardiography

Following the index procedure, mean EOA, mean and peak gradients at 1 year statistically improved more in the TAVR group than the AVR group.

- Mean EOA: 1.6cm² TAVR vs. 1.4 cm² AVR (p=0.0027)
- Mean mean gradient: 10.2 mmHg TAVR vs. 11.4 mmHg AVR (p=0.0131)
- Mean peak gradient: 19.4 mmHg TAVR vs. 21.3 mmHg AVR (p=0.0321)

However, the proportion of patients with moderate/severe paravalvular aortic regurgitation was higher in the TAVR group than the AVR group, i.e., 11.7% vs. 0.9% at 30 days (p < 0.0001), and 6.5% vs. 1.9% at 1 year (p < 0.0001).

Safety

Due to the different implant technique, different major complications were of interest and may have important consequences for the patients. Events of interest in the TAVR group comprise major vascular complications and stroke, and in the AVR group major bleeding and new onset atrial fibrillation.

Stroke

Early stroke (≤ 30 days from surgery) occurred more frequently in the TAVR group and late stroke (> 30 days from surgery) occurred more frequently in the AVR group, however, no statistical differences were observed. QoL in patients with stroke within the first 12 months improved throughout the follow-up and matched QoL in non-stroke patients at 1 year.

Major Vascular Complications



Major vascular complications were more likely in the TAVR group (at 1 year, 11.1% of TAVR patients and 3.8% of AVR patients experienced a major vascular event [p=0.0003]).

Major Bleeding

The incidence of major bleeding was higher in the AVR group (at 1 year, 15.8% of TAVR patients and 27.5% of AVR patients experienced major bleeding [p=0.0003]).

New Onset Atrial Fibrillation

New onset atrial fibrillation was more likely in the AVR group (at 1 year, 19.2% of AVR patients and 12.8% of TAVR patients experienced new onset atrial fibrillation [p=0.0320]).

Overall, 34.0% of TAVR patients and 43.8% of AVR patients experienced at least one major event of interest (stroke, major vascular events, major bleeding and/or new onset atrial fibrillation). In regards to patient outcome at 1 year, 11.6% of TAVR patients (40/344) that had a major event of interest died vs. 16.0% of AVR patients (50/313).

Note, all cause mortality and the composite endpoints of death/all stroke were similar for TAVR and AVR.

Safety Experience in Continued Access Patients

Patients were allowed non randomized continued access to this technology under the same provisions of the PARTNER study protocol including eligibility criteria, clinical event adjudication, core labs and Executive Committee oversight. At the time of data analyses, the expanded dataset included 1521 patients who either underwent TA-TAVR (n=822) or TF-TAVR (n=699) as reported in the clinical study report and briefing document. Procedural outcomes and the safety profile observed in this population appear to be at least as good as the results obtained in the randomized TAVR cohort.

Kaplan Meier rates for all cause mortality at 30 days and 1 year were lower in the NRCA group than the randomized cohort (i.e., in the transapical approach, 8.2% NRCA vs. 8.7% randomized TAVR at 30 days, 23.6% NRCA vs. 29.1% randomized TAVR at



1 year; 3.2% TF NRCA vs. 3.7% randomized TF TAVR at 30 days, 19.4% TF NRCA vs. 21.4% randomized TF TAVR at 1 year.

Risk management

Edwards has commenced a disciplined commercial rollout of this technology in the USA for the currently approved indication and is currently in line with the targeted number of centers to be trained in the first year of commercialization (150-250 centers). Sites are scrutinized through a detailed and step-wise process that includes presence of heart team (cardiac surgery, cardiology, echocardiography, and anesthesiology), infrastructure for imaging and sterile environment, ability to track and report clinical outcomes, multi-disciplinary valve clinic environment, support of administration to start a TAVR program, and procedure volume.

Edwards' commitment to training, ongoing education and tracking of procedure success is the foundation for the pace and quality of the commercialization process. The Edwards THV training program is multi-faceted and includes foundational didactic course, simulation training, device preparation and use training, case observation, peer proctoring, on-going support by field clinical specialist and continuing education.

This training program has been developed and refined over the past 5 years; over 2000 physicians have been trained, over 2000 cases have been proctored and more than 8000 cases have been supported globally. Subsequently a very high procedural success rate has been maintained as shown through the SOURCE Registry.

Based upon lessons learned from data analyses reported in the PMA and scientific literature, systematic use of imaging modalities such as computed tomographic angiography (CTA) studies to screen potential treatment candidates has been integrated into physician training in order to reduce procedure-related complications and optimize valve placement and positioning with TAVR.

Conclusions

The prespecified endpoint of non-inferiority for all cause mortality at one year between the gold standard of surgical aortic valve replacement and TAVR with Edwards SAPIEN THV was met.



All four secondary non-inferiority endpoints (time from randomization to the first occurrence of MACCE at one year, median total hospital days through one year, NYHA functional classification at one year, and 6MWT at one year) were met.

There were more early strokes (≤ 30 days of the index procedure) in the TAVR arm but more late strokes (> 30 days of the index procedure) in the AVR arm; however, the differences were not statistically significant. There were more vascular complications in the TAVR arm but more major bleeding events, and new onset atrial fibrillation in the AVR arm which were all statistically significant.

The rate and extent of recovery was faster in TAVR patients than AVR patients as evidenced by NYHA, 6MWT and QoL at 30 days. Duration of hospital stay from index procedure was shorter in the TAVR arm.

By study design to portray intended clinical practice and real world use, access approaches were not separately powered for non-inferiority testing. Despite this, analyses were performed for the two approaches. In both the ITT and AT populations, all cause mortality in the TAVR arm was not inferior to all cause mortality in the AVR arm at 1 year using the transfemoral approach. Non-inferiority could not be demonstrated in the transapical only population possibly due to the limited sample size of 200 patients.

As demonstrated during the study, 28/351 (8%) of patients randomly assigned to AVR either refused AVR or withdrew from the study vs. one patient (1/348, 0.3%) randomly assigned to TAVR who refused TAVR indicating that high risk surgical patients are very interested in an alternative option for the treatment of severe aortic stenosis.

When used in the high surgical risk population the benefits and risks associated with TAVR are not inferior to the risks and benefits associated with surgical AVR and therefore should be considered a safe and effective treatment option for this population.

In conclusion, all study endpoints were met including worst case analyses for the primary endpoint. The large body of continued access data suggests improvement with experience. Further analyses with all patients followed for a minimum of 2 years demonstrate longer term safety and efficacy of this technology.



2.0 Background

This Briefing Document reviews the results SAPIEN Valve Model 9000TFX for percutaneous transcatheter aortic valve replacement (TAVR) in high risk surgical patients with severe aortic stenosis. In the pivotal PARTNER trial, high-risk surgical patients were randomized to TAVR or traditional aortic valve replacement (AVR).

Also in the PARTNER trial, a separate cohort of inoperable patients was randomized to TAVR or standard care that could include balloon valve replacement (BAV) and results of this study have been presented previously (**Section 4.1**).

This briefing document presents the efficacy and safety findings observed in the high risk surgical cohort.

2.1 Aortic Valve Stenosis

Prolonged average life expectancy has resulted in an aging population and consequently, an increase in the number of patients with acquired, calcific, severe, symptomatic aortic stenosis (AS). The standard of care therapy for patients suffering from severe AS is aortic valve replacement surgery (AVR). However, in the aged population, many patients are too sick or have comorbidities that preclude the option for surgery [3].

Aortic stenosis is a progressive, debilitating and life-threatening disease if left untreated. Affected individuals are typically > 65 years of age. The pathology involves progressive calcification of the leaflet bodies which limits normal cusp opening during systole. Cellular aging and degeneration have been implicated in this form of the disease and diabetes mellitus and hypercholesterolemia are risk factors.

The pathophysiology of AS includes an increase in afterload, progressive hypertrophy of the left ventricle, and a decrease in systemic and coronary blood flow as consequences of valve obstruction. Typically, patients with AS are free from cardiovascular symptoms (e.g., angina, syncope and/or heart failure) until late in the course of the disease. However, once symptoms manifest, the prognosis is poor, especially when associated with congestive heart failure. Death in general, including sudden death, occurs primarily in symptomatic patients. Survival analyses have demonstrated that the interval from onset of symptoms to time of death is



approximately two years in patients with heart failure, three years in those with syncope, and five years in those with angina [4]. AVR has excellent long-term outcomes for patients with aortic valve stenosis including patients who were operable but had predicted high risk for surgery (by STS PROM > 10 [5]).

Grading the severity of AS is based on a variety of hemodynamic and natural history data. According to the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, AS is best described as a continuum. In patients with moderate-to-severe AS, valve area may decline up to 0.3cm² per year and the systolic pressure gradient across the valve can increase by as much as 15-19 mmHg per year, with a higher rate of progression observed in elderly patients with coronary artery disease (CAD) and chronic renal insufficiency. These guidelines were updated again in 2008 [6]. Relief of aortic valve obstruction typically results in an improvement of symptoms, hemodynamic parameters, and global left ventricle systolic function, as well as reversal of left ventricular hypertrophy [7-8].

Echocardiographic criteria for determining the severity of AS, as defined by the 2006 published practice guidelines of the joint ACC/AHA Task Force are described in Table 2.

Table 2. Criteria for Determining Severity of Aortic Stenosis

| Indicator | Mild | Moderate | Severe |
|---|------------------|----------|------------------|
| Jet velocity (m/s) | Less than 3.0 | 3.0-4.0 | Greater than 4.0 |
| Mean gradient (mmHg) | Less than 25 | 25-40 | Greater than 40 |
| Valve area (cm ²) | Greater than 1.5 | 1.0-1.5 | Less than 1.0 |
| Valve area index (cm ² /m ²) | | | Less than 0.6 |

2.2 Aortic Valve Replacement and Alternative Therapies

Treatment options for patients suffering from symptomatic aortic stenosis include palliation of symptoms without valve replacement (non-surgical standard therapy) or surgical aortic valve replacement (AVR). Treatment options are determined by patient risk for morbidity or mortality after surgery and patient choice. Non-surgical treatment options including balloon aortic valvuloplasty have been demonstrated to lead to shortened life expectancies and poor quality of life [9-11]. Patients considered poor



candidates for AVR typically present with significant morbidities or anatomical limitations (such as severely calcified aorta, chest wall radiation, etc) [12]. Also a state of frailty may lead to a patient and/or physician decision to forego surgery.

Surgical AVR has been demonstrated to have excellent long-term outcomes for patients with AS [13-16] including patients who were operable but had predicted high risk for surgery (by STS PROM > 10) [17-18].

2.3 Transcatheter Aortic Valve Replacement (TAVR)

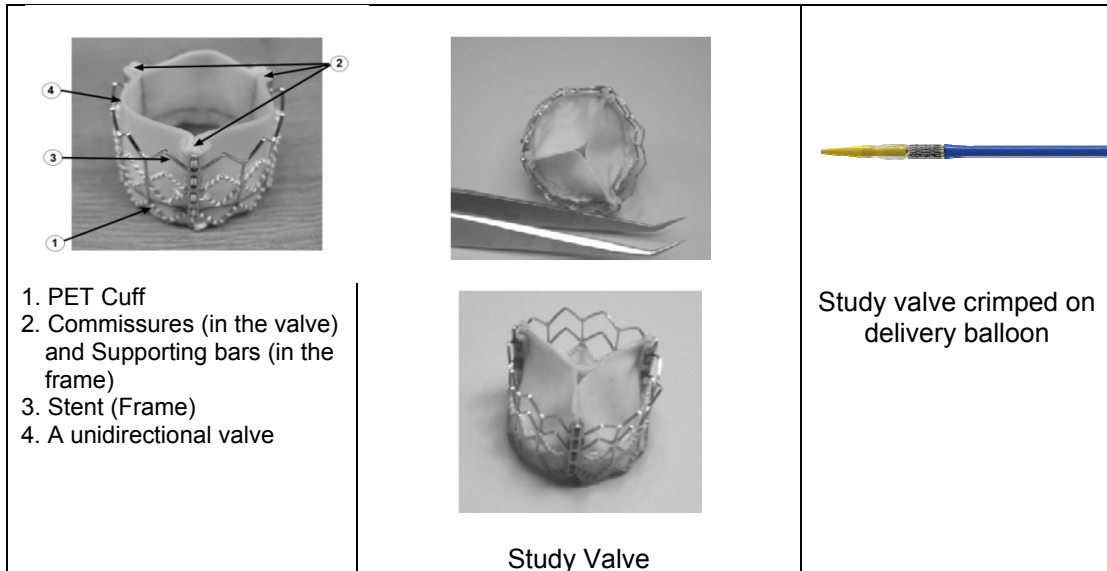
Transcatheter aortic valve replacement (TAVR) was first performed in man in 2002 [19] and was followed by European commercialization 2007 [20-21]. Today more than 20,000 patients have undergone TAVR worldwide and there is a proliferation of published literature supporting the safety and feasibility of the first generation balloon expandable system (SAPIEN). The Edwards THV clinical research program includes more than 9,000 patients enrolled in 10 clinical studies which include first in man, feasibility, pivotal randomized controlled trials and post market registries. Results from these trials have been publicly reported at scientific congresses and in journals [22-29]. The PARTNER Trial results have been published as well, i.e., inoperable patients with symptomatic AS (Cohort B, **Section 4.1**) [30], and the high risk surgical cohort (Cohort A) [31]. A description of the procedure is included in **Section 6.5**.



3.0 Device Description

The Edwards SAPIEN™ THV transcatheter heart valve, Model 9000TFX (bioprosthesis; Figure 2), is comprised of a radiopaque, stainless steel expandable support structure (stent), with an integrated unidirectional trileaflet tissue valve, and a polyethylene terephthalate (PET) fabric cuff. The valve tissue is fabricated from three equal sections of bovine pericardium that have been preserved in low concentration solutions of buffered glutaraldehyde to fully crosslink the tissue while preserving its flexibility and strength. The valve tissue component is firmly affixed to the frame within the fabric cuff at its inflow aspect and to attachment bars on the commissural posts at its outflow aspect using polytetrafluoroethylene (PTFE) sutures. The SAPIEN is available in 23mm and 26mm sizes. Other components of the SAPIEN Heart Valve System include a Crimper, RetroFlex Balloon Catheter and either the RetroFlex™ Delivery System for transfemoral delivery or the Ascendra Delivery System for transapical delivery, are further described in **Appendix B**.

Figure 2. Edwards SAPIEN™ Transcatheter Heart Valve



Sterilization

The SAPIEN Valve Model 9000TFX is sterilized by terminal liquid sterilization (TLS) in buffered glutaraldehyde solution. The RetroFlex 3 Delivery System, Ascendra Delivery System, RetroFlex Balloon Catheter, and Crimper are sterilized by ethylene oxide (EO). After sterilization, the devices are held in quarantine until sterility is



verified per process specifications. The TLS and EO processes have demonstrated Sterility Assurance Levels (SAL) exceeding the industry standard of 10^{-6} in validation studies.

Shelf Life

Packaging and product integrity studies were conducted to ensure that the shelf life for each package and product is maintained for a minimum of two (2) years for the SAPIEN Valve, RetroFlex 3 Delivery System, Ascendra Delivery System, RetroFlex Balloon Catheter, and Crimper.

Package Integrity

The packaging for the SAPIEN valve consists of a 3.8 oz jar, a lid and gasket closure system, and shelf and shipping containers. This system has been evaluated via physical testing and microbial challenge and was shown to maintain its sterile barrier following four years of real-time aging and exposure to temperature variations and simulated shipping conditions.

The RetroFlex 3 Delivery System, Ascendra Delivery System, RetroFlex Balloon Catheter, and Crimper are packaged in Tyvek pouches and shelf and shipping cartons. These systems have been evaluated and shown to maintain sterile barrier following two years of accelerated aging and exposure to temperature variations and simulated shipping conditions.

Product Integrity

SAPIEN Valve Biological Tissue: Edwards ThermaFix-processed bovine pericardial tissue has previously been validated and approved under Premarketing Application (PMA) application P860057 regarding the Carpentier-Edwards® PERIMOUNT® Pericardial Bioprosthesis product family. The tissue used for the SAPIEN valve is identical to the tissue used for the PERIMOUNT valve. Biochemical evaluation was conducted on tissue stored in glutaraldehyde solution for four years real time. All device specifications were met for moisture content, ninhydrin content, shrinkage temperature, and enzymatic digestion of tissue.



Histological examination of leaflets was conducted on leaflet samples from whole valves at zero-time and after two years of real-time aging. Results demonstrated that aging of tissue does not appear to impact the microstructure of bovine pericardial tissue used in the SAPIEN valve. A stress relaxation study was completed to compare cyclic load decay for tissue leaflet samples at zero-time to tissue leaflets at zero-time and after three years of real-time aging. No statistically significant difference was observed between groups.

SAPIEN Valve Nonbiological Components and Whole Valve Testing: Functionality of the SAPIEN valve's non-biologic components (polymers: valve holder, skirt, sleeve, and sutures; metallics: frame and frame samples) and whole-valve hydrodynamic and wear testing were completed after 2 years real-time aging.

Tensile testing of the frame met acceptance criteria. Corrosion resistance of the frame demonstrated higher resistance than the zero-time reference. Tensile testing of all polymer components met acceptance criteria relative to zero-time reference strengths. All valves passed the minimum hydrodynamic performance requirements for effective orifice area (EOA) and Regurgitant Fraction per ISO 5840:2005. The 2 year real-time aged SAPIEN valves survived durability testing out to 200 million cycles in accelerated wear testers under aortic pressure test conditions without failure, significant tissue wear or frame deformation and fracture. These valves offered a larger EOA and lower regurgitant fractions than those required per the minimum performance requirements of ISO 5840:2005 after 200 million cycles. This testing was included in the review of PMA100041 which was approved on November 2, 2011.

Delivery System and Accessories: Functionality and product integrity of the RetroFlex 3 Delivery System, Ascendra Delivery System, RetroFlex Balloon Catheter, and Crimper were demonstrated after following two years of accelerated aging and exposure to temperature variations and simulated shipping conditions.



4.0 Regulatory History and Development Program

Extensive preclinical testing (bench and animal studies) and clinical feasibility studies were conducted with both the transfemoral and transapical delivery system approaches. The PARTNER Trial, an IDE pivotal randomized-controlled clinical trial, was approved in March of 2007 and enrollment was initiated in April of 2007. The trial was designed to study the safety and efficacy of the Edwards SAPIEN THV and companion delivery systems, with the intention that this study would provide the data necessary for a PMA for commercialization in the US. The protocol was revised in December 2007 (prior to significant enrollment or site initiation). The revision entailed a sample size adjustment in the inoperable Cohort B from 250 to 350 patients based upon new information involving one-year assumptions for the primary endpoint. An additional endpoint (powered co-primary composite endpoint based on survival and rehospitalization) using the Finkelstein-Schoenfeld method was added to the trial design to include a clinically meaningful efficacy endpoint. Additionally, the transapical arm was approved for the high risk Cohort A. Subsequent protocol revisions have been modified in accordance to FDA interactions without impact to the design of the trial.

FDA approved the SAPIEN Transcatheter valve with the RetroFlex 3 delivery system for the non-operable patient population on November 2, 2011 under PMA 100041. The RetroFlex Dilator kit was cleared on April 13, 2010 through the 510(k) process (K093554). The RetroFlex-3 Introducer kit was cleared on July 10, 2010 (K093877).

4.1 Experience in Inoperable Patients

In the inoperable cohort, the two co-primary endpoints were (1) time from randomization to death over the duration of the trial and (2) composite of death or hospitalization if patient survived. All-cause mortality was 44.1% for TAVR vs. 66.5% with standard care (hazard ratio [HR] 0.51; 95% confidence interval [CI] 0.39, 0.68; $P < 0.001$). The risk of the composite endpoint of death from any cause or repeat hospitalization was 55% less with TAVR as compared with standard care (HR 0.45; 95% CI 0.35, 0.59; $P < 0.0001$) in the ITT population.



All prespecified secondary endpoints also favored TAVR specifically (1) time to first occurrence of MACCE within one year, (2) total hospital days through one year, (3) NYHA functional classification at one year and (4) 6MWT at one year. Sensitivity analyses of patients as they were treated, mortality at one year and cardiovascular mortality all favored TAVR. Mortality at 30 days was increased in the TAVR group. Over the first 30 days after randomization, 9 TAVR patients (5.0%) died vs. 5 standard-care patients (2.8%) in the ITT population. In the as-treated population, 11 TAVR patients (6.3%) died within 30 days of implant vs. 5 standard-care patients (2.8%) who died within 30 days of randomization. The increased mortality was secondary to procedural complications and stroke.

Prespecified adverse events were defined by protocol and adjudicated by a clinical endpoint committee. At 30 days, major vascular complications were more likely with TAVR (16.8% compared to 1.1%, $p<0.001$), as was the risk for stroke (7.3% compared to 1.7%, $p=0.02$). The safety experience in inoperable patients treated in feasibility studies was consistent with that observed in PARTNER study.

In summary, TAVR in inoperable aortic stenosis patients substantially increases survival compared to standard care. In addition, patient function characterized by quality of life instruments (Kansas City Cardiomyopathy Questionnaire, Short-Form-12 [SF-12], and EQ5D) as well as the 6MWT and NYHA Classification significantly improves at 30 days and 1 year after TAVR versus best medical management including balloon aortic valvuloplasty. TAVR is associated with an increased risk for stroke and procedure-related adverse events such as bleeding and vascular complications. Overall, the benefit from TAVR in inoperable patients with severe aortic stenosis is substantially greater than the risk. Additional 2 year data are provided in **Appendix I**. These 2 year data support the data observed at 1 year.

4.2 Worldwide Experience

Commercial distribution of the SAPIEN THV Model 9000TFX and accessories outside the US began in October 2007.

As of October 2011, over 20,000 patients in 42 countries worldwide had been implanted with the Edwards SAPIEN™ THV platform, (all outside United States countries are implanting second generation SAPIEN XT THV), with more than 9,000



patients enrolled in clinical studies ranging from first in man to post market registries. Implanted valve performance was remarkably consistent in all feasibility studies and procedure outcomes have improved with experience and device iterations [22-29].

Currently, the device is approved for distribution in the 27 member states under the European Union, Croatia, Iran, Israel, Jordan, Kuwait, Monaco, Norway, Russia, Saudi Arabia, Singapore, South Africa, Switzerland, Thailand, and Turkey. The SAPIEN valve and accessories have not been withdrawn from the market in any country for any reason related to the safety and efficacy of the device, but has now been replaced with second generation SAPIEN XT with NovaFlex and Ascendra 2 Delivery systems.



5.0 Preclinical Studies

5.1 *In Vitro* Testing

In vitro studies were performed for the Edwards SAPIEN THV Model 9000TFX and non-implantable accessories as recommended in the FDA's Draft Replacement Heart Valve Guidance (1994) and ISO 5840: Cardiovascular Implants- Cardiac Valve Prostheses (2005).

5.1.1 Biocompatibility Studies

Toxicology and biocompatibility testing for the SAPIEN THV Model 9000TFX and accessories was conducted in accordance with Good Laboratory Practices (21CFR §58) and ISO 10993-1: 2003 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing. Summaries of the test results for the SAPIEN THV Model 9000TFX are provided in Table 3. Test samples for the studies consisted of all patient-contacting portions of the device (direct and indirect contact) after all manufacturing processes including sterilant exposure. Similar tests for the RetroFlex 3 and Ascendra Delivery Systems, RetroFlex Balloon Catheter, and Crimper all showed acceptable results.

Table 3. Summary of Biocompatibility Testing – SAPIEN THV Model 9000TFX

| Test | Results |
|--|--|
| Cytotoxicity: Percent Inhibition of Cell Growth | Test article was non-inhibitory to cell growth at a sample concentration representative of the device's clinical application. Inhibitory to cell growth at elevated sample concentrations. |
| Cytotoxicity: Medium Eluate Method (MEM) | Test article sample was non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control. |
| Cytotoxicity: Agar Overlay Test | Solid samples of the stent frame were non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control. Cytotoxicity was observed in solid samples of the cloth, suture, and tissue material due to glutaraldehyde and formaldehyde residuals present in the solid sample. |
| Sensitization: Guinea Pig Maximization | No irritation was present on any of the test or control animals at 24- or 48-hour readings using saline and vegetable oil extracts. Non-sensitizing. |
| Irritation/Intracutaneous Toxicity: Rabbit Intracutaneous Reactivity | No evidence of irritation or abnormal effects over a 72-hour period as compared to negative controls. |
| Systemic Toxicity: USP Mouse Systemic Injection | No weight differences or observed systemic effects as compared to negative controls over 72 hour test period. |
| Systemic Toxicity: Material Mediated (Rabbit) Pyrogen Test | No temperature rise or abnormalities in any test or control animals. |
| Implantation Subacute / | No microscopic evidence of toxicity. |



| Test | Results |
|--|--|
| Subchronic Toxicity Chronic Toxicity | |
| Genotoxicity: Ames Test – Plate Incorporation | Test article extracts demonstrated no mutagenic potential under both the activated and non-activated conditions. |
| Genotoxicity: Chromosomal Aberration Assay | Test article extracts demonstrated no mutagenic potential under both the activated and non-activated conditions. |
| Genotoxicity: Mouse Micronucleus | Test article extracts were determined non-mutagenic. |
| Hemocompatibility: Hemolysis | No hemolytic effects observed under static conditions for both extract and solid samples. Material's extract did not adversely affect the clotting time and was determined compatible with plasma. |

5.1.2 SAPIEN Valve Hydrodynamic Performance

In vitro hydrodynamic performance studies of the SAPIEN Model 9000TFX bioprosthesis were completed to evaluate performance under steady- and pulsatile-flow testing conditions. Valves were evaluated after nominal deployment and after deployment into irregular shapes (under-deployed, oval deployed, and over-deployed). The studies were conducted in accordance with the FDA Draft Replacement Heart Valve Guidance (1994) or ISO 5840: Cardiovascular Implants-Cardiac Valve Prostheses (2005). Reference articles for the nominally deployed SAPIEN valve studies consisted of commercially available aortic valves; reference articles for the irregular studies consisted of nominally deployed SAPIEN valves. Across the studies, the following results were observed: the SAPIEN valve showed acceptable hemodynamics with pressure gradients and EOAs that were comparable to those of the reference valves. The test valve prevented significant transvalvular aortic back-flow during the diastolic phase (at various back-flow pressures). Hydrodynamics were acceptable, with a larger EOA and lower regurgitant fractions than required by ISO 5840:2005 acceptance criteria for aortic valves, and similar pressure drop to reference valves under pulsatile flow conditions. Aortic flow patterns throughout the entire cardiac cycle were characterized by broad central jet-like flows, no flow stasis during opening, and no retrograde jet-like flow. Pressure drop correlated with the Bernoulli relationship.

5.1.3 SAPIEN Valve Structural Performance

In vitro structural performance studies of the SAPIEN Model 9000TFX were performed in accordance with FDA Draft Replacement Heart Valve Guidance (1994).



Commercially available aortic valve replacements and Cordis Palmaz Genesis stents (for corrosion testing) were used as control articles in studies requiring concurrent testing of devices marketed in the US. After testing to 200 million cycles, all valves met the minimum EOA and Total Regurgitation Fraction requirements of ISO 5840:2005. After reaching the 200 million cycles, all valves are then subjected to test to failure at increasing pressures. All failures for both the test and reference valves occurred at pressures well beyond what would be experienced *in vivo*. Results of testing for resistance to lateral compressive loads, corrosion, and fatigue, even under simultaneous worst-case conditions, indicated acceptable valve performance. The following additional structural performance studies were completed with acceptable results: grain structure analysis, open circuit potential, material mechanical properties, fatigue life determination (Goodman), force on commissure.

5.1.4 SAPIEN Valve Design Specific Performance Studies

The following design-specific *in vitro* performance studies of the SAPIEN THV Model 9000TFX were completed with acceptable results: percent surface area, frame overexpansion safety factor investigation, frame foreshortening and recoil, frame radial strength, valve migration force, pulsatile flow migration, and radiopacity.

5.1.5 SAPIEN Valve Magnetic Resonance Imaging (MRI) Compatibility

Testing of this device in magnetic fields of 1.5 and 3.0 Tesla has shown that this device is MRI Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla or 3 Tesla
- Spatial gradient field of 2500 Gauss/cm or less.
- Maximum whole-body-averaged specific absorption rate (SAR) of 2 W/kg for 15 minutes of scanning.
- Normal mode operation, as defined in IEC 60601-2-33, of the MRI system.

5.1.6 Delivery System and Accessory Performance Testing

The following tests were performed for the RetroFlex 3 and Ascendra Delivery Systems and showed acceptable results: dimensional verification, visual inspection, simulated use, balloon characterization, bond strength, hemostasis, and migration.



The following tests were performed for the RetroFlex Balloon Catheter and showed acceptable results: dimensional verification, visual inspection, simulated use, balloon characterization, bond strength, and balloon compliance.

The following tests were performed for the Crimper and showed acceptable results: dimensional verification, visual inspection, and simulated use.

5.2 SAPIEN Valve Animal Studies

Feasibility studies were conducted in over 100 animals (porcine, bovine, canine and ovine) in an attempt to identify a suitable animal model and study feasibility of percutaneous delivery of the valve. The valves used in these studies were either early prototypes (equine and bovine) or the Cribier-Edwards™ Aortic Bioprosthesis, Model 9000. A chronic study was performed on this model of the valve in which 19 juvenile sheep with induced aortic insufficiency were treated. Fourteen (14) percutaneous implants of the 23 mm Model 9000 valve were attempted in the proximal descending aorta, with ten (10) successful animals (sacrificed between 10 - 21 weeks), three (3) procedure-related deaths, and one (1) non-related early death. Five (5) sheep were treated surgically with the control article, a commercially available pericardial bioprosthesis, with three (3) procedural deaths and two (2) sacrificed within 48 hours due to valve issues.

A chronic *in vivo* animal implantation study was conducted using the SAPIEN THV, Model 9000TFX in an adult ovine model. A total of 18 test article Model 9000TFX valves were implanted in the aortic position of 18 adult male sheep for a 10 week (n=9) and 20 week (n=9) evaluation study; three (3) of nine (9) animals survived to at least 10 weeks and six (6) of nine (9) survived to at least 20 weeks. Three (3) control articles were implanted in the aortic position of three (3) adult male sheep; two (2) control animals survived to at least 20 weeks and were clinically normal prior to explant; one (1) animal survived to less than 14 days. No control valves were evaluated at 10 weeks.

Clinical History: All 10-week and six 20-week sheep were clinically normal prior to explants.



Hemodynamic Performance: At 20 weeks, there were no differences from the average pre-explant peak gradients between the two groups for both normotensive and hypertensive readings, and no differences from the average post-implant and pre-explant cardiac outputs between the two groups. The six 20-week test valves had evidence of mild to moderate aortic valve insufficiency by echocardiography exams of paravalvular origin. One (1) of two (2) control valves had mild insufficiency.

Angiography evaluation at 20 weeks indicated that four (4) of six (6) test valves had Grade 1-2 regurgitation of undetermined origin, two (2) test valves had Grade 3-4 regurgitation with at least one for paravalvular origin, and one (1) control valve had Grade 3-4 regurgitation from undetermined location.

Histopathology: Results showed no apparent differences in tissue reactions (general healing, calcification, or morphology of the tissue/valve interface) between the test device and the control device.

Gross Observations: Normal healing with pliable leaflets and no thrombus were observed, with no evidence of infection or calcification when implanted for 20 weeks.



6.0 Clinical and Statistical Methodology of the PARTNER Study

6.1 Study Design

The PARTNER (**P**lacement of **AoRTic** **TraN**scathet**ER** Valves) trial identified two cohorts of patients with severe AS: (1) inoperable patients (Cohort B) and (2) patients at high risk for AVR (Cohort A). After stratification by cohort, patients were randomized and studied separately within each cohort. This Briefing Document focuses on the efficacy and safety experience in the high risk cohort; data involving the inoperable cohort are presented in **Section 4.1** and **Appendix I**. The FDA approved transfemoral delivery of the Edwards SAPIEN™ THV in inoperable patients on November 2, 2011.

The purpose of this trial involving Cohort A was to ascertain in the context of a randomized clinical trial whether TAVR is not inferior to AVR in respect to one-year mortality in high risk surgical patients with critical calcific AS.

The screening phase of the trial was designed to meet three objectives:

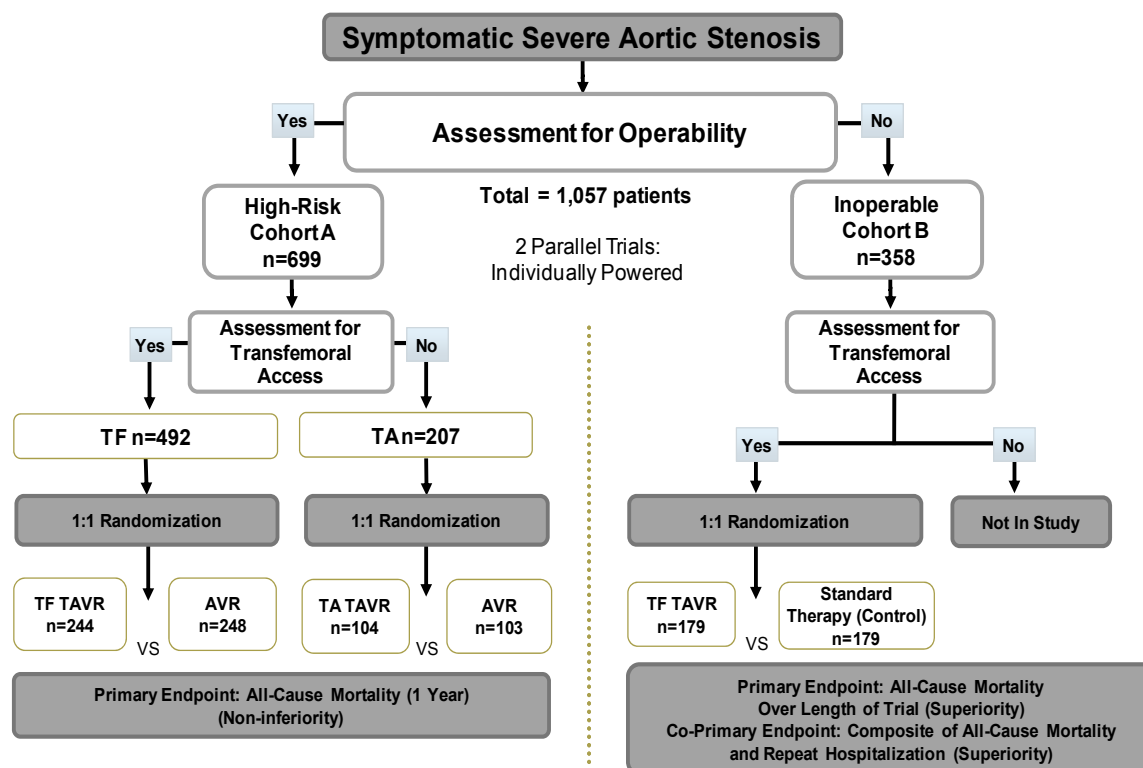
- determine patient eligibility
- determine surgical risk for stratification into the high risk cohort or inoperable cohort; and
- evaluate vascular access characteristics to determine eligibility for transfemoral delivery.

Figure 3 shows the randomized allocation of patients for both the inoperable and high-risk cohorts.

High surgical risk patients not eligible for transfemoral access who were randomly assigned to TAVR were treated by transapical access as a subset of the TAVR arm.



Figure 3. The PARTNER Trial Flow Chart



AVR=aortic valve replacement surgery, TA=transapical, TAVR=transcatheter aortic valve replacement, TF=transfemoral. Cohort A: high risk for AVR; Cohort B: inoperable patients.

In the high risk cohort, patients were enrolled from 23 centers in the US and two centers in Canada and one center in Germany. After initiation of the PARTNER Trial, some countries (including Canada and Germany) were able to access the technology through commercial or special access provisions and were no longer able to enroll in the trial.

Patients were randomized in both cohorts using a centralized computer system using a random, undisclosed variable block size by site. After determining eligibility, investigators entered patient-specific data into a central electronic case report form. Patient ID and randomized code were then populated into the case report form by computer and the investigator then received the computer-generated code to identify the randomly assigned procedure by refreshing the enrollment case report form. Thus, patients in the high risk cohort were randomized into two arms with AVR and TAVR as the intended treatment.



The primary endpoint for Cohort A was all cause mortality at 1 year. Additional endpoints examined improvement in symptomatology and cardiac function. Multiple prespecified safety endpoints were defined by protocol and events were adjudicated by a clinical endpoint committee (CEC; refer to **Section 6.10**). Additional information on clinical and statistical methodology is provided in the following sections.

6.2 Eligibility and Operability

Prior to classification of patients as high risk operable or inoperable, patients had to meet the fundamental enrollment criteria of severe, symptomatic, and calcific AS with quantifiable and documented source records. Upon meeting this fundamental criterion, the site investigator also verified that the patient met all inclusion criteria (**Section 6.2.1**) and none of the exclusion criteria (**Section 6.2.2**).

6.2.1 Patient Inclusion Criteria

Patients were required to meet the following inclusion criteria:

- Degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient > 40 mmHg, jet velocity greater than 4.0 m/s, or an initial aortic valve area (AVA) of < 0.8 cm² (or AVA index < 0.5 cm²/m²).
- Qualifying AVA baseline measurement had to be obtained within 45 days prior to enrollment. Enrollment was defined as the date that the Procedure Informed Consent was signed.
- Patient was symptomatic from his/her aortic valve stenosis as demonstrated by New York Heart Association (NYHA) Functional Class \geq II.
- The patient or the patient's legal representative had been informed of the nature of the study, agreed to its provisions and provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.
- The patient and the treating physician agreed that the patient was to return for all required post-procedure follow-up visits.

6.2.2 Patient Exclusion Criteria

Patients were excluded if any of the following conditions were present:

- Evidence of an acute MI ≤ 1 month before the intended treatment (defined as: Q wave MI, or non-Q wave MI with total CK elevation of CK-MB \geq twice normal



in the presence of MB elevation and/or troponin level elevation (World Health Organization [WHO] definition).

- Aortic valve was a congenital unicuspid or congenital bicuspid valve or was non-calcified.
- Mixed aortic valve disease (AS and aortic regurgitation with predominant aortic regurgitation >3+).
- Any therapeutic invasive cardiac procedure performed within 30 days of the index procedure, (or 6 months if the procedure was a drug-eluting coronary stent implantation).
- Pre-existing prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification, severe (greater than 3+) mitral insufficiency, or Gorlin syndrome.
- Blood dyscrasias as defined: leukopenia (white blood cells [WBC] <3000 mm³), acute anemia (hemoglobin [Hb] < 9 mg%), thrombocytopenia (platelet count <50,000 cells/mm³), history of bleeding diathesis, or coagulopathy.
- Untreated clinically significant coronary artery disease (CAD) requiring revascularization.
- Hemodynamic instability requiring inotropic support or mechanical heart assistance.
- Need for emergency surgery for any reason.
- Hypertrophic cardiomyopathy with or without obstruction.
- Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) <20%.
- Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
- Active peptic ulcer or upper gastrointestinal (GI) bleeding within the prior 3 months.
- A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately pre-medicated.
- Native aortic annulus size < 18 mm or > 25 mm as measured by echocardiogram.
- Patient had been offered surgery but refused surgery.
- Recent (within 6 months) cerebrovascular accident (CVA) and/or a transient ischemic attack (TIA).



- Renal insufficiency (creatinine > 3.0 mg/dL) and/or end-stage renal disease requiring chronic dialysis.
- Life expectancy < 12 months due to non-cardiac co-morbid conditions.
- Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5 cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta (applicable for transfemoral patients only).
- For transfemoral access only: Iliofemoral vessel characteristics that precluded safe placement of 22F or 24F introducer sheath such as severe obstructive calcification, severe tortuosity, or vessels size less than 7 mm in diameter.
- Currently participating in an investigational drug or another device study. [Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, were not considered investigational trials].
- Active bacterial endocarditis or other active infections.
- Bulky calcified aortic valve leaflets in close proximity to coronary ostia.

6.2.3 Operative Risk Assessment

Upon meeting all eligibility criteria, the site investigators (per site heart team assessment) then determined the patient’s risk for operative morbidity and mortality as follows:

- Patients deemed inoperable had documented evidence that the risk for mortality or serious irreversible morbidity was greater than 50% as determined by the examining cardiac surgeon investigator. Patients were typically deemed inoperable due to prohibitive medical or anatomical conditions (highly compromised respiratory disease, severe immunosuppressive diseases, “true” porcelain aorta, chest wall radiation or deformity, and multiple previous interventions in the presence of advanced multi-system dysfunction). Eligibility for the inoperable arm of the study was confirmed by peer review of two surgical investigators not affiliated with the site. Both had to conclude that the patient met the non-operability criteria.



- High risk patients were required to have co-morbidities such that the surgeon and cardiologist co-principal investigators (Co-PIs) concurred that the predicted risk of operative mortality was $\geq 15\%$ and/or a minimum STS score of 10. A candidate who did not meet the STS score criteria of ≥ 10 could be included in the study if a peer review by at least two surgeon investigators (not including the enrolling surgeon) concluded and documented that the patient's predicted risk of operative mortality was $\geq 15\%$. The surgeon's assessment of operative comorbidities not captured by the STS score was documented in the study case report form as well as in the patient medical record.

Screening included clinical evaluation, echocardiography, catheterization and vascular access assessment. Weekly, case review webcast presentations were held to adjudicate the cohort assignment and treatment strategy for each patient screened.

The STS risk calculator and EuroSCORE calculator are provided in **Appendix C**.

6.3 Study Endpoints

6.3.1 Primary Endpoint

The primary endpoint was defined as all-cause mortality at one year from randomization in the Intent-to-Treat (ITT) population. The one-sided definition of inferiority for this non-inferiority null hypothesis was $\Delta \geq 7.5$ percentage points.

6.3.2 Secondary Endpoints

Four secondary endpoints were defined by protocol with preplanned control of type one error:

- Time from randomization to the first occurrence of a Major Adverse Cardiac and Cerebrovascular Events (MACCE) event within one year. The MACCE definition comprised death, MI, stroke, and renal failure as defined by the protocol (definition of inferiority: $\Delta \geq +7.5$ %-points).
- Total hospital days through one year (definition of inferiority: $\Delta \geq +10$ days)
- NYHA functional classification at one year (definition of inferiority: $\Delta = \geq +0.25$)



- 6-minute walk test at one year (definition of inferiority: $\Delta \leq -70$ meters).

Prespecifional endpoints were predefined by protocol but no preplanned control of type one error:

- Functional improvement from baseline as measured per a) NYHA functional classification, b) EOA and c) 6-minute walk test at 30 days, six months, and one year
- Freedom from MACCE at 30 days, 6 and 12 months. MACCE definition included death, MI, stroke, and renal failure (per protocol definitions)
- Improved Quality of Life (QoL) from baseline at 30 days, 6 and 12 months
- Improved valve function demonstrated by a responder analysis showing the percentage of patients in each treatment group who have a greater than 50% improvement in EOA at 30 days, 6 months, and one year.

6.3.3 Prespecified Safety Endpoints

Protocol defined safety endpoints were collected, analyzed, and reported at 30 days or discharge (whichever was longer), at 6 months, and at 12 months:

- Annular dissection
- Aortic dissection
- Structural valve deterioration
- Non-structural dysfunction (including paravalvular leak)
- Valve thrombosis
- Embolism
- Bleeding events
- Operated valve endocarditis
- Conduction defects
- Ventricular injury
- Valve migration
- Hemolysis
- Vascular and access-related complications
- Mitral valve compromise



6.4 Investigator Training

Investigators were provided a written Training Manual and access to a password-protected training web site, which had patient clinical selection suggestions, procedural steps, potential complications and methods for prevention, the pacing protocol, access site angiograms and technique suggestions, and links to the current Instructions for Use and other important information.

Hands-on training was conducted using the Medical Simulation Corporation (MSC) Simantha™ simulator. The Investigator was first given a demonstration of the study valve and all specialty ancillary equipment. The Investigator then simulated two procedures to obtain a feel for the steps of the procedure and how all the equipment worked together.

A presentation was given on a web call with other participating investigators and members of the study Executive Committee that included patient selection, the steps of the procedure with in-depth discussion on the more challenging aspects (e.g., valve placement within the calcific native aortic valve), troubleshooting techniques, and challenging situations such as difficult anatomy (e.g., tortuous iliacs). This presentation included a review of cases including angiograms and echocardiograms of previous procedures.

Each investigator was required to attend a minimum of one live TAVR procedure performed by an experienced implanter and/or with an experienced implanter in attendance (proctoring). Each investigator naïve to the TAVR procedure performed two supervised TAVR procedures prior to participation in PARTNER trial.

An Edwards Clinical Specialist (trained on the device preparation and crimping procedure) was in attendance at all implant procedures. They were responsible for performing or overseeing the appropriate preparation of the THV delivery system and valve. All clinical sites had designated personnel that were trained on the preparation of the devices to ensure capability for device preparation by a non-Edwards staff member. The investigator was responsible for checking the placement and orientation of the valve on the balloon catheter prior to implantation.



6.5 Description of the TAVR Procedure

The transcatheter aortic valve replacement procedure (transfemoral approach) is performed in a cardiac operating room or hybrid catheterization lab under general anesthesia and fluoroscopic guidance. Delivery access is achieved through transfemoral cannulation. A balloon aortic valvuloplasty is performed prior to the SAPIEN valve implantation. The SAPIEN valve is then placed on its delivery system and crimped over a balloon to allow insertion into the body through the delivery sheath. The valve and delivery system are then inserted transfemorally through the sheath, and guided up to the aortic valve. Temporary pacing is performed to allow delivery of the valve in a stable environment. When the SAPIEN THV is correctly positioned, the balloon is inflated, expanding the new valve from its crimped mode to its fully functioning mode. The SAPIEN THV begins functioning immediately. Valve position and performance are immediately assessed by fluoroscopy and echocardiography.

During the transapical approach, a mini anterolateral left thoracotomy is made usually in the 6th intercostals space. The pericardium is opened, and a small transapical incision is made to accommodate the delivery catheter. A total of 1 bipolar or 2 unipolar epicardial pacing wires are placed on the left ventricle to pace the heart during valve placement. A balloon aortic valvuloplasty is performed prior to the SAPIEN valve implantation. The SAPIEN valve is then placed on a catheter across the native valve and uncrimped by balloon expansion of the stent. Cardiac output is momentarily stopped by the use of high rate pacing until the valve is correctly positioned. The SAPIEN THV begins functioning immediately. Valve position and performance are immediately assessed by fluoroscopy and echocardiography.

Antibiotic prophylaxis for endocarditis was administered per the recommendations of the American Heart Association.^a

^a Dajani AS et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA 1990;264(22):2919-22.



6.6 Anticoagulation

At this time, no published evidence-based recommendations for anticoagulation or antiplatelet regimens exist for the TAVR procedure. The anticoagulation regimen provided in the protocol recommended that all patients receive aspirin (75-100 mg daily) and clopidogrel (300 mg loading dose if patient was not currently taking clopidogrel and then 75 mg daily) prior to the procedure. Ticlopidine could be prescribed instead of clopidogrel at the investigator's discretion (Table 4). The activated clotting time (ACT) was monitored and anticoagulation was adjusted to keep the patient's ACT \geq 250 sec. The sheaths were removed when ACTs reached $<$ 150 sec after implantation of the study valve. Post hoc analysis of medication regimes after TAVR and investigator surveys indicated that the recommended regimen was not routinely followed post TAVR in the PARTNER trial due to concerns of bleeding in the elderly population.

Table 4. Recommended Concomitant Antiplatelet/Anticoagulation

| Medication | Pre-Procedure | During Catheterization | Post-Procedure | 30-Day Follow-up | 6-Month Follow-up |
|--------------------------|---|---|----------------|--------------------------|-----------------------|
| IV Heparin | PRN | 5000 IU Bolus, then as needed to achieve/maintain ACT \geq 250 sec. | | | |
| Aspirin | 75-100 mg QD | | 75-100 mg QD | 75-100 mg QD | 75-100 mg QD for life |
| Clopidogrel ^a | 300 mg po (if not on long-term therapy) | 75 mg po QD | 75 mg po QD | 75 mg po QD for 6 months | |

a. Ticlopidine could be used instead of clopidogrel at the Investigator's discretion.

6.7 Clinical Assessments and Patient Follow up Procedures

Patients undergoing TAVR or AVR were followed during the procedure, and on day 1 (up to 36 hours post-procedure), day 7 or discharge, whichever was later, at 1, 6, and 12 months and then yearly for a minimum of 5 years. Telephone follow-up was conducted after the last patient enrolled completed the 1 year visit (Table 5).



Table 5. Subject Schedule of Events

| | Baseline | During procedure | Day 1 (≤ 36 hrs post procedure) | Discharge / 7 D Follow Up ^a | 30 D Follow Up | 6 M Follow Up | 12 M Follow Up | Annual Follow Up ≥5 Yr | Telephone Follow-up 1 Yr Post Last Patient Enrolled ^b |
|---|----------|------------------|------------------------------------|---|----------------|---------------|----------------|---------------------------|--|
| Physical assessment and Patient interview | | | | | | | | | |
| Informed Consent | X | | | | | | | | |
| History | X | | | | | | | | |
| Physical Exam | X | | | X | X | X | X | X | |
| CCS Angina | X | | | X | X | X | X | X | |
| NYHA Class | X | | | X | X | X | X | X | |
| Current Medications | X | X | | X | X | X | X | X | |
| Event Assessment | | X | | X | X | X | X | X | X |
| NIH Stroke Score Assessment | X | | | X | X | X | X | X | |
| Mini Mental State Exam | X | | | | | | | | |
| STS Risk Score and Logistic EuroSCORE | X | | | | | | | | |
| Six Minute Walk Test | X | | | | X | X | X | | |
| Frailty Index ^c | X | | | | | | | | |
| Lab Measurements | | | | | | | | | |
| CBC with Differential and Platelet Count | X | | | | X | X | X | | |
| Troponins or CK, CK-MB | X | | X | | | | | | |
| Complete Metabolic Panel | X | | | | | X | X | | |
| Liver Panel | X | | | | | | | | |
| Albumin | X | | | | | | | | |
| BNP | X | | | X | X | X | X | X | |
| PTT or PT/INR if applicable | X | | | | X | X | X | | |
| Plasma Free Hemoglobin & Haptoglobin ^c | X | | | | X | X | X | | |



| | Baseline | During procedure | Day 1 (≤ 36 hrs post procedure) | Discharge / 7 D Follow Up ^a | 30 D Follow Up | 6 M Follow Up | 12 M Follow Up | Annual Follow Up ≥5 Yr | Telephone Follow-up 1 Yr Post Last Patient Enrolled ^b |
|--|----------------|------------------|------------------------------------|---|----------------|---------------|----------------|---------------------------|--|
| Non-Invasive Tests | | | | | | | | | |
| ECG | X | | | X | X | X | X | | |
| Chest X-ray | X ^d | | X | X | X | X | X | | |
| Echocardiogram – TTE or TEE ^e | X | | | X | X | X | X | X | |
| Invasive Tests | | | | | | | | | |
| Abdominal Aortogram | X ^f | | | | | | | | |
| Aortic arch angiogram | X | X | | | | | | | |
| Economics and Quality of Life Measures | | | | | | | | | |
| Kansas City Cardiomyopathy | X | | | | X | X | X | | |
| EuroQoL | X | | | | X | X | X | | |
| SF-12 | X | | | | X | X | X | | |

- Discharge/7 Day follow-up was required for patients undergoing TAVR or AVR. If patient was discharged over a weekend, the discharge tests were allowed to be completed on the last weekday prior to discharge.
- The additional telephone follow-up was performed for the purposes of determining patient survival post last follow-up only.
- If possible
- Chest x-ray within 90 days prior to the procedure.
- Transesophageal echocardiography (TEE) was performed if transthoracic echocardiography (TTE) examination was inadequate. TEE was accepted in place of TTE if performed for other reasons.
- All candidates underwent screening thoracic and abdominal aortograms or thoracic and abdominal CT angiograms with complete visualization of both iliacs and femorals to the aorta within 6 months of procedure.

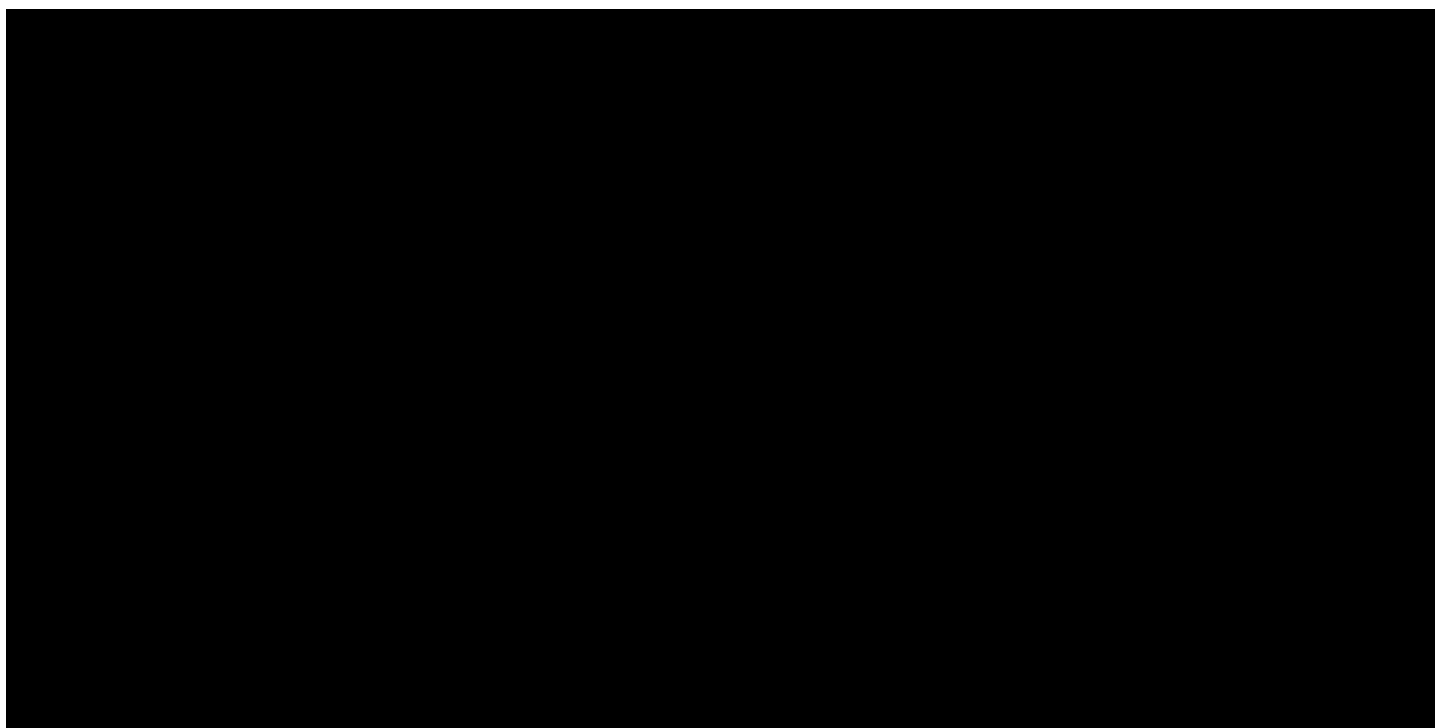


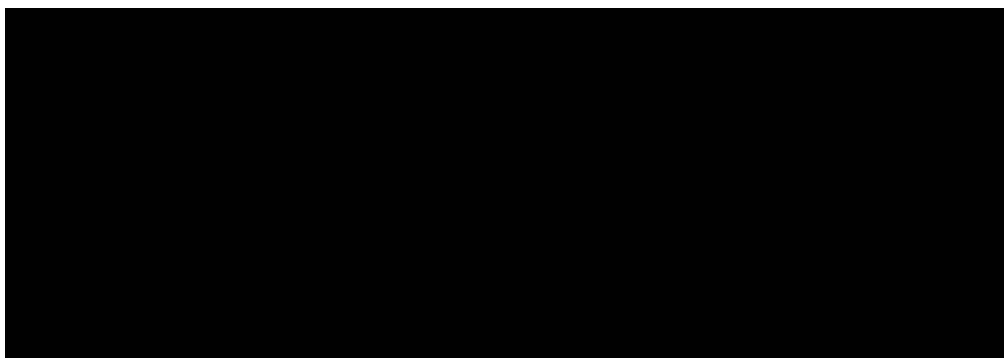
6.8 Adverse Event Definitions

Adverse events (AE) definitions were provided in the protocol, and have not changed since Version 1.0 released 2006. These adverse event definitions are provided in **Appendix D**. The pre-specified AE analysis uses these per protocol definitions.

The field has evolved greatly over the past five years. Since the study commenced, the Valve Academic Research Consortium (VARC) was established in response to the growing interest in TAVR by the medical community. Using a multi-disciplinary approach, VARC's objectives included the development of consensus involving standardized definitions for adverse events to be used in TAVR clinical trials [1-2]. The VARC definitions were employed by the Clinical Event Committee (CEC) of the PARTNER trial as outlined in their charter (**Appendix D**). In order to provide relevance of interpretation of the PARTNER Trial results with contemporary definitions, *post hoc* analyses including independently adjudicated endpoints are also included this briefing document.

6.9 Data Safety Monitoring Committee

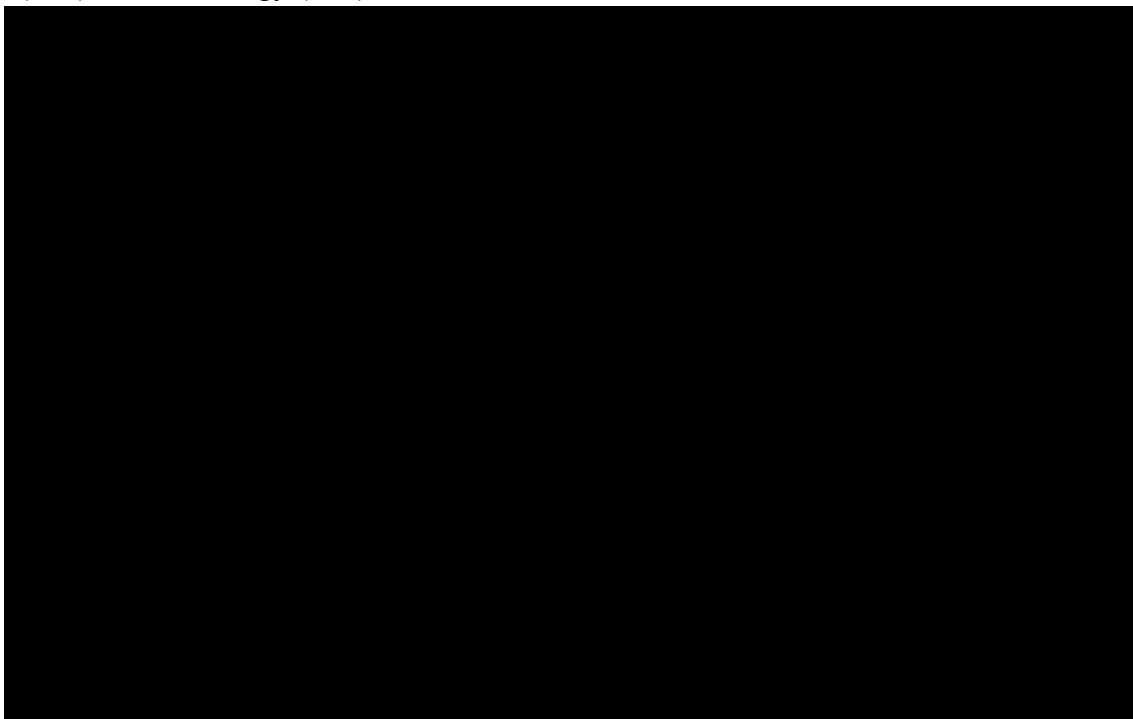


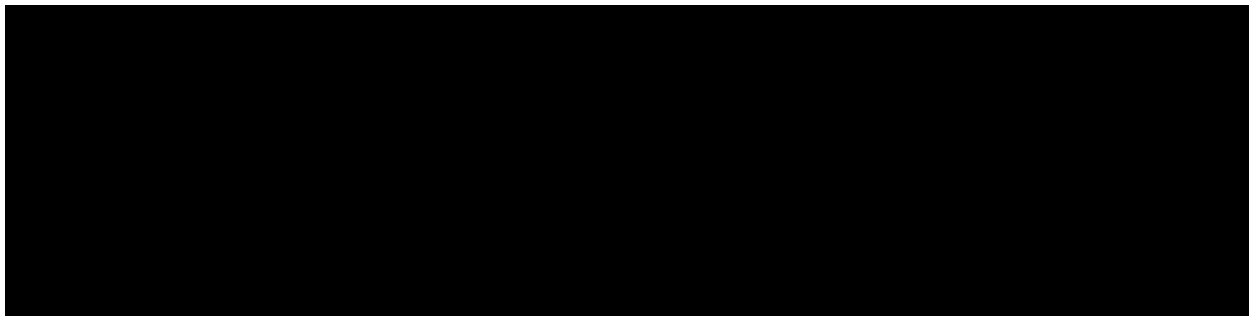


The DSMB could recommend stopping the trial for safety reasons, altering study conduct and changing eligibility criteria, but did not do so. The DSMB was not provided with statistical criteria for stopping the trial based on early evidence of distinct non-inferiority.

6.10 Clinical Evaluation Committee

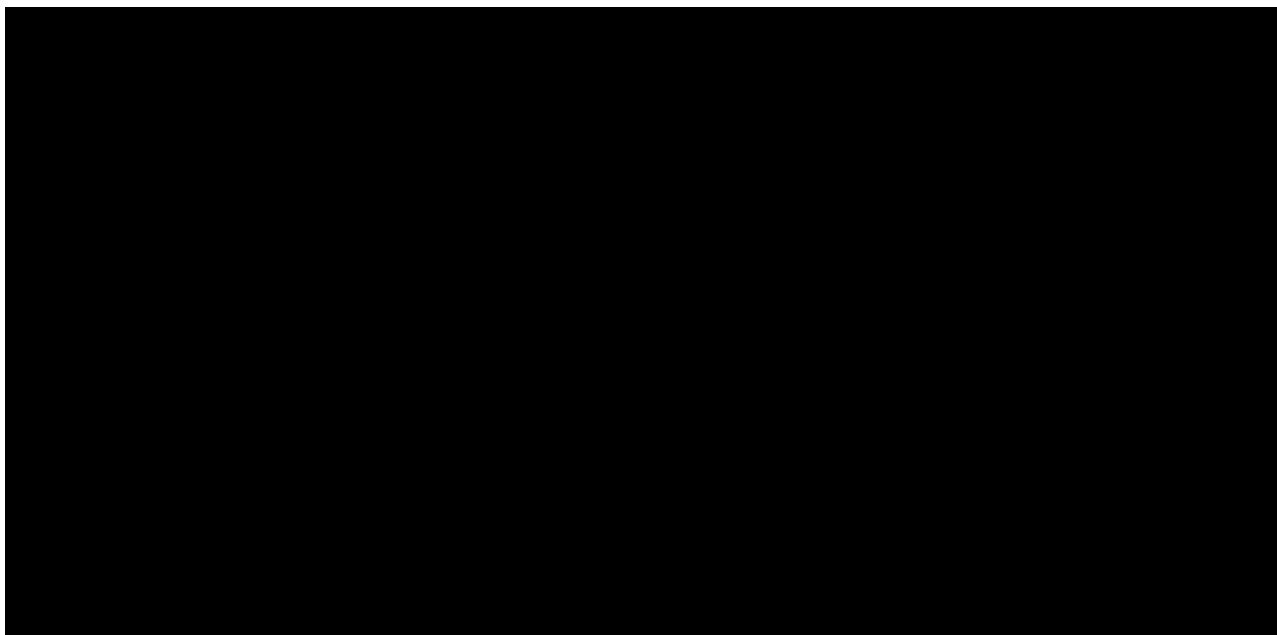
CEC members were university-based, specialty-trained physicians with relevant expertise: cardiac surgery (n=2), vascular surgery (n=1), cardiology (n=2), interventional cardiology (n=1), and neurology (n=1). The CEC members were:

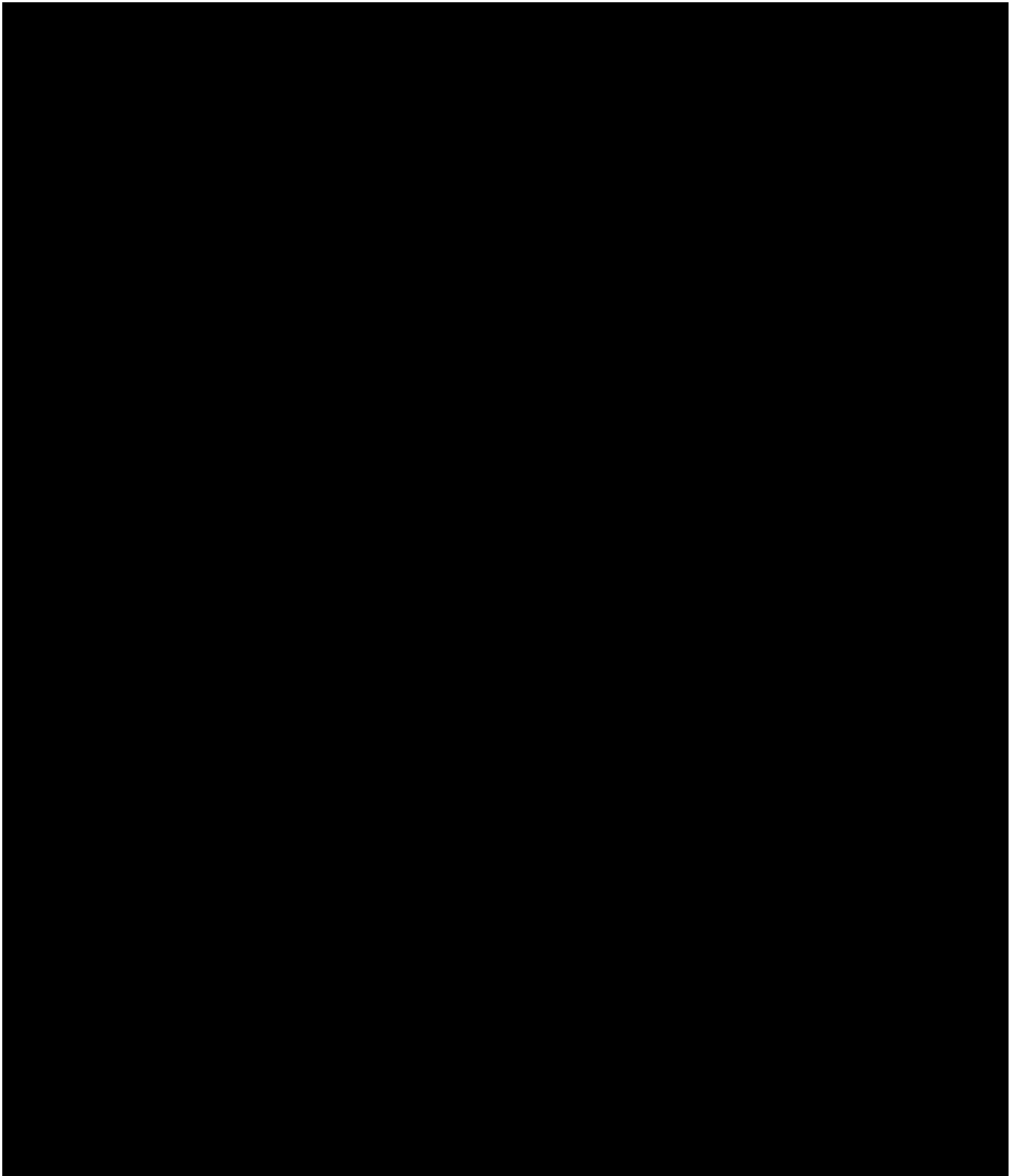




The CEC members remained constant throughout the trial duration and met on a regular basis throughout the study to adjudicate endpoint-related events reported during the trial. The CEC followed a charter for clinical endpoint adjudication and the charter remained constant throughout the trial with the exception of the *addition* of a post hoc adjudication of disability related to stroke and the addition of further adjudication for causes of death. Both of these post hoc amendments were applied per recommendation of the Executive Committee for purposes of interpretation of data and did not change the original adjudication of events per a priori charter. The key definitions used by the CEC harmonized to VARC definitions are located in **Appendix D**.

6.11 Statistical Methods







7.0 Disposition, Baseline and Study Procedure

7.1 Patient Disposition

Enrollment was initiated in the transfemoral high risk cohort in April, 2007 and in the transapical high risk cohort in April, 2008. Enrollment was completed in September, 2009. In order to capture the last patients enrolled with 2 year follow-up, the analysis close date was September 21, 2011. The date of the database extract was January 6, 2012.

Of the 3,996 patients screened for enrollment, 1,057 patients (26.5%) were randomized and 2,939 patients (73.5%) were screen failures. A total of 358 patients (9.0%) met the criteria for enrollment into the inoperable cohort and 699 patients (17.5%) met the criteria for enrollment into the high-risk cohort.

In the high-risk cohort, patients were first assigned to either transfemoral or transapical TAVR categories based on their vascular access, and were then randomized to either TAVR or AVR. A total of 492/699 (70.4%) were eligible for the transfemoral approach and 207/699 (29.6%) patients did not meet the criteria for transfemoral access and were assigned to the transapical approach.

ITT Population:

Overall, a total of 348/699 patients (49.8%) were randomly assigned to TAVR and 351/699 patients (50.2%) were randomized to AVR. The ITT population is the primary study population (Table 6).

Table 6. Intent-to-Treat Population – High Risk Cohort in the PARTNER Study

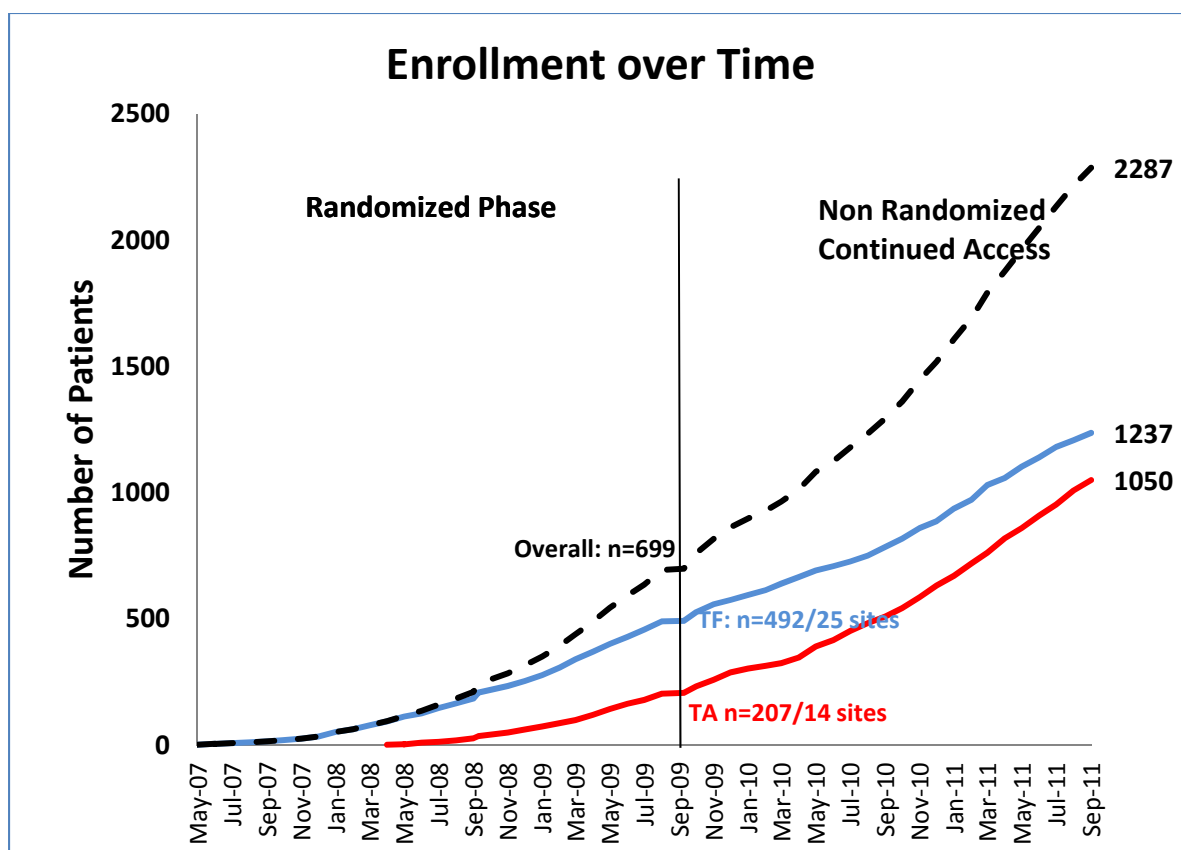
| | TAVR | AVR | Total |
|--------------|------|-----|-------|
| Transapical | 104 | 103 | 207 |
| Transfemoral | 244 | 248 | 492 |
| Pooled | 348 | 351 | 699 |



After enrollment in the randomized PMA cohort was complete, sites were able to enroll patients in a non-randomized continued access (NRCA) cohort. Eligible patients in the NRCA cohort underwent TAVR using the transfemoral approach or, if the characteristics of the patient's vasculature prohibited transfemoral access, using the transapical approach.

Table 87 in **Appendix F** shows the distribution of patients by site and arm. Enrollment accrual over time for the randomized clinical trial (PMA cohort) and continued access period stratified by approach is illustrated in Figure 4.

Figure 4. Enrollment Accrual over Time – High Risk Cohort in the PARTNER





AT Population:

As shown in Table 7, a total of 42 patients did not undergo TAVR nor AVR. Patients who did not undergo TAVR or AVR were excluded from the AT population. In the TAVR arm, two patients died prior to the procedure, one patient refused TAVR and one patient deteriorated prior to the procedure and was deemed too sick to undergo TAVR. In the AVR arm, five patients died prior to AVR, and five patients deteriorated prior to the procedure and were deemed too sick to undergo AVR. A total of 28 patients (8.0%) in the AVR arm either refused AVR or withdrew from the study. These patients are included in the primary ITT population.

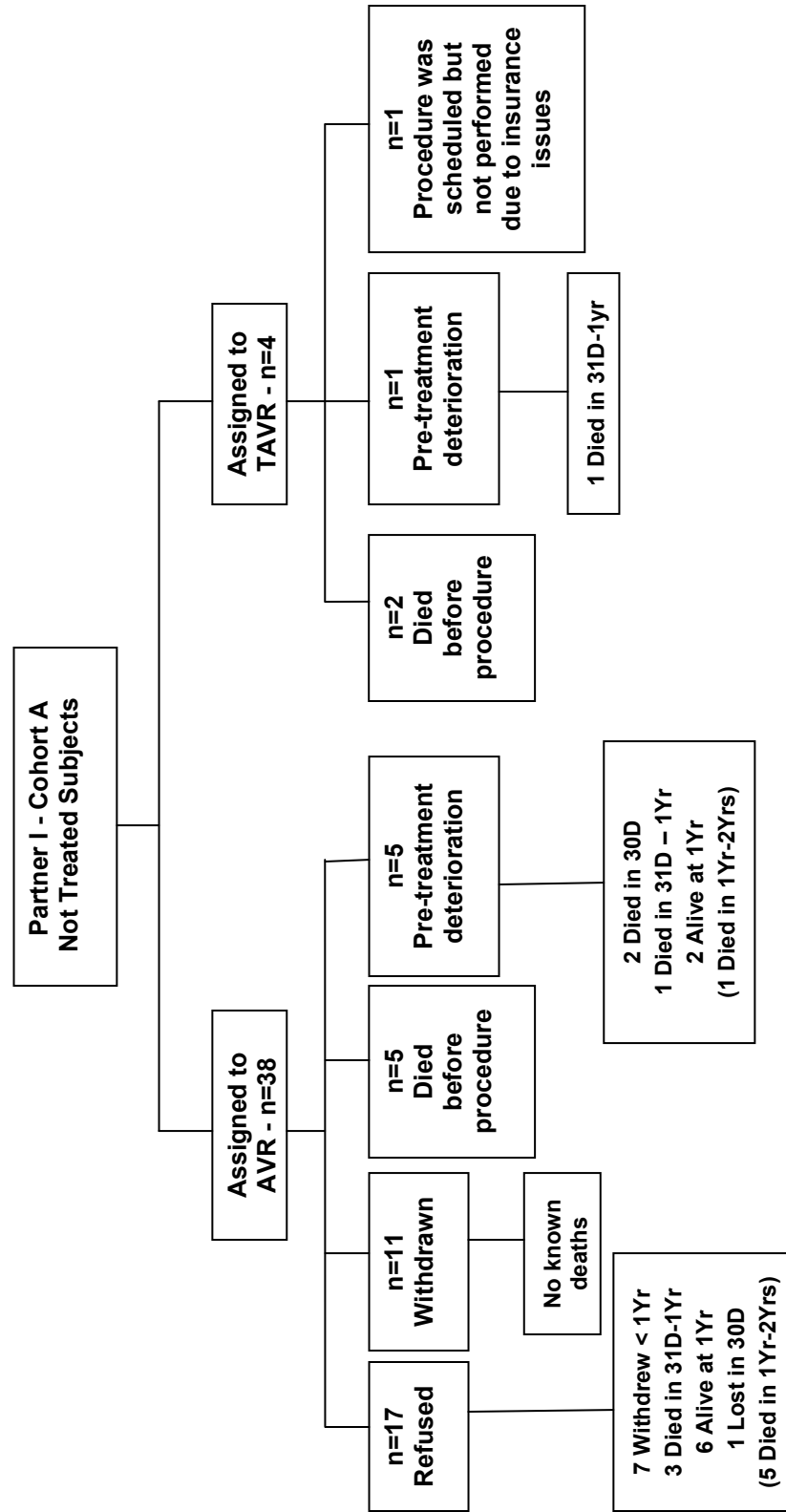
Table 7. Reasons for Not Undergoing the Randomly Assigned Treatment – High Risk Cohort in the PARTNER Study (ITT Population)

| Reason | Randomized to TAVR (N=348) | Randomized to AVR (N=351) |
|-----------------------------|-------------------------------|------------------------------|
| Died before the procedure | 2 (0.6%) | 5 (1.4%) |
| Refusal | 1 (0.3%) | 17 (4.8%) |
| Withdrawal | 0 (0%) | 11 (3.1%) |
| Pre-treatment deterioration | 1 (0.3%) | 5 (1.4%) |
| Total | 4 (1.1%) | 38 (10.8%) |

Figure 5 illustrates the outcome of the patients who did not undergo their randomly assigned treatment. Eight of the 17 patients (47.1%) who refused AVR died; 3 patients died within 1 year, and 5 patients died between 1 to 2 years of follow-up.



Figure 5. Outcome of Not Treated Patients – High Risk Cohort in the PARTNER Study (ITT Population)





Patients who did not undergo their randomly assigned treatment (TAVR or AVR) were excluded from the AT population (Table 8). No patients crossed over from one study arm (TAVR or AVR) into the other study arm (TAVR or AVR). Per protocol, TAVR patients who were converted to open heart surgery and underwent AVR remained in the TAVR arm since the TAVR procedure was started in all these patients.

Table 8. As Treated Population – High Risk Cohort in the PARTNER Study

| | TAVR | AVR | Total |
|--------------|------|-----|-------|
| Transapical | 104 | 92 | 196 |
| Transfemoral | 240 | 221 | 461 |
| Pooled | 344 | 313 | 657 |

Two patients () were initially randomized to TAVR using the transfemoral approach. Due to access problems, these patients received transapical TAVR. The AT implant approach was classified as TA-TAVR.

TAVR - Valve Implant Population:

A total of 18 TAVR patients were excluded from the valve implant population since either the THV was never implanted or did not remain *in situ* at the end of the index procedure (Table 9). The treatment received in these cases is provided in Table 9.

Table 9. TAVR Patients Excluded from the Valve Implant Population

| Reasons for Unsuccessful TAVR | Status | n | Treatment Received |
|--------------------------------|-------------------------------|-----------|--|
| Valve embolization | Did not remain <i>in situ</i> | 5 | Conversion to AVR (n=5) |
| TEE findings | Not implanted | 5 | AVR n=3; None n=1 ; BAV n=1 |
| Access problems | Not implanted | 4 | None n=2; late AVR n=1; converted to TA-TAVR n=1 |
| Died prior to valve deployment | Not implanted | 2 | Not Applicable |
| Femoral artery tear | Not implanted | 1 | Late AVR (n=1) |
| Large sigmoid septum | Not implanted | 1 | AVR (n=1) |
| Total | | 18 | |



Table 10 describes the classification of patients with respect to the assessment of the primary outcome as of September 21, 2011. At 1 year, 84 TAVR patients (24.1%) and 89 AVR patients (25.4%) had died. Three TAVR patients were censored at 1 year: two patients were lost to follow-up, and one patient had withdrawn. Twenty-six AVR patients were censored at 1 year: three patients were lost to follow-up, and 23 patients had withdrawn from the study.

Table 10. Classification of Patients with Respect to the Assessment of the Primary Outcome – High Risk Cohort in the PARTNER Study (ITT Population)

| Patient Status at 1 year ITT | Randomized | | Randomized Not Treated | |
|----------------------------------|------------------|-----|------------------------|-----|
| | TAVR | AVR | TAVR | AVR |
| Alive and at risk in KM analysis | 261 ^C | 236 | 1 | 7 |
| Died prior to 1 year | 84 | 89 | 3 | 11 |
| Lost | 2 | 3 | 0 | 1 |
| Withdrawn | 1 | 23 | 0 | 19 |
| Total Patients | 348 | 351 | 4 | 38 |

Source: Table 3.1

Lost patients were censored on the last date known alive. Withdrawn patients were censored on the withdrawal date. Table 88 in **Appendix F** lists the patients who either did not undergo their randomly assigned treatment (n=42) and/or patients that were censored at 1 year.

The mean (SD) follow-up time was 1.76 (0.95) years for TAVR patients and 1.58 (1.05) for AVR patients.

7.2 Demographic and Other Baseline Characteristics

Table 11 summarizes patient characteristics for the TAVR and AVR arms in the ITT population. Overall, the groups were balanced in most baseline characteristics. The only

^C After data lock, it was realized that the one-year follow-up data entry for one TAVR patient (██████████) was inconsistent. In analyses, this patient is censored prior to 1 year, however, the correct vital status is alive. Since the patient is a TAVR patient, any bias in the analysis will work against the TAVR arm of the trial. If this patient was to be counted as “alive”, the TAVR death rate at 1 year would decrease by 0.0001.



statistical significant difference was a higher incidence of creatinine > 2 mg/dL in the TAVR group. STS scores were assessed and recorded for each patient and reflect a high operative morbidity evidenced by a mean (SD) STS risk score of 11.8 (3.3) for TAVR patients and 11.7 (3.5) for AVR patients (higher number means greater risk; p=0.61).

Table 77 in **Appendix A** shows patient characteristics for the TAVR and AVR arms in the AT population and confirms the balance between groups.

Table 11. Demographic and Other Baseline Characteristics – High Risk Cohort in the PARTNER Trial (ITT Population)

| Characteristic | TAVR (n=348) | AVR (n=351) | Nominal p-value |
|---|-----------------|-----------------|--------------------|
| Age - years | 83.6 ± 6.8 | 84.5 ± 6.4 | 0.07 |
| Male sex - no./total no. (%) | 201/348 (57.8%) | 198/349 (56.7%) | 0.82 |
| Race | 348 | 349 | 0.63 |
| Asian | 2 (0.6%) | 0 (0.0%) | |
| Black | 11 (3.2%) | 8 (2.3%) | |
| Caucasian | 324 (93.1%) | 328 (94.0%) | |
| Hispanic | 9 (2.6%) | 9 (2.6%) | |
| Other | 2 (0.6%) | 4 (1.1%) | |
| STS score ^a | 11.8 ± 3.3 | 11.7 ± 3.5 | 0.61 |
| STS < 8 | 20 (5.7%) | 26 (7.4%) | |
| STS 8 - <10 | 46 (13.2%) | 57 (16.2%) | |
| STS 10 - < 15 | 229 (65.8%) | 219 (62.4%) | |
| STS ≥ 15 | 53 (15.2%) | 49 (14.0%) | |
| Logistic EuroSCORE ^b | 29.3 ± 16.5 | 29.2 ± 15.6 | 0.93 |
| NYHA class - no./total no. (%) | | | |
| II | 20/348 (5.7%) | 21/349 (6.0%) | >0.999 |
| III | 145/348 (41.7%) | 151/349 (43.3%) | 0.70 |
| IV | 183/348 (52.6%) | 177/349 (50.7%) | 0.65 |
| Coronary artery disease - no./total no. (%) | 260/348 (74.7%) | 266/349 (76.2%) | 0.66 |
| Previous MI - no./total no. (%) | 92/347 (26.5%) | 103/346 (29.8%) | 0.35 |
| Prior CABG - no./total no. (%) | 148/348 (42.5%) | 152/349 (43.6%) | 0.82 |
| Prior PCI - no./total no. (%) | 116/346 (33.5%) | 110/348 (31.6%) | 0.63 |
| Prior BAV - no./total no. (%) | 46/348 (13.2%) | 35/349 (10.0%) | 0.20 |
| Peripheral vascular disease - no./total no. (%) | 149/345 (43.2%) | 142/341 (41.6%) | 0.70 |
| Cerebral vascular disease - no./total no. (%) | 96/327 (29.4%) | 87/325 (26.8%) | 0.49 |
| COPD - no./total no. (%) | | | |
| Any | 152/348 (43.7%) | 151/351 (43.0%) | 0.88 |



| Characteristic | TAVR (n=348) | AVR (n=351) | Nominal p-value |
|---|-----------------|-----------------|--------------------|
| Oxygen dependent | 38/220 (17.3%) | 38/229 (16.6%) | 0.90 |
| Creatinine > 2mg/dL - no./total no. (%) | 37/343 (10.8%) | 22/344 (6.4%) | 0.04 |
| Atrial fibrillation - no./total no. (%) | 81/199 (40.7%) | 75/172 (43.6%) | 0.60 |
| Permanent pacemaker - no./total no. (%) | 69/348 (19.8%) | 76/349 (21.8%) | 0.58 |
| Pulmonary hypertension - no./total no. (%) | 126/295 (42.7%) | 111/302 (36.8%) | 0.15 |
| Frailty - no./total no. (%) ^c | 46/295 (15.6%) | 53/301 (17.6%) | 0.58 |
| Extensively calcified aorta - no./total no. (%) | 2/348 (0.6%) | 4/351 (1.1%) | 0.69 |
| Deleterious effects of chest-wall irradiation - no./total no. (%) | 3/348 (0.9%) | 3/351 (0.9%) | >0.999 |
| Chest-wall deformity - no./total no. (%) | 0/348 (0.0%) | 1/351 (0.3%) | >0.999 |
| Liver disease - no./total no. (%) | 8/348 (2.3%) | 11/349 (3.2%) | 0.64 |
| Echocardiographic Findings | | | |
| Aortic valve area – cm | 0.7 ± 0.2 | 0.6 ± 0.2 | 0.11 |
| Mean aortic valve gradient - mm Hg | 42.6 ± 14.6 | 43.5 ± 14.3 | 0.42 |
| Mean LVEF - % | 52.5 ± 13.5 | 53.1 ± 12.8 | 0.59 |
| Moderate or severe MR - no./total no. (%) ^d | 66/337 (19.6%) | 71/338 (21.0%) | 0.70 |

AVR= aortic valve replacement, BAV=balloon aortic valvuloplasty, CABG=coronary bypass grafting, COPD=chronic obstructive pulmonary disease, LVEF=left ventricular ejection fraction, MI=myocardial infarction, MR=mitral regurgitation, NYHA=New York Heart Association, PCI=percutaneous coronary intervention, STS=Society of Thoracic Surgeons, TAVR= transcatheter aortic valve replacement.

Categorical variables were analyzed using a two sided Fisher's exact test; continuous variables were analyzed using a two sided two sample t-test, ANOVA, or Wilcoxon rank-sum test, with multiple comparisons performed using Scheffé's method.

- The STS score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.
- The logistic EuroSCORE, which measures patient risk at the time of cardiovascular surgery, was calculated with the use of a logistic regression equation. Scores range from 0% to 100%, with higher scores indicating greater risk. A logistic EuroSCORE higher than 20% indicates very high surgical risk.
- Frailty was determined by the surgeons according to prespecified criteria.
- Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Baseline and demographic information involving other stratifications are provided in **Appendix A**.

7.3 Study Conduct

Visit compliance through 1 year was high (> 97.5%) in both groups (Table 89 in **Appendix F**).

In the transapical arm, the mean time to treatment in patients randomly assigned to the TAVR was 10.8 days vs. 20.5 days in the AVR group (Table 12).



Table 12. Time to Treatment – High Risk Cohort in the PARTNER Study (AT Population)

| Summary of Time to Treatment for AT Population | | | | | | |
|--|----------------------|------|-----------------------|------|-----------------|------|
| | Transapical Approach | | Transfemoral Approach | | Pooled Approach | |
| Summary | TAVR | AVR | TAVR | AVR | TAVR | AVR |
| Number of Subjects | 104 | 92 | 240 | 221 | 344 | 313 |
| Mean | 10.8 | 20.5 | 10.6 | 13.5 | 10.6 | 15.6 |
| Standard Deviation | 10.9 | 23.5 | 14.3 | 17.6 | 13.3 | 19.7 |
| Lower Quartile | 4.5 | 4.5 | 3 | 3 | 3.5 | 3 |
| Median | 7.0 | 12.5 | 7.0 | 8.0 | 7.0 | 9.0 |
| Upper Quartile | 13 | 30 | 13 | 16 | 13 | 22 |
| Minimum | 1 | 0 | 0 | 1 | 0 | 0 |
| Maximum | 65 | 143 | 143 | 165 | 143 | 165 |

7.4 Descriptive Findings from TAVR and AVR Procedures

7.4.1 Procedural Information and Events

Procedural data are provided in Table 13. The mean total procedure time (entry into catheterization [cath] lab/operating room [OR] to exit) and mean skin-to-skin time was shorter for the transapical approach than the transfemoral approach, while mean fluoroscopy duration was longer during the transapical approach. The mean total procedure time and skin-to-skin time was considerably longer for the AVR approach.

Most TF-TAVR patients (171/240 or 71.3%) had an incision for direct arterial access and 66/240 (27.5%) TF-TAVR patients had a percutaneous catheter puncture, and the approach was missing in 3 cases (3/240 or 1.3%). Two of the 66 patients (3.0%) with a percutaneous catheter puncture experienced a major vascular complication that required surgical intervention. Table 90 in **Appendix F** summarizes additional procedural parameters collected.

A full sternotomy was performed in 264 AVR procedures (264/313 or 84.3%); in 49 cases (49/313 = 15.7%), AVR was performed minimally invasively. The mean total cross clamp time was 73.5 min ± 28.7 min, and the mean pump time was 104.9 ± 41.4 min. In spite of the protocol, concomitant CABG was performed in 21 of 313 AVR cases



(6.7%; Table 91, **Appendix F**). In 16 AVR patients, an intra-aortic balloon pump was used. Note: None of the patients randomly assigned to AVR underwent TAVR.

Table 13. Procedural Data– High Risk Cohort in the PARTNER Study (AT Population)

| Measured Variable | TAVR (N = 344) | | AVR (N = 313) |
|--|--------------------------|--------------------------|--------------------|
| | Transapical (N = 104) | Transfemoral (N= 240) | |
| Total time in Cath Lab or OR in minutes [Mean (Min - Max)] | 224.9 (93 - 595) | 242.8 (0 - 624) | 323.7 (0 - 750) |
| Skin to skin time in minutes [Mean (Min - Max)] | 114 (9-904) | 141 (32-510) | 230.0 (169 - 295)† |
| Fluoroscopy time in minutes [Mean (Min - Max)] | 35 (5-945) | 30 (7-121) | 0 (0 - 0)† |
| Volume of contrast in mL [Mean (Min - Max)] | 104 (0-275) | 148 (15-507) | 0 (0 - 0)† |
| Use of Cannulation for Cardiopulmonary Bypass [n (%)] | 9 / 102 (8.8%) | 5 /234 (2.1%) | 313/313 (100%) |
| Use of general anesthesia [n (%)] | 102/102 (100%) | 240/240 (100%) | 309/309 (100%) |
| # of devices used | | | |
| 0 [n (%)] | 3/102 (2.9%) | 11/238 (4.6%) | na |
| 1 [n (%)] | 91/102 (89.2%) | 216/238 (90.8%) | 313/313 (100%) |
| 2 [n (%)] | 7/102 (6.9%) | 10/238 (4.2%) | na |
| 3 [n (%)] | 1/102 (1.0%) | 1/238 (0.4%) | na |
| More than one Valve Used [n (%)] | 3/104 (2.9%) | 4/240 (1.7%) | na |
| Emergent operation due to device or procedure [n (%)] | 1/104 (1.0%) | 3/240 (1.3%) | 12/313 (3.8%) |
| Valve Size | | | |
| 19 [n (%)] | na | na | 37/312 (11.9%) |
| 21 [n (%)] | na | na | 124/312 (39.7%) |
| 22 [n (%)] | na | na | 1/312 (0.3%) |
| 23 [n (%)] | 52/101 (51.5%) | 109/233 (46.8%) | 109/312 (34.9%) |
| 25 [n (%)] | na | na | 37/312 (11.9%) |
| 26 [n (%)] | 49/101 (48.5%) | 124/233 (53.3%) | Na |
| 27 [n (%)] | na | na | 3/312 (1.0%) |
| 29 [n (%)] | na | na | 1/312 (0.3%) |
| Adverse event during procedure [n (%)] | 20/102 (19.6%) | 51/240 (21.3%) | 46/313 (14.7%) |
| Device malfunction [n (%)] | 2/101 (2.0%) | 3/234 (1.3%) | na |
| Device Success (deployment, AVA >0.9, AI<3+, 1 valve) [n (%)] | 82/97 (84.5%) | 184/229 (80.4%) | na |
| Procedure Success (Device success, no MACCE <30d) [n (%)] | 73/97 (75.3%)‡ | 174/229 (76.0%)‡ | na |

na=not applicable

† Based on 7 total control subjects

‡ The denominator for Procedure Success is larger than the denominator for Device Success because it is known that 4 subjects with missing Device Success had Procedure Failures due to MACCE within 30 days of Index Procedure

Table 14 summarizes the procedural events and additional details are presented below. As shown, there were a total of 11 embolizations in the TAVR arm: five embolizations required conversion to AVR, four embolizations required the use of more than one valve, and two embolizations required stent or graft stabilization. During TAVR, TEE findings



required immediate conversion to AVR in three cases and the TAVR procedure was aborted in two cases.

Table 14. TAVR: Procedural Events – High Risk Cohort in the PARTNER Study (AT Population)

| Procedural Events | TAVR n=344 |
|---|--|
| More than one valve used | 7 (2.0%) Embolization n=4 Severe AR n=2 (including 1 device malfunction) Failure to cross n=1 |
| Immediate conversion to AVR | 9 (2.6%) Embolization n=5 Annulus size on TEE n=3 Large sigmoid septum n=1 |
| Aborted Procedures | 7 (2.0%) Failed access n=3 New TEE findings n=2 Died n=2 |
| Embolization requiring stent or graft stabilization | 2 (0.6%) |

7.4.1.1 TAVR - Device Malfunction

Device malfunction was defined as failure of the device to meet any of its performance specifications made in the labeling of the device or otherwise perform as intended. Five patients experienced device malfunction, four malfunctions involved the delivery system:

- Balloon rupture during valve implantation with no adverse sequelae (TA).
- Side arm broke off with no adverse sequelae (TF-RetroFlex).
- During the procedure, but prior to valve placement, the loader was pushed too far; the valve went through the sheath damaging the sheath and could not be advanced. The valve was recovered and returned to Edwards. No adverse events were caused by this malfunction (TF RetroFlex).
- Kinking of the sheath requiring insertion of another 22 Fr sheath with no adverse sequelae (TF RetroFlex).

One device malfunction involved the study valve:

- After placement of the first valve, TEE showed severe aortic valve regurgitation and 2 leaflets were not functioning. A second valve was implanted within the first valve (see More Than One Valve Used). The patient could not be weaned from the ventilator and died approx. 6 weeks later due to respiratory failure.



7.4.1.2 TAVR - More Than One Valve Used

In seven patients more than one valve was used. Two of the seven patients underwent a valve-in-valve procedure at the time of the index procedure:

- After successful deployment of the valve, the patient developed instantaneous hemodynamic collapse with 3+ aortic insufficiency (central and PVL) requiring a second valve implantation. The patient died approx. 2 weeks after the procedure.
- After first valve was placed, TEE showed severe aortic valve regurgitation and 2 leaflets were not functioning. A second valve was implanted within the first valve (see Device Malfunctions). The patient died approx. 6 weeks after the procedure.

The remaining five patients received more than one valve at the time of the index procedure due to embolization, or failure to cross:

- The first THV was implanted in left ventricular outflow tract (LVOT) with severe aortic insufficiency (no PVL) requiring deployment of 2nd valve. Vital status at the time of analysis: alive.
- Due to a heavily calcified native valve, it was not possible to cross and deploy the first THV successfully using the RF-1 system; this THV was deployed in the descending aorta and covered with a Palmaz-Schatz stent for stabilization. A 2nd THV was successfully advanced and deployed using RF-2 system. Vital status at the time of analysis: alive.
- Pacing capture was lost, PVC occurred and the device embolized. Subsequently, the first valve was secured in the descending aorta, and the second valve was implanted in the proper place. Vital status at the time of analysis: alive.
- Upon deployment, the valve landed high and there was severe AI with cardiac collapse. The patient was cannulated for CPB. A second valve was placed with excellent result and return of good function. However, the patient developed some ARDS with an ongoing ventilator requirement, and a tracheostomy was placed. The patient had worsening mental status and became unresponsive. Her DNR status was respected and the family made the decision to withdraw support. The patient died 1 month after the procedure.
- The first valve device slipped initially higher in the ascending part of the aorta and soon after it migrated in the descending aorta in a stable position; a 2nd valve was advanced through the first opened valve and deployed properly at the level of the native aortic valve. Vital status at the time of analysis: alive.

These 7 patients were included in the TAVR arm in both the ITT and AT populations.



7.4.1.3 TAVR Patients Who Underwent AVR

Eleven patients randomized to TAVR underwent AVR; nine patients underwent AVR immediately (during the index procedure) and two patients underwent late AVR, i.e., 3 month after the attempted TAVR procedure (Table 15). All 11 patients were classified as TAVR patients in the ITT population and AT population since the TAVR procedure was initiated in each case.

Table 15. TAVR Patient Who Underwent AVR – High Risk Cohort in the PARTNER Study

| Subject ID | Assigned Implant Approach | Reason for Conversion to AVR | Status at time of analysis |
|----------------------|---------------------------|--------------------------------------|--|
| Immediate AVR | | | |
| | TF-TAVR | Large sigmoid septum | Alive |
| | TF-TAVR | Annulus size was too large | Alive |
| | TF-TAVR | Annulus size was too large | Alive |
| | TF-TAVR | THV embolization | Alive |
| | TA-TAVR | THV embolization | Died approx. 8.5 months post procedure – cause unknown |
| | TA-TAVR | THV embolization | Alive |
| | TF-TAVR | Annulus size was too large | Alive |
| | TA-TAVR | THV embolization | Patient could not be weaned off bypass and died on the day of the procedure. |
| | TF-TAVR | THV embolization | Died 6 months post procedure due to non cardiovascular cause |
| Late AVR | | | |
| | TF-TAVR | Dissection – AVR 3 months later | Died 16 months post procedure – cause unknown |
| | TF-TAVR | Access problems – AVR 3 months later | Alive |

7.4.1.4 Aborted Procedures in TAVR Patients

In seven patients (five transfemoral and two transapical cases), the TAVR procedure was started but aborted:

- The procedure was aborted due to access problems, and no other intervention for AS was performed.



- Extensive calcification was discovered on TEE, and no other treatment was given for AS.
- The patient experienced a cardiac arrest when she was being transferred from the stretcher to the OR table. She was intubated and resuscitated, and it was decided to proceed with the transapical procedure. Due to the patient's anatomy (LV was posterior), the guidewire entered the RV instead of the LV which was confirmed by echo and the patient was placed on femoral-femoral bypass. While trying to reach the LV, bleeding from the mammary artery was observed which was subsequently ligated. However, after 82 minutes of cardiopulmonary bypass and consultation with the patient's family, the decision was made to stop the procedure and the patient was pronounced deceased.
- Severe mitral regurgitation was discovered on TEE, and the procedure was aborted. The patient underwent BAV, mitral valve replacement (MVR) and tricuspid annuloplasty.
- During surgical exposure of the apex, the patient experienced uncontrolled hemorrhage from the apex and expired.
- The procedure was aborted due to transfemoral access problems, and 30 days later, the patient underwent TA-TAVR.
- Cut down on the right femoral artery was performed, a 14F sheath was inserted and a valvuloplasty balloon was inflated in the aortic valve. Serial dilations of the right femoral arterial access site were performed with 16mm to 25mm dilators but the 22F delivery sheath could not be advanced into the aorta due to a combination of spasm and atherosclerosis. In spite of attempts to relieve the spasm with Verapamil and nitroglycerin and attempts to dilate the vessel, the sheath could not be advanced. Vascular cut down on the left femoral artery was performed, however, the same difficulties in trying to advance the sheath were encountered and the procedure was stopped without deployment of the valve.

These 7 patients were included in the TAVR arm in both the ITT and AT populations.



8.0 Efficacy

The primary endpoint in the high risk cohort was all cause mortality at 1 year in the ITT population. The one-sided definition of inferiority for this non-inferiority null hypothesis was $\Delta \geq 7.5\%$ -points. The primary analysis met the pre-defined non-inferiority success criterion.

All four secondary non-inferiority endpoints analyzed under type I error probability-control were met:

- 1) Time from randomization to the first occurrence of a MACCE event at one year. MACCE consisted of death, MI, stroke, and renal failure using per protocol definitions of each adverse event (definition of inferiority: $\Delta \geq +7.5\%$ -points);
- 2) Total hospital days through one year (definition of inferiority: $\Delta \geq +10$ days);
- 3) NYHA functional classification at one year (definition of inferiority: $\Delta = +0.25$);
- 4) Six minute walk test at one year (definition of inferiority: $\Delta \leq -70$ meters).

Table 16 summarizes the details of the primary analysis and secondary analyses. Sensitivity analyses are outlined below.



Table 16. Endpoints - High Risk Cohort in the PARTNER Randomized Study (ITT Population)

| Analysis | Endpoint | Inferiority Definition | AVR Arm Estimate | TAVR Arm Estimate | Absolute Difference (TAVR-AVR) | One-sided 95% Confidence Limit on Difference | P-value | Success |
|-----------|---|---------------------------|------------------|-------------------|--------------------------------|--|----------|---------|
| Primary | One-year all-cause mortality (Kaplan-Meier estimate) based on ITT | TAVR ≥7.5 %-points more | 26.8% | 24.3% | -2.5% | ≤ 2.99 | 0.0014 | Yes |
| Secondary | One-year MACCE (Kaplan-Meier estimate; no imputation – ITT) | TAVR ≥7.5 %-points more | 29.1% | 27.4% | -1.7% | ≤ 4.0 | 0.0040 | Yes |
| Secondary | Median Hospital Days through one-year (no imputation – ITT) | TAVR ≥10 days more | 18.8 | 16.3 | -3.0 | ≤ -2.00 | 0.0001 | Yes |
| Secondary | NYHA at one year (Completers analyses) | TAVR mean ≥0.25 higher | 1.70 | 1.70 | -0.01 | ≤ 0.11 | 0.0001 | Yes |
| Secondary | 6MWD at one year (Completers analyses) | TAVR mean ≤70 meters less | 169.8 | 165.0 | 4.88 | ≥ -18.51 | < 0.0001 | Yes |

6MWD=6 minute walk distance; AVR=aortic valve replacement; ITT=intent-to-treat; MACCE= major adverse cardiac and cerebrovascular events; NYHA=New York Heart Association; TAVR= transcatheter aortic valve replacement.
Per-protocol definitions - MACCE: Death; Myocardial Infarction = acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non-Q-wave MI; Renal Failure = Patient required chronic dialysis for greater than 30 days; Stroke = a neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction.

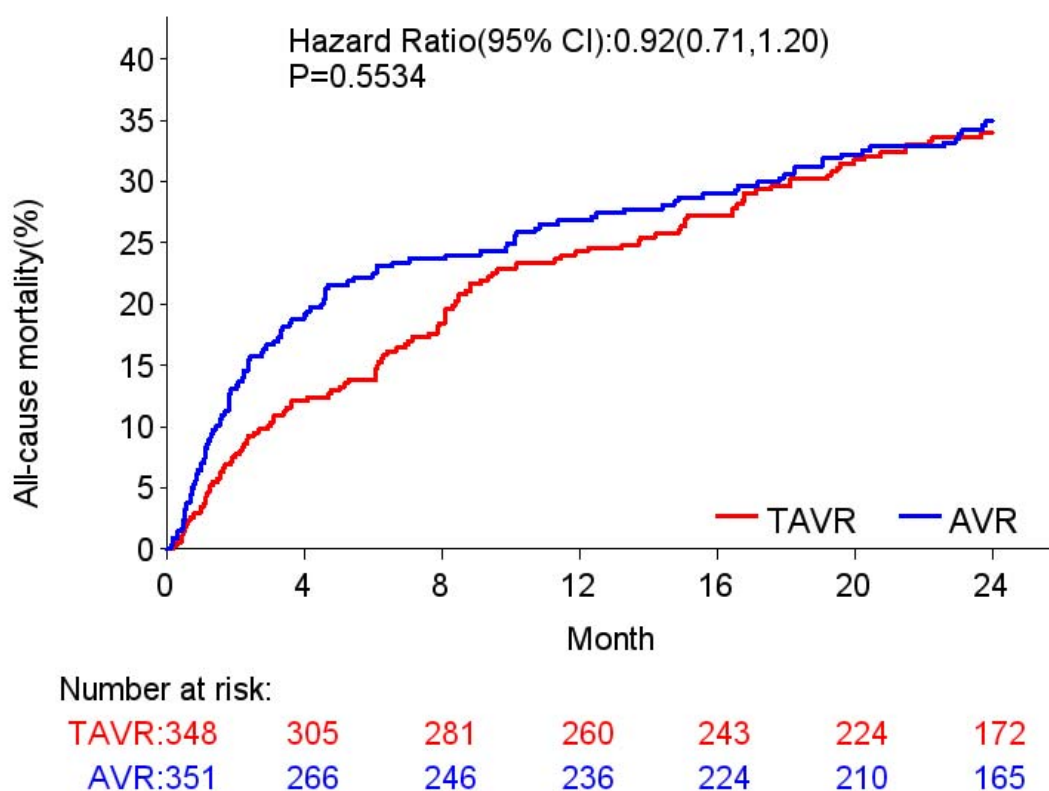


8.1 All Cause Mortality - ITT Population

Primary Endpoint

The primary endpoint was a non-inferiority analysis of all cause mortality at 1 year from randomization using the non-inferiority margin $\Delta = 0.075$. Figure 6 illustrates the mortality experience in the high surgical cohort for the ITT population out to 24 months.

Figure 6. All-Cause Mortality – High Risk Cohort in the PARTNER Study (ITT Population)



Hazard ratio at 2 years; p-value from log-rank test up to 24 months



Table 17 presents the primary endpoint analysis for the ITT population. The test was a one-sided non-inferiority test using the non-inferiority margin $\Delta=7.5\%$. At 1 year, the mortality difference (TAVR-AVR) was -2.53%, and the 95% one-sided upper CL for the difference was 2.99%. The p-value was 0.0014 indicating that the all cause mortality in the TAVR arm was not inferior to all cause mortality in the AVR arm at 1 year.

Table 17. Primary Endpoint Analysis - High Risk Cohort of the PARTNER Trial (ITT Population)

| Pooled Approaches: ITT - Actual Data Analysis | | |
|---|--------|--------|
| | AVR | TAVR |
| # patients died | 89 | 84 |
| # patients censored prior to 1 year | 26 | 4 |
| # patients known alive at 1 year | 236 | 260 |
| # Mortality at 1 year | 26.80% | 24.27% |
| # Standard error at 1 year | 2.44% | 2.31% |
| # Mortality difference (TAVR - AVR) | -2.53% | |
| # Standard error of difference | 3.35% | |
| # 95% 1-sided upper CL for difference | 2.99% | |
| Non-inferiority Delta | 7.50% | |
| # Z-score for primary endpoint test | 2.9909 | |
| # p-value for primary endpoint test | 0.0014 | |

Source: Table 7.1

8.1.1 Sensitivity Analysis of the Primary Endpoint

The primary endpoint analysis was repeated with various assumptions as to the treatment of patients who were censored prior to 1 year, or who did not receive the procedure (Table 18), specifically,

- AVR patients censored prior to one year were considered alive at 1 year, and TAVR patients censored prior to 1 year were considered dead as of the censoring date.



- AVR patients who did not receive the procedure were considered alive at 1 year, even if they were known to have died. Other censored patients remained censored.
- AVR patients who were censored prior to 1 year were considered alive at 1 year, and AVR patients who did not receive the procedure were also considered alive at 1 year. TAVR patients who were censored prior to 1 year were considered dead as of the censoring date.

All these assumptions are unfavorable to the TAVR arm. The intent of the sensitivity analyses was to find a tipping point; that is the point where the unfavorable assumptions would tip the primary endpoint away from statistical significance. Even with the worst case assumptions the primary endpoint passed; no tipping point was observed.

These sensitivity analyses confirm non-inferiority of the primary endpoint in the ITT population.

An alternate analysis using Peto errors instead of the Greenwood errors is presented (Table 19).



Table 18. Primary Endpoint Sensitivity Analyses - High Risk Cohort of the PARTNER Trial (ITT Population)

| | Sensitivity Analysis ITT A: Assume AVR censored alive at 1 year and TAVR censored dead at 1 year | | Sensitivity Analysis ITT B: Assume AVR who elected no procedure alive at 1 year | | Sensitivity Analysis ITT C: Assume AVR who withdrew or who elected no procedure alive at 1 year | |
|--|---|--------|--|--------|--|--------|
| | AVR | TAVR | AVR | TAVR | AVR | TAVR |
| # patients died (imputed for sensitivity analysis) | 89 | 88 | 86 | 84 | 86 | 88 |
| # patients censored prior to 1 year (imputed for sensitivity analysis) | 0 | 0 | 7 | 4 | 0 | 0 |
| # patients known alive at 1 year (imputed for sensitivity analysis) | 262 | 260 | 258 | 260 | 265 | 260 |
| # Mortality at 1 year | 25.36% | 25.29% | 24.72% | 24.27% | 24.50% | 25.29% |
| # Standard error at 1 year | 2.32% | 2.33% | 2.31% | 2.31% | 2.30% | 2.33% |
| # Mortality difference (TAVR - AVR) | -0.07% | | -0.45% | | 0.79% | |
| # Standard error of difference | 3.29% | | 3.27% | | 3.27% | |
| # 95% 1-sided upper CL for difference | 5.34% | | 4.92% | | 6.17% | |
| Non-inferiority Delta | 7.50% | | 7.50% | | 7.50% | |
| # Z-score for primary endpoint test | 2.3008 | | 2.4334 | | 2.0526 | |
| # p-value for primary endpoint test | 0.0107 | | 0.0075 | | 0.0201 | |

Source: Table 7.1



Table 19. Primary Endpoint Sensitivity Analysis Using Standard Errors and Peto Errors - High Risk Cohort of the PARTNER Trial (ITT Population)

| Comparison of primary endpoint analysis using Standard Errors and Peto Errors | | | | | | | | | | | | |
|---|-------------------------------------|-------------------------------|--------------------------------------|------------------------------|-------------------------------------|-------------------------------------|-----------------------------------|-----------------------------------|--|--|--|--------|
| | AVR standard error (Peto) at 1 year | TAVR standard error at 1 year | TAVR standard error (Peto) at 1 year | Standard Error of Difference | Standard Error (Peto) of Difference | 95% 1-sided lower CL for difference | Z-score for primary endpoint test | P-value for primary endpoint test | 95% 1-sided lower CL for difference (Peto) | Z-score for primary endpoint test (Peto) | P-value for primary endpoint test (Peto) | |
| AVR standard error at 1 year | 0.0244 | 0.0247 | 0.0231 | 0.0231 | 0.0335 | 0.0338 | -0.0299 | 2.9909 | 0.0014 | -0.0303 | 2.9657 | 0.0015 |



8.1.2 All Cause Mortality – AT Population

Non-inferiority was met in the as-treated population. As shown in Table 20, the all cause mortality difference was -1.53%, and the 95% one-sided lower CL for the difference was 4.02%, which was below the pre-specified non-inferiority margin of 7.5%. The non-inferiority p-value was 0.0037 indicating that the all cause mortality in the TAVR AT arm was not inferior to the all cause mortality in the AVR AT arm at 1 year.

Table 20. Primary Endpoint Analysis – High Risk Cohort of the PARTNER Trial (AT Population)

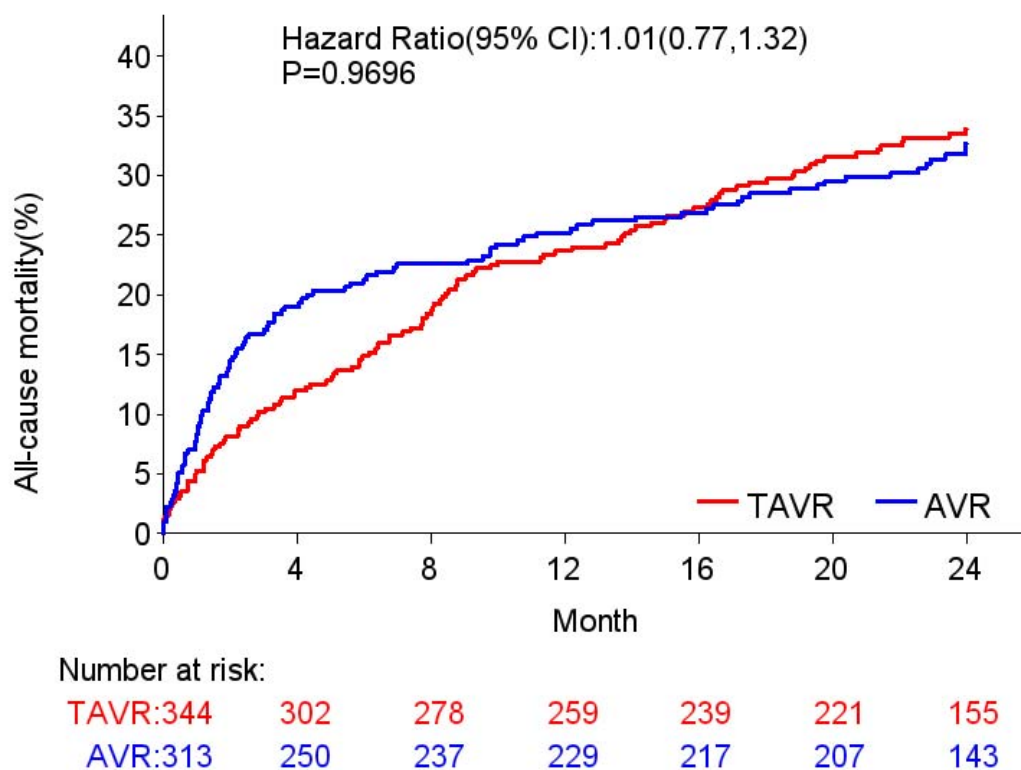
| Pooled Approaches: AT: Actual Data Analysis | | |
|--|--------|--------|
| | AVR | TAVR |
| # patients died (imputed for sensitivity analysis) | 78 | 81 |
| # patients censored prior to 1 year (imputed for sensitivity analysis) | 6 | 4 |
| # patients known alive at 1 year (imputed for sensitivity analysis) | 229 | 259 |
| # Mortality at 1 year | 25.21% | 23.68% |
| # Standard error at 1 year | 2.47% | 2.30% |
| # Mortality difference (TAVR - AVR) | -1.53% | |
| # Standard error of difference | 3.37% | |
| # 95% 1-sided upper CL for difference | 4.02% | |
| # Z-score for primary endpoint test | 2.6748 | |
| # p-value for primary endpoint test | 0.0037 | |

Source: Table 7.1

Figure 7 shows the all cause mortality experience in the AT population.



Figure 7. All-Cause Mortality – High Risk Cohort in the PARTNER Study (AT Population)



Hazard ratio at 2 years; p-value from log-rank test up to 24 months

A sensitivity analysis assuming that AVR patients censored at 1 year were alive and TAVR patients censored at 1 year were dead, resulted in a survival difference (TAVR-AVR) of -0.21% (95% one-sided lower CL for the difference of 5.34%) and p-value of 0.0112.

Thus, in the AT population, the all cause mortality in the TAVR arm was not inferior to the all cause mortality in the AVR arm at 1 year and confirm the findings in the ITT population.



8.1.3 Multivariate Analyses of All Cause Mortality

Proportional Hazard Regression (PHR) analysis of predictors of mortality of death over the course of the trial was performed. Each model contained the trial arm and single additional covariate. Trial arm was forced into the model. As shown in Table 21, the following predictors of mortality in the entire study population were identified: BMI, liver disease, mean gradient, STS risk score and moderate to severe mitral regurgitation. Trial arm was not a predictor of mortality.

Table 21. Proportional Hazards Regression Analysis of Predictors of Death over the Course of the Trial: Multivariable Model - High Risk Cohort in the PARTNER Study (ITT Population)

| Label | Hazard Ratio | 95% Lower Confidence Limit for Hazard Ratio | 95% Upper Confidence Limit for Hazard Ratio | Pr > ChiSq |
|---|--------------|---|---|------------|
| Test Arm | 0.889 | 0.700 | 1.129 | 0.3345 |
| Body Mass Index (lbs/in ²) | 0.961 | 0.939 | 0.983 | 0.0006 |
| Non-CV Conditions: Liver disease | 2.283 | 1.303 | 4.002 | 0.0039 |
| Mean Gradient mmHg/10 | 0.889 | 0.814 | 0.971 | 0.0090 |
| STS Risk Score | 1.040 | 1.005 | 1.076 | 0.0257 |
| Moderate or Severe Mitral Regurgitation -- Baseline | 1.362 | 1.023 | 1.813 | 0.0343 |

In the TAVR arm, the following predictors of mortality were identified: BMI, mean gradient, baseline creatinine and other vascular stent of PTA (arterial; Table 22).

Table 22. Proportional Hazards Regression Analysis of Predictors of Death over the Course of the Trial: Multivariable Model - High Risk Cohort in the PARTNER Study (ITT TAVR Population)

| Label | Hazard Ratio | 95% Lower Confidence Limit for Hazard Ratio | 95% Upper Confidence Limit for Hazard Ratio | Pr > ChiSq |
|--|--------------|---|---|------------|
| Body Mass Index (lbs/in ²) | 0.934 | 0.903 | 0.965 | <.0001 |
| Mean Gradient mmHg/10 | 0.818 | 0.717 | 0.932 | 0.0026 |
| Baseline Creatinine | 1.065 | 1.008 | 1.124 | 0.0235 |
| CV Surgery: Other vascular stent of PTA (arterial) | 1.884 | 1.036 | 3.425 | 0.0378 |



Moderate – severe mitral regurgitation, prior CABG, STS risk score and liver disease were predictive of mortality in the AVR arm (Table 23).

Table 23. Proportional Hazards Regression Analysis of Predictors of Death over the Course of the Trial: Multivariable Model - High Risk Cohort in the PARTNER Study (ITT AVR Population)

| Label | Hazard Ratio | 95% Lower Confidence Limit for Hazard Ratio | 95% Upper Confidence Limit for Hazard Ratio | Pr > ChiSq |
|---|--------------|---|---|------------|
| Moderate or Severe Mitral Regurgitation -- Baseline | 1.869 | 1.266 | 2.760 | 0.0017 |
| CV Surgery: CABG | 0.572 | 0.401 | 0.817 | 0.0021 |
| STS Risk Score | 1.071 | 1.022 | 1.122 | 0.0042 |
| Non-CV Conditions: Liver disease | 2.587 | 1.196 | 5.594 | 0.0157 |

8.2 Secondary Endpoints

8.2.1 Time from Randomization to the First Occurrence of MACCE at 1 Year (ITT Population)

MACCE consisted of death, MI, stroke, and renal failure using per protocol definitions of each adverse event. The MACCE null hypothesis was that ITT TAVR subjects (pooled transapical and transfemoral) at 1 year were not worse than the ITT AVR subjects (i.e., the one-sided non-inferiority margin for this non-inferiority null hypothesis was $\Delta = 0.075$).

The KM event rate for time from randomization to the first occurrence of MACCE at 1 year was 27.4% with TAVR as compared to 29.1% with AVR in the ITT population. The difference (TAVR-AVR) was -1.7 (two sided 90% CI -7.4, 4.0), $p=0.0040$, so non-inferiority was met.

At 30 days, the KM rates in the ITT population were 8.9% and 9.7%, for TAVR vs. AVR respectively (Table 24).



Table 24. Secondary Endpoint Analysis: Time from Randomization to the first Occurrence of MACCE (Per Protocol Definitions) at One Year – High Risk Cohort in the PARTNER Study (ITT Population)

| | | Cohort A Randomized Patients -- ITT Population | |
|--|------------------------|---|-----------------|
| | | Pooled Approaches | |
| Statistics | Event | AVR (N=351) | TAVR (N=348) |
| No. of patients | | 351 | 348 |
| No. of person-years | | 253.4 | 281.9 |
| No. of patients with event (%) | Early event (days<=30) | 33(9.4%) | 31(8.9%) |
| | Event at 1 year | 97(27.6%) | 95(27.3%) |
| | Late event (days>30) | 64(18.2%) | 64(18.4%) |
| Event rate per 100 pys | Early event (days<=30) | 122.77 | 114.09 |
| | Event at 1 year | 38.28 | 33.70 |
| | Late event (days>30) | 28.25 | 25.12 |
| KM event rate at 30 days (95%CI)(%) | Event | 9.7(6.5,12.8) | 8.9(5.9,11.9) |
| KM event rate at 1 year (95%CI)(%) | Event | 29.1(24.2,34.0) | 27.4(22.7,32.1) |
| Difference (Test-Control) in KM event rate (Two-sided 90% CI)(%) | Event | | -1.7(-7.4,4.0) |
| Probability for non-inferiority test | Event | | 0.0040 |

Source: Table 8.1

For a non-inferiority test, the non-inferiority margin of 7.5% was pre-specified

Difference and its two-sided 90% confidence interval were calculated by a Z-test.

Per-protocol definitions - MACCE: Death; Myocardial Infarction = acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI; Renal Failure = Patient required chronic dialysis for greater than 30 days; Stroke = a neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction

The breakdown of MACCE events at one year is provided in Table 25. Death was the main contributor to the MACCE event rate. Myocardial infarction and renal failure were numerically higher in the AVR arm, and stroke was numerically higher in the TAVR arm. A total of 20 TAVR patients (6.0%) vs. 10 AVR patients (3.2%) experienced a stroke by one year. Although, not significantly different, this imbalance is further explored in **Section 9.2**.



Table 25. MACCE Events (Per Protocol Definitions) at One Year – High Risk Cohort in the PARTNER Study (ITT Population)

| | Patients in group | Events | Patient with Event* | KM Event rate at 1 year |
|-----------------------|-------------------|--------|---------------------|-------------------------|
| Death | | | | |
| AVR | 351 | 89 | 89 | 26.8% |
| TAVR | 348 | 84 | 84 | 24.3% |
| Myocardial infarction | | | | |
| AVR | 351 | 2 | 2 | 0.6% |
| TAVR | 348 | 0 | 0 | 0.0% |
| Renal failure | | | | |
| AVR | 351 | 11 | 10 | 3.4% |
| TAVR | 348 | 8 | 8 | 2.4% |
| Stroke | | | | |
| AVR | 351 | 10 | 10 | 3.2% |
| TAVR | 348 | 20 | 20 | 6.0% |
| MACCE | | | | |
| AVR | 351 | 112 | 97 | 29.1% |
| TAVR | 348 | 112 | 95 | 27.4% |

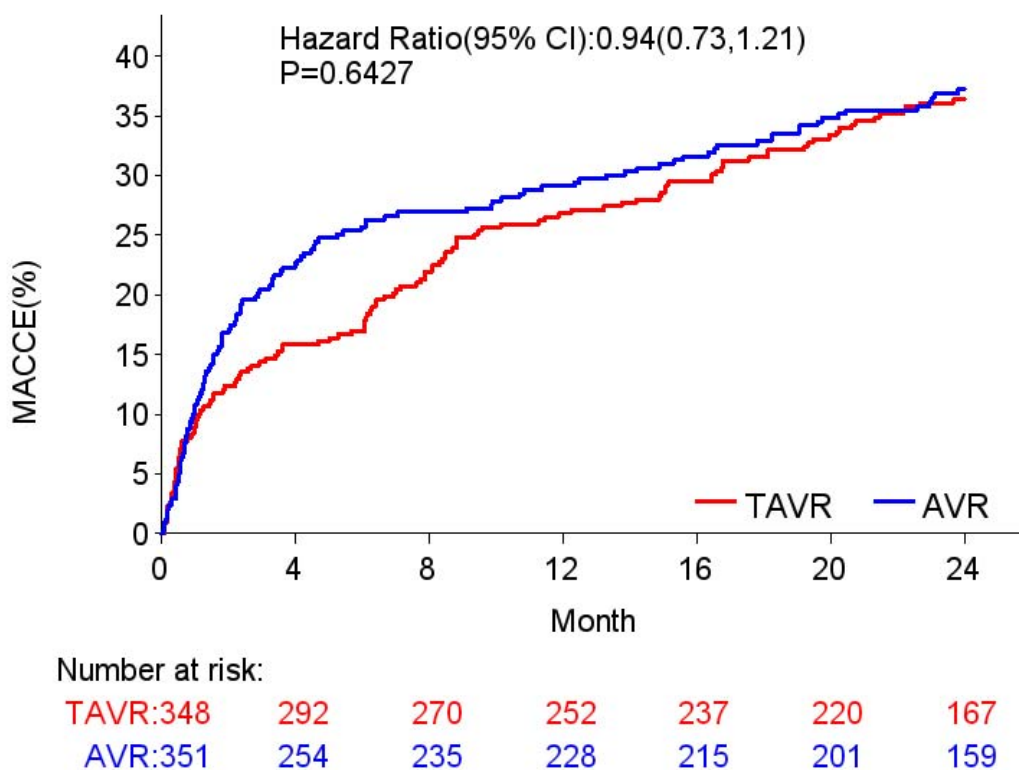
Source: Table 5.3

* Patients could experience more than one event.

Figure 8 illustrates the first occurrence of a MACCE event through 2 years. Figure 9 shows MI, Figure 10 shows renal failure and Figure 11 located in **Section 9.2** presents stroke.



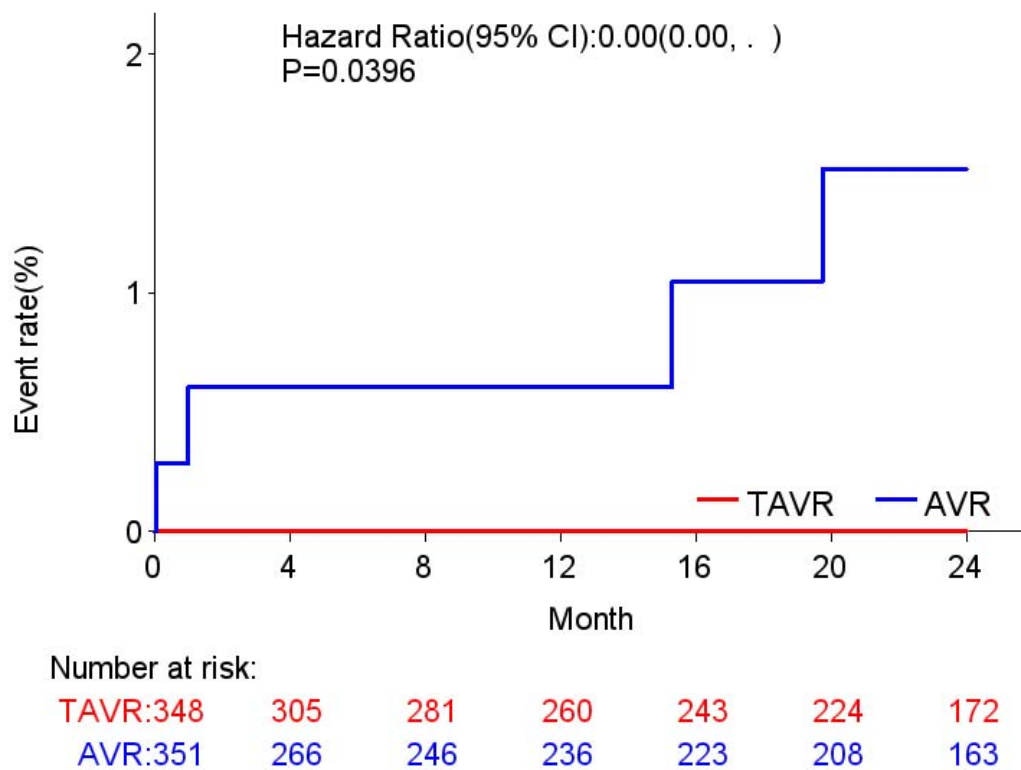
Figure 8. First Occurrence of MACCE (Per Protocol Definitions) at One Year – High Risk Cohort in the PARTNER Study (ITT Population)



Hazard ratio at 2 years; p-value from log-rank test up to 24 months



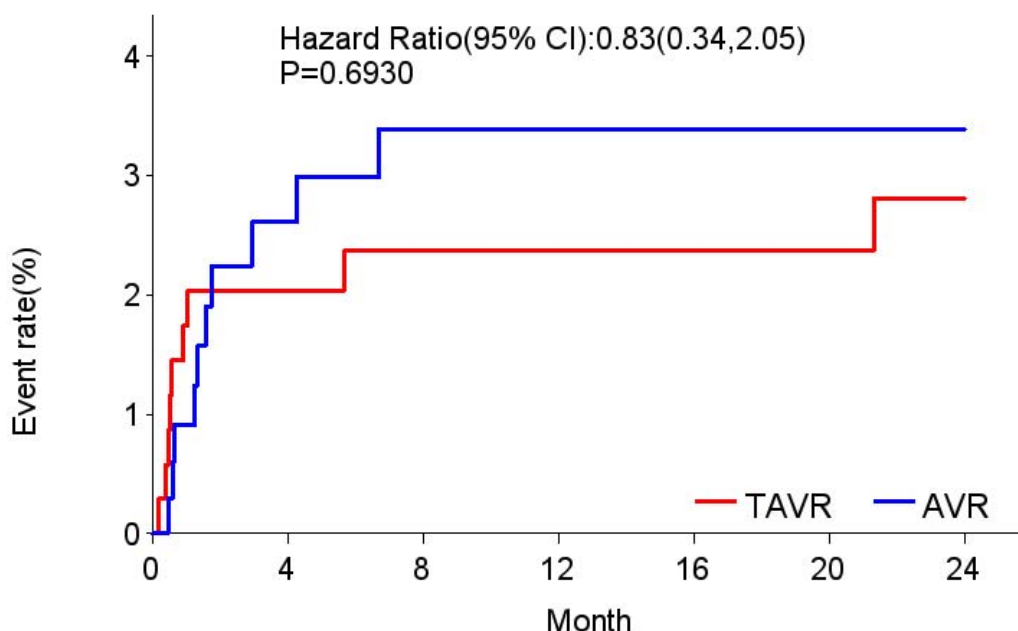
Figure 9. Myocardial Infarction – High Risk Cohort in the PARTNER Study (ITT Population)



Hazard ratio at 2 years; p-value from log-rank test up to 24 months



Figure 10. Renal Failure – High Risk Cohort in the PARTNER Study (ITT Population)



Number at risk:

| | | | | | | |
|----------|-----|-----|-----|-----|-----|-----|
| TAVR:348 | 304 | 280 | 260 | 243 | 224 | 171 |
| AVR:351 | 260 | 241 | 234 | 222 | 208 | 163 |

Hazard ratio at 2 years; p-value from log-rank test up to 24 months

8.2.2 Time from Procedure to the First Occurrence of MACCE at 1 Year (AT Population)

In the AT population, the KM rate for time from procedure to the first occurrence of MACCE at 1 year was 26.6% for the pooled TAVR group and 27.4% for the pooled AVR arm (probability for non-inferiority test $p=0.0083$).

In both the ITT and AT populations, the time from randomization to first occurrence of MACCE at 1 year in the pooled TAVR arm was not inferior to the time from randomization to first occurrence of MACCE at 1 year in the pooled AVR arm.



8.2.3 Total Hospital Days Through One Year (ITT Population)

The null hypothesis was that median hospital days for the TAVR group was greater than the median hospital days for the AVR group plus 10 (i.e., the one-sided non-inferiority margin for this non-inferiority null hypothesis was $\Delta = 10$). Observed days were used for this analysis. Since more AVR patients than TAVR patients died during the first year, and considerably more AVR patients than TAVR patients withdrew from the study, any bias in this analysis favors the AVR group.

During year 1, patients in the TAVR group of the ITT population spent fewer days in the hospital than AVR patients (mean [SD], 16.3 [18.0] vs. 18.8 [22.9] days, respectively; Table 26). The median difference was -3.00 days (90% two sided bootstrapped CI -4.50, -2.00), $p=0.0001$ thus non inferiority was met.

Table 26. Secondary Endpoint Analysis: Total Hospital Days through One Year - High Risk Cohort in the PARTNER Study (ITT Population)

| Statistics | Cohort A Randomized Patients -- ITT Population | |
|--|--|--------------------|
| | Pooled Approaches | |
| | AVR (N=351) | TAVR (N=348) |
| n | 351 | 348 |
| Mean | 18.75 | 16.32 |
| SD | 22.577 | 17.978 |
| Minimum | 0.00 | 0.00 |
| Q1 | 8.00 | 6.00 |
| Median | 13.00 | 10.00 |
| Q3 | 22.00 | 20.00 |
| Maximum | 280.00 | 187.00 |
| Median difference (TAVR-AVR)(Two-sided 90% CI) | | -3.00(-4.50,-2.00) |
| One-sided P-value from bootstrap test | | 0.0001 |

Source: Table 8.2

For a non-inferiority test, the non-inferiority margin of 10 days was pre-specified.

Median difference and its two-sided 90% confidence interval were calculated by a bootstrap approach with 10,000 repetitions.

Additional analyses involving hospitalization are presented in Table 27. Days alive and out of hospital were 297 days for TAVR vs. 279 days for AVR. The percentage of patients with repeat hospitalizations through 1 year was 17.7% in the TAVR arm and 18.6% in the AVR arm. At the time of the index procedure, mean days in the ICU was 4.1 days for TAVR vs. 6.3 days for AVR, and mean duration of entire hospitalization (including ICU stay) was 8.8 days for TAVR vs. 14.1 days for AVR.



Table 27. Additional Analyses Involving Hospitalization Through 1 Year - High Risk Cohort in the PARTNER Study (ITT Population)

| Statistics | Cohort A Randomized Patients -- ITT Population | |
|---|--|-----------------|
| | Pooled Approaches | |
| | AVR (N=351) | TAVR (N=348) |
| Days Alive and Out of Hospital | | |
| n | 350 | 346 |
| Mean ± SD | 278.8 ± 131.0 | 296.9 ± 110.8 |
| Repeat Hospitalization (%) | 17.7 | 18.6 |
| Mean Days in ICU (Index Procedure) | 6.3 | 4.1 |
| Mean Days in Hospital (Index Procedure) | 8.8 | 14.1 |

8.2.4 Total Hospital Days Through 1 Year (AT Population)

In the pooled AT population, the same trend was observed (15.1 [18.0] days in the TAVR group vs. 19.4 [22.9] days in the AVR group); median difference (TAVR-AVR) -5.00 (two sided 90% CI -7.00, -3.00), one-sided p-value from bootstrap test < 0.0001.

The median hospital days through 1 year in the pooled TAVR arm was not inferior to the median hospital days through 1 year in the pooled AVR arm in both the ITT and AT populations.

8.2.5 NYHA Functional Class at One Year (ITT Population)

Table 28 summarizes the NYHA classification at one year for the ITT population. The non-inferiority testing was based on NYHA as a continuous variable. The two-sample t-statistic used $\Delta = 0.25$. The difference between treatment groups was -0.01 (two sided 90% CI -0.12, 0.11), $p=0.0001$ indicating that non-inferiority was met.

Four sensitivity analyses in the ITT population were performed for NYHA to account for missing data in various ways.

In sensitivity analysis 1, death was imputed as NYHA=5, all observed values were used, and there was no imputation for missing reasons other than death. The resulting difference between treatment groups was -0.11 (two sided 90% CI -0.32, 0.10, $p=0.0023$) indicating that non-inferiority was met.

In sensitivity analysis 2, values obtained before the window remained missing in this analysis. Where an in-window value was not available, the earliest value obtained after



the window was used, if any such values were available. Dead patients were imputed as NYHA=5. The resulting difference between treatment groups was -0.15 (two sided 90% CI -0.37, 0.07, p=0.0014) indicating that non-inferiority was met

In sensitivity analysis 3, the main analysis was repeated treating death as a simple category NYHA "class 5," all observed values were used, and NYHA was assigned class 4 for missing reasons other than death. The resulting difference between treatment groups was -0.19 (two sided 90% CI -0.39, 0.01, p=0.0001) indicating that non-inferiority was met.

Sensitivity analysis 4, performed at the direction of the FDA, imputed all patients in the TAVR arm with NYHA data missing for reasons other than death to NYHA IV (n=37), and all patients in the AVR arm with data missing for reasons other than death to have NYHA I (n=14). The resulting difference between treatment groups was 0.13 (two sided 90% CI -0.07, 0.33, p=0.1548) indicating that for this extreme analysis non-inferiority was not demonstrated.

Table 28. Secondary Endpoint Analysis: NYHA at One Year - High Risk Cohort in the PARTNER Study (ITT Population)

| | | Cohort A Randomized Patients -- ITT Population | |
|------------------------|---|--|-------------------|
| | | Pooled Approaches | |
| Analysis | Statistics | AVR (N=351) | TAVR (N=348) |
| Descriptive Analysis | n | 226 | 250 |
| | Mean | 1.70 | 1.70 |
| | SD | 0.763 | 0.773 |
| | Class I | 103(29.3%) | 119(34.2%) |
| | Class II | 93(26.5%) | 93(26.7%) |
| | Class III | 24(6.8%) | 33(9.5%) |
| | Class IV | 6(1.7%) | 5(1.4%) |
| | Death | 88(25.1%) | 83(23.9%) |
| | Unknown | 37(10.5%) | 15(4.3%) |
| Main Analysis | Difference (TAVR-AVR)(Two-sided 90% CI) | | -0.01(-0.12,0.11) |
| | Probability for non-inferiority test | | 0.0001 |
| Sensitivity Analysis 1 | Difference (TAVR-AVR)(Two-sided 90% CI) | | -0.11(-0.32,0.10) |
| | Probability for non-inferiority test | | 0.0023 |
| Sensitivity Analysis 2 | Difference (TAVR-AVR)(Two-sided 90% CI) | | -0.15(-0.37,0.07) |
| | Probability for non-inferiority test | | 0.0014 |
| Sensitivity Analysis 3 | Difference (TAVR-AVR)(Two-sided 90% CI) | | -0.19(-0.39,0.01) |
| | Probability for non-inferiority test | | 0.0001 |
| Sensitivity Analysis 4 | Difference (TAVR-AVR)(Two-sided 90% CI) | | 0.13(-0.07,0.33) |
| | Probability for non-inferiority test | | 0.1548 |

Source: Table 8.3



For a non-inferiority test, the non-inferiority margin of 0.25 was pre-specified.
Mean difference and its two-sided 90% confidence interval were calculated by a t-test
Main Analysis: (1) No imputation for death. (2) In-window values only. (3) No imputation for missing for reasons other than death.
Sensitivity Analysis 1: (1) NYHA=5 for death. (2) All observed values. (3) No imputation for missing for reasons other than death.
Sensitivity Analysis 2: (1) NYHA=5 for death. (2) In-window values only. (3) Where an in-window value is not available, use the earliest available value obtained after the window.
Sensitivity Analysis 3: (1) NYHA=5 for death. (2) All observed values. (3) NYHA=4 for missing for reasons other than death.
Sensitivity Analysis 4: (1) NYHA=5 for death. (2) All observed values. (3) NYHA=4 for missing for reasons other than death in the TAVR arm and NYHA=1 in the AVR arm.

8.2.6 NYHA Functional Class at One Year (AT Population)

In the AT population, the mean difference in NYHA at 1 year (TAVR-AVR) was 0.02 (two sided 90% CI -0.10, 0.13), $p=0.0005$ indicating that non-inferiority was met in the AT population as well.

Sensitivity analyses in the pooled AT population resulted in similar findings observed in the pooled ITT population (Table 29).

Table 29. Secondary Endpoint Analysis: NYHA at One Year High Risk Cohort in the PARTNER Study (AT Population)

| | | Cohort A Randomized Patients -- AT Population | |
|------------------------|---|---|-------------------|
| | | Pooled Approaches | |
| Analysis | Statistics | AVR (N=313) | TAVR (N=344) |
| Descriptive Analysis | n | 220 | 249 |
| | Mean | 1.67 | 1.69 |
| | SD | 0.742 | 0.770 |
| | Class I | 103(32.9%) | 119(34.6%) |
| | Class II | 91(29.1%) | 93(27.0%) |
| | Class III | 21(6.7%) | 32(9.3%) |
| | Class IV | 5(1.6%) | 5(1.5%) |
| | Death | 77(24.6%) | 80(23.3%) |
| | Unknown | 16(5.1%) | 15(4.4%) |
| Main Analysis | Difference (TAVR-AVR)(Two-sided 90% CI) | | 0.02(-0.10,0.13) |
| | Probability for non-inferiority test | | 0.0005 |
| Sensitivity Analysis 1 | Difference (TAVR-AVR)(Two-sided 90% CI) | | -0.04(-0.25,0.17) |
| | Probability for non-inferiority test | | 0.0112 |
| Sensitivity Analysis 2 | Difference (TAVR-AVR)(Two-sided 90% CI) | | -0.08(-0.30,0.14) |
| | Probability for non-inferiority test | | 0.0073 |
| Sensitivity Analysis 3 | Difference (TAVR-AVR)(Two-sided 90% CI) | | -0.05(-0.25,0.15) |
| | Probability for non-inferiority test | | 0.0077 |
| Sensitivity Analysis 4 | Difference (TAVR-AVR)(Two-sided 90% CI) | | 0.10(-0.10,0.31) |
| | Probability for non-inferiority test | | 0.1186 |

Source: Table 8.3

For a non-inferiority test, the non-inferiority margin of 0.25 was pre-specified.
Mean difference and its two-sided 90% confidence interval were calculated by a t-test



Main Analysis: (1) No imputation for death. (2) In-window values only. (3) No imputation for missing for reasons other than death.

Sensitivity Analysis 1: (1) NYHA=5 for death. (2) All observed values. (3) No imputation for missing for reasons other than death.

Sensitivity Analysis 2: (1) NYHA=5 for death. (2) In-window values only. (3) Where an in-window value is not available, use the earliest available value obtained after the window.

Sensitivity Analysis 3: (1) NYHA=5 for death. (2) All observed values. (3) NYHA=4 for missing for reasons other than death.

Sensitivity Analysis 4: (1) NYHA=5 for death. (2) All observed values. (3) NYHA=4 for missing for reasons other than death in the TAVR arm and NYHA=1 in the AVR arm.

8.2.7 6-Minute Walk Test at One Year (ITT Population)

The 6MWT null hypothesis was that ITT pooled TAVR arm had 6MWD, on average, at least 70 meters less by year 1 than the ITT AVR arm (i.e., the one-sided non-inferiority margin for this non-inferiority null hypothesis was $\Delta = 70$ meters). Note, 37 patients were not part of this analysis, since the 6MWT was added after the start of the trial or these patients were unable to perform the test due to medical reasons.

Table 30 summarizes the 6MWT at one year for the ITT population. At 1 year, the mean (SD) 6MWD was 165.0 (128.4) meters (range 0 to 575.5 meters) in the TAVR group and 169.8 (134.4) meters (range 0 to 457.2 meters) in the AVR group. The mean difference was 4.88 (two sided 90% CI -18.51, 28.27) $p < 0.0001$, thus non-inferiority was met.

Four sensitivity analyses involving 6MWT were performed to account for 6MWT data missing for reasons other than death (Table 30). In sensitivity analysis 1, 6MWD was assigned -1 for death, all observed values were used, and there was no imputation for missing for reasons other than death. The resulting difference between treatment groups was -9.40 (two sided 90% CI -27.87, 9.07, $p < 0.0001$).

In sensitivity analysis 2, all dead patients were assigned a distance of -1. Only-in-window values were used. Where an in-window value was not available, the earliest value obtained after the window was used, if any such values were available. The resulting difference between treatment groups was -8.86 (two sided 90% CI -28.17, 10.45, $p < 0.0001$).

In sensitivity analysis 3, all dead patients were assigned a distance of -1, all observed values were used, and 6MWD was assigned a distance of 0 for missing for reasons other than death. The resulting difference between treatment groups was -22.44 (two sided 90% CI -38.09, -6.79, $p < 0.0001$).



In sensitivity analysis 4, all dead patients were assigned a distance of -1, and all observed values were used. The missing for reasons other than death for AVR were assigned the highest distance actually observed in the AVR arm (i.e., 457.2 m; n=112), and the missing for reasons other than death for the TAVR arm were zero (n=66). The resulting difference between treatment groups was 101.31 (two sided 90% CI 80.93, 121.68, p=0.0058).

Table 30. Secondary Endpoint Analysis: 6MWT at One Year – High Risk Cohort in the PARTNER Study (ITT Population)

| Analysis | Statistics | Pooled Approaches | |
|------------------------|---|-------------------|----------------------|
| | | AVR (N=351) | TAVR (N=348) |
| Descriptive Analysis | n | 150 | 198 |
| | Mean | 169.84 | 164.96 |
| | SD | 134.407 | 128.405 |
| | Minimum | 0.00 | 0.00 |
| | Q1 | 14.00 | 70.07 |
| | Median | 176.13 | 154.03 |
| | Q3 | 280.00 | 251.76 |
| | Maximum | 457.20 | 575.46 |
| | Performed in window | 113(32.2%) | 156(44.8%) |
| | Performed outside window | 31(8.8%) | 27(7.8%) |
| | Missing due to death | 83(23.6%) | 79(22.7%) |
| | Missing due to protocol or medical reason | 37(10.5%) | 42(12.1%) |
| | Missing otherwise | 80(22.8%) | 35(10.1%) |
| | Visit missed for other reason | 7(2.0%) | 9(2.6%) |
| Main Analysis | Difference (AVR-TAVR)(Two-sided 90% CI) | | 4.88(-18.51,28.27) |
| | Probability for non-inferiority test | | <.0001 |
| Sensitivity Analysis 1 | Difference (AVR-TAVR)(Two-sided 90% CI) | | -9.40(-27.87,9.07) |
| | Probability for non-inferiority test | | <.0001 |
| Sensitivity Analysis 2 | Difference (AVR-TAVR)(Two-sided 90% CI) | | -8.86(-28.17,10.45) |
| | Probability for non-inferiority test | | <.0001 |
| Sensitivity Analysis 3 | Difference (AVR-TAVR)(Two-sided 90% CI) | | -22.44(-38.09,-6.79) |
| | Probability for non-inferiority test | | <.0001 |
| Sensitivity Analysis 4 | Difference (AVR-TAVR)(Two-sided 90% CI) | | 101.31(80.93,121.68) |
| | Probability for non-inferiority test | | 0.0058 |

Source: Table 8.4

For a non-inferiority test, the non-inferiority margin of 70 meters was pre-specified.

Mean difference and its two-sided 90% confidence interval were calculated by a t-test.

Sensitivity Analysis 1: McMahon and Harrel strategy was used to deal with missing values for patients who were not known deceased before one year.

Main Analysis: (1) No imputation for death. (2) In-window values only. (3) No imputation for missing for reasons other than death.

Sensitivity Analysis 1: (1) 6MWT=-1 for death. (2) All observed values. (3) No imputation for missing for reasons other than death.

Sensitivity Analysis 2: (1) 6MWT=-1 for death. (2) In-window values only. (3) Where an in-window value is not available, use the earliest available value obtained after the window.

Sensitivity Analysis 3: (1) 6MWT=-1 for death. (2) All observed values. (3) 6MWT=0 for missing for reasons other than death.

Sensitivity Analysis 4: (1) 6MWT=-1 for death. (2) All observed values. (3) 6MWT=0 for missing for reasons other than death in the TAVR arm and 6MWT=457.2 m in the AVR arm, the highest value observed in the AVR arm.



8.2.8 6-Minute Walk Test at One Year (AT Population)

Table 31 summarizes the 6MWT at one year for the AT population. At 1 year, the mean (SD) 6MWD was 165.0 (128.4) meters (range 0 to 575.5 meters) in the pooled TAVR group and 172.3 (134.2) meters (range 0 to 457.2 meters) in the pooled AVR group. The mean difference was 7.34 (two sided 90% CI -16.21, 30.89), $p < 0.0001$, thus non-inferiority was met in the AT population as well.

Sensitivity analyses of the 6MWT in the AT population resulted in similar findings as observed in the ITT population (Table 31).

Table 31. Secondary Endpoint Analysis: 6MWT at One Year - High Risk Cohort in the PARTNER Study (AT Population)

| Analysis | Statistics | Pooled Approaches | |
|------------------------|---|-------------------|---------------------|
| | | AVR (N=313) | TAVR (N=344) |
| Descriptive Analysis | n | 146 | 198 |
| | Mean | 172.30 | 164.96 |
| | SD | 134.186 | 128.405 |
| | Minimum | 0.00 | 0.00 |
| | Q1 | 15.00 | 70.07 |
| | Median | 178.50 | 154.03 |
| | Q3 | 282.61 | 251.76 |
| | Maximum | 457.20 | 575.46 |
| | Performed in window | 111(35.5%) | 156(45.3%) |
| | Performed outside window | 30(9.6%) | 26(7.6%) |
| | Missing due to death | 73(23.3%) | 76(22.1%) |
| | Missing due to protocol or medical reason | 35(11.2%) | 42(12.2%) |
| | Missing otherwise | 58(18.5%) | 35(10.2%) |
| | Visit missed for other reason | 6(1.9%) | 9(2.6%) |
| Main Analysis | Difference (AVR-TAVR)(Two-sided 90% CI) | | 7.34(-16.21,30.89) |
| | Probability for non-inferiority test | | <.0001 |
| Sensitivity Analysis 1 | Difference (AVR-TAVR)(Two-sided 90% CI) | | -4.89(-23.83,14.05) |
| | Probability for non-inferiority test | | <.0001 |
| Sensitivity Analysis 2 | Difference (AVR-TAVR)(Two-sided 90% CI) | | -4.32(-24.13,15.49) |
| | Probability for non-inferiority test | | <.0001 |
| Sensitivity Analysis 3 | Difference (AVR-TAVR)(Two-sided 90% CI) | | -15.21(-31.63,1.22) |
| | Probability for non-inferiority test | | <.0001 |
| Sensitivity Analysis 4 | Difference (AVR-TAVR)(Two-sided 90% CI) | | 91.42(70.97,111.88) |
| | Probability for non-inferiority test | | 0.0425 |

Source: Table 8.4

For a non-inferiority test, the non-inferiority margin of 70 meters was pre-specified.

Mean difference and its two-sided 90% confidence interval were calculated by a t-test.

Sensitivity Analysis 1: McMahon and Harrel strategy was used to deal with missing values for patients who were not known deceased before one year.

Main Analysis: (1) No imputation for death. (2) In-window values only. (3) No imputation for missing for reasons other than death.

Sensitivity Analysis 1: (1) 6MWT=-1 for death. (2) All observed values. (3) No imputation for missing for reasons other than death.



Sensitivity Analysis 2: (1) 6MWT=-1 for death. (2) In-window values only. (3) Where an in-window value is not available, use the earliest available value obtained after the window.

Sensitivity Analysis 3: (1) 6MWT=-1 for death. (2) All observed values. (3) 6MWT=0 for missing for reasons other than death.

Sensitivity Analysis 4: (1) 6MWT=-1 for death. (2) All observed values. (3) 6MWT=0 for missing for reasons other than death in the TAVR arm and 6MWT=457.20 in the AVR arm, the highest value observed in the AVR arm.

At 30 days, TAVR patients walked farther than AVR patients (mean [SD] 6MWD was 143.1 [129.0] meters in the TAVR arm vs. 104.8 [116.8] meters in AVR arm (Table 92, **Appendix F**).

9.0 Safety Findings in PARTNER High Risk Cohort

9.1 Protocol-Defined Adverse Events

Table 32 shows protocol-defined AEs (see **Appendix D** for definitions) that occurred within 30 days, 31 days - 1 year, and > 1 year following the index procedure. The day of the index procedure was considered Day 0.

Conservatively, sites reported endocarditis for five TAVR and five AVR patients. However, in three patients (two TAVR and one AVR patients), there were no definitive clinical signs of endocarditis; in one AVR patient, endocarditis of the tricuspid valve was suspected but not confirmed. Therefore, in each trial arm, there were three confirmed cases of endocarditis. Only one patient with endocarditis required explant (see **Section 9.1.1**).

Adverse events of high incidence consisted of:

- A total of 116/313 AVR patients (37.1%) vs. 145/344 TAVR patients (42.2%) experienced an infection (p=0.3680)
- A total of 56/313 AVR patients (17.9%) vs. 78/344 TAVR patients (22.7%) were rehospitalized for symptoms of aortic stenosis (p=0.2573).

The following statistically significant differences were observed:

- Perivalvular leak at 31 days – 1 year interval (KM rate 1.5% in TAVR vs. 0.0% in AVR, p=0.0246)



- Sternal wounds infection at 31 days – 1 year interval (KM rate 0.0% in TAVR vs. 2.5% in AVR, $p=0.0076$)

These significant differences are anticipated due to the differences in implant technique, specifically during TAVR the THV is deployed within the native aortic valve without the ability to surgically correct any perivalvular leak observed on intra-procedural echo. A sternotomy is performed during AVR only and has the potential an associated sternal wound infection.

Note, although no significant difference were found involving stroke, stroke is evaluated in depth in **Section 9.2**.



Table 32. Protocol-Defined Adverse Events – High Risk Cohort in the PARTNER Study (AT Population)

| Per Protocol AE Randomized PMA Cohort A (AT) -- Pooled Approaches | | | | | | | | | | | | | | | |
|---|--|--------------|----------------------|------------|----------------------|--------------------------|--------------------------------------|--------|----------------------|-------------------------|-------------------------------------|--------|----------------------|--------------------------------------|--------|
| | | Total Events | | <= 30 days | | | 31 days - 1 year | | | > 1 year | | Trial | | | |
| | | Total events | Patients with event* | Events | Patients with event* | KM Event rate at 30 days | P-value for point in time at 30 days | Events | Patients with event* | KM Event rate at 1 year | P-value for point in time at 1 year | Events | Patients with event* | Log-rank p-value for length of trial | |
| Annular dissection | | | | | | | | | | | | | | | |
| AVR | | 313 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . | |
| TAVR | | 344 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . | |
| Aortic Dissection | | | | | | | | | | | | | | | |
| AVR | | 313 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . | |
| TAVR | | 344 | 1 | 1 | 1 | 0.3% | 0.3166 | 0 | 0 | 0.3% | 0.3166 | 0 | 0 | 0.3401 | |
| Aortic Stenosis | | | | | | | | | | | | | | | |
| AVR | | 313 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . | |
| TAVR | | 344 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . | |
| Bleeding event | | | | | | | | | | | | | | | |
| AVR | | 313 | 44 | 39 | 7 | 6 | 1.9% | . | 21 | 20 | 9.8% | . | 16 | 14 | . |
| TAVR | | 344 | 43 | 38 | 10 | 10 | 3.0% | 0.3902 | 18 | 18 | 8.3% | 0.5388 | 15 | 13 | 0.4798 |
| Device migration | | | | | | | | | | | | | | | |
| AVR | | 313 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| TAVR | | 344 | 1 | 1 | 1 | 1 | 0.3% | 0.3166 | 0 | 0 | 0.3% | 0.3166 | 0 | 0 | 0.3401 |
| Embolic event | | | | | | | | | | | | | | | |
| AVR | | 313 | 4 | 4 | 3 | 3 | 1.0% | . | 0 | 0 | 1.0% | . | 1 | 1 | . |
| TAVR | | 344 | 6 | 6 | 5 | 5 | 1.5% | 0.5443 | 1 | 1 | 1.8% | 0.3458 | 0 | 0 | 0.6421 |
| Hemolysis | | | | | | | | | | | | | | | |
| AVR | | 313 | 1 | 1 | 0 | 0 | 0.0% | . | 1 | 1 | 0.4% | . | 0 | 0 | . |
| TAVR | | 344 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | 0.3164 | 0 | 0 | 0.2817 |



| Per Protocol AE Randomized PMA Cohort A (AT) -- Pooled Approaches | | | | | | | | | | | | | | |
|---|-------------------|--------------|----------------------|------------|----------------------|--------------------------|--------------------------------------|------------------|----------------------|-------------------------|-------------------------------------|----------|----------------------|--------------------------------------|
| | | Total Events | | <= 30 days | | | | 31 days - 1 year | | | | > 1 year | | Trial |
| | Patients in group | Total events | Patients with event* | Events | Patients with event* | KM Event rate at 30 days | P-value for point in time at 30 days | Events | Patients with event* | KM Event rate at 1 year | P-value for point in time at 1 year | Events | Patients with event* | Log-rank p-value for length of trial |
| | | | | | | | | | | | | | | |
| Hemorrhagic/Vascular event | | | | | | | | | | | | | | |
| | 313 | 105 | 91 | 100 | 87 | 27.8% | . | 3 | 3 | 28.6% | . | 2 | 2 | . |
| | 344 | 133 | 94 | 110 | 84 | 24.5% | 0.3332 | 12 | 10 | 26.8% | 0.6248 | 11 | 7 | 0.5460 |
| Infection (including Endocarditis) | | | | | | | | | | | | | | |
| | 313 | 197 | 116 | 78 | 65 | 21.4% | . | 64 | 48 | 34.2% | . | 55 | 36 | . |
| | 344 | 270 | 145 | 73 | 63 | 18.7% | 0.3911 | 103 | 71 | 35.9% | 0.6515 | 94 | 54 | 0.3680 |
| Myocardial infarction | | | | | | | | | | | | | | |
| | 313 | 6 | 6 | 1 | 1 | 0.3% | . | 0 | 0 | 0.3% | . | 5 | 5 | . |
| | 344 | 2 | 2 | 0 | 0 | 0.0% | 0.3165 | 0 | 0 | 0.0% | 0.3165 | 2 | 2 | 0.1254 |
| Nonstructural valve dysfunction | | | | | | | | | | | | | | |
| | 313 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| | 344 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| Perforation or damage to myocardium | | | | | | | | | | | | | | |
| | 313 | 2 | 2 | 2 | 2 | 0.6% | . | 0 | 0 | 0.6% | . | 0 | 0 | . |
| | 344 | 3 | 3 | 2 | 2 | 0.6% | 0.9247 | 1 | 1 | 1.0% | 0.6509 | 0 | 0 | 0.7372 |
| Peripheral Vascular Disease | | | | | | | | | | | | | | |
| | 313 | 1 | 1 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 1 | 1 | . |
| | 344 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | 0.2988 |
| | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | 313 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| | 344 | 5 | 5 | 3 | 3 | 0.9% | 0.0819 | 2 | 2 | 1.5% | 0.0246 | 0 | 0 | 0.0356 |
| Rehospitalization for symptoms of aortic stenosis | | | | | | | | | | | | | | |
| | 313 | 76 | 56 | 18 | 18 | 6.1% | . | 37 | 29 | 16.6% | . | 21 | 16 | . |



| Per Protocol AE Randomized PMA Cohort A (AT) -- Pooled Approaches | | | | | | | | | | | | | | | |
|---|---------------------|--------------|----------------------|------------|----------------------|--------------------------|--------------------------------------|------------------|----------------------|-------------------------|-------------------------------------|----------|----------------------|--------------------------------------|--------|
| | | Total Events | | <= 30 days | | | | 31 days - 1 year | | | | > 1 year | | Trial | |
| | Patients in group | Total events | Patients with event* | Events | Patients with event* | KM Event rate at 30 days | P-value for point in time at 30 days | Events | Patients with event* | KM Event rate at 1 year | P-value for point in time at 1 year | Events | Patients with event* | Log-rank p-value for length of trial | |
| | TAVR | 344 | 103 | 78 | 19 | 18 | 5.4% | 0.7142 | 49 | 40 | 17.3% | 0.8184 | 35 | 30 | 0.2573 |
| | Renal failure | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | AVR | 313 | 11 | 10 | 7 | 6 | 2.0% | . | 4 | 4 | 3.5% | . | 0 | 0 | . |
| | TAVR | 344 | 8 | 8 | 6 | 6 | 1.8% | 0.8407 | 1 | 1 | 2.1% | 0.2898 | 1 | 1 | 0.4541 |
| Renal insufficiency | | | | | | | | | | | | | | | |
| | AVR | 313 | 26 | 24 | 18 | 18 | 5.8% | . | 7 | 7 | 7.8% | . | 1 | 1 | . |
| | TAVR | 344 | 26 | 26 | 19 | 19 | 5.6% | 0.8921 | 3 | 3 | 6.6% | 0.5790 | 4 | 4 | 0.8995 |
| Sternal wound infection | | | | | | | | | | | | | | | |
| | AVR | 313 | 7 | 7 | 3 | 3 | 1.0% | . | 4 | 4 | 2.5% | . | 0 | 0 | . |
| | TAVR | 344 | 0 | 0 | 0 | 0 | 0.0% | 0.0818 | 0 | 0 | 0.0% | 0.0076 | 0 | 0 | 0.0045 |
| Stroke | | | | | | | | | | | | | | | |
| | AVR | 313 | 18 | 17 | 8 | 8 | 2.6% | . | 1 | 1 | 3.0% | . | 9 | 8 | . |
| | TAVR | 344 | 23 | 23 | 15 | 15 | 4.4% | 0.2064 | 4 | 4 | 5.8% | 0.0887 | 4 | 4 | 0.5113 |
| Transient ischemic attack (TIA) | | | | | | | | | | | | | | | |
| | AVR | 313 | 7 | 6 | 1 | 1 | 0.3% | . | 3 | 3 | 1.5% | . | 3 | 3 | . |
| | TAVR | 344 | 10 | 10 | 3 | 3 | 0.9% | 0.3572 | 5 | 5 | 2.7% | 0.3592 | 2 | 2 | 0.4486 |
| | Valvular thrombosis | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | AVR | 313 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| | TAVR | 344 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| Endocarditis (Site) | | | | | | | | | | | | | | | |
| | AVR | 313 | 7 | 5 | 1 | 1 | 0.3% | . | 2 | 2 | 1.1% | . | 4 | 2 | . |
| | TAVR | 344 | 5 | 5 | 0 | 0 | 0.0% | 0.3165 | 3 | 3 | 1.0% | 0.9514 | 2 | 2 | 0.8302 |
| MACCE | | | | | | | | | | | | | | | |

KM=Kaplan-Meier, MACCE= Major Adverse Cardiac and Cerebrovascular Events (death, stroke, MI, and renal failure), TIA=transient ischemic attack

Death, MI, Renal Failure, and Stroke using the event definitions above.



9.1.1 Explant

One patient underwent explant. Patient () underwent transfemoral TAVR on 9 June 2009. On 1 June 2010, the patient was re-admitted with symptoms of fever for past 4-6 months, weight loss (approx. 20 pounds), fatigue, thrombocytopenia, and weakness. He had fallen and injured his right forearm, the skin was torn and grossly infected. Echocardiography showed vegetation and perforation of the prosthetic aortic valve, and the patient was diagnosed with fungal (histoplasmosis) endocarditis. On June 14, 2010 the valve was explanted and replaced with a 21mm Carpentier-Edwards Magna prosthetic valve. The patient was discharged on IV antibiotics to a long-term acute facility on June 25, 2010.

9.2 Stroke

Stroke was defined a neurological deficit lasting ≥ 24 hours , or lasting < 24 hours with a brain imaging showing infarction. TIA was defined as a fully reversible neurologic event lasting < 24 hours with no evidence of infarction on imaging if performed.

Stroke ascertainment during the trial was achieved by daily clinical examination at the bedside, performing a NIH Stroke Scale (NIHSS) exam by a certified examiner at baseline, 7 days or discharge (whichever was sooner), 30 days, 6 months, 12 months, and annually for 5 years. Imaging with CT or MRI was performed when neurological status changed or NIHSS scale increased. All site-reported neurological events were adjudicated by the CEC. The CEC classified neurological events including stroke and TIA.

In the ITT population, a total of 44 strokes for 43 patients were reported through all follow-up; 24 TAVR patients and 19 AVR patients. In addition, a total of 17 TIAs were reported for 16 patients; 10 TAVR patients and 6 AVR patients (Table 33). In the AT population, 41 strokes were reported in 40 patients through the entire follow-up; 23 TAVR patients and 17 AVR patients.

Stroke narratives and Qol and NIHSS score for all patients who experienced a stroke within 1 year are located in **Appendix G**.



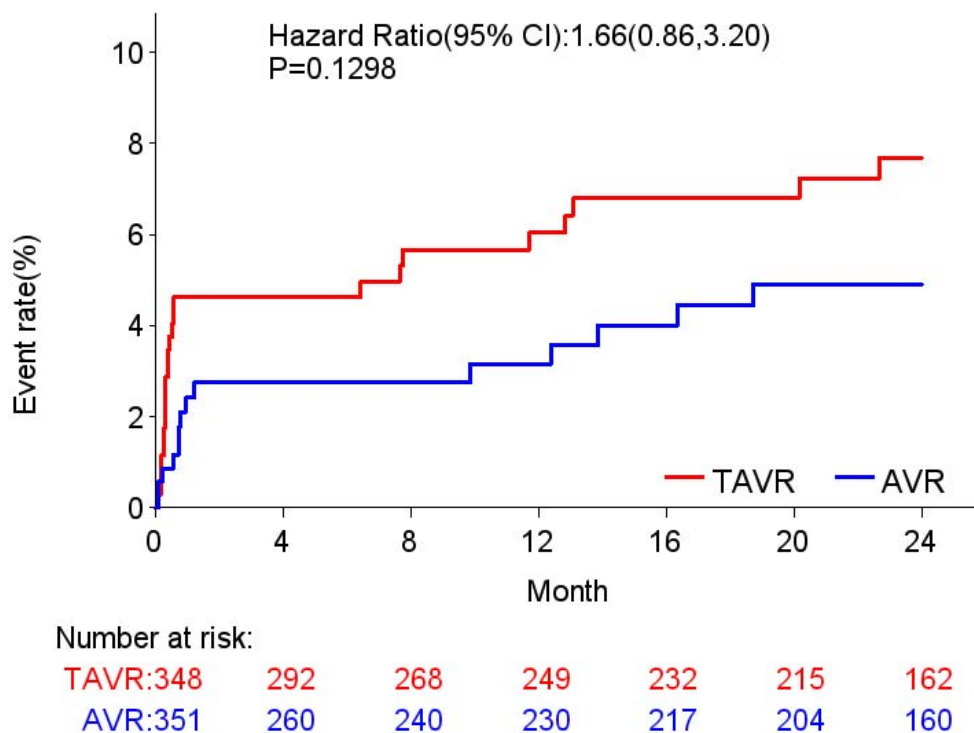
Table 33. Neurological Events - High Risk Cohort in the PARTNER Study (ITT Population)

| | Pooled TAVR n=348 | | Pooled AVR n=351 | |
|---------------------------|----------------------|----------------------|---------------------|----------------------|
| | Total Events | Patients with Events | Total Events | Patients with Events |
| Stroke | 24 | 24 | 20 | 19 |
| Transient Ischemic Attack | 10 | 10 | 7 | 6 |

Source: Table 5.3

Figure 11 illustrates the stroke rate over time. Both groups had higher rates of stroke in the first month with the TAVR group having a larger increase. Strokes were classified as early stroke (≤ 30 days from surgery) and late stroke (>30 days from surgery). The early stroke rate was 4.4% in the TAVR arm and 2.6% in the AVR arm. The absolute percentage difference was 1.8% (95% CI -1.0%, 4.6%), $p=0.2880$ (Table 34). After the first month, there was little difference between groups.

Figure 11. Stroke – High Risk Cohort in the PARTNER Study (ITT Population)



Hazard ratio at 2 years; p-value from log-rank test up to 24 months



Table 34. Early Stroke (≤ 30 days) - High Risk Cohort in the PARTNER Study (AT Population)

| | n | % of AT Patients | p-value* | Difference in stroke proportions and 95% CI |
|------|----|------------------|----------|---|
| TAVR | 15 | 4.4 | 0.2880 | 1.8% (-1.0%, 4.6%) |
| AVR | 8 | 2.6 | | |

Fischer's exact p-value

The cumulative incidence to first stroke truncated at 30 days is shown in Figure 12. The hazard ratio for periprocedural stroke in the TAVR arm compared to the AVR arm was 1.31 (95% CI 0.73, 2.44).

Figure 12. Cumulative Incidence of First Stroke Truncated at 30 Days – High Risk Cohort in the PARTNER Study (AT Population)
1st Stroke Cumulative Incidence (PMA AT)
Stroke Hazard Ratio = 1.31 (95% CI 0.73 to 2.44)
Truncated at 30 Days

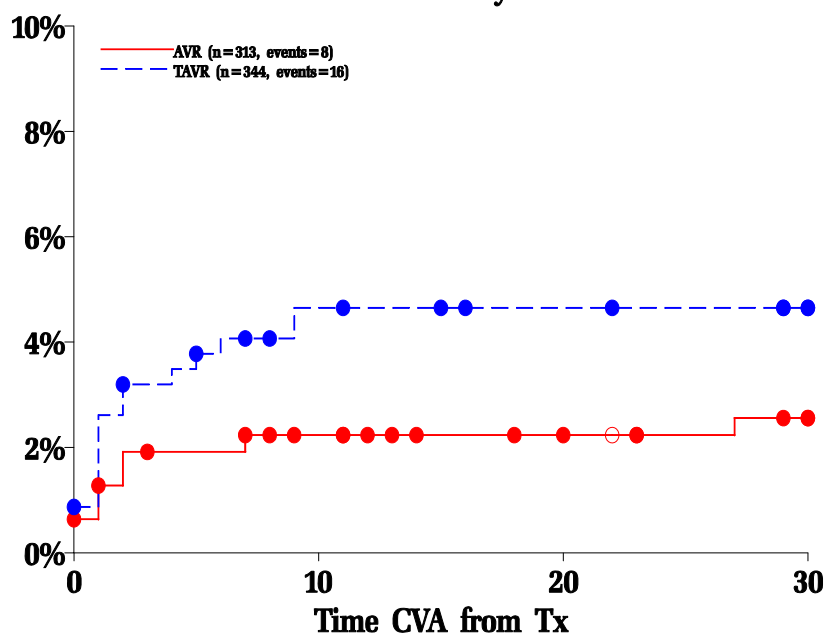
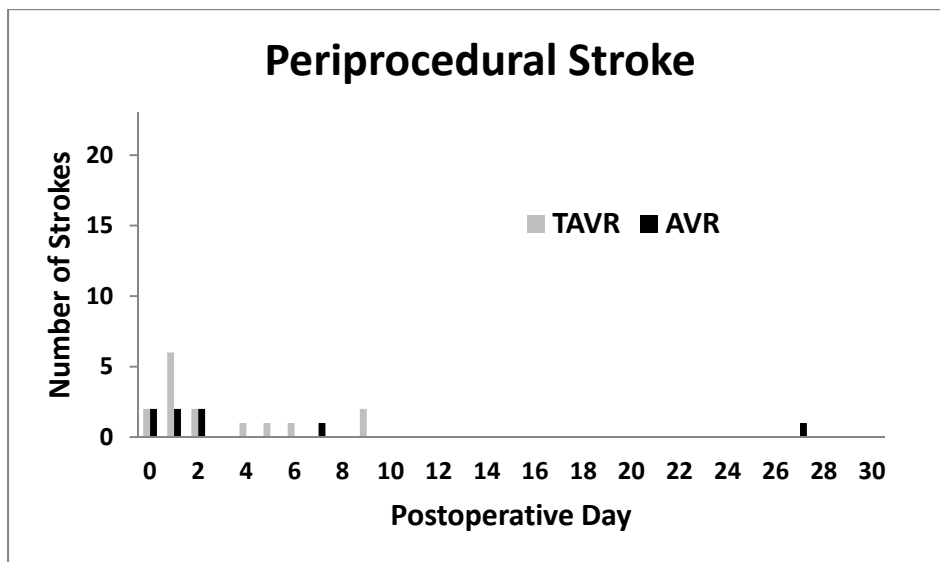


Figure 13 illustrates the timing of early stroke in the AT population. Most strokes in the TAVR arm and AVR arm occurred within 5 days following the procedure.



Figure 13. Timing of Early Stroke (≤ 30 Days) – High Risk Cohort in the PARTNER Study (AT Population)



One stroke occurred prior to TF TAVR.

Table 35 presents the NIHSS at 30 days for patients who experienced stroke. At 30 days, of the 10 TAVR patients that experienced a stroke and were assessed at 30 days, five patients (50%) had a NIHSS score between 0-1, three patients (30%) had a NIHSS score between 2-8, one patient (10%) had a NIHSS score ≥ 9 , and one patient (10%) had died. At 30 days, of the 5 AVR patients that experienced a stroke and were assessed at 30 days, two patients (40%) had a NIHSS score between 0-1, two patients (40%) had a NIHSS score between 2-8, and one patient (20%) had died.

Table 35. NIHSS at 30 Days - High Risk Cohort in the PARTNER Study (AT Population)

| NIHSS at 30 Days | TAVR | AVR |
|------------------|-----------|----------|
| 0-1 | 5 (50%) | 2 (40%) |
| 2-8 | 3 (30%) | 2 (40%) |
| ≥ 9 | 1 (10%) | 0 (0.0%) |
| Death | 1 (10%) | 1 (20%) |
| Total | 10 (100%) | 5 (100%) |



No difference was observed involving late stroke; 8 TAVR patients and 9 AVR patients experienced a late stroke. The absolute percentage difference was -0.6% (95% CI -3.0%, 1.9%), $p=0.807$ (Table 36).

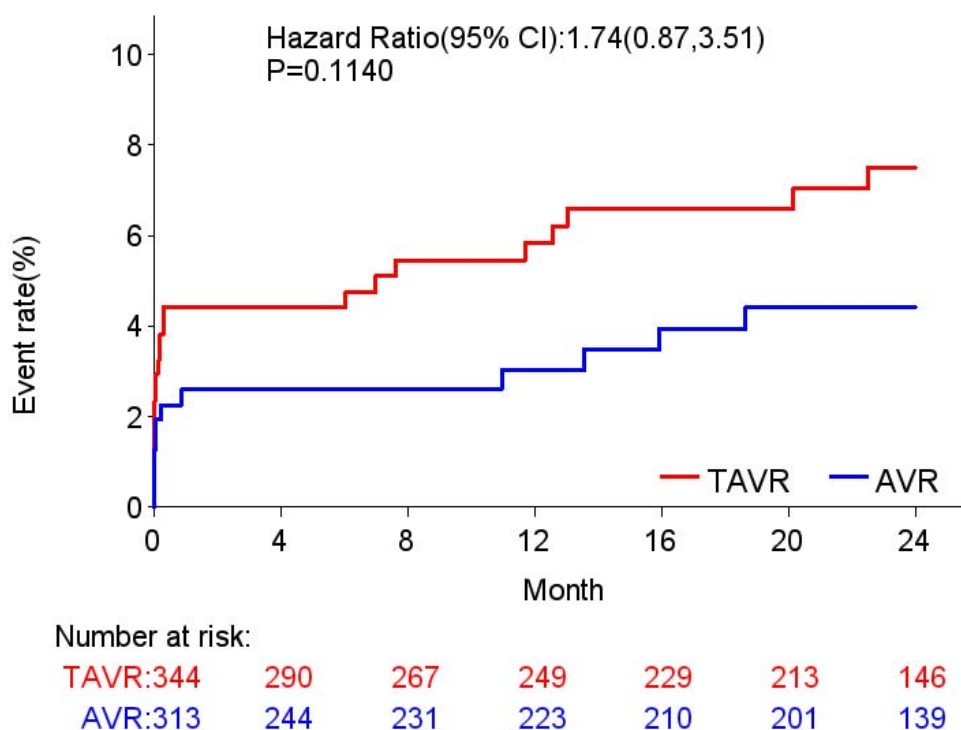
Table 36. Late Stroke (> 30 days) - High Risk Cohort in the PARTNER Study (AT Population)

| | n | % of AT Patients | p-value* | Difference in stroke proportions and 95% CI |
|------|---|------------------|----------|---|
| TAVR | 8 | 2.3 | 0.807 | -0.6% (-3.0%, 1.9%) |
| AVR | 9 | 2.9 | | |

Fischer's exact p-value

Figure 14 illustrates the time to stroke analysis, and confirms that the difference in stroke incidence occurs within 30 days, followed by a low and similar incidence of stroke in both arms. Figure 15 present the timing of late stroke (> 30 days after the index procedure).

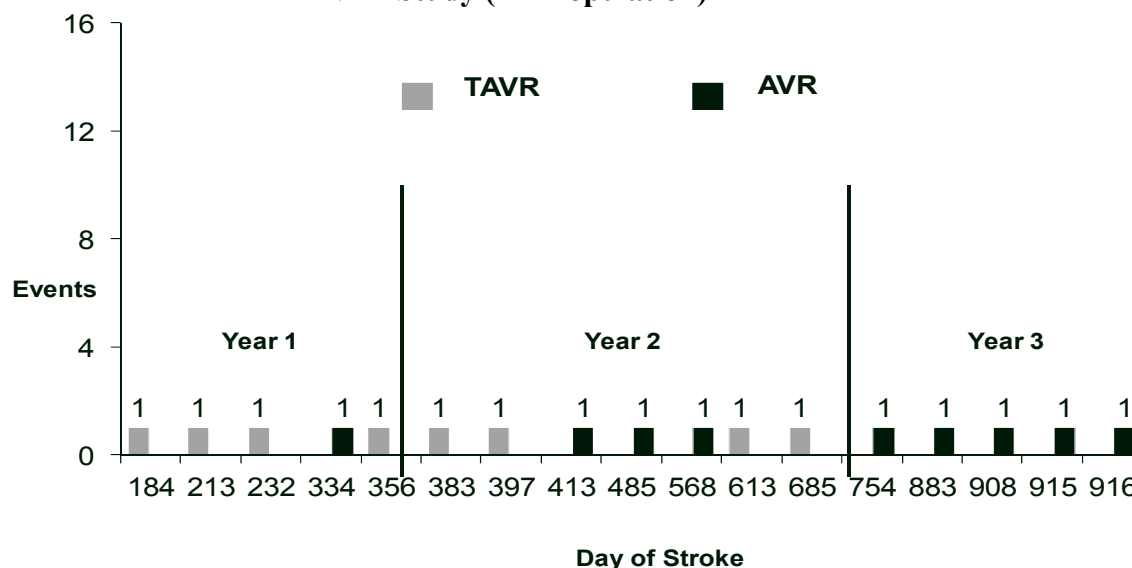
Figure 14. Stroke – High Risk Cohort in the PARTNER Study (AT Population)



Hazard ratio at 2 years; p-value from log-rank test up to 24 months



Figure 15. Timing of Late Stroke (> 30 days) – High Risk Cohort in the PARTNER Study (AT Population)



In order to assess the impact of stroke on the patients' quality of life, Table 37 presents the pairwise SF-12 physical scores in patients who experienced and did not experience stroke over time by treatment group. The SF-12 physical instrument is the most sensitive QoL instrument to the effects of stroke from a disability perspective that was administered in the study. Patients undergoing TAVR who experienced a stroke had similar SF-12 physical scores as TAVR patients who did not experience a stroke at 1, 6 and 12 months. However, AVR patients who experienced a stroke had worse SF-12 physical scores at 1 and 6 months but recovered to baseline at 1 year.

Table 37. Pairwise Comparison of SF-12 Physical Score - High Risk Cohort in the PARTNER Study (AT Population)

| | Stroke | | No Stroke | |
|-----------|--------|----------------------------|-----------|----------------------------|
| TAVR | n | Paired Difference (95% CI) | n | Paired Difference (95% CI) |
| 1 month | 12 | 6.5 (1.4, 11.6) | 248 | 4.2 (3.0, 5.5) |
| 6 month | 12 | 5.5 (1.0, 10.0) | 229 | 6.3 (4.9, 7.8) |
| 12 months | 10 | 7.3 (-1.1, 15.8) | 211 | 6.5 (5.0, 8.1) |
| AVR | n | Paired Difference (95% CI) | n | Paired Difference (95% CI) |
| 1 month | 4 | -9.0 (-31.6, 13.6) | 205 | 2.1 (0.6, 3.6) |
| 6 month | 5 | -1.0 (-10.7, 8.7) | 182 | 7.4 (5.7, 9.0) |
| 12 months | 4 | -0.8 (-18.9, 17.4) | 176 | 5.8 (4.1, 7.6) |



In spite of the low number of strokes, a multivariate model was fitted in order to identify predictors of early and late stroke. During the multivariable modeling process, fifty (50) total non-treatment variables were considered – forty-one (41) site-collected baseline variables, one (1) electrocardiogram variable (baseline atrial fibrillation), four (4) echocardiographic variables (baseline AV area, baseline ejection fraction, baseline mean gradient, first post-procedure PV leak grade), three (3) procedural variables (anesthesia time, rapid pacing during deployment, procedural hypotension), and one (1) site learning curve variable. Stepwise logistic regression was used to select predictor variables, and treatment was forced into the model but was not a predictor for early or late stroke.

As shown in Table 38, patients with any kind of prior cardiovascular intervention were 4 times more likely to have an early stroke (≤ 30 days) of the index procedure ($p=0.056$).

The only significant predictor of late stroke was gender ($p=0.0129$). As expected in elderly patients, females have a significantly higher risk of stroke.

In regards to stroke overall, Cox regression was performed to take time to stroke into account. Peripheral vascular disease was the only significant predictor of stroke ($p=0.0077$). Patients with peripheral vascular disease had a 3 times higher risk of stroke. Prior cardiovascular intervention or gender which were predictors of early and late stroke respectively, were not MV predictors of stroke throughout the follow up.

Table 38. Significant Multivariate Predictors of Stroke - High Risk Cohort in the PARTNER Study (AT Population)

| Early Stroke - Effect^a | p-value | Odds Ratio | Lower 95% CL | Upper 95% CL |
|--|----------------|-------------------|---------------------|---------------------|
| TAVR vs. AVR | 0.2142 | 1.742 | 0.726 | 4.176 |
| Previous Cardiovascular Intervention | 0.0560 | 4.041 | 0.937 | 17.427 |
| Late Stroke - Effect^b | p-value | Odds Ratio | Lower 95% CL | Upper 95% CL |
| TAVR vs. AVR | 0.6718 | 0.809 | 0.304 | 2.153 |
| Male vs. Female | 0.0129 | 0.23 | 0.072 | 0.733 |
| Stroke (Early and Late) - Effect | p-value | Odds Ratio | Lower 95% CL | Upper 95% CL |
| TAVR vs. AVR | 0.0739 | 2.224 | 0.926 | 5.345 |
| Previous Cardiovascular Intervention | 0.1528 | 2.238 | 0.742 | 6.751 |
| Male vs. Female | 0.2772 | 0.635 | 0.28 | 1.44 |
| Peripheral Vascular Disease | 0.0077 | 3.058 | 1.344 | 6.961 |

a. N=657 data points used; n=23 early stroke and n=634 not early stroke

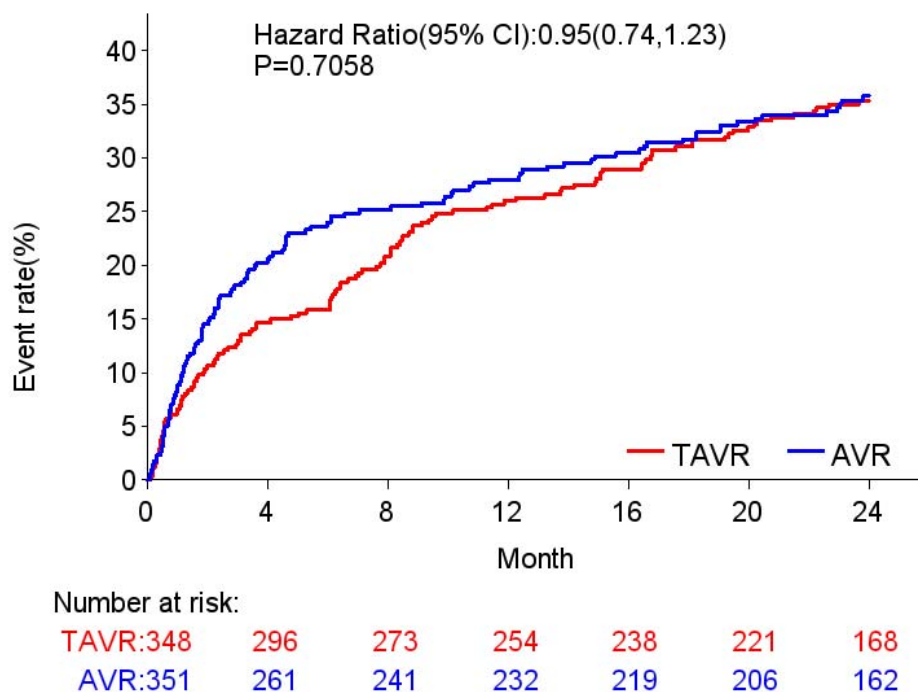
b. N=625 data points used; n=17 late stroke and n=608 not late stroke

c. N=648 data points used; n=40 stroke and n=608 not stroke



Finally, Figure 16 illustrates the death or stroke rate over time.

Figure 16. Death or Stroke at 24 Months – High Risk Cohort in the PARTNER Study (AT Population)



Hazard ratio at 2 years; p-value from log-rank test up to 24 months

9.3 Safety Events Stratified by Implant Approach

Table 39 shows protocol-defined AEs reported for the transfemoral cohort. The incidence of perivalvular leak was higher in the TF-TAVR group than the TF-AVR group (2.2% TF-TAVR vs. 0.0% TF-AVR, $p=0.0240$) during the 31 day – 1 year interval.

Table 40 shows protocol-defined AEs reported for the transapical cohort. The incidence of bleeding, hemorrhagic/vascular events and sternal wound infection was significantly lower for the TAVR group compared to the AVR group, specifically:

- Bleeding events during the 31 day to 1 year interval (4.1% TAVR vs. 16.6% AVR, $p=0.0075$)



- Hemorrhagic/vascular events reported within 30 days (14.5% TAVR vs. 28.3% AVR, $p=0.0183$)
- Sternal wound infection during the 31 day to 1 year interval (0% TAVR vs. 5.1% AVR, $p=0.0411$)



Table 39. Protocol-Defined Adverse Events – Transfemoral Approach - High Risk Cohort in the PARTNER Study (AT Population)

| Per Protocol AE Randomized PMA Cohort A (AT) -- Transfemoral Approach | | | | | | | | | | | | | | | |
|---|-------------------|--------------|----------------------|------------|----------------------|--------------------------|--------------------------------------|------------------|----------------------|-------------------------|-------------------------------------|----------|----------------------|--------------------------------------|--------|
| | | Total Events | | <= 30 days | | | | 31 days - 1 year | | | | > 1 year | Trial | | |
| | Patients in group | Total events | Patients with event* | Events | Patients with event* | KM Event rate at 30 days | P-value for point in time at 30 days | Events | Patients with event* | KM Event rate at 1 year | P-value for point in time at 1 year | Events | Patients with event* | Log-rank p-value for length of trial | |
| Annular dissection | | | | | | | | | | | | | | | |
| | AVR | 221 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| | TAVR | 240 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| Aortic Dissection | | | | | | | | | | | | | | | |
| | AVR | 221 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| | TAVR | 240 | 1 | 1 | 1 | 1 | 0.4% | 0.3163 | 0 | 0 | 0.4% | 0.3163 | 0 | 0 | 0.3373 |
| Aortic Stenosis | | | | | | | | | | | | | | | |
| | AVR | 221 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| | TAVR | 240 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| Bleeding event | | | | | | | | | | | | | | | |
| | AVR | 221 | 27 | 24 | 4 | 3 | 1.4% | . | 10 | 10 | 6.9% | . | 13 | 11 | . |
| | TAVR | 240 | 37 | 33 | 7 | 7 | 2.9% | 0.2387 | 17 | 17 | 9.9% | 0.2730 | 13 | 12 | 0.4594 |
| Device migration | | | | | | | | | | | | | | | |
| | AVR | 221 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| | TAVR | 240 | 1 | 1 | 1 | 1 | 0.4% | 0.3163 | 0 | 0 | 0.4% | 0.3163 | 0 | 0 | 0.3373 |
| Embolic event | | | | | | | | | | | | | | | |
| | AVR | 221 | 2 | 2 | 1 | 1 | 0.5% | . | 0 | 0 | 0.5% | . | 1 | 1 | . |
| | TAVR | 240 | 1 | 1 | 1 | 1 | 0.4% | 0.9653 | 0 | 0 | 0.4% | 0.9653 | 0 | 0 | 0.5075 |
| Hemolysis | | | | | | | | | | | | | | | |



| Per Protocol AE Randomized PMA Cohort A (AT) -- Transfemoral Approach | | | | | | | | | | | | | | |
|---|-------------------|--------------|----------------------|--------|----------------------|--------------------------|--------------------------------------|--------|----------------------|-------------------------|-------------------------------------|--------|----------------------|--------------------------------------|
| | Total Events | | <= 30 days | | | | 31 days - 1 year | | | | > 1 year | | Trial | |
| | Patients in group | Total events | Patients with event* | Events | Patients with event* | KM Event rate at 30 days | P-value for point in time at 30 days | Events | Patients with event* | KM Event rate at 1 year | P-value for point in time at 1 year | Events | Patients with event* | Log-rank p-value for length of trial |
| AVR | 221 | 1 | 1 | 0 | 0 | 0.0% | . | 1 | 1 | 0.5% | . | 0 | 0 | . |
| TAVR | 240 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | 0.3161 | 0 | 0 | 0.2775 |
| Hemorrhagic/Vascular event | | | | | | | | | | | | | | |
| AVR | 221 | 74 | 65 | 70 | 61 | 27.6% | . | 2 | 2 | 28.7% | . | 2 | 2 | . |
| TAVR | 240 | 106 | 73 | 94 | 69 | 28.8% | 0.7782 | 5 | 5 | 30.2% | 0.7164 | 7 | 4 | 0.8715 |
| Infection (including Endocarditis) | | | | | | | | | | | | | | |
| AVR | 221 | 137 | 81 | 52 | 42 | 19.6% | . | 45 | 34 | 31.9% | . | 40 | 26 | . |
| TAVR | 240 | 174 | 97 | 41 | 37 | 15.6% | 0.2684 | 65 | 48 | 32.7% | 0.8707 | 68 | 37 | 0.6095 |
| Myocardial infarction | | | | | | | | | | | | | | |
| AVR | 221 | 4 | 4 | 1 | 1 | 0.5% | . | 0 | 0 | 0.5% | . | 3 | 3 | . |
| TAVR | 240 | 2 | 2 | 0 | 0 | 0.0% | 0.3162 | 0 | 0 | 0.0% | 0.3162 | 2 | 2 | 0.3845 |
| Nonstructural valve dysfunction | | | | | | | | | | | | | | |
| AVR | 221 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| TAVR | 240 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| Perforation or damage to myocardium | | | | | | | | | | | | | | |
| AVR | 221 | 1 | 1 | 1 | 1 | 0.5% | . | 0 | 0 | 0.5% | . | 0 | 0 | . |
| TAVR | 240 | 2 | 2 | 1 | 1 | 0.4% | 0.9535 | 1 | 1 | 0.9% | 0.5400 | 0 | 0 | 0.6245 |
| Peripheral Vascular Disease | | | | | | | | | | | | | | |
| AVR | 221 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| TAVR | 240 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| Perivalvular leak | | | | | | | | | | | | | | |



| Per Protocol AE Randomized PMA Cohort A (AT) -- Transfemoral Approach | | | | | | | | | | |
|---|-------------------|----------------------|------------|----------------------|--------------------------|--------------------------------------|------------------|----------------------|-------------------------|-------------------------------------|
| | Total Events | | <= 30 days | | | | 31 days - 1 year | | | Trial |
| | Patients in group | Patients with event* | Events | Patients with event* | KM Event rate at 30 days | P-value for point in time at 30 days | Events | Patients with event* | KM Event rate at 1 year | P-value for point in time at 1 year |
| AVR | 221 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . |
| TAVR | 240 | 5 | 3 | 3 | 1.3% | 0.0813 | 2 | 2 | 2.2% | 0.0240 |
| Rehospitalization for symptoms of aortic stenosis | | | | | | | | | | |
| AVR | 221 | 52 | 39 | 12 | 5.8% | . | 28 | 22 | 17.3% | . |
| TAVR | 240 | 75 | 55 | 14 | 5.5% | 0.9175 | 35 | 29 | 17.6% | 0.9386 |
| Renal failure | | | | | | | | | | |
| AVR | 221 | 5 | 5 | 2 | 0.9% | . | 3 | 3 | 2.6% | . |
| TAVR | 240 | 6 | 6 | 4 | 1.7% | 0.4874 | 1 | 1 | 2.1% | 0.7495 |
| Renal insufficiency | | | | | | | | | | |
| AVR | 221 | 19 | 17 | 13 | 6.0% | . | 6 | 6 | 8.2% | . |
| TAVR | 240 | 13 | 13 | 7 | 2.9% | 0.1173 | 2 | 2 | 3.9% | 0.0649 |
| Sternal wound infection | | | | | | | | | | |
| AVR | 221 | 3 | 3 | 2 | 0.9% | . | 1 | 1 | 1.4% | . |
| TAVR | 240 | 0 | 0 | 0 | 0.0% | 0.1554 | 0 | 0 | 0.0% | 0.0813 |
| Stroke | | | | | | | | | | |
| AVR | 221 | 8 | 8 | 3 | 1.4% | . | 0 | 0 | 1.4% | . |
| TAVR | 240 | 11 | 11 | 8 | 3.3% | 0.1586 | 1 | 1 | 3.8% | 0.0959 |
| Transient ischemic attack (TIA) | | | | | | | | | | |
| AVR | 221 | 2 | 2 | 0 | 0.0% | . | 1 | 1 | 0.6% | . |
| TAVR | 240 | 6 | 6 | 3 | 1.3% | 0.0813 | 2 | 2 | 2.3% | 0.1460 |
| Valvular thrombosis | | | | | | | | | | |
| AVR | 221 | 2 | 2 | 0 | 0.0% | . | 1 | 1 | 0.6% | . |
| TAVR | 240 | 6 | 6 | 3 | 1.3% | 0.0813 | 2 | 2 | 2.3% | 0.1460 |



| Per Protocol AE Randomized PMA Cohort A (AT) -- Transfemoral Approach | | | | | | | | | | |
|---|-------------------|--------------|----------------------|--------|----------------------|--------------------------|--------------------------------------|--------|----------------------|--------------------------------------|
| | Total Events | | <= 30 days | | | 31 days - 1 year | | | > 1 year | Trial |
| | Patients in group | Total events | Patients with event* | Events | Patients with event* | KM Event rate at 30 days | P-value for point in time at 30 days | Events | Patients with event* | Log-rank p-value for length of trial |
| AVR | 221 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | . |
| TAVR | 240 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | . |
| Endocarditis (Site) | | | | | | | | | | |
| AVR | 221 | 6 | 4 | 0 | 0 | 0.0% | . | 2 | 4 | 2 |
| TAVR | 240 | 4 | 4 | 0 | 0 | 0.0% | . | 2 | 2 | 0.8504 |
| MACCE | | | | | | | | | | |
| AVR | 221 | 101 | 88 | 24 | 23 | 10.4% | . | 40 | 38 | 31 |
| TAVR | 240 | 104 | 91 | 21 | 17 | 7.1% | 0.2036 | 44 | 42 | 37 |

KM=Kaplan-Meier, MACCE= Major Adverse Cardiac and Cerebrovascular Events (death, stroke, MI, and renal failure), TIA=transient ischemic attack

Source: Table 5.3

* Patients could experience more than one event.

Bleeding Event

Any episode of major internal or external bleeding that caused death, hospitalization or permanent injury (e.g., vision loss) or necessitated transfusion of greater than 3 units PRBCs or pericardiocentesis procedure.

Peripheral embolic event

A peripheral embolic event was an operative, autopsy or clinically documented embolus that produced symptoms from complete or partial obstruction or a peripheral (noncerebral) artery.

Hemorrhagic Vascular Complication

Hematoma at access site >5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or **any** transfusion during or related to the index procedure.

Stroke

A neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction

TIA

A fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction

Myocardial Infarction

Acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI

Renal Failure

Patient required chronic dialysis for greater than 30 days

Renal Insufficiency

Creatinine level above 3.5

MACCE

Death, MI, Renal Failure, and Stroke using the event definitions above.



Table 40. Protocol-Defined Adverse Events – Transapical Approach - High Risk Cohort in the PARTNER Study (AT Population)

| Per Protocol AE Randomized PMA Cohort A (AT) -- Transapical Approach | | | | | | | | | | | | | | | |
|--|-------------------|--------------|----------------------|------------|----------------------|--------------------------|--------------------------------------|------------------|----------------------|-------------------------|-------------------------------------|----------|----------------------|--------------------------------------|--------|
| | | Total Events | | <= 30 days | | | | 31 days - 1 year | | | | > 1 year | | Trial | |
| | Patients in group | Total events | Patients with event* | Events | Patients with event* | KM Event rate at 30 days | P-value for point in time at 30 days | Events | Patients with event* | KM Event rate at 1 year | P-value for point in time at 1 year | Events | Patients with event* | Log-rank p-value for length of trial | |
| Annular dissection | | | | | | | | | | | | | | | |
| | AVR | 92 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| | TAVR | 104 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| Aortic Dissection | | | | | | | | | | | | | | | |
| | AVR | 92 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| | TAVR | 104 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| Aortic Stenosis | | | | | | | | | | | | | | | |
| | AVR | 92 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| | TAVR | 104 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| Bleeding event | | | | | | | | | | | | | | | |
| | AVR | 92 | 17 | 15 | 3 | 3 | 3.3% | . | 11 | 10 | 16.6% | . | 3 | 3 | . |
| | TAVR | 104 | 6 | 5 | 3 | 3 | 3.0% | 0.9118 | 1 | 1 | 4.1% | 0.0075 | 2 | 1 | 0.0091 |
| Device migration | | | | | | | | | | | | | | | |
| | AVR | 92 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| | TAVR | 104 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . | 0 | 0 | . |
| Embolic event | | | | | | | | | | | | | | | |
| | AVR | 92 | 2 | 2 | 2 | 2 | 2.2% | . | 0 | 0 | 2.2% | . | 0 | 0 | . |
| | TAVR | 104 | 5 | 5 | 4 | 4 | 4.0% | 0.4701 | 1 | 1 | 5.2% | 0.2693 | 0 | 0 | 0.3247 |
| Hemolysis | | | | | | | | | | | | | | | |



| Per Protocol AE Randomized PMA Cohort A (AT) -- Transapical Approach | | | | | | | | | | | |
|--|-------------------|--------------|----------------------|------------|----------------------|--------------------------|--------------------------------------|------------------|----------------------|-------------------------|--------|
| | Patients in group | Total Events | | <= 30 days | | | | 31 days - 1 year | | | Trial |
| | | Total events | Patients with event* | Events | Patients with event* | KM Event rate at 30 days | P-value for point in time at 30 days | Events | Patients with event* | KM Event rate at 1 year | |
| AVR | 92 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . |
| TAVR | 104 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . |
| Hemorrhagic/Vascular event | | | | | | | | | | | |
| AVR | 92 | 31 | 26 | 30 | 26 | 28.3% | . | 1 | 1 | 28.3% | . |
| TAVR | 104 | 27 | 21 | 16 | 15 | 14.5% | 0.0183 | 7 | 5 | 19.2% | 0.1601 |
| Infection (including Endocarditis) | | | | | | | | | | | |
| AVR | 92 | 60 | 35 | 26 | 23 | 25.7% | . | 19 | 14 | 39.6% | . |
| TAVR | 104 | 96 | 48 | 32 | 26 | 25.9% | 0.9765 | 38 | 23 | 43.8% | 0.3440 |
| Myocardial infarction | | | | | | | | | | | |
| AVR | 92 | 2 | 2 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . |
| TAVR | 104 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | 0.1300 |
| Nonstructural valve dysfunction | | | | | | | | | | | |
| AVR | 92 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . |
| TAVR | 104 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . |
| Perforation or damage to myocardium | | | | | | | | | | | |
| AVR | 92 | 1 | 1 | 1 | 1 | 1.1% | . | 0 | 0 | 1.1% | . |
| TAVR | 104 | 1 | 1 | 1 | 1 | 1.0% | 0.9308 | 0 | 0 | 1.0% | 0.9307 |
| Peripheral Vascular Disease | | | | | | | | | | | |
| AVR | 92 | 1 | 1 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . |
| TAVR | 104 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | 0.3045 |
| Perivalvular leak | | | | | | | | | | | |



| Per Protocol AE Randomized PMA Cohort A (AT) -- Transapical Approach | | | | | | | | | | | |
|--|-------------------|--------------|----------------------|------------|----------------------|--------------------------|--------------------------------------|------------------|----------------------|-------------------------|--------|
| | Patients in group | Total Events | | <= 30 days | | | | 31 days - 1 year | | | Trial |
| | | Total events | Patients with event* | Events | Patients with event* | KM Event rate at 30 days | P-value for point in time at 30 days | Events | Patients with event* | KM Event rate at 1 year | |
| AVR | 92 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . |
| TAVR | 104 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . |
| Rehospitalization for symptoms of aortic stenosis | | | | | | | | | | | |
| AVR | 92 | 24 | 17 | 6 | 6 | 6.8% | . | 9 | 7 | 14.9% | . |
| TAVR | 104 | 28 | 23 | 5 | 5 | 5.1% | 0.6135 | 14 | 11 | 16.7% | 0.5536 |
| Renal failure | | | | | | | | | | | |
| AVR | 92 | 6 | 5 | 5 | 4 | 4.5% | . | 1 | 1 | 5.7% | . |
| TAVR | 104 | 2 | 2 | 2 | 2 | 2.0% | 0.3395 | 0 | 0 | 2.0% | 0.1929 |
| Renal insufficiency | | | | | | | | | | | |
| AVR | 92 | 7 | 7 | 5 | 5 | 5.5% | . | 1 | 1 | 6.9% | . |
| TAVR | 104 | 13 | 13 | 12 | 12 | 11.9% | 0.1123 | 1 | 1 | 13.1% | 0.2252 |
| Sternal wound infection | | | | | | | | | | | |
| AVR | 92 | 4 | 4 | 1 | 1 | 1.2% | . | 3 | 3 | 5.1% | . |
| TAVR | 104 | 0 | 0 | 0 | 0 | 0.0% | 0.3144 | 0 | 0 | 0.0% | 0.0331 |
| Stroke | | | | | | | | | | | |
| AVR | 92 | 10 | 9 | 5 | 5 | 5.5% | . | 1 | 1 | 7.0% | . |
| TAVR | 104 | 12 | 12 | 7 | 7 | 7.0% | 0.6775 | 3 | 3 | 10.8% | 0.6618 |
| Transient ischemic attack (TIA) | | | | | | | | | | | |
| AVR | 92 | 5 | 4 | 1 | 1 | 1.1% | . | 2 | 2 | 3.9% | . |
| TAVR | 104 | 4 | 4 | 0 | 0 | 0.0% | 0.3146 | 3 | 3 | 3.7% | 0.8890 |
| Valvular thrombosis | | | | | | | | | | | |



| Per Protocol AE Randomized PMA Cohort A (AT) -- Transapical Approach | | | | | | | | | | | |
|--|-------------------|--------------|----------------------|------------|----------------------|--------------------------|--------------------------------------|------------------|----------------------|-------------------------|--------------------------------------|
| | Patients in group | Total Events | | <= 30 days | | | | 31 days - 1 year | | | Log-rank p-value for length of trial |
| | | Total events | Patients with event* | Events | Patients with event* | KM Event rate at 30 days | P-value for point in time at 30 days | Events | Patients with event* | KM Event rate at 1 year | |
| AVR | 92 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . |
| TAVR | 104 | 0 | 0 | 0 | 0 | 0.0% | . | 0 | 0 | 0.0% | . |
| Endocarditis (Site) | | | | | | | | | | | |
| AVR | 92 | 1 | 1 | 1 | 1 | 1.1% | . | 0 | 0 | 1.1% | . |
| TAVR | 104 | 1 | 1 | 0 | 0 | 0.0% | 0.3146 | 1 | 1 | 1.2% | 0.9322 |
| MACCE | | | | | | | | | | | |
| AVR | 92 | 54 | 39 | 17 | 14 | 15.2% | . | 18 | 17 | 29.6% | . |
| TAVR | 104 | 58 | 49 | 18 | 17 | 16.4% | 0.8270 | 24 | 23 | 34.8% | 0.5593 |

KM=Kaplan-Meier; MACCE= Major Adverse Cardiac and Cerebrovascular Events (death, stroke, MI, and renal failure), TIA=transient ischemic attack
Source: Table 5.3
* Patients could experience more than one event.

Bleeding Event
Any episode of major internal or external bleeding that caused death, hospitalization or permanent injury (e.g., vision loss) or necessitated transfusion of greater than 3 units PRBCs or pericardiocentesis procedure.

Peripheral embolic event
A peripheral embolic event was an operative, autopsy or clinically documented embolus that produced symptoms from complete or partial obstruction or a peripheral (noncerebral) artery.

Hemorrhagic Vascular Complication
Hematoma at access site >5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or **any** transfusion during or related to the index procedure. .

Stroke
A neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction

TIA
A fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction

Myocardial Infarction
Acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI

Renal Failure
Patient required chronic dialysis for greater than 30 days

Renal Insufficiency
Creatinine level above 3.5

MACCE
Death, MI, Renal Failure, and Stroke using the event definitions above.



9.4 CEC-Adjudicated Adverse Events

Table 94 in **Appendix F** shows the reported adverse events that were adjudicated by the CEC for the pooled AT population (see **Appendix D** for definitions).

Significant differences observed are associated with the procedural approach, i.e., TAVR vs. AVR. Depending on the event, one of the two TAVR approaches is associated with the event (e.g., vascular events are associated with TF-TAVR).

The major vascular event rate was 11.1% for TAVR and 3.8% for AVR at 30 days and one year ($p=0.0003$). The log rank p-value for major vascular event for length of trial was 0.0003. Subsequent treatment of vascular events also accounted for a significantly higher incidence of arterial vascular procedure at each time interval and over the entire trial in the TAVR arm as compared to the AVR arm.

In contrast major bleeding and sternal wound infection were higher in the AVR arm, e.g., the major bleeding rate was 10.8% for TAVR vs. 23.0% for AVR at 30 days ($p<0.0001$), and 15.8% for TAVR vs. 27.5% for AVR at one year ($p=0.0003$). The log rank p-value for major bleeding for length of trial was 0.0003. All hemorrhagic events were statistically higher in the AVR arm at 30 days, the 31 day to 1 year interval, and length of trial.

9.4.1 Death in Patients who Experienced Major CEC Adjudicated Adverse Events of Interest

As shown, due to the different implant technique, different major complications are of interest and may have important consequences in patients. Events of interest in the TAVR group include major vascular complications and stroke and in the AVR group major bleeding and new onset atrial fibrillation.

Table 41 provides patients who experienced those major complications and their 1 year vital status; at 1 year, 40 TAVR patients (11.6%) had died and 50 AVR patients (16.0%) had died.



Table 41. CEC-Adjudicated Adverse Events – Impact of Major Complications on 1 Year Mortality – High Risk Cohort in the PARTNER Study (AT Population)

| Complication | At 1 year | | | | | | | |
|-------------------------|---------------------------|--------------------------------|-------------------------------|--|--------------------------|--------------------------------|-------------------------------|--|
| | As Treated TAVR (n = 344) | | | | As Treated AVR (n = 313) | | | |
| | Patients with event | Percent of patients with event | Patients with event and death | Percent of patients with event and death | Patients with event | Percent of patients with event | Patients with event and death | Percent of patients with event and death |
| Stroke | 19 | 5.5% | 9 | 2.6% | 9 | 2.9% | 3 | 1.0% |
| Major Vascular Event | 38 | 11.0% | 14 | 4.1% | 12 | 3.8% | 5 | 1.6% |
| New Atrial Fibrillation | 44 | 12.8% | 14 | 4.1% | 60 | 19.2% | 18 | 5.8% |
| Major Bleeding | 52 | 15.1% | 18 | 5.2% | 84 | 26.8% | 36 | 11.5% |
| All above events | 117 | 34.0% | 40 | 11.6% | 137 | 43.8% | 50 | 16.0% |

Source: Table wxyz

| | |
|-----------------------|---|
| Stroke | A neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction. |
| Vascular Complication | Any of the following: Access Site Hematoma at access site > 5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular perforation, vascular dissection, gastro-intestinal ischemia. Major: thoracic aortic dissection; access site or access-related vascular injury leading to death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention; distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage. Minor: Vascular event that did not meet the criteria for major vascular complication. |
| Hemorrhagic Event | Major bleeding: Any episode of major internal or external bleeding that caused death, hospitalization or permanent injury (e.g., vision loss) or necessitated transfusion of greater than 3 units PRBCs within a 24 hour period, pericardiocentesis, open and/or endovascular procedure for repair or hemostasis. Minor bleeding: Bleeding event that did not meet the criteria for major bleed. |

9.5 Instructions For Use (IFU) - FDA Definition of Bleeding

Ad hoc, bleeding events were analyzed using FDA's definition for bleeding, specifically "Bleeding event defined as ≥ 2 units of blood within the index procedure." The results of these analyses were included in the IFU and are shown in Table 95 through Table 97 in **Appendix F**.



10.0 Additional Analyses in the Partner I High Risk Cohort

10.1 Additional Analyses Related to the Primary Endpoint

Table 42 presents several composite endpoints including death for the ITT population using CEC definitions. Previously, mortality at 30 days and 1 year were described. The log-rank p-value for death over the length of trial was 0.3101.

The CEC classified all causes of deaths as cardiovascular (cardiac), non-cardiovascular, or unknown. No significant differences in KM event rate of cardiac death were observed within 30 days, and the 31 days - 1 year interval. Figure 17 illustrates cardiovascular mortality. Over the duration of the study, the risk of death due to cardiovascular causes was not significantly different between the TAVR and AVR arms ($p=0.4810$).

The KM event rates for death/all stroke were similar for TAVR and AVR within 30 days (i.e., 7.8% vs. 8.5%, $p=0.7228$), and the 31 days - 1 year interval (27.4% vs. 28.6%, $p=0.7432$). Figure 16 illustrates all cause mortality/all stroke (log-rank p-value over the length of trial $p=0.6955$).

The differences in KM event rates for death/all vascular events within 30 days were significant in favor of the AVR arm (9.6% AVR vs. 19.3% TAVR, $p=0.0003$). And a similar trend was observed during the 31 days – 1 year interval (29.3% vs. 36.0%, $p=0.0632$).

The differences in KM event rates for death/all bleeding events within 30 days were significant in favor of the TAVR arm (16.7% TAVR vs. 24.7% AVR, $p=0.0086$), while the differences in KM event rates for death/all bleeding events failed to reach significance between 31 days and 1 year (37.5% TAVR vs. 42.5% AVR, $p=0.1806$).

In regards to major bleeding, a significant difference was observed within 30 days only (12.6% in the TAVR arm vs. 23.0% in the AVR arm, $p=0.0003$); a similar trend was observed in the 31 days to 1 year interval ($p=0.0701$).

No significant differences in KM event rates of death or rehospitalization were observed comparing the study arms.



Table 42. Death and Composite Endpoints - High Risk Cohort in the PARTNER Study (ITT Population)

| Randomized PMA Cohort A (ITT) -- Pooled Approaches | | | | | | | | | | | | |
|--|--------------|----------------------|--------|----------------------|--------------------------|--|--------|----------------------|-------------------------|---------------------------------------|----------|----------------------|
| | | Total Events | | <= 30 days | | | | 31 days - 1 year | | | > 1 year | |
| Patients in group | Total events | Patients with event* | Events | Patients with event* | KM Event rate at 30 days | P-value for point in time at 30 days** | Events | Patients with event* | KM Event rate at 1 year | P-value for point in time at 1 year** | Events | Patients with event* |
| Death | | | | | | | | | | | | |
| AVR | 351 | 137 | 22 | 22 | 6.5% | . | 67 | 67 | 26.8% | . | 48 | 48 |
| TAVR | 348 | 133 | 12 | 12 | 3.4% | 0.0689 | 72 | 72 | 24.3% | 0.4506 | 49 | 49 |
| Cardiac Death | | | | | | | | | | | | |
| AVR | 351 | 78 | 10 | 10 | 3.0% | . | 30 | 30 | 13.0% | . | 38 | 38 |
| TAVR | 348 | 76 | 11 | 11 | 3.2% | 0.9019 | 36 | 36 | 14.3% | 0.6268 | 29 | 29 |
| Death/All Stroke | | | | | | | | | | | | |
| AVR | 351 | 157 | 30 | 29 | 8.5% | . | 69 | 68 | 28.6% | . | 58 | 49 |
| TAVR | 348 | 157 | 28 | 27 | 7.8% | 0.7228 | 76 | 74 | 27.4% | 0.7432 | 53 | 52 |
| Death/All Vascular | | | | | | | | | | | | |
| AVR | 351 | 155 | 37 | 33 | 9.6% | . | 70 | 68 | 29.3% | . | 48 | 48 |
| TAVR | 348 | 207 | 82 | 67 | 19.3% | 0.0003 | 75 | 73 | 36.0% | 0.0632 | 50 | 50 |
| Death/Major Vascular | | | | | | | | | | | | |
| AVR | 351 | 151 | 35 | 31 | 9.0% | . | 68 | 68 | 28.8% | . | 48 | 48 |
| TAVR | 348 | 181 | 58 | 46 | 13.2% | 0.0808 | 73 | 72 | 31.4% | 0.4519 | 50 | 50 |
| Death/All Bleeding | | | | | | | | | | | | |
| AVR | 351 | 260 | 101 | 85 | 24.7% | . | 95 | 77 | 42.5% | . | 64 | 55 |
| TAVR | 348 | 223 | 61 | 58 | 16.7% | 0.0086 | 99 | 86 | 37.5% | 0.1806 | 63 | 56 |



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| Randomized PMA Cohort A (ITT) -- Pooled Approaches | | | | | | | | | | | | | |
|--|-------------------|--------------|----------------------|------------|----------------------|--------------------------|--|------------------|----------------------|-------------------------|---------------------------------------|----------------------|---------------------------------------|
| | | Total Events | | <= 30 days | | | | 31 days - 1 year | | | > 1 year | Trial | |
| | Patients in group | Total events | Patients with event* | Events | Patients with event* | KM Event rate at 30 days | P-value for point in time at 30 days** | Events | Patients with event* | KM Event rate at 1 year | P-value for point in time at 1 year** | Patients with event* | Log-rank p-value for length of trial# |
| Death/Major Bleeding | | | | | | | | | | | | | |
| AVR | 351 | 249 | 180 | 94 | 79 | 23.0% | . | 92 | 77 | 40.7% | . | 63 | 54 |
| TAVR | 348 | 204 | 164 | 46 | 44 | 12.6% | 0.0003 | 96 | 84 | 34.0% | 0.0701 | 62 | 56 |
| Death or Rehospitalization | | | | | | | | | | | | | |
| AVR | 351 | 225 | 169 | 35 | 34 | 10.0% | . | 118 | 98 | 37.7% | . | 72 | 60 |
| TAVR | 348 | 243 | 177 | 29 | 25 | 7.2% | 0.1901 | 129 | 101 | 34.9% | 0.4540 | 85 | 69 |
| | | | | | | | | | | | | | 0.8362 |

Source: Table 7.3

* Patients could experience more than one event.

** p-value for point in time: Comparison of the KM estimates at that one point in time; the comparison treats the estimates as normal variables

Log-rank p-value for length of trial = the log-rank p-value over the entire time period, from start to analysis close date.

Stroke

A neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction.

Vascular Complication

Any of the following: Access Site Hematoma at access site > 5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular perforation, vascular dissection, gastro-intestinal ischemia.

Major: thoracic aortic dissection; access site or access-related vascular injury leading to death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention; distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.

Minor: Vascular event that did not meet the criteria for major vascular complication.

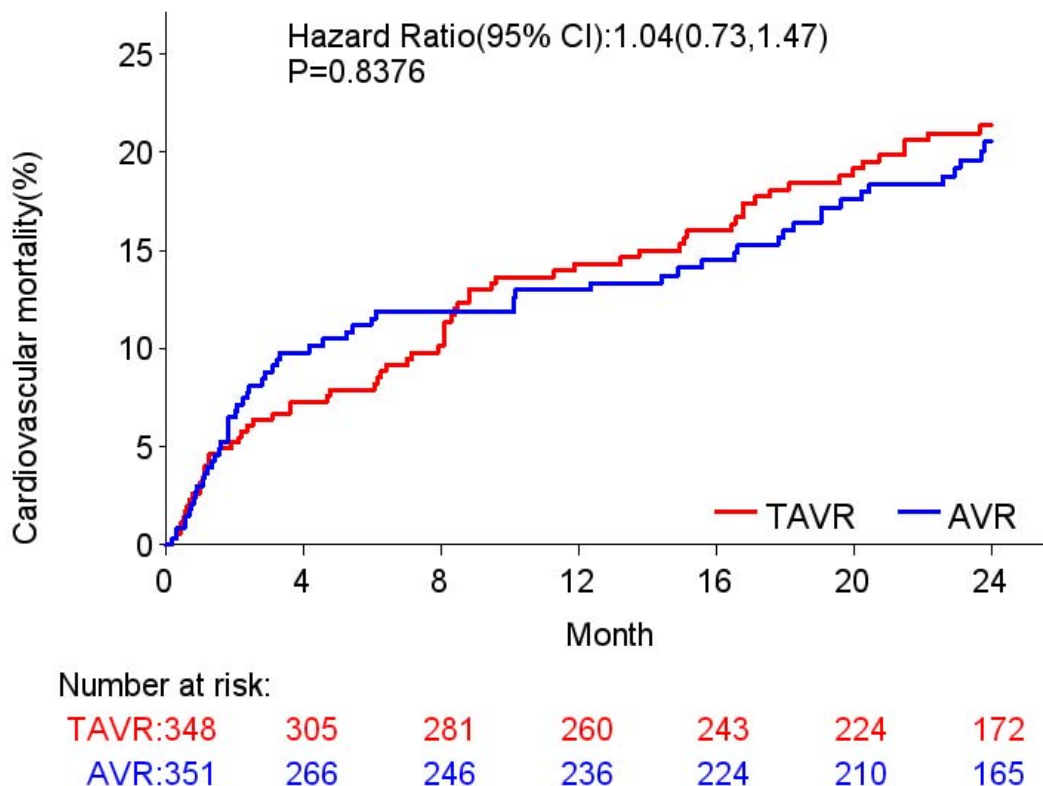
Hemorrhagic Event

Major bleeding: Any episode of major internal or external bleeding that caused death, hospitalization or permanent injury (e.g., vision loss) or necessitated transfusion of greater than 3 units PRBCs within a 24 hour period, pericardiocentesis procedure, open and/or endovascular procedure for repair or hemostasis.

Minor bleeding: Bleeding event that did not meet the criteria for major bleed.



Figure 17. Cardiac Mortality – High Risk Cohort in the PARTNER Study (ITT Population)



Hazard ratio at 2 years; p-value from log-rank test up to 24 months

10.2 NYHA Classification

Table 43 presents the cross tabulation of NYHA from baseline and 1 Year for the TAVR patients; 91.2% of patients improved, 8.0% had no change, and in two patients (0.4%), the NYHA class worsened.



Table 43. Cross Tabulation of NYHA from Baseline at 1 Year in TAVR Patients (AT Population)

| NYHA | 1 Year | | | | | | |
|-----------|---------|----------|-----------|----------|------|---------|-------|
| Baseline | Class I | Class II | Class III | Class IV | Died | Missing | Total |
| Class I | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Class II | 7 | 4 | 1 | 0 | 6 | 2 | 20 |
| Class III | 54 | 43 | 12 | 1 | 29 | 5 | 144 |
| Class IV | 58 | 46 | 19 | 4 | 45 | 8 | 180 |
| Died | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Missing | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 119 | 93 | 32 | 5 | 80 | 15 | 344 |

Table 44 presents the cross tabulation of NYHA from baseline and 1 Year for the AVR patients; 91.4%, improved, 7.3%, had no change, and in three patients (1.4%), the NYHA class worsened.

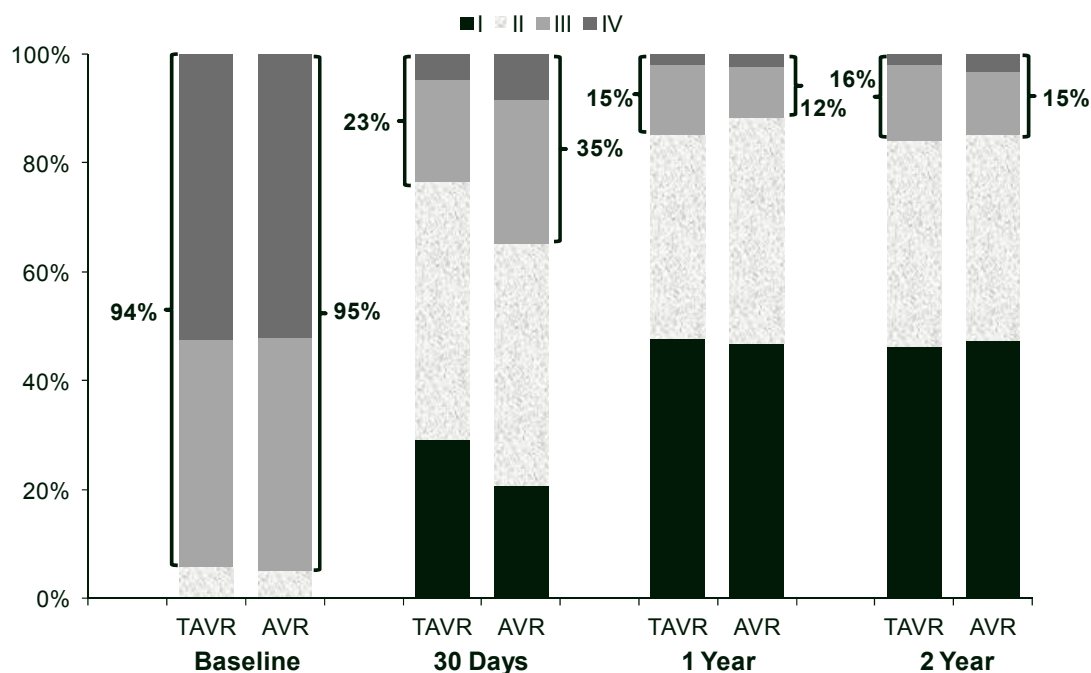
Table 44. Cross Tabulation of NYHA from Baseline at 1 Year in AVR Patients (AT Population)

| NYHA | 1 Year | | | | | | |
|-----------|---------|----------|-----------|----------|------|---------|-------|
| Baseline | Class I | Class II | Class III | Class IV | Died | Missing | Total |
| Class I | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Class II | 6 | 3 | 2 | 0 | 3 | 2 | 16 |
| Class III | 47 | 42 | 9 | 1 | 30 | 5 | 134 |
| Class IV | 50 | 46 | 10 | 4 | 44 | 9 | 163 |
| Died | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Missing | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 103 | 91 | 21 | 5 | 77 | 16 | 313 |

Figure 18 shows the distribution of cardiac symptom severity based on NYHA classification at several time points during the first year and second year of the PARTNER study. At 30 days, TAVR was more likely to reduce symptoms to NYHA class I or II (68.4% of TAVR patients were in NYHA I or II vs. 55.0% AVR).



Figure 18. NYHA Symptoms Over Time – High Risk Cohort in the PARTNER Study (ITT Population)



At the time of the database extract, all (alive) patients were followed for at least 2 years. Table 45 summarizes the NYHA classification at two year for the ITT population.

Table 45. NYHA at Two Years - High Risk Cohort in the PARTNER Study (ITT Population)

| | | Cohort A Randomized Patients -- ITT Population | |
|----------------------|------------|--|--------------|
| | | Pooled Approaches | |
| Analysis | Statistics | AVR (N=351) | TAVR (N=348) |
| Descriptive Analysis | n | 183 | 199 |
| | Mean | 1.70 | 1.72 |
| | SD | 0.799 | 0.779 |
| | Class I | 87(24.8%) | 92(26.4%) |
| | Class II | 69(19.7%) | 75(21.6%) |
| | Class III | 21(6.0%) | 28(8.0%) |
| | Class IV | 6(1.7%) | 4(1.1%) |
| | Death | 115(32.8%) | 117(33.6%) |
| | Unknown | 53(15.1%) | 32(9.2%) |

Source: Table 8.3a



Table 46 summarizes the NYHA data at two year for the AT population.

Table 46. NYHA at Two Years - High Risk Cohort in the PARTNER Study (AT Population)

| | | Cohort A Randomized Patients -- AT Population | |
|----------------------|------------|---|--------------|
| | | Pooled Approaches | |
| Analysis | Statistics | AVR (N=313) | TAVR (N=344) |
| Descriptive Analysis | n | 182 | 199 |
| | Mean | 1.71 | 1.72 |
| | SD | 0.799 | 0.779 |
| | Class I | 86(27.5%) | 92(26.7%) |
| | Class II | 69(22.0%) | 75(21.8%) |
| | Class III | 21(6.7%) | 28(8.1%) |
| | Class IV | 6(1.9%) | 4(1.2%) |
| | Death | 98(31.3%) | 114(33.1%) |
| | Unknown | 33(10.5%) | 31(9.0%) |

Source: Table 8.3a

10.3 6 MWT

Table 47 summarizes the 6MWT over time for the AT population. Data that are missing for medical reason(s) were imputed as 0 meters. The mean 6MWD in the TAVR group was 108.5 meters at baseline, 143.1 meters at 30 days, 171.5 meters at 6 months and 162.7 meters at 1 year. The mean 6MWD in the AVR group was 107.6 meters at baseline, 104.8 meters at 30 days, 185.5 meters at 6 months and 168.9 meters at 1 year.

Table 47. 6MWT (AT Population)

| | | | Cohort A Randomized Patients -- As Treated (AT) Population | | | | | |
|----------------|----------|------------|--|--------------|-----------------------|--------------|-------------------|--------------|
| | | | Transapical Approach | | Transfemoral Approach | | Pooled Approaches | |
| Parameter | Visit | Statistics | AVR (N=92) | TAVR (N=104) | AVR (N=221) | TAVR (N=240) | AVR (N=313) | TAVR (N=344) |
| TOTAL DISTANCE | BASELINE | n | 83 | 96 | 190 | 213 | 273 | 309 |
| | | Mean | 115.17 | 98.21 | 104.26 | 113.11 | 107.58 | 108.48 |
| | | SD | 116.856 | 104.064 | 112.875 | 122.116 | 113.995 | 116.843 |
| | | Minimum | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | | Q1 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | | Median | 90.00 | 87.50 | 72.15 | 76.20 | 75.00 | 82.00 |
| | | Q3 | 198.00 | 157.28 | 194.00 | 186.50 | 195.00 | 180.00 |
| | | Maximum | 450.00 | 424.89 | 415.00 | 549.00 | 450.00 | 549.00 |



| | | | Cohort A Randomized Patients -- As Treated (AT) Population | | | | | |
|-----------|---------|------------|--|-----------------|-----------------------|-----------------|-------------------|-----------------|
| Parameter | Visit | Statistics | Transapical Approach | | Transfemoral Approach | | Pooled Approaches | |
| | | | AVR (N=92) | TAVR (N=104) | AVR (N=221) | TAVR (N=240) | AVR (N=313) | TAVR (N=344) |
| | 30 DAY | n | 65 | 79 | 143 | 179 | 208 | 258 |
| | | Mean | 113.33 | 113.42 | 100.97 | 156.22 | 104.83 | 143.11 |
| | | SD | 118.617 | 117.548 | 116.142 | 131.991 | 116.775 | 129.037 |
| | | Minimum | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | | Q1 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | | Median | 80.00 | 91.44 | 73.00 | 158.00 | 75.08 | 125.20 |
| | | Q3 | 201.00 | 180.00 | 180.00 | 245.20 | 190.00 | 240.00 |
| | | Maximum | 459.00 | 429.00 | 494.00 | 480.00 | 494.00 | 480.00 |
| | 6 MONTH | n | 51 | 65 | 113 | 169 | 164 | 234 |
| | | Mean | 195.16 | 154.36 | 181.12 | 178.11 | 185.49 | 171.52 |
| | | SD | 124.075 | 126.932 | 145.173 | 141.329 | 138.730 | 137.626 |
| | | Minimum | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | | Q1 | 110.00 | 35.05 | 54.80 | 0.00 | 70.05 | 0.00 |
| | | Median | 216.71 | 150.00 | 180.00 | 177.00 | 192.93 | 165.00 |
| | | Q3 | 270.00 | 236.22 | 296.57 | 285.00 | 286.91 | 278.00 |
| | | Maximum | 525.00 | 435.00 | 547.00 | 540.00 | 547.00 | 540.00 |
| | 1 YEAR | n | 48 | 64 | 115 | 153 | 163 | 217 |
| | | Mean | 165.42 | 154.61 | 168.90 | 166.05 | 167.88 | 162.68 |
| | | SD | 132.506 | 136.309 | 134.297 | 122.107 | 133.372 | 126.249 |
| | | Minimum | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | | Q1 | 36.58 | 6.81 | 0.00 | 90.00 | 0.00 | 70.07 |
| | | Median | 179.07 | 132.50 | 177.00 | 165.00 | 177.00 | 151.70 |
| | | Q3 | 275.31 | 250.00 | 280.00 | 247.00 | 280.00 | 247.00 |
| | | Maximum | 448.36 | 575.46 | 457.20 | 540.10 | 457.20 | 575.46 |

Missing for medical reasons was given a value of zero.

Source: Table 6.8

Table 48 provides the change in 6MWD from baseline at 1 Year. The mean improvement was 46.1 ± 128.6 meters in the TAVR arm, and 47.2 ± 129.7 meters in the AVR arm. The difference in change from baseline between TAVR and AVR was not significant ($p=0.9378$).



Table 48. Improvement in 6MWT (AT Population)

| Statistics | Baseline AVR | Baseline TAVR | 1 Year AVR | 1 Year TAVR | Change from Baseline AVR | Change from Baseline TAVR | P-Value for Change from Baseline between TAVR & AVR |
|------------|--------------|---------------|------------|-------------|--------------------------|---------------------------|---|
| N | 273 | 309 | 163 | 217 | 151 | 203 | 0.9378 |
| Mean | 107.6 | 108.5 | 167.9 | 162.7 | 47.2 | 46.1 | . |
| SD | 114 | 116.84 | 133.37 | 126.25 | 129.74 | 128.63 | . |
| Min | 0 | 0 | 0 | 0 | -270 | -421 | . |
| Median | 75 | 82 | 177 | 151.7 | 23 | 33 | . |
| Max | 450 | 549 | 457.2 | 575.5 | 349.9 | 358.8 | . |

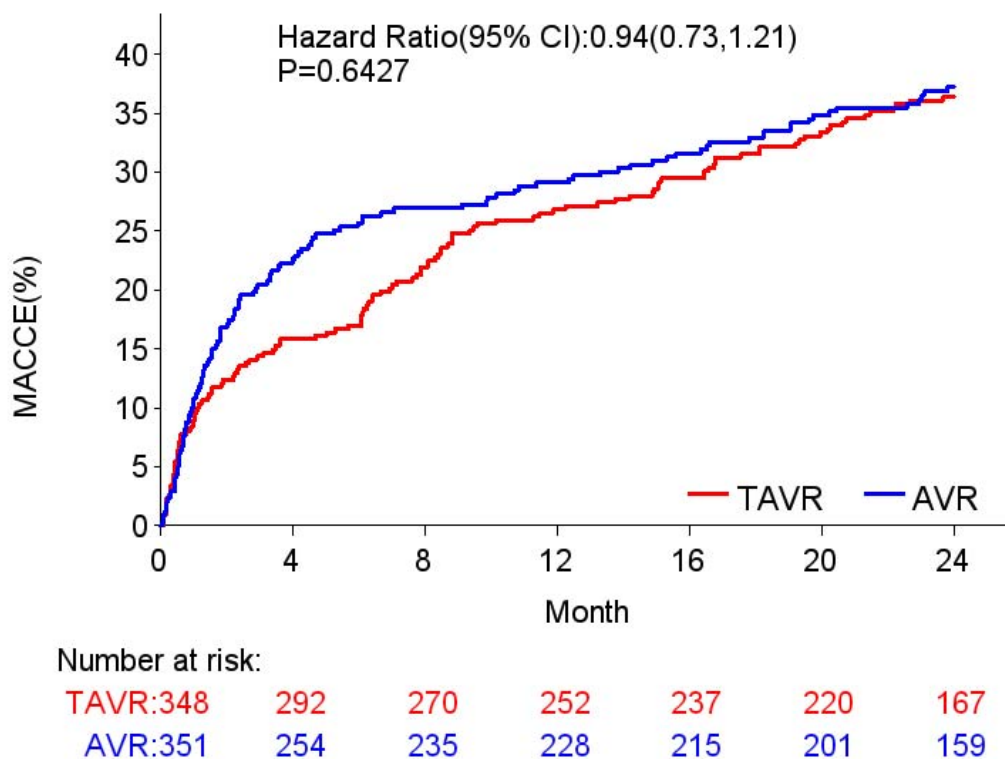
Missing for medical reasons is given a value of zero

10.4 Time from Randomization to First Occurrence of MACCE (Per Protocol Definitions)

In the TAVR arm, the KM rate from time from randomization to first occurrence of MACCE 9.9% at 30 days, 26.6% at 1 year and 37.1% at 2 years. In the AVR arm, the KM rate from time from randomization to first occurrence of MACCE 11.8% at 30 days, 27.4% at 1 year and 35.2% at 2 years. Figure 19 shows the KM rate of first occurrence of a MACCE event during the study.



Figure 19. First Occurrence of a MACCE (Per Protocol Definitions) during the Study – High Risk Cohort in the PARTNER Study (ITT Population)



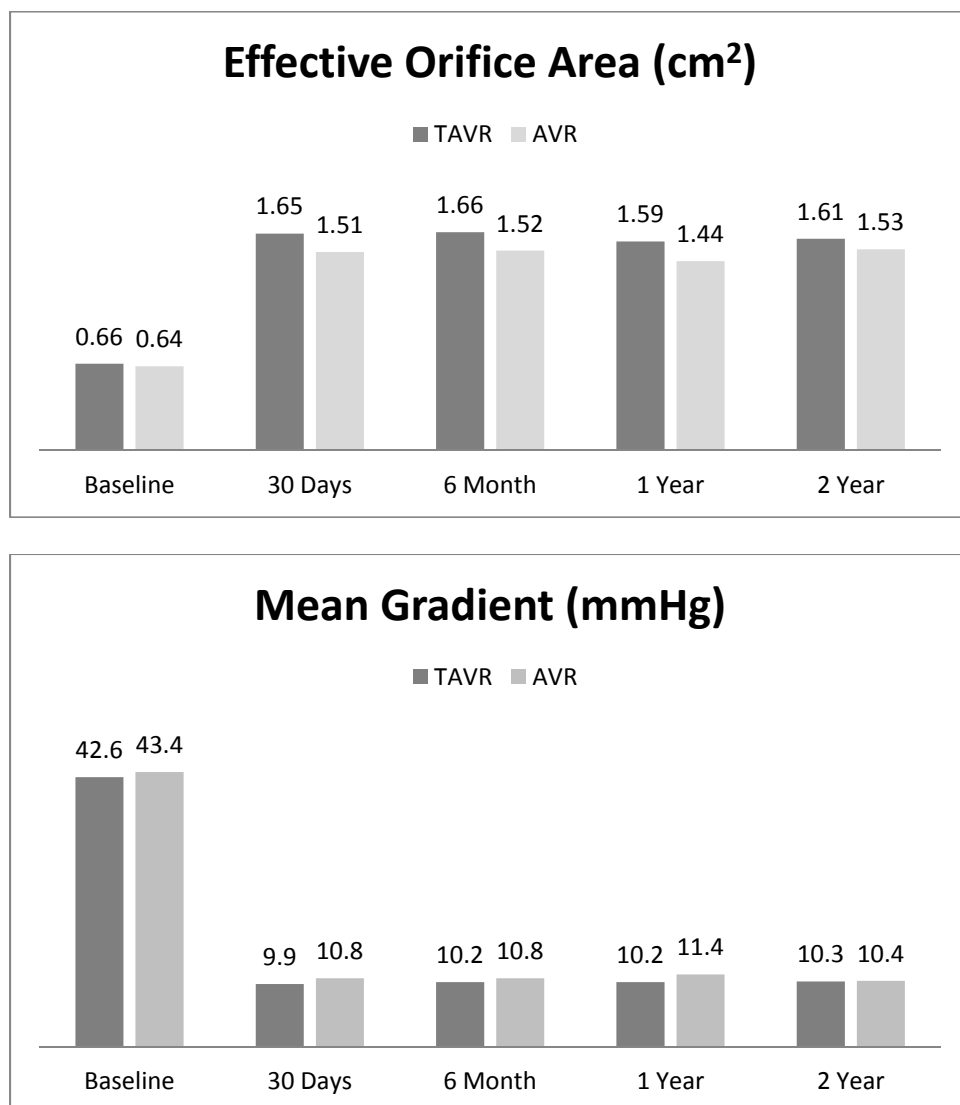
Hazard ratio at 2 years; p-value from log-rank test up to 24 months

10.5 Echocardiography Findings

Observed echocardiographic parameters over time are presented in Table 93 in **Appendix F**. Figure 20 illustrates the improvement in mean EOA and mean gradient over time for both trial arms.



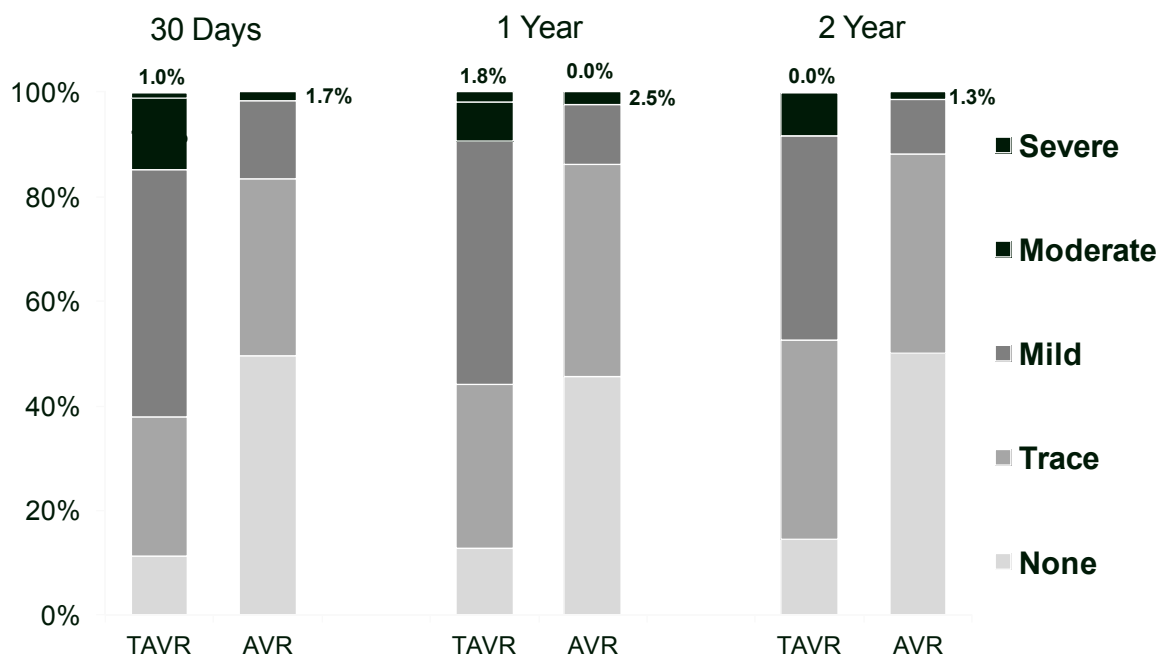
Figure 20. Effective Orifice Area and Mean Gradient Over Time– High Risk Cohort in the PARTNER Study (AT Population)



Total aortic regurgitation, which includes both central aortic regurgitation and paravalvular regurgitation, was assessed at 30 days, one year and two years (Figure 21). There is a significant difference between TAVR and AVR, such that more patients with TAVR have either moderate or severe aortic regurgitation. At one year and two years these numbers decreased somewhat, but still there is a meaningful difference between TAVR and AVR.



Figure 21. Total Aortic Regurgitation – High Risk Cohort in the PARTNER Study (AT Population)



A total of 205 TAVR patients had PV leak data at 30 days and 1 year (Table 49). In accordance with peer-reviewed publications, PV leak progression was defined as a worsening of ≥ 2 grades. At 1 year, PV leak improved in 28.1%; PV leak did not change in 50.4%; PV leak progressed in 1.6% and 19.9% of patients with PV leak died.

Table 49. PV Leak Changes: Results from the Core Laboratory – High Risk Cohort in the PARTNER Study (TAVR AT Population)

| | 1 Year | | | | | | |
|----------|--------|-------|------|----------|--------|------|-------|
| 30 Day | None | Trace | Mild | Moderate | Severe | Dead | Total |
| None | 36 | 10 | 4 | 0 | 0 | 9 | 59 |
| Trace | 20 | 17 | 13 | 0 | 0 | 11 | 61 |
| Mild | 12 | 24 | 40 | 5 | 0 | 23 | 104 |
| Moderate | 1 | 4 | 10 | 7 | 0 | 8 | 30 |
| Severe | 0 | 0 | 0 | 1 | 1 | 1 | 3 |
| Total | 69 | 55 | 67 | 13 | 1 | 52 | 257 |



All cause mortality was stratified by PV leak, respectively all cause mortality stratified none-trace vs. mild-severe PV leak (Figure 22) and all cause mortality stratified by none-trace vs. mild vs. moderate-severe PV leak (Figure 23). Finally, mortality in patients with none-trace total aortic regurgitation is presented in Figure 24. The potential for one year mortality of less than 15% in this population is encouraging and points to further potential of this procedure in high risk patients. Based upon this observation, continued efforts and focus on minimizing post-procedural aortic regurgitation are warranted.

Figure 22. All Cause Mortality Stratified by First PV Leak - TAVR: None-Trace vs. Mild-Severe (AT Population)

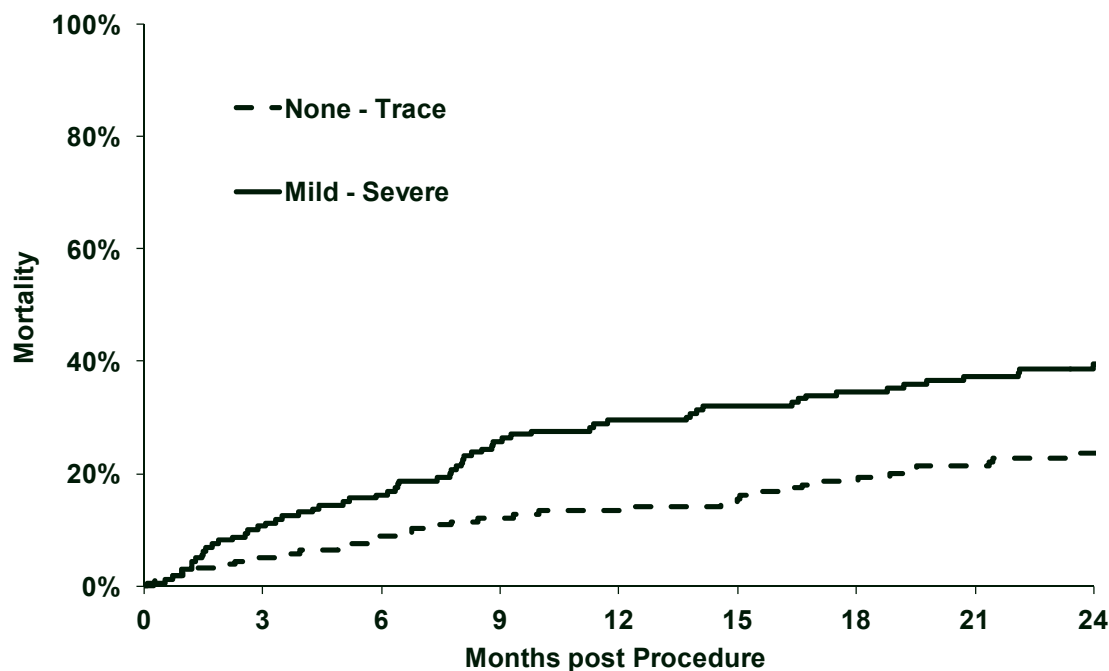




Figure 23. Mortality by First PV Leak - TAVR: None-Trace vs. Mild vs. Moderate-Severe (AT Population)

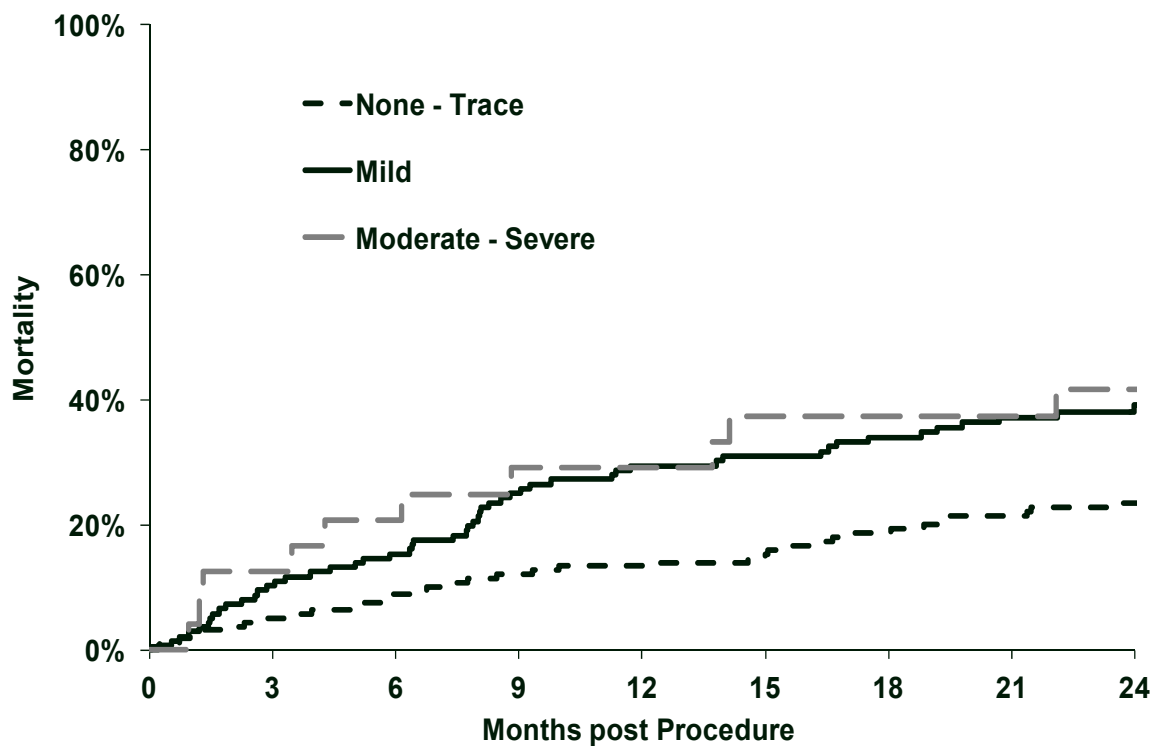
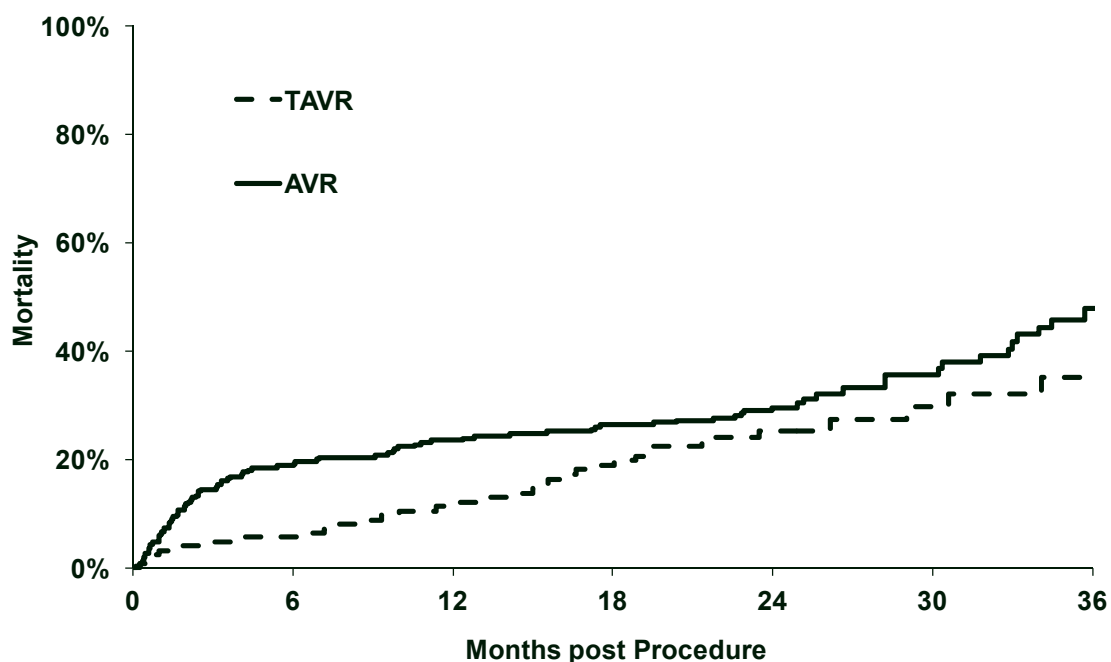




Figure 24. Mortality in Patient with None-Trace Total Aortic Regurgitation High Risk Cohort in the PARTNER Study (AT Population)



Statistically significant differences were observed for EOA index, and EOA at discharge, 30 days, 6 month and 1 year, for mean gradient at discharge, 30 day and 1 year, and for peak gradient at discharge and 1 year in favor of the TAVR (Table 50).



Table 50. Comparison of Echocardiogram Results from Core Laboratory – High Risk Cohort in the PARTNER Study (AT Population)

| Echo Parameter | Visit | AVR (N=313) | TAVR (N=344) | P-value ^a |
|--|-----------|----------------|-----------------|----------------------|
| Cardiac Index (L/min/m ²) | BASELINE | 179,2.3(0.8) | 185,2.2(0.7) | 0.4807 |
| | 30 DAY | 96,2.3(0.7) | 122,2.3(0.7) | 0.8071 |
| | 6 MONTH | 80,2.2(0.6) | 109,2.3(0.7) | 0.4805 |
| | 1 YEAR | 77,2.2(0.8) | 101,2.2(0.6) | 0.8616 |
| | 2 YEAR | 41,2.2(0.6) | 43,2.1(0.6) | 0.2788 |
| | DISCHARGE | 102,2.3(0.6) | 131,2.6(0.8) | 0.0006 |
| AV Area Index (cm ² /m ²) | BASELINE | 293,0.4(0.1) | 317,0.4(0.1) | 0.3207 |
| | 30 DAY | 205,0.8(0.2) | 268,0.9(0.3) | 0.0016 |
| | 6 MONTH | 160,0.8(0.3) | 229,0.9(0.3) | 0.0095 |
| | 1 YEAR | 144,0.8(0.2) | 212,0.9(0.3) | 0.0032 |
| | 2 YEAR | 71,0.8(0.3) | 89,0.9(0.3) | 0.0631 |
| | DISCHARGE | 212,0.8(0.3) | 253,0.9(0.3) | 0.0009 |
| AV Area (EOA) (cm ²) | BASELINE | 295,0.6(0.2) | 318,0.7(0.2) | 0.2754 |
| | 30 DAY | 228,1.5(0.4) | 278,1.6(0.5) | 0.0017 |
| | 6 MONTH | 166,1.5(0.5) | 235,1.7(0.5) | 0.0116 |
| | 1 YEAR | 153,1.4(0.5) | 220,1.6(0.5) | 0.0027 |
| | 2 YEAR | 75,1.5(0.5) | 91,1.6(0.4) | 0.2592 |
| | DISCHARGE | 240,1.5(0.5) | 289,1.6(0.5) | 0.0004 |
| AV Mean Gradient (mmHg) | BASELINE | 300,43.4(14.3) | 326,42.6(14.5) | 0.4865 |
| | 30 DAY | 232,10.8(5.0) | 286,9.9(4.8) | 0.0422 |
| | 6 MONTH | 171,10.8(4.8) | 246,10.2(4.3) | 0.1829 |
| | 1 YEAR | 157,11.4(5.3) | 228,10.2(4.3) | 0.0131 |
| | 2 YEAR | 75,10.4(4.7) | 96,10.3(5.5) | 0.9193 |
| | DISCHARGE | 257,11.9(5.4) | 303,10.9(4.6) | 0.0107 |
| AV Peak Gradient (mmHg) | BASELINE | 300,73.2(24.2) | 326,70.8(23.5) | 0.2022 |
| | 30 DAY | 232,20.6(8.9) | 286,19.5(9.0) | 0.1574 |
| | 6 MONTH | 171,20.3(8.6) | 246,19.7(8.1) | 0.4208 |
| | 1 YEAR | 157,21.3(9.4) | 228,19.4(7.9) | 0.0321 |
| | 2 YEAR | 75,19.1(8.5) | 96,19.2(9.5) | 0.9338 |
| | DISCHARGE | 257,23.4(10.2) | 303,20.9(8.5) | 0.0018 |

a. From t-test for continuous variables.

AV=aortic valve

Data presented as n, mean (SD).

Source: Table 6.5a



Figure 25 presents the mean ejection fraction at baseline stratified in different subgroups, including patients that had preserved LV function greater than 50%; patients with slight reduction, 40 to 49%; and more severe degrees of reduction, 30 to 39%, and 20 to 20%. Data show no difference in baseline left ventricular function for both groups.

Figure 25. Mean Ejection Fraction (EF) at Baseline – High Risk Cohort in the PARTNER Study (AT Population)

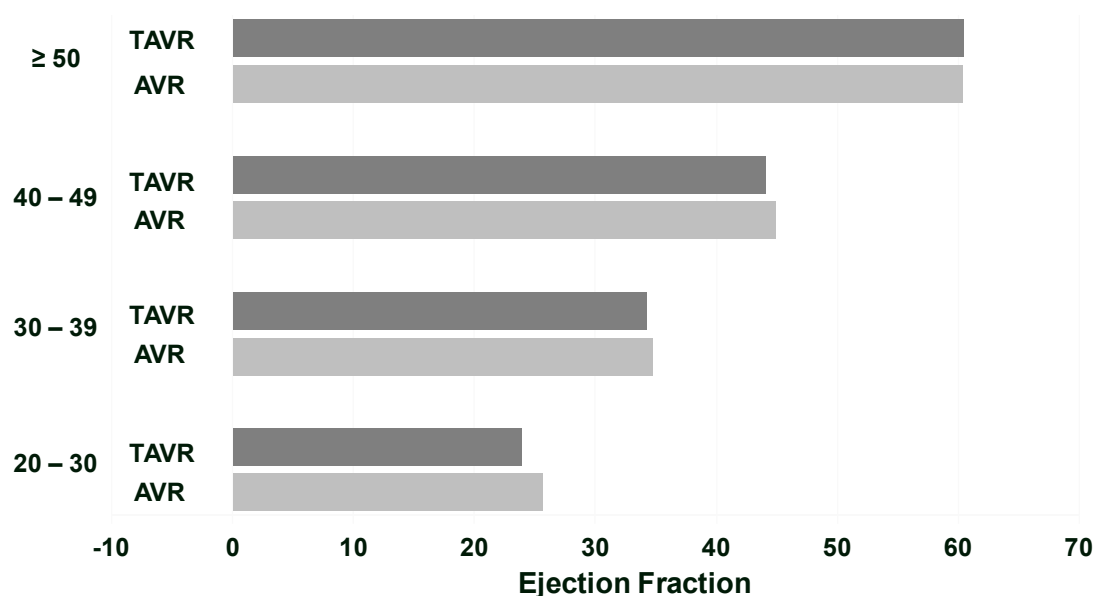
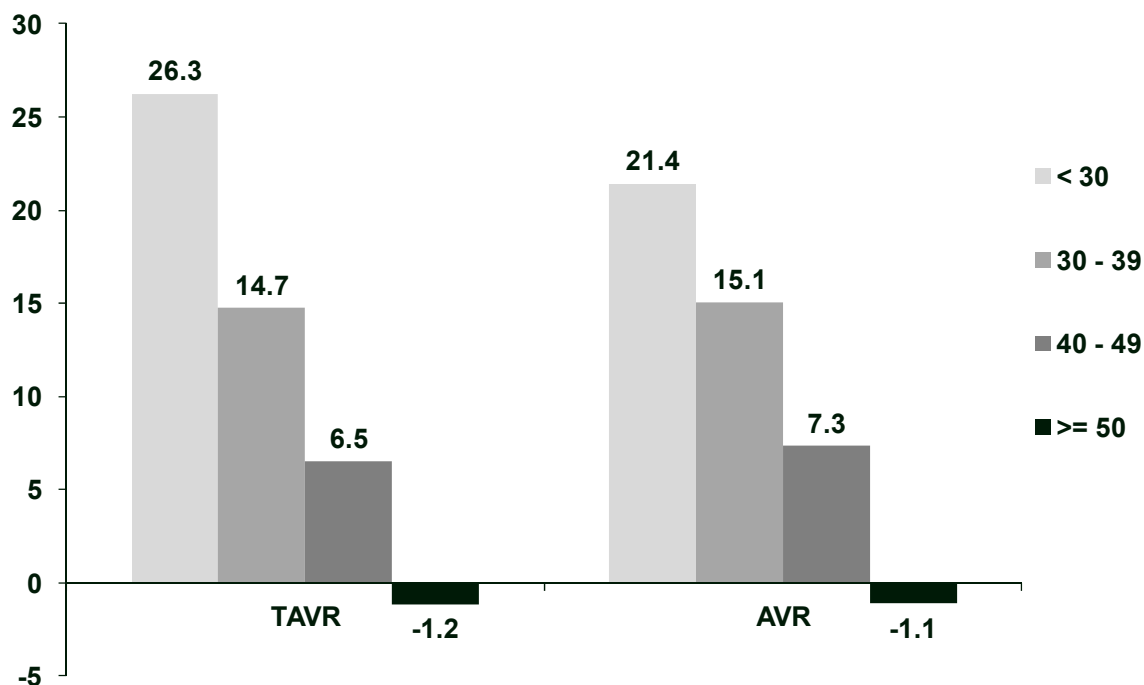


Figure 26 presents the mean change in EF at 1 year stratified by baseline EF. In patients with reduced LV function, there is an improvement or an increase in the ejection fraction at 1 year for both treatment arms that actually increases the more baseline EF is depressed. Patients who started with a baseline ejection fraction of 20 to 30% by the end of the year had similar LV function as those patients who started with normal ejection fraction. This observation involves the reversibility of left ventricular function, and myocardial contractile reserve in many of these patients with aortic stenosis, which is equally benefited by AVR and TAVR patients.



Figure 26. Mean Change in EF at 1 Year Stratified by Baseline EF – High Risk Cohort in the PARTNER Study (AT Population)



10.6 Quality of Life

The quality of life analysis was performed by academic investigators at the Harvard Clinical Research Institute (Boston, MA) and the Health Economics and Technology Assessment Group at Saint Luke's Mid America Heart Institute (Kansas City, MO). Disease-specific health status was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ).^d The KCCQ consists of 23 questions addressing 5 health domains from the patient's perspective pertaining to heart failure: symptoms, physical limitation, social limitation, self-efficacy, and quality of life. These individual scales are combined into an overall summary

^d Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol* 2000;35:1245-55.



scale, with values ranging from 0-100; higher scores indicate lesser symptoms and better quality of life (QoL). The KCCQ has undergone extensive validation and has been shown to independently predict mortality and health care costs in heart failure populations.^{e,f} Among outpatients with heart failure, small, moderate, or large clinical improvements as rated by treating physicians corresponded with changes in the KCCQ summary score of approximately 5, 10, and 20 points, respectively.^g

Generic health status was evaluated using the Medical Outcomes Study Short-Form 12 (SF-12) Health Survey.^h The SF-12 was derived from the original SF-36 health survey by selecting those items having the greatest explanatory power. The physical and mental summary scores for the SF-12 have been shown to correlate highly with the same summary scales from the SF-36; they are scaled to overall population norms of 50 and standard deviations of 10; higher scores are better. Multiple groups have agreed that minimal clinically important changes in the mental and physical summary scores are roughly 2-2.5 points.^{i,j} EQ-5DTM is a generic instrument for assessment of utilities and quality-adjusted life years. The scores range from 0 to 1 (0=death; 1= perfect health). Assessments were performed by self-administered questionnaires at baseline, 1, 6 and 12 months.

^e Soto GE, Jones P, Weintraub WS, Krumholz HM, Spertus JA. Prognostic value of health status in patients with heart failure after acute myocardial infarction. *Circulation* 2004;110:546-51.

^f Chan PS, Soto G, Jones PG, et al. Patient health status and costs in heart failure: insights from the eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS). *Circulation* 2009;119:398-407.

^g Spertus J, Peterson E, Conard MW, et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. *Am Heart J* 2005;150:707-15.

^h Ware J, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220-33.

ⁱ Wyrwich KW, Spertus JA, Kroenke K, Tierney WM, Babu AN, Wolinsky FD. Clinically important differences in health status for patients with heart disease: an expert consensus panel report. *Am Heart J* 2004;147:615-22.

^j Ware J, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. Determining important differences in scores. In: *User's Manual for the SF-36v2 Health Survey*. Lincoln, RI: QualityMetric Incorporated; 2007.



At baseline, mean KCCQ summary scores were markedly depressed (39.6 ± 21.8 and 44.5 ± 21.8 in the TAVR and AVR groups, respectively). Significant, statistical changes were noted at almost every time point for each treatment group, except for the SF-12 mental score and EQ-5D utilities at 1 month in the AVR group (Table 51). The differences between treatment groups according to mixed effects models by treatment approach are presented in Table 52. Several significant, statistical differences were noted at the 1 month visit only in favor of TAVR.

Table 51. Quality of Life – Within Grouped Comparison from Paired t-test - High Risk Cohort in the PARTNER Study

| Scale/Timepoint | TAVR Group | | | AVR Group | | |
|---------------------------|------------|----------------------------|----------------------|-----------|----------------------------|----------------------|
| | N | Paired Difference (95% CI) | P-value ^a | N | Paired Difference (95% CI) | P-value ^a |
| KCCQ Summary | | | | | | |
| 1 month | 274 | 20.5 (17.4, 23.7) | <.0001 | 218 | 12.2 (8.3, 16.0) | <.0001 |
| 6 months | 254 | 28.1 (24.6, 31.7) | <.0001 | 195 | 27.1 (23.4, 30.7) | <.0001 |
| 12 months | 231 | 29.0 (25.4, 32.6) | <.0001 | 195 | 25.2 (21.0, 29.4) | <.0001 |
| KCCQ Physical Limitations | | | | | | |
| 1 month | 238 | 11.8 (7.7, 15.9) | <.0001 | 183 | 2.7 (-2.2, 7.7) | 0.2722 |
| 6 months | 224 | 19.3 (15.3, 23.4) | <.0001 | 179 | 19.4 (14.8, 24.0) | <.0001 |
| 12 months | 205 | 17.9 (13.5, 22.4) | <.0001 | 171 | 13.6 (8.9, 18.2) | <.0001 |
| KCCQ Total Symptoms | | | | | | |
| 1 month | 273 | 18.3 (15.0, 21.6) | <.0001 | 217 | 12.6 (8.6, 16.6) | <.0001 |
| 6 months | 252 | 22.5 (19.0, 26.0) | <.0001 | 194 | 24.7 (21.2, 28.1) | <.0001 |
| 12 months | 228 | 24.3 (20.7, 27.9) | <.0001 | 192 | 21.9 (17.7, 26.1) | <.0001 |
| KCCQ Self-Efficacy | | | | | | |
| 1 month | 273 | 5.4 (2.3, 8.4) | 0.0005 | 217 | 4.6 (1.1, 8.0) | 0.0091 |
| 6 months | 252 | 7.0 (4.0, 10.0) | <.0001 | 192 | 6.6 (2.8, 10.3) | 0.0007 |
| 12 months | 231 | 5.9 (2.6, 9.2) | 0.0005 | 192 | 4.7 (0.8, 8.6) | 0.0186 |
| KCCQ Quality of Life | | | | | | |
| 1 month | 273 | 28.8 (25.0, 32.6) | <.0001 | 215 | 19.5 (15.0, 24.0) | <.0001 |
| 6 months | 252 | 36.5 (32.5, 40.5) | <.0001 | 193 | 34.3 (30.0, 38.6) | <.0001 |
| 12 months | 230 | 39.1 (35.1, 43.2) | <.0001 | 188 | 34.9 (30.1, 39.6) | <.0001 |
| KCCQ Social Limitation | | | | | | |
| 1 month | 220 | 19.8 (14.9, 24.6) | <.0001 | 161 | 9.4 (3.5, 15.2) | 0.0019 |
| 6 months | 207 | 30.5 (25.2, 35.9) | <.0001 | 163 | 28.4 (23.2, 33.6) | <.0001 |
| 12 months | 190 | 33.6 (28.2, 39.0) | <.0001 | 150 | 28.2 (21.7, 34.7) | <.0001 |
| SF-12 Physical | | | | | | |
| 1 month | 260 | 4.3 (3.1, 5.5) | <.0001 | 210 | 2.0 (0.5, 3.4) | 0.0100 |
| 6 months | 242 | 6.2 (4.8, 7.6) | <.0001 | 191 | 7.1 (5.5, 8.7) | <.0001 |
| 12 months | 221 | 6.6 (5.1, 8.1) | <.0001 | 185 | 5.6 (4.0, 7.3) | <.0001 |
| SF-12 Mental | | | | | | |
| 1 month | 260 | 2.8 (1.3, 4.3) | 0.0004 | 210 | 0.3 (-1.6, 2.2) | 0.7495 |
| 6 months | 242 | 4.6 (3.0, 6.2) | <.0001 | 191 | 3.9 (2.1, 5.7) | <.0001 |



| | | | | | | |
|------------------------|-----|-----------------------------|--------|-----|-----------------------------|--------|
| 12 months | 221 | 4.6 (2.9, 6.3) | <.0001 | 185 | 4.4 (2.6, 6.3) | <.0001 |
| EQ-5D Utilities | | | | | | |
| 1 month | 266 | 0.0483 (0.0198, 0.0769) | 0.0010 | 212 | 0.0141 (-0.0180, 0.0462) | 0.3882 |
| 6 months | 242 | 0.0834 (0.0533, 0.1135) | <.0001 | 188 | 0.0794 (0.0456, 0.1133) | <.0001 |
| 12 months | 221 | 0.0806 (0.0500, 0.1113) | <.0001 | 183 | 0.0718 (0.0374, 0.1061) | 0.0001 |

KCCQ=Kansas City Cardiomyopathy Questionnaire, SF-12=Short Form-12.

a. From paired t-test.

Minimum clinically important differences were as follows: KCCQ Summary - 6 points; SF-12 Physical - 2 points; SF-12 Mental - 2 points; EQ-5D utilities - undefined.

Source: Original CSR Table 93.

Table 52. Quality of Life – Differences between Treatment Groups in QoL Measures over Time According to Longitudinal Mixed Effects Models – High Risk Cohort in the PARTNER Study

| Scale/Timepoint | Predicted Mean Values (95% CI) | | Predicted Mean Difference (TAVR-AVR), 95% CI | P-value ^a |
|---------------------------|--------------------------------|--------------------|--|----------------------|
| | TAVR | AVR | | |
| KCCQ Summary | | | | |
| 1 month | 58.6 (54.8, 62.5) | 53.2 (48.9, 57.4) | 5.5 (1.2, 9.8) | 0.0126 |
| 6 months | 65.9 (62.1, 69.7) | 68.5 (64.3, 72.6) | -2.6 (-6.7, 1.6) | 0.2230 |
| 12 months | 65.7 (61.8, 69.6) | 66.2 (62.0, 70.4) | -0.5 (-4.8, 3.8) | 0.8186 |
| KCCQ Physical Limitations | | | | |
| 1 month | 52.4 (47.5, 57.2) | 46.0 (40.7, 51.3) | 6.4 (0.8, 11.9) | 0.0239 |
| 6 months | 59.7 (55.1, 64.2) | 62.7 (57.7, 67.6) | -3.0 (-8.0, 2.0) | 0.2345 |
| 12 months | 56.8 (52.1, 61.6) | 56.4 (51.3, 61.5) | 0.4 (-4.8, 5.6) | 0.8801 |
| KCCQ Total Symptoms | | | | |
| 1 month | 64.9 (61.3, 68.5) | 61.5 (57.6, 65.5) | 3.4 (-0.7, 7.4) | 0.1056 |
| 6 months | 68.8 (65.3, 72.3) | 73.9 (70.1, 77.8) | -5.2 (-9.1, -1.3) | 0.0093 |
| 12 months | 69.6 (66.0, 73.2) | 70.9 (67.0, 74.8) | -1.3 (-5.3, 2.7) | 0.5291 |
| KCCQ Self-Efficacy | | | | |
| 1 month | 82.1 (79.1, 85.1) | 80.9 (77.6, 84.2) | 1.2 (-2.4, 4.7) | 0.5183 |
| 6 months | 84.4 (81.4, 87.3) | 83.5 (80.2, 86.7) | 0.9 (-2.5, 4.3) | 0.6058 |
| 12 months | 83.7 (80.6, 86.8) | 82.4 (79.1, 85.8) | 1.2 (-2.4, 4.9) | 0.5049 |
| KCCQ Quality of Life | | | | |
| 1 month | 62.1 (57.8, 66.5) | 56.4 (51.6, 61.2) | 5.7 (0.8, 10.7) | 0.0231 |
| 6 months | 69.8 (65.6, 73.9) | 72.0 (67.4, 76.6) | -2.2 (-6.8, 2.4) | 0.3475 |
| 12 months | 71.5 (67.2, 75.8) | 71.4 (66.7, 76.1) | 0.1 (-4.7, 5.0) | 0.9575 |
| KCCQ Social Limitation | | | | |
| 1 month | 51.3 (45.8, 56.9) | 45.3 (39.1, 51.5) | 6.1 (-0.4, 12.5) | 0.0678 |
| 6 months | 62.8 (57.4, 68.2) | 66.0 (60.1, 71.9) | -3.3 (-9.3, 2.8) | 0.2915 |
| 12 months | 65.0 (59.4, 70.7) | 65.4 (59.2, 71.5) | -0.4 (-6.8, 6.1) | 0.9153 |
| SF-12 Physical | | | | |
| 1 month | 33.6 (32.1, 35.1) | 32.1 (30.4, 33.7) | 1.5 (-0.1, 3.1) | 0.0682 |
| 6 months | 35.5 (34.0, 37.1) | 37.2 (35.4, 38.9) | -1.6 (-3.4, 0.2) | 0.0776 |
| 12 months | 35.4 (33.7, 37.1) | 35.6 (33.8, 37.4) | -0.2 (-2.2, 1.8) | 0.8732 |



| | | | | |
|------------------------|-----------------------------|-----------------------------|------------------------------|--------|
| SF-12 Mental | | | | |
| 1 month | 49.6 (48.0, 51.3) | 47.1 (45.2, 48.9) | 2.6 (0.6, 4.5) | 0.0098 |
| 6 months | 51.0 (49.3, 52.6) | 50.8 (49.0, 52.6) | 0.1 (-1.7, 2.0) | 0.8836 |
| 12 months | 51.4 (49.7, 53.0) | 51.7 (50.0, 53.5) | -0.4 (-2.3, 1.5) | 0.6860 |
| EQ-5D Utilities | | | | |
| 1 month | 0.7036 (0.6688, 0.7385) | 0.6754 (0.6372, 0.7135) | 0.0283 (-0.0103, 0.0668) | 0.1503 |
| 6 months | 0.7359 (0.7034, 0.7684) | 0.7458 (0.7099, 0.7817) | -0.0099 (-0.0442, 0.0244) | 0.5701 |
| 12 months | 0.7264 (0.6912, 0.7616) | 0.7210 (0.6828, 0.7592) | 0.0054 (-0.0336, 0.0443) | 0.7865 |

a. From longitudinal mixed effects models.

Minimum clinically important differences were as follows: KCCQ Summary - 6 points; SF-12 Physical - 2 points; SF-12 Mental - 2 points; EQ-5D utilities - undefined.

10.7 Mixed Model Analyses

In order to account for values at different time points, mixed model, using repeated measures, analyses were performed to assess functional improvement from baseline as measured by NYHA functional classification, EOA, and 6-minute walk test at 30 days, 6 months, 1 year and 2 years (Table 53).



Table 53. Summary of Mixed Model Analyses of Prespecified Exploratory Analyses: NYHA, EOA, and 6MWT – High Risk Cohort in the PARTNER Study (ITT Population)

| | No of Patients ^a | LS Mean (95% CI) | | Treatment Difference | |
|--|-----------------------------|-----------------------|-----------------------|-------------------------------------|----------------------|
| Visit | | TAVR | AVR | Point Estimate and two-sided 90% CI | p-value ^b |
| NYHA Classification Value ^c | | | | | |
| 30 days | 323,293 | 2.19(2.04,2.35) | 2.53(2.37,2.70) | -0.34(-0.53,-0.15) | <.0001 |
| 6 months | 334,298 | 2.32(2.16,2.47) | 2.54(2.37,2.70) | -0.22(-0.41,-0.03) | <.0001 |
| 1 year | 333,314 | 2.51(2.35,2.67) | 2.61(2.45,2.78) | -0.10(-0.29,0.09) | 0.0022 |
| 2 years | 316,298 | 2.89(2.73,3.05) | 2.92(2.76,3.09) | -0.03(-0.22,0.16) | 0.0152 |
| EOA (cm ²) | | | | | |
| 30 days | 263,214 | 1.65(1.44,1.86) | 1.50(1.27,1.74) | 0.14(-0.17,0.46) | 0.3727 |
| 6 months | 221,161 | 1.66(1.43,1.89) | 1.52(1.25,1.79) | 0.14(-0.21,0.49) | 0.4334 |
| 1 year | 210,150 | 1.61(1.38,1.85) | 1.42(1.14,1.69) | 0.20(-0.17,0.56) | 0.2938 |
| 2 years | 90,74 | 1.66(1.30,2.02) | 1.54(1.15,1.94) | 0.12(-0.42,0.65) | 0.6672 |
| 6-Minute Walk Test ^d | | | | | |
| 30 days | 248,192 | 144.29(130.42,158.16) | 108.00(92.36,123.64) | 36.29(18.76,53.83) | 0.0016 |
| 6 months | 220,153 | 163.95(149.44,178.46) | 173.26(156.20,190.31) | -9.30(-28.09,9.48) | <.0001 |
| 1 year | 203,154 | 149.30(134.38,164.22) | 153.89(136.88,170.91) | -4.60(-23.58,14.39) | <.0001 |

EOA=effective orifice area, NYHA=New York Heart Association.

a. Number of patients in the TAVR group, number of patients in the AVR group.

b. Probability for non-inferiority test.

c. NYHA: Death was treated as NYHA=5 in the analysis; for a non-inferiority test, the non-inferiority margin of 0.25 was pre-specified.

d. For a non-inferiority test, the non-inferiority margin of 70 meters was pre-specified.

Source: Tables 9.1 - 9.3

10.8 Responder Analyses

Since the post-procedural changes in EOA and 6-minute walk test between visits are correlated, a generalized estimation equation (GEE) analyses were performed to compare the differences in these outcomes among different visit intervals.

Table 54 shows the results of an EOA responder analysis in which responders were defined as those who had a greater than 50% improvement in EOA from baseline. The likelihood



(odds ratio [OR]) of such improvement was 1.10 (p=0.0291), 1.21 (p=0.0020), and 1.23 (p=0.0035)-fold higher among TAVR vs. AVR patients at the 1 month, 6 month, and 1 year visits, respectively (Table 54). The OR was slightly greater at each visit in a responder analysis in which improvement was defined as an EOA increase of 100% or reaching an EOA of $> 1.5 \text{ cm}^2$ (data not shown).

Table 54. Responder Analysis Based on Improvement in Effective Orifice Area – High Risk Cohort in the PARTNER Study (ITT Population)

| | Descriptive Analysis | | | | | |
|----------|----------------------|--|-----|--|---------------------------------|----------------------|
| | TAVR | | AVR | | GEE Model Analysis ^a | |
| Visit | n | n (%) Patients with Improvement ^b | n | n (%) Patients with Improvement ^b | Odds Ratio (95% CI) | P-value ^c |
| 30 days | 279 | 237 (85%) | 241 | 188 (78%) | 1.10(1.01,1.20) | 0.0291 |
| 6 months | 271 | 197 (73%) | 236 | 139 (59%) | 1.21(1.07,1.36) | 0.0020 |
| 1 year | 293 | 190 (65%) | 238 | 120 (50%) | 1.23(1.07,1.41) | 0.0035 |

EOA=effective orifice area, GEE=generalized estimation equation.

a. GEE model included treatment, visit, interaction between treatment and visit as fixed effects, and patient as random effect.

b. For the EOA improvement analysis, improved meant an increase of 50% or greater from the baseline value.

c. From Wald chi-square p-values from GEE model with "type=exch."

Note: A patient with a missing follow-up value due to death was considered to not have improved. Missing values for other reasons were considered neither improved nor not improved.

Table 55 shows the results of a 6-minute walk test responder analysis in which responders were defined as those who had an increase of ≥ 70 meters from the baseline value. The likelihood (OR) of such improvement was 2.25 (p=0.0002), 1.18 (p=0.2837), and 1.16 (p=0.3178)-fold higher among TAVR vs. AVR patients at the 1 month, 6 month, and 1 year visits, respectively. However, only 1 out of 4 TAVR patients were responders based on this definition.



Table 55. Responder Analysis Based on Improvement in 6-Minute Walk Test – High Risk Cohort in the PARTNER Study (ITT Population)

| | Descriptive Analysis | | | | | |
|----------|----------------------|--|-----|--|---------------------------------|----------------------|
| | TAVR | | AVR | | GEE Model Analysis ^a | |
| Visit | n | n (%) Patients with Improvement ^b | n | n (%) Patients with Improvement ^b | Odds Ratio (95% CI) | P-value ^c |
| 30 days | 264 | 67 (25%) | 219 | 25 (11%) | 2.25(1.46,3.44) | 0.0002 |
| 6 months | 270 | 72 (27%) | 228 | 49 (21%) | 1.18(0.87,1.60) | 0.2837 |
| 1 year | 286 | 76 (27%) | 242 | 55 (23%) | 1.16(0.86,1.57) | 0.3178 |

GEE=generalized estimation equation.

- a. GEE model included treatment, visit, interaction between treatment and visit as fixed effects, and patient as random effect.
- b. For the 6-minute walk test analysis, improvement analysis, improved meant an increase of ≥ 70 meters from the baseline value. If the patient was unable to perform the walk test for a medical reason the value 0 meters was used for the analysis.
- c. From Wald chi-square p-values from GEE model with "type=exch."

Note: A patient with a missing follow-up value due to death was considered not to have improved. Missing values for other reasons were considered neither improved nor not improved.



10.9 Descriptive Analyses Stratified by Implant Approach

10.9.1 All Cause Mortality Stratified by Implant Approach – ITT Population

The effect of the TAVR approach was assessed (Figure 27). The point estimates are below the non-inferiority margin of 7.5.

Figure 27 All Cause Mortality at 1 Year by Surgical Approach - High Risk Cohort in the PARTNER Randomized Study (ITT Population)

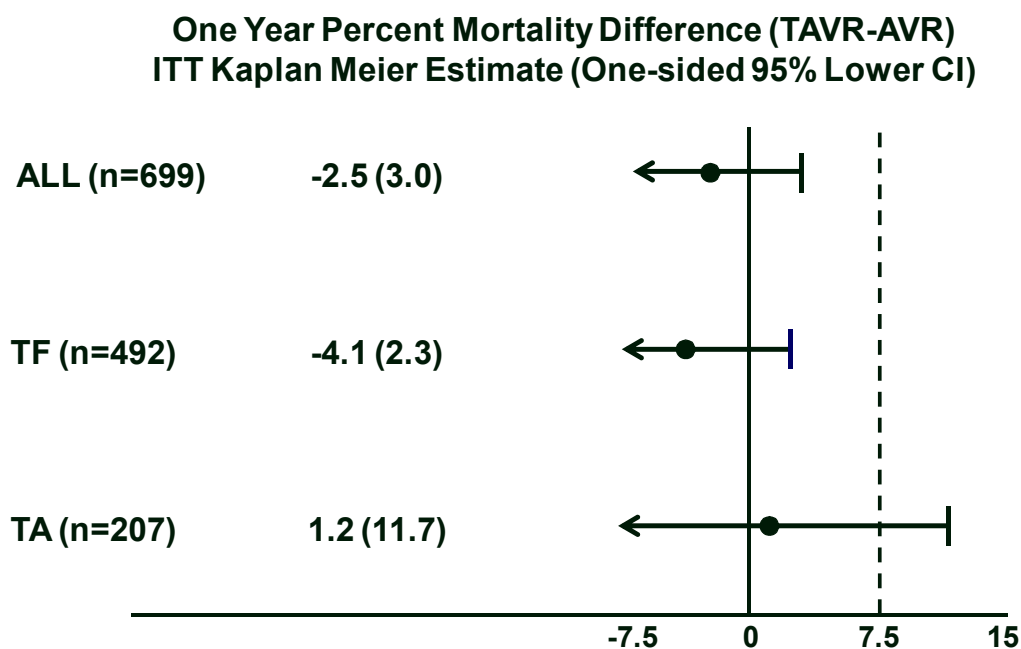


Table 56 presents the all cause mortality analysis for the transfemoral ITT population. The survival difference (TAVR-AVR) was -4.12%, and the 95% one-sided upper CL for the difference was 2.34%. The p-value was 0.0015 indicating that all cause mortality in the TAVR arm was not inferior to all cause mortality in the AVR arm at 1 year using the transfemoral approach.



Table 56. All Cause Mortality: Transfemoral Approach – High Risk Cohort in the PARTNER Study (ITT Population)

| Transfemoral Approach: ITT: Actual Data Analysis | | |
|--|--------|--------|
| | AVR | TAVR |
| # patients died (imputed for sensitivity analysis) | 62 | 54 |
| # patients censored prior to 1 year (imputed for sensitivity analysis) | 18 | 3 |
| # patients known alive at 1 year (imputed for sensitivity analysis) | 168 | 187 |
| # Mortality at 1 year | 26.36% | 22.24% |
| # Standard error at 1 year | 2.88% | 2.67% |
| # Mortality difference (TAVR - AVR) | -4.12% | |
| # Standard error of difference | 3.93% | |
| # 95% 1-sided upper CL for difference | 2.34% | |
| # Z-score for primary endpoint test | 2.9595 | |
| # p-value for primary endpoint test | 0.0015 | |

Source: Table 7.1

As shown in Table 57, several sensitivity analyses involving all cause mortality for the transfemoral ITT population were performed and all analyses showed non-inferiority.



Table 57. All Cause Mortality Sensitivity Analyses: Transfemoral Approach - High Risk Cohort of the PARTNER Trial (ITT Population)

| | Sensitivity Analysis ITT A: Assume AVR censored alive at 1 year and TAVR censored dead at 1 year | | Sensitivity Analysis ITT B: Assume AVR who elected no procedure alive at 1 year | | Sensitivity Analysis ITT C: Assume AVR who withdrew or who elected no procedure alive at 1 year | |
|--|---|--------|--|--------|--|--------|
| | AVR | TAVR | AVR | TAVR | AVR | TAVR |
| # patients died (imputed for sensitivity analysis) | 62 | 57 | 60 | 54 | 60 | 57 |
| # patients censored prior to 1 year (imputed for sensitivity analysis) | 0 | 0 | 5 | 3 | 0 | 0 |
| # patients known alive at 1 year (imputed for sensitivity analysis) | 186 | 187 | 183 | 187 | 188 | 187 |
| # Mortality at 1 year | 25.00% | 23.36% | 24.43% | 22.24% | 24.19% | 23.36% |
| # Standard error at 1 year | 2.75% | 2.71% | 2.74% | 2.67% | 2.72% | 2.71% |
| # Mortality difference (TAVR - AVR) | -1.64% | | -2.19% | | -0.83% | |
| # Standard error of difference | 3.86% | | 3.83% | | 3.84% | |
| # 95% 1-sided upper CL for difference | 4.71% | | 4.11% | | 5.48% | |
| # Z-score for primary endpoint test | 2.3678 | | 2.5301 | | 2.1710 | |
| # p-value for primary endpoint test | 0.0089 | | 0.0057 | | 0.0150 | |

Source: Table 7.1



Table 58 presents the all cause mortality analysis for the transapical ITT population. The survival difference (TAVR-AVR) was 1.18%, and the 95% one-sided lower CL for the difference was 11.69% ($p=0.1614$), therefore, non-inferiority was not met.

Table 58. All Cause Mortality: Transapical Approach – High Risk Cohort in the PARTNER Study (ITT Population)

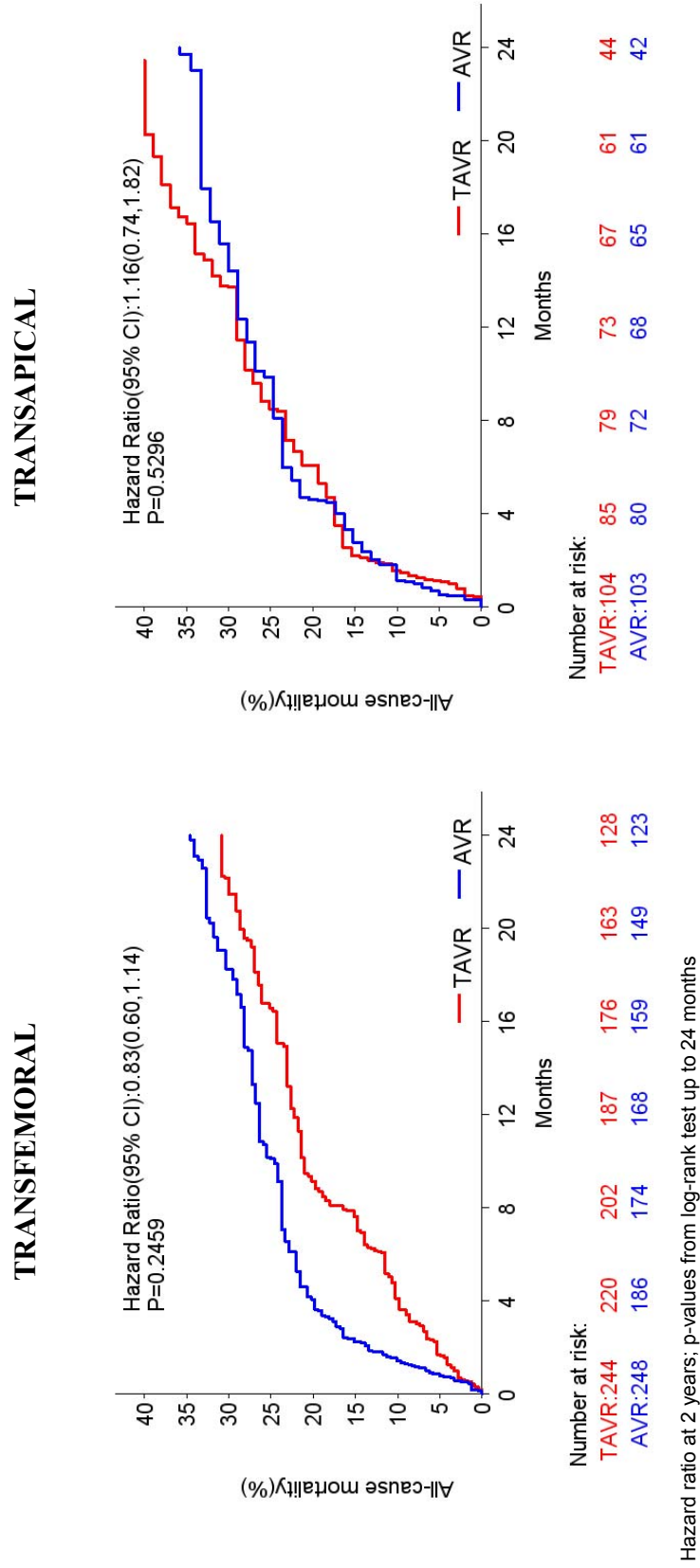
| Transapical Approach: ITT: Actual Data Analysis | | |
|--|--------|--------|
| | AVR | TAVR |
| # patients died (imputed for sensitivity analysis) | 27 | 30 |
| # patients censored prior to 1 year (imputed for sensitivity analysis) | 8 | 1 |
| # patients known alive at 1 year (imputed for sensitivity analysis) | 68 | 73 |
| # Mortality at 1 year | 27.86% | 29.04% |
| # Standard error at 1 year | 4.56% | 4.47% |
| # Mortality difference (TAVR - AVR) | 1.18% | |
| # Standard error of difference | 6.39% | |
| # 95% 1-sided upper CL for difference | 11.69% | |
| # Z-score for primary endpoint test | 0.9888 | |
| # p-value for primary endpoint test | 0.1614 | |

Source: Table 7.1

Figure 28 presents the all cause mortality stratified by implant approach for the ITT population.



Figure 28. All-Cause Mortality Stratified by Implant Approach – High Risk Cohort in the PARTNER Study (ITT Population)





10.9.2 All Cause Mortality Stratified by Implant Approach – AT Population

Similar results involving all cause mortality were obtained in the AT population for each implant approach (Table 59 and Table 60).

Table 59. All-Cause Mortality: Transfemoral Approach – High Risk Cohort in the PARTNER Study (AT Population)

| Transfemoral Approach: AT: Actual Data Analysis | | |
|--|--------|--------|
| | AVR | TAVR |
| # patients died (imputed for sensitivity analysis) | 55 | 51 |
| # patients censored prior to 1 year (imputed for sensitivity analysis) | 4 | 3 |
| # patients known alive at 1 year (imputed for sensitivity analysis) | 162 | 186 |
| # Mortality at 1 year | 25.18% | 21.35% |
| # Standard error at 1 year | 2.94% | 2.65% |
| # Mortality difference (TAVR - AVR) | -3.83% | |
| # Standard error of difference | 3.96% | |
| # 95% 1-sided upper CL for difference | 2.68% | |
| # Z-score for primary endpoint test | 2.8618 | |
| # p-value for primary endpoint test | 0.0021 | |

Source: Table 7.1

Table 60. All-Cause Mortality: Transapical Approach – High Risk Cohort in the PARTNER Study (AT Population)

| Transapical Approach: AT: Actual Data Analysis | | |
|--|--------|--------|
| | AVR | TAVR |
| # patients died (imputed for sensitivity analysis) | 23 | 30 |
| # patients censored prior to 1 year (imputed for sensitivity analysis) | 2 | 1 |
| # patients known alive at 1 year (imputed for sensitivity analysis) | 67 | 73 |
| # Mortality at 1 year | 25.28% | 29.07% |
| # Standard error at 1 year | 4.56% | 4.47% |
| # Mortality difference (TAVR - AVR) | 3.79% | |
| # Standard error of difference | 6.39% | |
| # 95% 1-sided upper CL for difference | 14.29% | |
| # Z-score for primary endpoint test | 0.5816 | |
| # p-value for primary endpoint test | 0.2804 | |

Source: Table 7.1



In both the ITT and AT populations, all cause mortality in the TAVR arm was not inferior to all cause mortality in the AVR arm at 1 year using the transfemoral approach. Non-inferiority could not be demonstrated in the transapical only population possibly due to the limited sample size of 200 patients. Note, the trial was not powered to demonstrate non-inferiority in the transapical approach when analyzed in isolation.

10.9.3 Time from Randomization to the First Occurrence of MACCE at 1 Year by Implant Approach (ITT Population)

In the ITT transfemoral population, the KM event rate for time from randomization to the first occurrence of a MACCE event at one year was 24.7% for the TAVR group and 28.0% for the AVR group; these KM rates were 33.8% for the TAVR group and 31.8% for the AVR group in the transapical ITT population. Note: per-protocol definitions for MACCE were used; see footnote in Table 61.

10.9.4 Time from Procedure to the First Occurrence of MACCE at 1 Year by Implant Approach (AT Population)

As shown in Table 61, the KM event rate for time from procedure to the first occurrence of a MACCE event at 1 year was 23.0% for the TAVR group and 26.5% for the AVR group in the transfemoral AT population; these rates were 34.8% for the TAVR group and 29.6% for the AVR group in the transapical AT population.



Table 61. Time from Procedure to the First Occurrence of a MACCE (Per Protocol Definitions) at One Year – High Risk Cohort in the PARTNER Study Stratified by Implant Approach (AT Population)

| | | Cohort A Randomized Patients -- As Treated Population | | | |
|-------------------------------------|-----------------------|---|-----------------|-----------------------|-----------------|
| | | Transapical Approach | | Transfemoral Approach | |
| Statistics | Event | AVR (N=92) | TAVR (N=104) | AVR (N=221) | TAVR (N=240) |
| No. of patients | | 92 | 104 | 221 | 240 |
| No. of person-years | | 67.7 | 76.7 | 171.3 | 202.6 |
| No. of patients with event (%) | Early event (days≤30) | 14(15.2%) | 17(16.3%) | 23(10.4%) | 17(7.1%) |
| | Event at 1 year | 27(29.3%) | 36(34.6%) | 58(26.2%) | 55(22.9%) |
| | Late event (days>30) | 13(14.1%) | 19(18.3%) | 35(15.8%) | 38(15.8%) |
| Event rate per 100 pys | Early event (days≤30) | 207.11 | 224.97 | 136.51 | 91.45 |
| | Event at 1 year | 39.91 | 46.97 | 33.86 | 27.15 |
| | Late event (days>30) | 21.34 | 27.50 | 22.66 | 20.65 |
| KM event rate at 30 days (95%CI)(%) | Event | 15.2(7.9,22.6) | 16.4(9.2,23.5) | 10.4(6.4,14.5) | 7.1(3.8,10.3) |
| KM event rate at 1 year (95%CI)(%) | Event | 29.6(20.2,39.0) | 34.8(25.6,44.0) | 26.5(20.7,32.4) | 23.0(17.7,28.4) |

Per-protocol definitions - MACCE: Death; Myocardial Infarction= acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI; Renal Failure: Patient required chronic dialysis for greater than 30 days; Stroke= a neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction

Source: Table 8.1.

10.9.5 Total Hospital Days Through 1 Year by Implant Approach (ITT Population)

In the transfemoral ITT population, the mean number of hospital days through 1 year was 15.8 ± 19.8 days for the TAVR group vs. 18.6 ± 23.6 days in the AVR group. In the transapical ITT population, the mean (SD) number of hospital days through 1 year was 17.5 (12.6) days for the TAVR group, and 19.0 (21.0) days for the AVR group.

10.9.6 Total Hospital Days Through 1 Year by Implant Approach (AT Population)

Table 62 summarizes the total hospital days through one year stratified by implant approach. In the transfemoral AT population, the mean number of hospital days through 1 year was 14.4 ± 19.8 days for the TAVR group, and 19.1 ± 23.6 days for the AVR group. In the transapical AT population, the mean number of hospital days through 1 year was 16.6 ± 12.8 days for the TAVR group, and 20.1 ± 21.5 days for the AVR group.



Table 62. Total Hospital Days through One Year – High Risk Cohort in the PARTNER Study Stratified by Implant Approach (AT Population)

| Statistics | Cohort A Randomized Patients -- As Treated Population | | | |
|------------|---|-----------------|-----------------------|-----------------|
| | Transapical Approach | | Transfemoral Approach | |
| | AVR (N=92) | TAVR (N=104) | AVR (N=221) | TAVR (N=240) |
| n | 92 | 104 | 221 | 240 |
| Mean | 20.06 | 16.63 | 19.13 | 14.44 |
| SD | 21.534 | 12.754 | 23.547 | 19.845 |
| Minimum | 3.00 | 0.00 | 0.00 | 0.00 |
| Q1 | 9.50 | 7.00 | 8.00 | 4.00 |
| Median | 15.00 | 13.00 | 13.00 | 7.00 |
| Q3 | 23.00 | 22.00 | 23.00 | 16.13 |
| Maximum | 184.00 | 57.00 | 275.00 | 186.00 |

Source: Table 8.2

In both the transapical and transfemoral TAVR groups, the mean total hospital days through 1 year was lower than mean total hospital days through 1 year in their corresponding AVR groups.

10.9.7 NYHA Functional Class at One Year by Implant Approach (ITT Population)

In the ITT population, the mean (SD) NYHA classification at 1 year was 1.68 (0.77) in the TAVR arm and 1.75 (0.77) in the AVR arm of the transfemoral population. The mean (SD) NYHA classification was 1.73 (0.80) in the TAVR arm and 1.60 (0.75) in the AVR arm of the transapical ITT population at one year.

10.9.8 NYHA Functional Class at One Year by Implant Approach (AT Population)

Table 63 summarizes the NYHA classification at one year stratified by implant approach for the AT population. At 1 year, the mean (SD) NYHA classification was 1.69 (0.77) in the TAVR arm and 1.71 (0.74) in the AVR arm of the transfemoral AT population. The



mean (SD) NYHA classification was 1.70 (0.79) in the TAVR arm and 1.59 (0.75) in the AVR arm of the transapical AT population at one year.

Table 63. NYHA at One Year – High Risk Cohort in the PARTNER Study Stratified by Implant Approach (AT Population)

| Statistics | Cohort A Randomized Patients -- As Treated Population | | | |
|------------|---|-----------------|-----------------------|-----------------|
| | Transapical Approach | | Transfemoral Approach | |
| | AVR (N=92) | TAVR (N=104) | AVR (N=221) | TAVR (N=240) |
| n | 64 | 70 | 156 | 179 |
| Mean | 1.59 | 1.70 | 1.71 | 1.69 |
| SD | 0.750 | 0.787 | 0.738 | 0.766 |
| Class I | 35(38.0%) | 34(32.7%) | 68(30.8%) | 85(35.4%) |
| Class II | 21(22.8%) | 24(23.1%) | 70(31.7%) | 69(28.8%) |
| Class III | 7(7.6%) | 11(10.6%) | 14(6.3%) | 21(8.8%) |
| Class IV | 1(1.1%) | 1(1.0%) | 4(1.8%) | 4(1.7%) |
| Death | 22(23.9%) | 29(27.9%) | 55(24.9%) | 51(21.3%) |
| Unknown | 6(6.5%) | 5(4.8%) | 10(4.5%) | 10(4.2%) |

Source: Table 8.3

10.9.9 6-Minute Walk Test at One Year by Implant Approach (ITT Population)

In the transfemoral ITT population, the mean (SD) 6MWD at one year was 164.5 (124.8) meters in the TAVR group and 172.1 (134.9) meters in the AVR group. In the transapical arm, the mean (SD) 6MWD was 166.1 (138.0) meters in the TAVR group and 164.5 (134.6) meters in the AVR group.

10.9.10 6-Minute Walk at One Year Test by Implant Approach (AT Population)

Table 64 summarizes the 6MWT at one year for the AT population stratified by implant approach. At 1 year, the mean (SD) 6MWD was 164.9 (125.2) meters in the TAVR group and 174.0 (135.0) meters in the AVR group of the transfemoral arm. In the transapical arm, the mean (SD) 6MWD was 165.0 (137.0) meters in the TAVR group and 168.3 (133.8) meters in the AVR group.



Table 64. 6MWT at One Year – High Risk Cohort in the PARTNER Study Stratified by Implant Approach (AT Population)

| Statistics | Cohort A Randomized Patients -- As Treated Population | | | |
|---|---|-----------------|-----------------------|-----------------|
| | Transapical Approach | | Transfemoral Approach | |
| | AVR (N=92) | TAVR (N=104) | AVR (N=221) | TAVR (N=240) |
| n | 43 | 58 | 103 | 140 |
| Mean | 168.29 | 165.03 | 173.97 | 164.92 |
| SD | 133.781 | 136.979 | 134.973 | 125.194 |
| Minimum | 0.00 | 0.00 | 0.00 | 0.00 |
| Q1 | 73.15 | 53.00 | 14.00 | 71.55 |
| Median | 175.26 | 148.00 | 180.00 | 164.50 |
| Q3 | 283.46 | 274.30 | 280.00 | 247.00 |
| Maximum | 448.36 | 575.46 | 457.20 | 540.10 |
| Performed in window | 33(35.9%) | 46(44.2%) | 78(35.3%) | 110(45.8%) |
| Performed outside window | 6(6.5%) | 6(5.8%) | 24(10.9%) | 20(8.3%) |
| Missing due to death | 22(23.9%) | 29(27.9%) | 51(23.1%) | 47(19.6%) |
| Missing due to protocol or medical reason | 10(10.9%) | 12(11.5%) | 25(11.3%) | 30(12.5%) |
| Missing otherwise | 21(22.8%) | 11(10.6%) | 37(16.7%) | 24(10.0%) |
| Visit missed for other reason | 0(0%) | 0(0%) | 6(2.7%) | 9(3.8%) |

Source: Table 8.4

10.9.11 Quality of Life Stratified by Implant Approach

In the transfemoral arm, significant, statistical changes were noted at every time point for the TF TAVR group. In the TF AVR group, KCCQ physical limitations, the SF-12 mental score and EQ-5D utilities at 1 month were not statistically significant (Table 65). Similar to the pooled cohort, differences between treatment groups according to mixed effects models revealed several significant, statistical differences at the 1 month visit only for the transfemoral approach in favor of TF TAVR (Table 67).



In the transapical arm, KCCQ physical limitations at 1 months, KCCQ social limitation at 1 month. SF-12 mental at 1 month and EQ-5D utilities at 1 and 6 months did not change significantly within the TAVR arm. KCCQ physical limitations at 1 month, KCCQ self efficacy at 1 month, KCCQ social limitation at 1 months, SF-12 physical and mental scores at 1 month and EQ-5D utilities at 1 and 12 month did not change significantly within the TA AVR arm (Table 66). In the transapical arm, differences between treatment groups according to mixed effects models revealed several significant, statistical differences predominantly at the 6 month visit in favor of TA AVR (Table 68).

In summary, among high surgical risk patients, both surgical and transcatheter AVR resulted in substantial improvement in disease-specific and generic HRQOL over 1 year follow-up. Although the extent of improvement at 1 year was similar with TAVR and AVR, there were important differences in the rate and extent of recovery at the earlier time points:

- For patients eligible for the TF approach, TAVR resulted in substantial QOL benefits compared with AVR at 1 month with similar QOL at later time points
- For patients eligible only for the TA approach, QOL tended to be better with AVR at 1 and 6 months, but was similar at 12 months

Thus both groups (TF-TAVR and TA-TAVR) become comparable to AVR but TF-TAVR tends to achieve most of its QoL improvement earlier than TA-TAVR.



Table 65. Quality of Life – Within Grouped Comparison from Paired t-test - High Risk Cohort in the PARTNER Study – Transfemoral Approach

| Scale/Timepoint | TAVR Group | | | AVR Group | | |
|---------------------------|------------|----------------------------|---------|-----------|----------------------------|---------|
| | N | Paired Difference (95% CI) | P-value | N | Paired Difference (95% CI) | P-value |
| KCCQ Summary | | | | | | |
| 1 month | 197 | 23.7 (20.1, 27.3) | <.0001 | 157 | 12.1 (7.4, 16.7) | <.0001 |
| 6 months | 183 | 29.8 (25.9, 33.8) | <.0001 | 139 | 26.9 (22.4, 31.5) | <.0001 |
| 12 months | 165 | 28.7 (24.4, 33.1) | <.0001 | 136 | 26.8 (21.8, 31.7) | <.0001 |
| KCCQ Physical Limitations | | | | | | |
| 1 month | 175 | 15.2 (10.4, 20.0) | <.0001 | 132 | 3.2 (-2.7, 9.0) | 0.2877 |
| 6 months | 163 | 21.9 (17.2, 26.7) | <.0001 | 127 | 20.2 (14.5, 25.9) | <.0001 |
| 12 months | 150 | 18.9 (13.5, 24.2) | <.0001 | 117 | 14.4 (8.9, 19.9) | <.0001 |
| KCCQ Total Symptoms | | | | | | |
| 1 month | 196 | 20.4 (16.7, 24.2) | <.0001 | 157 | 12.8 (7.9, 17.8) | <.0001 |
| 6 months | 182 | 24.8 (20.8, 28.8) | <.0001 | 139 | 24.3 (20.2, 28.5) | <.0001 |
| 12 months | 164 | 24.8 (20.5, 29.0) | <.0001 | 133 | 23.3 (18.3, 28.4) | <.0001 |
| KCCQ Self-Efficacy | | | | | | |
| 1 month | 196 | 4.8 (1.3, 8.3) | 0.0077 | 156 | 5.2 (0.9, 9.5) | 0.0184 |
| 6 months | 181 | 6.8 (3.2, 10.3) | 0.0002 | 136 | 6.2 (1.4, 10.9) | 0.0110 |
| 12 months | 165 | 4.8 (0.9, 8.8) | 0.0171 | 133 | 5.0 (0.2, 9.8) | 0.0418 |
| KCCQ Quality of Life | | | | | | |
| 1 month | 196 | 31.5 (27.4, 35.6) | <.0001 | 154 | 18.9 (13.5, 24.4) | <.0001 |
| 6 months | 181 | 38.2 (33.7, 42.8) | <.0001 | 137 | 34.0 (28.7, 39.3) | <.0001 |
| 12 months | 165 | 38.1 (33.6, 42.7) | <.0001 | 130 | 37.3 (31.6, 42.9) | <.0001 |
| KCCQ Social Limitation | | | | | | |
| 1 month | 159 | 24.7 (19.3, 30.1) | <.0001 | 115 | 12.0 (4.9, 19.1) | 0.0010 |
| 6 months | 149 | 31.8 (25.7, 37.9) | <.0001 | 115 | 28.3 (22.0, 34.6) | <.0001 |
| 12 months | 140 | 33.3 (26.9, 39.8) | <.0001 | 103 | 30.6 (22.8, 38.4) | <.0001 |
| SF-12 Physical | | | | | | |
| 1 month | 184 | 5.0 (3.5, 6.4) | <.0001 | 149 | 2.6 (0.7, 4.4) | 0.0061 |
| 6 months | 172 | 6.7 (5.0, 8.3) | <.0001 | 134 | 7.2 (5.1, 9.2) | <.0001 |
| 12 months | 155 | 6.3 (4.5, 8.2) | <.0001 | 127 | 6.1 (4.2, 8.1) | <.0001 |
| SF-12 Mental | | | | | | |
| 1 month | 184 | 4.3 (2.5, 6.1) | <.0001 | 149 | -0.3 (-2.6, 2.1) | 0.8174 |
| 6 months | 172 | 5.1 (3.2, 7.0) | <.0001 | 134 | 4.0 (1.6, 6.3) | 0.0010 |
| 12 months | 155 | 5.0 (3.1, 7.0) | <.0001 | 127 | 4.7 (2.4, 6.9) | 0.0001 |
| EQ-5D Utilities | | | | | | |
| 1 month | 192 | 0.0753 (0.0425, 0.1082) | <.0001 | 154 | 0.0162 (-0.0239, 0.0564) | 0.4258 |
| 6 months | 176 | 0.0987 (0.0654, 0.1321) | <.0001 | 136 | 0.0854 (0.0439, 0.1270) | 0.0001 |
| 12 months | 160 | 0.0872 (0.0507, 0.1238) | <.0001 | 129 | 0.0809 (0.0402, 0.1216) | 0.0001 |



Table 66. Quality of Life – Within Grouped Comparison from Paired t-test - High Risk Cohort in the PARTNER Study – Transapical Approach

| Scale/Timepoint | TAVR Group | | | AVR Group | | |
|---------------------------|------------|----------------------------|---------|-----------|----------------------------|---------|
| | N | Paired Difference (95% CI) | P-value | N | Paired Difference (95% CI) | P-value |
| KCCQ Summary | | | | | | |
| 1 month | 77 | 12.5 (6.1, 19.0) | 0.0002 | 61 | 12.5 (5.5, 19.5) | 0.0007 |
| 6 months | 71 | 23.8 (16.4, 31.2) | <.0001 | 56 | 27.3 (21.0, 33.7) | <.0001 |
| 12 months | 66 | 29.6 (23.2, 36.1) | <.0001 | 59 | 21.6 (13.8, 29.4) | <.0001 |
| KCCQ Physical Limitations | | | | | | |
| 1 month | 63 | 2.4 (-4.9, 9.7) | 0.5204 | 51 | 1.7 (-7.7, 11.1) | 0.7199 |
| 6 months | 61 | 12.4 (4.3, 20.5) | 0.0034 | 52 | 17.3 (9.6, 25.0) | <.0001 |
| 12 months | 55 | 15.5 (7.4, 23.6) | 0.0003 | 54 | 11.7 (3.2, 20.3) | 0.0083 |
| KCCQ Total Symptoms | | | | | | |
| 1 month | 77 | 12.9 (6.2, 19.6) | 0.0003 | 60 | 12.1 (5.6, 18.5) | 0.0004 |
| 6 months | 70 | 16.6 (9.3, 23.9) | <.0001 | 55 | 25.6 (19.2, 32.0) | <.0001 |
| 12 months | 64 | 23.1 (16.2, 30.0) | <.0001 | 59 | 18.7 (11.2, 26.3) | <.0001 |
| KCCQ Self-Efficacy | | | | | | |
| 1 month | 77 | 6.8 (0.8, 12.8) | 0.0259 | 61 | 2.9 (-2.3, 8.0) | 0.2689 |
| 6 months | 71 | 7.6 (1.5, 13.6) | 0.0150 | 56 | 7.6 (1.6, 13.6) | 0.0143 |
| 12 months | 66 | 8.5 (2.5, 14.6) | 0.0065 | 59 | 4.0 (-2.8, 10.9) | 0.2428 |
| KCCQ Quality of Life | | | | | | |
| 1 month | 77 | 22.1 (13.7, 30.5) | <.0001 | 61 | 20.9 (13.1, 28.7) | <.0001 |
| 6 months | 71 | 32.1 (23.6, 40.6) | <.0001 | 56 | 34.8 (27.4, 42.2) | <.0001 |
| 12 months | 65 | 41.7 (33.1, 50.2) | <.0001 | 58 | 29.5 (20.7, 38.2) | <.0001 |
| KCCQ Social Limitation | | | | | | |
| 1 month | 61 | 6.9 (-3.2, 17.0) | 0.1771 | 46 | 2.8 (-7.9, 13.4) | 0.6037 |
| 6 months | 58 | 27.4 (16.4, 38.4) | <.0001 | 48 | 28.6 (19.1, 38.1) | <.0001 |
| 12 months | 50 | 34.2 (24.0, 44.5) | <.0001 | 47 | 22.8 (11.0, 34.7) | 0.0003 |
| SF-12 Physical | | | | | | |
| 1 month | 76 | 2.8 (0.6, 5.0) | 0.0133 | 61 | 0.5 (-2.1, 3.0) | 0.7080 |
| 6 months | 70 | 5.2 (2.5, 7.8) | 0.0002 | 57 | 7.0 (4.4, 9.6) | <.0001 |
| 12 months | 66 | 7.1 (4.5, 9.8) | <.0001 | 58 | 4.5 (1.2, 7.8) | 0.0080 |
| SF-12 Mental | | | | | | |
| 1 month | 76 | -0.8 (-3.7, 2.2) | 0.5968 | 61 | 1.7 (-1.4, 4.8) | 0.2695 |
| 6 months | 70 | 3.3 (0.2, 6.5) | 0.0357 | 57 | 3.7 (1.0, 6.3) | 0.0079 |
| 12 months | 66 | 3.6 (0.1, 7.0) | 0.0417 | 58 | 3.9 (0.6, 7.2) | 0.0213 |
| EQ-5D Utilities | | | | | | |
| 1 month | 74 | -0.0217 (-0.0769, 0.0336) | 0.4367 | 58 | 0.0085 (-0.0428, 0.0597) | 0.7424 |
| 6 months | 66 | 0.0427 (-0.0231, 0.1084) | 0.1995 | 52 | 0.0638 (0.0059, 0.1216) | 0.0314 |
| 12 months | 61 | 0.0633 (0.0058, 0.1208) | 0.0314 | 54 | 0.0500 (-0.0158, 0.1157) | 0.1336 |



Table 67. Quality of Life – Differences between Treatment Groups in QoL Measures over Time According to Longitudinal Mixed Effects Models – High Risk Cohort in the PARTNER Study – Transfemoral Approach

| Scale/Timepoint | Predicted Mean Values (95% CI) | | Predicted Mean Difference (TAVR-AVR), 95% CI | P-value |
|---------------------------|--------------------------------|--------------------------|--|---------|
| | TAVI | AVR | | |
| KCCQ Summary | | | | |
| 1 month | 63.0 (58.8, 67.2) | 53.1 (48.5, 57.7) | 9.9 (4.9, 14.9) | 0.0001 |
| 6 months | 68.2 (64.1, 72.3) | 68.7 (64.2, 73.2) | -0.5 (-5.3, 4.4) | 0.8502 |
| 12 months | 66.9 (62.7, 71.2) | 68.1 (63.5, 72.8) | -1.2 (-6.3, 3.9) | 0.6402 |
| KCCQ Physical Limitations | | | | |
| 1 month | 57.2 (51.9, 62.4) | 46.3 (40.5, 52.0) | 10.9 (4.5, 17.4) | 0.0010 |
| 6 months | 63.2 (58.3, 68.1) | 63.7 (58.3, 69.1) | -0.5 (-6.3, 5.4) | 0.8728 |
| 12 months | 59.6 (54.5, 64.8) | 57.4 (51.7, 63.0) | 2.3 (-3.9, 8.5) | 0.4691 |
| KCCQ Total Symptoms | | | | |
| 1 month | 68.0 (64.1, 72.0) | 61.4 (57.1, 65.7) | 6.6 (1.9, 11.4) | 0.0064 |
| 6 months | 71.6 (67.8, 75.4) | 73.7 (69.5, 77.9) | -2.1 (-6.7, 2.5) | 0.3716 |
| 12 months | 71.4 (67.4, 75.3) | 72.4 (68.1, 76.7) | -1.1 (-5.8, 3.7) | 0.6632 |
| KCCQ Self-Efficacy | | | | |
| 1 month | 82.5 (79.2, 85.8) | 79.9 (76.3, 83.6) | 2.6 (-1.5, 6.7) | 0.2191 |
| 6 months | 85.0 (81.8, 88.1) | 81.9 (78.3, 85.4) | 3.1 (-0.9, 7.1) | 0.1288 |
| 12 months | 83.9 (80.5, 87.3) | 81.3 (77.6, 85.1) | 2.5 (-1.8, 6.9) | 0.2477 |
| KCCQ Quality of Life | | | | |
| 1 month | 65.8 (61.1, 70.6) | 56.0 (50.8, 61.2) | 9.8 (4.0, 15.6) | 0.0009 |
| 6 months | 72.1 (67.5, 76.6) | 71.8 (66.8, 76.8) | 0.3 (-5.2, 5.7) | 0.9277 |
| 12 months | 71.5 (66.8, 76.2) | 73.4 (68.3, 78.6) | -1.9 (-7.6, 3.8) | 0.5033 |
| KCCQ Social Limitation | | | | |
| 1 month | 58.1 (52.0, 64.2) | 47.6 (40.7, 54.4) | 10.6 (3.0, 18.2) | 0.0066 |
| 6 months | 64.3 (58.4, 70.2) | 67.3 (60.7, 73.8) | -2.9 (-10.1, 4.3) | 0.4267 |
| 12 months | 65.4 (59.3, 71.5) | 68.3 (61.4, 75.1) | -2.9 (-10.5, 4.8) | 0.4638 |
| SF-12 Physical | | | | |
| 1 month | 34.7 (33.0, 36.3) | 32.7 (30.9, 34.4) | 2.0 (0.1, 3.9) | 0.0415 |
| 6 months | 36.2 (34.4, 37.9) | 37.1 (35.2, 39.0) | -0.9 (-3.0, 1.2) | 0.4111 |
| 12 months | 35.9 (34.0, 37.8) | 36.2 (34.2, 38.3) | -0.4 (-2.8, 2.0) | 0.7655 |
| SF-12 Mental | | | | |
| 1 month | 52.1 (50.3, 53.9) | 46.7 (44.7, 48.7) | 5.4 (3.1, 7.7) | 0.0000 |
| 6 months | 52.2 (50.4, 54.0) | 51.0 (49.0, 53.0) | 1.2 (-1.0, 3.5) | 0.2817 |
| 12 months | 52.8 (51.0, 54.6) | 52.3 (50.3, 54.3) | 0.4 (-1.8, 2.7) | 0.6948 |
| EQ-5D Utilities | | | | |
| 1 month | 0.7369 (0.6988, 0.7749) | 0.6759 (0.6344, 0.7173) | 0.0610 (0.0160, 0.1060) | 0.0080 |
| 6 months | 0.7556 (0.7204, 0.7907) | 0.7438 (0.7051, 0.7826) | 0.0117 (-0.0286, 0.0520) | 0.5676 |
| 12 months | 0.7458 (0.7074, 0.7843) | 0.7179 (0.6759, 0.7599) | 0.0279 (-0.0181, 0.0739) | 0.2335 |



Table 68. Quality of Life – Differences between Treatment Groups in QoL Measures over Time According to Longitudinal Mixed Effects Models – High Risk Cohort in the PARTNER Study – Transapical Approach

| Scale/Timepoint | Predicted Mean Values (95% CI) | | Predicted Mean Difference (TAVR-AVR), 95% CI | P-value |
|---------------------------|--------------------------------|--------------------------|--|---------|
| | TAVR | AVR | | |
| KCCQ Summary | | | | |
| 1 month | 50.5 (44.7, 56.4) | 56.4 (49.8, 62.9) | -5.8 (-13.9, 2.2) | 0.1548 |
| 6 months | 62.9 (57.3, 68.6) | 70.9 (64.5, 77.3) | -7.9 (-15.7, -0.2) | 0.0444 |
| 12 months | 65.5 (59.6, 71.5) | 64.8 (58.3, 71.2) | 0.8 (-7.2, 8.8) | 0.8491 |
| KCCQ Physical Limitations | | | | |
| 1 month | 43.7 (36.1, 51.3) | 49.4 (41.0, 57.9) | -5.8 (-16.3, 4.8) | 0.2828 |
| 6 months | 54.5 (47.6, 61.4) | 64.1 (56.5, 71.6) | -9.6 (-18.9, -0.2) | 0.0443 |
| 12 months | 53.8 (46.4, 61.1) | 57.9 (50.2, 65.6) | -4.1 (-13.8, 5.6) | 0.4057 |
| KCCQ Total Symptoms | | | | |
| 1 month | 59.5 (54.0, 65.0) | 64.7 (58.4, 70.9) | -5.1 (-12.8, 2.5) | 0.1896 |
| 6 months | 64.1 (58.7, 69.4) | 77.2 (71.2, 83.2) | -13.2 (-20.5, -5.9) | 0.0004 |
| 12 months | 67.8 (62.2, 73.3) | 70.1 (64.1, 76.0) | -2.3 (-9.7, 5.2) | 0.5472 |
| KCCQ Self-Efficacy | | | | |
| 1 month | 80.6 (75.9, 85.3) | 83.1 (77.8, 88.5) | -2.6 (-9.2, 4.1) | 0.4501 |
| 6 months | 82.5 (77.9, 87.0) | 87.1 (82.0, 92.2) | -4.6 (-10.9, 1.7) | 0.1514 |
| 12 months | 82.8 (77.9, 87.7) | 84.8 (79.5, 90.0) | -2.0 (-8.7, 4.7) | 0.5604 |
| KCCQ Quality of Life | | | | |
| 1 month | 54.9 (48.3, 61.6) | 59.6 (52.1, 67.1) | -4.7 (-13.9, 4.5) | 0.3173 |
| 6 months | 66.1 (59.8, 72.4) | 74.5 (67.4, 81.6) | -8.4 (-17.0, 0.2) | 0.0565 |
| 12 months | 73.9 (67.3, 80.5) | 69.1 (61.9, 76.2) | 4.8 (-4.0, 13.7) | 0.2829 |
| KCCQ Social Limitation | | | | |
| 1 month | 38.1 (29.5, 46.7) | 43.8 (34.0, 53.7) | -5.8 (-17.9, 6.4) | 0.3523 |
| 6 months | 63.2 (54.9, 71.4) | 67.0 (57.8, 76.1) | -3.8 (-15.1, 7.5) | 0.5078 |
| 12 months | 69.0 (60.1, 77.9) | 62.9 (53.4, 72.4) | 6.1 (-5.9, 18.1) | 0.3174 |
| SF-12 Physical | | | | |
| 1 month | 31.8 (29.6, 34.0) | 31.6 (29.1, 34.0) | 0.3 (-2.7, 3.3) | 0.8479 |
| 6 months | 34.9 (32.5, 37.4) | 38.3 (35.6, 41.0) | -3.3 (-6.7, -0.0) | 0.0487 |
| 12 months | 35.3 (32.6, 37.9) | 35.1 (32.2, 38.0) | 0.2 (-3.5, 3.8) | 0.9176 |
| SF-12 Mental | | | | |
| 1 month | 45.3 (42.7, 47.8) | 49.6 (46.7, 52.4) | -4.3 (-7.9, -0.8) | 0.0176 |
| 6 months | 49.5 (47.0, 52.0) | 52.0 (49.2, 54.8) | -2.5 (-6.0, 1.0) | 0.1585 |
| 12 months | 49.5 (47.0, 52.0) | 52.0 (49.3, 54.7) | -2.5 (-5.9, 0.9) | 0.1459 |
| EQ-5D Utilities | | | | |
| 1 month | 0.6399 (0.5873, 0.6926) | 0.6969 (0.6372, 0.7567) | -0.0570 (-0.1299, 0.0159) | 0.1250 |
| 6 months | 0.7073 (0.6592, 0.7554) | 0.7725 (0.7181, 0.8268) | -0.0652 (-0.1303, -0.0001) | 0.0496 |
| 12 months | 0.6985 (0.6446, 0.7524) | 0.7497 (0.6911, 0.8084) | -0.0512 (-0.1241, 0.0216) | 0.1677 |



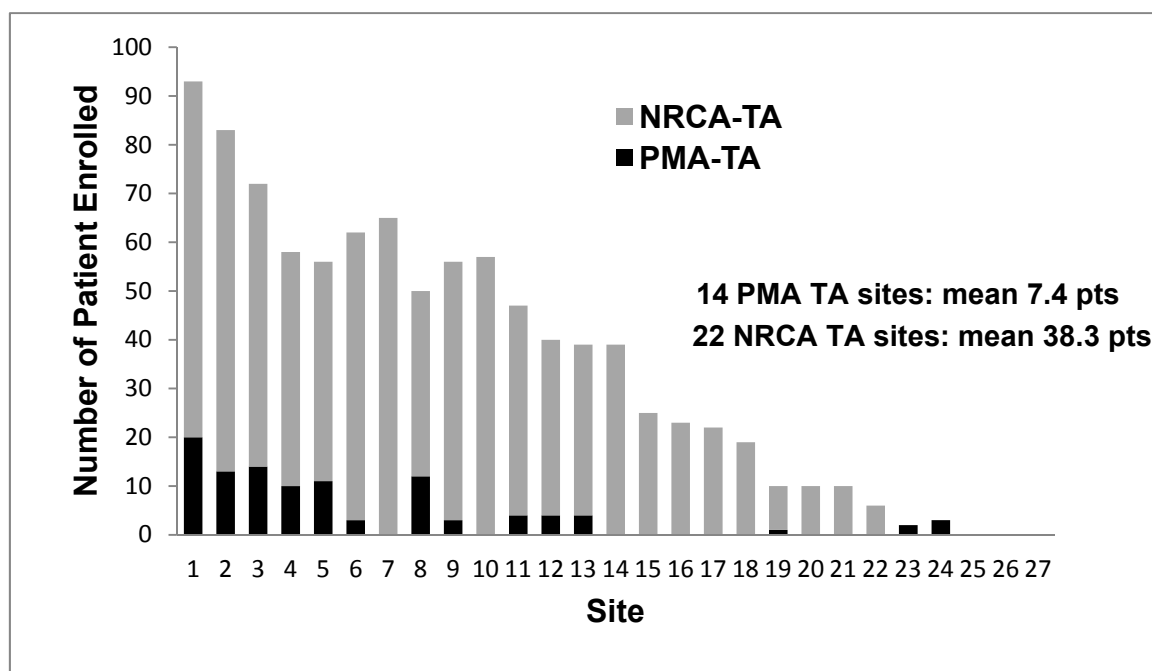
11.0 Other Experience in High Risk Patients

11.1 Non-Randomized Continued-Access (NRCA) Patients

After the PMA enrollment was completed, US sites were allowed to continue TAVR under a non-randomized continued-access (NRCA) protocol. Enrollment in the NRCA started in June, 2008 and is ongoing. As of September 21, 2011, a total of 1588 NRCA ITT patients were enrolled (Table 98 **Appendix F**).

Figure 29 presents the enrollment of the transapical TAVR patients. During the randomized PMA phase, a total of 14 sites enrolled transapical patients (mean 7.4 patients/site). A total of 22 sites enrolled transapical NRCA patients (mean 38.3 patients/site).

Figure 29. Transapical Enrollment per Site (ITT Population)





At the time of database extract, CEC adjudication of all reported death and strokes was 100%. In addition, all patients that had reached their 1 year follow-up were 100% monitored. Adjudication for other events is ongoing.

The as-treated NRCA population comprises 1521 NRCA patients (i.e., 822 transapical and 699 transfemoral TAVR patients). Mean (SD) age at screening was 85.5 (6.3) years for pooled NRCA AT patients. Overall, slightly more patients were male (51.2%), and the vast majority was Caucasian (94.9%). Prior cardiovascular intervention was common, e.g., 44.1% of NRCA patients underwent prior CABG, 43.8% underwent prior PCI and 26.5% had prior BAV. The mean (SD) STS risk score was 11.8 (3.8) and the mean (SD) logistic EuroSCORE was 28.4 (47.7). The vast majority were in NYHA class III (47.7%) or NYHA class IV (47.6%).

Table 69 compares the demographic and baseline characteristics of the high risk randomized TAVR patients vs. the NRCA patients. Compared to the randomized TAVR patients, the age of NRCA patients was slightly higher and more NRCA patients were female. In addition, NRCA patients had a higher incidence of CAD, prior PCI and prior BAV and lower incidence of pulmonary hypertension and frailty compared to the randomized TAVR patients.

Table 69. Demographic and Baseline Characteristics - High Risk Randomized TAVR Patients vs. Non Randomized Continued-Access Patients (AT Population)

| Characteristic | PMA (TAVR) (N=344) | NRCA (N=1521) | Nominal P-Value |
|------------------------------|-----------------------|------------------|--------------------|
| Age - years | 84.4 ± 6.3 | 85.5 ± 6.3 | 0.0000 |
| Male sex - no./total no. (%) | 198/344 (57.6%) | 777/1519 (51.2%) | 0.04 |
| Race | 344 | 1519 | 0.34 |
| Asian | 2 (0.6%) | 15 (1.0%) | |
| Black | 11 (3.2%) | 26 (1.7%) | |
| Caucasian | 320 (93.0%) | 1441 (94.9%) | |
| Hispanic | 9 (2.6%) | 27 (1.8%) | |
| Other | 2 (0.6%) | 10 (0.7%) | |
| STS score | 11.7 ± 3.4 | 11.8 ± 3.8 | 0.87 |



| Characteristic | PMA (TAVR) (N=344) | NRCA (N=1521) | Nominal P-Value |
|---|-----------------------|--------------------|--------------------|
| Logistic EuroSCORE | 29.2 ± 15.2 | 28.4 ± 47.7 | 0.73 |
| NYHA class - no./total no. (%) | 344/344 (100.0%) | 1518/1518 (100.0%) | >0.999 |
| II | 20/344 (5.8%) | 70/1518 (4.6%) | 0.33 |
| III | 144/344 (41.9%) | 724/1518 (47.7%) | 0.06 |
| IV | 180/344 (52.3%) | 722/1518 (47.6%) | 0.12 |
| Coronary artery disease - no./total no. (%) | 258/344 (75.0%) | 1213/1518 (79.9%) | 0.05 |
| Previous MI - no./total no. (%) | 92/343 (26.8%) | 399/1511 (26.4%) | 0.89 |
| Prior CABG - no./total no. (%) | 146/344 (42.4%) | 670/1519 (44.1%) | 0.59 |
| Prior PCI - no./total no. (%) | 115/342 (33.6%) | 665/1518 (43.8%) | 0.0005 |
| Prior BAV - no./total no. (%) | 46/344 (13.4%) | 400/1509 (26.5%) | 0.0000 |
| Peripheral vascular disease - no./total no. (%) | 148/341 (43.4%) | 694/1502 (46.2%) | 0.37 |
| Cerebral vascular disease - no./total no. (%) | 96/323 (29.7%) | 400/1499 (26.7%) | 0.27 |
| COPD - no./total no. (%) | | | |
| Any | 150/344 (43.6%) | 657/1521 (43.2%) | 0.90 |
| Oxygen dependent | 38/218 (17.4%) | 174/904 (19.2%) | 0.56 |
| Creatinine > 2mg/dL - no./total no. (%) | 37/340 (10.9%) | 139/1503 (9.2%) | 0.36 |
| Atrial fibrillation - no./total no. (%) | 80/196 (40.8%) | 120/279 (43.0%) | 0.64 |
| Permanent pacemaker - no./total no. (%) | 69/344 (20.1%) | 345/1517 (22.7%) | 0.31 |
| Pulmonary hypertension - no./total no. (%) | 126/291 (43.3%) | 553/1514 (36.5%) | 0.03 |
| Frailty - no./total no. (%) | 46/291 (15.8%) | 157/1515 (10.4%) | 0.01 |
| Extensively calcified aorta - no./total no. (%) | 2/344 (0.6%) | 16/1515 (1.1%) | 0.55 |
| Deleterious effects of chest-wall irradiation - no./total no. (%) | 3/344 (0.9%) | 6/1515 (0.4%) | 0.22 |
| Chest-wall deformity - no./total no. (%) | 0/344 (0.0%) | 7/1515 (0.5%) | 0.36 |
| Liver disease - no./total no. (%) | 8/344 (2.3%) | 37/1516 (2.4%) | >0.999 |
| Echocardiographic Findings | | | |
| Aortic valve area - cm ² | 0.6 ± 0.2 | 0.7 ± 0.2 | 0.86 |
| Mean aortic valve gradient - mm Hg | 43.4 ± 14.3 | 44.6 ± 15.0 | 0.05 |
| Mean LVEF - % | 53.3 ± 12.6 | 53.0 ± 13.0 | 0.67 |
| Moderate or severe MR - no./total no. (%) | 65/333 (19.5%) | 144/646 (22.3%) | 0.32 |

Table 84 and Table 85 in **Appendix A** provide the demographic and baseline characteristics of the high risk randomized TAVR patients vs. the NRCA patients for the



transapical and transfemoral approach respectively. The mean (SD) follow-up time in the NRCA group was 0.59 (0.5) years. Visit compliance was high, i.e., 98.9% at 30 days, 96.1% at 6 months, and 93.2% at 1 year.

Table 70 provides the procedural parameters for the randomized TAVR and NRCA patients. The mean time in the cath lab, total procedure time and fluoroscopy time was considerably shorter in NRCA patients that underwent TF-TAVR as compared to randomized patients that underwent TF-TAVR.

The proportion of patients requiring conversion to open heart surgery was lower and the proportion of patients with the study valve in the correct location was higher in NRCA patients than the proportions reported for randomized patients.

Table 70. Procedural Parameters – Randomized TAVR and NRCA Patients (AT Population)

| Variable/Statistic | As Treated Patients | | | |
|---|--------------------------|---------------------------|--------------------------|---------------------------|
| | Randomized TAVR | | NRCA | |
| | Transapical (n = 104) | Transfemoral (n = 240) | Transapical (n = 822) | Transfemoral (n = 699) |
| Time in Cath Lab (min) | | | | |
| N | 102 | 239 | 820 | 699 |
| Mean | 224.93 | 242.85 | 235.51 | 219.34 |
| Std Dev | 76.52 | 90.73 | 72.53 | 76.00 |
| Lower Quartile | 172.00 | 196.00 | 195.50 | 184.00 |
| Median | 211.50 | 232.00 | 225.00 | 212.00 |
| Upper Quartile | 250.00 | 269.00 | 264.00 | 246.00 |
| Total procedure time (skin-to-skin) (min) | | | | |
| N | 100 | 234 | 819 | 693 |
| Mean | 113.76 | 141.41 | 121.78 | 114.37 |
| Std Dev | 101.96 | 81.09 | 67.53 | 52.89 |
| Lower Quartile | 67.50 | 92.00 | 80.00 | 80.00 |
| Median | 94.00 | 120.00 | 106.00 | 99.00 |
| Upper Quartile | 121.50 | 163.00 | 142.00 | 134.00 |
| Fluoroscopy Total time (min) | | | | |
| N | 88 | 218 | 789 | 668 |



| | As Treated Patients | | | |
|--|--------------------------|---------------------------|--------------------------|---------------------------|
| | Randomized TAVR | | NRCA | |
| Variable/Statistic | Transapical (n = 104) | Transfemoral (n = 240) | Transapical (n = 822) | Transfemoral (n = 699) |
| Mean | 35.03 | 29.81 | 14.75 | 25.16 |
| Std Dev | 139.69 | 14.98 | 34.11 | 17.98 |
| Lower Quartile | 10.00 | 21.00 | 9.00 | 16.00 |
| Median | 12.00 | 26.00 | 11.00 | 22.00 |
| Upper Quartile | 17.00 | 35.00 | 16.00 | 29.00 |
| Volume of contrast media (ml) | | | | |
| N | 89 | 223 | 799 | 677 |
| Mean | 104.28 | 148.00 | 101.35 | 139.78 |
| Std Dev | 51.42 | 90.22 | 78.77 | 151.86 |
| Lower Quartile | 70.00 | 85.00 | 56.00 | 75.00 |
| Median | 100.00 | 130.00 | 84.00 | 118.00 |
| Upper Quartile | 140.00 | 200.00 | 125.00 | 170.00 |
| Derived Device Size | | | | |
| Count | 101 | 233 | 812 | 697 |
| 23 | 52 (51.5%) | 109 (46.8%) | 434 (53.4%) | 366 (52.5%) |
| 26 | 49 (48.5%) | 124 (53.2%) | 378 (46.6%) | 330 (47.3%) |
| Missing | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.1%) |
| Was the patient cannulated for cardiopulmonary bypass? | | | | |
| Count | 102 | 234 | 821 | 698 |
| No | 93 (91.2%) | 229 (97.9%) | 736 (89.6%) | 688 (98.6%) |
| Yes | 9 (8.8%) | 5 (2.1%) | 85 (10.4%) | 10 (1.4%) |
| Did the patient require IABP during procedure? | | | | |
| Count | 102 | 234 | 821 | 698 |
| No | 94 (92.2%) | 230 (98.3%) | 759 (92.4%) | 687 (98.4%) |
| Yes | 8 (7.8%) | 4 (1.7%) | 62 (7.6%) | 11 (1.6%) |
| Was a conversion to open heart surgery performed? | | | | |
| Count | 102 | 234 | 820 | 698 |
| No | 99 (97.1%) | 228 (97.4%) | 811 (98.9%) | 686 (98.3%) |
| Yes | 3 (2.9%) | 6 (2.6%) | 9 (1.1%) | 12 (1.7%) |
| Number of Aortic valve prosthesis | | | | |
| Count | 102 | 238 | 822 | 699 |
| 0 | 3 (2.9%) | 11 (4.6%) | 72 (8.8%)* | 69 (9.9%)* |



| | As Treated Patients | | | |
|--|--------------------------|---------------------------|--------------------------|---------------------------|
| | Randomized TAVR | | NRCA | |
| Variable/Statistic | Transapical (n = 104) | Transfemoral (n = 240) | Transapical (n = 822) | Transfemoral (n = 699) |
| 1 | 91 (89.2%) | 216 (90.8%) | 717 (87.2%) | 596 (85.3%) |
| 2 | 7 (6.9%) | 10 (4.2%) | 30 (3.6%) | 32 (4.6%) |
| 3 | 1 (1.0%) | 1 (0.4%) | 3 (0.4%) | 2 (0.3%) |
| Did any adverse event occur during procedure? | | | | |
| Count | 102 | 240 | 820 | 697 |
| No | 82 (80.4%) | 189 (78.8%) | 676 (82.4%) | 536 (76.9%) |
| Yes | 20 (19.6%) | 51 (21.3%) | 144 (17.6%) | 161 (23.1%) |
| Did a device malfunction occur during procedure | | | | |
| Count | 101 | 234 | 821 | 697 |
| No | 99 (98.0%) | 231 (98.7%) | 817 (99.5%) | 693 (99.4%) |
| Yes | 2 (2.0%) | 3 (1.3%) | 4 (0.5%) | 4 (0.6%) |
| Was the study valve successfully delivered? | | | | |
| Count | 102 | 235 | 822 | 699 |
| No | 6 (5.9%) | 7 (3.0%) | 7 (0.9%) | 5 (0.7%) |
| Yes | 96 (94.1%) | 228 (97.0%) | 815 (99.1%) | 694 (99.3%) |
| Study valve correct location and position? | | | | |
| Count | 100 | 233 | 818 | 698 |
| No | 4 (4.0%) | 5 (2.1%) | 8 (1.0%) | 8 (1.1%) |
| Yes | 96 (96.0%) | 228 (97.9%) | 810 (99.0%) | 690 (98.9%) |
| Study valve remained correct? | | | | |
| Count | 100 | 231 | 817 | 697 |
| No | 4 (4.0%) | 4 (1.7%) | 6 (0.7%) | 6 (0.9%) |
| Yes | 96 (96.0%) | 227 (98.3%) | 811 (99.3%) | 691 (99.1%) |
| TF Delivery: RetroFlex Catheter/RetroFlex Catheter II? | | | | |
| Count | | 224 | | 620 |
| RetroFlex Catheter | | 127 (56.7%) | | 6 (1.0%) |
| RetroFlex II Catheter | | 71 (31.7%) | | 1 (0.2%) |
| RetroFlex III Catheter | | 26 (11.6%) | | 613 (98.9%) |

Source: Table 13.1

* This includes patients who were not implanted yet at the time of database extract.



Thirteen of the 1521 NRCA patients (0.9%) experienced a device malfunction:

- Seven patients (0.5%; [REDACTED], [REDACTED] underwent valve-in-valve implantation since one of the leaflets of the originally implanted valve did not function properly.
- In patient [REDACTED] the balloon catheter ruptured; the nosecone of the Retroflex 3 separated requiring cut down for removal.
- Patient [REDACTED] experienced aortic insufficiency and underwent valve in valve implantation.
- In patient [REDACTED], the introducer sheath placed was kinked; the sheath was removed and a new sheath was placed.
- One patient [REDACTED] experienced perforation of the aorta due to a kink in the delivery system.
- In patient [REDACTED], one cusp of the valve remained open post-deployment. There was very low systemic end-diastolic pressure (equilibration LV=Ao), but there was a dicrotic notch. This was immediately rectified when pig tail injection inside THV stent done; Ao end-diastolic pressure went from 20-30 to 60 mmHg. Ao root injection showed mild-mod AR. By TEE small posterior paravalvular AR and very tiny central AR jet. No gradient post-TAVR.
- In one patient [REDACTED] an immobile leaflet started working after an Amplatz catheter and extra stiff Amplatz wire were advanced into the left ventricle eliminating the observed aortic insufficiency and need for a second valve.

At the time of the database extract, a total of 260/1521 (17.1%) NRCA patients had died. The cause of death was cardiovascular related in 43.5% (113/260; Table 71).



Table 71. Causes of Death – High Risk NRCA Patients (AT Population)

| | Cohort A Continued Access Patients -- As Treated (AT) Population | | |
|---|--|-----------------------|-------------------|
| | Transapical Approach | Transfemoral Approach | Pooled Approaches |
| Variable | NRCA (n = 822) | NRCA (n = 699) | NRCA (n = 1521) |
| Cardiovascular | 69 | 44 | 113 |
| Arrhythmia | 2 (2.9%) | 2 (4.5%) | 4 (3.5%) |
| CNS event | 3 (4.3%) | 8 (18.2%) | 11 (9.7%) |
| Congestive heart failure (CHF) | 14 (20.3%) | 6 (13.6%) | 20 (17.7%) |
| Endocarditis of prosthetic study valve | 1 (1.4%) | 3 (6.8%) | 4 (3.5%) |
| Myocardial infarction (MI) | 5 (7.2%) | 0 (0.0%) | 5 (4.4%) |
| Non-cerebral hemorrhage | 1 (1.4%) | 1 (2.3%) | 2 (1.8%) |
| Other | 2 (2.9%) | 0 (0.0%) | 2 (1.8%) |
| Peripheral arterial disease/abdominal aortic aneurysm | 0 (0.0%) | 1 (2.3%) | 1 (0.9%) |
| Peripheral arterial embolism (not cerebral, not PE) | 1 (1.4%) | 0 (0.0%) | 1 (0.9%) |
| Sudden, unexpected or unexplained death | 7 (10.1%) | 4 (9.1%) | 11 (9.7%) |
| Unknown cardiovascular | 28 (40.6%) | 18 (40.9%) | 46 (40.7%) |
| Vascular complication | 5 (7.2%) | 1 (2.3%) | 6 (5.3%) |
| Non-Cardiovascular | 56 | 30 | 86 |
| Accidental | 1 (1.8%) | 1 (3.3%) | 2 (2.3%) |
| Infection/sepsis | 17 (30.4%) | 12 (40.0%) | 29 (33.7%) |
| Malignancy | 2 (3.6%) | 1 (3.3%) | 3 (3.5%) |
| Other | 13 (23.2%) | 2 (6.7%) | 15 (17.4%) |
| Renal disease | 5 (8.9%) | 3 (10.0%) | 8 (9.3%) |
| Unknown non-cardiovascular | 18 (32.1%) | 11 (36.7%) | 29 (33.7%) |
| Cause of unknown or unclassified death | | | |
| Unknown | 32 | 29 | 61 |
| Not Specified | 32 (100.0%) | 29 (100.0%) | 61 (100.0%) |
| Total Deaths | 157 | 103 | 260 |

Source: Table7.4

Kaplan Meier rates for all cause mortality at 30 days and 1 year were lower in the NRCA group than the randomized cohort (i.e., in the transapical approach, 8.2% NRCA vs. 8.7%



randomized TAVR at 30 days, 23.6% NRCA vs. 29.1% randomized TAVR at 1 year; 3.2% TF NRCA vs. 3.7% randomized TF TAVR at 30 days, 19.4% TF NRCA vs. 21.4% randomized TF TAVR at 1 year; Table 72).

Table 72. All Cause Mortality – Randomized TAVR and NRCA Patients by Implant Approach (AT Population)

| | | Total Events | | 30 day events | | | 1 year events | | |
|----------------------------|-------------------|--------------|---------------------|---------------|---------------------|--------------------------|---------------|---------------------|-------------------------|
| | Patients in group | Total events | Patients with event | Events | Patients with event | KM Event rate at 30 days | Events | Patients with event | KM Event rate at 1 year |
| ALL CAUSE MORTALITY | | | | | | | | | |
| Pooled | | | | | | | | | |
| NRCA | 1521 | 260 | 260 | 88 | 88 | 5.9% | 244 | 244 | 21.6% |
| Randomized TAVR | 344 | 130 | 130 | 18 | 18 | 5.2% | 81 | 81 | 23.7% |
| Randomized AVR | 313 | 120 | 120 | 25 | 25 | 8.0% | 78 | 78 | 25.2% |
| Transapical | | | | | | | | | |
| NRCA | 822 | 157 | 157 | 66 | 66 | 8.2% | 148 | 148 | 23.6% |
| Randomized TAVR | 104 | 45 | 45 | 9 | 9 | 8.7% | 30 | 30 | 29.1% |
| Randomized AVR | 92 | 36 | 36 | 7 | 7 | 7.6% | 23 | 23 | 25.3% |
| Transfemoral | | | | | | | | | |
| NRCA | 699 | 103 | 103 | 22 | 22 | 3.2% | 96 | 96 | 19.4% |
| Randomized TAVR | 240 | 85 | 85 | 9 | 9 | 3.7% | 51 | 51 | 21.4% |
| Randomized AVR | 221 | 84 | 84 | 18 | 18 | 8.2% | 55 | 55 | 25.2% |

Source: Table 5.0

All-cause mortality for randomized TAVR, randomized AVR and NRCA TAVR patients is illustrated in Figure 30; all-cause mortality stratified by surgical approach for randomized TAVR, randomized AVR and NRCA TAVR patients is presented in Figure 31.



Figure 30. All-Cause Mortality – High Risk Randomized TAVR, Randomized AVR and NRCA TAVR Patients (AT Population)

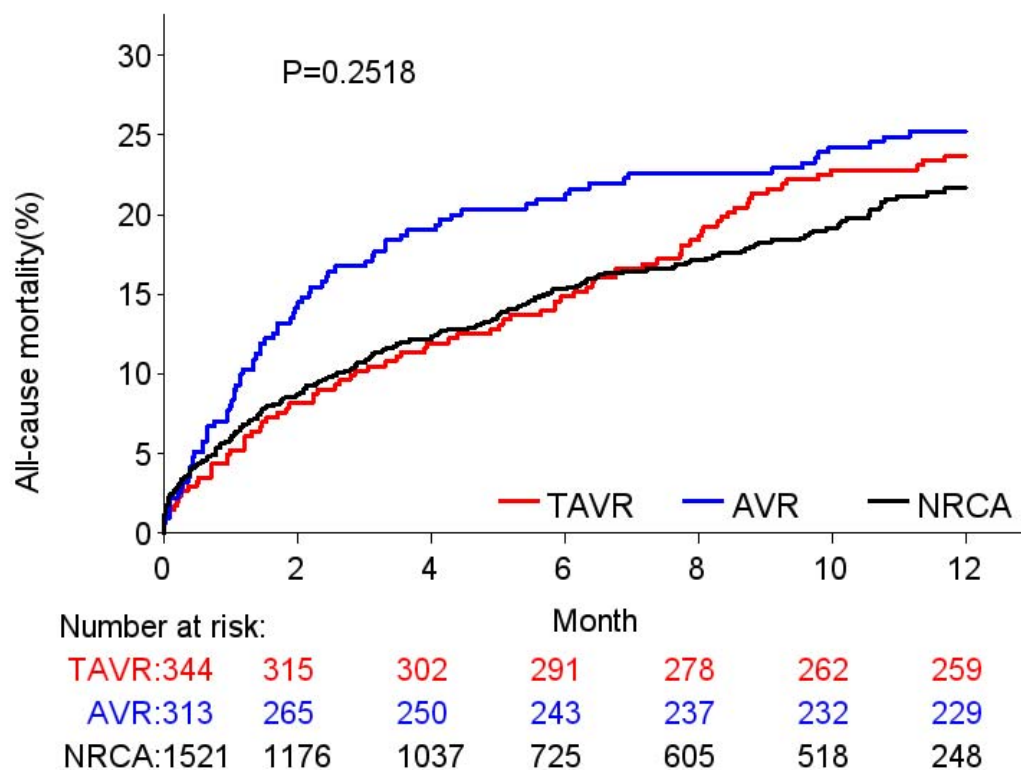




Figure 31. All-Cause Mortality– High Risk Randomized TAVR, Randomized AVR and NRCA TAVR Patients Stratified by Implant Approach (AT Population)

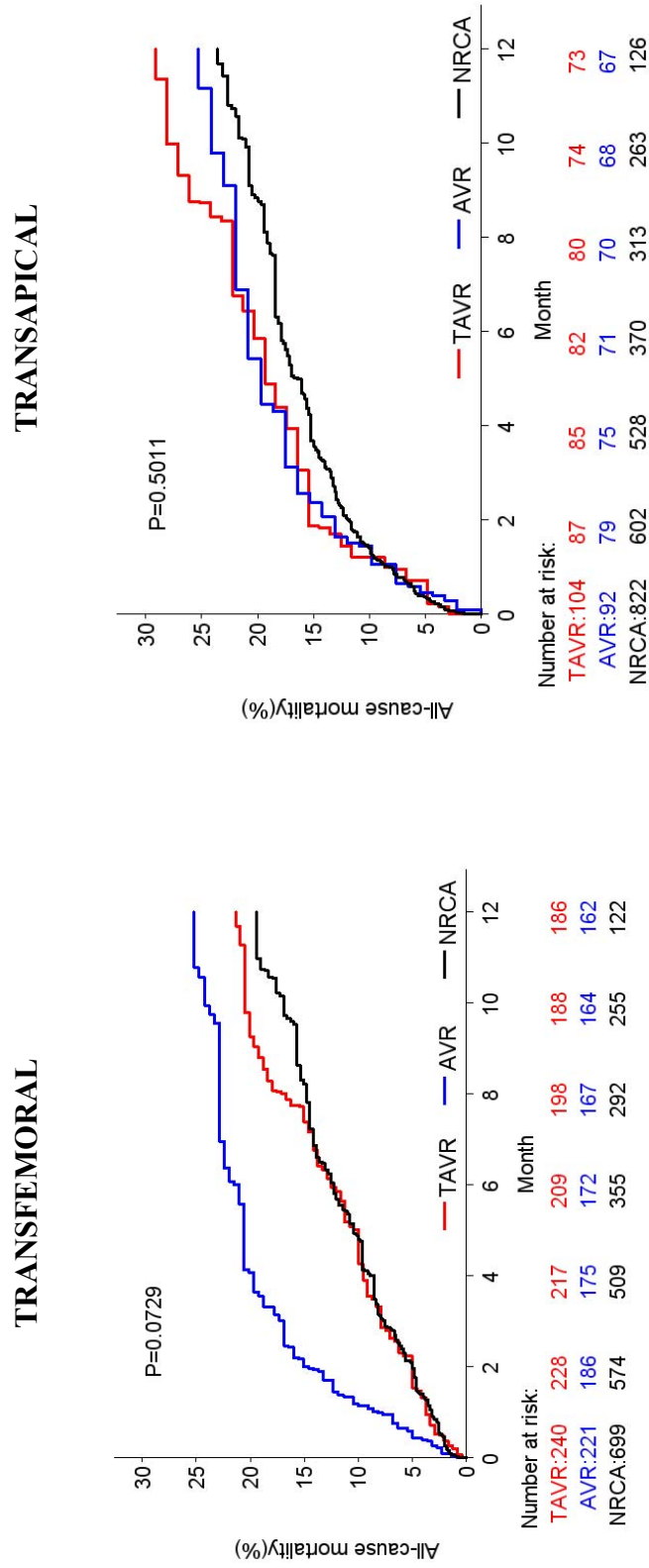
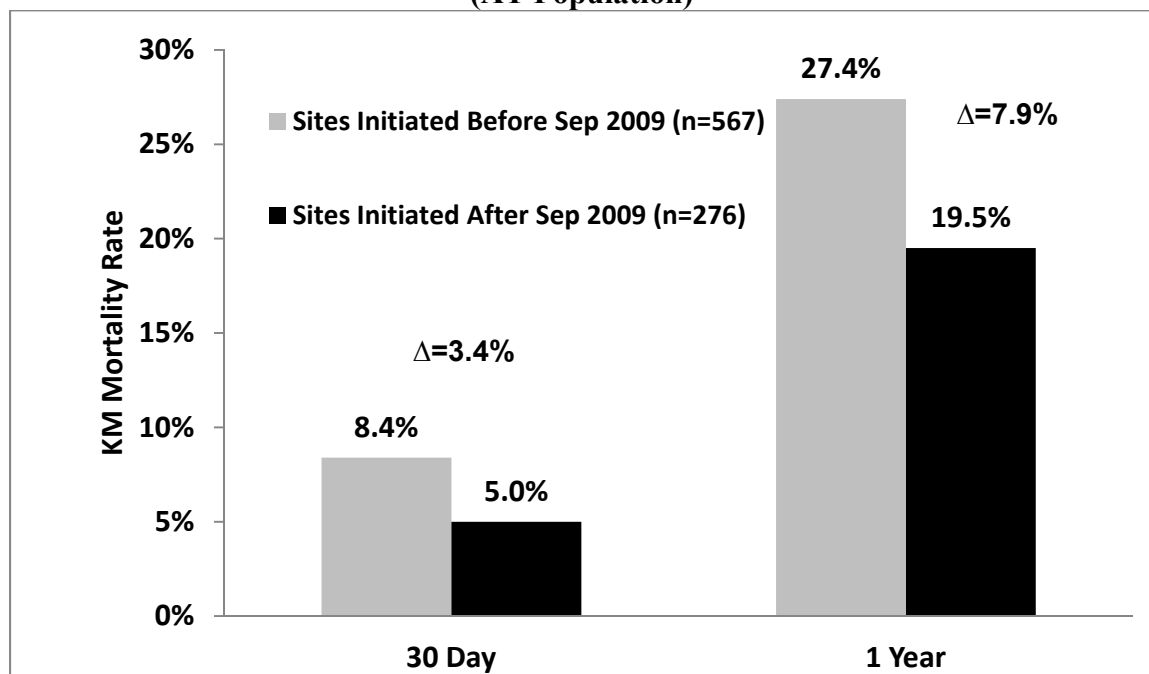




Figure 32 shows the impact of accumulated transapical experience on mortality. A total of 14 sites were initiated before September 2009, and an additional 14 sites were initiated after September 2009. Mortality rates decreased in sites that were initiated later suggesting that transmission of accumulated knowledge to later adopting sites through training and education leads to comparable results to those obtained in more experienced centers.

Figure 32 Impact of Accumulated Transapical Site Experience on Mortality (AT Population)





As shown in Table 73, the transapical stroke rate in the NRCA group was considerably lower than the stroke rate reported for the randomized TAVR arm:

- Transapical NRCA stroke rate 2.0% vs. 7.0% randomized TAVR at 30 days
- Transapical NRCA stroke rate 3.7% vs. 10.8% randomized TAVR at 1 year

The transfemoral stroke rate in the NRCA group was higher than the stroke rate reported for the randomized TF TAVR arm at 30 days (4.4% vs. 3.3%) and 1 year (5.7% vs. 3.8%).

In the pooled population, the stroke rate in the NRCA group was lower than the stroke rate reported for the randomized TAVR arm at 30 days and 1 year.

Table 73. Stroke – Randomized TAVR and NRCA Patients (AT Population)

| | | Total Events | | 30 day events | | | 1 year events | | |
|---------------------|-------------------|--------------|---------------------|---------------|---------------------|--------------------------|---------------|---------------------|-------------------------|
| | Patients in group | Total events | Patients with event | Events | Patients with event | KM Event rate at 30 days | Events | Patients with event | KM Event rate at 1 year |
| STROKE | | | | | | | | | |
| Pooled | | | | | | | | | |
| NRCA | 1521 | 62 | 60 | 48 | 46 | 3.1% | 60 | 58 | 4.6% |
| Randomized TAVR | 344 | 23 | 23 | 15 | 15 | 4.4% | 19 | 19 | 5.8% |
| Randomized AVR | 313 | 18 | 17 | 8 | 8 | 2.6% | 9 | 9 | 3.0% |
| Transapical | | | | | | | | | |
| NRCA | 822 | 24 | 23 | 17 | 16 | 2.0% | 23 | 22 | 3.7% |
| Randomized TAVR | 104 | 12 | 12 | 7 | 7 | 7.0% | 10 | 10 | 10.8% |
| Randomized AVR | 92 | 10 | 9 | 5 | 5 | 5.5% | 6 | 6 | 7.0% |
| Transfemoral | | | | | | | | | |
| NRCA | 699 | 38 | 37 | 31 | 30 | 4.4% | 37 | 36 | 5.7% |
| Randomized TAVR | 240 | 11 | 11 | 8 | 8 | 3.3% | 9 | 9 | 3.8% |
| Randomized AVR | 221 | 8 | 8 | 3 | 3 | 1.4% | 3 | 3 | 1.4% |

Source: Table 5.2



Stroke at 30 days for randomized TAVR, randomized AVR and NRCA TAVR patients is illustrated in Figure 33; stroke at 30 days stratified by surgical approach for randomized TAVR, randomized AVR and NRCA TAVR patients is presented in Figure 31.

Figure 33. All Stroke at 30 Days– High Risk Randomized TAVR, Randomized AVR and NRCA TAVR Patients (AT Population)

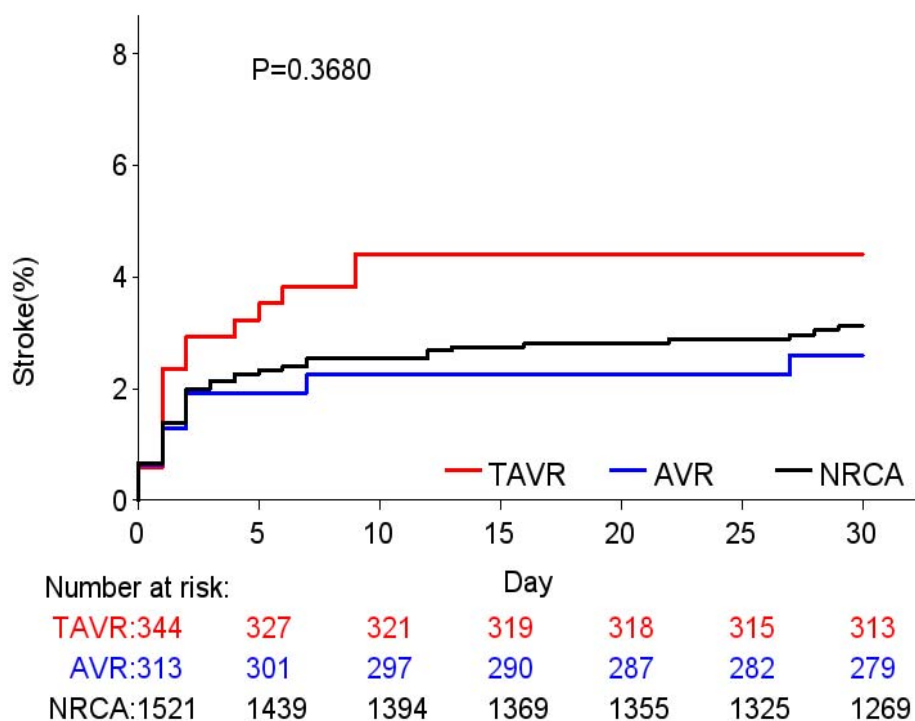




Figure 34. All Stroke at 30 Days– High Risk Randomized AVR, Randomized TAVR Patients, and NRCA TAVR Patients Stratified by Implant Approach (AT Population)

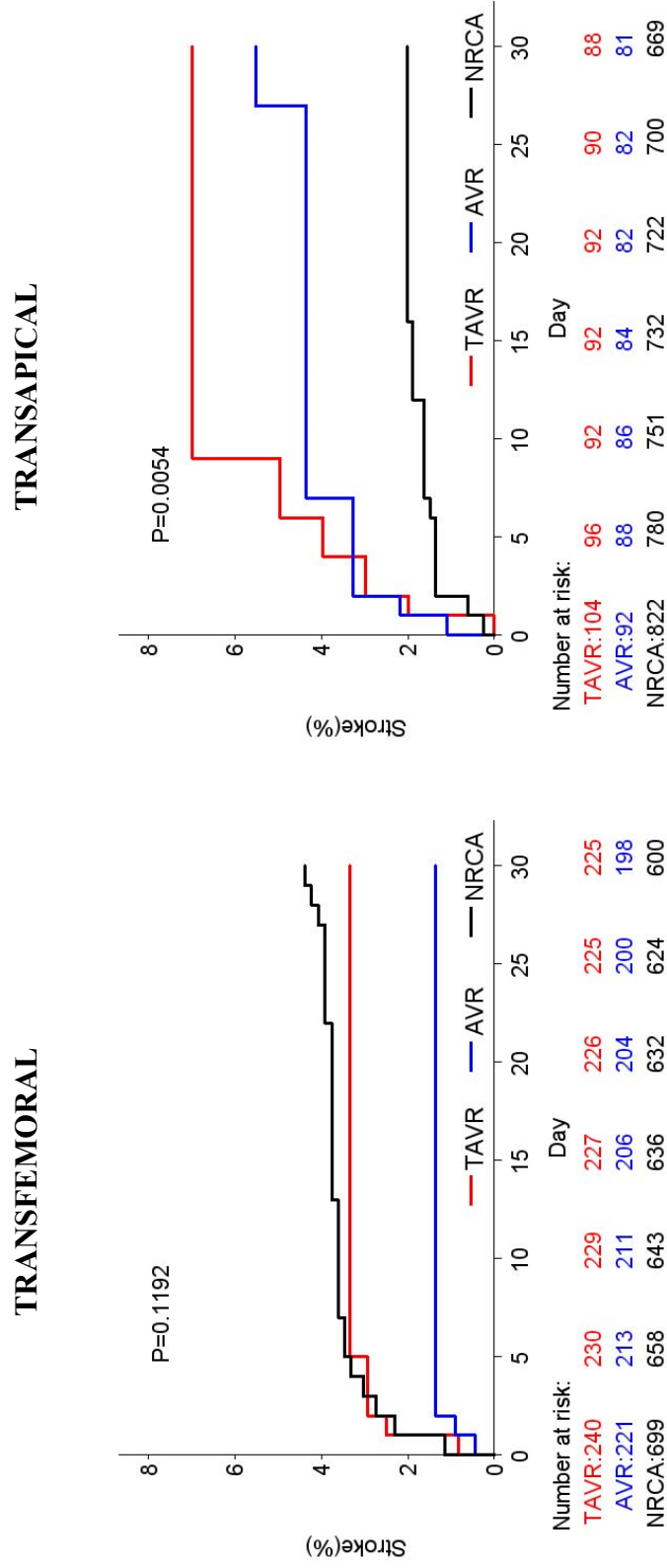
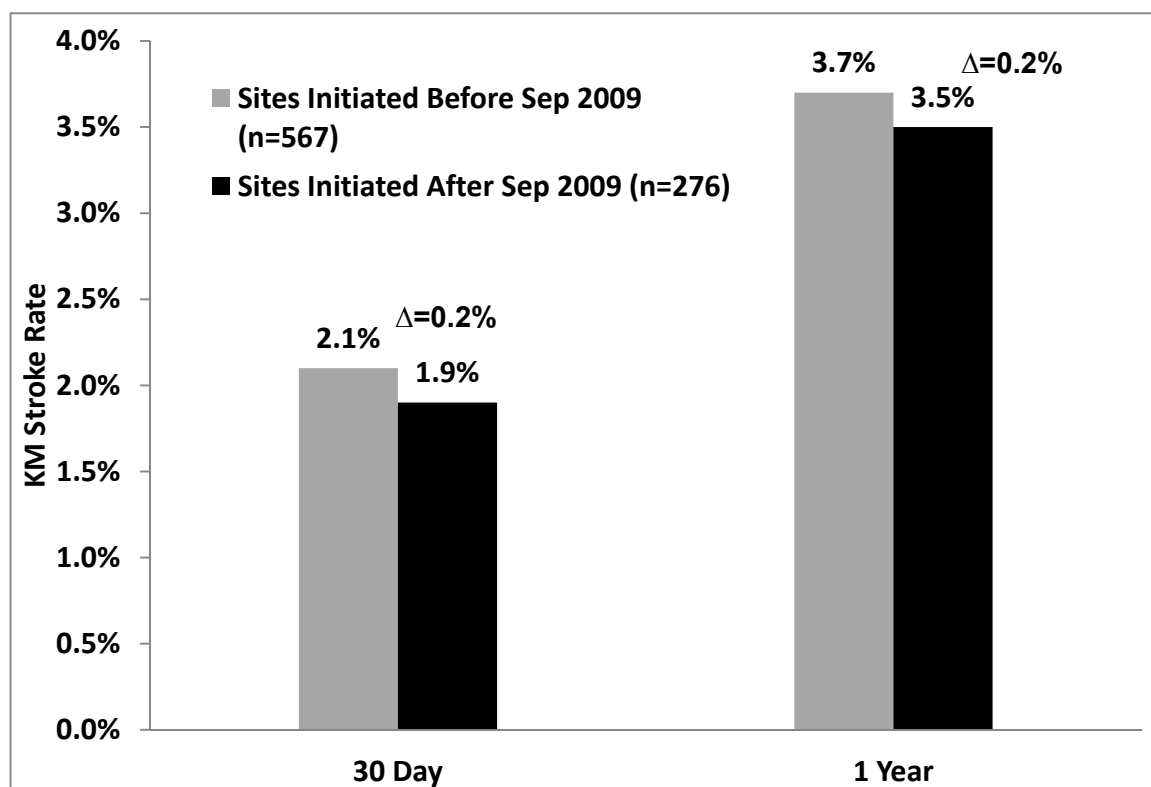




Figure 35 shows the impact of accumulated transapical experience on stroke. Stroke rates decreased in sites that were initiated later suggesting that transmission of accumulated knowledge to later adopting sites through training and education leads to comparable results to those obtained in more experienced centers.

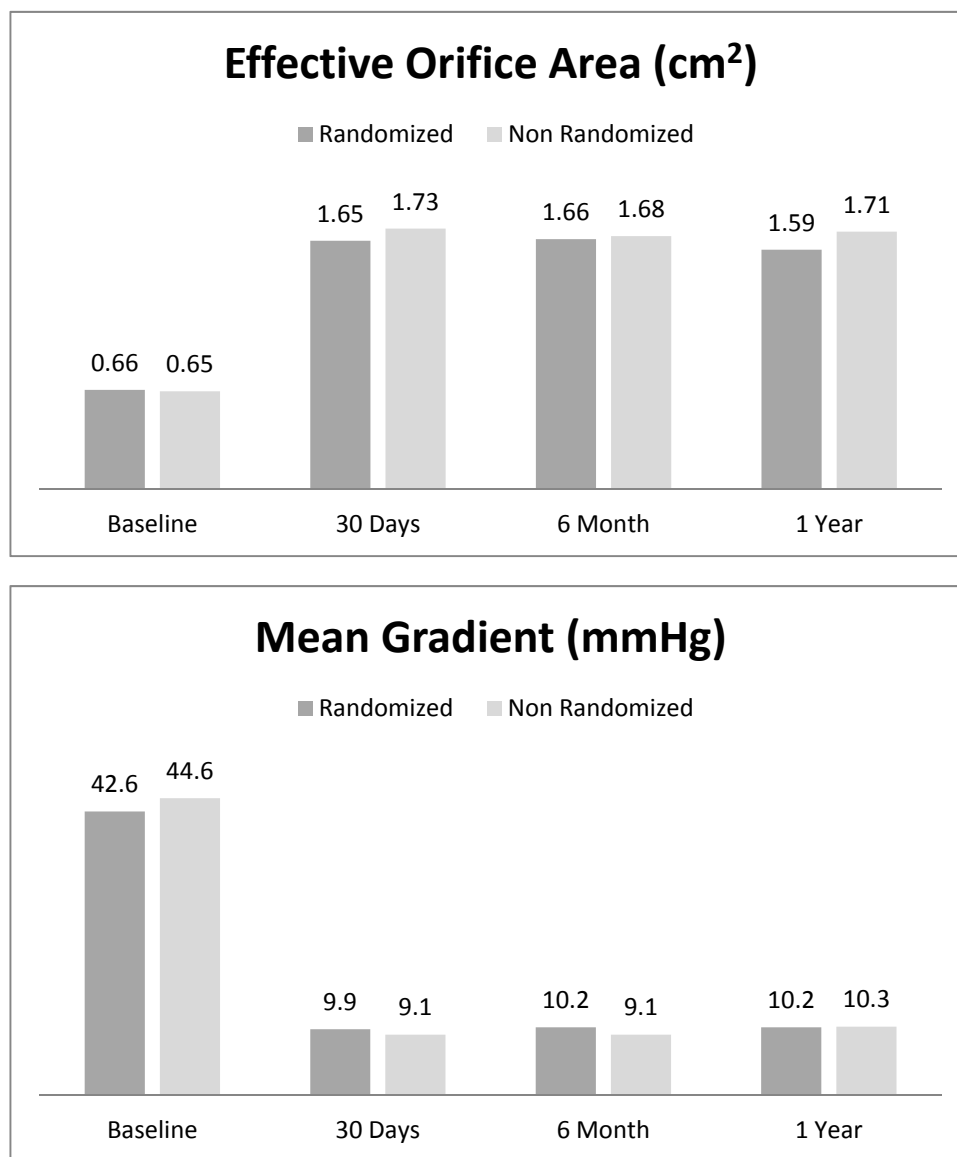
Figure 35 Impact of Accumulated Transapical Site Experience on Stroke (AT Population)



Mean EOA and mean gradient among the randomized TAVR arm and NCRA cohort are illustrated in Figure 36. In the NCRA group, moderate to severe paravalvular leak was reported for 13.2% at 30 days, 12.6% at 6 months and 12.9% at 1 year (Table 99 – **Appendix F**).



Figure 36. Echocardiography Data – High Risk Randomized TAVR vs. Non Randomized, Continued-Access Patients (AT Population)





The proportion of NRCA patients in NYHA class I and II was 4.7% at baseline, 72.4% at 30 days, 73.2% at 6 months, and 59.7% at 1 year (Table 74)

Table 74. NYHA by Visit – High Risk Randomized TAVR and NRCA Patients (AT Population)

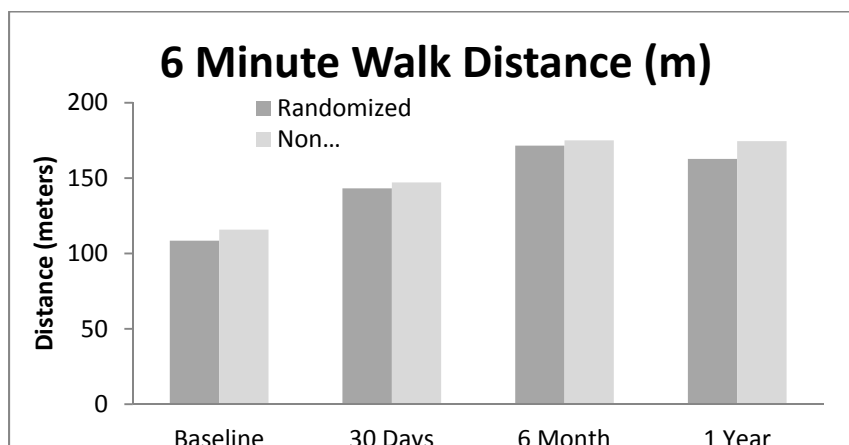
| Visit | Statistics | Cohort A Randomized Patients -- AT | | | Cohort A Continued Access Patients -- AT | | |
|----------|----------------|------------------------------------|-----------------------|-------------------|--|-----------------------|-------------------|
| | | Transapical Approach | Transfemoral Approach | Pooled Approaches | Transapical Approach | Transfemoral Approach | Pooled Approaches |
| | | TAVR (N=104) | TAVR (N=240) | TAVR (N=344) | NRCA (N=822) | NRCA (N=699) | NRCA (N=1521) |
| BASELINE | n | 104 | 240 | 344 | 822 | 696 | 1518 |
| | NYHA Class I | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.3) | 2 (0.1) |
| | NYHA Class II | 8 (7.7) | 12 (5.0) | 20 (5.8) | 43 (5.2) | 27 (3.9) | 70 (4.6) |
| | NYHA Class III | 42 (40.4) | 102 (42.5) | 144 (41.9) | 411 (50.0) | 313 (45.0) | 724 (47.7) |
| | NYHA Class IV | 54 (51.9) | 126 (52.5) | 180 (52.3) | 368 (44.8) | 354 (50.9) | 722 (47.6) |
| | Dead | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 30 DAY | n | 97 | 226 | 323 | 793 | 678 | 1471 |
| | NYHA Class I | 14 (14.4) | 76 (33.6) | 90 (27.9) | 268 (33.8) | 245 (36.1) | 513 (34.9) |
| | NYHA Class II | 44 (45.4) | 101 (44.7) | 145 (44.9) | 289 (36.4) | 300 (44.2) | 589 (40.0) |
| | NYHA Class III | 25 (25.8) | 33 (14.6) | 58 (18.0) | 134 (16.9) | 97 (14.3) | 231 (15.7) |
| | NYHA Class IV | 7 (7.2) | 7 (3.1) | 14 (4.3) | 36 (4.5) | 15 (2.2) | 51 (3.5) |
| | Dead | 7 (7.2) | 9 (4.0) | 16 (5.0) | 66 (8.3) | 21 (3.1) | 87 (5.9) |
| 6 MONTH | n | 98 | 232 | 330 | 676 | 585 | 1261 |
| | NYHA Class I | 30 (30.6) | 82 (35.3) | 112 (33.9) | 281 (41.6) | 239 (40.9) | 520 (41.2) |
| | NYHA Class II | 31 (31.6) | 93 (40.1) | 124 (37.6) | 191 (28.3) | 212 (36.2) | 403 (32.0) |
| | NYHA Class III | 14 (14.3) | 25 (10.8) | 39 (11.8) | 60 (8.9) | 46 (7.9) | 106 (8.4) |
| 1 YEAR | NYHA Class IV | 3 (3.1) | 5 (2.2) | 8 (2.4) | 6 (0.9) | 8 (1.4) | 14 (1.1) |
| | Dead | 20 (20.4) | 27 (11.6) | 47 (14.2) | 138 (20.4) | 80 (13.7) | 218 (17.3) |
| | n | 99 | 230 | 329 | 450 | 374 | 824 |
| | NYHA Class I | 34 (34.3) | 85 (37.0) | 119 (36.2) | 152 (33.8) | 138 (36.9) | 290 (35.2) |
| | NYHA Class II | 24 (24.2) | 69 (30.0) | 93 (28.3) | 98 (21.8) | 104 (27.8) | 202 (24.5) |
| | NYHA Class III | 11 (11.1) | 21 (9.1) | 32 (9.7) | 27 (6.0) | 16 (4.3) | 43 (5.2) |
| | NYHA Class IV | 1 (1.0) | 4 (1.7) | 5 (1.5) | 5 (1.1) | 6 (1.6) | 11 (1.3) |
| | Dead | 29 (29.3) | 51 (22.2) | 80 (24.3) | 168 (37.3) | 110 (29.4) | 278 (33.7) |

Source: Table 6.6

During a 6-minute walk test, NRCA patients walked, on average, further at 3 months, 6 months, and 1 year, than they did at baseline (Figure 37).



Figure 37. 6-Minute Walk Distance – High Risk Randomized TAVR vs. NRCA Patients (AT Population)



Source: Table 6.8

Per protocol defined AEs for the NRCA patients are presented in Table 75. The most common event was infection. At 1 year, the proportion of patients with MACCE (death, stroke, myocardial infarction and renal failure) was 22.5% in the transfemoral NRCA group and 25.3% in the transapical NRCA group.

Table 75. Adverse Events (Per Protocol Definitions) – High Risk NRCA Patients (AT Population)

| Per Protocol AE Non-Randomized Continued Access Cohort A (AT) | | | | | | | | | | | |
|---|-------------------|--------------|---------------------|------------|---------------------|--------------------------|------------------|---------------------|-------------------------|----------|---------------------|
| | | Total Events | | <= 30 days | | | 31 days - 1 year | | | > 1 year | |
| | Patients in group | Total events | Patients with event | Events | Patients with event | KM Event rate at 30 days | Events | Patients with event | KM Event rate at 1 year | Events | Patients with event |
| Annular dissection | | | | | | | | | | | |
| NRCA: TA | 822 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| NRCA: TF | 699 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| Aortic Dissection | | | | | | | | | | | |
| NRCA: TA | 822 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| NRCA: TF | 699 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| Aortic Stenosis | | | | | | | | | | | |
| NRCA: TA | 822 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| NRCA: TF | 699 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |



| Per Protocol AE Non-Randomized Continued Access Cohort A (AT) | | | | | | | | | | | |
|---|-------------------|--------------|---------------------|------------|---------------------|--------------------------|------------------|---------------------|-------------------------|----------|---------------------|
| | | Total Events | | <= 30 days | | | 31 days - 1 year | | | > 1 year | |
| | Patients in group | Total events | Patients with event | Events | Patients with event | KM Event rate at 30 days | Events | Patients with event | KM Event rate at 1 year | Events | Patients with event |
| Bleeding event | | | | | | | | | | | |
| NRCA: TA | 822 | 31 | 26 | 8 | 8 | 1.1% | 23 | 19 | 5.7% | 0 | 0 |
| NRCA: TF | 699 | 25 | 23 | 5 | 5 | 0.7% | 19 | 19 | 5.2% | 1 | 1 |
| Device migration | | | | | | | | | | | |
| NRCA: TA | 822 | 2 | 2 | 2 | 2 | 0.2% | 0 | 0 | 0.2% | 0 | 0 |
| NRCA: TF | 699 | 3 | 3 | 3 | 3 | 0.4% | 0 | 0 | 0.4% | 0 | 0 |
| Embolic event | | | | | | | | | | | |
| NRCA: TA | 822 | 7 | 6 | 7 | 6 | 0.8% | 0 | 0 | 0.8% | 0 | 0 |
| NRCA: TF | 699 | 8 | 8 | 8 | 8 | 1.2% | 0 | 0 | 1.2% | 0 | 0 |
| Hemolysis | | | | | | | | | | | |
| NRCA: TA | 822 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| NRCA: TF | 699 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| Hemorrhagic/Vascular event | | | | | | | | | | | |
| NRCA: TA | 822 | 70 | 55 | 59 | 46 | 5.7% | 11 | 10 | 7.9% | 0 | 0 |
| NRCA: TF | 699 | 82 | 63 | 73 | 59 | 8.5% | 9 | 8 | 9.5% | 0 | 0 |
| Infection (including Endocarditis) | | | | | | | | | | | |
| NRCA: TA | 822 | 340 | 244 | 194 | 155 | 20.0% | 128 | 103 | 37.0% | 18 | 16 |
| NRCA: TF | 699 | 228 | 164 | 111 | 92 | 13.8% | 113 | 88 | 29.1% | 4 | 4 |
| Myocardial infarction | | | | | | | | | | | |
| NRCA: TA | 822 | 10 | 10 | 5 | 5 | 0.6% | 2 | 2 | 1.0% | 3 | 3 |
| NRCA: TF | 699 | 4 | 4 | 2 | 2 | 0.3% | 2 | 2 | 0.6% | 0 | 0 |
| Nonstructural valve dysfunction | | | | | | | | | | | |
| NRCA: TA | 822 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| NRCA: TF | 699 | 5 | 5 | 5 | 5 | 0.7% | 0 | 0 | 0.7% | 0 | 0 |
| Perforation or damage to myocardium | | | | | | | | | | | |
| NRCA: TA | 822 | 7 | 7 | 7 | 7 | 0.9% | 0 | 0 | 0.9% | 0 | 0 |
| NRCA: TF | 699 | 2 | 2 | 2 | 2 | 0.3% | 0 | 0 | 0.3% | 0 | 0 |
| Peripheral Vascular Disease | | | | | | | | | | | |
| NRCA: TA | 822 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| NRCA: TF | 699 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| Perivalvular leak | | | | | | | | | | | |



| Per Protocol AE Non-Randomized Continued Access Cohort A (AT) | | | | | | | | | | | |
|---|-------------------|--------------|---------------------|------------|---------------------|--------------------------|------------------|---------------------|-------------------------|----------|---------------------|
| | | Total Events | | <= 30 days | | | 31 days - 1 year | | | > 1 year | |
| | Patients in group | Total events | Patients with event | Events | Patients with event | KM Event rate at 30 days | Events | Patients with event | KM Event rate at 1 year | Events | Patients with event |
| NRCA: TA | 822 | 21 | 21 | 18 | 18 | 2.2% | 3 | 3 | 3.2% | 0 | 0 |
| NRCA: TF | 699 | 21 | 18 | 16 | 14 | 2.0% | 4 | 4 | 2.8% | 1 | 1 |
| Rehospitalization for symptoms of aortic stenosis | | | | | | | | | | | |
| NRCA: TA | 822 | 84 | 61 | 24 | 21 | 2.8% | 50 | 43 | 10.9% | 10 | 7 |
| NRCA: TF | 699 | 69 | 55 | 19 | 19 | 2.9% | 48 | 39 | 10.9% | 2 | 2 |
| Renal failure | | | | | | | | | | | |
| NRCA: TA | 822 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| NRCA: TF | 699 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| Renal insufficiency | | | | | | | | | | | |
| NRCA: TA | 822 | 67 | 65 | 60 | 59 | 7.5% | 5 | 5 | 8.6% | 2 | 2 |
| NRCA: TF | 699 | 27 | 24 | 18 | 16 | 2.3% | 9 | 8 | 4.3% | 0 | 0 |
| Sternal wound infection | | | | | | | | | | | |
| NRCA: TA | 822 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| NRCA: TF | 699 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| Stroke | | | | | | | | | | | |
| NRCA: TA | 822 | 24 | 23 | 17 | 16 | 2.0% | 6 | 6 | 3.7% | 1 | 1 |
| NRCA: TF | 699 | 38 | 37 | 31 | 30 | 4.4% | 6 | 6 | 5.7% | 1 | 1 |
| Transient ischemic attack (TIA) | | | | | | | | | | | |
| NRCA: TA | 822 | 7 | 5 | 3 | 3 | 0.4% | 2 | 1 | 0.6% | 2 | 1 |
| NRCA: TF | 699 | 4 | 4 | 2 | 2 | 0.3% | 2 | 2 | 0.6% | 0 | 0 |
| Valvular thrombosis | | | | | | | | | | | |
| NRCA: TA | 822 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| NRCA: TF | 699 | 0 | 0 | 0 | 0 | 0.0% | 0 | 0 | 0.0% | 0 | 0 |
| Endocarditis (Site) | | | | | | | | | | | |
| NRCA: TA | 822 | 4 | 4 | 0 | 0 | 0.0% | 3 | 3 | 0.6% | 1 | 1 |
| NRCA: TF | 699 | 2 | 2 | 0 | 0 | 0.0% | 2 | 2 | 0.4% | 0 | 0 |
| MACCE | | | | | | | | | | | |
| NRCA: TA | 822 | 187 | 172 | 87 | 79 | 9.8% | 87 | 84 | 25.3% | 13 | 11 |
| NRCA: TF | 699 | 143 | 125 | 55 | 49 | 7.1% | 80 | 74 | 22.5% | 8 | 7 |

KM=Kaplan-Meier, TA=transapical, TF=transfemoral.

Source: Table 5.3

Bleeding Event

Any episode of major internal or external bleeding that caused death, hospitalization or permanent



| | |
|-----------------------------------|---|
| | injury (e.g., vision loss) or necessitated transfusion of greater than 3 units PRBCs or pericardiocentesis procedure. |
| Peripheral embolic event | A peripheral embolic event was an operative, autopsy or clinically documented embolus that produced symptoms from complete or partial obstruction of a peripheral (noncerebral) artery. |
| Hemorrhagic Vascular Complication | Hematoma at access site >5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. . |
| Stroke | A neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction |
| TIA | A fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction |
| Myocardial Infarction | Acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI |
| Renal Failure | Patient required chronic dialysis for greater than 30 days |
| Renal Insufficiency | Creatinine level above 3.5 |
| MACCE | Death, MI, Renal Failure, and Stroke using the event definitions above. |

11.2 Roll-in Patients from PARTNER Study

For the purposes of investigator training, which included two proctored TAVR procedures, there were 2 roll-in patients with successful delivery of the Edwards SAPIEN THV to its intended location per delivery approach per new clinical site. For scheduling purposes, all roll-in patients (n=41) were scheduled to undergo TAVR. Results for these patients were not pooled with any other group for analysis.

As of September 21, 2011 a total of 38 of the 41 roll-in patients were included in the AT population; 19 transapical and 19 transfemoral patients. Data reported in this Briefing Document involve the AT roll-in population only. The mean (SD) age of the roll-in cohort was 83.7 (7.5) years. Twenty-three of the 38 patients (60.5%) were male, and most (30/38, 78.9%) were Caucasian. They were primarily in NYHA class III (n=20, 52.6%) or NYHA class IV (n=15, 39.5%). Most patients (32/38 or 84.2%) had undergone prior cardiovascular intervention/surgery. The mean (SD) STS Risk Score was 11.6 (4.0) and logistic EuroSCORE was 27.8 (17.7). In the roll-in cohort, the mean (SD) follow-up time was 1.8 (1.0) years. There was excellent follow-up compliance through 3 years (100% at each visit).

At 30 days, the KM death rates were 5.3% for transfemoral patients and 15.8% for the transapical patients; these rates were 21.1% and 26.3% respectively at 1 year. Of the 20



roll-in patients who had died at the time of the database extract on September 21, 2011, a total of ten (10) patients had died due to cardiovascular causes, eight (8) patients had died due to non cardiovascular causes and in two patients the cause of death was not specified.

The proportion of patients with NYHA class I and II increased from 7.9% at baseline to 57.8% at 30 days, 68.4% at 6 months, 60.5% at 1 year, and 52.6% at 2 years. Results of the 6-minute walk test improved almost 50% from baseline to 1 year (mean = 129.2 meters at baseline, 162.4 meters at 30 days, 183.3 meters at 6 months, and 192.3 meters at 1 year).

A total of 25 per protocol defined MACCE events (i.e., death, stroke, MI or renal failure) were reported for 21 patients which included 3 strokes in 2 patients who both underwent TAVR using the transapical approach.



12.0 Post-Marketing Safety Experience

12.1 European Registry – Two Consecutive Years of Post Approval Enrollment, 1-Year Results

Edwards received approval for commercialization of SAPIEN in Europe in 2007 and for SAPIEN XT in 2010 and subsequently initiated two post-approval registries (SOURCE and SOURCE XT); more than 5,000 patients have been enrolled to date.

In the SOURCE Registry, the follow-up rates at the initial sites were 99% at 30 days and 98% at one year (n=2307 patients; 920 transfemoral TAVR and 1387 transapical TAVR). At baseline, the patients who underwent transapical TAVR had a significantly higher prevalence of multiple comorbidities (e.g., renal insufficiency – 31.1% vs. 24.9% for transfemoral patients; peripheral vascular disease – 26.4% vs. 10.2%, respectively; porcelain aorta – 10.2% vs. 4.0%, respectively; carotid artery stenosis > 50% – 15.1% vs. 6.8%, respectively; multivessel coronary disease – 36.6% vs. 21.7%, respectively) and higher logistic EuroSCORE (mean = 27.6 vs. 23.9, respectively). They had also undergone CABG (25.5% vs. 15.4%) and AVR (1.7% vs. 0.3%, respectively) more commonly prior to study enrollment.

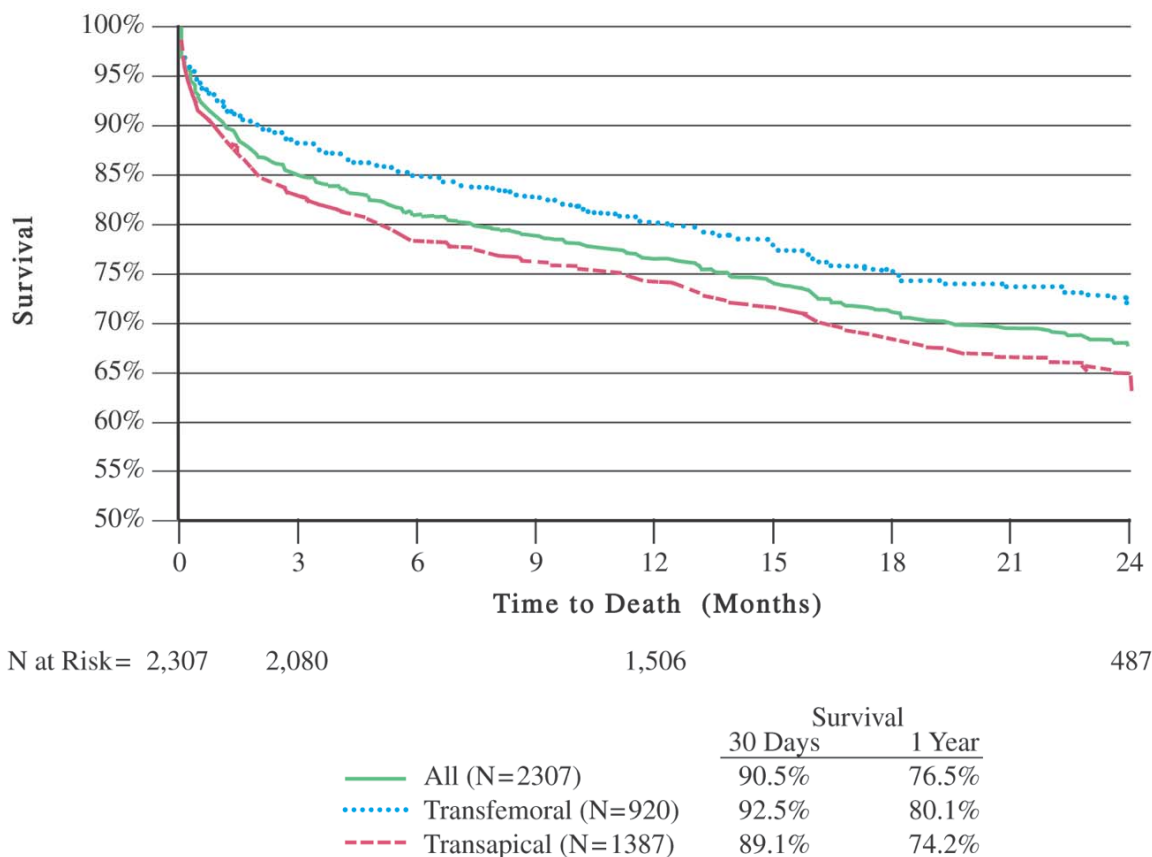
Procedural success rate (defined as one valve implanted, aortic regurgitation < 2+, and patient left procedure room alive) was 93.0% for transfemoral TAVR and 92.2% for transapical TAVR. At 30 days, there was no difference based on implantation approach for incident stroke (2.7%), aortic regurgitation > 2+/perivalvular leakage (4.2%), or need for a pacemaker (7.0%). The incidence of a major bleeding event was significantly greater among patients having transapical TAVR (3.9% vs. 2.3%), whereas the incidence of vascular access-related complications was significantly higher among patients having transfemoral TAVR (major: 11.3% vs. 2.0%; minor: 10.4% vs. 1.0%).

Figure 38 shows two-year outcomes. Early major vascular access-related complications (i.e., limb-threatening ischemia, vessel rupture requiring additional unplanned vascular surgery or interventional treatment; major vascular access-related adverse events included aortic dissection and annular dissection) were a significant risk factor for 30-day



and 1-year mortality ($P<0.001$ for both TAVR approaches). More than half (51.6%) of deaths up to 1 year had a non-cardiac etiology and were related to baseline comorbidities.

Figure 38. Kaplan-Meier Survival - SOURCE Registry



The 30-day mortality rate among transfemoral TAVR patients in the SOURCE registry was 7.5%, which compares with rates in Cohort B of the PARTNER US trial of 5.0% for patients considered inoperable and 3.3% for high-risk patients. The respective 1-year mortality rates were 19.9% in SOURCE vs. 30.7% and 22.2% in PARTNER US.

The 30-day mortality rate for transapical TAVR patients in the SOURCE registry was 10.9% compared to 8.7% of transapical patients in Cohort A of the PARTNER US trial.



The 1-year mortality rates were 25.9% in the SOURCE Registry and 29.1% in the PARTNER US Cohort A respectively.

In a comparison of procedures performed in the 15 months immediately after approval in Europe (November 2007 to January 2009; N=1038) to those performed more recently (February 2009 to December 2009; N=1269), procedural success (91.7% vs. 93.2%), vascular complications (major 6.6% vs. 5.0%), and survival (76.0% vs. 77.0% at 1 year; 67.5% vs. 67.8% at 2 years) were similar between the periods. The cardiac comorbidities of patients prior to TAVR increased over time (heart failure, 27.5% vs. 34.4%; multivessel disease, 24.8% vs. 35.1%; previous AVR, 0.2% vs. 2.0%; all $P<0.001$) and their logistic EuroSCORE decreased (27.6 vs. 25.0, $P<0.001$). Implantation via the transapical approach became even more common (55.4% vs. 64.0%).

Data recently presented at the European Association of Cardiothoracic Surgeons meeting (October, 2011) showed low rates of adverse events after one year as depicted in the Table 76. Freedom from death at 2-years is 65.3% with the majority of deaths in the second year being non-cardiac in nature (46.7%) versus cardiac (40.0%).

Table 76. SOURCE Registry Transapical Adverse Events

| | KM Freedom from Events | | |
|--------------------------|------------------------|----------|----------|
| Term | 30 Days | < 1 Year | > 1 Year |
| Myocardial Infarction | 99.5% | 98.7% | 98.4% |
| Endocarditis | 99.9% | 99.3% | 99.1% |
| Valve Thrombosis | 99.9% | 99.9% | 99.9% |
| Any Stroke | 97.3% | 95.1% | 93.8% |
| Stroke/Ischemic | 97.3% | 95.4% | 94.3% |
| Stroke/Hemorrhagic | 100.0% | 99.9% | 99.8% |
| Stroke/Unknown | 100.0% | 99.7% | 99.7% |
| Renal failure & dialysis | 92.9% | 92.1% | 91.8% |
| New Pacemaker | 92.4% | 91.7% | 90.9% |



12.2 Experience with SAPIENXT

Edwards has introduced SAPIEN XT THV into OUS markets to broaden indication, improve procedure outcomes and potentially complications. Therefore, additional experience in the related SAPIEN XT THV and the NovaFlex delivery catheter for transfemoral cases as well as the Ascendra 2 system for transapical cases is provided in **Appendix J**.



13.0 Risk Management Program

13.1 Measures to Mitigate Stroke Risk after TAVR

Since recognizing the increased frequency and likely etiologies of strokes associated with TAVR, several measures will be described to mitigate stroke risk, including changes in procedural factors, technology enhancements, and modifications of anticoagulation regimens. Best procedural practices which are now generally utilized in all TAVR procedures are:

- Careful anesthesia control to maintain BP in a tight range to avoid episodes of hypotension or hypertension
- Reducing the number and duration of rapid-RV pacing to avoid sustained hypotension
- Reducing the size and number of pre-dilations with valvuloplasty balloons
- Minimizing THV catheter manipulations across the native diseased aortic valve prior to deployment

In addition, the introduction of the new SAPIEN XT THV and the NovaFlex delivery catheter for transfemoral cases (as well as the Ascendra 2 system for transapical cases) may provide important technical advantages (**Appendix J**).

Finally, the anticoagulation regimens employed in these elderly patients with multiple comorbidities and frequent arrhythmias have not been well standardized. After counseling of several experts and polling all PARTNER investigators, the Steering Committee has devised a more rigorous program of tiered anticoagulation treatment based upon patient risk stratas which will be integrated in the labeling.

13.2 Measures to Mitigate Vascular Complications after TAVR

Clinical operators have been proactive in devising strategies to reduce vascular complications after TAVR and these strategies will be integrated in the labeling. A critical insight has been the systematic use of computed tomographic angiography (CTA) studies to screen potential treatment candidates. Based upon the composite analysis of



cross-sectional iliac and femoral artery dimensions, circumferential calcification (including location), and vessel tortuosity, experienced TAVR operators have significantly improved case selection criteria. The procedure has also been modified, such that early recognition of complications are managed more effectively (reducing bleeding and other clinical sequelae) and careful percutaneous access and closure techniques have been incorporated based upon increased operator experience. A more subtle procedural modification has been operator preference to select alternative transapical access in borderline cases where peripheral vascular anatomy is suboptimal. Lastly, and likely of greatest importance, is the clear recognition that improved technology with lower profile sheaths (Figure 56) can reduce vascular complications.

A recent “in press” manuscript from Vancouver^k clearly describes the impact of experience and new technology on the frequency and impact of vascular complications after TAVR. In this study, 137 consecutive patients were compared from two treatment periods, wherein the more recently treated patients had careful computed tomographic angiographic screening, percutaneous repair techniques, and smaller caliber sheaths. In these more recently treated patients, major vascular complications decreased from 8% to 1% ($p = 0.06$), minor vascular complications decreased from 24% to 8% ($p < 0.01$), major bleeding fell from 14% to 1% ($p < 0.01$) and unplanned surgery decreased from 28% to 2% ($p < 0.01$). A minimal artery diameter smaller than the external sheath diameter, moderate or severe calcification, and peripheral vascular disease were associated with higher vascular complication rates.

During training, the combined experiences of previous studies will be applied and rigorously enforced to reduce vascular complications. It will be recommended for all patients to undergo careful screening CTA studies, operator technique training will be emphasized (see **Section 13.3**, including percutaneous access and closure methods) and,

^k Toggweiler S, Gurvitch R, Leipsic J, Wood DA, Willson AB, Binder RK, Cheung A, Ye J, Webb JG. Percutaneous Aortic Valve Replacement. Vascular Outcomes with a Fully Percutaneous Procedure.



in the near future, availability of the lower profile SAPIEN XT and NovaFlex system devices should facilitate sheath entry and removal.

13.3 Physician Training

Pre-procedural screening is critical in determining patient appropriateness for TAVR and mitigating potential procedural complications. Edwards has developed detailed training materials for physicians, with a focus on the SAPIEN Transcatheter Heart Valve, RetroFlex 3 Transfemoral Delivery System, Ascendra Delivery System, patient screening, and their interrelationship.

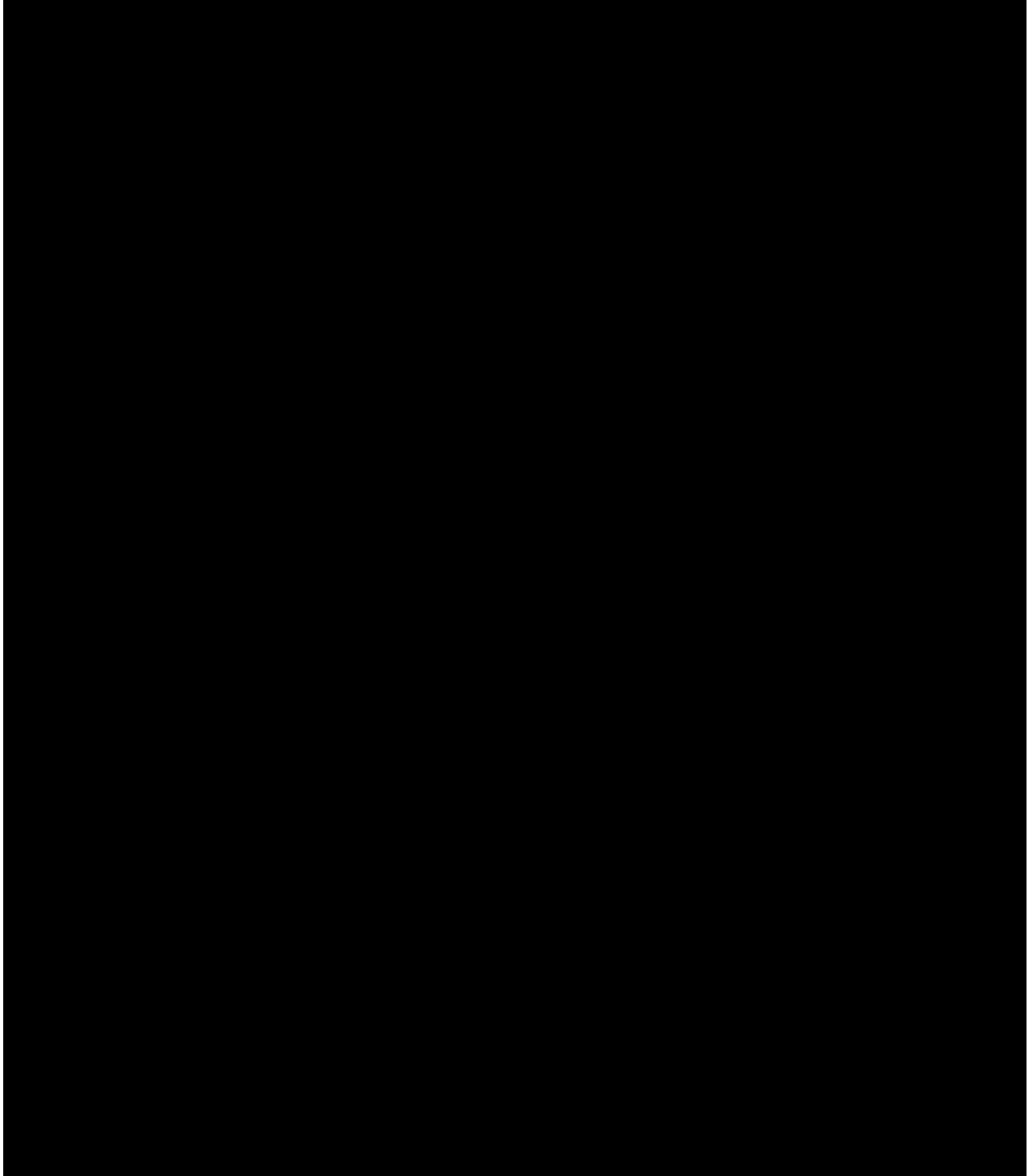
The Training Materials provide extensive information on patient screening such that suitable candidates for TAVR are identified. After qualifying on the basis of severe symptomatic aortic stenosis (definition provided), patients will need various imaging tests to assess if they are appropriate candidates for SAPIEN. Imaging will assess the following points, as discussed in the Training Materials:

- Is the aortic valvular complex suitable?
- Are the peripheral vessels and aortic arch (angulation and stenosis) suitable?
- Coronary arteries - is coronary revascularization necessary prior to valve implantation?
- Left ventricle – function and anatomy

The Training Materials include sections on: pre-procedure Device Preparation; Procedure and Techniques (e.g., room set-up, anesthesia, patient preparation, valve size selection, access options, puncture site, balloon valvuloplasty, and a step-by-step explanation of the TAVR procedure), followed by instructions on post-implantation valve position, aortic regurgitation assessments, delivery system/sheath removal, and closure options. The Training Materials also provide multiple post-procedure considerations in the form of aortogram images and accompanying text/tips.



13.4 Proposed PARTNER Post-Approval Study in the United States





13.5 Edwards' Commitment to Responsible Commercialization

The Edwards SAPIEN valve was commercialized launched in Europe in Q4, 2007. Globally, there are about 400 heart centers implanting the Edwards SAPIEN valve and over 15,000 patients have been treated. Each of the 400 heart centers has completed Edwards training program. Our focus is on ensuring excellent patient outcomes.

The key to commercialization efforts is Edwards' commitment to training. In each heart center, the existence of a heart team comprised of both interventional cardiologist as well as cardiac surgeons is required. Edwards has declined to commercialize centers where cardiac surgery support was not available.

The Edwards THV training program is multi-faceted and includes:

- Foundational didactic course
- Simulation training
- Device preparation and use training
- Case observation
- Peer proctoring
- On-going support by the Field Clinical Specialist
- Continuing education

After site selection and prior to training, the heart team requirements will be reviewed at an initial meeting. Sites are then provided with the training manual along with specific radiologic and echo training videos. Lastly, the site begins the patient screening process and an eLearning test.

After pre-training, the site attends a formal two day training course at one of our training sites. The first day of the training focuses on the heart team, patient screening, operative



assessment, echo, and vascular screening. The site is also expected to present two screened cases for review. The cases brought by the site are important as it transfers the learning of screening to real life examples. In addition, step-by-step case management and decision making process are addressed. Day two focuses on potential complications as early detection and proper management. Followed by a hands-on session with device demonstrations to explain not only the function, but the design intent of the system. Device preparation and handling are also covered. Lastly, the team proceeds to simulation training which is a key part of the program. The simulators are custom for the Edwards- SAPIEN program and allow the operator to practice the procedural steps. The system is very sophisticated and captures critical metrics such as contrast usage and trains the site on terminology specific to the procedure.

After the two day training course, the heart team is ready to perform their first cases and moves to the proctor phase. Each site is proctored until the proctor and the Edwards Field Clinical Specialist determine the site is ready to be proctor independent. A site is proctored for a minimum of 2 cases; the average number of proctored cases is 5. After the proctoring phase is complete, the heart team is still supported by the Edwards Field Clinical specialists. The clinical specialist is available and can arrange a proctor if needed and is there until they are deemed ready for compete independence, but not less than 20 cases after proctoring.

Edwards Field Clinical Specialists are primarily trained cath lab technicians or certified Physicians Assistants. Field Clinical Specialists provide device preparation training and support, training updates, arrange proctor assistance, or screening support for complex cases, and ultimately decide when the site is ready for full independence.

After a site is fully independent, the Field Clinical Specialist will still attend cases periodically. Additionally, Edwards provides 24/7 tech support, continuing education and training through a web portal.

This training program has been developed and refined over the past 4 years; over 1600 physicians have been trained, over 1500 cases have been procured and more than 8000



cases have been supported. Subsequently a very high procedural success rate has been maintained as shown through the SOURCE Registry.

Sites are vetted through a detailed process. Factors evaluated include:

- Presence of heart team (cardiac surgery, cardiology, echocardiography, anesthesiology)
- Infrastructure for imaging and sterile environment
- Ability to track and report clinical outcomes
- Multi-disciplinary valve clinic environment
- Support of administration to start a TAVR program
- Procedure volume

Also taking into account are PCI volume, AVR volume, dedicated staff, presence of a valve clinical, and facilities. Based on Edwards' experience in both the PARTNER trial and the commercial sites in Europe, site selection criteria have been refined to better predict what sites will develop a successful TAVR program.

In conclusion, Edwards' plans involve a very disciplined rollout of this technology. While there are over 2000 intervention centers and 1200 cardiac surgery programs, between 150-250 centers will be trained in the first year of commercialization. The pace will be dictated based on maintaining high procedural outcomes. Additionally, the heart teams will be trained to document the patient's operable status in the patient medical record.



14.0 Conclusions

When used in the high surgical risk population the benefits and risks associated with TAVR are not inferior to the risks and benefits associated with surgical AVR and therefore should be considered a safe and effective treatment option for this population.



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16.0 Appendices



Appendix A. Additional Supportive Analyses

Additional Analyses of Demographic and Baseline Characteristics

Demographic and baseline characteristics for various study groups are provided below.

Table 77. Demographic and Other Baseline Characteristics – High Risk Cohort in the PARTNER Study (AT Population)

| Characteristic | TAVR (N=344) | AVR (N=313) | Nominal p-value |
|---|-----------------|-----------------|--------------------|
| Age - years | 83.6 ± 6.8 | 84.4 ± 6.3 | 0.12 |
| Male sex - no./total no. (%) | 198/344 (57.6%) | 179/313 (57.2%) | 0.94 |
| Race | 344 | 313 | 0.70 |
| Asian | 2 (0.6%) | 0 (0.0%) | |
| Black | 11 (3.2%) | 7 (2.2%) | |
| Caucasian | 320 (93.0%) | 294 (93.9%) | |
| Hispanic | 9 (2.6%) | 9 (2.9%) | |
| Other | 2 (0.6%) | 3 (1.0%) | |
| STS score | 11.8 ± 3.3 | 11.7 ± 3.4 | 0.65 |
| Logistic EuroSCORE | 29.4 ± 16.5 | 29.2 ± 15.2 | 0.90 |
| NYHA class - no./total no. (%) | | | |
| II | 20/344 (5.8%) | 16/313 (5.1%) | 0.73 |
| III | 144/344 (41.9%) | 134/313 (42.8%) | 0.81 |
| IV | 180/344 (52.3%) | 163/313 (52.1%) | >0.999 |
| Coronary artery disease - no./total no. (%) | 258/344 (75.0%) | 241/313 (77.0%) | 0.58 |
| Previous MI - no./total no. (%) | 92/343 (26.8%) | 90/310 (29.0%) | 0.54 |
| Prior CABG - no./total no. (%) | 146/344 (42.4%) | 139/313 (44.4%) | 0.64 |
| Prior PCI - no./total no. (%) | 115/342 (33.6%) | 101/312 (32.4%) | 0.74 |
| Prior BAV - no./total no. (%) | 46/344 (13.4%) | 32/313 (10.2%) | 0.23 |
| Peripheral vascular disease - no./total no. (%) | 148/341 (43.4%) | 132/307 (43.0%) | 0.94 |
| Cerebral vascular disease - no./total no. (%) | 96/323 (29.7%) | 79/292 (27.1%) | 0.48 |
| COPD - no./total no. (%) | | | |
| Any | 150/344 (43.6%) | 138/313 (44.1%) | 0.94 |
| Oxygen dependent | 38/218 (17.4%) | 34/204 (16.7%) | 0.90 |
| Creatinine > 2mg/dL - no./total no. (%) | 37/340 (10.9%) | 20/313 (6.4%) | 0.05 |
| Atrial fibrillation - no./total no. (%) | 80/196 (40.8%) | 68/154 (44.2%) | 0.59 |
| Permanent pacemaker - no./total no. (%) | 69/344 (20.1%) | 70/313 (22.4%) | 0.50 |



| Characteristic | TAVR (N=344) | AVR (N=313) | Nominal p-value |
|---|-----------------|----------------|--------------------|
| Pulmonary hypertension - no./total no. (%) | 126/291 (43.3%) | 95/268 (35.4%) | 0.07 |
| Frailty - no./total no. (%) | 46/291 (15.8%) | 49/267 (18.4%) | 0.43 |
| Extensively calcified aorta - no./total no. (%) | 2/344 (0.6%) | 2/313 (0.6%) | >0.999 |
| Deleterious effects of chest-wall irradiation - no./total no. (%) | 3/344 (0.9%) | 2/313 (0.6%) | >0.999 |
| Chest-wall deformity - no./total no. (%) | 0/344 (0.0%) | 1/313 (0.3%) | 0.48 |
| Liver disease - no./total no. (%) | 8/344 (2.3%) | 9/313 (2.9%) | 0.81 |
| Echocardiographic Findings | | | |
| Aortic valve area - cm ² | 0.7 ± 0.2 | 0.6 ± 0.2 | 0.28 |
| Mean aortic valve gradient - mm Hg | 42.6 ± 14.5 | 43.4 ± 14.3 | 0.49 |
| Mean LVEF - % | 52.6 ± 13.5 | 53.3 ± 12.6 | 0.48 |
| Moderate or severe MR - no./total no. (%) | 65/333 (19.5%) | 63/303 (20.8%) | 0.69 |

Table 78. Demographic and Baseline Characteristics Males vs. Females – High Risk Cohort in the PARTNER Study (ITT Population)

| Characteristic | Males (N=399) | Females (N=298) | Nominal p-Value |
|---|------------------|--------------------|--------------------|
| Age - years | 83.4 ± 7.0 | 84.9 ± 6.0 | 0.0035 |
| Race | 399 | 298 | 0.0046 |
| Asian | 1 (0.3%) | 1 (0.3%) | |
| Black | 5 (1.3%) | 14 (4.7%) | |
| Caucasian | 383 (96.0%) | 269 (90.3%) | |
| Hispanic | 8 (2.0%) | 10 (3.4%) | |
| Other | 2 (0.5%) | 4 (1.3%) | |
| STS score | 11.6 ± 3.6 | 11.9 ± 3.1 | 0.23 |
| Logistic EuroSCORE | 30.9 ± 16.9 | 27.2 ± 14.6 | 0.0027 |
| NYHA class - no./total no. (%) | 399/399 (100.0%) | 298/298 (100.0%) | |
| II | 22/399 (5.5%) | 19/298 (6.4%) | 0.63 |
| III | 169/399 (42.4%) | 127/298 (42.6%) | >0.999 |
| IV | 208/399 (52.1%) | 152/298 (51.0%) | 0.82 |
| Coronary artery disease - no./total no. (%) | 334/399 (83.7%) | 192/298 (64.4%) | <0.001 |
| Previous MI - no./total no. (%) | 137/396 (34.6%) | 58/297 (19.5%) | <0.001 |
| Prior CABG - no./total no. (%) | 241/399 (60.4%) | 59/298 (19.8%) | <0.001 |



| Characteristic | Males (N=399) | Females (N=298) | Nominal p-Value |
|---|------------------|--------------------|--------------------|
| Prior PCI - no./total no. (%) | 145/397 (36.5%) | 81/297 (27.3%) | 0.01 |
| Prior BAV - no./total no. (%) | 42/399 (10.5%) | 39/298 (13.1%) | 0.34 |
| Peripheral vascular disease - no./total no. (%) | 184/392 (46.9%) | 107/294 (36.4%) | 0.0063 |
| Cerebral vascular disease - no./total no. (%) | 109/377 (28.9%) | 74/275 (26.9%) | 0.60 |
| COPD - no./total no. (%) | | | |
| Any | 183/399 (45.9%) | 120/298 (40.3%) | 0.14 |
| Oxygen dependent | 37/264 (14.0%) | 39/185 (21.1%) | 0.06 |
| Creatinine > 2mg/dL - no./total no. (%) | 46/395 (11.6%) | 13/292 (4.5%) | 0.0008 |
| Atrial fibrillation - no./total no. (%) | 97/239 (40.6%) | 59/132 (44.7%) | 0.44 |
| Permanent pacemaker - no./total no. (%) | 108/399 (27.1%) | 37/298 (12.4%) | <0.001 |
| Pulmonary hypertension - no./total no. (%) | 131/349 (37.5%) | 104/246 (42.3%) | 0.27 |
| Frailty - no./total no. (%) | 40/348 (11.5%) | 57/246 (23.2%) | 0.0002 |
| Extensively calcified aorta - no./total no. (%) | 4/399 (1.0%) | 2/298 (0.7%) | >0.999 |
| Deleterious effects of chest-wall irradiation - no./total no. (%) | 4/399 (1.0%) | 2/298 (0.7%) | >0.999 |
| Chest-wall deformity - no./total no. (%) | 1/399 (0.3%) | 0/298 (0.0%) | >0.999 |
| Liver disease - no./total no. (%) | 12/399 (3.0%) | 7/298 (2.3%) | 0.65 |
| Echocardiographic Findings | | | |
| Aortic valve area - cm ² | 0.7 ± 0.2 | 0.6 ± 0.2 | <0.001 |
| Mean aortic valve gradient - mm Hg | 40.4 ± 12.7 | 46.5 ± 15.9 | <0.001 |
| Mean LVEF - % | 50.3 ± 13.1 | 56.1 ± 12.5 | <0.001 |
| Moderate or severe MR - no./total no. (%) | 69/386 (17.9%) | 68/289 (23.5%) | 0.08 |

As shown in Table 79, a higher incidence of increased creatinine (> 2mg/dL) and a larger aortic valve area at baseline were reported for the TF TAVR arm as compared to the TF AVR arm.



Table 79. Demographic and Baseline Characteristics for Transfemoral TAVR and AVR Arms – High Risk Cohort in the PARTNER Study (ITT Population)

| Characteristic | TF-TAVR (N=244) | TF- AVR (N=248) | Nominal p-value |
|---|--------------------|--------------------|--------------------|
| Age - years | 83.9 ± 6.7 | 84.9 ± 6.6 | 0.11 |
| Male sex - no./total no. (%) | 148/244 (60.7%) | 136/247 (55.1%) | 0.23 |
| Race | 244 | 247 | 0.12 |
| Asian | 2 (0.8%) | 0 (0.0%) | |
| Black | 9 (3.7%) | 5 (2.0%) | |
| Caucasian | 229 (93.9%) | 230 (93.1%) | |
| Hispanic | 2 (0.8%) | 8 (3.2%) | |
| Other | 2 (0.8%) | 4 (1.6%) | |
| STS score | 11.8 ± 3.2 | 11.6 ± 3.5 | 0.44 |
| Logistic EuroSCORE | 29.1 ± 16.7 | 29.0 ± 15.6 | 0.96 |
| NYHA class - no./total no. (%) | | | |
| II | 13/244 (5.3%) | 17/247 (6.9%) | 0.57 |
| III | 102/244 (41.8%) | 107/247 (43.3%) | 0.78 |
| IV | 129/244 (52.9%) | 123/247 (49.8%) | 0.53 |
| Coronary artery disease - no./total no. (%) | 184/244 (75.4%) | 181/247 (73.3%) | 0.61 |
| Previous MI - no./total no. (%) | 65/243 (26.7%) | 63/244 (25.8%) | 0.84 |
| Prior CABG - no./total no. (%) | 96/244 (39.3%) | 96/247 (38.9%) | 0.93 |
| Prior PCI - no./total no. (%) | 84/242 (34.7%) | 68/247 (27.5%) | 0.10 |
| Prior BAV - no./total no. (%) | 33/244 (13.5%) | 24/247 (9.7%) | 0.21 |
| Peripheral vascular disease - no./total no. (%) | 85/242 (35.1%) | 84/242 (34.7%) | >0.999 |
| Cerebral vascular disease - no./total no. (%) | 58/231 (25.1%) | 59/231 (25.5%) | >0.999 |
| COPD - no./total no. (%) | | | |
| Any | 105/244 (43.0%) | 107/248 (43.1%) | >0.999 |
| Oxygen dependent | 29/155 (18.7%) | 28/163 (17.2%) | 0.77 |
| Creatinine > 2mg/dL - no./total no. (%) | 31/241 (12.9%) | 13/243 (5.3%) | 0.0043 |
| Atrial fibrillation - no./total no. (%) | 51/141 (36.2%) | 56/134 (41.8%) | 0.39 |
| Permanent pacemaker - no./total no. (%) | 48/244 (19.7%) | 59/247 (23.9%) | 0.28 |
| Pulmonary hypertension - no./total no. (%) | 80/191 (41.9%) | 80/201 (39.8%) | 0.68 |
| Frailty - no./total no. (%) | 30/191 (15.7%) | 35/200 (17.5%) | 0.68 |
| Extensively calcified aorta - no./total no. (%) | 0/244 (0.0%) | 2/248 (0.8%) | 0.50 |



| Characteristic | TF-TAVR (N=244) | TF- AVR (N=248) | Nominal p-value |
|---|--------------------|--------------------|--------------------|
| Deleterious effects of chest-wall irradiation - no./total no. (%) | 1/244 (0.4%) | 2/248 (0.8%) | >0.999 |
| Chest-wall deformity - no./total no. (%) | 0/244 (0.0%) | 0/248 (0.0%) | 0.30 |
| Liver disease - no./total no. (%) | 6/244 (2.5%) | 11/247 (4.5%) | 0.32 |
| Echocardiographic Findings | | | |
| Aortic valve area - cm ² | 0.7 ± 0.2 | 0.6 ± 0.2 | 0.02 |
| Mean aortic valve gradient - mm Hg | 43.1 ± 14.9 | 44.6 ± 14.5 | 0.25 |
| Mean LVEF - % | 52.2 ± 14.0 | 52.8 ± 13.6 | 0.61 |
| Moderate or severe MR - no./total no. (%) | 47/237 (19.8%) | 50/238 (21.0%) | 0.82 |

When comparing the TA ITT arms, the TA TAVR arm had a lower incidence of previous MI, and higher incidence of pulmonary hypertension (Table 80).

Table 80. Demographic and Baseline Characteristics for Transapical TAVR and AVR Arms – High Risk Cohort in the PARTNER Study (ITT Population)

| Characteristic | TA- TAVR (N=104) | TA-AVR (N=103) | Nominal p-value |
|---|---------------------|-------------------|--------------------|
| Age - years | 82.9 ± 7.0 | 83.6 ± 5.8 | 0.40 |
| Male sex - no./total no. (%) | 53/104 (51.0%) | 62/102 (60.8%) | 0.16 |
| Race | 104 | 102 | 0.12 |
| Asian | 0 (0.0%) | 0 (0.0%) | |
| Black | 2 (1.9%) | 3 (2.9%) | |
| Caucasian | 95 (91.3%) | 98 (96.1%) | |
| Hispanic | 7 (6.7%) | 1 (1.0%) | |
| Other | 0 (0.0%) | 0 (0.0%) | |
| STS score | 11.8 ± 3.6 | 11.9 ± 3.4 | 0.82 |
| Logistic EuroSCORE | 29.9 ± 16.1 | 29.7 ± 15.7 | 0.94 |
| NYHA class - no./total no. (%) | | | |
| II | 7/104 (6.7%) | 4/102 (3.9%) | 0.54 |
| III | 43/104 (41.3%) | 44/102 (43.1%) | 0.89 |
| IV | 54/104 (51.9%) | 54/102 (52.9%) | 0.89 |
| Coronary artery disease - no./total no. (%) | 76/104 (73.1%) | 85/102 (83.3%) | 0.09 |
| Previous MI - no./total no. (%) | 27/104 (26.0%) | 40/102 (39.2%) | 0.05 |



| Characteristic | TA- TAVR (N=104) | TA-AVR (N=103) | Nominal p-value |
|--|---------------------|-------------------|--------------------|
| Prior CABG - no./total no. (%) | 52/104 (50.0%) | 56/102 (54.9%) | 0.49 |
| Prior PCI - no./total no. (%) | 32/104 (30.8%) | 42/101 (41.6%) | 0.11 |
| Prior BAV - no./total no. (%) | 13/104 (12.5%) | 11/102 (10.8%) | 0.83 |
| Peripheral vascular disease - no./total no. (%) | 64/103 (62.1%) | 58/99 (58.6%) | 0.67 |
| Cerebral vascular disease - no./total no. (%) | 38/96 (39.6%) | 28/94 (29.8%) | 0.17 |
| COPD - no./total no. (%) | | | |
| Any | 47/104 (45.2%) | 44/103 (42.7%) | 0.78 |
| Oxygen dependent | 9/65 (13.8%) | 10/66 (15.2%) | >0.999 |
| Creatinine > 2mg/dL - no./total no. (%) | 6/102 (5.9%) | 9/101 (8.9%) | 0.44 |
| Atrial fibrillation - no./total no. (%) | 30/58 (51.7%) | 19/38 (50.0%) | >0.999 |
| Permanent pacemaker - no./total no. (%) | 21/104 (20.2%) | 17/102 (16.7%) | 0.59 |
| Pulmonary hypertension - no./total no. (%) | 46/104 (44.2%) | 31/101 (30.7%) | 0.06 |
| Frailty - no./total no. (%) | 16/104 (15.4%) | 18/101 (17.8%) | 0.71 |
| Extensively calcified aorta - no./total no. (%) | 2/104 (1.9%) | 2/103 (1.9%) | >0.999 |
| Deleterious effects of chest-wall irradiation - no./total no. (%) | 2/104 (1.9%) | 1/103 (1.0%) | >0.999 |
| Chest-wall deformity - no./total no. (%) | 0/104 (0.0%) | 1/103 (1.0%) | 0.50 |
| Liver disease - no./total no. (%) | 2/104 (1.9%) | 0/102 (0.0%) | 0.50 |
| Echocardiographic Findings | | | |
| Aortic valve area - cm2 | 0.7 ± 0.2 | 0.7 ± 0.2 | 0.73 |
| Mean aortic valve gradient - mm Hg | 41.4 ± 13.9 | 40.7 ± 13.5 | 0.72 |
| Mean LVEF - % | 53.3 ± 12.4 | 53.6 ± 10.8 | 0.85 |
| Moderate or severe MR - no./total no. (%) | 19/100 (19.0%) | 21/100 (21.0%) | 0.86 |

As discussed, high risk surgical patients who were not eligible for the transfemoral approach were eligible for transapical access. Table 81 summarizes the demographic and baseline characteristics involving the transfemoral eligible vs. the transapical eligible patients. As expected, transapical eligible patients had a higher incidence of prior CABG and peripheral vascular disease. Additionally, the incidence of cerebrovascular disease was higher in transapical eligible patients while their mean aortic valve gradient was lower as compared to transfemoral eligible patients.



Table 81. Demographic and Baseline Characteristics for Pooled Transapical (AVR + TAVR) vs. Pooled Transfemoral (TAVR + AVR) – High Risk Cohort in the PARTNER Study (ITT Population)

| Characteristic | TA (AVR + TAVR) (N=207) | TF (AVR + TAVR) (N=492) | Nominal p-value |
|---|----------------------------|----------------------------|--------------------|
| Age - years | 83.2 ± 6.5 | 84.4 ± 6.7 | 0.03 |
| Male sex - no./total no. (%) | 115/206 (55.8%) | 284/491 (57.8%) | 0.67 |
| Race | 206 | 491 | 0.30 |
| Asian | 0 (0.0%) | 2 (0.4%) | |
| Black | 5 (2.4%) | 14 (2.9%) | |
| Caucasian | 193 (93.7%) | 459 (93.5%) | |
| Hispanic | 8 (3.9%) | 10 (2.0%) | |
| Other | 0 (0.0%) | 6 (1.2%) | |
| STS score | 11.8 ± 3.5 | 11.7 ± 3.3 | 0.70 |
| Logistic EuroSCORE | 29.8 ± 15.9 | 29.1 ± 16.1 | 0.61 |
| NYHA class - no./total no. (%) | | | |
| II | 11/206 (5.3%) | 30/491 (6.1%) | 0.86 |
| III | 87/206 (42.2%) | 209/491 (42.6%) | >0.999 |
| IV | 108/206 (52.4%) | 252/491 (51.3%) | 0.80 |
| Coronary artery disease - no./total no. (%) | 161/206 (78.2%) | 365/491 (74.3%) | 0.33 |
| Previous MI - no./total no. (%) | 67/206 (32.5%) | 128/487 (26.3%) | 0.10 |
| Prior CABG - no./total no. (%) | 108/206 (52.4%) | 192/491 (39.1%) | 0.0014 |
| Prior PCI - no./total no. (%) | 74/205 (36.1%) | 152/489 (31.1%) | 0.21 |
| Prior BAV - no./total no. (%) | 24/206 (11.7%) | 57/491 (11.6%) | >0.999 |
| Peripheral vascular disease - no./total no. (%) | 122/202 (60.4%) | 169/484 (34.9%) | 0.0000 |
| Cerebral vascular disease - no./total no. (%) | 66/190 (34.7%) | 117/462 (25.3%) | 0.02 |
| COPD - no./total no. (%) | | | |
| Any | 91/207 (44.0%) | 212/492 (43.1%) | 0.87 |
| Oxygen dependent | 19/131 (14.5%) | 57/318 (17.9%) | 0.41 |
| Creatinine > 2mg/dL - no./total no. (%) | 15/203 (7.4%) | 44/484 (9.1%) | 0.55 |
| Atrial fibrillation - no./total no. (%) | 49/96 (51.0%) | 107/275 (38.9%) | 0.04 |
| Permanent pacemaker - no./total no. (%) | 38/206 (18.4%) | 107/491 (21.8%) | 0.36 |
| Pulmonary hypertension - no./total no. (%) | 77/205 (37.6%) | 160/392 (40.8%) | 0.48 |
| Frailty - no./total no. (%) | 34/205 (16.6%) | 65/391 (16.6%) | >0.999 |
| Extensively calcified aorta - no./total no. (%) | 4/207 (1.9%) | 2/492 (0.4%) | 0.07 |



| Characteristic | TA (AVR + TAVR) (N=207) | TF (AVR + TAVR) (N=492) | Nominal p-value |
|---|----------------------------|----------------------------|--------------------|
| Deleterious effects of chest-wall irradiation - no./total no. (%) | 3/207 (1.4%) | 3/492 (0.6%) | 0.37 |
| Chest-wall deformity - no./total no. (%) | 1/207 (0.5%) | 0/492 (0.0%) | 0.30 |
| Liver disease - no./total no. (%) | 2/206 (1.0%) | 17/491 (3.5%) | 0.08 |
| Echocardiographic Findings | | | |
| Aortic valve area - cm ² | 0.7 ± 0.2 | 0.6 ± 0.2 | 0.17 |
| Mean aortic valve gradient - mm Hg | 41.0 ± 13.7 | 43.9 ± 14.7 | 0.02 |
| Mean LVEF - % | 53.5 ± 11.6 | 52.5 ± 13.8 | 0.40 |
| Moderate or severe MR - no./total no. (%) | 40/200 (20.0%) | 97/475 (20.4%) | >0.999 |

Since more AVR than TAVR patients did not undergo their randomly assigned treatment, the non treated AVR patients were compared to treated AVR patients (Table 82), and the non treated AVR patients who refused AVR or withdrew from the study were compared to treated AVR patients (Table 83). Except for aortic valve area, no consistent significant differences were observed.

Table 82. Demographic and Baseline Characteristics for Not Treated AVR vs. Treated AVR Patients – High Risk Cohort in the PARTNER Study (ITT Population)

| Characteristic | Non-Treated AVR (N=38) | Treated AVR (N=313) | Nominal p-value |
|--------------------------------|---------------------------|------------------------|--------------------|
| Age - years | 85.5 ± 6.6 | 84.4 ± 6.3 | 0.21 |
| Male sex - no./total no. (%) | 19/36 (52.8%) | 179/313 (57.2%) | 0.87 |
| Race | 36 | 313 | 0.66 |
| Asian | 0 (0.0%) | 0 (0.0%) | |
| Black | 1 (2.8%) | 7 (2.2%) | |
| Caucasian | 34 (94.4%) | 294 (93.9%) | |
| Hispanic | 0 (0.0%) | 9 (2.9%) | |
| Other | 1 (2.8%) | 3 (1.0%) | |
| STS score | 11.6 ± 4.3 | 11.7 ± 3.4 | 0.82 |
| Logistic EuroSCORE | 29.5 ± 20.4 | 29.2 ± 15.2 | 0.96 |
| NYHA class - no./total no. (%) | 36/36 (100.0%) | 313/313 (100.0%) | . |
| II | 5/36 (13.9%) | 16/313 (5.1%) | 0.08 |
| III | 17/36 (47.2%) | 134/313 (42.8%) | 0.74 |



| Characteristic | Non-Treated AVR (N=38) | Treated AVR (N=313) | Nominal p-value |
|---|---------------------------|------------------------|--------------------|
| IV | 14/36 (38.9%) | 163/313 (52.1%) | 0.26 |
| Coronary artery disease - no./total no. (%) | 25/36 (69.4%) | 241/313 (77.0%) | 0.26 |
| Previous MI - no./total no. (%) | 13/36 (36.1%) | 90/310 (29.0%) | 0.59 |
| Prior CABG - no./total no. (%) | 13/36 (36.1%) | 139/313 (44.4%) | 0.51 |
| Prior PCI - no./total no. (%) | 9/36 (25.0%) | 101/312 (32.4%) | 0.38 |
| Prior BAV - no./total no. (%) | 3/36 (8.3%) | 32/313 (10.2%) | 0.61 |
| Peripheral vascular disease - no./total no. (%) | 10/34 (29.4%) | 132/307 (43.0%) | 0.09 |
| Cerebral vascular disease - no./total no. (%) | 8/33 (24.2%) | 79/292 (27.1%) | 0.45 |
| COPD - no./total no. (%) | | | |
| Any | 13/38 (34.2%) | 138/313 (44.1%) | 0.34 |
| Oxygen dependent | 4/25 (16.0%) | 34/204 (16.7%) | >0.999 |
| Creatinine > 2mg/dL - no./total no. (%) | 2/31 (6.5%) | 20/313 (6.4%) | 0.76 |
| Atrial fibrillation - no./total no. (%) | 7/18 (38.9%) | 68/154 (44.2%) | 0.82 |
| Permanent pacemaker - no./total no. (%) | 6/36 (16.7%) | 70/313 (22.4%) | 0.43 |
| Pulmonary hypertension - no./total no. (%) | 16/34 (47.1%) | 95/268 (35.4%) | 0.74 |
| Frailty - no./total no. (%) | 4/34 (11.8%) | 49/267 (18.4%) | 0.37 |
| Extensively calcified aorta - no./total no. (%) | 2/38 (5.3%) | 2/313 (0.6%) | 0.05 |
| Deleterious effects of chest-wall irradiation - no./total no. (%) | 1/38 (2.6%) | 2/313 (0.6%) | 0.31 |
| Chest-wall deformity - no./total no. (%) | 0/38 (0.0%) | 1/313 (0.3%) | >0.999 |
| Liver disease - no./total no. (%) | 2/36 (5.6%) | 9/313 (2.9%) | 0.30 |
| Echocardiographic Findings | | | |
| Aortic valve area - cm ² | 0.6 ± 0.2 | 0.6 ± 0.2 | 0.02 |
| Mean aortic valve gradient - mm Hg | 44.2 ± 14.5 | 43.4 ± 14.3 | 0.69 |
| Mean LVEF - % | 50.7 ± 14.9 | 53.3 ± 12.6 | 0.18 |
| Moderate or severe MR - no./total no. (%) | 8/35 (22.9%) | 63/303 (20.8%) | 0.68 |



Table 83. Demographic and Baseline Characteristics for Treated AVR vs. Not Treated AVR Patients who Refused and Withdrew – High Risk Cohort in the PARTNER Study (ITT Population)

| Characteristic | Non-Treated AVR Who Refused or Withdrew (N=28) | Treated AVR (N=313) | Nominal p-value |
|---|--|---------------------|-----------------|
| Age - years | 85.5 ± 5.8 | 84.4 ± 6.3 | 0.25 |
| Male sex - no./total no. (%) | 12/26 (46.2%) | 179/313 (57.2%) | 0.31 |
| Race | 26 | 313 | 0.27 |
| Asian | 0 (0.0%) | 0 (0.0%) | |
| Black | 1 (3.8%) | 7 (2.2%) | |
| Caucasian | 24 (92.3%) | 294 (93.9%) | |
| Hispanic | 0 (0.0%) | 9 (2.9%) | |
| Other | 1 (3.8%) | 3 (1.0%) | |
| STS score | 11.3 ± 2.5 | 11.7 ± 3.4 | 0.50 |
| Logistic EuroSCORE | 30.9 ± 19.6 | 29.2 ± 15.2 | 0.66 |
| NYHA class - no./total no. (%) | 26/26 (100.0%) | 313/313 (100.0%) | . |
| II | 5/26 (19.2%) | 16/313 (5.1%) | 0.01 |
| III | 12/26 (46.2%) | 134/313 (42.8%) | 0.69 |
| IV | 9/26 (34.6%) | 163/313 (52.1%) | 0.11 |
| Coronary artery disease - no./total no. (%) | 19/26 (73.1%) | 241/313 (77.0%) | 0.82 |
| Previous MI - no./total no. (%) | 10/26 (38.5%) | 90/310 (29.0%) | 0.27 |
| Prior CABG - no./total no. (%) | 9/26 (34.6%) | 139/313 (44.4%) | 0.42 |
| Prior PCI - no./total no. (%) | 4/26 (15.4%) | 101/312 (32.4%) | 0.09 |
| Prior BAV - no./total no. (%) | 2/26 (7.7%) | 32/313 (10.2%) | 0.76 |
| Peripheral vascular disease - no./total no. (%) | 8/24 (33.3%) | 132/307 (43.0%) | 0.41 |
| Cerebral vascular disease - no./total no. (%) | 5/25 (20.0%) | 79/292 (27.1%) | 0.50 |
| COPD - no./total no. (%) | | | |
| Any | 10/28 (35.7%) | 138/313 (44.1%) | 0.44 |
| Oxygen dependent | 4/18 (22.2%) | 34/204 (16.7%) | 0.52 |
| Creatinine > 2mg/dL - no./total no. (%) | 2/23 (8.7%) | 20/313 (6.4%) | >0.999 |
| Atrial fibrillation - no./total no. (%) | 4/11 (36.4%) | 68/154 (44.2%) | 0.77 |
| Permanent pacemaker - no./total no. (%) | 4/26 (15.4%) | 70/313 (22.4%) | 0.63 |
| Pulmonary hypertension - no./total no. (%) | 11/25 (44.0%) | 95/268 (35.4%) | 0.68 |
| Frailty - no./total no. (%) | 4/25 (16.0%) | 49/267 (18.4%) | >0.999 |
| Extensively calcified aorta - no./total no. (%) | 1/28 (3.6%) | 2/313 (0.6%) | 0.22 |



| Characteristic | Non-Treated AVR Who Refused or Withdrew (N=28) | Treated AVR (N=313) | Nominal p-value |
|---|--|---------------------|-----------------|
| Deleterious effects of chest-wall irradiation - no./total no. (%) | 0/28 (0.0%) | 2/313 (0.6%) | >0.999 |
| Chest-wall deformity - no./total no. (%) | 0/28 (0.0%) | 1/313 (0.3%) | >0.999 |
| Liver disease - no./total no. (%) | 1/26 (3.8%) | 9/313 (2.9%) | 0.52 |
| Echocardiographic Findings | | | |
| Aortic valve area - cm ² | 0.6 ± 0.2 | 0.6 ± 0.2 | 0.14 |
| Mean aortic valve gradient - mm Hg | 44.2 ± 13.0 | 43.4 ± 14.3 | 0.69 |
| Mean LVEF - % | 53.5 ± 12.7 | 53.3 ± 12.6 | 0.77 |
| Moderate or severe MR - no./total no. (%) | 6/26 (23.1%) | 63/303 (20.8%) | 0.80 |

Table 84 compares the randomized TA-TAVR patients to the continued access TA-TAVR patients. No differences in mean STS and Logistic EuroSCOREs were noted. The NRCA TA-TAVR patients had a higher incidence of coronary artery disease, prior PCI and prior BAV and lower incidence of cerebral vascular disease and pulmonary hypertension compared to the randomized TA-TAVR patients.

Table 84. Demographic and Baseline Characteristics for TA-TAVR Patients - Randomized vs. Non Randomized Continued Access Patients (AT Population)

| Characteristic | PMA (TA-TAVR) (N=104) | NRCA (TA-TAVR) (N=822) | Nominal P-Value |
|--------------------------------|-----------------------|------------------------|-----------------|
| Age - years | 83.4 ± 5.5 | 84.7 ± 6.3 | 0.0073 |
| Male sex - no./total no. (%) | 53/104 (51.0%) | 383/822 (46.6%) | 0.41 |
| Race | 104 | 822 | >0.999 |
| Asian | 0 (0.0%) | 9 (1.1%) | |
| Black | 2 (1.9%) | 9 (1.1%) | |
| Caucasian | 95 (91.3%) | 788 (95.9%) | |
| Hispanic | 7 (6.7%) | 12 (1.5%) | |
| Other | 0 (0.0%) | 4 (0.5%) | |
| STS score | 12.1 ± 3.5 | 12.2 ± 4.5 | 0.29 |
| Logistic EuroSCORE | 29.9 ± 15.1 | 28.4 ± 16.6 | 0.40 |
| NYHA class - no./total no. (%) | 104/104 (100.0%) | 822/822 (100.0%) | . |
| II | 8/104 (7.7%) | 43/822 (5.2%) | 0.36 |
| III | 42/104 (40.4%) | 411/822 (50.0%) | 0.08 |



| Characteristic | PMA (TA-TAVR) (N=104) | NRCA (TA-TAVR) (N=822) | Nominal P-Value |
|---|--------------------------|---------------------------|--------------------|
| IV | 54/104 (51.9%) | 368/822 (44.8%) | 0.18 |
| Coronary artery disease - no./total no. (%) | 77/104 (74.0%) | 690/821 (84.0%) | 0.02 |
| Previous MI - no./total no. (%) | 28/104 (26.9%) | 236/819 (28.8%) | 0.73 |
| Prior CABG - no./total no. (%) | 51/104 (49.0%) | 416/822 (50.6%) | 0.84 |
| Prior PCI - no./total no. (%) | 33/104 (31.7%) | 391/821 (47.6%) | 0.0024 |
| Prior BAV - no./total no. (%) | 13/104 (12.5%) | 242/818 (29.6%) | 0.0002 |
| Peripheral vascular disease - no./total no. (%) | 65/103 (63.1%) | 495/813 (60.9%) | 0.75 |
| Cerebral vascular disease - no./total no. (%) | 40/96 (41.7%) | 248/812 (30.5%) | 0.04 |
| COPD - no./total no. (%) | | | |
| Any | 46/104 (44.2%) | 371/822 (45.1%) | 0.92 |
| Oxygen dependent | 9/65 (13.8%) | 89/507 (17.6%) | 0.60 |
| Creatinine > 2mg/dL - no./total no. (%) | 7/103 (6.8%) | 73/815 (9.0%) | 0.58 |
| Atrial fibrillation - no./total no. (%) | 31/58 (53.4%) | 56/133 (42.1%) | 0.16 |
| Permanent pacemaker - no./total no. (%) | 21/104 (20.2%) | 178/820 (21.7%) | 0.80 |
| Pulmonary hypertension - no./total no. (%) | 48/104 (46.2%) | 291/819 (35.5%) | 0.04 |
| Frailty - no./total no. (%) | 16/104 (15.4%) | 83/819 (10.1%) | 0.13 |
| Extensively calcified aorta - no./total no. (%) | 2/104 (1.9%) | 13/819 (1.6%) | 0.68 |
| Deleterious effects of chest-wall irradiation - no./total no. (%) | 2/104 (1.9%) | 3/819 (0.4%) | 0.10 |
| Chest-wall deformity - no./total no. (%) | 0/104 (0.0%) | 3/819 (0.4%) | >0.999 |
| Liver disease - no./total no. (%) | 2/104 (1.9%) | 22/820 (2.7%) | >0.999 |
| Echocardiographic Findings | | | |
| Aortic valve area - cm2 | 0.7 ± 0.2 | 0.6 ± 0.2 | 0.84 |
| Mean aortic valve gradient - mm Hg | 40.5 ± 12.9 | 44.0 ± 15.1 | 0.17 |
| Mean LVEF - % | 53.5 ± 10.9 | 53.3 ± 12.8 | 0.85 |
| Moderate or severe MR - no./total no. (%) | 19/100 (19.0%) | 72/336 (21.4%) | 0.68 |

Table 85 compares the randomized TF-TAVR patients to the continued access TF-TAVR patients. The mean STS score was slightly lower in the NRCA TF-TAVR patients compared to randomized TF-TAVR patients. The NRCA TF-TAVR patients had a higher incidence of prior BAV than randomized TF-TAVR patients.



Table 85. Demographic and Baseline Characteristics for TF-TAVR Patients - Randomized vs. Non Randomized Continued Access Patients (AT Population)

| Characteristic | PMA (TF-TAVR) (N=240) | NRCA (TF-TAVR) (N=699) | Nominal P-Value |
|---|--------------------------|---------------------------|--------------------|
| Age - years | 84.8 ± 6.6 | 86.3 ± 6.2 | 0.0000 |
| Male sex - no./total no. (%) | 145/240 (60.4%) | 394/697 (56.5%) | 0.33 |
| Race | 240 | 697 | 0.47 |
| Asian | 2 (0.8%) | 6 (0.9%) | |
| Black | 9 (3.8%) | 17 (2.4%) | |
| Caucasian | 225 (93.8%) | 653 (93.7%) | |
| Hispanic | 2 (0.8%) | 15 (2.2%) | |
| Other | 2 (0.8%) | 6 (0.9%) | |
| STS score | 11.5 ± 3.3 | 11.3 ± 2.8 | 0.0075 |
| Logistic EuroSCORE | 28.9 ± 15.2 | 28.5 ± 68.5 | 0.89 |
| NYHA class - no./total no. (%) | 240/240 (100.0%) | 696/696 (100.0%) | >0.999 |
| II | 12/240 (5.0%) | 27/696 (3.9%) | 0.46 |
| III | 102/240 (42.5%) | 313/696 (45.0%) | 0.55 |
| IV | 126/240 (52.5%) | 354/696 (50.9%) | 0.71 |
| Coronary artery disease - no./total no. (%) | 181/240 (75.4%) | 523/697 (75.0%) | 0.93 |
| Previous MI - no./total no. (%) | 64/239 (26.8%) | 163/692 (23.6%) | 0.34 |
| Prior CABG - no./total no. (%) | 95/240 (39.6%) | 254/697 (36.4%) | 0.40 |
| Prior PCI - no./total no. (%) | 82/238 (34.5%) | 274/697 (39.3%) | 0.19 |
| Prior BAV - no./total no. (%) | 33/240 (13.8%) | 158/691 (22.9%) | 0.0022 |
| Peripheral vascular disease - no./total no. (%) | 83/238 (34.9%) | 199/689 (28.9%) | 0.09 |
| Cerebral vascular disease - no./total no. (%) | 56/227 (24.7%) | 152/687 (22.1%) | 0.47 |
| COPD - no./total no. (%) | | | |
| Any | 104/240 (43.3%) | 286/699 (40.9%) | 0.54 |
| Oxygen dependent | 29/153 (19.0%) | 85/397 (21.4%) | 0.56 |
| Creatinine > 2mg/dL - no./total no. (%) | 30/237 (12.7%) | 66/688 (9.6%) | 0.22 |
| Atrial fibrillation - no./total no. (%) | 49/138 (35.5%) | 64/146 (43.8%) | 0.18 |
| Permanent pacemaker - no./total no. (%) | 48/240 (20.0%) | 167/697 (24.0%) | 0.21 |
| Pulmonary hypertension - no./total no. (%) | 78/187 (41.7%) | 262/695 (37.7%) | 0.35 |
| Frailty - no./total no. (%) | 30/187 (16.0%) | 74/696 (10.6%) | 0.05 |
| Extensively calcified aorta - no./total no. (%) | 0/240 (0.0%) | 3/696 (0.4%) | 0.57 |



| Characteristic | PMA (TF-TAVR) (N=240) | NRCA (TF-TAVR) (N=699) | Nominal P-Value |
|--|--------------------------|---------------------------|--------------------|
| Deleterious effects of chest-wall irradiation - no./total no. (%) | 1/240 (0.4%) | 3/696 (0.4%) | >0.999 |
| Chest-wall deformity - no./total no. (%) | 0/240 (0.0%) | 4/696 (0.6%) | 0.58 |
| Liver disease - no./total no. (%) | 6/240 (2.5%) | 15/696 (2.2%) | 0.80 |
| Echocardiographic Findings | | | |
| Aortic valve area - cm ² | 0.6 ± 0.2 | 0.7 ± 0.2 | 0.84 |
| Mean aortic valve gradient - mm Hg | 44.6 ± 14.8 | 45.2 ± 14.9 | 0.09 |
| Mean LVEF - % | 53.3 ± 13.3 | 52.6 ± 13.3 | 0.71 |
| Moderate or severe MR - no./total no. (%) | 46/233 (19.7%) | 72/310 (23.2%) | 0.35 |



Appendix B. Device Description

Overview

In the transapical procedure, the SAPIEN is mounted and crimped onto a balloon catheter and inserted through the apex of the left ventricle and is expanded and implanted within the diseased aortic valve.

Transapical implantation of the SAPIEN valve requires the following Edwards accessory devices:

- Ascendra Balloon Catheter for delivery and deployment of the SAPIEN valve
- Ascendra Balloon Aortic Valvuloplasty Catheter for valvuloplasty of the heart valve prior to implanting the SAPIEN valve
- Crimper, which is used to crimp the SAPIEN valve on the Ascendra Balloon Catheter
- Ascendra Introducer Sheath Set

In the transfemoral procedure, the SAPIEN is mounted and crimped onto a balloon catheter and inserted in the femoral artery through a small incision in the groin and is expanded and implanted within the diseased aortic valve.

Transfemoral implantation of the SAPIEN valve requires the following Edwards accessory devices:

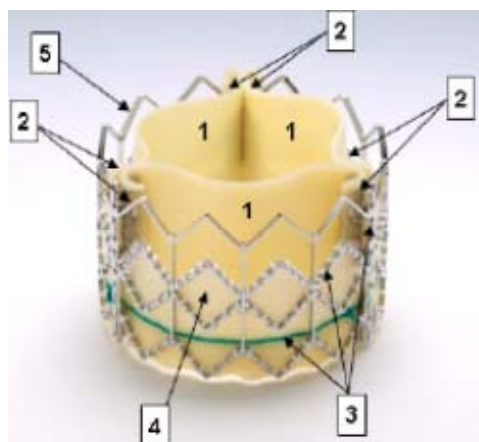
- RetroFlex 3 Delivery System for delivery and deployment of the SAPIEN valve
- RetroFlex Balloon Catheter for valvuloplasty of the heart valve prior to implanting the SAPIEN valve
- Crimper, which is used to crimp the SAPIEN valve on the RetroFlex 3 Delivery System
- RetroFlex 3 Introducer Sheath Set cleared under 510(k) K093877
- RetroFlex Dilator Kit cleared under 510(k) K093554



Edwards SAPIEN Transcatheter Heart Valve, Model 9000TFX

The Edwards SAPIEN Transcatheter Heart Valve (bioprosthesis), shown in Figure 39, is comprised of a balloon-expandable, radiopaque, stainless steel (316L) frame, three bovine pericardial tissue leaflets, and a polyethylene terephthalate (PET) fabric. The bioprosthesis is treated according to the Carpentier-Edwards ThermaFix process, packaged, and terminally sterilized in glutaraldehyde. The device is available in size 23mm and 26mm.

Figure 39. Edwards SAPIEN Transcatheter Heart Valve



1. Bovine Pericardium Leaflet
2. Stainless Steel 5-hole Bars with cloth covers
3. Sutures
4. Fabric Skirt
5. Stainless Steel Frame

Primary packaging for the valve consist of a glutaraldehyde filled jar, a holder which is used to secure the valve and serial number I.D. tag within the jar, and a lid which is use to seal the contents within the jar and maintain a sterile barrier. A tamper evident band is placed around the outside of the jar/lid. The primary packaging assembly is placed in the secondary packaging, which consists of a shelf carton with a temperature sensor. This shelf carton assembly is placed in final tertiary packaging which consists of a Styrofoam enclosure placed in a shipping carton. Additional thermal protection is used for shipments intended for extreme weather conditions by placing gel packs within the Styrofoam enclosures.



Principles of Operation: Edwards SAPIEN Transcatheter Heart Valve

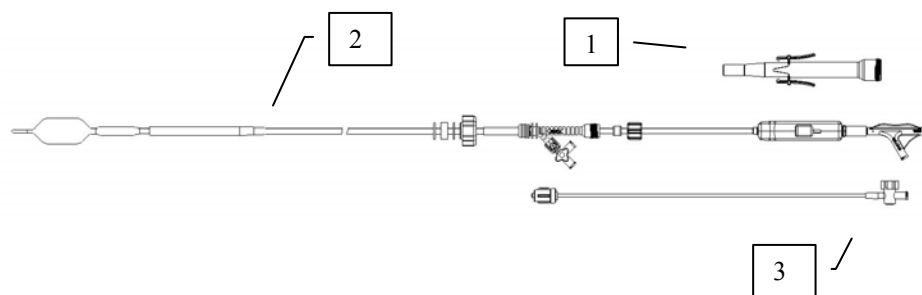
The SAPIEN valve's frame and bovine pericardial leaflets are designed to withstand the stresses incurred during crimping, expansion, and in service within the body. The SAPIEN valve operates similarly to the native aortic valve by preventing backflow from the aorta into the left ventricle during diastole. During normal valve functioning, the aortic valve cusps open as a result of ventricular contraction when the pressure in the left ventricle exceeds that of the aorta. Blood flows through the open aortic valve from the left ventricle to the aorta during systole. Following the emptying of the left ventricle, the elevated pressures present in the distended aorta pushes blood back toward the left ventricle, which causes the leaflets to close, thereby preventing the flow of blood back into the ventricle during diastole.

Transapical: Ascendra Balloon Catheter, Models 9100BCL23 and 9100BCL26

The Ascendra Balloon Catheter, shown in Figure 40, consists of a balloon catheter, loader, and optional extension tubing. Two radiopaque markers on the balloon serve as indicators for bioprosthesis placement during crimping, as well as visualization of the balloon. The catheter has a deflecting mechanism to steer the balloon. The loader allows for the delivery of the crimped bioprosthesis through the introducer sheath hemostasis valves. The balloon is inflated by connecting an inflation device directly or indirectly (using the supplied extension tubing) to the balloon inflation luer port of the catheter. The device is supplied sterile for single use only. The Ascendra Balloon Catheter is compatible with a 0.035" guidewire.



Figure 40. Ascendra Balloon Catheter



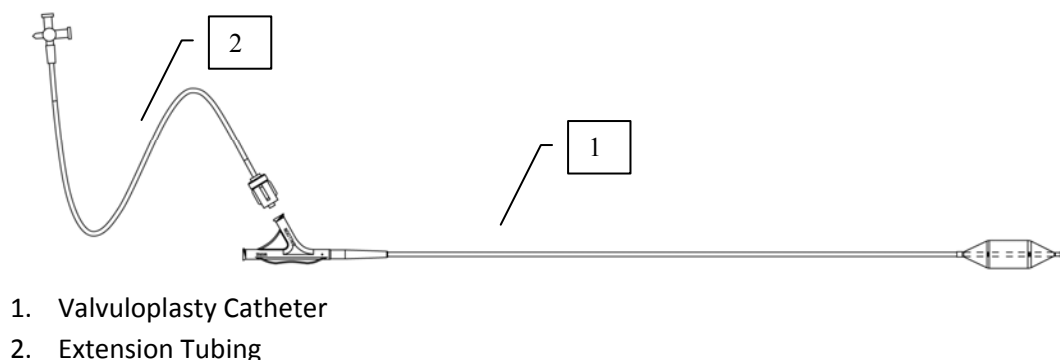
1. Loader
2. Balloon Catheter
3. Extension Tubing

Transapical: Ascendra Balloon Aortic Valvuloplasty Catheter, Model 9100BAVC

The Ascendra Balloon Aortic Valvuloplasty Catheter, shown in Figure 41, is a coaxial designed catheter with a distal inflatable balloon intended to predilate the stenotic aortic valve prior to implantation of the Edwards SAPIEN THV bioprosthesis. Two radiopaque marker bands indicate the dilating section of the balloon and aid in balloon placement. At the proximal end of the catheter, there is a standard “Y” connector for balloon inflation and a guidewire lumen. An inflation device may be connected directly or indirectly (using the supplied extension tubing) to the balloon inflation luer port of the catheter. The balloon is inflated by injecting a diluted contrast medium solution through the luer port (marked “BALLOON”) on the “Y” connector. The device is supplied sterile for single use only. The Ascendra Balloon Aortic Valvuloplasty Catheter is compatible with a 0.035” guidewire.



Figure 41. Ascendra Balloon Aortic Valvuloplasty Catheter



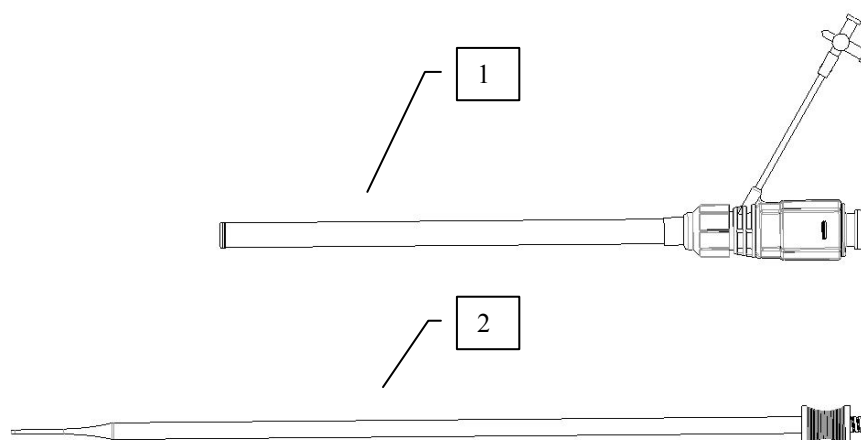
Transapical: Ascendra Introducer Sheath Set, Model 9100IS

The Ascendra Introducer Sheath Set, shown in Figure 42, is used for the introduction and removal of devices used with the Edwards SAPIEN transcatheter heart valve. It consists of two components, sheath and introducer. The device is supplied sterile for single use only. The Ascendra Introducer Sheath Set is compatible with a 0.035" guidewire.

The sheath has an inner diameter of 26F and a length of 21cm. A radiopaque marker is located at the sheath tip for visualization. There are printed non-radiopaque depth markings on the distal end of the body that may be used to verify the depth of the sheath in the ventricle. The proximal end includes a side port and three hemostasis valves. The introducer has an outer diameter of 0.326" and a length of 39cm.



Figure 42. Ascendra Introducer Sheath Set



1. Sheath
2. Introducer

Principles of Operation: Transapical Implantation

The Ascendra Balloon Catheter is used to advance the bioprosthesis over a .035” guidewire, through the Ascendra introducer sheath, and into the body. The pusher tip is located just proximal to the balloon and sits behind the crimped bioprosthesis. The pusher tip supports the bioprosthesis during insertion and placement throughout the procedure. A 26F loader is packaged with the balloon catheter and placed over the bioprosthesis during device preparation. The 26F loader covers the crimped valve as it is inserted into the Ascendra sheath. The Ascendra Balloon Catheter can be deflected using the deflection mechanism on the proximal end to aid in valve placement.

The proximal end of the catheter encompasses a series of functional parts that help control or deploy the bioprosthesis in the anatomy. These components include the pusher nut, deflecting handle, and inflation y-connector. The pusher nut is used to control the pusher tip and is able to lock in both distal and proximal positions. The deflecting handle



allows for articulation of the distal end of the catheter. The balloon inflation “Y” (also provided with balloon extension tubing) allows for the inflation and deflation of the balloon for bioprosthesis deployment.

The distal end of the catheter encompasses a series of functional parts that aid in the delivery of the bioprosthesis. These components are the guidewire lumen, balloon, loader, and pusher tip. The guidewire lumen allows the catheter to track over a preplaced guidewire within the anatomy. The balloon expands a pre-crimped valve within the target site. The loader covers the balloon and crimped bioprosthesis assembly and aids in the insertion of the balloon catheter into the sheath. The pusher tip is used to stabilize the crimped bioprosthesis as it is advanced into the loader, through the sheath, and into the anatomy. The pusher is retracted in order to free the balloon prior to bioprosthesis deployment.

The Ascendra Balloon Aortic Valvuloplasty catheter is a coaxial designed catheter with a distal inflatable balloon intended to predilate the stenotic aortic valve prior to implantation of the Edwards SAPIEN THV bioprosthesis. Two radiopaque marker bands indicate the dilating section of the balloon and aid in balloon placement. At the proximal end of the catheter, there is a standard “Y” connector for balloon inflation and a guidewire lumen. An inflation device may be connected directly or indirectly (using the supplied extension tubing) to the balloon inflation port of the catheter. The balloon is inflated by injecting a diluted contrast medium solution through the balloon inflation port (marked “BALLOON”) on the “Y” connector.

The Ascendra Introducer Sheath Set is used for the introduction and removal of devices used with the Edwards SAPIEN transcatheter heart valve. It consists of two components, sheath and introducer. The device is supplied sterile for single use only. The Ascendra Introducer Sheath Set is compatible with a 0.035” guidewire.

The introducer is inserted in the sheath during device preparation. The sheath/introducer is inserted over a guidewire through a thoracic incision into the left ventricle. The introducer is then removed from the sheath and replaced with the interventional device.

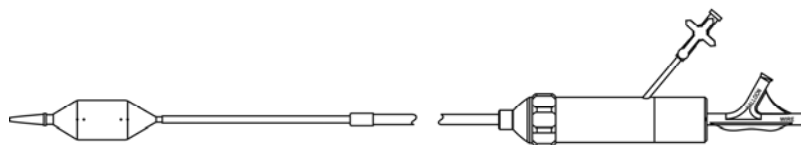


The sheath has an inner diameter of 26F and a length of 21cm. A radiopaque marker is located at the sheath tip for visualization when inserting the sheath. There are printed non-radiopaque depth markings on the distal end of the body that can be used to gauge the depth of distal end of the sheath within the ventricle. The proximal end includes housing with a side port and three hemostasis valves. The introducer has an outer diameter of 0.326” and a length of 39cm.

Transfemoral: RetroFlex 3 Delivery System, Models 9120FS23, 9120FS26

The RetroFlex 3 Delivery System, shown in Figure 43, includes a rotating wheel within the handle for articulation of flex catheter, a tapered tip at the distal end of the delivery system to facilitate crossing the native valve, a balloon for deployment of the bioprosthesis, and radiopaque markers. The device is supplied sterile for single use only.

Figure 43. RetroFlex 3 Delivery System



Transfemoral: RetroFlex Balloon Catheter, Models 9120BC20, 9120BC23

The RetroFlex Balloon Catheter, shown in Figure 44, is used for valvuloplasty of a stenotic cardiac valve prior to implantation of a transcatheter heart valve. The device consists of a shaft and balloon with radiopaque markers indicating working length of the balloon. At the proximal end of the device, there is a standard “Y-connector” for balloon inflation and guidewire insertion. The device is supplied sterile for single use only.



Figure 44. RetroFlex Balloon Catheter



Principles of Operation: Transfemoral Implantation

The SAPIEN valve is a bioprosthesis designed for transfemoral implantation in patients with severe aortic stenosis. This minimally invasive approach will be performed under local and/or general anesthesia using sterile technique, and using echocardiographic and fluoroscopic guidance for visualization.

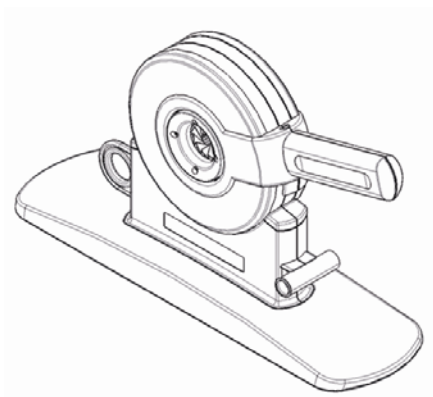
Prior to implantation, the native annulus is predilated with the RetroFlex Balloon Catheter to ease crossing of the bioprosthesis. The SAPIEN valve is carefully mounted and crimped onto a steerable, articulated balloon delivery catheter (RetroFlex 3 Delivery system) using the specially designed crimping device (Crimper). Following dilation of the femoral artery and placement of a sheath, the RetroFlex 3 Delivery System with mounted SAPIEN valve is inserted into the femoral artery and advanced across the native stenotic aortic valve. The steerable and articulating capabilities of the RetroFlex 3 delivery system facilitates correct positioning of the SAPIEN valve across the native valve. Balloon inflation and deflation expands and deploys the SAPIEN valve within the native valve.

Transfemoral/Transapical: Crimper, Models 9100CR23, 9100CR26

The Crimper, shown in Figure 45, is comprised of a housing and a compression mechanism, creating an aperture that is opened and closed by means of a handle located on the housing. The crimper includes a balloon gauge to verify diameter of an inflated balloon catheter and a crimp gauge to verify collapsed diameter of the device. The device is supplied sterile for single use only.



Figure 45. Crimper





Appendix C. STS Score and EuroSCORE Calculators

The STS risk calculator takes the following factors into account:

VALVE (AV Repl, MV Repl, MV Repair)

B. Demographics

- Patient Age (140)
- Gender (150)
- Race Black (192)
- Race Asian (193)
- Ethnicity (199)

D. Risk Factors

- Weight (350)
- Height (360)
- Diabetes (400)
- Diabetes Control (410)
- Last Preop Creatinine Level (430)
- Renal Failure-Dialysis (450)
- Hypertension (460)
- Infectious Endocarditis Type (500)
- Chronic Lung Disease (510)
- Immunosuppressive Treatment (520)
- Peripheral Arterial Disease (530)
- Cerebrovascular Disease (540)
- Cerebrovascular Accident (552)

E. Previous Interventions

- Previous CAB (600)
- Previous Valve (610)
- Previous PCI Interval (670)

F. Preoperative Cardiac Status

- Previous Myocardial Infarction Timing (760)
- Heart Failure (770)
- Classification-NYHA (775)
- Cardiac Presentation on Admission (791)
- Cardiogenic Shock (810)
- Resuscitation (830)
- Arrhythmia Afib / Aflutter (853)

G. Preoperative Medications

- Inotropes (970)

H. Hemodynamics and Cath

- Number of Diseased Vessels (1050)
- Left Main Disease (1060)
- Ejection Fraction (1080)
- Aortic Stenosis (1120)
- Mitral Stenosis (1140)
- Aortic Insufficiency (1170)
- Mitral Insufficiency (1180)



Tricuspid Insufficiency (1190)

I. Operative

Incidence (1230)

Status (1240)


IABP-Timing (1440)

K. Valve Surgery

Mitral Procedure (1640)

Note, the STS Risk Calculator was changed in January, 2008.



| EuroSCORE Risk Profile | | | |
|--|-------|---------------------------------|---|
| | | Additive EuroSCORE Φ | Logistic EuroSCORE $\beta_i \quad X_i$ |
| | | | |
| | | | |
| Patient Factors | | | |
| Age | #REF! | #REF! | #REF! |
| Sex | | 1 | 0.3304052 |
| Chronic pulmonary disease | | 1 | 0.4931341 |
| Extracardiac arteriopathy | | 2 | 0.6558917 |
| Neurological dysfunction | | 2 | 0.841626 |
| Previous cardiac surgery | | 3 | 1.002625 |
| Serum creatinine >200 $\mu\text{mol/L}$ | | 2 | 0.6521653 |
| Active endocarditis | | 3 | 1.101265 |
| Critical preoperative state | | 3 | 0.9058132 |
| | | | |
| Cardiac Factors | | | |
| Unstable angina | | 2 | 0.5677075 |
| LV dysfunction moderate or LVEF 30-50% | | 1 | 0.4191643 |
| LV dysfunction poor or LVEF<30 | | 3 | 1.094443 |
| Recent myocardial infarct | | 2 | 0.5460218 |
| Pulmonary hypertension | | 2 | 0.7676924 |
| | | | |
| Operation Factors | | | |
| Emergency | | 2 | 0.7127953 |
| Other than isolated CABG | | 2 | 0.5420364 |
| Surgery on thoracic aorta | | 3 | 1.159787 |
| Postinfarct septal rupture | | 4 | 1.462009 |
| | | | |
|  EuroSCORE | | $\Sigma\Phi$ | $e^{(-4.789594 + \Sigma\beta_i X_i)} / 1 + e^{(-4.789594 + \Sigma\beta_i X_i)}$ |
| Downloaded from http://euroscore.org | | | |



Appendix D. Adverse Event Definitions

The adverse event definitions as specified in the protocol are provided in Table 86.

Table 86. Protocol Defined Adverse Events

| | |
|--|---|
| Annular Dissection | Disruption or tear of the valve annulus extending to the aorta caused by mechanical injury from oversizing a balloon or the valve device itself |
| Aortic Dissection | Aortic dissection defined as Type A or B dissections that required surgical or percutaneous intervention. |
| Aortic Stenosis | Aortic stenosis was classified as “severe” when the following were present: <ul style="list-style-type: none"> • Jet velocity greater than 4.0 m/s • Mean gradient greater than 40mmHg • Valve area less than 1.0 cm² • Valve area index less than 0.6cm²/m² |
| Bleeding Event | Any episode of major internal or external bleeding that caused death, hospitalization or permanent injury (e.g., vision loss) or necessitated transfusion of greater than 3 units PRBCs or pericardiocentesis procedure. The complication <i>bleeding event</i> applied to all patients whether or not they were taking anticoagulants or antiplatelet drugs, since bleeding events could occur in patients who were not receiving anticoagulants. Embolic stroke complicated by bleeding was classified as a neurologic event under <i>embolism</i> and was not included as a separate bleeding event. Hemorrhage that required 2 or more units of transfusion within the index procedure was reported as serious adverse events. |
| Cerebrovascular Accident (CVA) | See “Embolism” |
| Conversion To Bypass | Conversion to cardiopulmonary bypass was defined when patient was cannulated <u>and</u> heparinized |
| Death (See Also “Sudden Death” And “Valve-Related Death”) | In general deaths were classified as cardiac or non-cardiac and procedure/valve-related. <i>Cardiac death</i> was defined as all deaths resulting from cardiac causes. This category included valve-related deaths (including sudden unexplained deaths) and non-valve related cardiac deaths (e.g., congestive heart failure, acute myocardial infarction, documented fatal arrhythmias.) <i>Non-cardiac death</i> was defined as a death not due to cardiac causes (as defined above). <i>Procedure-related death</i> : Deaths directly related to the procedure or complications thereof or any death occurring ≤ 30 days of the procedure were classified as procedure-related. <i>Valve-related death</i> : Death caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, operated valvular endocarditis, or death related to reoperation of an operated valve. |



| | |
|--------------------------|--|
| | <p>Sudden, unexplained, unexpected deaths of patients with an operated valve were included as valve-related mortality. Deaths caused by heart failure in patients with advanced myocardial disease and satisfactorily functioning cardiac valves were not included. Specific causes of valve-related deaths were designated and reported.</p> <p><i>Sudden death:</i> Sudden, unexpected, unexplained death. The cause of these deaths was unknown and the relationship to an operated valve was also unknown. Therefore, these deaths were reported as a separate category of valve-related mortality if the cause could not be determined by clinical data or autopsy.</p> |
| Device Malfunction | <p>The failure of a device to meet any of its performance specifications or otherwise perform as intended. Performance specifications included all claims made in the labeling of the device.</p> |
| Device Migration | <p>Device migration was defined x-ray confirmed movement of the study valve from its initial implantation site such that there was a change in valve orientation within the aortic outflow track resulting in a new echo-confirmed flow disturbance (pre- and post- filmed documentation).</p> |
| Embolism | <p>Free flowing blood clot or lesion material that was located in the systemic or pulmonary circulation.</p> <p>Any embolic event that occurred in the absence of infection after the immediate perioperative period (when anesthesia-induced unconsciousness was completely reversed).</p> <p>A <i>neurologic event</i> included any new, temporary or permanent focal or global neurologic deficit.</p> <p>A <i>transient ischemic attack (TIA)</i> was a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.</p> <p>A <i>stroke</i> or <i>permanent neurologic event</i> lasted ≥ 24 hours, or lasted < 24 hours with a brain imaging study showing infarction.</p> <p>Patients who did not awake or who awoke after operation with a new stroke were excluded in tabulations of valve-related morbidity. Psychomotor deficits were classified as adverse events if they were newly noted post baseline.</p> <p>A peripheral embolic event was an operative, autopsy or clinically documented embolus that produced symptoms from complete or partial obstruction of a peripheral (non-cerebral) artery. Patients who awoke with a myocardial infarction were excluded. Patients who had a myocardial infarction after the perioperative period were also excluded unless a coronary arterial embolus was shown to be the cause of the infarction by operation, autopsy or clinical investigation. Emboli proven to consist of non-thrombotic material (e.g., atherosclerosis, myxoma) were excluded.</p> |
| Emergent Bypass Surgery | <p>Emergent bypass surgery was defined as urgent or emergent coronary bypass surgery < 30 days of the index treatment.</p> |
| Emergent Cardiac Surgery | <p>Emergent Salvage: The patient underwent cardiopulmonary resuscitation (CPR) en route to the operating room or prior to anesthesia induction</p> <p>Emergent: The patient's clinical status included any of the following:</p> <ol style="list-style-type: none">1) Ischemic dysfunction of any of the following: a) ongoing ischemia including rest angina despite maximal medical therapy (medical and/or IABP); b) Acute Evolving Myocardial Infarction within 24 hours before surgery or c) |



| | |
|---|--|
| | <p>pulmonary edema requiring intubation</p> <p>2) Mechanical dysfunction (either of the following): a) shock with circulatory support; or b) shock without circulatory support</p> <p>Urgent:</p> <p>ALL of the following conditions were met:</p> <ul style="list-style-type: none">a) Not elective statusb) Not emergent statusc) Procedure required during same hospitalization in order to minimize chance of further clinical deteriorationd) Worsening, sudden chest pain, CHF, acute myocardial infarction (AMI), anatomy, IABP, unstable angina with intravenous nitroglycerin or rest angina were included <p>Elective:</p> <p>The patient's cardiac function was stable in the days or weeks prior to the operation. The procedure could be deferred without increased risk of compromised cardiac outcome.</p> |
| Endocarditis (Operated Valvular Endocarditis) | <p>Any infection involving an operated valve.</p> <p>The diagnosis of operated valvular endocarditis was based on customary clinical criteria including an appropriate combination of positive blood cultures, clinical signs and histologic confirmation of endocarditis at reoperation or autopsy.</p> <p>Morbidity associated with active infection, such as valve thrombosis, thrombotic embolus, bleeding event or paravalvular leak was included under this category and was not included in other categories of morbidity.</p> |
| Explant (See Also "Reoperation") | Removal of the investigational valve implant for any reason. |
| Hemodynamic Collapse | Hemodynamic collapse was defined when the SBP dropped below 40mmHg or when there was electromechanical dissociation. |
| Hemolysis | <ul style="list-style-type: none">• Plasma Hgb > 40 on two consecutive measurements within 24 hours. Laboratory values meeting this criteria were listed as a major adverse event, or• Clinical diagnosis of hemolysis evidenced by laboratory testing such as serial hemoglobin, serum LDH, haptoglobin, serum bilirubin and/or urine bilirubin levels |
| Hemorrhage | <p>See "Bleeding event"</p> <p>Events which were excluded were those due to liver disease, myocardial infarction, or systemic infection.</p> <p>Reported as major or minor as defined below:</p> <ul style="list-style-type: none">• Major: Required intervention.• Minor: Did not require intervention. |
| Hemorrhagic Vascular Complication | <p>Vascular complications included the following:</p> <ol style="list-style-type: none">1. Hematoma at access site >5 cm |



| | |
|--|---|
| | <ol style="list-style-type: none"> 2. False aneurysm 3. Arterio-venous fistula 4. Retroperitoneal bleeding 5. Peripheral ischemia/nerve injury 6. Any transfusion required was reported as a vascular complication unless for a clinical indication clearly other than catheterization complication. 7. Vascular surgical repair |
| Infection | Known infection requiring intravenous antibiotics for other than prophylaxis, and/or extended hospitalization. |
| Mitral Valve Compromise | Mitral valve compromise defined as mitral injury producing a 1+ increase in mitral regurgitation. |
| Myocardial Infarction | <p>Any of the following criteria met the definition of MI:</p> <ol style="list-style-type: none"> 1) Any Acute MI demonstrated by autopsy 2) Any emergent PCI performed for acute ST-elevation myocardial infarction 3) Any administration of thrombolytics for acute myocardial infarction 4) Clinical peri-procedural MI (up through 7 complete days post index procedure): <ul style="list-style-type: none"> ▪ Periprocedural Q-wave MI: Development of new pathologic Q waves in 2 or more contiguous leads with elevation of CK-MB or CK in absence of CK-MB data. New Q waves in the absence of symptoms or elevated markers were NOT considered an MI. ▪ Periprocedural Non-Q-wave MI: Documented signs or symptoms of ischemia and/or new ischemic changes on ECG AND CK-MB elevation > 10 X ULN. In the absence of CK-MB data, CK should be used. In the absence of CK-MB data, CK could be used with the same > 10 X ULN criteria. 5) Clinical non-procedural MI <ul style="list-style-type: none"> ○ Q-wave MI: Development of new pathologic Q waves in 2 or more contiguous leads with elevation of CK, CK-MB or Troponin in clinical setting with signs or symptoms of myocardial ischemia. ○ Non-Q-wave MI: Elevation of CK > 2 times ULN with elevation of CK-MB or Troponin in clinical setting with signs or symptoms of myocardial ischemia. |
| Nonstructural Dysfunction | <p>An abnormality, which was not intrinsic to the prosthetic valve (i.e. valve was structurally normal) resulting in stenosis or regurgitation.</p> <p>Examples of nonstructural dysfunction included entrapment by pannus, tissue or suture, paravalvular leak, inappropriate sizing or positioning, residual leak or obstruction from valve implantation or repair, and clinically important hemolytic anemia.</p> <p>See “paravalvular leak” for additional definitions</p> |
| Paravalvular Leak (See Also “Nonstructural Dysfunction”) | <p>Leakage due to a separation of the prosthetic valve from the annulus.</p> <p>Any evidence of leakage of blood around the device. Diagnosis of paravalvular leak could be obtained from echo; however, definitive diagnosis was obtained at reoperation, explant, or autopsy.</p> <p>Primary paravalvular leak</p> |

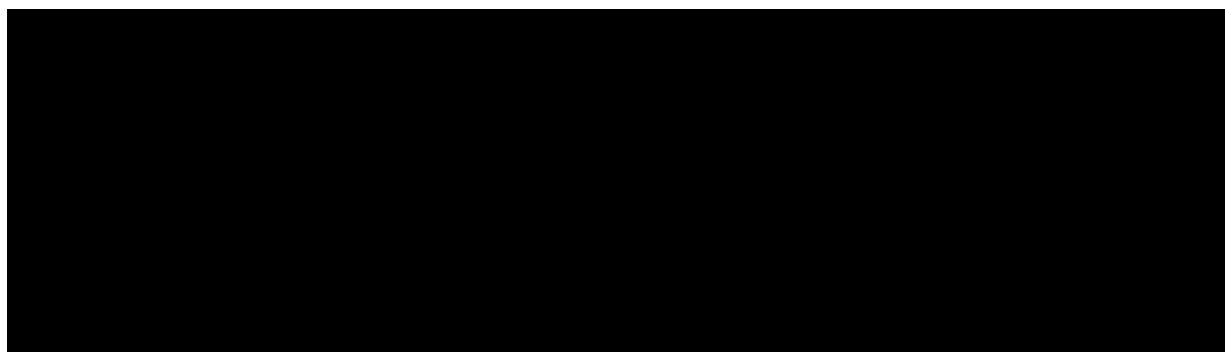


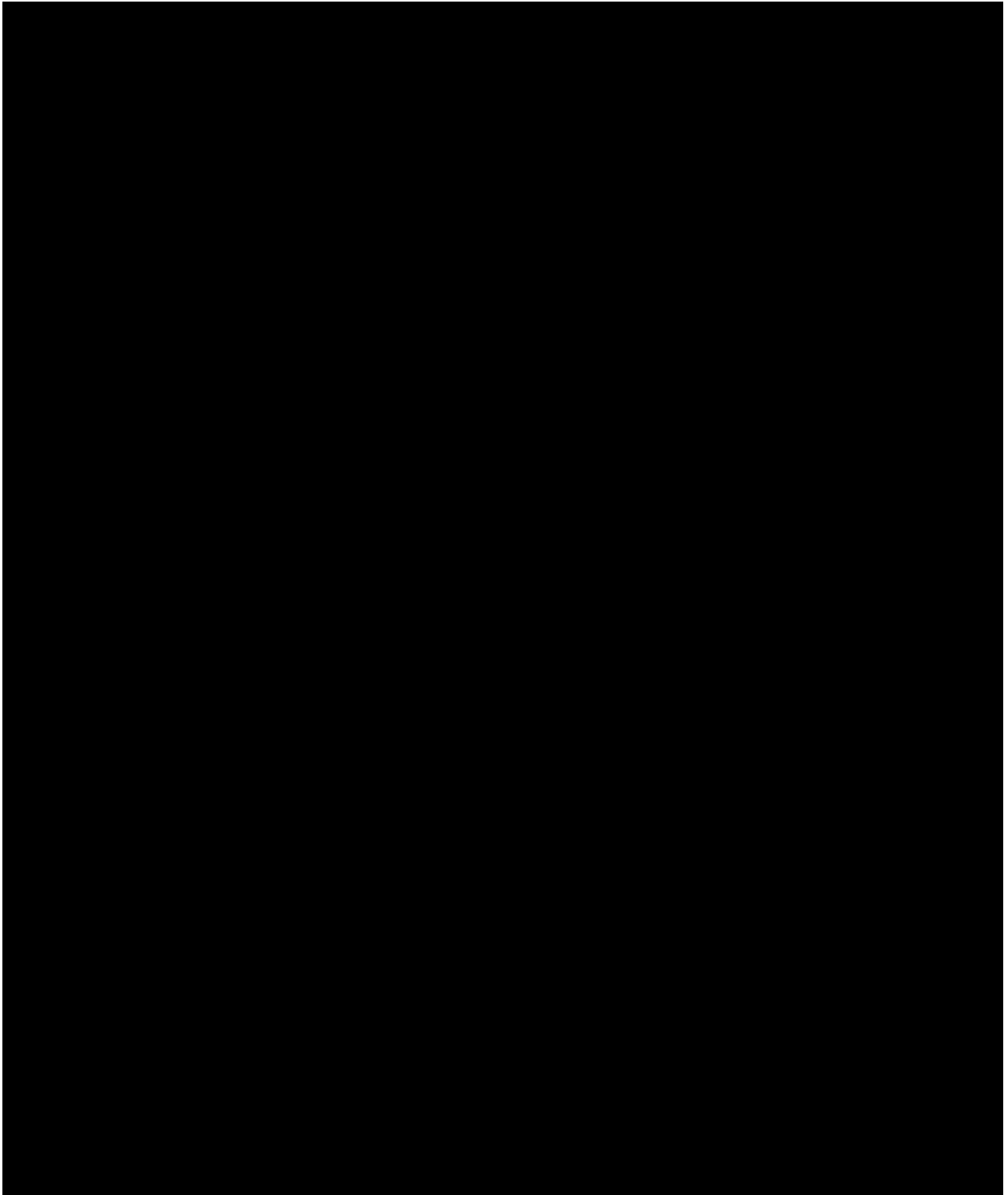
| | |
|---|--|
| | <p>Defined as any evidence of leakage of blood around the prosthesis between the device and the native annulus.</p> <p>Primary paravalvular leaks were stratified by the following:</p> <p>All leaks: evidence of moderate to severe paravalvular insufficiency by echocardiography</p> <p>Minor leaks: A paravalvular leak graded < 3+ aortic insufficiency and did not require surgical intervention</p> <p>Major leaks: A paravalvular leak graded ≥3+ aortic insufficiency or required surgical intervention</p> |
| Perforation of the Free Myocardial Wall | <p>These perforations were categorized according to the severity:</p> <p>Clinical perforation: Coronary perforation requiring additional treatment outside the protocol, or resulting in significant pericardial effusions, urgent open-chest surgery or death. "Clinical perforation" applied if either catheter drainage or open drainage was required.</p> <p>Pericardial hemorrhage/tamponade: Perforation with hemodynamic evidence of tamponade or pericardial hemorrhage.</p> |
| Peripheral Thromboembolic Event | See "Embolism" |
| Renal Failure | Patient required chronic dialysis for greater than 30 days |
| Renal Insufficiency | Creatinine level above 3.5 |
| Reintervention | Any intervention that repaired, altered or replaced a previously operated valve. |
| Sternal Wound Infection | <p>Deep sternal infection involving muscle, bone, and/or mediastinum</p> <p>Required to have one of the following:</p> <ol style="list-style-type: none">1) Wound opened with excision of tissue (I&D)2) Positive culture3) Treatment with antibiotics. <p>Infection that was contiguous with the sternum on imaging constituted involvement of the sternum.</p> |
| Stroke | A neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction |
| Structural Valvular Deterioration (SVD) | <p>Any change in valve function (a decrease of one NYHA functional class or more) of an operated valve resulting from an intrinsic abnormality of the valve that caused stenosis or regurgitation.</p> <p>Structural valve deterioration included operated valve dysfunction or deterioration <i>exclusive of infection or thrombosis</i> as determined by reoperation, autopsy or clinical investigation. The term structural deterioration referred to changes intrinsic to the valve, such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep and suture line disruption of components (e.g. leaflets, chordae) of an operated valve.</p> |
| Sudden Death (See Also "Death") | <p>Sudden, unexpected, unexplained death. The cause of these deaths was unknown and the relationship to an operated valve was also unknown.</p> <p>Therefore, these deaths should be reported as a separate category of valve-related mortality if the cause could not be determined by clinical data or</p> |

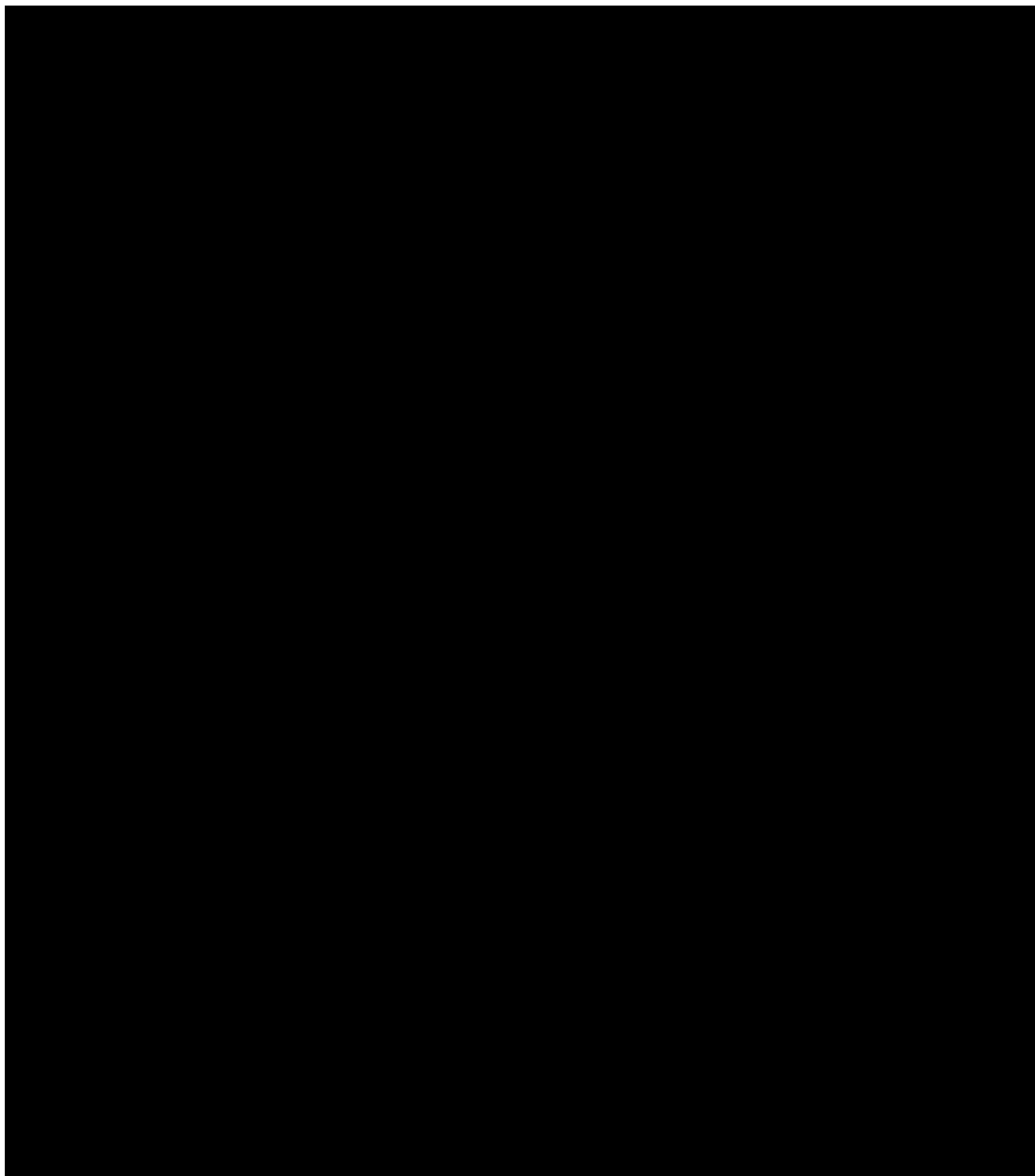


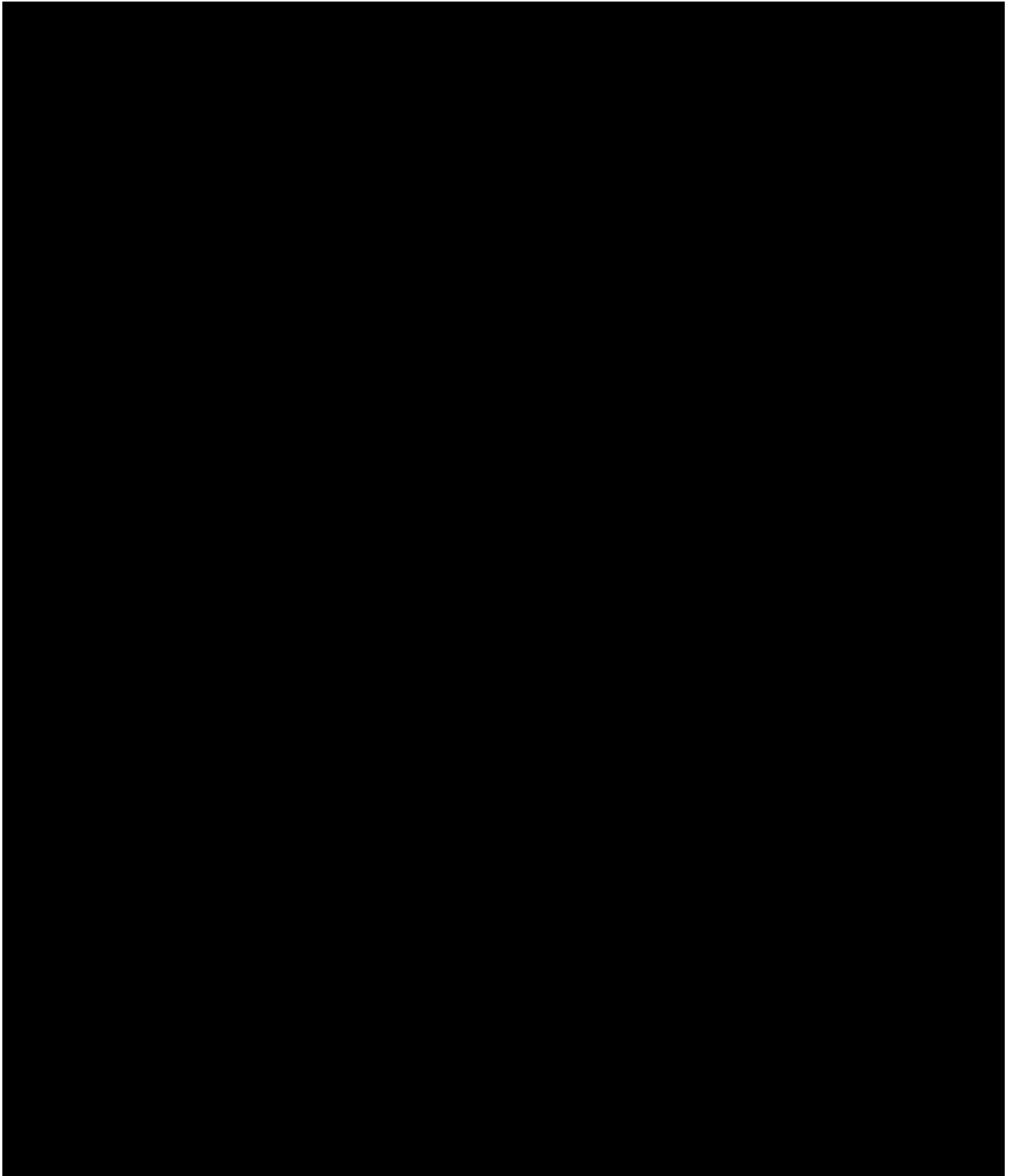
| | |
|---|---|
| | autopsy. |
| Thromboembolic Event | See “embolism” |
| Thrombus (Valve Thrombosis) | <p>An aggregation of platelet, fibrin, clotting factors, and other cellular elements exclusive of infection.</p> <p>Valve thrombosis was defined as any thrombus in the absence of infection attached to or near an operated valve that occluded part of the blood flow path or that interfered with function of the valve. A valve related thrombus was confirmed by operation, autopsy, or diagnostically by such methods as echocardiography, angiocardiology, or magnetic resonance imaging.</p> |
| Transient Ischemic Attack (TIA) | See “embolism” |
| Traumatic Cardiac Microangiopathic Hemolytic Anemia | <p>The intravascular fragmentation of red blood cells characterized by low hemoglobin levels, schizocytes consisting of helmet cells, triangle cells and other fragmented forms. The red cells could show hypochromia if iron deficiency due to urinary loss of hemoglobin or hemosiderin was present. The plasma hemoglobin level was elevated and the serum haptoglobin concentration was diminished or absent. Hemosiderinuria was a constant finding, but hemoglobinuria may vary from none to large amounts. Serum LDH activity could be elevated. The leukocyte count could be normal or slightly elevated and the platelet count could be diminished. This anemic event was exclusive of infection or autoimmune disease. The anemia was considered mild if controlled by iron replacement, and severe if transfusion was necessary.</p> |
| Valve-Related Mortality (See Also “Death”) | <p>Death caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, operated valvular endocarditis, or death related to reoperation of an operated valve. Sudden, unexplained, unexpected deaths of patients with an operated valve were included as valve-related mortality. Deaths caused by heart failure in patients with advanced myocardial disease and satisfactorily functioning cardiac valves were not included. Specific causes of valve-related deaths were designated and reported.</p> |

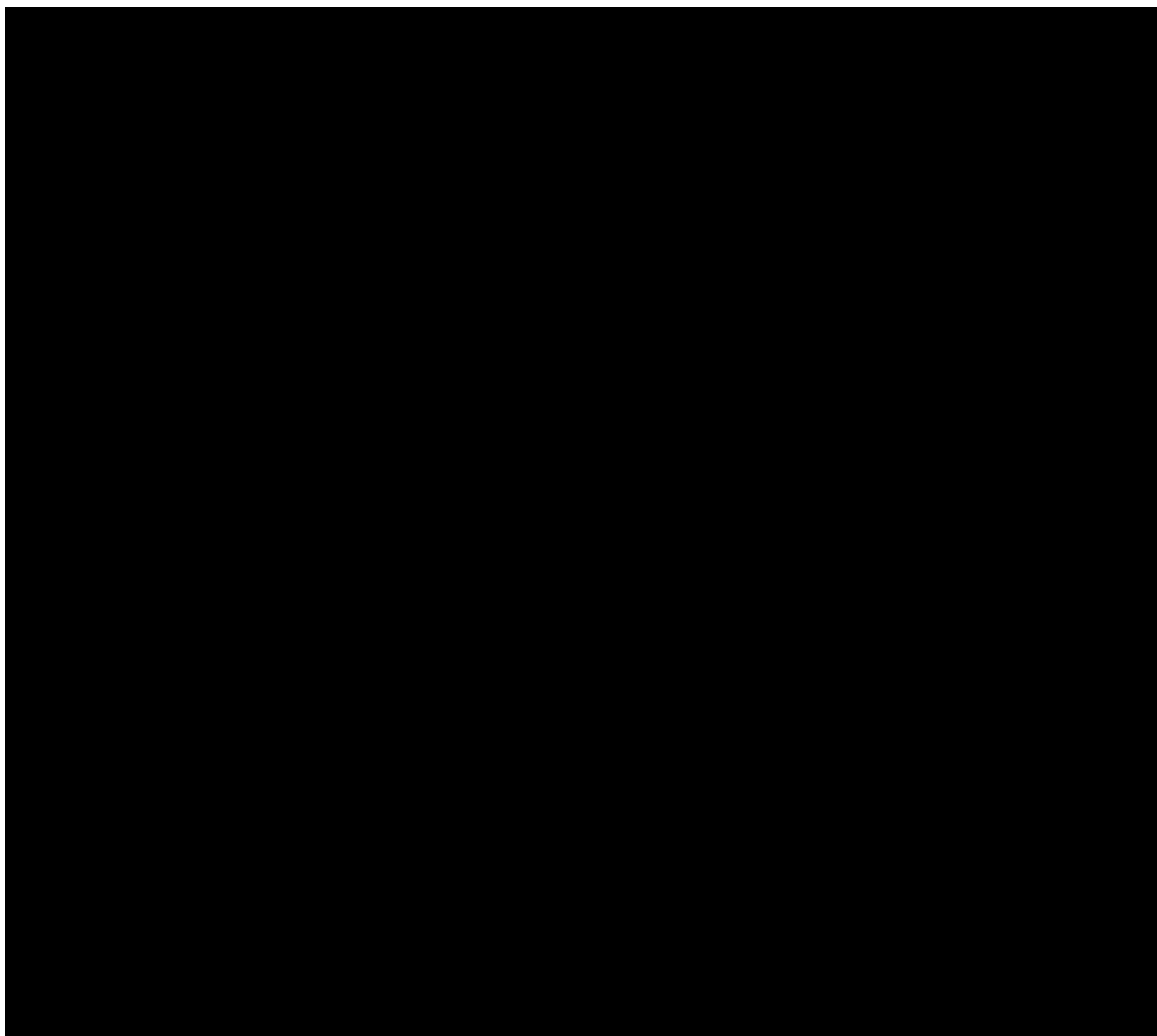
The adverse event definitions used by the CEC in accordance with VARC are provided below:





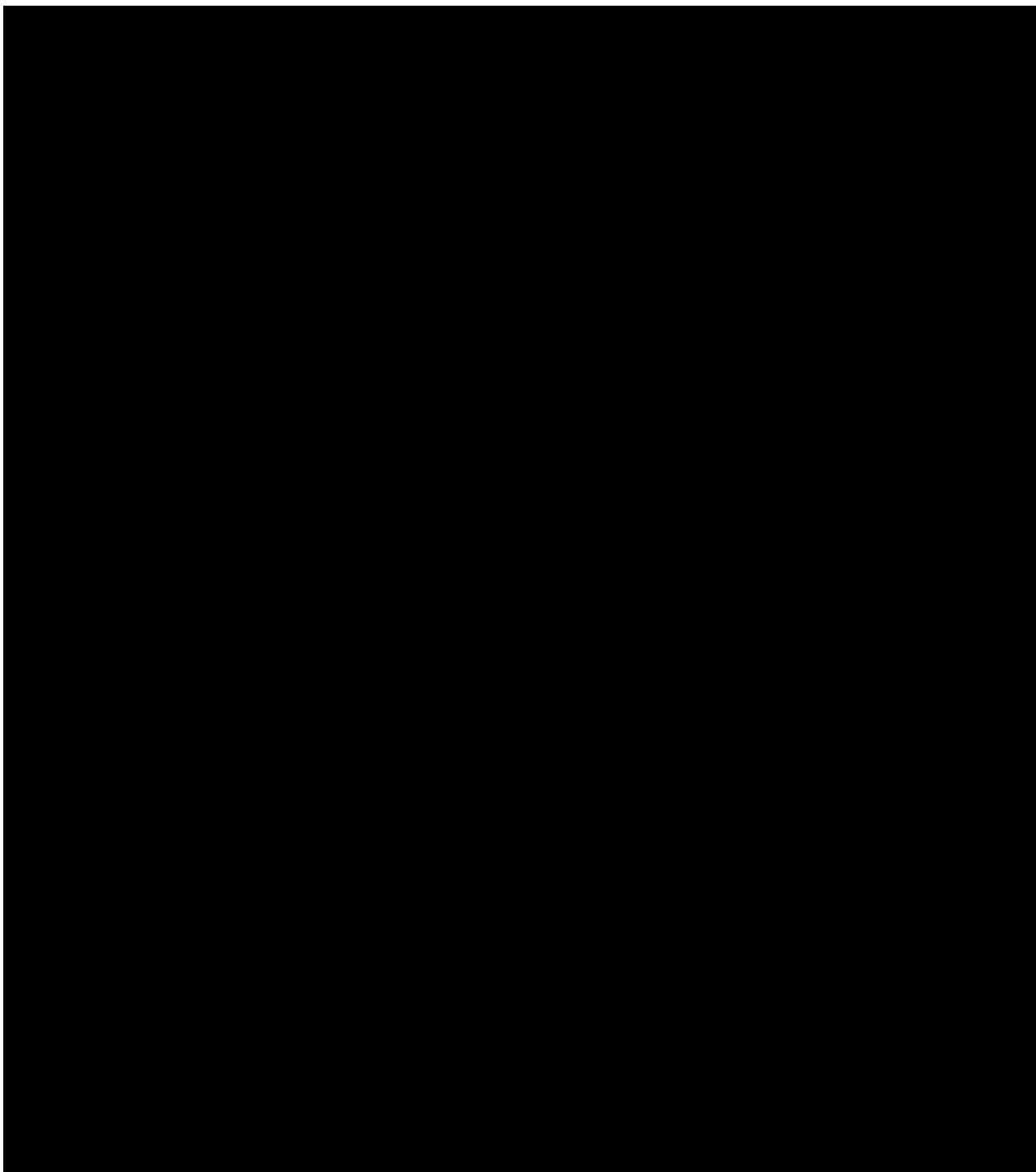


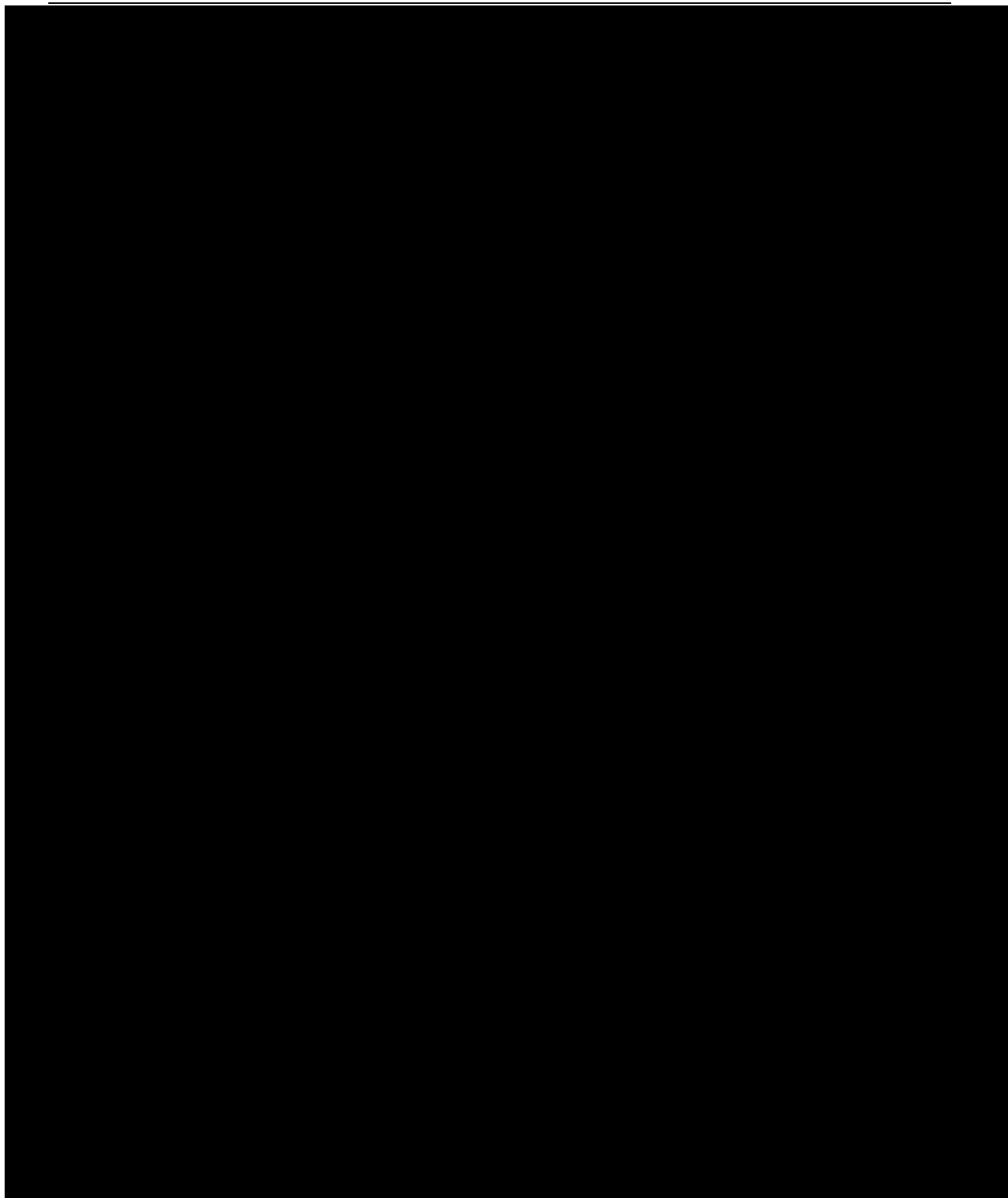


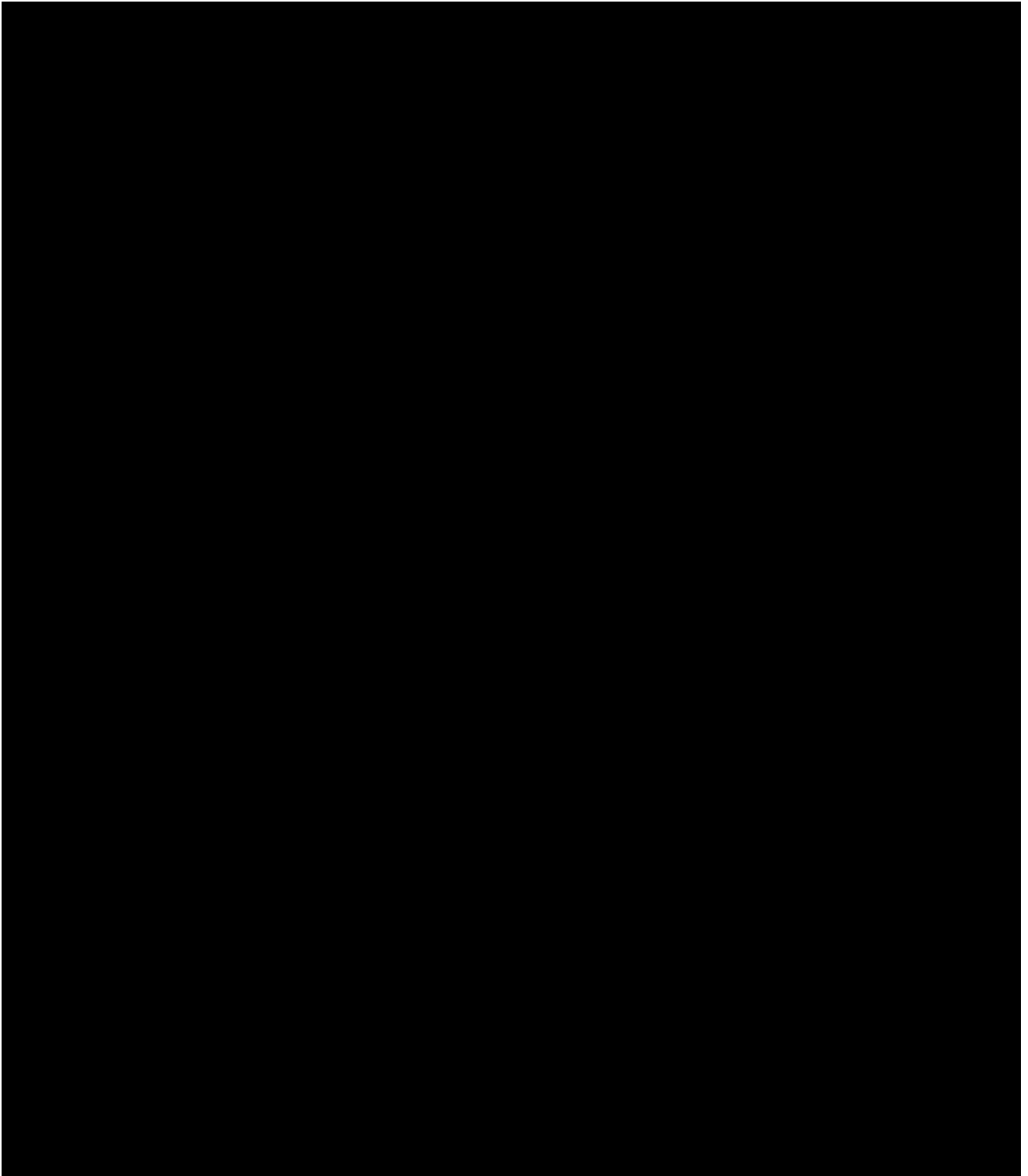


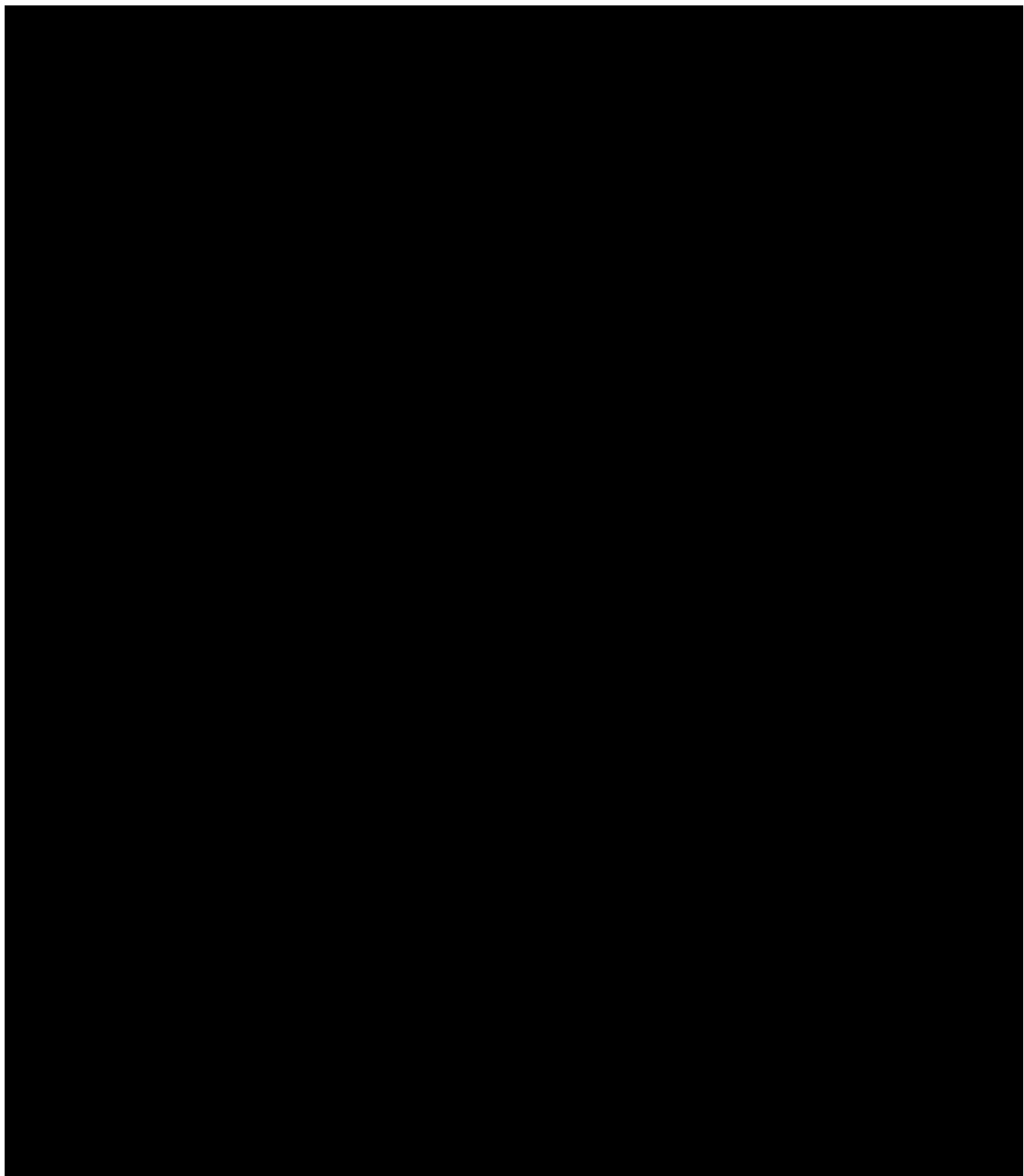


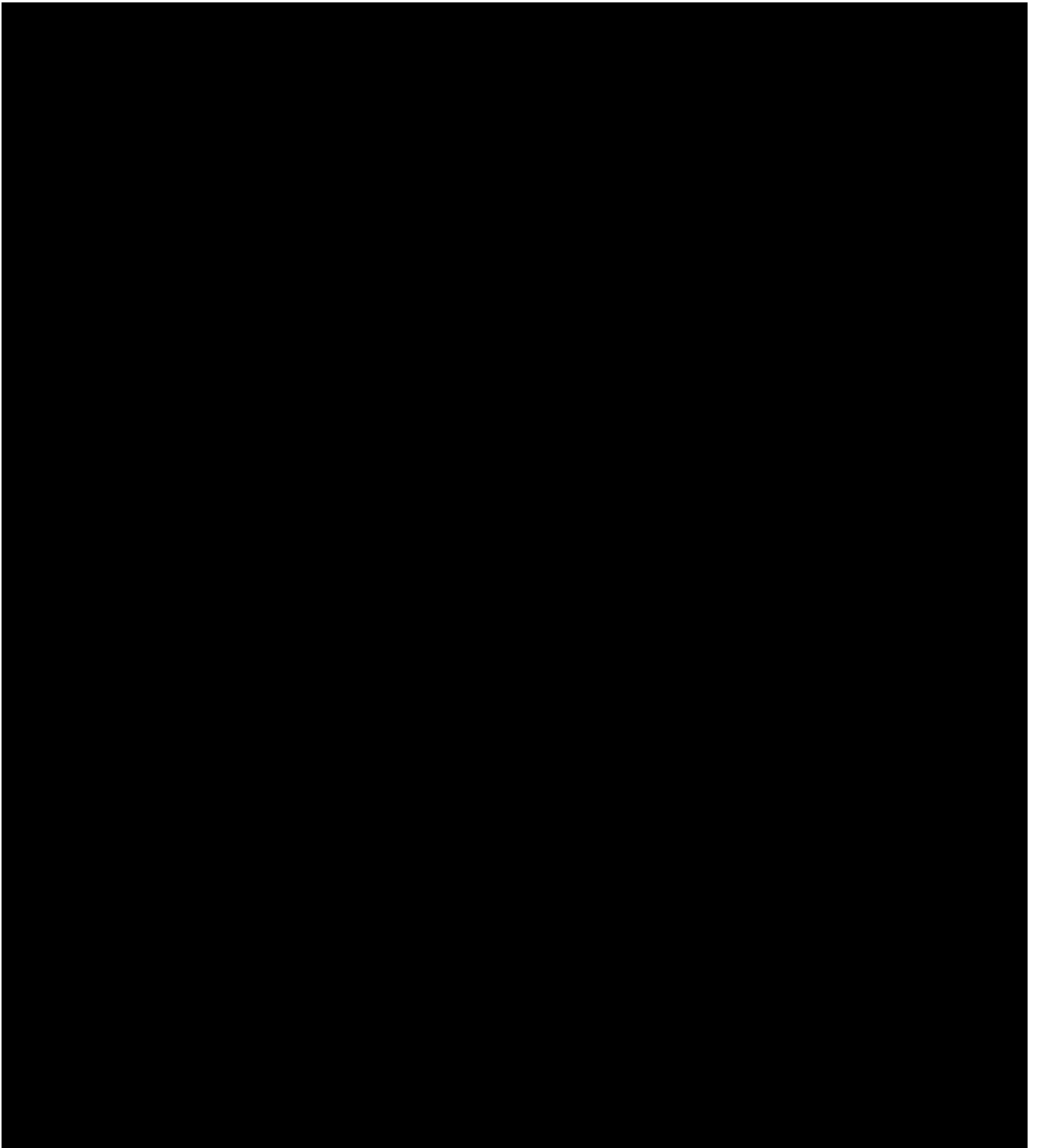
Appendix E. Statistical Methods

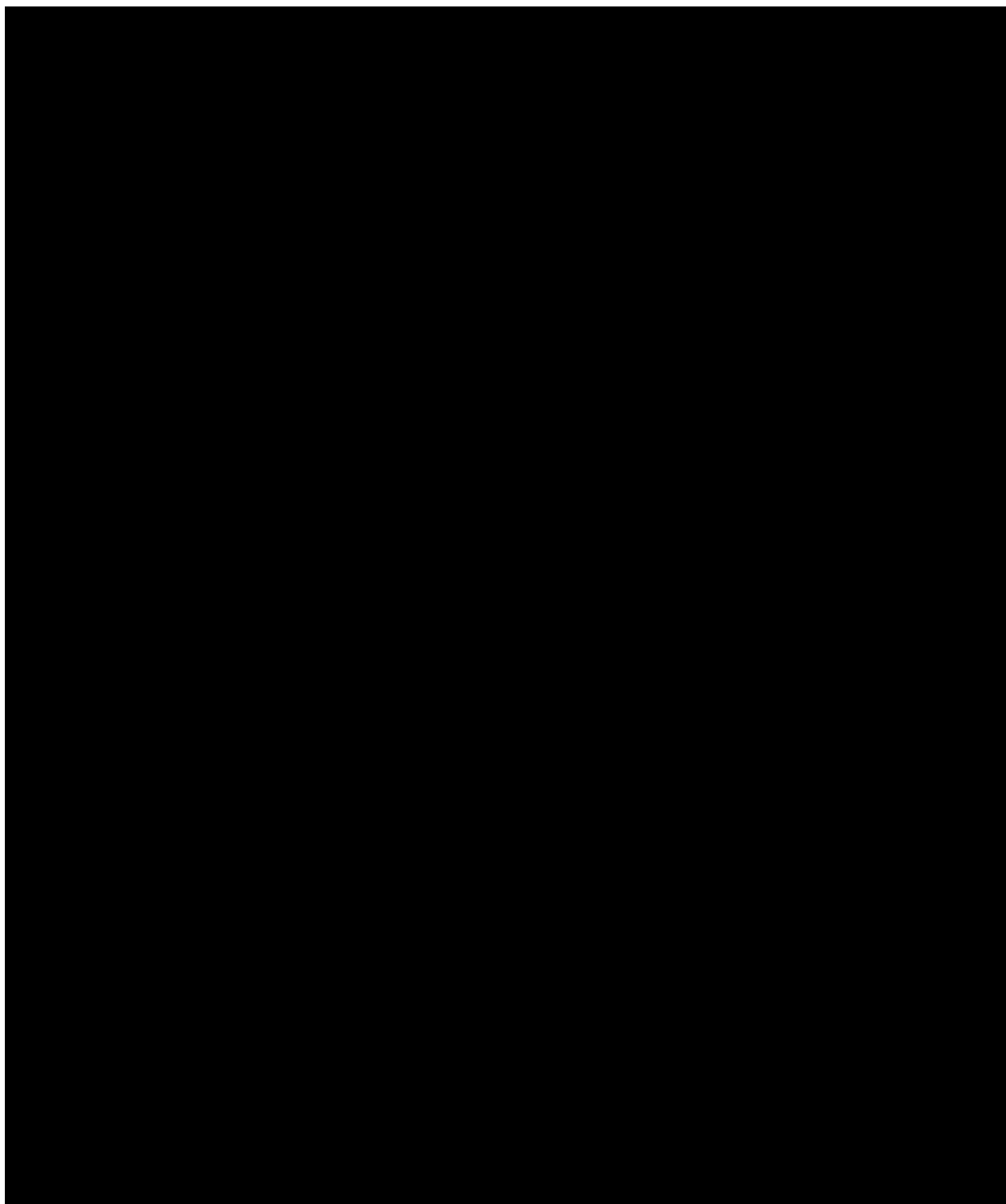


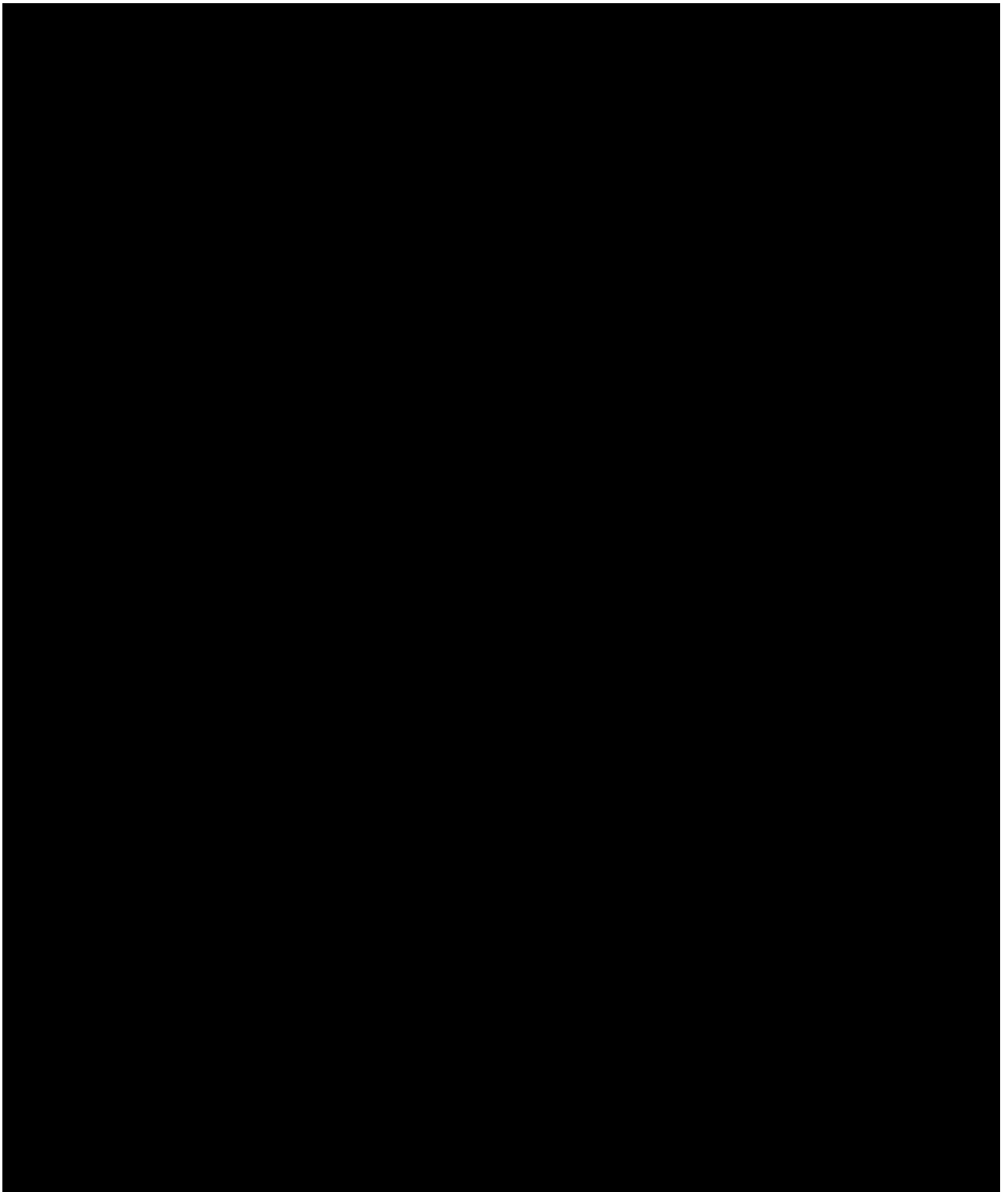


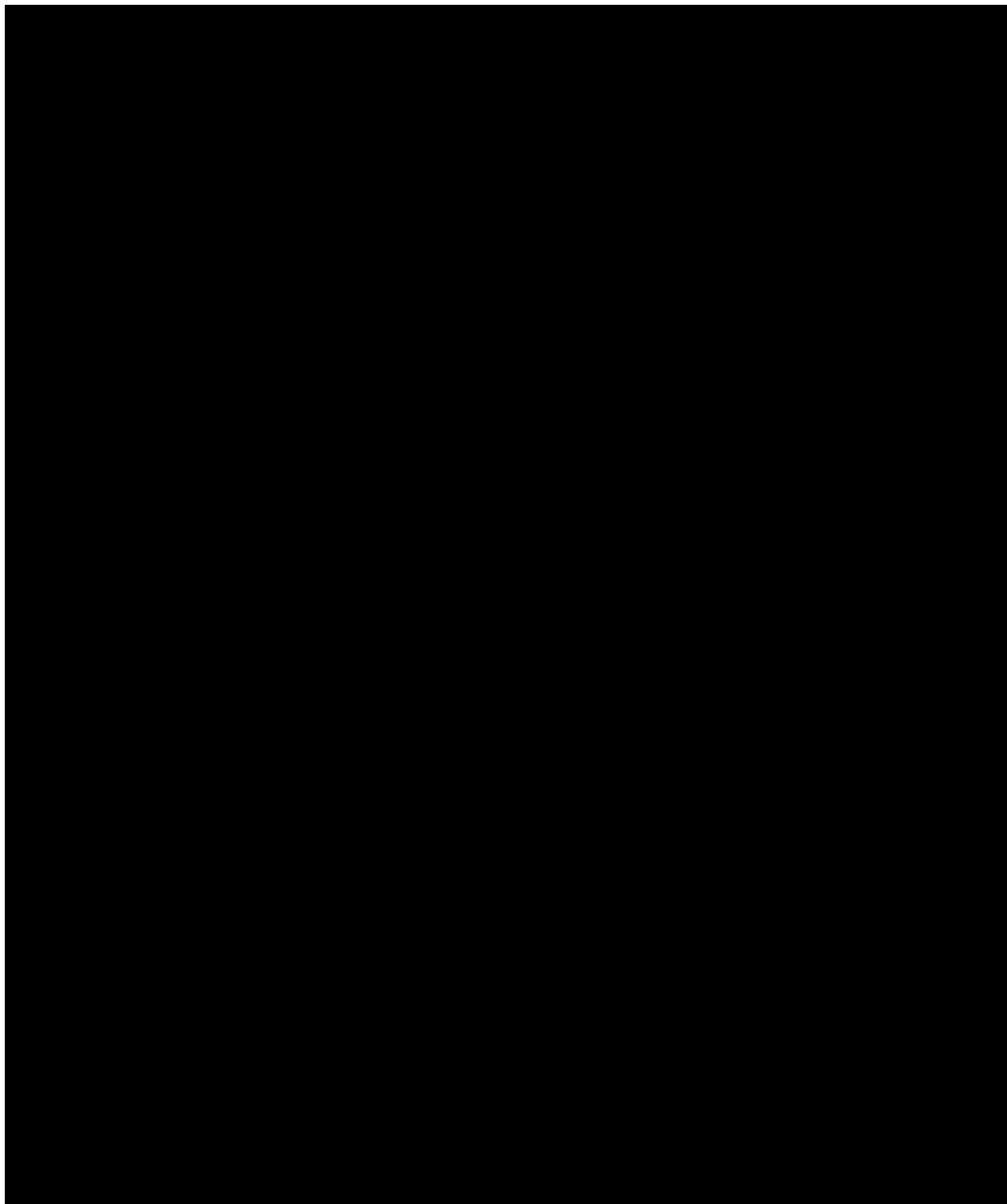


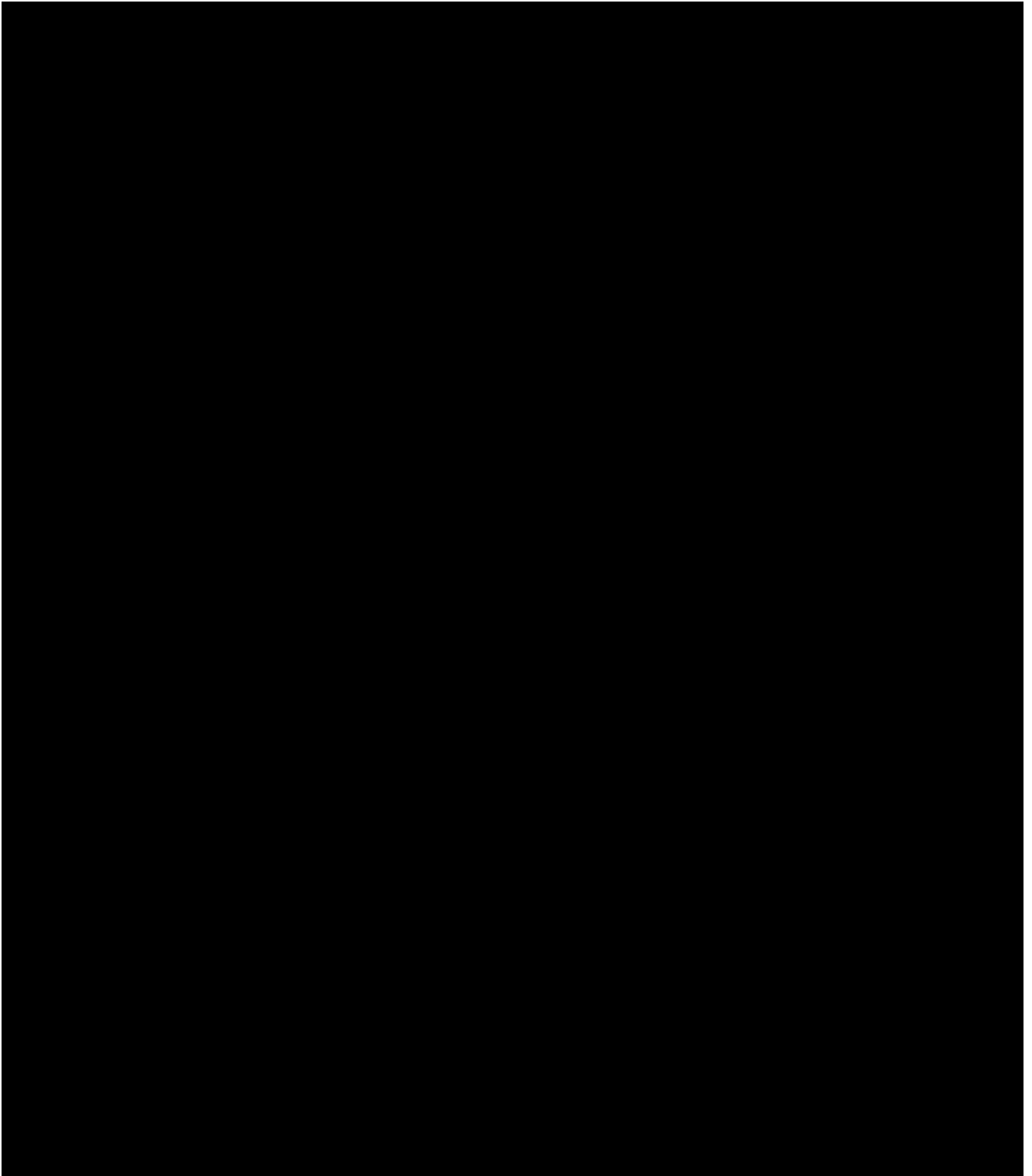


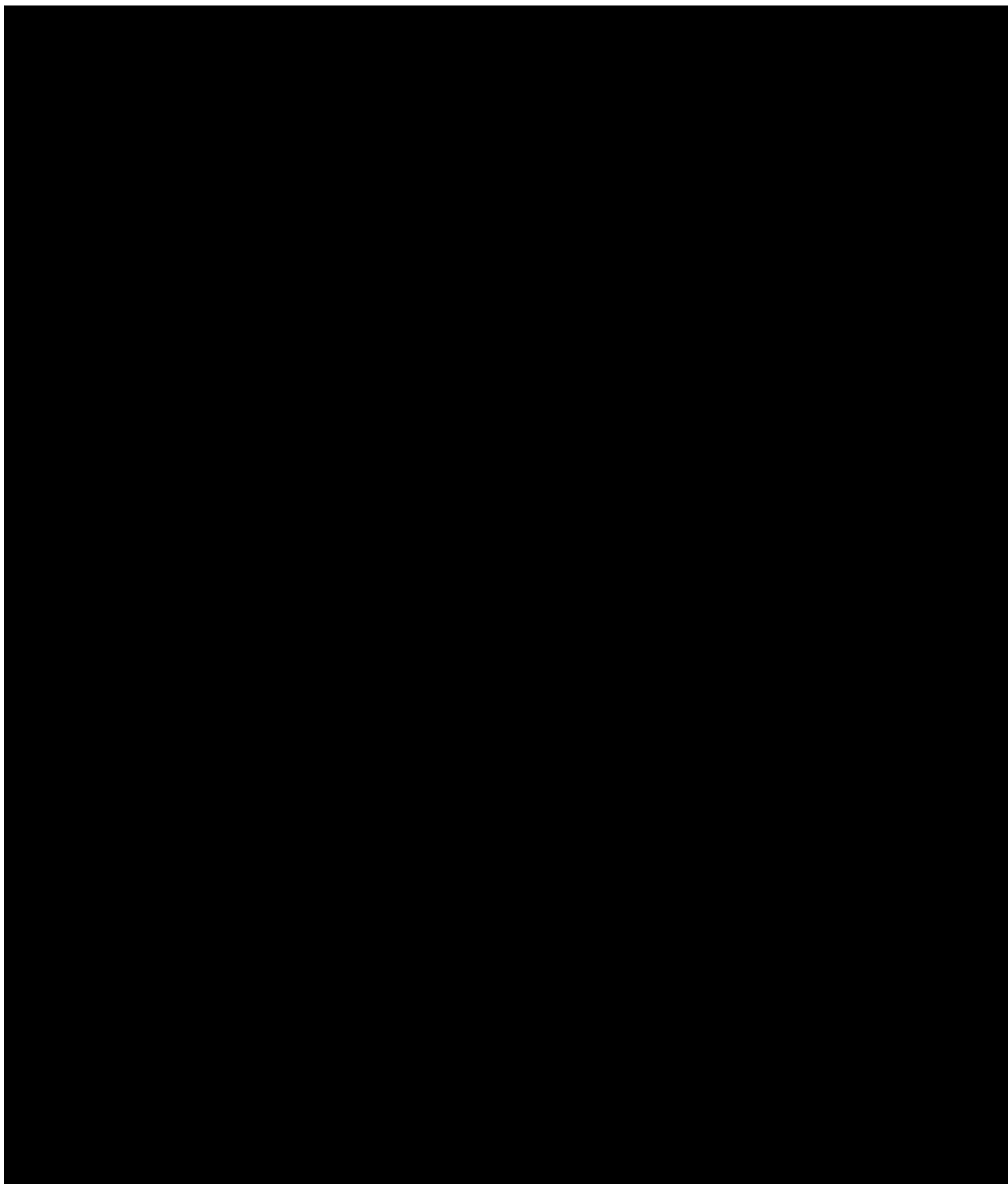


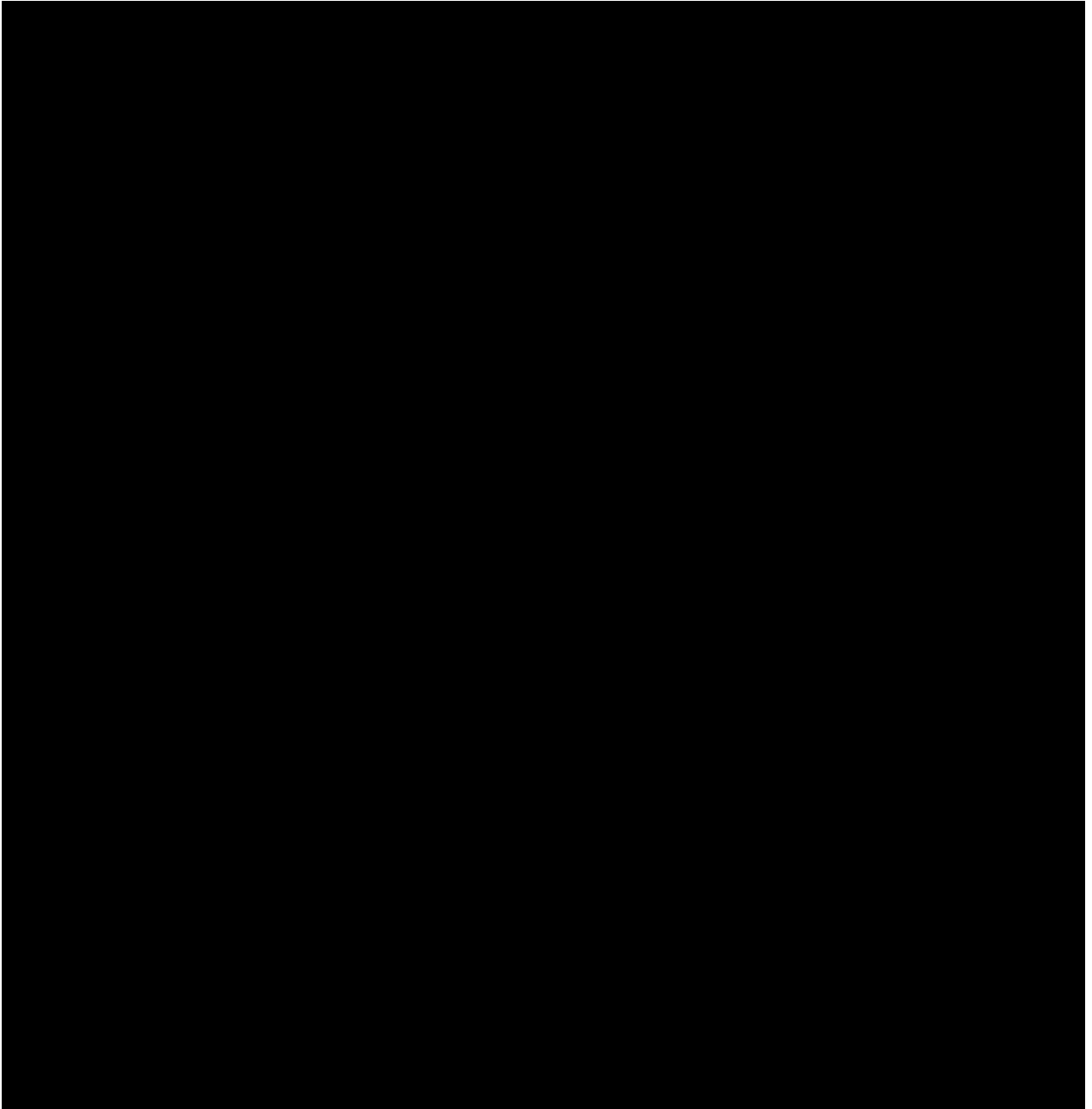














Appendix F. Additional Tables – High Risk Cohort

Table 87. Patient Enrollment by Site and Treatment Group - High Risk Cohort in the PARTNER Study (ITT Population)

| Cohort A Counts -- Intent to Treat (ITT) | | | | | | | | | |
|--|----------------------|------|-----------------------|------|-------------------|------|-----------------|---------------------|----------|
| | Randomized Patients | | | | | | Trial Total | | |
| | Transapical Approach | | Transfemoral Approach | | Pooled Approaches | | | | |
| Site | AVR | TAVR | AVR | TAVR | AVR | TAVR | Rando- mized | Non Rando- mized | Cohort A |
| Barnes | 2 | 4 | 9 | 9 | 11 | 13 | 24 | 63 | 87 |
| Boston Mass General | 0 | 0 | 8 | 7 | 8 | 7 | 15 | 83 | 98 |
| Brigham Womens | 0 | 0 | 1 | 1 | 1 | 1 | 2 | 29 | 31 |
| Cedars Sinai | 12 | 12 | 47 | 45 | 59 | 57 | 116 | 127 | 243 |
| Cleveland Clinic | 11 | 11 | 13 | 12 | 24 | 23 | 47 | 93 | 140 |
| Columbia | 12 | 13 | 36 | 36 | 48 | 49 | 97 | 129 | 226 |
| Cornell | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 61 | 62 |
| Dallas | 20 | 20 | 27 | 28 | 47 | 48 | 95 | 135 | 230 |
| Emory | 15 | 14 | 19 | 19 | 34 | 33 | 67 | 94 | 161 |
| Evanston | 0 | 0 | 2 | 2 | 2 | 2 | 4 | 22 | 26 |
| Evanston Northwestern | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Intermountain | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 46 | 47 |
| Laval | 3 | 2 | 2 | 1 | 5 | 3 | 8 | 0 | 8 |
| Leipzig | 0 | 0 | 4 | 3 | 4 | 3 | 7 | 2 | 9 |
| Mayo | 0 | 0 | 3 | 3 | 3 | 3 | 6 | 65 | 71 |
| Miami | 1 | 3 | 11 | 10 | 12 | 13 | 25 | 83 | 108 |
| Northwestern | 4 | 4 | 6 | 6 | 10 | 10 | 20 | 68 | 88 |
| Ochsner | 0 | 0 | 1 | 1 | 1 | 1 | 2 | 23 | 25 |
| Pennsylvania | 13 | 10 | 14 | 15 | 27 | 25 | 52 | 100 | 152 |
| Scripps | 0 | 0 | 3 | 4 | 3 | 4 | 7 | 106 | 113 |
| StLukes | 0 | 1 | 7 | 5 | 7 | 6 | 13 | 21 | 34 |
| Stanford | 5 | 4 | 7 | 7 | 12 | 11 | 23 | 84 | 107 |
| Toronto | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| U of Washington | 0 | 0 | 2 | 3 | 2 | 3 | 5 | 36 | 41 |
| Vancouver | 2 | 3 | 7 | 7 | 9 | 10 | 19 | 0 | 19 |
| Virginia | 0 | 0 | 2 | 1 | 2 | 1 | 3 | 38 | 41 |



| Cohort A Counts -- Intent to Treat (ITT) | | | | | | | | | |
|--|----------------------|------|-----------------------|------|-------------------|------|-----------------|---------------------|----------|
| | Randomized Patients | | | | | | Trial Total | | |
| | Transapical Approach | | Transfemoral Approach | | Pooled Approaches | | | | |
| Site | AVR | TAVR | AVR | TAVR | AVR | TAVR | Rando- mized | Non Rando- mized | Cohort A |
| Washington DC | 3 | 3 | 17 | 17 | 20 | 20 | 40 | 121 | 161 |
| Total | 103 | 104 | 248 | 244 | 351 | 348 | 699 | 1629 | 2328 |

Source: Table 1.1

Table 88. Listing of Patients Who Either Did NOT Undergo the Randomly Assigned Treatment and/or Were Censored at 1 Year – High Risk Cohort in the PARTNER Study (ITT Population)

| Subject | Trial Arm | Non Treatment? | Censored at 1 year? |
|---------|-----------|----------------------------------|---|
| | AVR | Yes, refused | Yes, withdrawn |
| | AVR | Yes, refused | Yes, withdrawn |
| | AVR | Yes, withdrawn | Yes, withdrawn |
| | AVR | Yes, refused | No, died in 31 days – 1 year |
| | AVR | Yes, died before procedure | No, died within 30days |
| | AVR | Yes, died before procedure | No, died within 30days |
| | AVR | Yes, withdrawn | Yes, withdrawn |
| | AVR | Yes, pre-treatment deterioration | No, died in 31 days – 1 year |
| | AVR | Yes, refused | Yes, withdrawn |
| | AVR | Yes, pre-treatment deterioration | No - alive (died in 1 year – 2 years) |
| | AVR | Yes, refused | Yes, withdrawn |
| | AVR | No | Yes, withdrawn (withdrew after treatment; no reason provided) |
| | AVR | Yes, pre-treatment deterioration | No, died within 30 days |
| | AVR | No | Yes, lost to follow-up |
| | AVR | Yes, refused | No |
| | TAVR | No | Yes, withdrawn (no reason provided) |
| | AVR | Yes, refused | Yes, withdrawn |
| | AVR | Yes, refused | Yes, withdrawn |
| | AVR | Yes, pre-treatment deterioration | No, died within 30 days |
| | AVR | Yes, refused | No, alive (died in 1 year – 2 years) |
| | AVR | Yes, withdrawn | Yes, withdrawn |
| | TAVR | No | Yes, lost |



| Subject | Trial Arm | Non Treatment? | Censored at 1 year? |
|---------|-----------|--|--|
| | TAVR | No | Yes, alive and censored at 1 year |
| | AVR | No | Yes, withdrawn (patient objected to the time required to complete the f/u visit) |
| | AVR | Yes, withdrawn | Yes, withdrawn |
| | TAVR | Yes, pre-treatment deterioration | No, died in 31 days – 1 year |
| | AVR | Yes, withdrawn | Yes, withdrawn |
| | AVR | Yes, refused | No, alive (died in 1year - 2years) |
| | AVR | Yes, died before procedure | No, died within 30 days |
| | AVR | Yes, died before procedure | No, died in 31days - 1year |
| | AVR | No | Yes, withdrawn (patient has surgery at a non-PARTNER site and withdrew from the study after treatment) |
| | TAVR | Yes, procedure scheduled but not done due to insurance problem | No |
| | TAVR | Yes, died before procedure | No, died within 30 days |
| | TAVR | No | Yes, lost |
| | TAVR | Yes, died before procedure | No, died within 30 days |
| | AVR | Yes, refused | No, died in 31 days – 1 year |
| | AVR | Yes, refused | No, died in 31 days – 1 year |
| | AVR | Yes, refused | Yes, withdrawn |
| | AVR | Yes, died before procedure | No, died within 30 days |
| | AVR | Yes, withdrawn | Yes, withdrawn |
| | AVR | Yes, withdrawn | Yes, withdrawn |
| | AVR | Yes, refused | Yes, lost |
| | AVR | Yes, withdrawn | Yes, withdrawn |
| | AVR | No | Yes, withdrawn (no reason provided) |
| | AVR | Yes, refused | No, alive (died in 1 year – 2 years) |
| | AVR | Yes, pre-treatment deterioration | Yes, withdrawn |
| | AVR | Yes, withdrawn | Yes, withdrawn |
| | AVR | No | Yes, lost |
| | AVR | Yes, withdrawn | Yes, withdrawn |
| | AVR | Yes, withdrawn | Yes, withdrawn |

^P After data lock, it was realized that the one-year follow-up data entry for one TAVR patient () was inconsistent. In analyses, this patient is censored prior to 1 year, however, the correct vital status is alive. Since the patient is a TAVR patient, any bias in the analysis will work against the TAVR arm of the trial. If this patient was to be counted as “alive”, the TAVR death rate at 1 year would decrease by 0.0001.



| Subject | Trial Arm | Non Treatment? | Censored at 1 year? |
|---------|-----------|----------------|--------------------------------------|
| | AVR | Yes, refused | No, alive (died in 1 year – 2 years) |
| | AVR | Yes, refused | No, alive (died in 1 year – 2 years) |

Table 89. Compliance at Each Visit – High Risk Cohort in the PARTNER Study (ITT Population)

| | | | Cohort A Randomized Patients -- Intent to Treat (ITT) Population | |
|---------|---------------------------|--|--|--------------|
| | | | Pooled Approaches | |
| Visit | Variable | Subgroups | AVR (N=351) | TAVR (N=348) |
| 30 DAY | Total Patients | n | 351 | 348 |
| | Total Eligible Patients | n | 292 | 328 |
| | | Done -- Timing unknown | 0(0%) | 0(0%) |
| | | Missed visit | 6(2.1%) | 2(0.6%) |
| | | Overdue | 1(0.3%) | 3(0.9%) |
| | | Done in window | 212(72.6%) | 277(84.5%) |
| | | Done out of window | 73(25.0%) | 46(14.0%) |
| | Total Ineligible patients | n | 59 | 20 |
| | | Lost to follow-up | 0(0%) | 0(0%) |
| | | Withdrew before visit | 2(3.4%) | 0(0%) |
| 6 MONTH | | Not due not done | 30(50.8%) | 4(20.0%) |
| | | Died before visit | 27(45.8%) | 16(80.0%) |
| | Visit compliance | (done in window + done out of window)/eligible | 285(97.6%) | 323(98.5%) |
| | Total Patients | n | 351 | 348 |
| | Total Eligible Patients | n | 253 | 297 |
| | | Done -- Timing unknown | 0(0%) | 0(0%) |
| | | Missed visit | 5(2.0%) | 1(0.3%) |
| | | Overdue | 1(0.4%) | 1(0.3%) |
| | | Done in window | 168(66.4%) | 233(78.5%) |
| | | Done out of window | 79(31.2%) | 62(20.9%) |
| 1 YEAR | Total Ineligible patients | n | 98 | 51 |
| | | Lost to follow-up | 1(1.0%) | 1(2.0%) |
| | | Withdrew before visit | 22(22.4%) | 0(0%) |
| | | Not due not done | 0(0%) | 0(0%) |
| | | Died before visit | 75(76.5%) | 50(98.0%) |
| | Visit compliance | (done in window + done out of window)/eligible | 247(97.6%) | 295(99.3%) |
| | Total Patients | n | 351 | 348 |
| | Total Eligible Patients | n | 237 | 262 |
| | | Done -- Timing unknown | 0(0%) | 0(0%) |
| | | Missed visit | 0(0%) | 1(0.4%) |
| | | Overdue | 0(0%) | 1(0.4%) |
| | | Done in window | 206(86.9%) | 233(88.9%) |
| | | Done out of window | 31(13.1%) | 27(10.3%) |
| | Total Ineligible patients | n | 114 | 86 |



| | | | Cohort A Randomized Patients -- Intent to Treat (ITT) Population | |
|--------|------------------|--|---|-----------------|
| | | | Pooled Approaches | |
| Visit | Variable | Subgroups | AVR (N=351) | TAVR (N=348) |
| 2 YEAR | | Lost to follow-up | 3(2.6%) | 2(2.3%) |
| | | Withdrew before visit | 23(20.2%) | 1(1.2%) |
| | | Not due not done | 0(0%) | 0(0%) |
| | | Died before visit | 88(77.2%) | 83(96.5%) |
| | | (done in window + done out of window)/eligible | 237(100%) | 260(99.2%) |
| | | Total Patients n | 351 | 348 |
| | | Total Eligible Patients n | 208 | 226 |
| | | Done -- Timing unknown | 0(0%) | 0(0%) |
| | | Missed visit | 0(0%) | 1(0.4%) |
| | | Overdue | 9(4.3%) | 13(5.8%) |
| 3 YEAR | | Done in window | 180(86.5%) | 202(89.4%) |
| | | Done out of window | 19(9.1%) | 10(4.4%) |
| | | Total Ineligible patients n | 143 | 122 |
| | | Lost to follow-up | 3(2.1%) | 3(2.5%) |
| | | Withdrew before visit | 25(17.5%) | 2(1.6%) |
| | | Not due not done | 0(0%) | 0(0%) |
| | | Died before visit | 115(80.4%) | 117(95.9%) |
| | | (done in window + done out of window)/eligible | 199(95.7%) | 212(93.8%) |
| | | Total Patients n | 351 | 348 |
| | | Total Eligible Patients n | 72 | 73 |
| | | Done -- Timing unknown | 0(0%) | 0(0%) |
| | | Missed visit | 0(0%) | 3(4.1%) |
| | | Overdue | 20(27.8%) | 15(20.5%) |
| | | Done in window | 49(68.1%) | 48(65.8%) |
| | | Done out of window | 3(4.2%) | 7(9.6%) |
| | | Total Ineligible patients n | 279 | 275 |
| | | Lost to follow-up | 3(1.1%) | 3(1.1%) |
| | | Withdrew before visit | 27(9.7%) | 4(1.5%) |
| | | Not due not done | 114(40.9%) | 134(48.7%) |
| | | Died before visit | 135(48.4%) | 134(48.7%) |
| | Visit compliance | (done in window + done out of window)/eligible | 52(72.2%) | 55(75.3%) |

Visit windows: 30 days ± 7 days; 6 month: 180 days ± 14 days; 1 year ± 30 days; 2 years ± 45 days; 3 years ± 45 days.

Visit performed in window + Visit performed out of window = % compliance
Eligible Patient

Source: Table 3.2



Table 90. Procedural Parameters – High Risk Cohort in the PARTNER Study (AT Population)

| Variable/Statistic | TAVR | |
|---|--------------------------|---------------------------|
| | Transapical (n = 104) | Transfemoral (n = 240) |
| Days randomization to procedure | | |
| N | 104 | 240 |
| Mean | 10.77 | 10.55 |
| Std Dev | 10.93 | 14.25 |
| Lower Quartile | 4.50 | 3.00 |
| Median | 7.00 | 7.00 |
| Upper Quartile | 13.00 | 13.00 |
| Time in Cath Lab (min) | | |
| N | 102 | 239 |
| Mean | 224.93 | 242.85 |
| Std Dev | 76.52 | 90.73 |
| Lower Quartile | 172.00 | 196.00 |
| Median | 211.50 | 232.00 |
| Upper Quartile | 250.00 | 269.00 |
| Total procedure time (skin-to-skin) (min) | | |
| N | 100 | 234 |
| Mean | 113.76 | 141.41 |
| Std Dev | 101.96 | 81.09 |
| Lower Quartile | 67.50 | 92.00 |
| Median | 94.00 | 120.00 |
| Upper Quartile | 121.50 | 163.00 |
| Fluoroscopy Total time (min) | | |
| N | 88 | 218 |
| Mean | 35.03 | 29.81 |
| Std Dev | 139.69 | 14.98 |
| Lower Quartile | 10.00 | 21.00 |
| Median | 12.00 | 26.00 |
| Upper Quartile | 17.00 | 35.00 |
| Volume of contrast media (ml) | | |
| N | 89 | 223 |



| Variable/Statistic | TAVR | |
|--|--------------------------|---------------------------|
| | Transapical (n = 104) | Transfemoral (n = 240) |
| Mean | 104.28 | 148.00 |
| Std Dev | 51.42 | 90.22 |
| Lower Quartile | 70.00 | 85.00 |
| Median | 100.00 | 130.00 |
| Upper Quartile | 140.00 | 200.00 |
| Derived Device Size | | |
| Count | 101 | 233 |
| 23 | 52 (51.5%) | 109 (46.8%) |
| 26 | 49 (48.5%) | 124 (53.2%) |
| 29 | 0 (0.0%) | 0 (0.0%) |
| Was the patient cannulated for cardiopulmonary bypass? | | |
| Count | 102 | 234 |
| No | 93 (91.2%) | 229 (97.9%) |
| Yes | 9 (8.8%) | 5 (2.1%) |
| Did the patient require IABP during procedure? | | |
| Count | 102 | 234 |
| No | 94 (92.2%) | 230 (98.3%) |
| Yes | 8 (7.8%) | 4 (1.7%) |
| Was a conversion to open heart surgery performed? | | |
| Count | 102 | 234 |
| No | 99 (97.1%) | 228 (97.4%) |
| Yes ^a | 3 (2.9%) | 6 (2.6%) |
| Number of Aortic valve prosthesis | | |
| Count | 102 | 238 |
| 0 | 3 (2.9%) | 11 (4.6%) |
| 1 | 91 (89.2%) | 216 (90.8%) |
| 2 ^b | 7 (6.9%) | 10 (4.2%) |
| 3 ^c | 1 (1.0%) | 1 (0.4%) |
| Did any adverse event occur during procedure? | | |
| Count | 102 | 240 |
| No | 82 (80.4%) | 189 (78.8%) |
| Yes | 20 (19.6%) | 51 (21.3%) |
| Did a device malfunction occur during procedure | | |



| Variable/Statistic | TAVR | |
|--|--------------------------|---------------------------|
| | Transapical (n = 104) | Transfemoral (n = 240) |
| Count | 101 | 234 |
| No | 99 (98.0%) | 231 (98.7%) |
| Yes | 2 (2.0%) | 3 (1.3%) |
| Was the study valve successfully delivered? | | |
| Count | 102 | 235 |
| No | 6 (5.9%) | 7 (3.0%) |
| Yes | 96 (94.1%) | 228 (97.0%) |
| Study valve correct location and position? | | |
| Count | 100 | 233 |
| No | 4 (4.0%) | 5 (2.1%) |
| Yes | 96 (96.0%) | 228 (97.9%) |
| Study valve remained correct? | | |
| Count | 100 | 231 |
| No | 4 (4.0%) | 4 (1.7%) |
| Yes | 96 (96.0%) | 227 (98.3%) |
| TF Delivery: RetroFlex Catheter/RetroFlex Catheter II? | | |
| Count | 0 | 224 |
| RetroFlex Catheter | | 127 (56.7%) |
| RetroFlex II Catheter | | 71 (31.7%) |
| RetroFlex III Catheter | | 26 (11.6%) |

Source: Table 13.1

a. Conversion to open heart surgery (n=9):

b. Two valves (n=17):

c. Three valves (n=2):



Table 91. Procedural Parameters – AVR Group in the PARTNER Study (AT Population)

| Variable/Statistic | AVR (n = 313) |
|---------------------------------------|------------------|
| Days randomization to procedure | |
| N | 313 |
| Mean | 15.58 |
| Std Dev | 19.72 |
| Lower Quartile | 3.00 |
| Median | 9.00 |
| Upper Quartile | 22.00 |
| Concomitant Procedure: CABG | |
| Count | 313 |
| No | 292 (93.3%) |
| Yes | 21 (6.7%) |
| Valve Size | |
| Count | 312 |
| 19 | 37 (11.9%) |
| 21 | 124 (39.7%) |
| 22 | 1 (0.3%) |
| 23 | 109 (34.9%) |
| 25 | 37 (11.9%) |
| 26 | 0 (0.0%) |
| 27 | 3 (1.0%) |
| 29 | 1 (0.3%) |
| Total cross clamp time of aorta (min) | |
| N | 294 |
| Mean | 73.48 |
| Std Dev | 28.66 |
| Lower Quartile | 57.00 |
| Median | 66.50 |
| Upper Quartile | 82.00 |
| Pump time (min) | |
| N | 283 |
| Mean | 104.94 |
| Std Dev | 41.41 |



| Variable/Statistic | AVR (n = 313) |
|---|------------------|
| Lower Quartile | 79.00 |
| Median | 95.00 |
| Upper Quartile | 121.00 |
| Did any adverse event occur during procedure? | |
| Count | 313 |
| No | 267 (85.3%) |
| Yes | 46 (14.7%) |

Source: Table 13.1



Table 92. 6MWT - High Risk Cohort in the PARTNER Study (AT Population)

| | | | Cohort A Randomized Patients -- As Treated (AT) Population | | | | | |
|----------------|----------|------------|--|--------------|-----------------------|--------------|-------------------|--------------|
| Parameter | Visit | Statistics | Transapical Approach | | Transfemoral Approach | | Pooled Approaches | |
| | | | Control (N=92) | Test (N=104) | Control (N=221) | Test (N=240) | Control (N=313) | Test (N=344) |
| TOTAL DISTANCE | BASELINE | n | 83 | 96 | 190 | 213 | 273 | 309 |
| | | Mean | 115.17 | 98.21 | 104.26 | 113.11 | 107.58 | 108.48 |
| | | SD | 116.856 | 104.064 | 112.875 | 122.116 | 113.995 | 116.843 |
| | | Minimum | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | | Q1 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | | Median | 90.00 | 87.50 | 72.15 | 76.20 | 75.00 | 82.00 |
| | | Q3 | 198.00 | 157.28 | 194.00 | 186.50 | 195.00 | 180.00 |
| | | Maximum | 450.00 | 424.89 | 415.00 | 549.00 | 450.00 | 549.00 |
| | 30 DAY | n | 65 | 79 | 143 | 179 | 208 | 258 |
| | | Mean | 113.33 | 113.42 | 100.97 | 156.22 | 104.83 | 143.11 |
| | | SD | 118.617 | 117.548 | 116.142 | 131.991 | 116.775 | 129.037 |
| | | Minimum | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | | Q1 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | | Median | 80.00 | 91.44 | 73.00 | 158.00 | 75.08 | 125.20 |
| | | Q3 | 201.00 | 180.00 | 180.00 | 245.20 | 190.00 | 240.00 |
| | 6 MONTH | Maximum | 459.00 | 429.00 | 494.00 | 480.00 | 494.00 | 480.00 |
| | | n | 51 | 65 | 113 | 169 | 164 | 234 |
| | | Mean | 195.16 | 154.36 | 181.12 | 178.11 | 185.49 | 171.52 |
| | | SD | 124.075 | 126.932 | 145.173 | 141.329 | 138.730 | 137.626 |
| | | Minimum | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | | Q1 | 110.00 | 35.05 | 54.80 | 0.00 | 70.05 | 0.00 |
| | | Median | 216.71 | 150.00 | 180.00 | 177.00 | 192.93 | 165.00 |
| | | Q3 | 270.00 | 236.22 | 296.57 | 285.00 | 286.91 | 278.00 |
| | | Maximum | 525.00 | 435.00 | 547.00 | 540.00 | 547.00 | 540.00 |
| | 1 YEAR | n | 48 | 64 | 115 | 153 | 163 | 217 |
| | | Mean | 165.42 | 154.61 | 168.90 | 166.05 | 167.88 | 162.68 |
| | | SD | 132.506 | 136.309 | 134.297 | 122.107 | 133.372 | 126.249 |
| | | Minimum | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | | Q1 | 36.58 | 6.81 | 0.00 | 90.00 | 0.00 | 70.07 |
| | | Median | 179.07 | 132.50 | 177.00 | 165.00 | 177.00 | 151.70 |
| | | Q3 | 275.31 | 250.00 | 280.00 | 247.00 | 280.00 | 247.00 |
| | | Maximum | 448.36 | 575.46 | 457.20 | 540.10 | 457.20 | 575.46 |

Source: Table 6.8



Table 93. Summary of Echocardiogram Results from Core Laboratory – High Risk Cohort in the PARTNER Study (AT Population)

| | | | Cohort A Randomized Patients -- As Treated (AT) Population | |
|--------------------------|-----------|------------|--|--------------|
| | | | Pooled Approaches | |
| Parameter | Visit | Statistics | AVR (N=313) | TAVR (N=344) |
| Cardiac Index (L/min/m2) | BASELINE | n | 179 | 185 |
| | | Mean | 2.28 | 2.23 |
| | | SD | 0.791 | 0.704 |
| | 30 DAY | n | 96 | 122 |
| | | Mean | 2.33 | 2.30 |
| | | SD | 0.704 | 0.742 |
| | 6 MONTH | n | 80 | 109 |
| | | Mean | 2.21 | 2.27 |
| | | SD | 0.599 | 0.685 |
| | 1 YEAR | n | 77 | 101 |
| | | Mean | 2.18 | 2.20 |
| | | SD | 0.822 | 0.627 |
| | 2 YEAR | n | 41 | 43 |
| | | Mean | 2.25 | 2.11 |
| | | SD | 0.601 | 0.568 |
| AV Area Index (cm2/m2) | DISCHARGE | n | 102 | 131 |
| | | Mean | 2.27 | 2.59 |
| | | SD | 0.624 | 0.759 |
| | BASELINE | n | 293 | 317 |
| | | Mean | 0.35 | 0.36 |
| | | SD | 0.104 | 0.108 |
| | 30 DAY | n | 205 | 268 |
| | | Mean | 0.84 | 0.92 |
| | | SD | 0.237 | 0.277 |
| | 6 MONTH | n | 160 | 229 |
| | | Mean | 0.84 | 0.91 |
| | | SD | 0.285 | 0.290 |
| | 1 YEAR | n | 144 | 212 |
| | | Mean | 0.80 | 0.88 |
| | | SD | 0.248 | 0.273 |
| AV Area (EOA) (cm2) | 2 YEAR | n | 71 | 89 |
| | | Mean | 0.83 | 0.91 |
| | | SD | 0.267 | 0.264 |
| | DISCHARGE | n | 212 | 253 |
| | | Mean | 0.81 | 0.90 |
| | | SD | 0.264 | 0.287 |
| | BASELINE | n | 295 | 318 |
| | | Mean | 0.64 | 0.66 |
| | | SD | 0.188 | 0.199 |
| | 30 DAY | n | 228 | 278 |



| | | | Cohort A Randomized Patients -- As Treated (AT) Population | |
|-------------------------|-----------|------------|--|--------------|
| Parameter | Visit | Statistics | Pooled Approaches | |
| | | | AVR (N=313) | TAVR (N=344) |
| | | Mean | 1.51 | 1.65 |
| | | SD | 0.428 | 0.503 |
| | 6 MONTH | n | 166 | 235 |
| | | Mean | 1.52 | 1.66 |
| | | SD | 0.530 | 0.524 |
| | 1 YEAR | n | 153 | 220 |
| | | Mean | 1.44 | 1.59 |
| | | SD | 0.466 | 0.481 |
| | 2 YEAR | n | 75 | 91 |
| | | Mean | 1.53 | 1.61 |
| | | SD | 0.481 | 0.444 |
| | DISCHARGE | n | 240 | 289 |
| | | Mean | 1.46 | 1.62 |
| | | SD | 0.463 | 0.510 |
| AV Mean Gradient (mmHg) | BASELINE | n | 300 | 326 |
| | | Mean | 43.38 | 42.58 |
| | | SD | 14.350 | 14.504 |
| | 30 DAY | n | 232 | 286 |
| | | Mean | 10.78 | 9.90 |
| | | SD | 5.027 | 4.768 |
| | 6 MONTH | n | 171 | 246 |
| | | Mean | 10.81 | 10.22 |
| | | SD | 4.797 | 4.306 |
| | 1 YEAR | n | 157 | 228 |
| | | Mean | 11.43 | 10.21 |
| | | SD | 5.286 | 4.267 |
| | 2 YEAR | n | 75 | 96 |
| | | Mean | 10.36 | 10.28 |
| | | SD | 4.682 | 5.476 |
| | DISCHARGE | n | 257 | 303 |
| | | Mean | 11.95 | 10.87 |
| | | SD | 5.351 | 4.616 |
| AV Peak Gradient (mmHg) | BASELINE | n | 300 | 326 |
| | | Mean | 73.25 | 70.81 |
| | | SD | 24.208 | 23.522 |
| | 30 DAY | n | 232 | 286 |
| | | Mean | 20.59 | 19.47 |
| | | SD | 8.899 | 8.959 |
| | 6 MONTH | n | 171 | 246 |
| | | Mean | 20.32 | 19.65 |
| | | SD | 8.643 | 8.056 |
| | 1 YEAR | n | 157 | 228 |
| | | Mean | 21.28 | 19.36 |



| | | | Cohort A Randomized Patients -- As Treated (AT) Population | |
|------------------------------------|-----------|------------|--|--------------|
| Parameter | Visit | Statistics | Pooled Approaches | |
| | | | AVR (N=313) | TAVR (N=344) |
| | | SD | 9.445 | 7.922 |
| | 2 YEAR | n | 75 | 96 |
| | | Mean | 19.09 | 19.20 |
| | | SD | 8.470 | 9.491 |
| | DISCHARGE | n | 257 | 303 |
| | | Mean | 23.41 | 20.93 |
| | | SD | 10.165 | 8.470 |
| Paravalvular Aortic Regurgitation | 30 DAY | n | 233 | 290 |
| | | NONE | 170 (73.0) | 65 (22.4) |
| | | TRACE | 41 (17.6) | 70 (24.1) |
| | | MILD | 16 (6.9) | 117 (40.3) |
| | | MODERATE | 2 (0.9) | 31 (10.7) |
| | | SEVERE | 0 (0.0) | 3 (1.0) |
| | | NA | 4 (1.7) | 4 (1.4) |
| | 6 MONTH | n | 175 | 248 |
| | | NONE | 141 (80.6) | 63 (25.4) |
| | | TRACE | 22 (12.6) | 56 (22.6) |
| | | MILD | 12 (6.9) | 93 (37.5) |
| | | MODERATE | 0 (0.0) | 26 (10.5) |
| | | SEVERE | 0 (0.0) | 2 (0.8) |
| | | NA | 0 (0.0) | 8 (3.2) |
| | 1 YEAR | n | 157 | 228 |
| | | NONE | 123 (78.3) | 73 (32.0) |
| | | TRACE | 24 (15.3) | 57 (25.0) |
| | | MILD | 7 (4.5) | 78 (34.2) |
| | | MODERATE | 3 (1.9) | 14 (6.1) |
| | | SEVERE | 0 (0.0) | 1 (0.4) |
| | | NA | 0 (0.0) | 5 (2.2) |
| | 2 YEAR | n | 77 | 97 |
| | | NONE | 61 (79.2) | 35 (36.1) |
| | | TRACE | 8 (10.4) | 27 (27.8) |
| | | MILD | 5 (6.5) | 27 (27.8) |
| | | MODERATE | 1 (1.3) | 6 (6.2) |
| | | SEVERE | 0 (0.0) | 0 (0.0) |
| | | | 2 (2.6) | 2 (2.1) |
| | DISCHARGE | n | 266 | 325 |
| | | NONE | 210 (78.9) | 81 (24.9) |
| | | TRACE | 34 (12.8) | 80 (24.6) |
| | | MILD | 11 (4.1) | 130 (40.0) |
| | | MODERATE | 1 (0.4) | 21 (6.5) |
| | | SEVERE | 0 (0.0) | 2 (0.6) |
| | | NA | 10 (3.8) | 11 (3.4) |
| Transvalvular Aortic Regurgitation | BASELINE | n | 303 | 333 |



| | | | Cohort A Randomized Patients -- As Treated (AT) Population | |
|----------------------------|-----------|------------|--|--------------|
| Parameter | Visit | Statistics | Pooled Approaches | |
| | | | AVR (N=313) | TAVR (N=344) |
| | | NONE | 43 (14.2) | 37 (11.1) |
| | | TRACE | 85 (28.1) | 96 (28.8) |
| | | MILD | 129 (42.6) | 173 (52.0) |
| | | MODERATE | 38 (12.5) | 20 (6.0) |
| | | SEVERE | 5 (1.7) | 4 (1.2) |
| | | NA | 3 (1.0) | 3 (0.9) |
| | 30 DAY | n | 233 | 290 |
| | | NONE | 127 (54.5) | 104 (35.9) |
| | | TRACE | 79 (33.9) | 107 (36.9) |
| | | MILD | 22 (9.4) | 76 (26.2) |
| | | MODERATE | 2 (0.9) | 3 (1.0) |
| | | SEVERE | 0 (0.0) | 0 (0.0) |
| | | NA | 3 (1.3) | 0 (0.0) |
| | 6 MONTH | n | 175 | 248 |
| | | NONE | 100 (57.1) | 97 (39.1) |
| | | TRACE | 58 (33.1) | 98 (39.5) |
| | | MILD | 17 (9.7) | 44 (17.7) |
| | | MODERATE | 0 (0.0) | 5 (2.0) |
| | | SEVERE | 0 (0.0) | 0 (0.0) |
| | | NA | 0 (0.0) | 4 (1.6) |
| | 1 YEAR | n | 157 | 228 |
| | | NONE | 86 (54.8) | 82 (36.0) |
| | | TRACE | 59 (37.6) | 94 (41.2) |
| | | MILD | 12 (7.6) | 47 (20.6) |
| | | MODERATE | 0 (0.0) | 2 (0.9) |
| | | SEVERE | 0 (0.0) | 1 (0.4) |
| | | NA | 0 (0.0) | 2 (0.9) |
| | 2 YEAR | n | 77 | 97 |
| | | NONE | 43 (55.8) | 34 (35.1) |
| | | TRACE | 29 (37.7) | 40 (41.2) |
| | | MILD | 4 (5.2) | 21 (21.6) |
| | | MODERATE | 0 (0.0) | 2 (2.1) |
| | | SEVERE | 0 (0.0) | 0 (0.0) |
| | | NA | 1 (1.3) | 0 (0.0) |
| | DISCHARGE | n | 266 | 325 |
| | | NONE | 151 (56.8) | 122 (37.5) |
| | | TRACE | 91 (34.2) | 118 (36.3) |
| | | MILD | 17 (6.4) | 75 (23.1) |
| | | MODERATE | 1 (0.4) | 5 (1.5) |
| | | SEVERE | 0 (0.0) | 0 (0.0) |
| | | NA | 6 (2.3) | 5 (1.5) |
| Total Aortic Regurgitation | BASELINE | n | 303 | 333 |
| | | NONE | 43 (14.2) | 37 (11.1) |



| Parameter | Visit | Statistics | Cohort A Randomized Patients -- As Treated (AT) Population | |
|-----------|-----------|------------|--|--------------|
| | | | Pooled Approaches | |
| | | | AVR (N=313) | TAVR (N=344) |
| | | TRACE | 85 (28.1) | 96 (28.8) |
| | | MILD | 129 (42.6) | 173 (52.0) |
| | | MODERATE | 38 (12.5) | 20 (6.0) |
| | | SEVERE | 5 (1.7) | 4 (1.2) |
| | | NA | 3 (1.0) | 3 (0.9) |
| | 30 DAY | n | 233 | 291 |
| | | NONE | 114 (48.9) | 33 (11.3) |
| | | TRACE | 78 (33.5) | 77 (26.5) |
| | | MILD | 34 (14.6) | 138 (47.4) |
| | | MODERATE | 4 (1.7) | 40 (13.7) |
| | | SEVERE | 0 (0.0) | 3 (1.0) |
| | | NA | 3 (1.3) | 0 (0.0) |
| | 6 MONTH | n | 175 | 248 |
| | | NONE | 87 (49.7) | 32 (12.9) |
| | | TRACE | 63 (36.0) | 65 (26.2) |
| | | MILD | 23 (13.1) | 111 (44.8) |
| | | MODERATE | 2 (1.1) | 34 (13.7) |
| | | SEVERE | 0 (0.0) | 2 (0.8) |
| | | NA | 0 (0.0) | 4 (1.6) |
| | 1 YEAR | n | 158 | 228 |
| | | NONE | 72 (45.6) | 29 (12.7) |
| | | TRACE | 64 (40.5) | 71 (31.1) |
| | | MILD | 18 (11.4) | 105 (46.1) |
| | | MODERATE | 4 (2.5) | 17 (7.5) |
| | | SEVERE | 0 (0.0) | 4 (1.8) |
| | | NA | 0 (0.0) | 2 (0.9) |
| | 2 YEAR | n | 77 | 97 |
| | | NONE | 38 (49.4) | 14 (14.4) |
| | | TRACE | 29 (37.7) | 37 (38.1) |
| | | MILD | 8 (10.4) | 38 (39.2) |
| | | MODERATE | 1 (1.3) | 8 (8.2) |
| | | SEVERE | 0 (0.0) | 0 (0.0) |
| | | NA | 1 (1.3) | 0 (0.0) |
| | DISCHARGE | n | 266 | 327 |
| | | NONE | 141 (53.0) | 47 (14.4) |
| | | TRACE | 92 (34.6) | 82 (25.1) |
| | | MILD | 24 (9.0) | 160 (48.9) |
| | | MODERATE | 3 (1.1) | 31 (9.5) |
| | | SEVERE | 0 (0.0) | 2 (0.6) |
| | | NA | 6 (2.3) | 5 (1.5) |

Source: Table 6.5



Table 94. CEC-Adjudicated Adverse Events – High Risk Cohort in the PARTNER Study (AT Population)

| CEC Adjudicated Events Randomized PMA Cohort A (AT) -- Pooled Approaches | | | | | | | | | | | | | | |
|--|-------------------|--------------|---------------------|--------|---------------------|--------------------------|--------------------------------------|--------|---------------------|-------------------------|-------------------------------------|--------|---------------------|--------------------------------------|
| Total Events | | | <= 30 days | | | | 31 days - 1 year | | | | > 1 year | | Trial | |
| | Patients in group | Total events | Patients with event | Events | Patients with event | KM Event rate at 30 days | P-value for point in time at 30 days | Events | Patients with event | KM Event rate at 1 year | P-value for point in time at 1 year | Events | Patients with event | Log-rank p-value for length of trial |
| Arterial Vascular Procedure | | | | | | | | | | | | | | |
| | 313 | 12 | 12 | 9 | 9 | 2.9% | . | 1 | 1 | 3.3% | . | 2 | 2 | . |
| | 344 | 64 | 52 | 48 | 44 | 12.8% | <.0001 | 8 | 6 | 14.5% | <.0001 | 8 | 6 | <.0001 |
| New Permanent Pacemaker | | | | | | | | | | | | | | |
| | 313 | 19 | 19 | 14 | 14 | 4.6% | . | 2 | 2 | 5.3% | . | 3 | 3 | . |
| | 344 | 22 | 22 | 16 | 16 | 4.7% | 0.9329 | 4 | 4 | 6.1% | 0.6737 | 2 | 2 | 0.8869 |
| Stroke or TIA | | | | | | | | | | | | | | |
| | 313 | 25 | 22 | 9 | 8 | 2.6% | . | 4 | 4 | 4.3% | . | 12 | 11 | . |
| | 344 | 33 | 33 | 18 | 18 | 5.3% | 0.0749 | 9 | 9 | 8.5% | 0.0335 | 6 | 6 | 0.2511 |
| TIA | | | | | | | | | | | | | | |
| | 313 | 7 | 6 | 1 | 1 | 0.3% | . | 3 | 3 | 1.5% | . | 3 | 3 | . |
| | 344 | 10 | 10 | 3 | 3 | 0.9% | 0.3572 | 5 | 5 | 2.7% | 0.3592 | 2 | 2 | 0.4486 |
| Stroke | | | | | | | | | | | | | | |
| | 313 | 18 | 17 | 8 | 8 | 2.6% | . | 1 | 1 | 3.0% | . | 9 | 8 | . |
| | 344 | 23 | 23 | 15 | 15 | 4.4% | 0.2064 | 4 | 4 | 5.8% | 0.0887 | 4 | 4 | 0.5113 |
| Hemorrhagic | | | | | | | | | | | | | | |



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| CEC Adjudicated Events Randomized PMA Cohort A (AT) -- Pooled Approaches | | | | | | | | | | | | | | |
|--|-------------------|--------------|---------------------|------------|---------------------|--------------------------|--------------------------------------|------------------|---------------------|-------------------------|-------------------------------------|----------|---------------------|--------------------------------------|
| | | Total Events | | <= 30 days | | | | 31 days - 1 year | | | | > 1 year | | Trial |
| | Patients in group | Total events | Patients with event | Events | Patients with event | KM Event rate at 30 days | P-value for point in time at 30 days | Events | Patients with event | KM Event rate at 1 year | P-value for point in time at 1 year | Events | Patients with event | Log-rank p-value for length of trial |
| AVR | 313 | 117 | 100 | 85 | 78 | 24.9% | | 17 | 16 | 29.8% | | 15 | 13 | |
| TAVR | 344 | 90 | 79 | 54 | 53 | 15.5% | 0.0026 | 22 | 22 | 20.7% | 0.0087 | 14 | 12 | 0.0078 |
| Major Bleed | | | | | | | | | | | | | | |
| AVR | 313 | 106 | 93 | 78 | 72 | 23.0% | | 14 | 14 | 27.5% | | 14 | 12 | |
| TAVR | 344 | 71 | 62 | 38 | 37 | 10.8% | <.0001 | 20 | 20 | 15.8% | 0.0003 | 13 | 11 | 0.0003 |
| MI | | | | | | | | | | | | | | |
| AVR | 313 | 6 | 6 | 1 | 1 | 0.3% | | 0 | 0 | 0.3% | | 5 | 5 | |
| TAVR | 344 | 2 | 2 | 0 | 0 | 0.0% | 0.3165 | 0 | 0 | 0.0% | 0.3165 | 2 | 2 | 0.1254 |
| Vascular | | | | | | | | | | | | | | |
| AVR | 313 | 17 | 16 | 15 | 14 | 4.5% | | 2 | 2 | 5.2% | | 0 | 0 | |
| TAVR | 344 | 72 | 62 | 70 | 60 | 17.5% | <.0001 | 1 | 1 | 17.8% | <.0001 | 1 | 1 | <.0001 |
| Major Vascular | | | | | | | | | | | | | | |
| AVR | 313 | 13 | 12 | 13 | 12 | 3.8% | | 0 | 0 | 3.8% | | 0 | 0 | |
| TAVR | 344 | 46 | 39 | 45 | 38 | 11.1% | 0.0003 | 0 | 0 | 11.1% | 0.0003 | 1 | 1 | 0.0003 |
| Rehospitalization | | | | | | | | | | | | | | |
| AVR | 313 | 76 | 56 | 18 | 18 | 6.1% | | 37 | 29 | 16.6% | | 21 | 16 | |
| TAVR | 344 | 103 | 78 | 19 | 18 | 5.4% | 0.7142 | 49 | 40 | 17.3% | 0.8184 | 35 | 30 | 0.2573 |
| Renal Failure | | | | | | | | | | | | | | |



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| CEC Adjudicated Events Randomized PMA Cohort A (AT) -- Pooled Approaches | | | | | | | | | | | |
|--|-------------------|--------------|---------------------|--------|---------------------|--------------------------|--------------------------------------|--------|---------------------|-------------------------------------|--------------------------------------|
| | Total Events | | <= 30 days | | | | 31 days - 1 year | | | > 1 year | Trial |
| | Patients in group | Total events | Patients with event | Events | Patients with event | KM Event rate at 30 days | P-value for point in time at 30 days | Events | Patients with event | P-value for point in time at 1 year | Log-rank p-value for length of trial |
| AVR | 313 | 19 | 19 | 14 | 14 | 4.6% | . | 5 | 0 | . | . |
| TAVR | 344 | 19 | 19 | 13 | 13 | 3.8% | 0.6483 | 4 | 2 | 0.4774 | 0.7076 |
| Sternal Wound Infection | | | | | | | | | | | |
| AVR | 313 | 7 | 7 | 3 | 3 | 1.0% | . | 4 | 0 | . | . |
| TAVR | 344 | 0 | 0 | 0 | 0 | 0.0% | 0.0818 | 0 | 0 | 0.0076 | 0.0045 |

KM=Kaplan-Meier, MI=myocardial infarction; TIA=transient ischemic attack.
Source: Table 5.2

^a In the original PMA report, it was stated that a total of 20 TAVR patients experienced a stroke and 7 TAVR patients had a TIA at 1 year. This stroke rate included patient who experienced a neurologic event. Due to the absence of source documentation, the event was classified as stroke for analysis. On 7 September 2011, the CEC was able to classify the event as a TIA based on obtained source documentation. Subsequently, there are now 19 TAVR patients who experienced stroke and 8 TAVR patients with TIA at 1 year.

| | |
|-----------------------------|---|
| Aortic Valve Reintervention | Any operation that repairs alters or replaces a previously operated valve. (Aortic balloon valvuloplasty; open aortic valve replacement; open revision of existing aortic valve without replacement; implantation of percutaneous aortic valve; or other) |
| Arterial Vascular Procedure | Any surgical, endovascular(or other) arterial vascular procedure |
| Bradyarrhythmic event | Bradyarrhythmia requiring a permanent pacemaker implantation |
| CNS Event | Stroke: A neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction TIA: A fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction |
| Vascular Complication | Any of the following: Access Site Hematoma at access site > 5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular perforation, vascular dissection, gastro-intestinal ischemia. Major: thoracic aortic dissection; access site or access-related vascular injury leading to death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention; distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage. |



| | |
|-------------------------|---|
| Embololic Event | Minor: Vascular event that did not meet the criteria for major vascular complication. Embololic Events are defined as radiographic or clinical evidence of an embolic event. |
| Hemorrhagic Event | Major bleeding: Any episode of major internal or external bleeding that caused death, hospitalization or permanent injury (e.g., vision loss) or necessitated transfusion of greater than 3 units PRBCs within a 24 hour period, pericardiocentesis, open and/or endovascular procedure for repair or hemostasis. Minor bleeding: Bleeding event that did not meet the criteria for major bleed. |
| Myocardial Infarction | Acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI |
| Rehospitalization | Hospitalization for symptoms of heart failure, angina or syncope due to aortic valve disease requiring aortic valve intervention or intensified medical management. |
| Renal Failure | Renal Failure requiring initiation of any dialysis. |
| Sternal Wound Infection | Deep sternal infection involves muscle, bone, and/or mediastinum (with the imaging constituting an involvement of the sternum). Must have one of the following conditions: Wound opened with excision of tissue (I&D); Positive Culture; Treatment with antibiotics. |



Table 95. Instructions for Use (IFU) - Clinical Outcomes in the Pooled TAVR and AVR Groups Up to 2 Years (AT Population)

| Outcome | 30 Days | | | | 31 Days - 1 Year | | | | 1 Year - 2 Years | | | |
|---|-------------------|---------------------|------------------|-------------------|-------------------|---------------------|------------------|-------------------|-------------------|---------------------|------------------|-------------------|
| | Pooled TAVR N=344 | KM Event rate TAVR* | Pooled AVR N=313 | KM Event rate AVR | Pooled TAVR N=344 | KM Event rate TAVR* | Pooled AVR N=313 | KM Event rate AVR | Pooled TAVR N=344 | KM Event rate TAVR* | Pooled AVR N=313 | KM Event rate AVR |
| Death | 18 | 5.2% | 25 | 8.0% | 63 | 23.7% | 53 | 25.2% | 33 | 33.9% | 21 | 32.7% |
| Death from cardiovascular cause ^a | 14 | 4.1% | 9 | 2.9% | 30 | 13.6% | 24 | 11.5% | 20 | 20.8% | 16 | 18.5% |
| Repeat hospitalization ^b | 18 | 5.4% | 18 | 6.1% | 40 | 17.3% | 29 | 16.6% | 15 | 23.8% | 9 | 20.8% |
| Death from any cause or repeat hospitalization ^b | 35 | 10.2% | 43 | 13.8% | 86 | 33.9% | 74 | 35.5% | 48 | 46.2% | 33 | 44.4% |
| TIA ^d | 3 | 0.9% | 1 | 0.3% | 5 | 2.7% | 3 | 1.5% | 2 | 3.6% | 2 | 2.7% |
| All Stroke ^c | 15 | 4.4% | 8 | 2.6% | 4 | 5.8% | 1 | 3.0% | 4 | 7.5% | 3 | 4.4% |
| Myocardial Infarction ^g | | | | | | | | | | | | |
| All | 0 | 0.0% | 1 | 0.3% | 0 | 0.0% | 0 | 0.3% | 2 | 0.0% | 0 | 1.3% |
| Peri-procedural | 0 | 0.0% | 1 | 0.3% | 0 | 0.0% | 0 | 0.3% | 0 | 0.0% | 0 | 0.3% |
| Hemorrhagic Vascular Complication ^f | 84 | 24.5% | 87 | 27.8% | 10 | 26.8% | 3 | 28.6% | 3 | 28.0% | 2 | 29.4% |
| Major Vascular Complication ⁱ | 38 | 11.1% | 12 | 3.8% | 0 | 11.1% | 0 | 3.8% | 1 | 11.4% | 0 | 3.8% |
| Renal Failure ^h | 13 | 3.8% | 14 | 4.6% | 4 | 5.2% | 5 | 6.5% | 2 | 6.0% | 0 | 6.5% |
| Renal Insufficiency | 19 | 5.6% | 18 | 5.8% | 3 | 6.6% | 7 | 7.8% | 4 | 8.1% | 1 | 8.3% |
| Bleeding Event ^e | 35 | 10.2% | 89 | 28.4% | 0 | 10.2% | 0 | 28.4% | 0 | 10.2% | 0 | 28.4% |
| Cardiac reintervention | | | | | | | | | | | | |
| Balloon aortic valvuloplasty | 0 | N/A | 0 | N/A | 2 | N/A | 0 | N/A | 0 | N/A | 0 | N/A |
| Repeat TAVR | 0 | N/A | 0 | N/A | 0 | N/A | 0 | N/A | 0 | N/A | 0 | N/A |



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| | 30 Days | | | | 31 Days - 1 Year | | | | 1 Year - 2 Years | | | |
|--------------------------------------|-------------------|---------------------|------------------|-------------------|-------------------|---------------------|------------------|-------------------|-------------------|---------------------|------------------|-------------------|
| | Pooled TAVR N=344 | KM Event rate TAVR* | Pooled AVR N=313 | KM Event rate AVR | Pooled TAVR N=344 | KM Event rate TAVR* | Pooled AVR N=313 | KM Event rate AVR | Pooled TAVR N=344 | KM Event rate TAVR* | Pooled AVR N=313 | KM Event rate AVR |
| Outcome | | | | | | | | | | | | |
| Aortic-valve replacement | 7 | N/A | 0 | N/A | 1 | N/A | 0 | N/A | 1 | N/A | 0 | N/A |
| Endocarditis | 0 | 0.0% | 1 | 0.3% | 3 | 1.0% | 2 | 1.1% | 1 | 1.5% | 0 | 1.1% |
| New Atrial Fibrillation ^l | 30 | N/A | 57 | N/A | 14 | N/A | 3 | N/A | N/A | N/A | N/A | N/A |
| New pacemaker | 16 | 4.7% | 14 | 4.6% | 4 | 6.1% | 2 | 5.3% | 2 | 6.9% | 3 | 6.8% |

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.
N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.
Data presented as n (%) of patient unless otherwise specified.

a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.
d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.
e. Bleeding event was defined as ≥ 2 units within the index procedure.
f. Hemorrhagic vascular complications were defined as a hematoma at the access site >5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure.
g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non-Q-wave MI.
h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).
i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.
j. New atrial fibrillation as defined by ECG corelab.



Table 96. Instructions for Use (IFU) – Clinical Outcomes in the Transfemoral Group Up to 2 Years (AT Population)

| Outcome | 30 Days | | | | 31 Days - 1 Year | | | | 1 Year - 2 Years | | | |
|---|---------------------|---------------------------|--------------|----------------------|---------------------|---------------------------|--------------|----------------------|---------------------|---------------------------|--------------|----------------------|
| | TF TAVR N=240 | KM Event rate TAVR* | AVR N=221 | KM Event rate AVR | TF TAVR N=240 | KM Event rate TAVR* | AVR N=221 | KM Event rate AVR | TF TAVR N=240 | KM Event rate TAVR* | AVR N=221 | KM Event rate AVR |
| Death | 9 | 3.7% | 18 | 8.2% | 42 | 21.4% | 37 | 25.2% | 21 | 30.7% | 13 | 31.6% |
| Death from cardiovascular cause ^a | 8 | 3.3% | 7 | 3.2% | 19 | 12.0% | 17 | 11.8% | 14 | 19.0% | 9 | 17.3% |
| Repeat hospitalization ^b | 13 | 5.5% | 12 | 5.8% | 29 | 17.6% | 22 | 17.3% | 8 | 22.4% | 4 | 19.8% |
| Death from any cause or repeat hospitalization ^b | 21 | 8.7% | 30 | 13.6% | 59 | 31.8% | 52 | 35.3% | 31 | 42.2% | 18 | 42.2% |
| TIA ^d | 3 | 1.3% | 0 | 0.0% | 2 | 2.3% | 1 | 0.6% | 1 | 2.8% | 1 | 1.4% |
| All Stroke ^c | 8 | 3.3% | 3 | 1.4% | 1 | 3.8% | 0 | 1.4% | 2 | 5.0% | 1 | 2.0% |
| Myocardial Infarction ^g | | | | | | | | | | | | |
| All | 0 | 0.0% | 1 | 0.5% | 0 | 0.0% | 0 | 0.5% | 1 | 0.0% | 0 | 1.1% |
| Peri-procedural | 0 | 0.0% | 1 | 0.5% | 0 | 0.0% | 0 | 0.5% | 0 | 0.0% | 0 | 0.5% |
| Hemorrhagic Vascular Complication ^f | 69 | 28.8% | 61 | 27.6% | 5 | 30.2% | 2 | 28.7% | 1 | 30.7% | 2 | 29.8% |
| Major Vascular Complication ⁱ | 34 | 14.2% | 7 | 3.2% | 0 | 14.2% | 0 | 3.2% | 1 | 14.7% | 0 | 3.2% |
| Renal Failure ^h | 8 | 3.4% | 7 | 3.2% | 3 | 4.7% | 4 | 5.5% | 2 | 5.8% | 0 | 5.5% |
| Renal Insufficiency | 7 | 2.9% | 13 | 6.0% | 2 | 3.9% | 6 | 8.2% | 4 | 5.9% | 0 | 8.2% |
| Bleeding Event ^e | 27 | 11.3% | 63 | 28.5% | 0 | 11.3% | 0 | 28.5% | 0 | 11.3% | 0 | 28.5% |
| Cardiac reintervention | | | | | | | | | | | | |
| Balloon aortic valvuloplasty | 0 | N/A | 0 | N/A | 2 | N/A | 0 | N/A | 0 | N/A | 0 | N/A |
| Repeat TAVR | 0 | N/A | 0 | N/A | 0 | N/A | 0 | N/A | 0 | N/A | 0 | N/A |



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| Outcome | 30 Days | | | | 31 Days - 1 Year | | | | 1 Year - 2 Years | | | |
|--------------------------------------|---------------------|---------------------------|--------------|----------------------|---------------------|---------------------------|--------------|----------------------|---------------------|---------------------------|--------------|----------------------|
| | TF TAVR N=240 | KM Event rate TAVR* | AVR N=221 | KM Event rate AVR | TF TAVR N=240 | KM Event rate TAVR* | AVR N=221 | KM Event rate AVR | TF TAVR N=240 | KM Event rate TAVR* | AVR N=221 | KM Event rate AVR |
| Aortic-valve replacement | 4 | N/A | 0 | N/A | 1 | N/A | 0 | N/A | 1 | N/A | 0 | N/A |
| Endocarditis | 0 | 0.0% | 0 | 0.0% | 2 | 1.0% | 2 | 1.1% | 1 | 1.6% | 0 | 1.1% |
| New Atrial Fibrillation ^l | 19 | N/A | 42 | N/A | 11 | N/A | 2 | N/A | N/A | N/A | N/A | N/A |
| New pacemaker | 11 | 4.6% | 9 | 4.2% | 3 | 6.0% | 0 | 4.2% | 2 | 7.2% | 3 | 6.2% |

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.
N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.
Data presented as n (%) of patient unless otherwise specified.

a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.
d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.
e. Bleeding event is defined as ≥ 2 units within the index procedure.
f. Hemorrhagic vascular complications are defined as a hematoma at the access site >5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.
g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non-Q-wave MI.
h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).
i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.
j. New atrial fibrillation as defined by ECG corelab



Table 97. Instructions for Use (IFU) – Clinical Outcomes in the Transapical Group Up to 2 Years (AT Population)

| Outcome | 30 Days | | | | 31 Days - 1 Year | | | | 1 Year - 2 Years | | | |
|---|---------------------|---------------------------|-------------|----------------------|---------------------|---------------------------|-------------|----------------------|---------------------|---------------------------|-------------|----------------------|
| | TA TAVR N=104 | KM Event rate TAVR* | AVR N=92 | KM Event rate AVR | TA TAVR N=104 | KM Event rate TAVR8 | AVR n=92 | KM Event rate AVR | TA TAVR N=104 | KM Event rate TAVR* | AVR N=92 | KM Event rate AVR |
| Death | 9 | 8.7% | 7 | 7.6% | 21 | 29.1% | 16 | 25.3% | 12 | 41.3% | 8 | 35.5% |
| Death from cardiovascular cause ^a | 6 | 5.8% | 2 | 2.2% | 11 | 17.4% | 7 | 10.8% | 6 | 25.2% | 7 | 21.6% |
| Repeat hospitalization ^b | 5 | 5.1% | 6 | 6.8% | 11 | 16.7% | 7 | 14.9% | 7 | 27.4% | 5 | 23.3% |
| Death from any cause or repeat hospitalization ^b | 14 | 13.5% | 13 | 14.1% | 27 | 38.7% | 22 | 36.3% | 17 | 55.3% | 15 | 49.6% |
| TIA ^d | 0 | 0.0% | 1 | 1.1% | 3 | 3.7% | 2 | 3.9% | 1 | 5.8% | 1 | 5.6% |
| All Stroke ^c | 7 | 7.0% | 5 | 5.5% | 3 | 10.8% | 1 | 7.0% | 2 | 13.8% | 2 | 10.0% |
| Myocardial Infarction ^g | | | | | | | | | | | | |
| All | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 0.0% | 0 | 15.5% |
| Peri-procedural | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| Hemorrhagic Vascular Complication ⁱ | 15 | 14.5% | 26 | 28.3% | 5 | 19.2% | 1 | 28.3% | 2 | 22.0% | 0 | 28.3% |
| Major Vascular Complication ⁱ | 4 | 3.9% | 5 | 5.4% | 0 | 3.9% | 0 | 5.4% | 0 | 3.9% | 0 | 5.4% |
| Renal Failure ^h | 5 | 5.0% | 7 | 7.7% | 1 | 6.2% | 1 | 8.9% | 0 | 6.2% | 0 | 8.9% |
| Renal Insufficiency | 12 | 11.9% | 5 | 5.5% | 1 | 13.1% | 1 | 6.9% | 0 | 13.1% | 1 | 8.4% |
| Bleeding Event ^e | 8 | 7.7% | 26 | 28.3% | 0 | 7.7% | 0 | 28.3% | 0 | 7.7% | 0 | 28.3% |
| Cardiac reintervention | | | | | | | | | | | | |
| Balloon aortic valvuloplasty | 0 | N/A | 0 | N/A | 0 | N/A | 0 | N/A | 0 | N/A | 0 | N/A |
| Repeat TAVR | 0 | N/A | 0 | N/A | 0 | N/A | 0 | N/A | 0 | N/A | 0 | N/A |
| Aortic-valve replacement | 3 | N/A | 0 | N/A | 0 | N/A | 0 | N/A | 0 | N/A | 0 | N/A |



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| | 30 Days | | | | 31 Days - 1 Year | | | | 1 Year - 2 Years | | | |
|--------------------------------------|---------------------|---------------------------|-------------|----------------------|---------------------|---------------------------|-------------|----------------------|---------------------|---------------------------|-------------|----------------------|
| Outcome | TA TAVR N=104 | KM Event rate TAVR* | AVR N=92 | KM Event rate AVR | TA TAVR N=104 | KM Event rate TAVR8 | AVR n=92 | KM Event rate AVR | TA TAVR N=104 | KM Event rate TAVR* | AVR N=92 | KM Event rate AVR |
| Endocarditis | 0 | 0.0% | 1 | 1.1% | 1 | 1.2% | 0 | 1.1% | 0 | 1.2% | 0 | 1.1% |
| New Atrial Fibrillation ¹ | 11 | N/A | 15 | N/A | 3 | N/A | 1 | N/A | | | | |
| New pacemaker | 5 | 5.0% | 5 | 5.6% | 1 | 6.2% | 2 | 8.1% | 0 | 6.2% | 0 | 8.1% |

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.

N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.

Data presented as n (%) of patient unless otherwise specified.

a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.

b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).

c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.

d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.

e. Bleeding event is defined as ≥ 2 units within the index procedure.

f. Hemorrhagic vascular complications are defined as a hematoma at the access site >5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.

g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non-Q-wave MI.

h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).

i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.

j. New atrial fibrillation as defined by ECG corelab



Table 98. Enrollment - High Risk Non Randomized Roll-In and Continued Access Patients (ITT Population)

| | Non-Randomized Patients | | | | | | Trial Total | | |
|-----------------------|-------------------------|------------------|-----------------------|------------------|-------------------|------------------|-------------|----------------|----------|
| | Transapical Approach | | Transfemoral Approach | | Pooled Approaches | | | | |
| Site | Roll-in | Continued Access | Roll-in | Continued Access | Roll-in | Continued Access | Rando-mized | Non Randomized | Cohort A |
| Barnes | 2 | 43 | 0 | 18 | 2 | 61 | 24 | 63 | 87 |
| Boston Mass General | 0 | 57 | 1 | 25 | 1 | 82 | 15 | 83 | 98 |
| Brigham Womens | 0 | 10 | 0 | 19 | 0 | 29 | 2 | 29 | 31 |
| Cedars Sinai | 2 | 38 | 0 | 87 | 2 | 125 | 116 | 127 | 243 |
| Cleveland Clinic | 0 | 45 | 0 | 48 | 0 | 93 | 47 | 93 | 140 |
| Columbia | 0 | 70 | 0 | 59 | 0 | 129 | 97 | 129 | 226 |
| Cornell | 0 | 23 | 3 | 35 | 3 | 58 | 1 | 61 | 62 |
| Dallas | 0 | 73 | 1 | 61 | 1 | 134 | 95 | 135 | 230 |
| Emory | 2 | 58 | 0 | 34 | 2 | 92 | 67 | 94 | 161 |
| Evanston | 0 | 10 | 0 | 12 | 0 | 22 | 4 | 22 | 26 |
| Evanston Northwestern | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Intermountain | 0 | 25 | 1 | 20 | 1 | 45 | 1 | 46 | 47 |
| Laval | 0 | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 8 |
| Leipzig | 0 | 0 | 2 | 0 | 2 | 0 | 7 | 2 | 9 |
| Mayo | 0 | 39 | 2 | 24 | 2 | 63 | 6 | 65 | 71 |
| Miami | 2 | 59 | 0 | 22 | 2 | 81 | 25 | 83 | 108 |
| Northwestern | 2 | 36 | 2 | 28 | 4 | 64 | 20 | 68 | 88 |
| Ochsner | 0 | 6 | 2 | 15 | 2 | 21 | 2 | 23 | 25 |
| Pennsylvania | 2 | 48 | 1 | 49 | 3 | 97 | 52 | 100 | 152 |
| Scripps | 0 | 65 | 1 | 40 | 1 | 105 | 7 | 106 | 113 |
| St Lukes | 2 | 9 | 2 | 8 | 4 | 17 | 13 | 21 | 34 |
| Stanford | 2 | 35 | 0 | 47 | 2 | 82 | 23 | 84 | 107 |
| Toronto | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| U of Washington | 1 | 22 | 1 | 12 | 2 | 34 | 5 | 36 | 41 |
| Vancouver | 0 | 0 | 0 | 0 | 0 | 0 | 19 | 0 | 19 |
| Virginia | 0 | 19 | 1 | 18 | 1 | 37 | 3 | 38 | 41 |
| Washington DC | 2 | 53 | 2 | 64 | 4 | 117 | 40 | 121 | 161 |
| Total | 19 | 843 | 22 | 745 | 41 | 1588 | 699 | 1629 | 2328 |

Source: Table 1.1



Table 99. Echocardiography Data – High Risk Non Randomized, Continued-Access Patients (AT Population)

| Cohort A Continued Access Patients -- As Treated (AT) Population | | | | | |
|--|----------|------------|----------------------|-----------------------|-------------------|
| | | | Transapical Approach | Transfemoral Approach | Pooled Approaches |
| Echo Core Lab Parameters | Visit | Statistics | NRCA (N=822) | NRCA (N=699) | NRCA (N=1521) |
| AV Area (EOA) (cm2) | BASELINE | n | 326 | 302 | 628 |
| | | Mean | 0.65 | 0.66 | 0.65 |
| | | SD | 0.194 | 0.210 | 0.202 |
| | 30 DAY | n | 281 | 275 | 556 |
| | | Mean | 1.67 | 1.79 | 1.73 |
| | | SD | 0.493 | 0.532 | 0.515 |
| | 6 MONTH | n | 206 | 195 | 401 |
| | | Mean | 1.64 | 1.71 | 1.68 |
| | | SD | 0.477 | 0.457 | 0.468 |
| | 1 YEAR | n | 46 | 71 | 117 |
| | | Mean | 1.70 | 1.72 | 1.71 |
| | | SD | 0.529 | 0.427 | 0.468 |
| AV Mean Gradient (mmHg) | BASELINE | n | 335 | 305 | 640 |
| | | Mean | 43.98 | 45.20 | 44.56 |
| | | SD | 15.110 | 14.872 | 14.998 |
| | 30 DAY | n | 285 | 286 | 571 |
| | | Mean | 8.79 | 9.48 | 9.13 |
| | | SD | 3.539 | 3.998 | 3.788 |
| | 6 MONTH | n | 207 | 201 | 408 |
| | | Mean | 8.62 | 9.58 | 9.09 |
| | | SD | 3.597 | 3.767 | 3.709 |
| | 1 YEAR | n | 47 | 73 | 120 |
| | | Mean | 9.73 | 10.68 | 10.31 |
| | | SD | 3.753 | 4.324 | 4.120 |
| AV Peak Gradient (mmHg) | BASELINE | n | 335 | 305 | 640 |
| | | Mean | 71.31 | 72.95 | 72.10 |
| | | SD | 24.122 | 23.175 | 23.671 |
| | 30 DAY | n | 285 | 286 | 571 |
| | | Mean | 16.76 | 17.86 | 17.31 |
| | | SD | 6.412 | 7.315 | 6.895 |
| | 6 MONTH | n | 207 | 201 | 408 |
| | | Mean | 16.25 | 17.92 | 17.07 |
| | | SD | 6.438 | 6.876 | 6.702 |
| | 1 YEAR | n | 47 | 73 | 120 |
| | | Mean | 18.74 | 20.36 | 19.73 |
| | | SD | 6.763 | 8.246 | 7.711 |
| Paravalvular Aortic Regurgitation | BASELINE | n | 335 | 310 | 645 |
| | | NONE | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| | | TRACE | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | | MILD | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | | MODERATE | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | | SEVERE | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | | NA | 334 (99.7) | 310 (100) | 644 (99.8) |
| | 30 DAY | n | 291 | 293 | 584 |
| | | NONE | 69 (23.7) | 40 (13.7) | 109 (18.7) |
| | | | | | |



| Cohort A Continued Access Patients -- As Treated (AT) Population | | | | | |
|--|----------|------------|----------------------|-----------------------|-------------------|
| | | | Transapical Approach | Transfemoral Approach | Pooled Approaches |
| Echo Core Lab Parameters | Visit | Statistics | NRCA (N=822) | NRCA (N=699) | NRCA (N=1521) |
| | | TRACE | 99 (34.0) | 82 (28.0) | 181 (31.0) |
| | | MILD | 102 (35.1) | 112 (38.2) | 214 (36.6) |
| | | MODERATE | 20 (6.9) | 54 (18.4) | 74 (12.7) |
| | | SEVERE | 0 (0.0) | 3 (1.0) | 3 (0.5) |
| | | NA | 1 (0.3) | 2 (0.7) | 3 (0.5) |
| | 6 MONTH | n | 209 | 204 | 413 |
| | | NONE | 56 (26.8) | 37 (18.1) | 93 (22.5) |
| | | TRACE | 70 (33.5) | 44 (21.6) | 114 (27.6) |
| | | MILD | 67 (32.1) | 86 (42.2) | 153 (37.0) |
| | | MODERATE | 15 (7.2) | 34 (16.7) | 49 (11.9) |
| | | SEVERE | 1 (0.5) | 2 (1.0) | 3 (0.7) |
| | | NA | 0 (0.0) | 1 (0.5) | 1 (0.2) |
| | 1 YEAR | n | 48 | 76 | 124 |
| | | NONE | 18 (37.5) | 14 (18.4) | 32 (25.8) |
| | | TRACE | 12 (25.0) | 17 (22.4) | 29 (23.4) |
| | | MILD | 14 (29.2) | 32 (42.1) | 46 (37.1) |
| | | MODERATE | 3 (6.3) | 11 (14.5) | 14 (11.3) |
| | | SEVERE | 0 (0.0) | 2 (2.6) | 2 (1.6) |
| | | NA | 1 (2.1) | 0 (0.0) | 1 (0.8) |
| Transvalvular Aortic Regurgitation | BASELINE | n | 335 | 310 | 645 |
| | | NONE | 30 (9.0) | 32 (10.3) | 62 (9.6) |
| | | TRACE | 121 (36.1) | 103 (33.2) | 224 (34.7) |
| | | MILD | 156 (46.6) | 135 (43.5) | 291 (45.1) |
| | | MODERATE | 24 (7.2) | 32 (10.3) | 56 (8.7) |
| | | SEVERE | 3 (0.9) | 4 (1.3) | 7 (1.1) |
| | | NA | 1 (0.3) | 4 (1.3) | 5 (0.8) |
| | 30 DAY | n | 291 | 293 | 584 |
| | | NONE | 140 (48.1) | 130 (44.4) | 270 (46.2) |
| | | TRACE | 122 (41.9) | 116 (39.6) | 238 (40.8) |
| | | MILD | 29 (10.0) | 43 (14.7) | 72 (12.3) |
| | | MODERATE | 0 (0.0) | 2 (0.7) | 2 (0.3) |
| | | SEVERE | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | | NA | 0 (0.0) | 2 (0.7) | 2 (0.3) |
| | 6 MONTH | n | 209 | 204 | 413 |
| | | NONE | 96 (45.9) | 83 (40.7) | 179 (43.3) |
| | | TRACE | 77 (36.8) | 85 (41.7) | 162 (39.2) |
| | | MILD | 33 (15.8) | 34 (16.7) | 67 (16.2) |
| | | MODERATE | 3 (1.4) | 0 (0.0) | 3 (0.7) |
| | | SEVERE | 0 (0.0) | 1 (0.5) | 1 (0.2) |
| | | NA | 0 (0.0) | 1 (0.5) | 1 (0.2) |
| | 1 YEAR | n | 48 | 76 | 124 |
| | | NONE | 19 (39.6) | 31 (40.8) | 50 (40.3) |
| | | TRACE | 15 (31.3) | 32 (42.1) | 47 (37.9) |
| | | MILD | 13 (27.1) | 11 (14.5) | 24 (19.4) |
| | | MODERATE | 0 (0.0) | 2 (2.6) | 2 (1.6) |
| | | SEVERE | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | | NA | 1 (2.1) | 0 (0.0) | 1 (0.8) |
| Total Aortic Regurgitation | BASELINE | n | 336 | 312 | 648 |



| Cohort A Continued Access Patients -- As Treated (AT) Population | | | | | |
|--|---------|------------|----------------------|-----------------------|-------------------|
| | | | Transapical Approach | Transfemoral Approach | Pooled Approaches |
| Echo Core Lab Parameters | Visit | Statistics | NRCA (N=822) | NRCA (N=699) | NRCA (N=1521) |
| | | NONE | 30 (8.9) | 32 (10.3) | 62 (9.6) |
| | | TRACE | 122 (36.3) | 103 (33.0) | 225 (34.7) |
| | | MILD | 156 (46.4) | 137 (43.9) | 293 (45.2) |
| | | MODERATE | 24 (7.1) | 32 (10.3) | 56 (8.6) |
| | | SEVERE | 3 (0.9) | 4 (1.3) | 7 (1.1) |
| | | NA | 1 (0.3) | 4 (1.3) | 5 (0.8) |
| | 30 DAY | n | 291 | 293 | 584 |
| | | NONE | 43 (14.8) | 23 (7.8) | 66 (11.3) |
| | | TRACE | 107 (36.8) | 77 (26.3) | 184 (31.5) |
| | | MILD | 121 (41.6) | 128 (43.7) | 249 (42.6) |
| | | MODERATE | 20 (6.9) | 60 (20.5) | 80 (13.7) |
| | | SEVERE | 0 (0.0) | 3 (1.0) | 3 (0.5) |
| | | NA | 0 (0.0) | 2 (0.7) | 2 (0.3) |
| | 6 MONTH | n | 209 | 205 | 414 |
| | | NONE | 34 (16.3) | 20 (9.8) | 54 (13.0) |
| | | TRACE | 78 (37.3) | 47 (22.9) | 125 (30.2) |
| | | MILD | 74 (35.4) | 97 (47.3) | 171 (41.3) |
| | | MODERATE | 22 (10.5) | 37 (18.0) | 59 (14.3) |
| | | SEVERE | 1 (0.5) | 3 (1.5) | 4 (1.0) |
| | | NA | 0 (0.0) | 1 (0.5) | 1 (0.2) |
| | 1 YEAR | n | 48 | 77 | 125 |
| | | NONE | 12 (25.0) | 7 (9.1) | 19 (15.2) |
| | | TRACE | 12 (25.0) | 21 (27.3) | 33 (26.4) |
| | | MILD | 20 (41.7) | 33 (42.9) | 53 (42.4) |
| | | MODERATE | 3 (6.3) | 14 (18.2) | 17 (13.6) |
| | | SEVERE | 0 (0.0) | 2 (2.6) | 2 (1.6) |
| | | NA | 1 (2.1) | 0 (0.0) | 1 (0.8) |

Source: Table 6.5

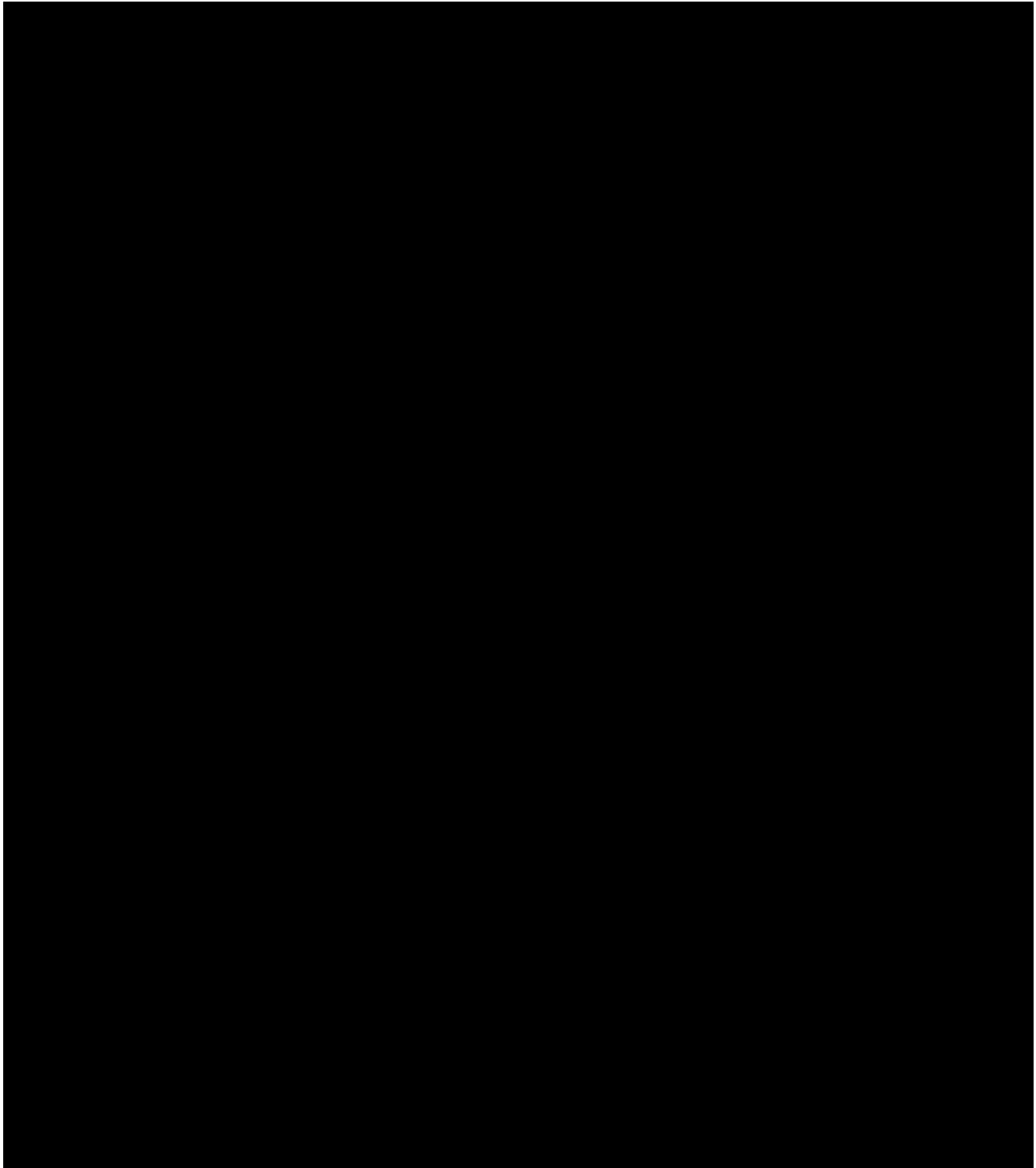


Appendix G. Narratives for PARTNER High Risk Surgical Patients Who Experienced a CEC-Adjudicated Stroke within 1 Year of the Index Procedure

NOTE:

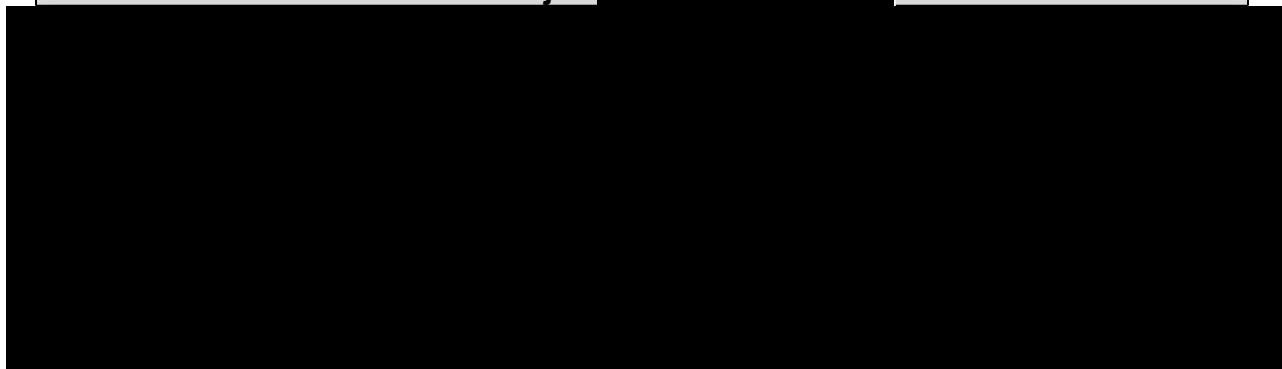
The narratives were prepared by the CEC.

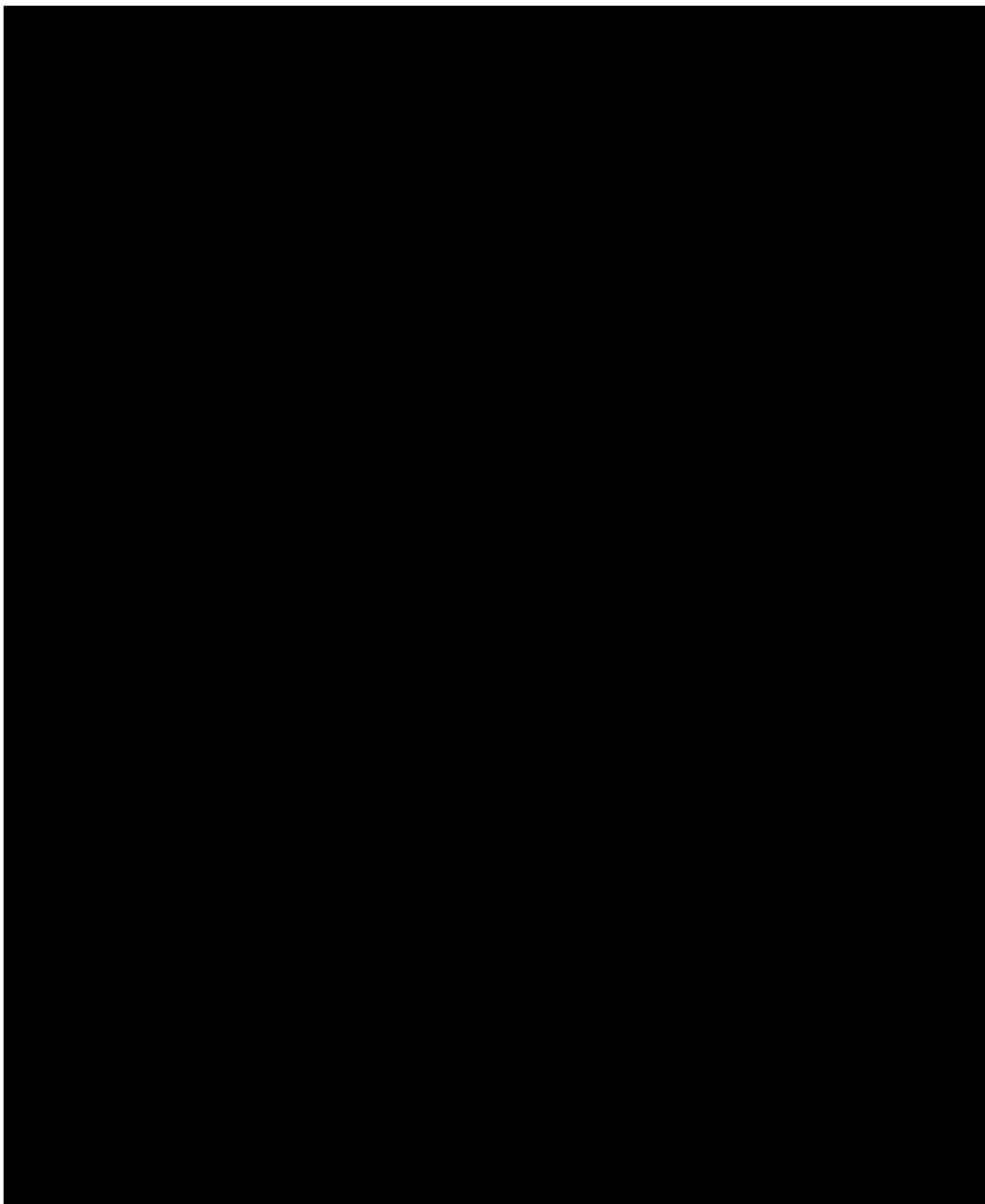
A table with QoL data if available post stroke, was compiled for each patient and added to each narrative as appropriate.

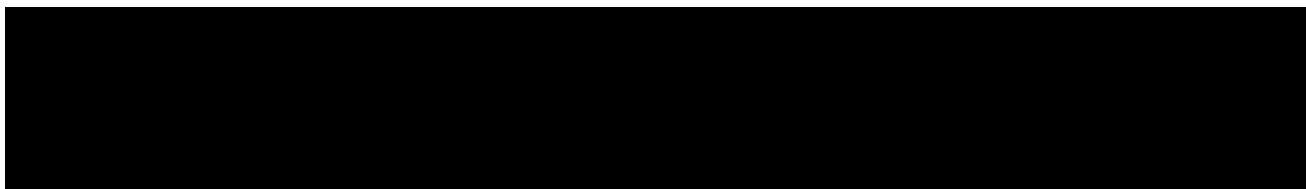


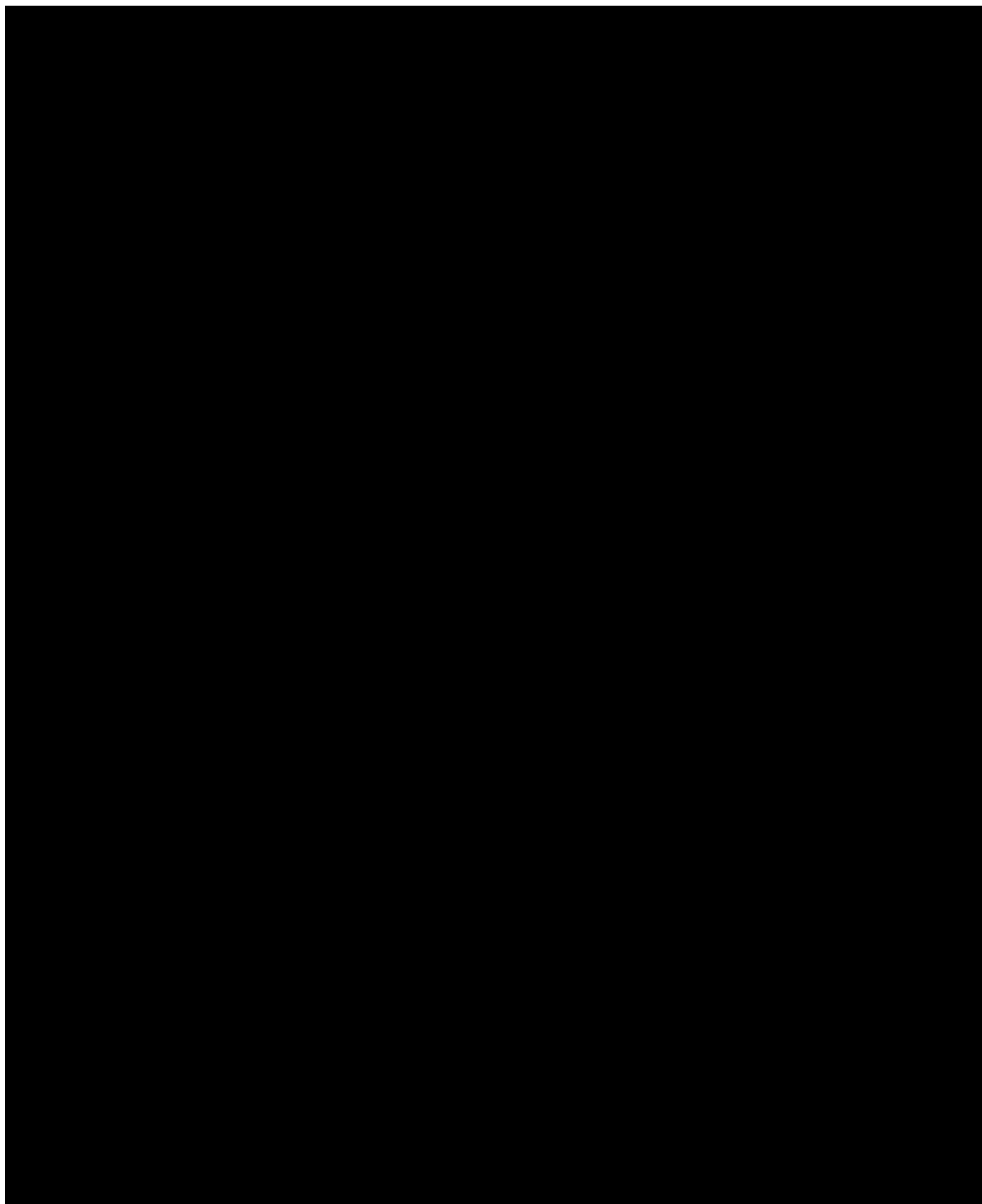


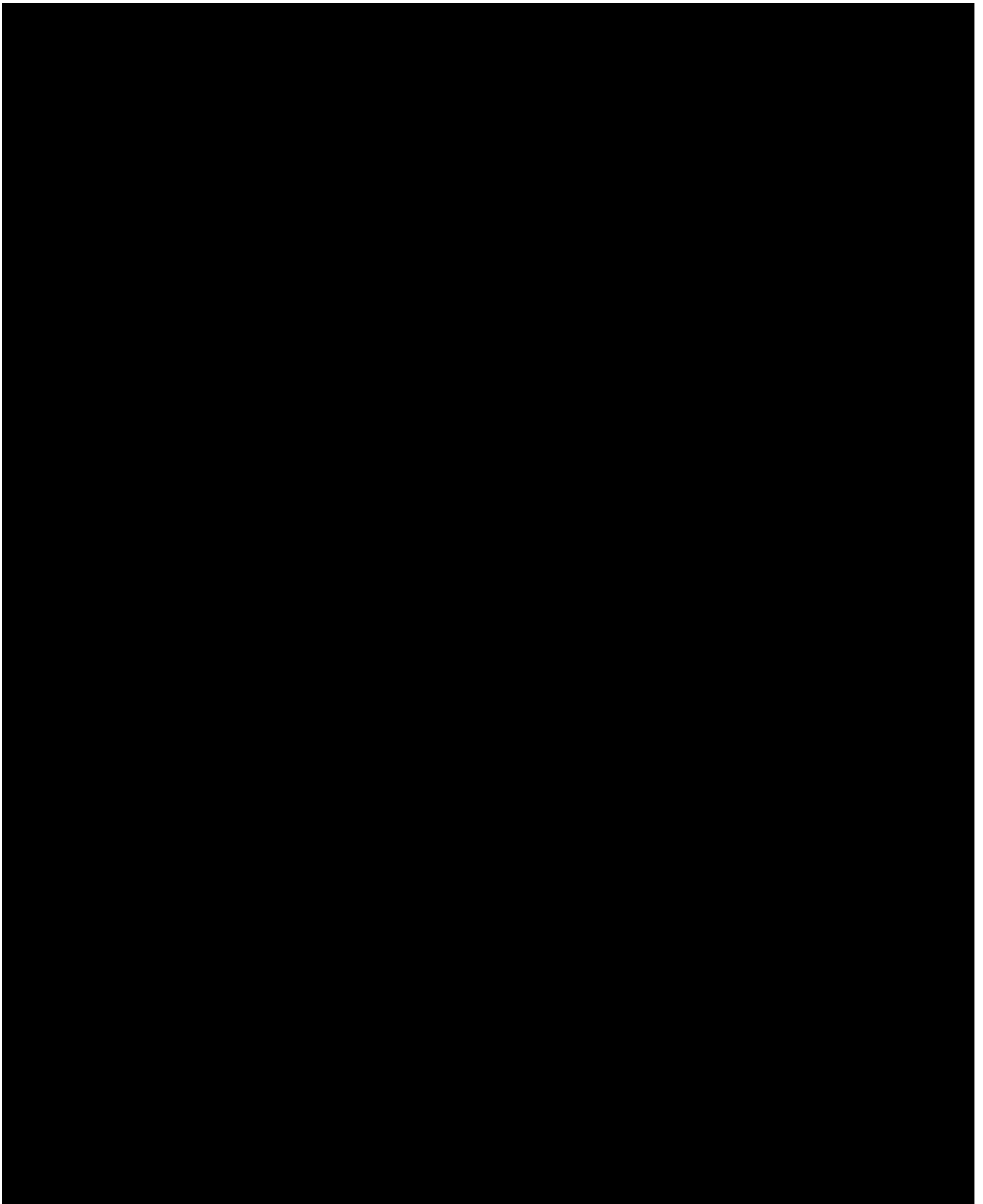
TAVR Subject







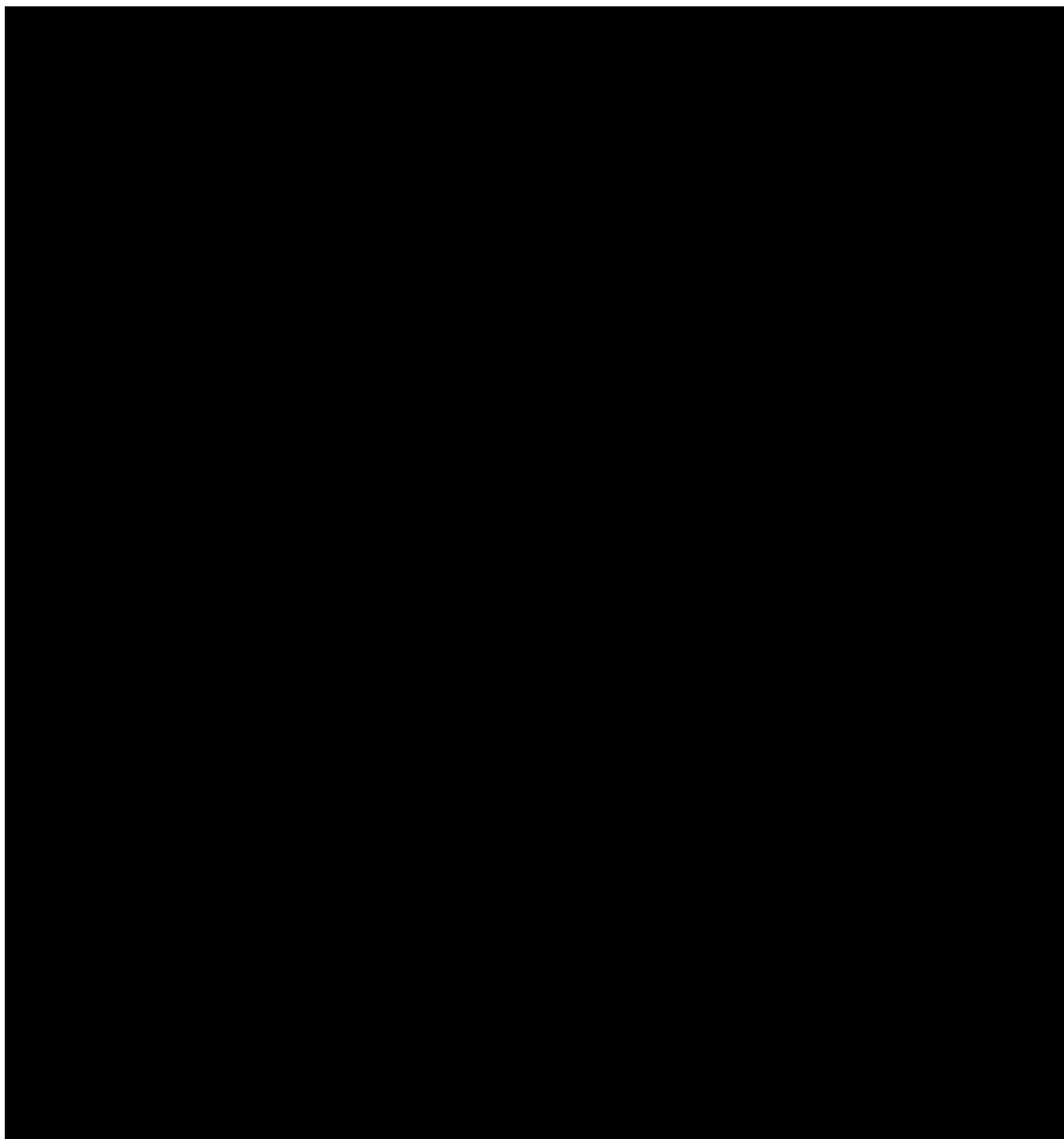


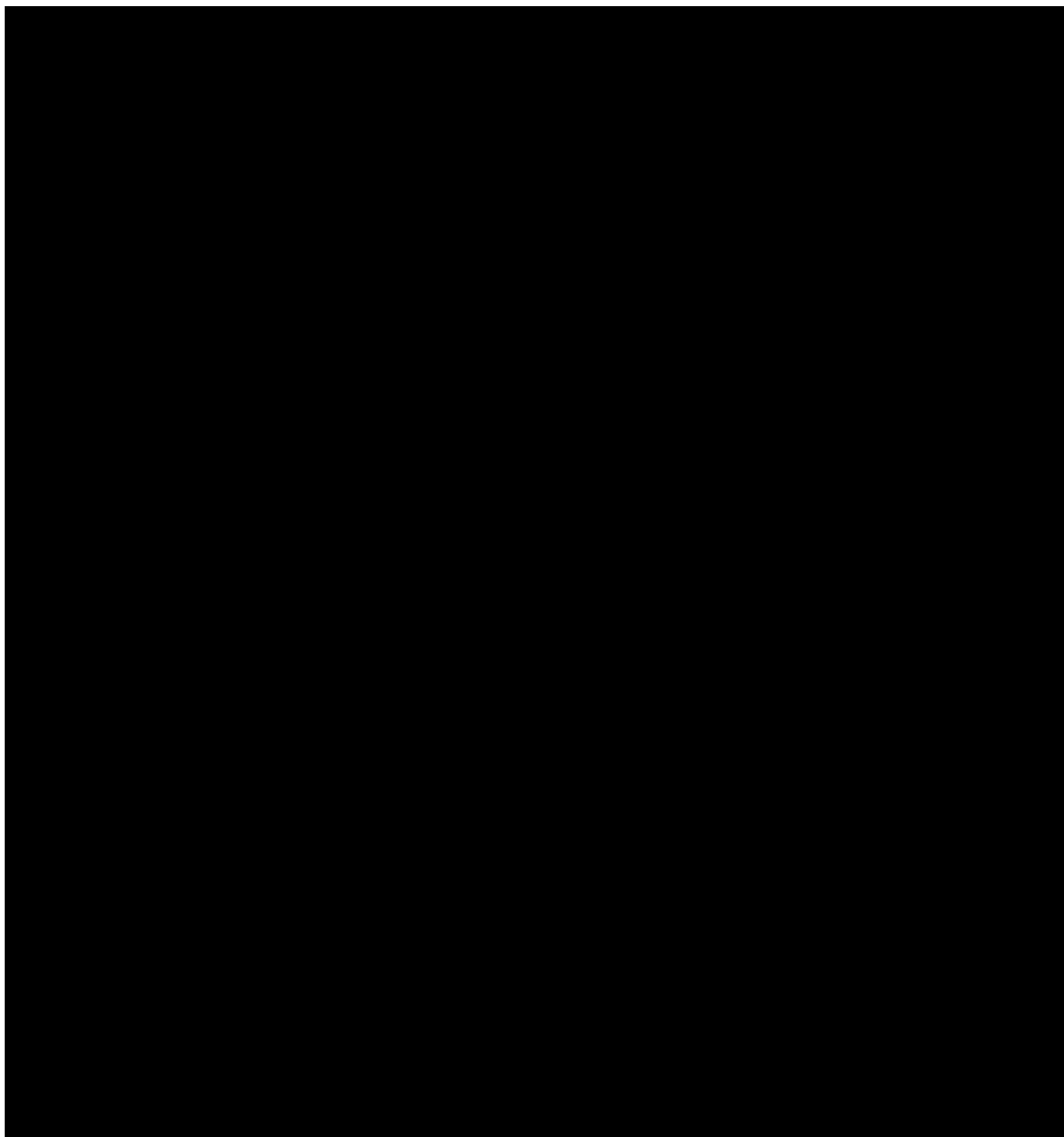


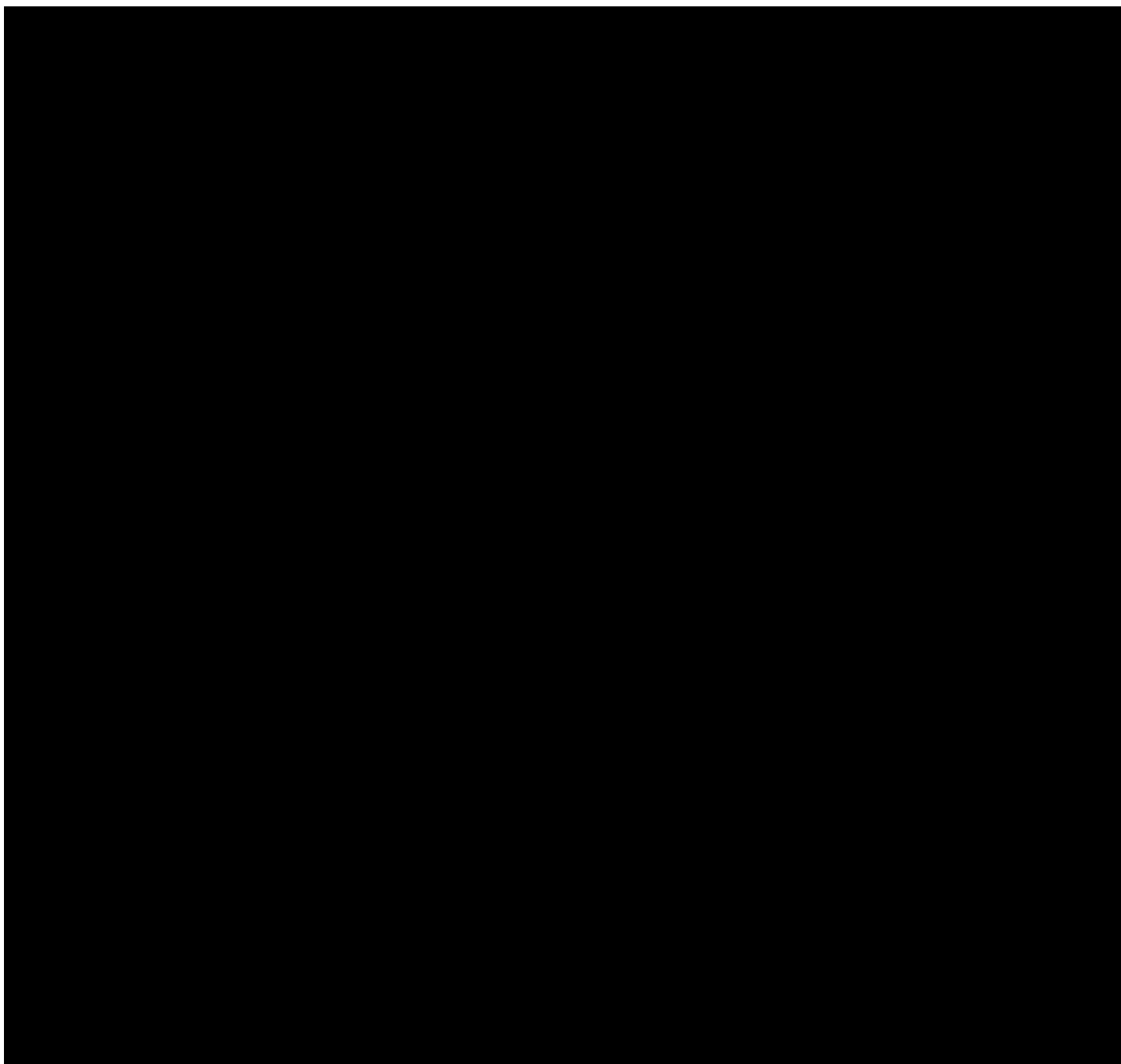


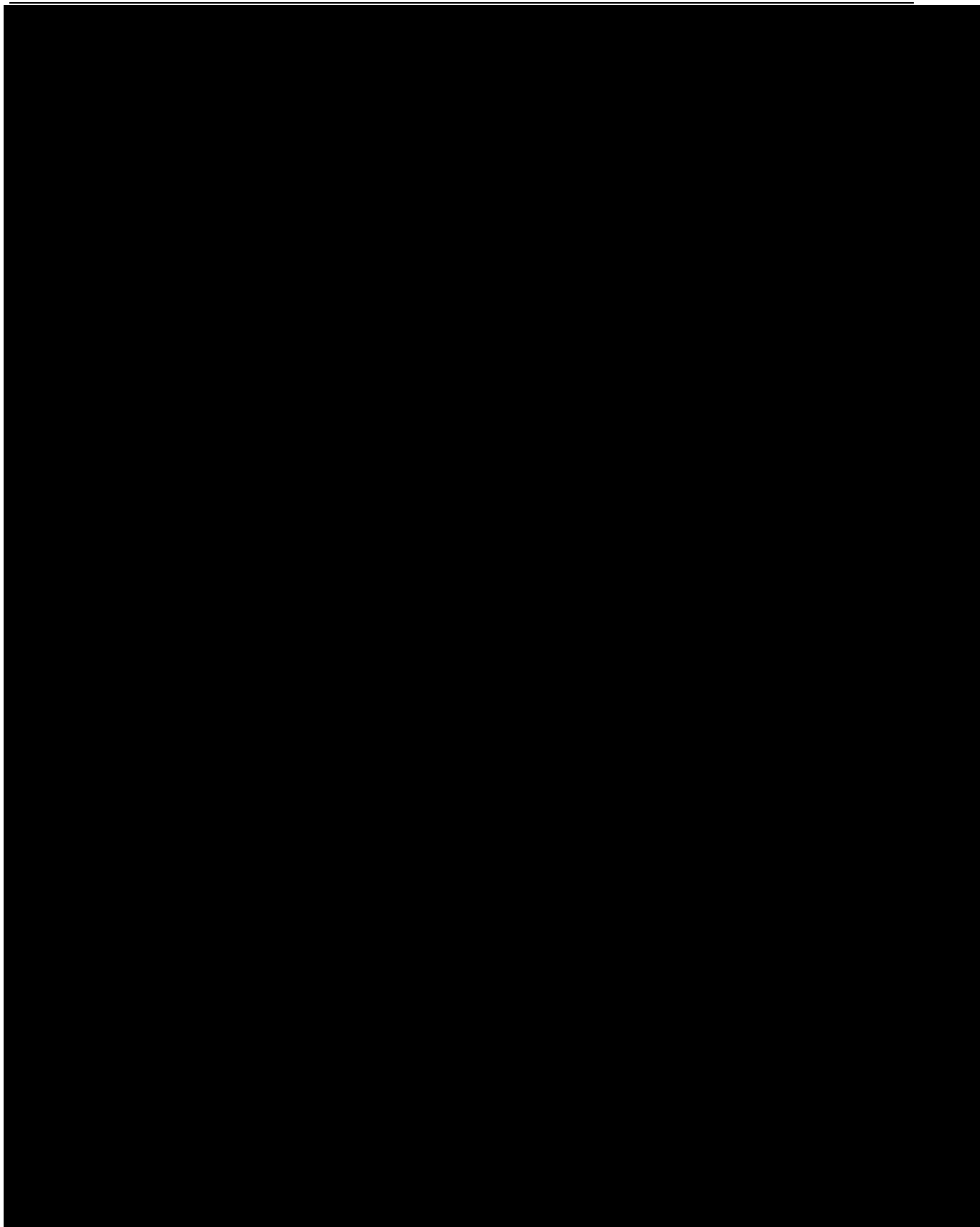
The **Embohc event** on 23 Jan 2009 was nositively adiudicated by the CEC. This event was a

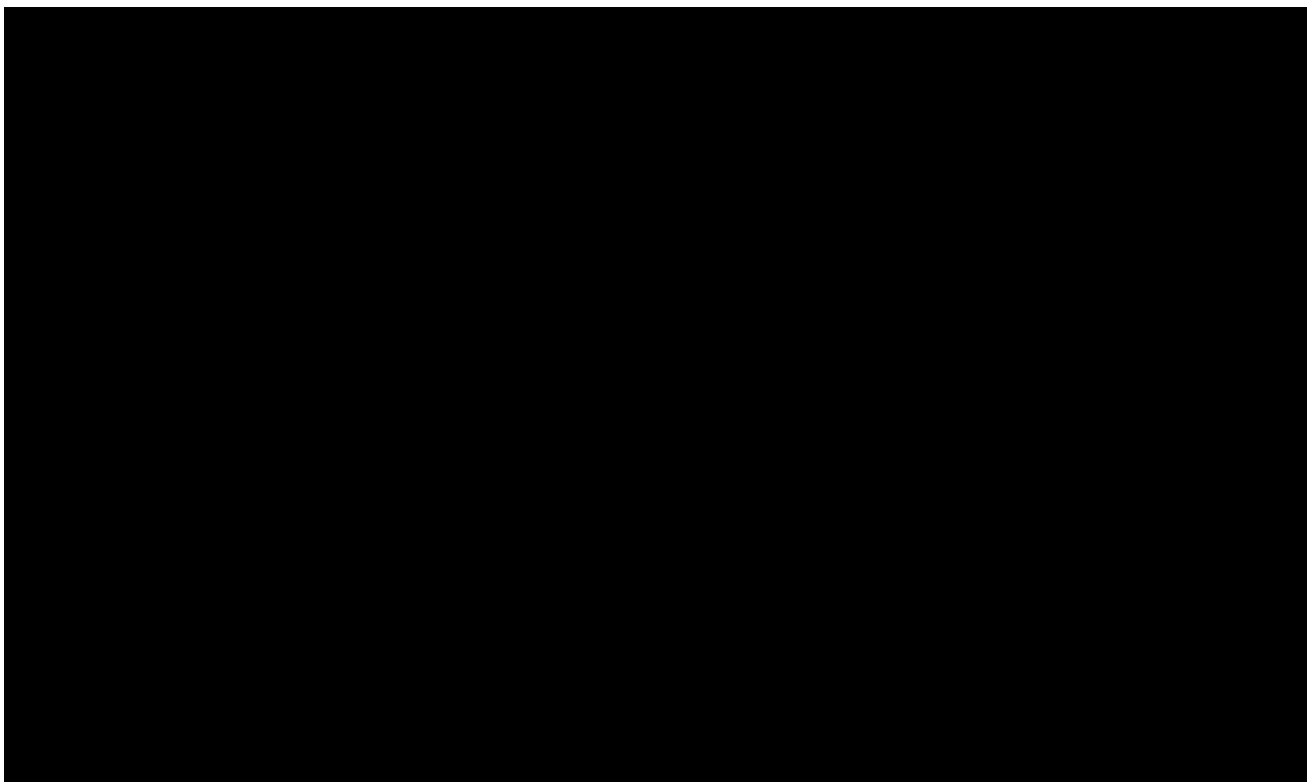
A large rectangular area of the page is completely blacked out, indicating that the content has been redacted. This area covers the majority of the page's body text.

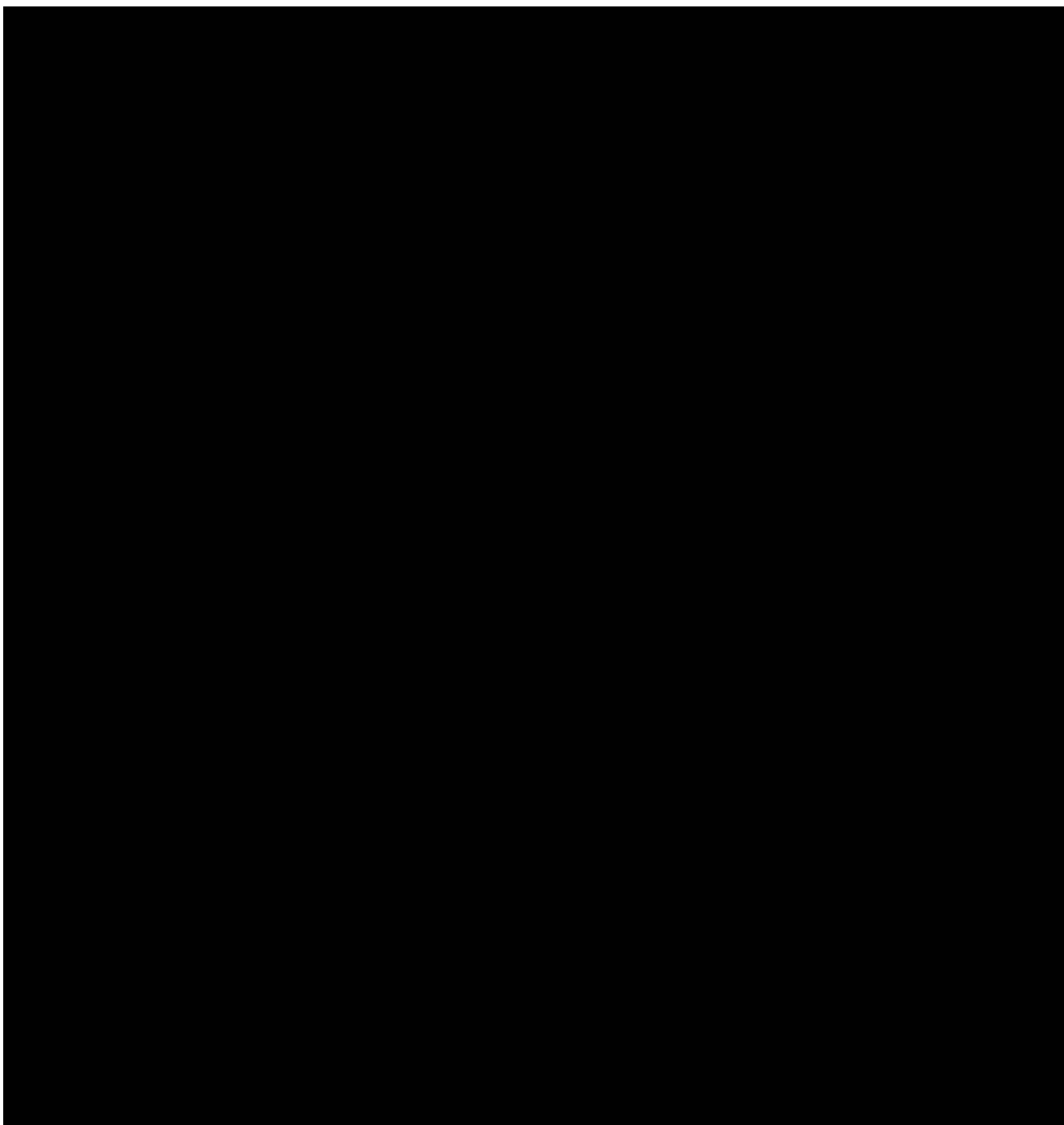




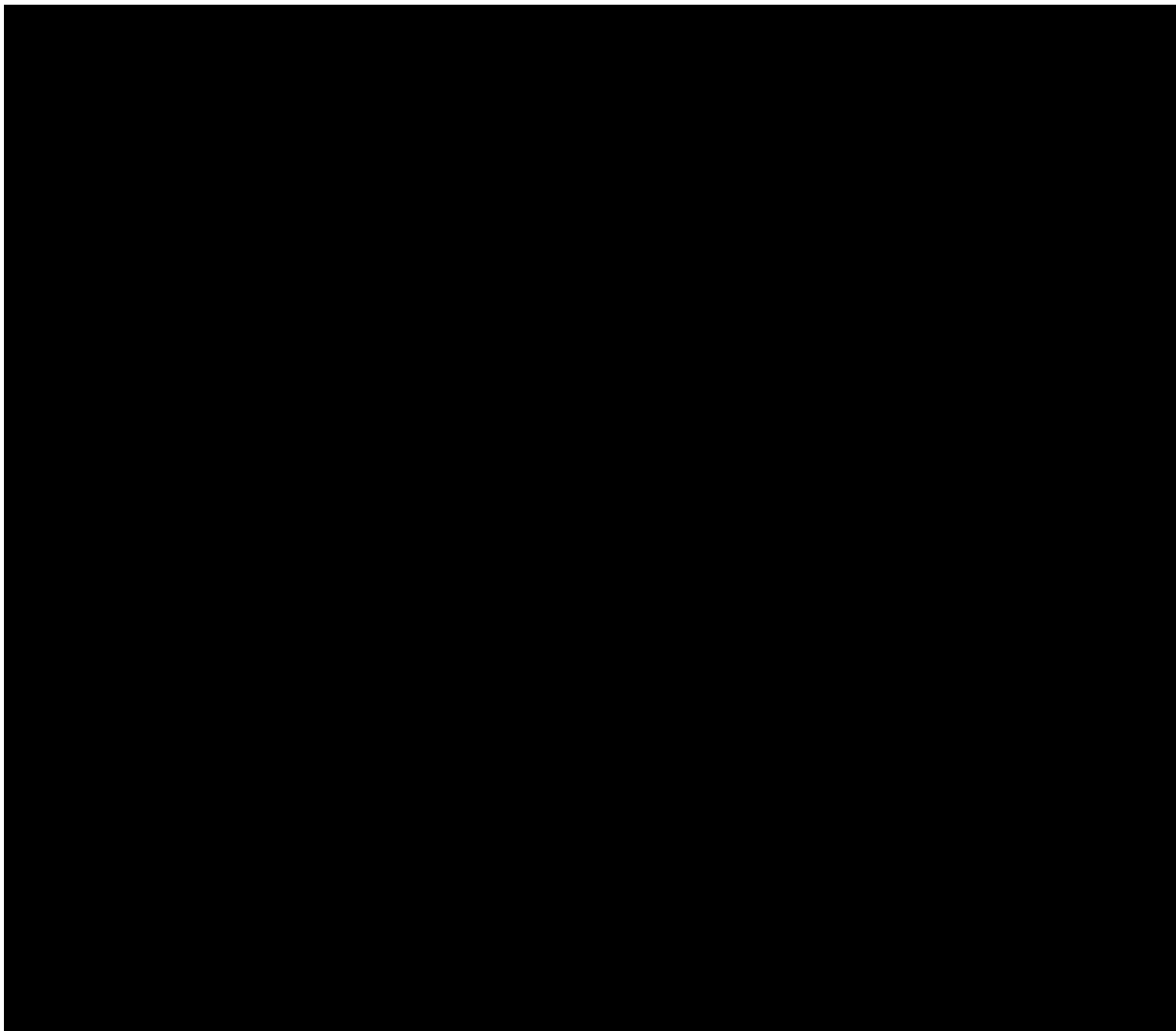


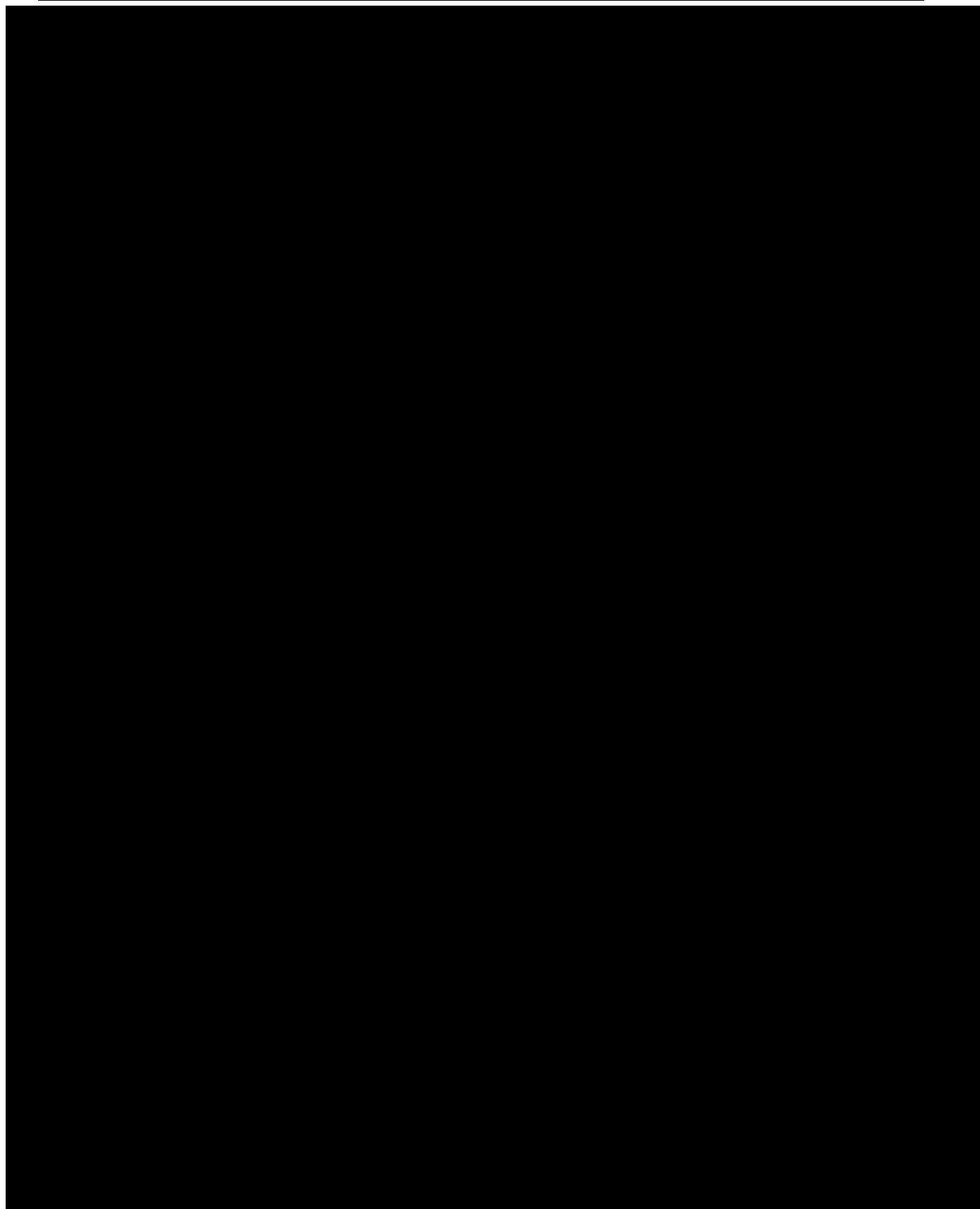


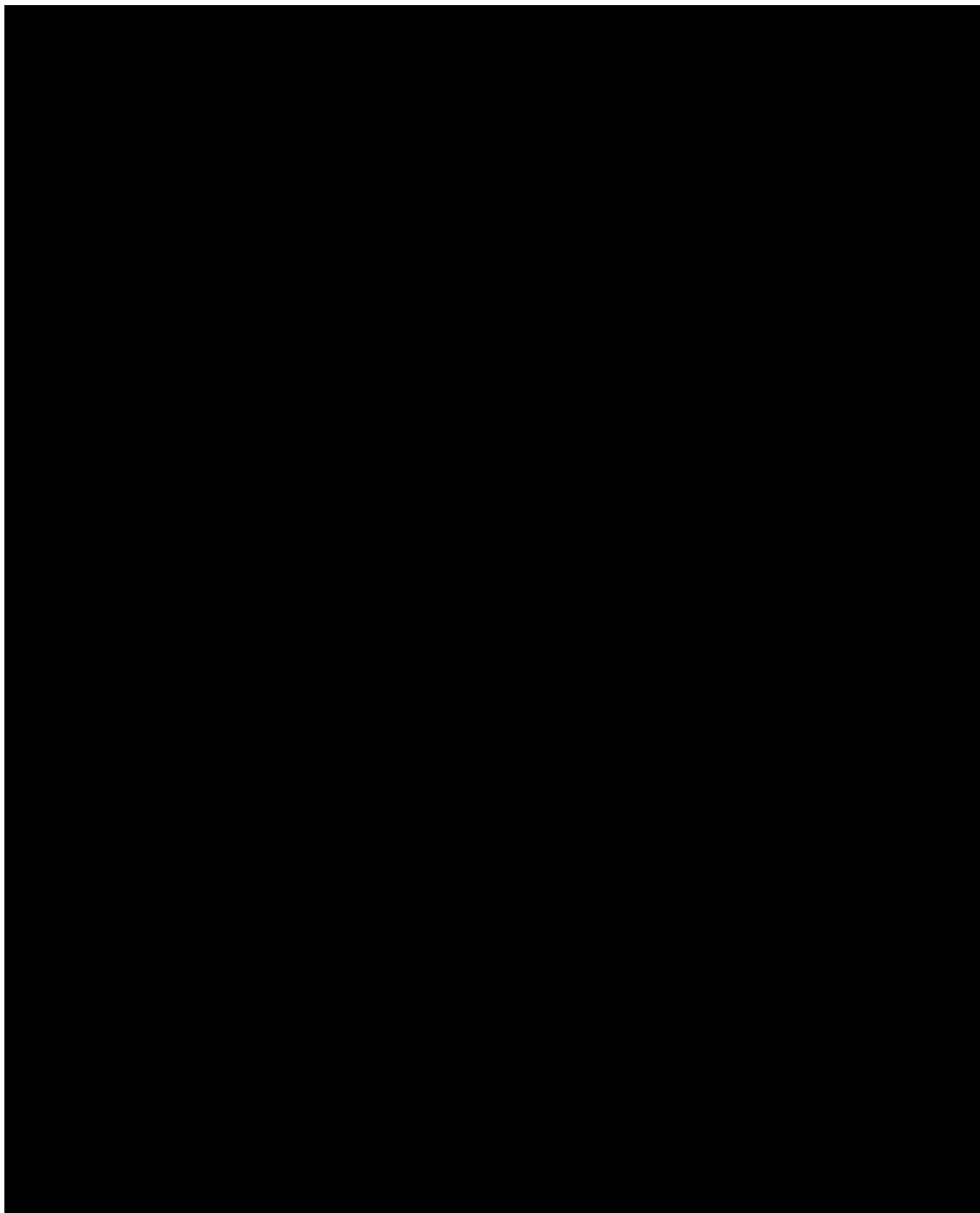


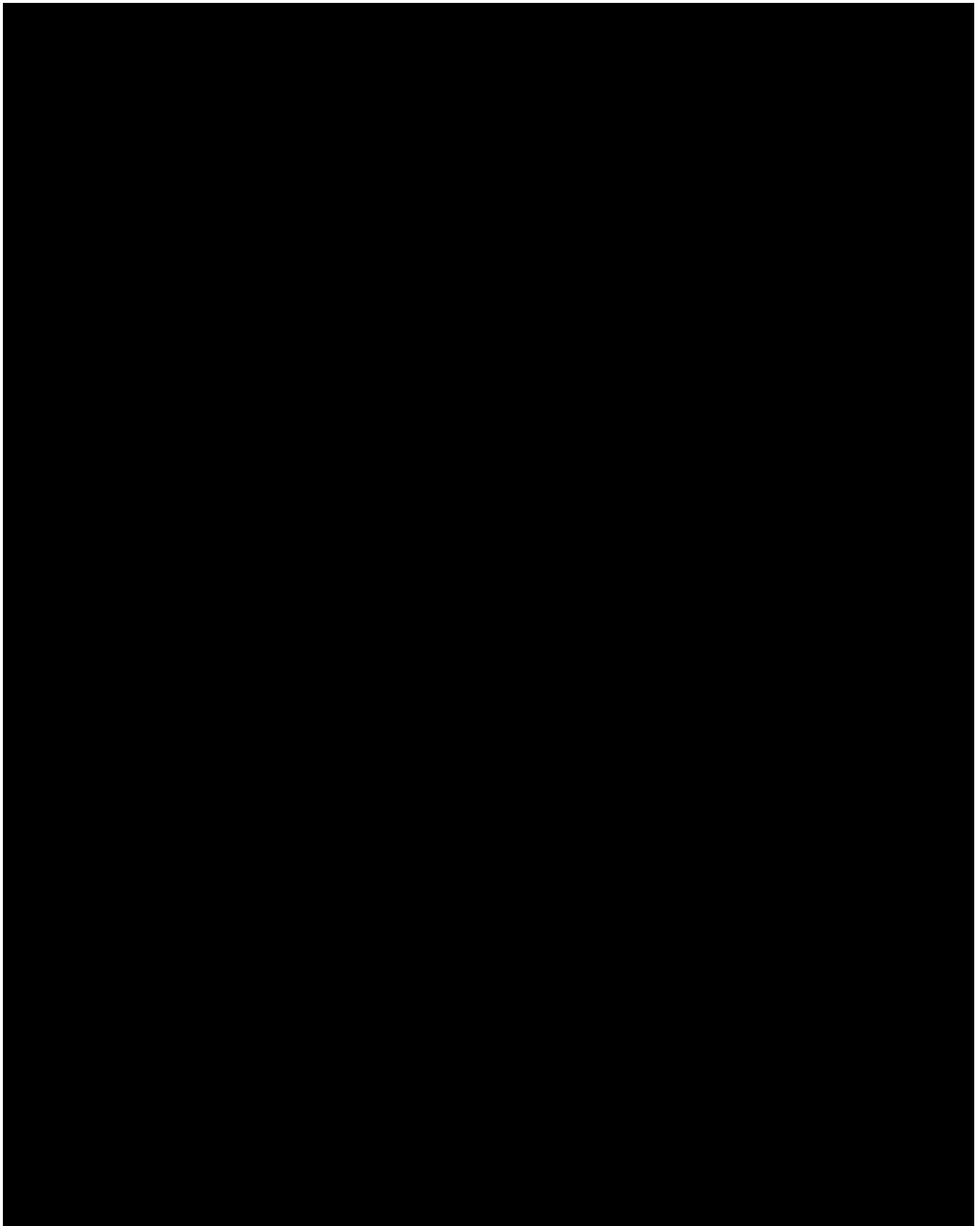


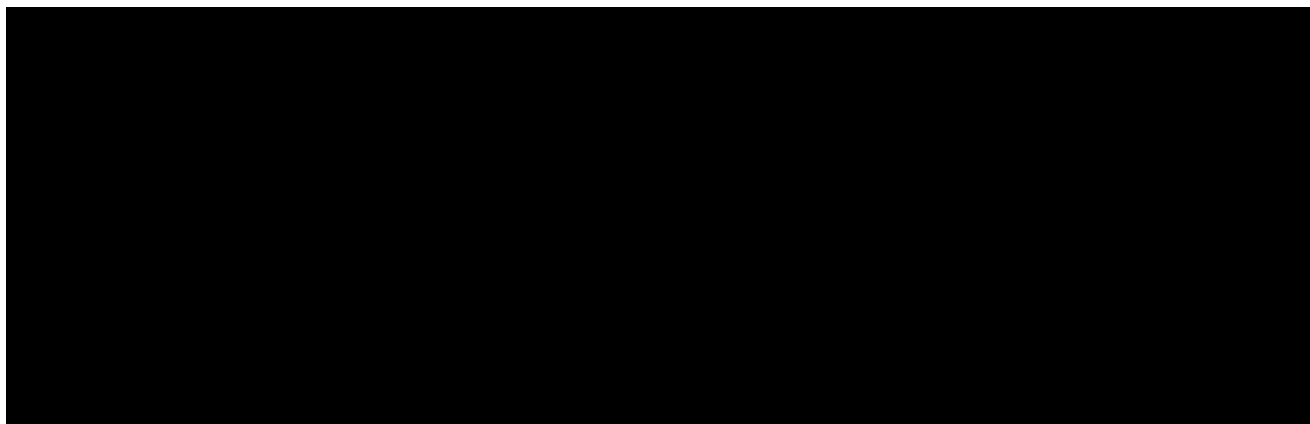


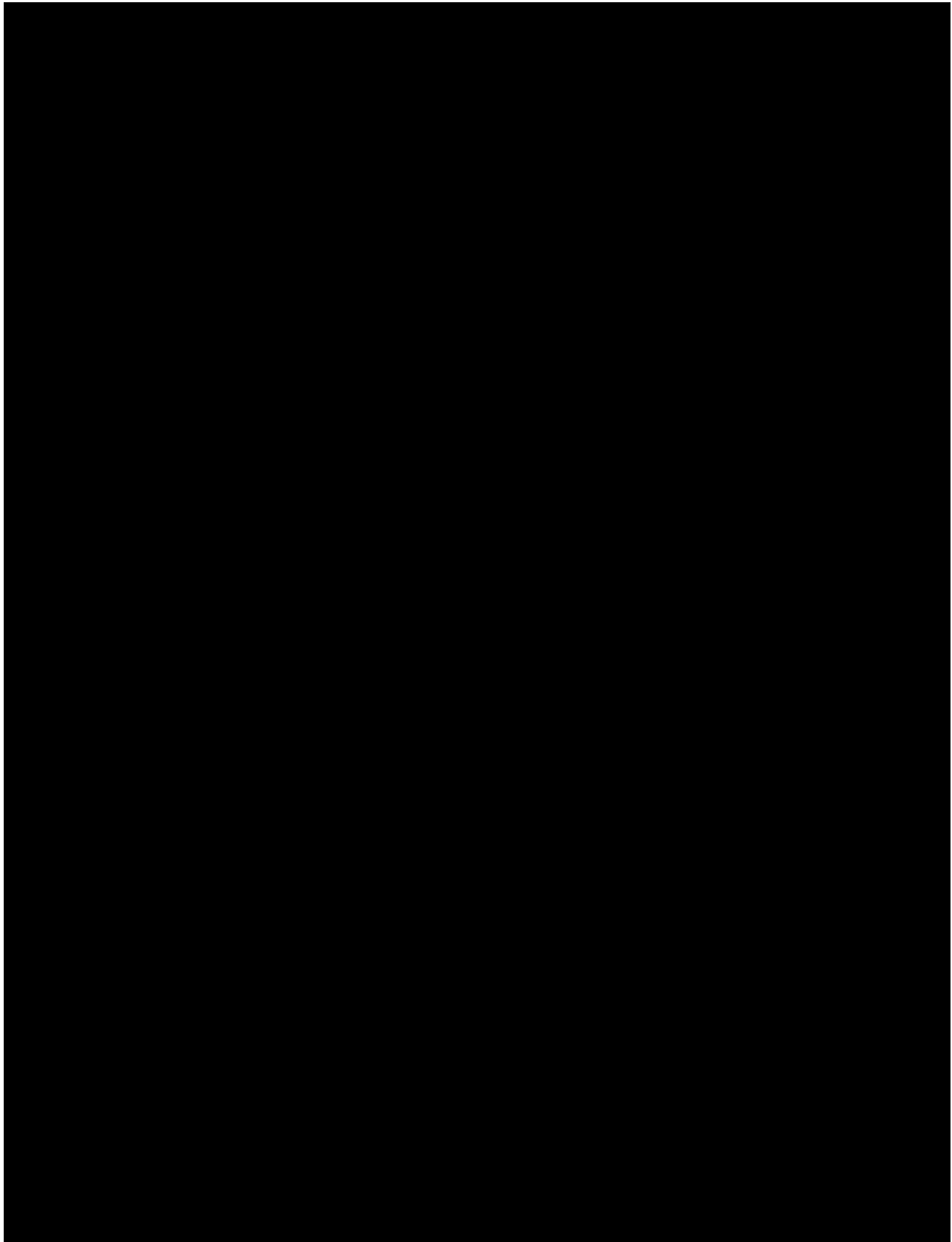


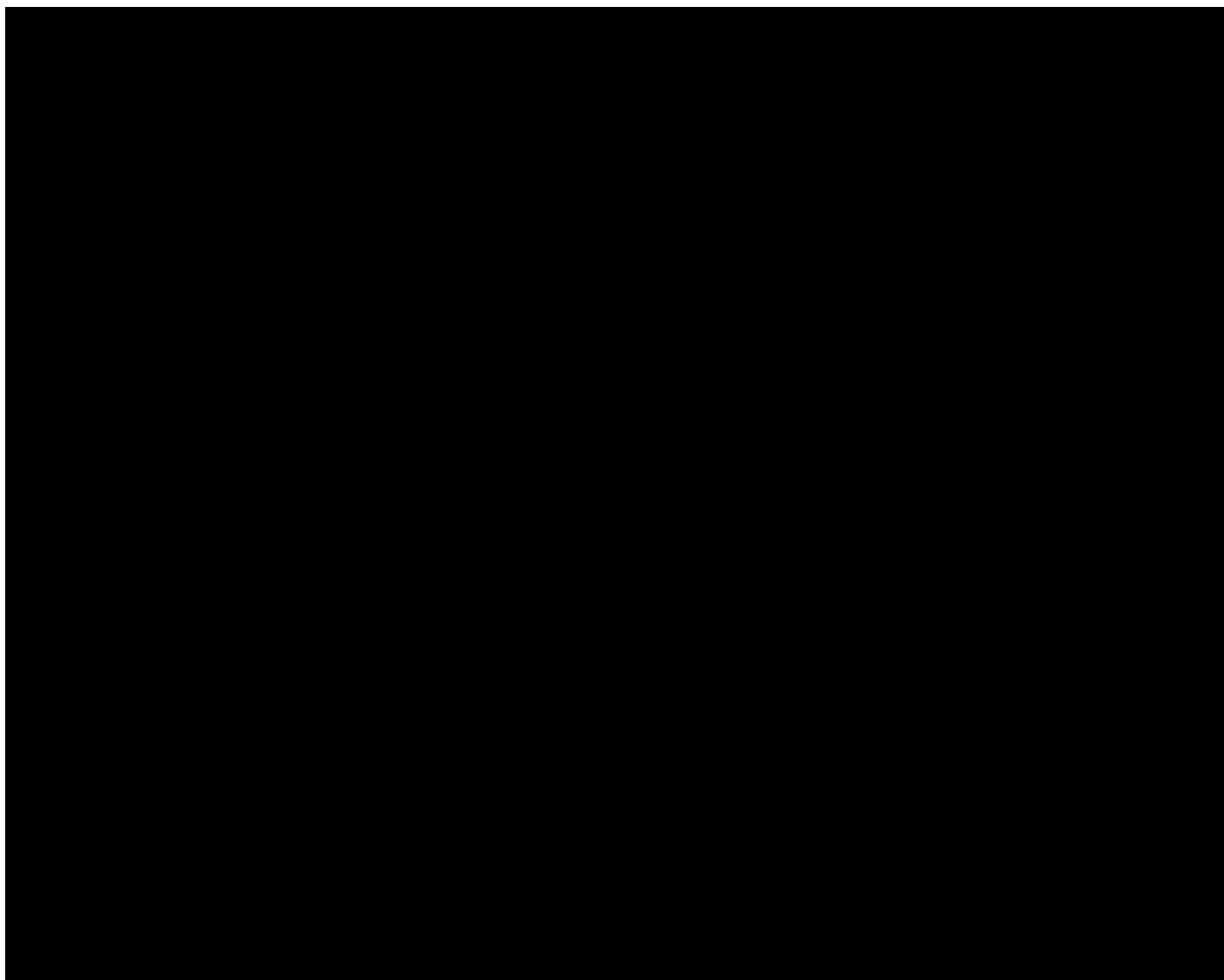


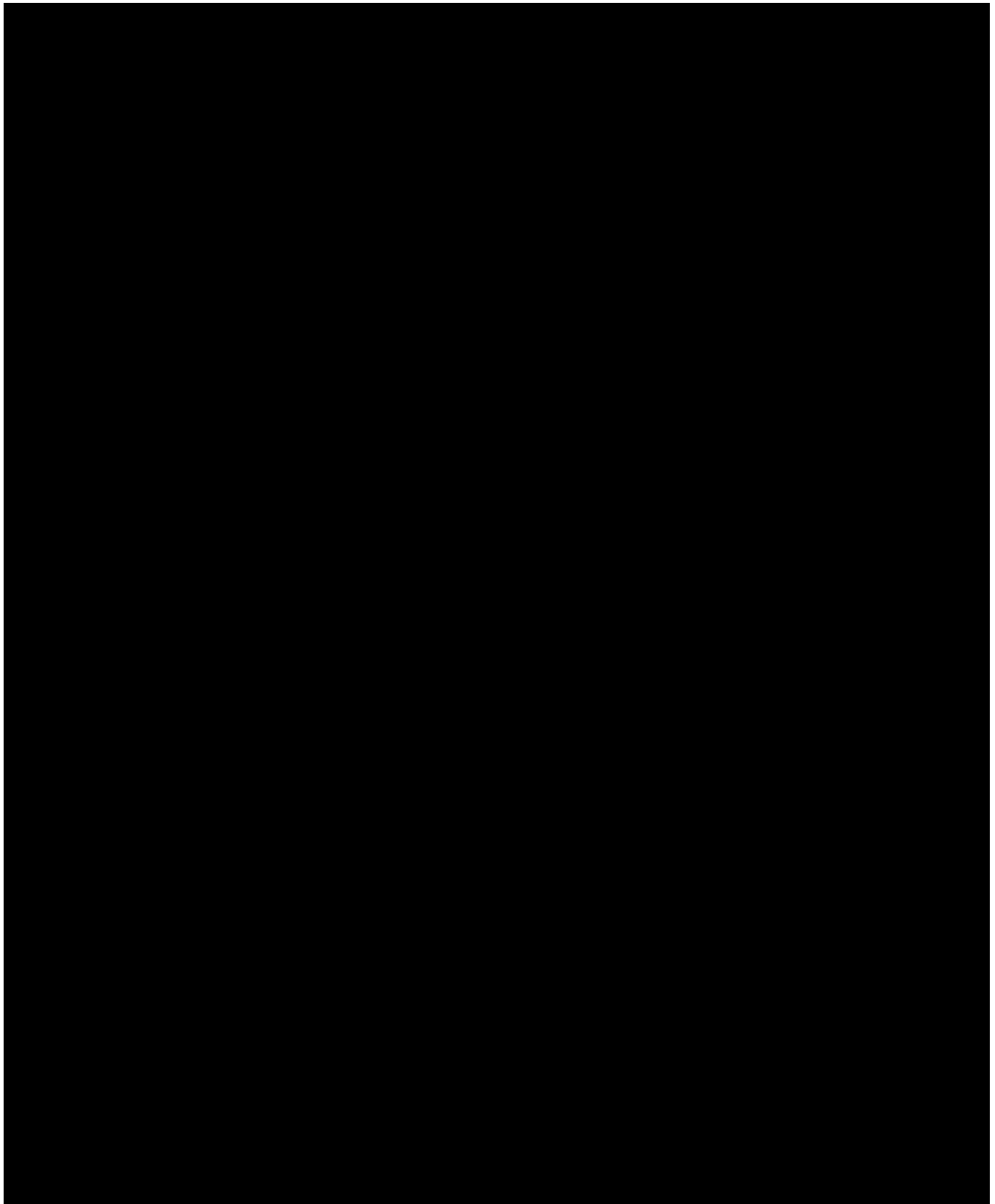


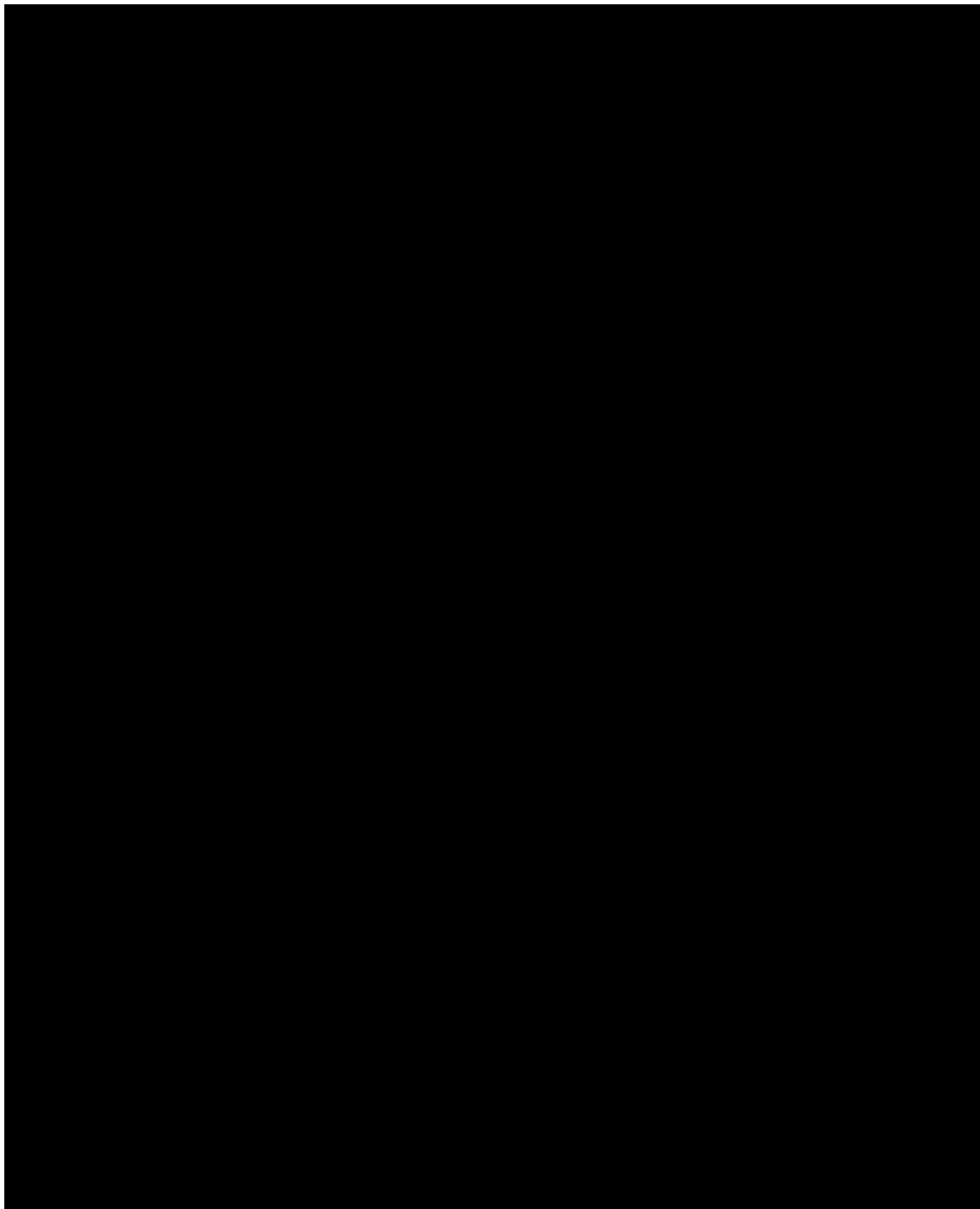






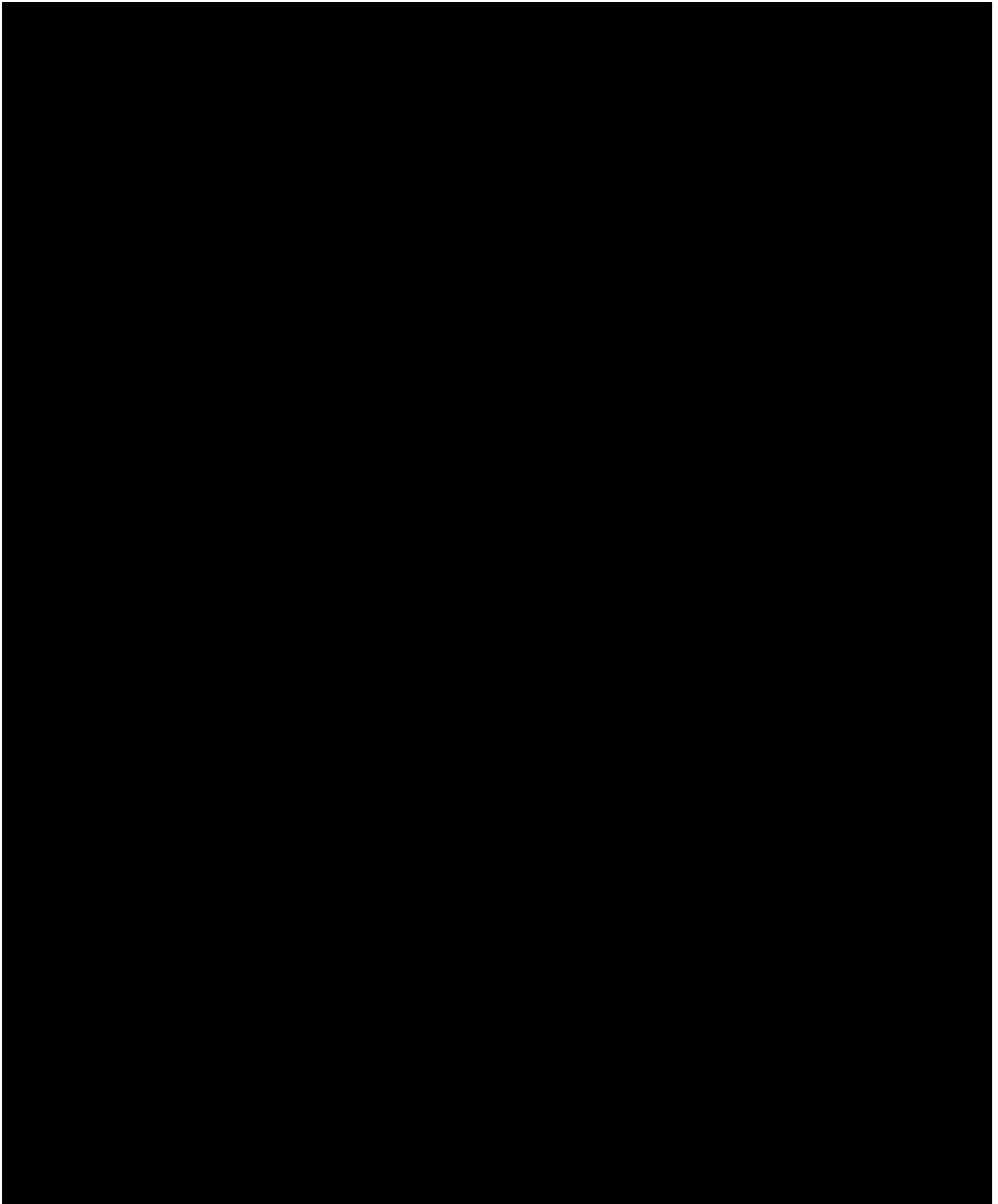


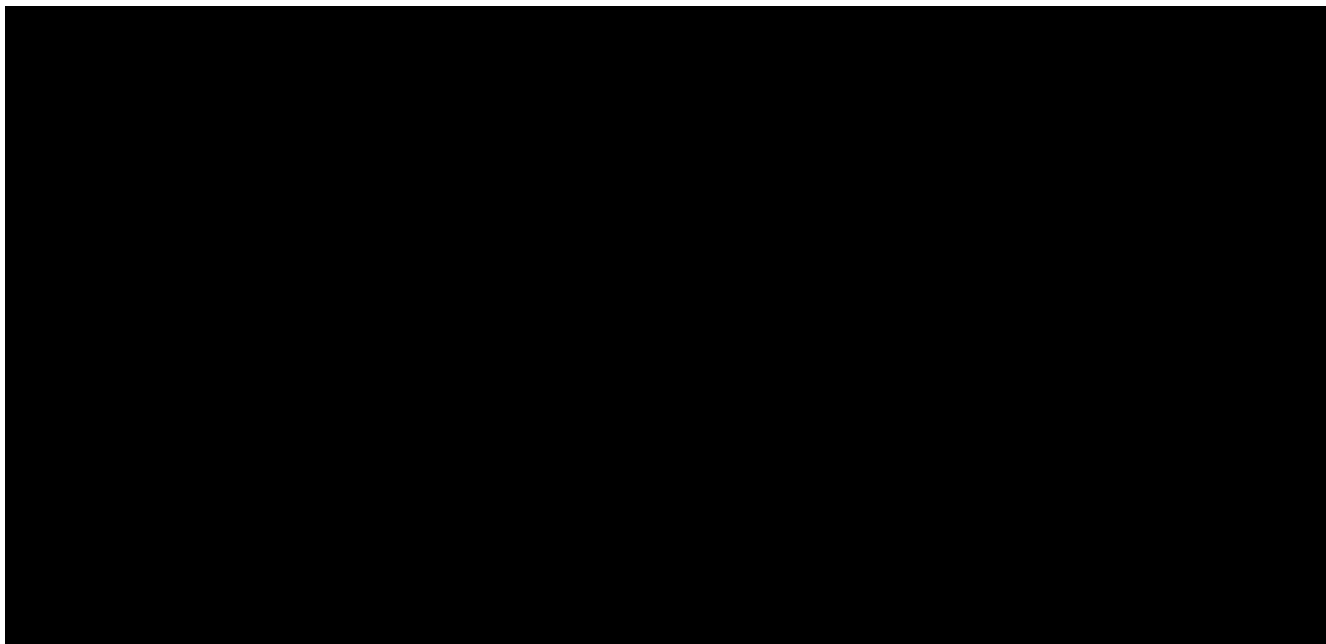


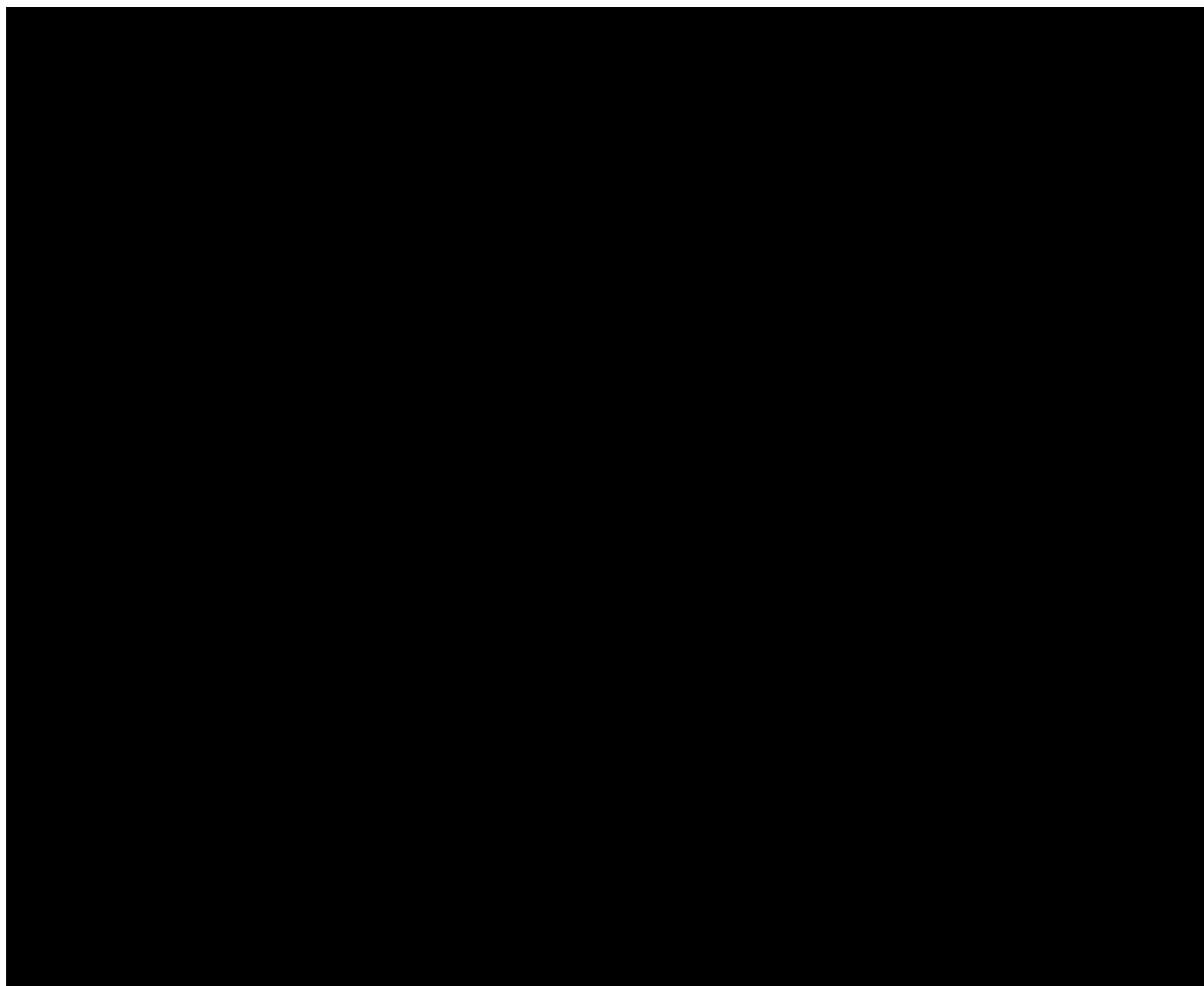


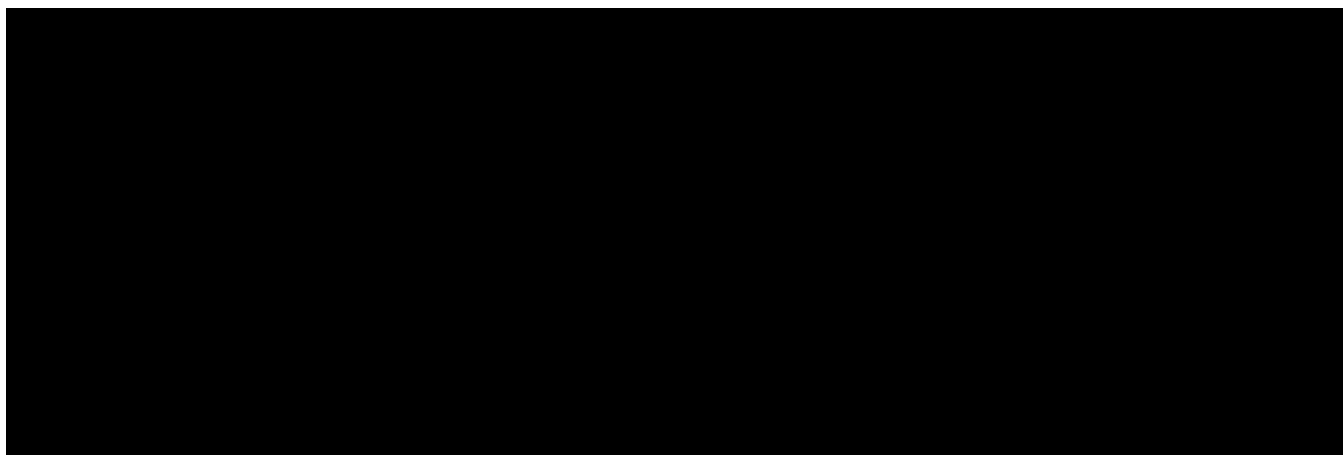


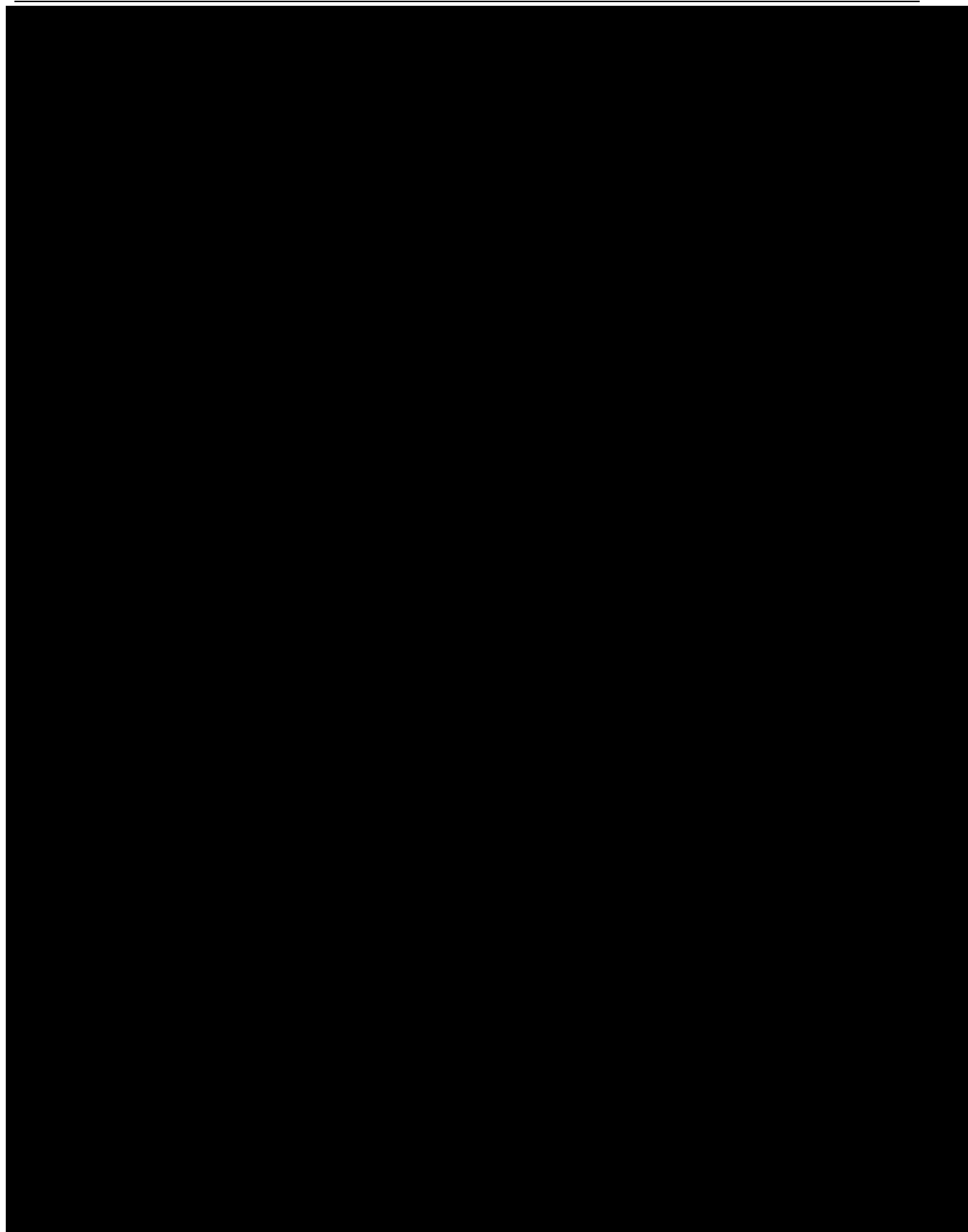
| | | | | | | | | | | |
|--|--|--|--|--|--|--|--|--|--|--|
| | | | | | | | | | | |
|--|--|--|--|--|--|--|--|--|--|--|

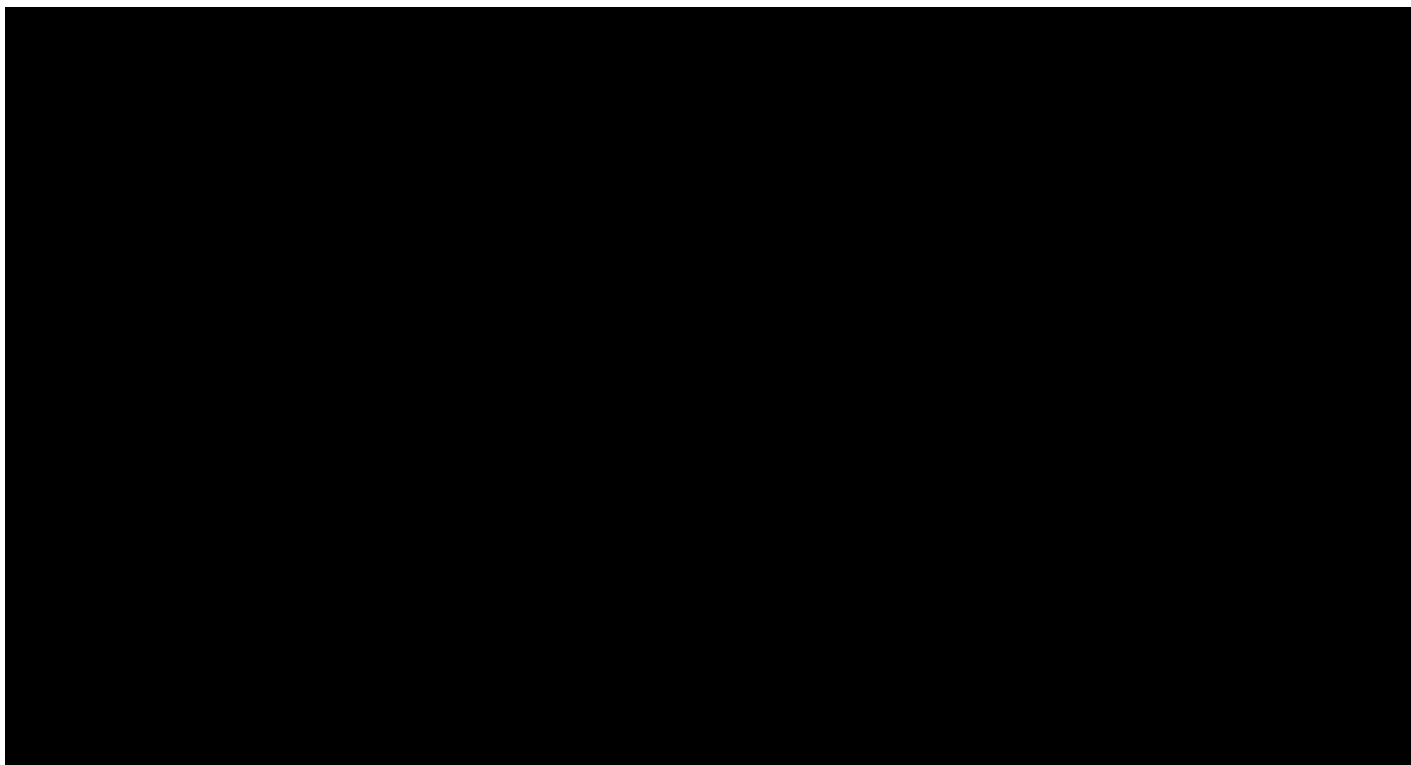


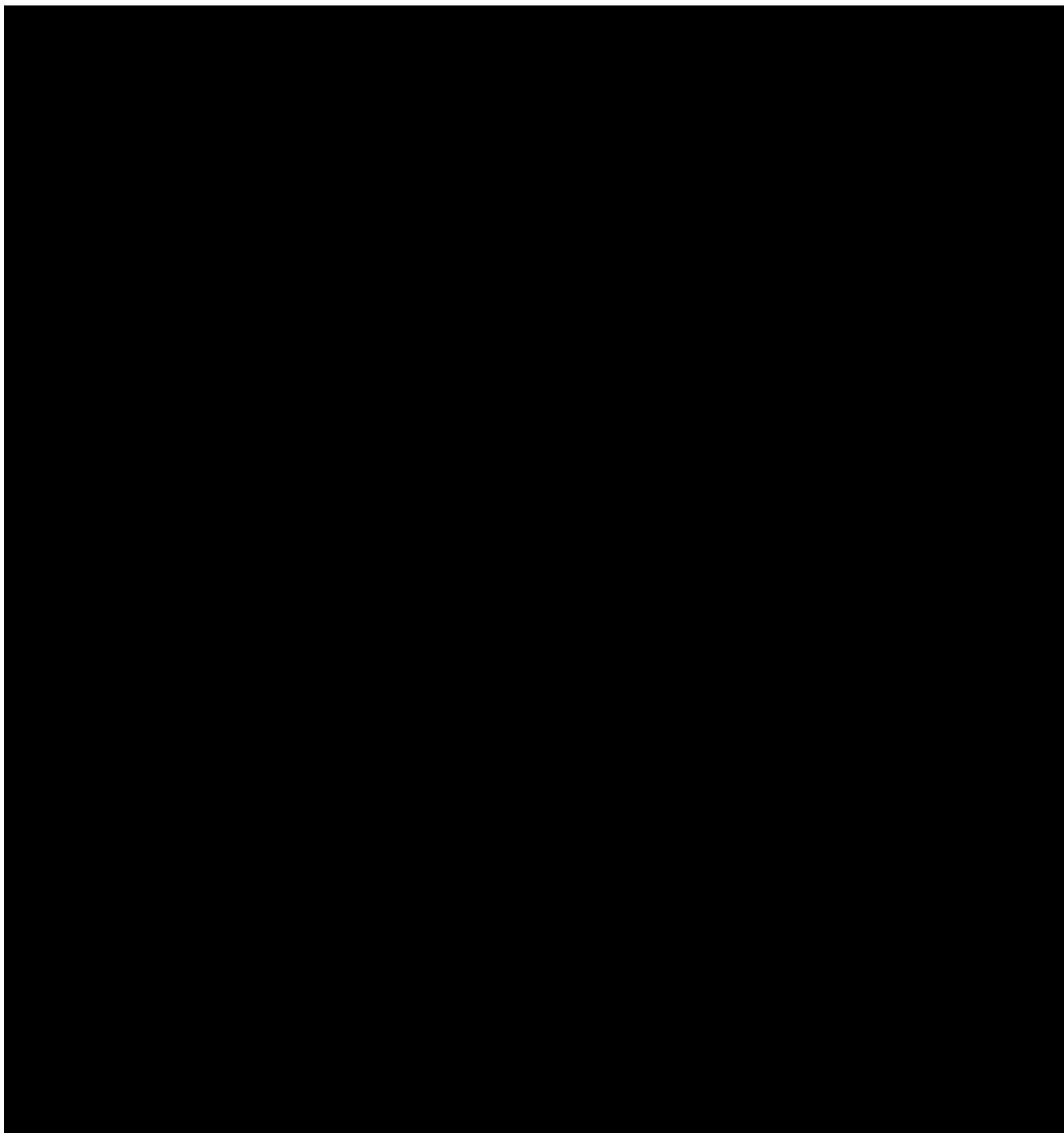


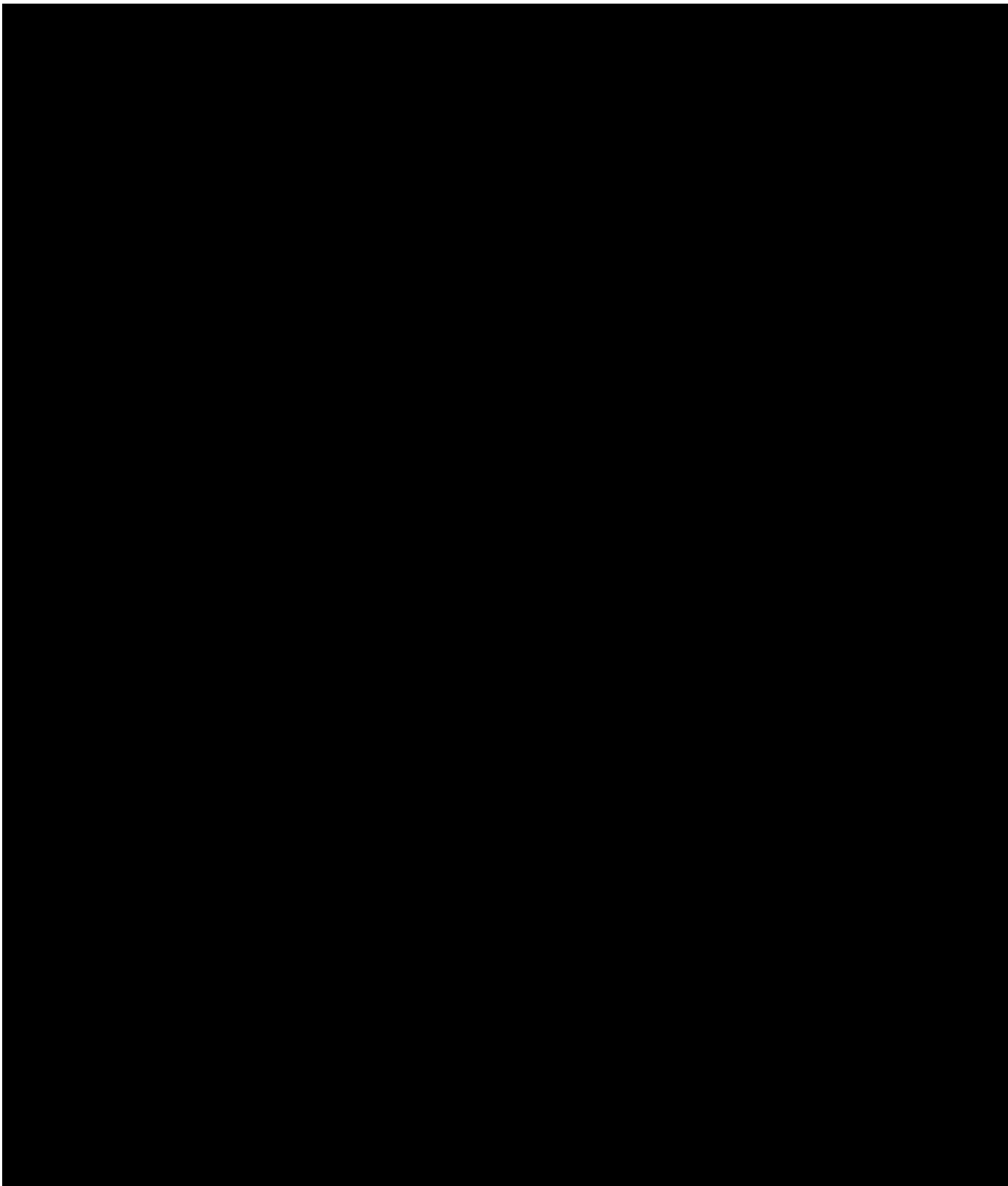


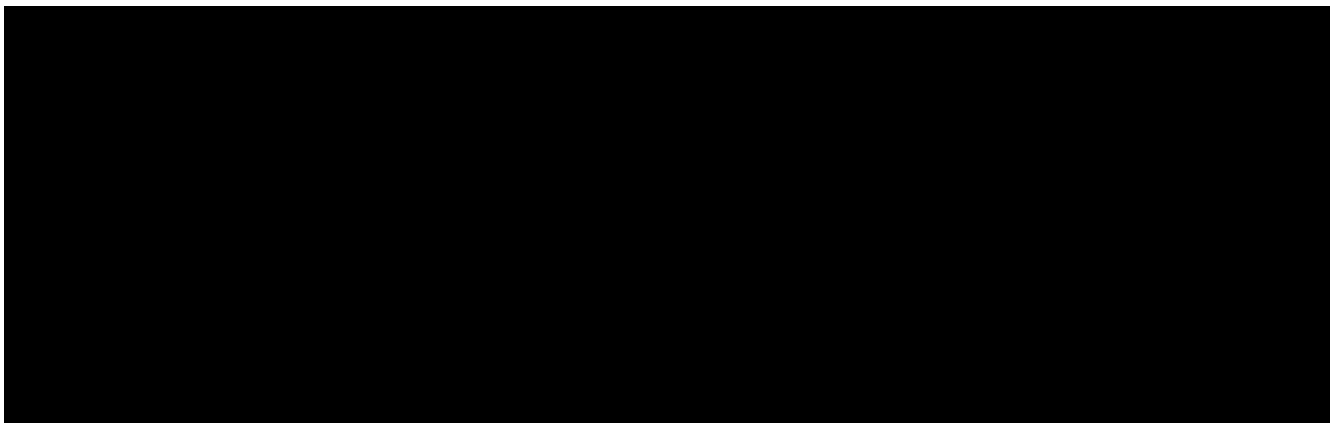


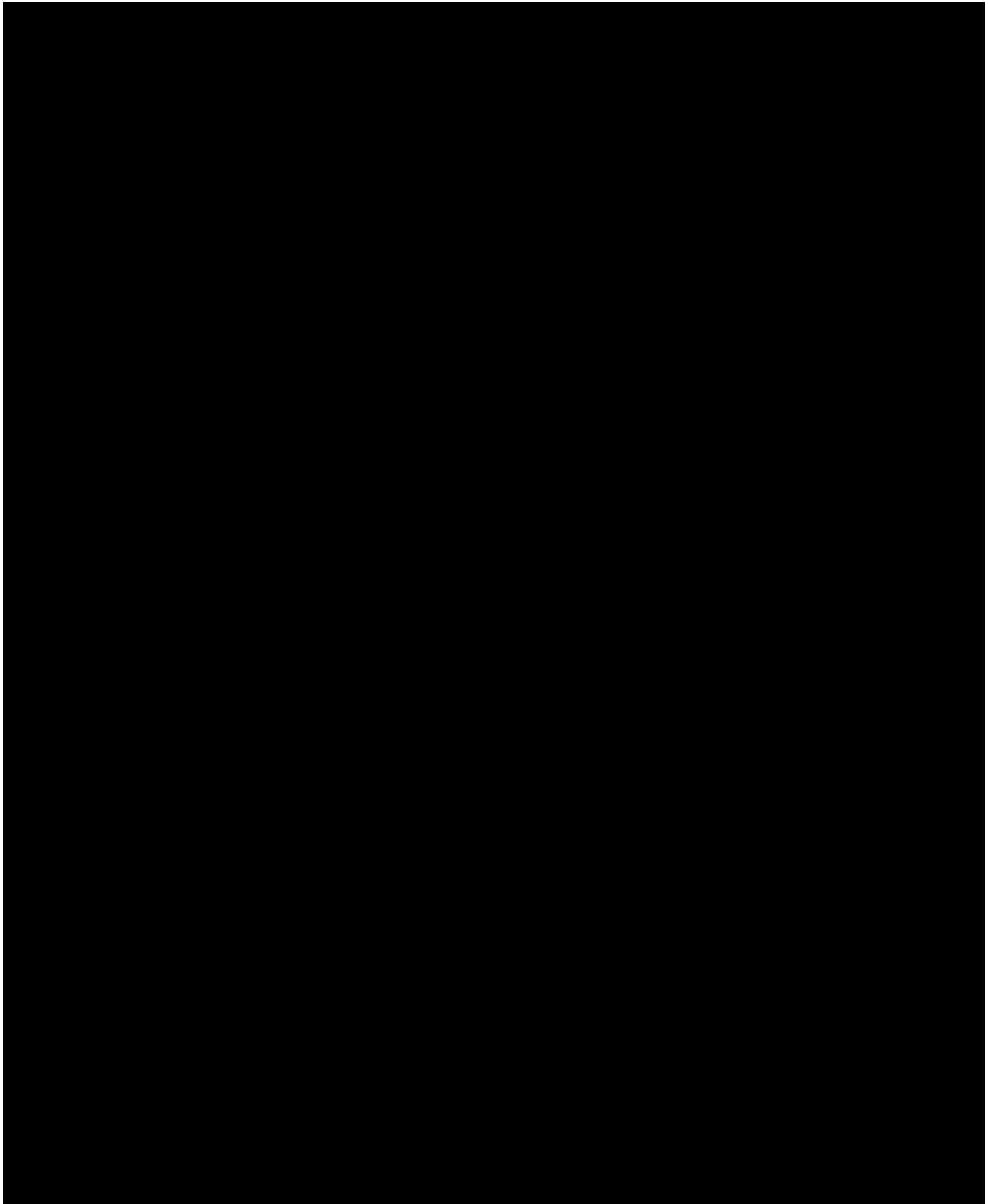


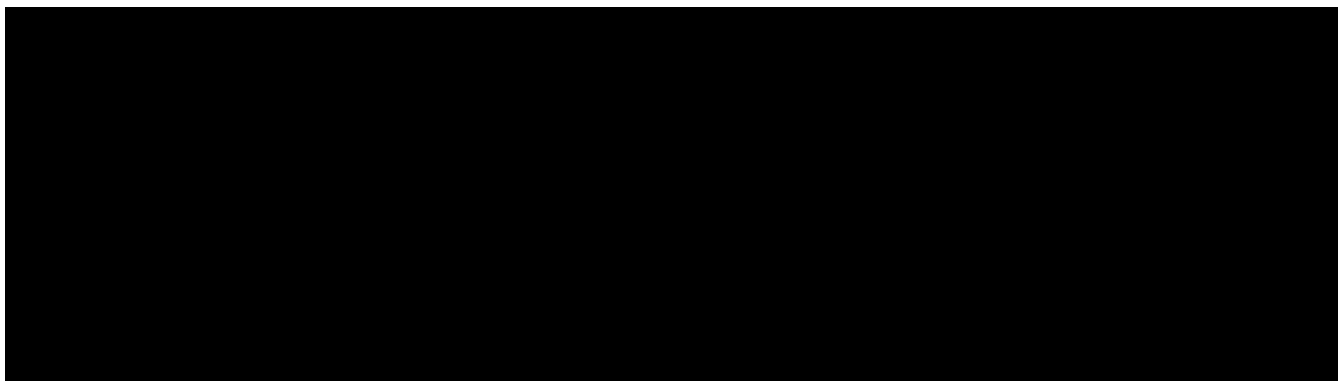


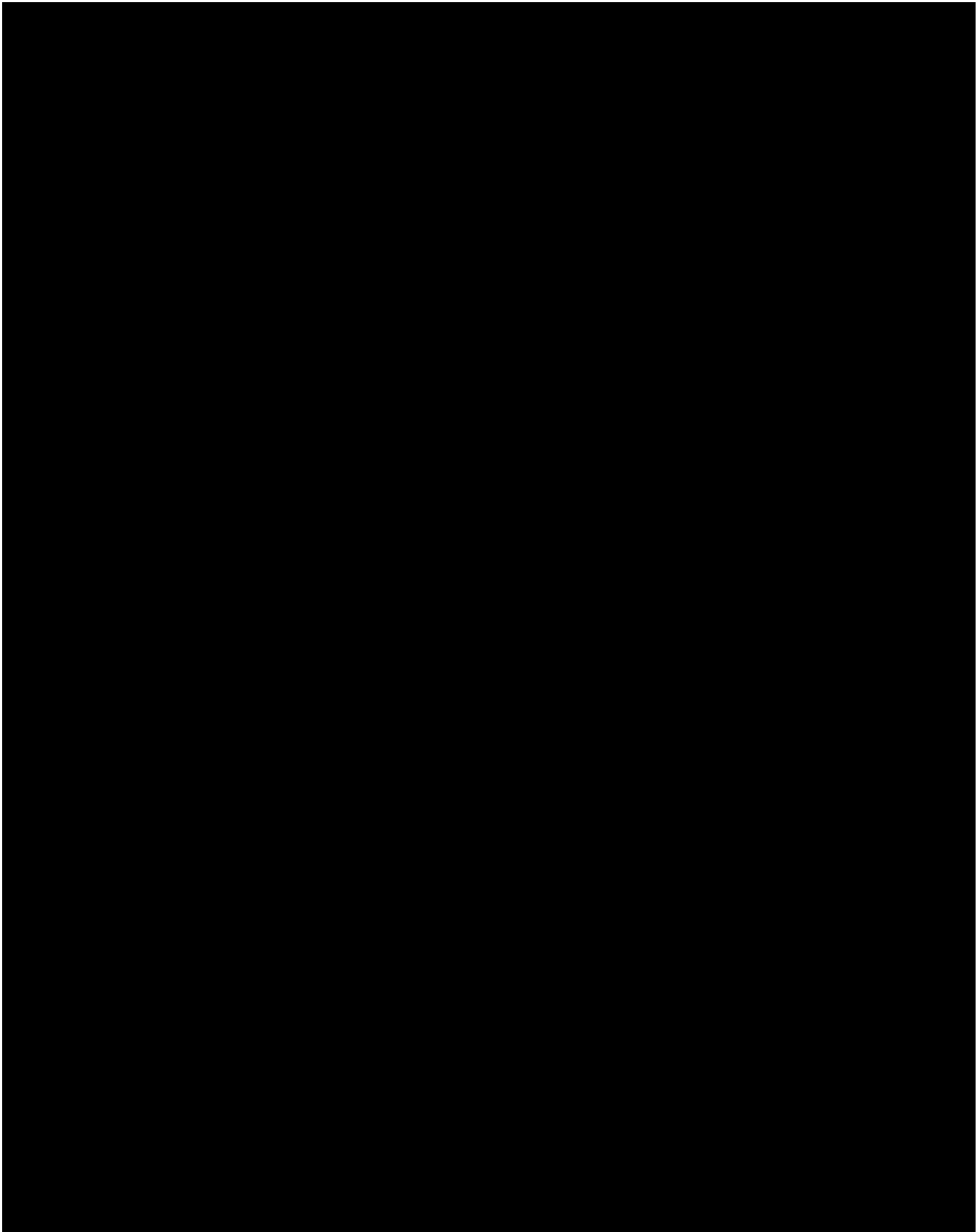


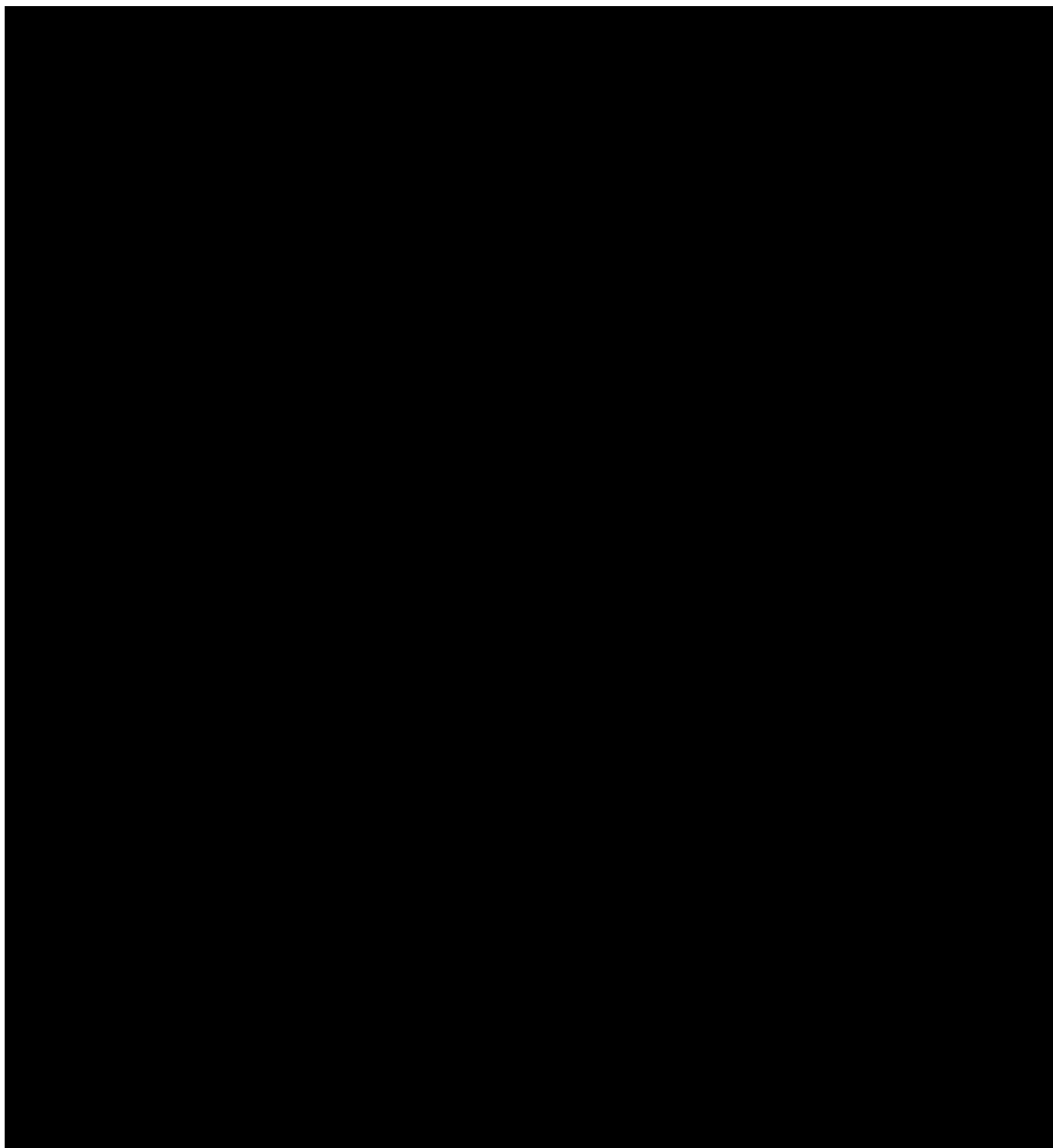


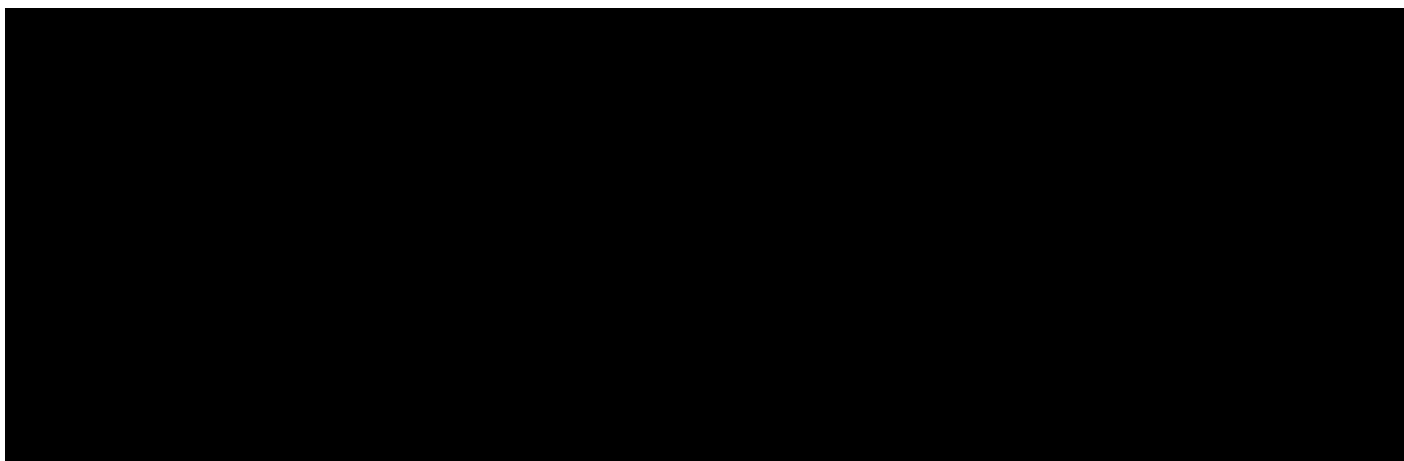


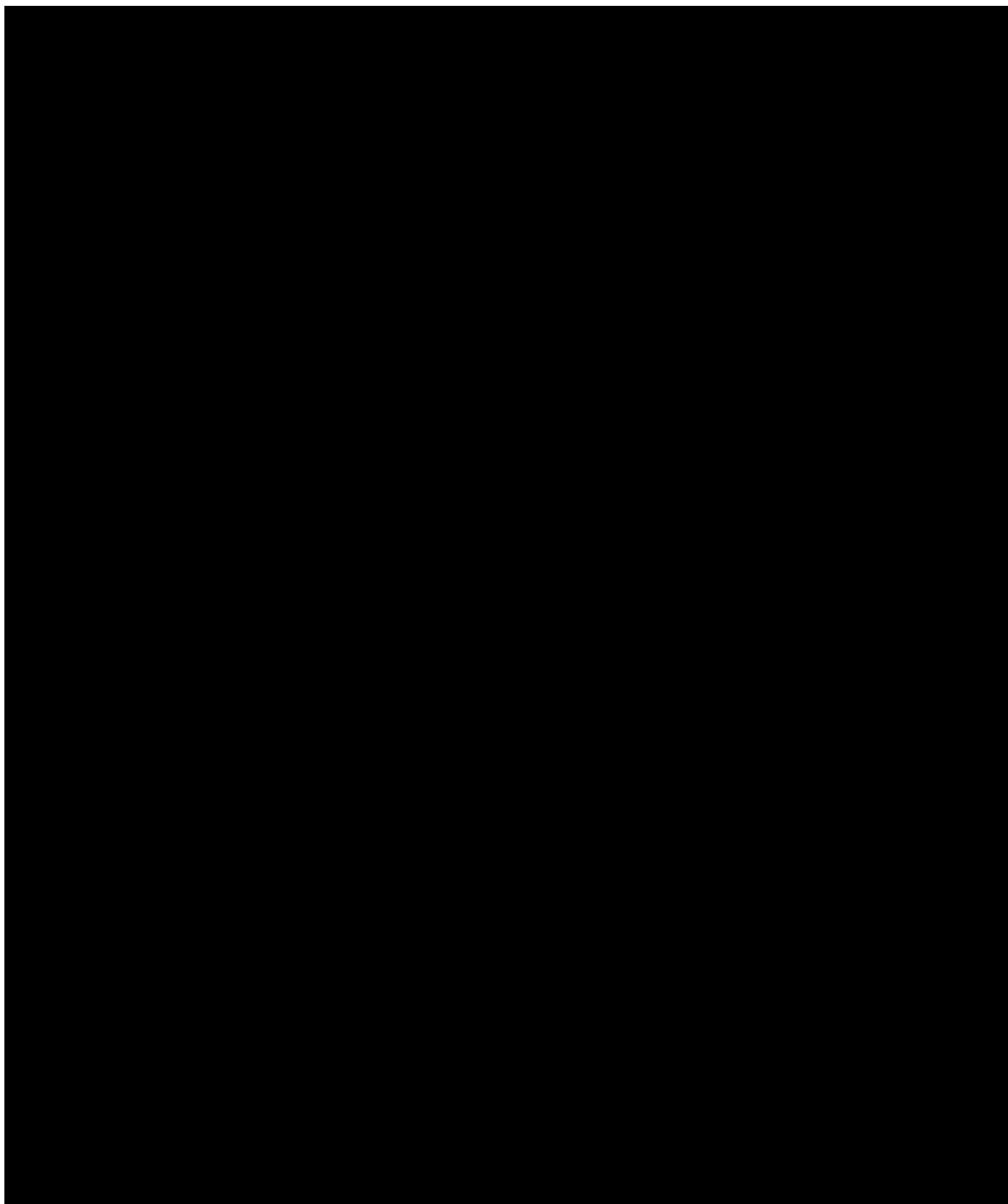


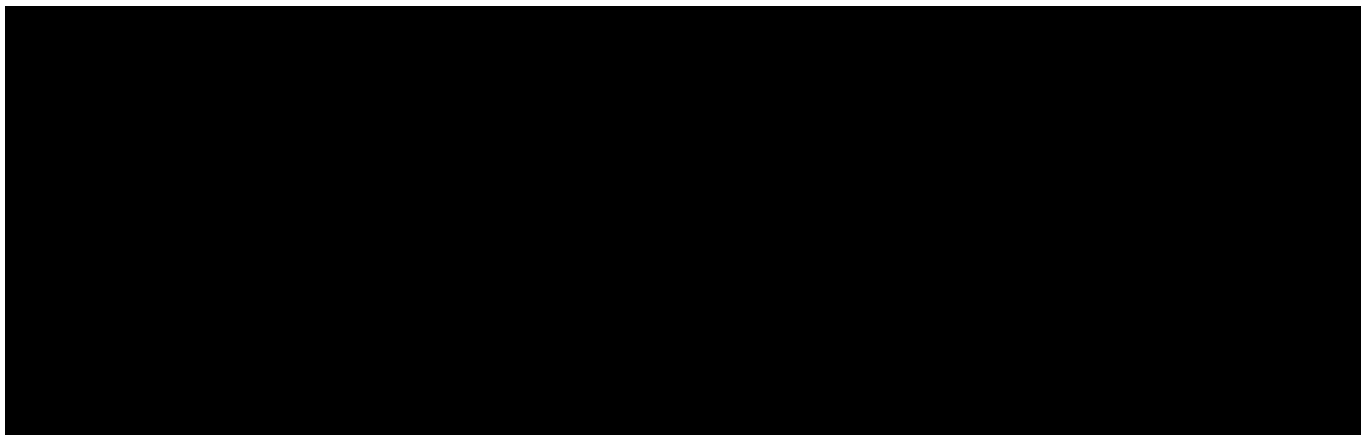


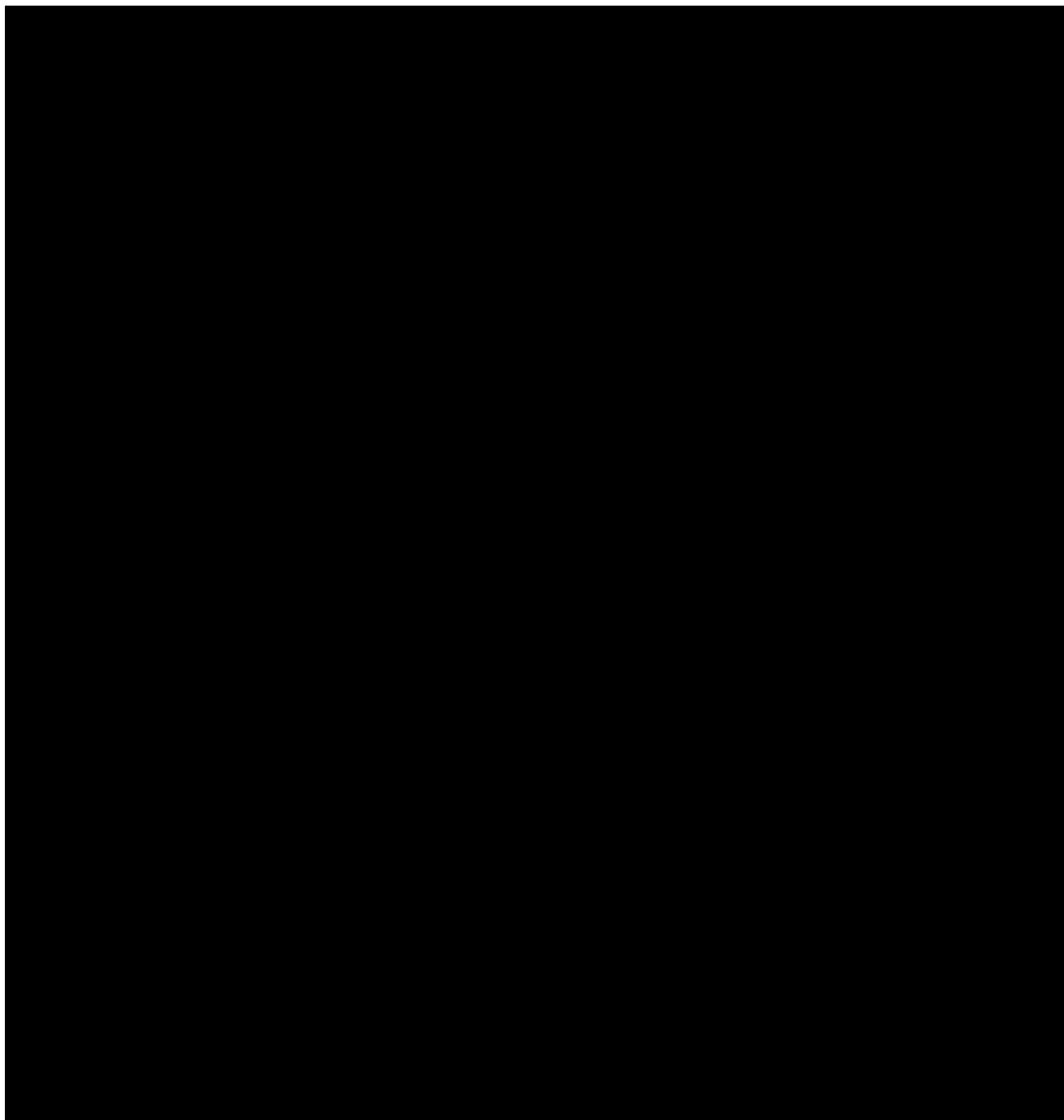


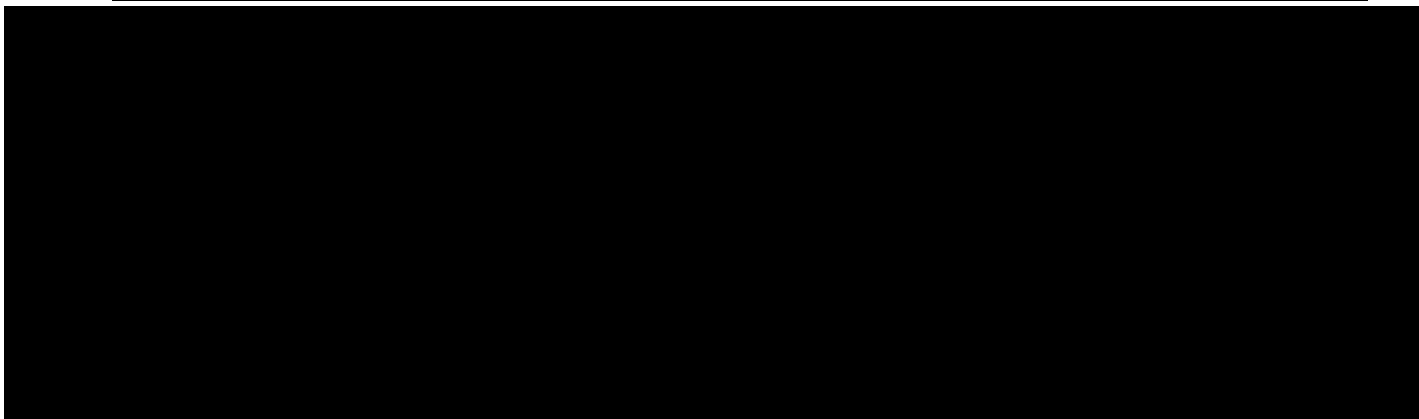


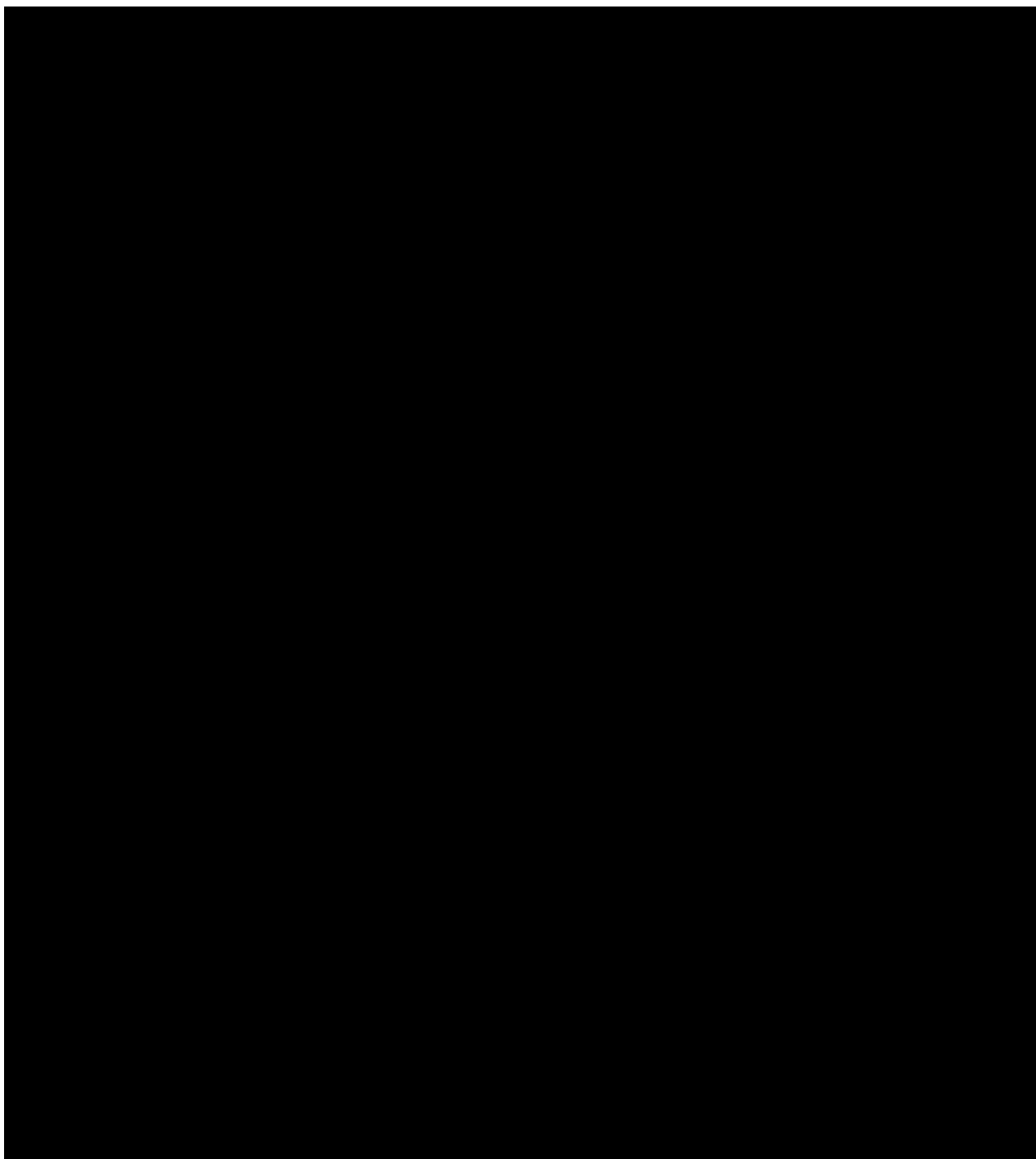


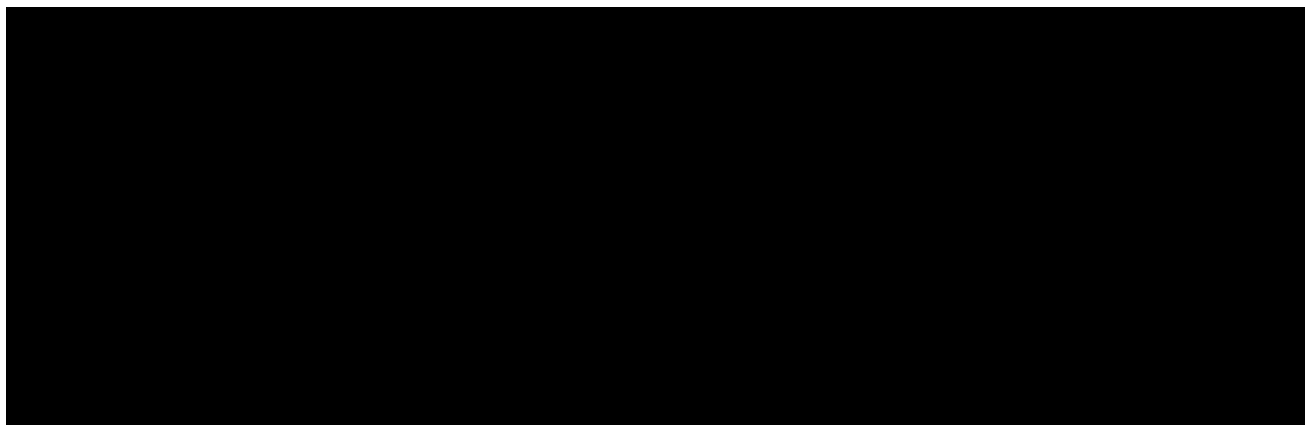


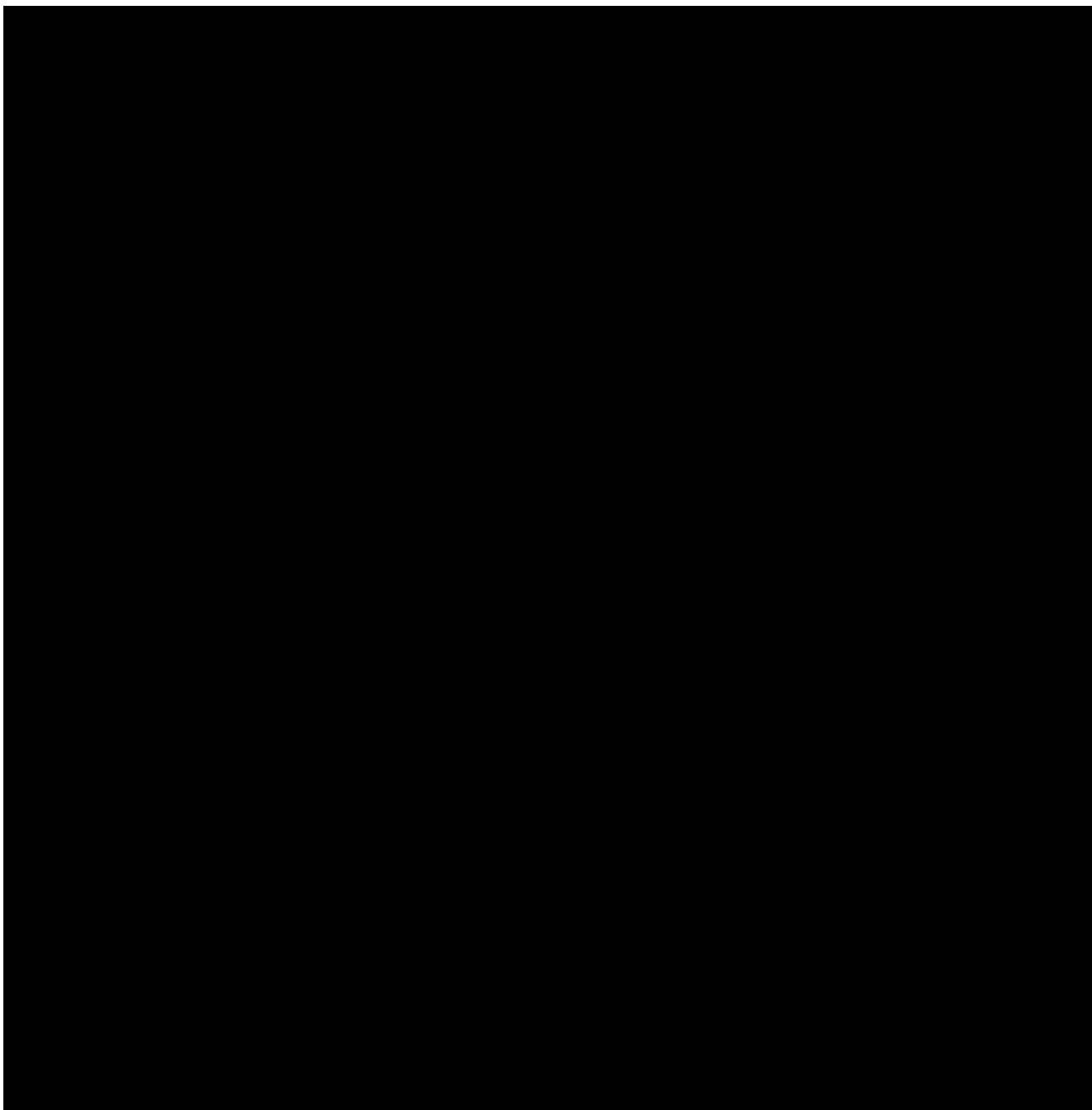


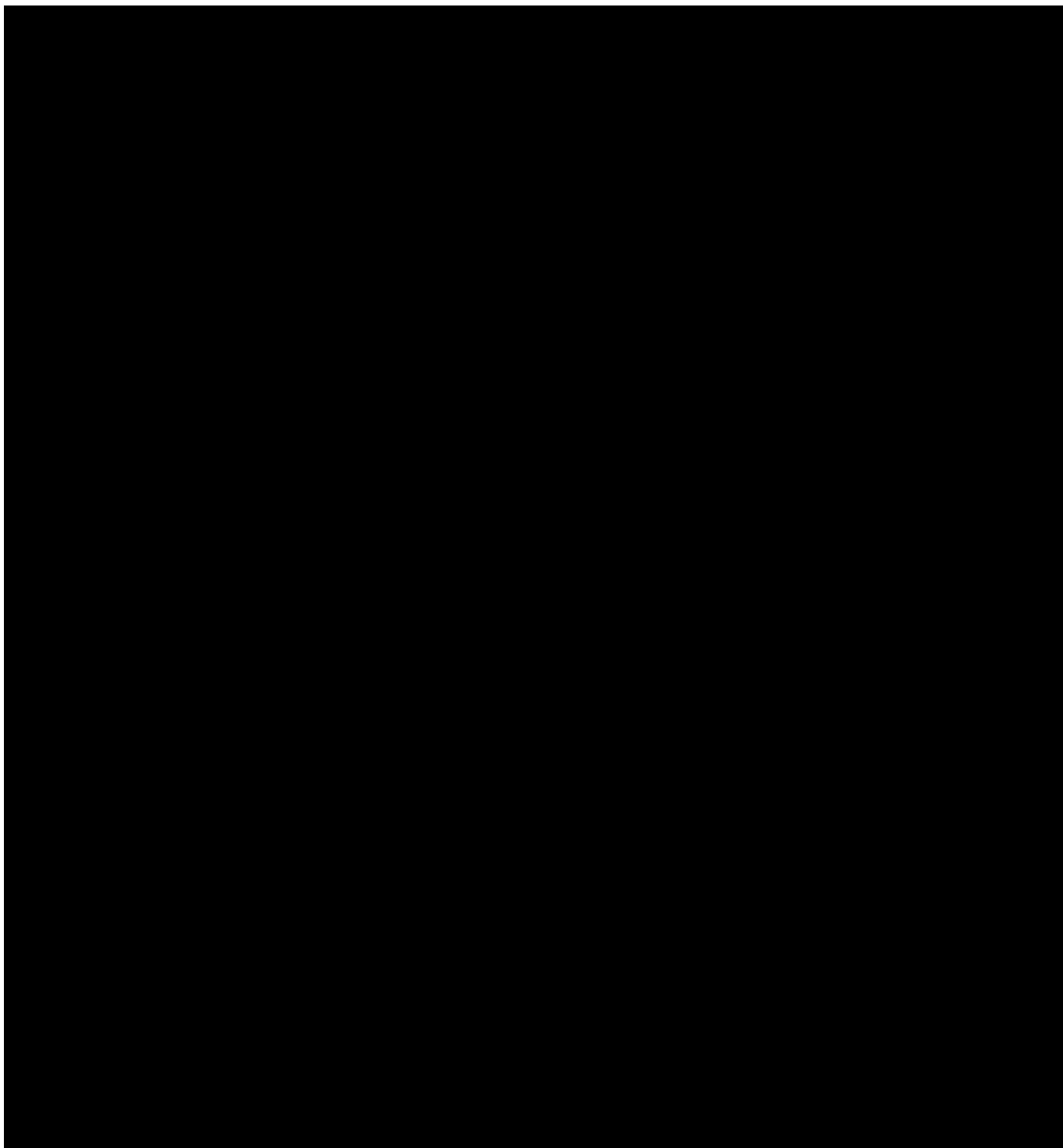


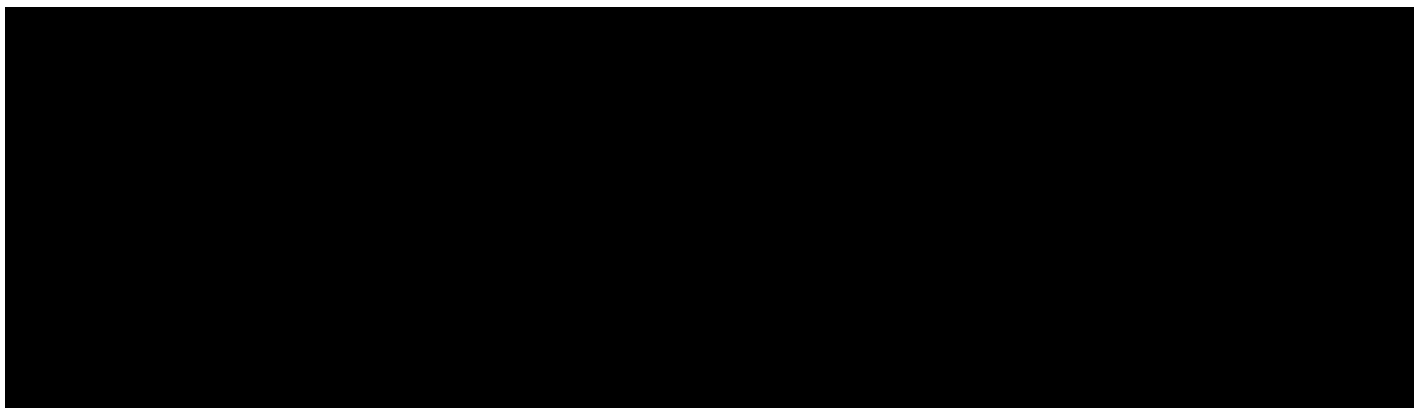


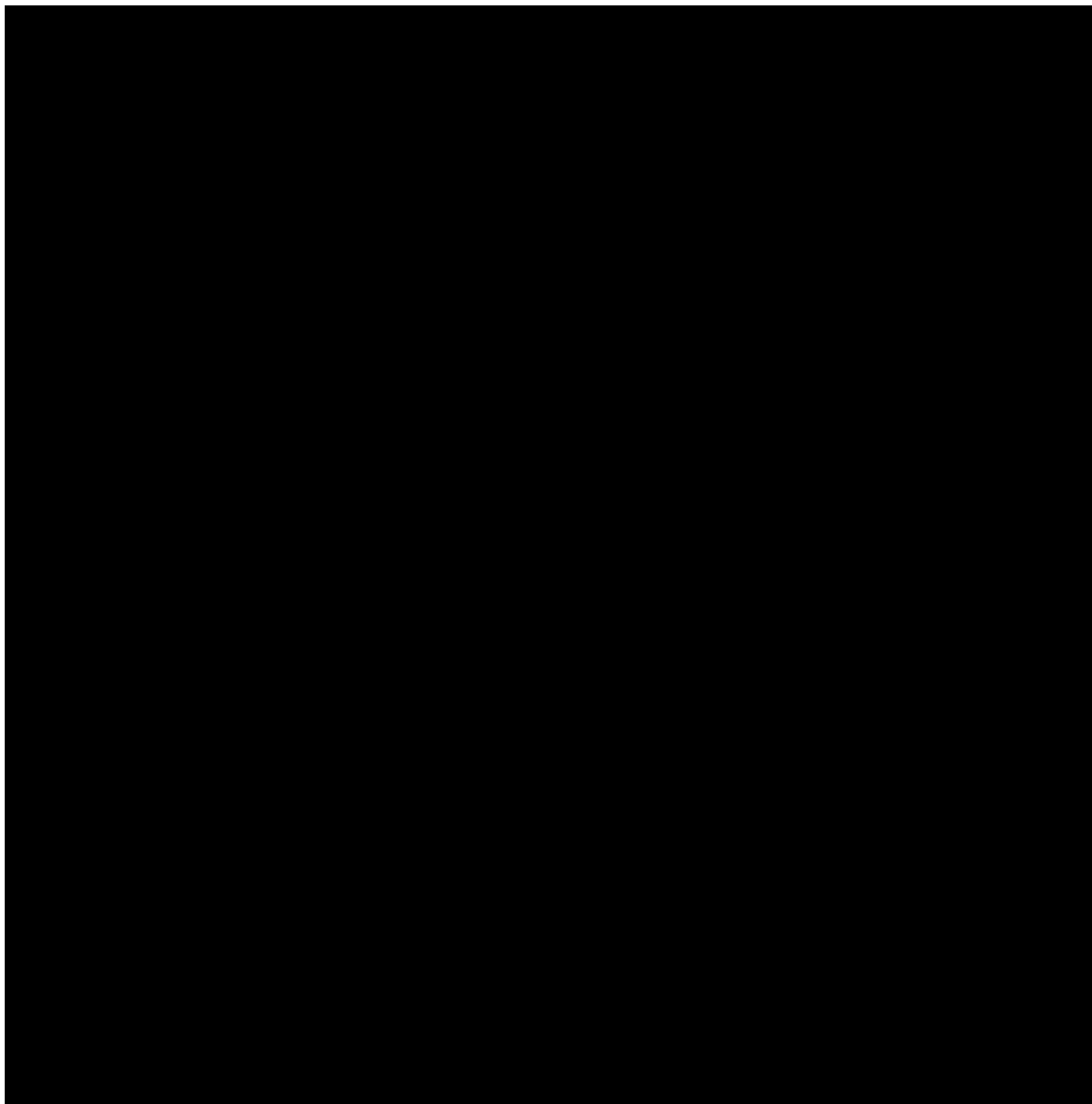


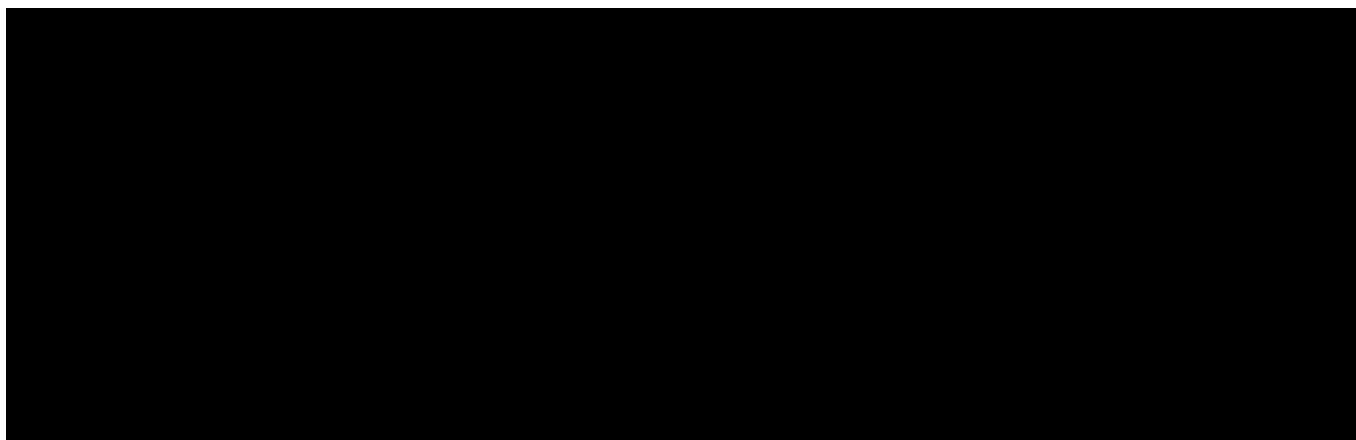


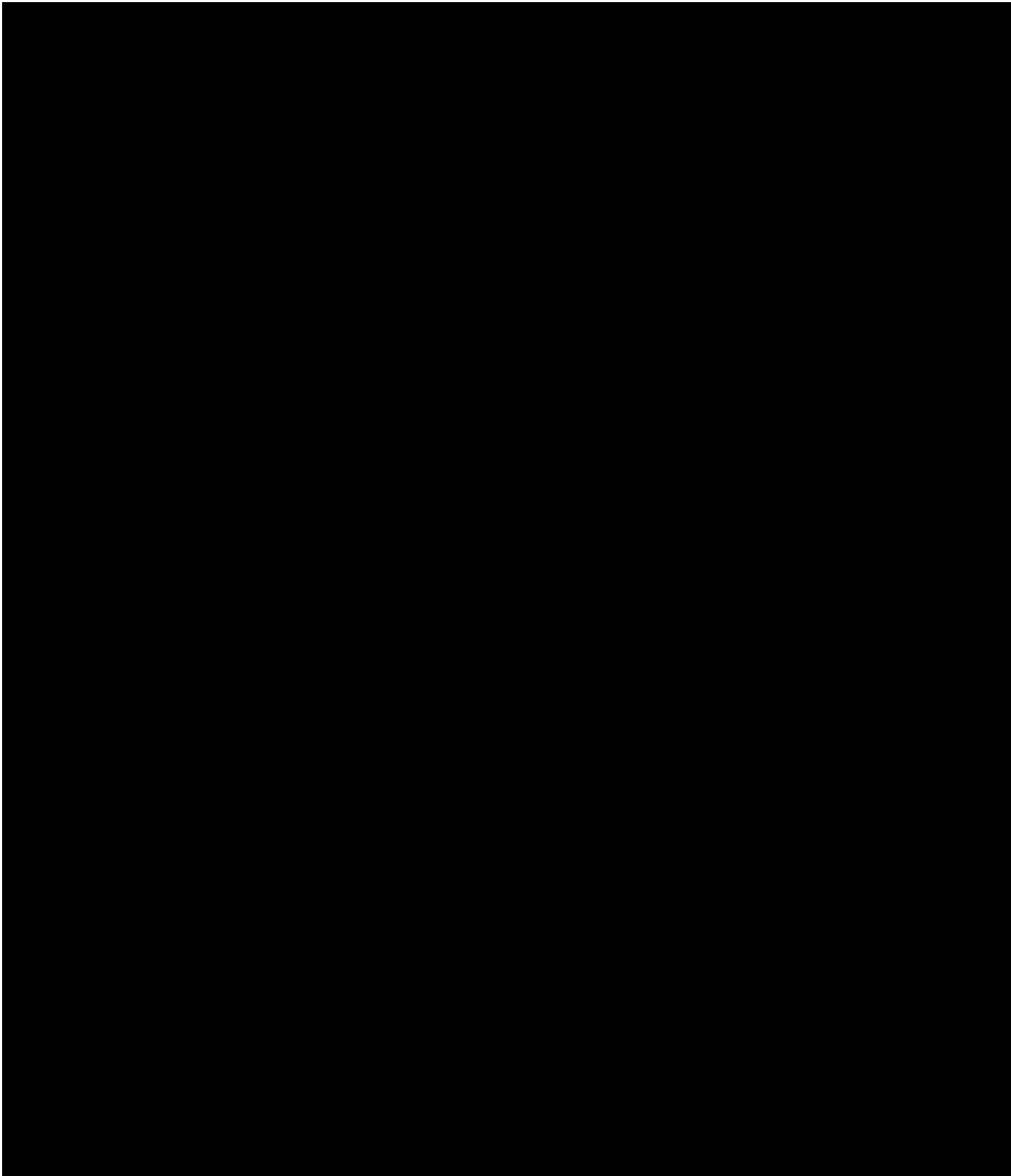


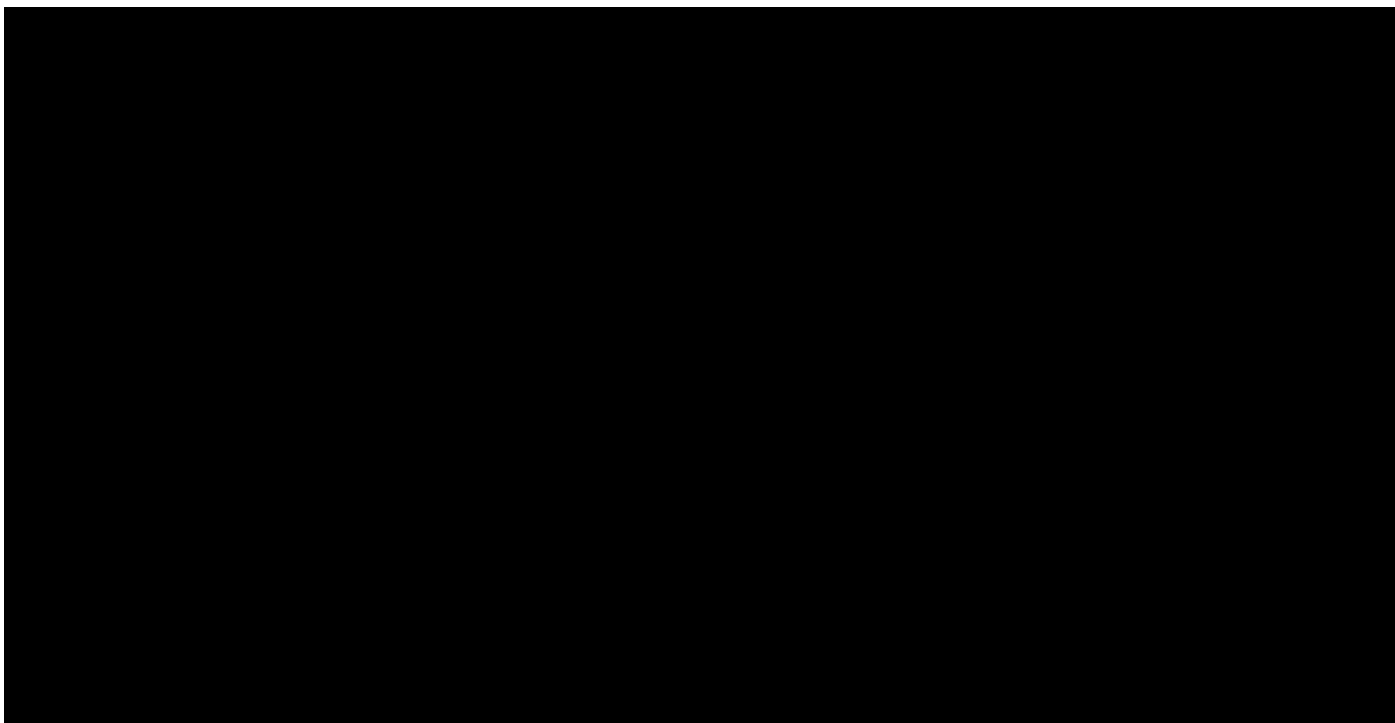










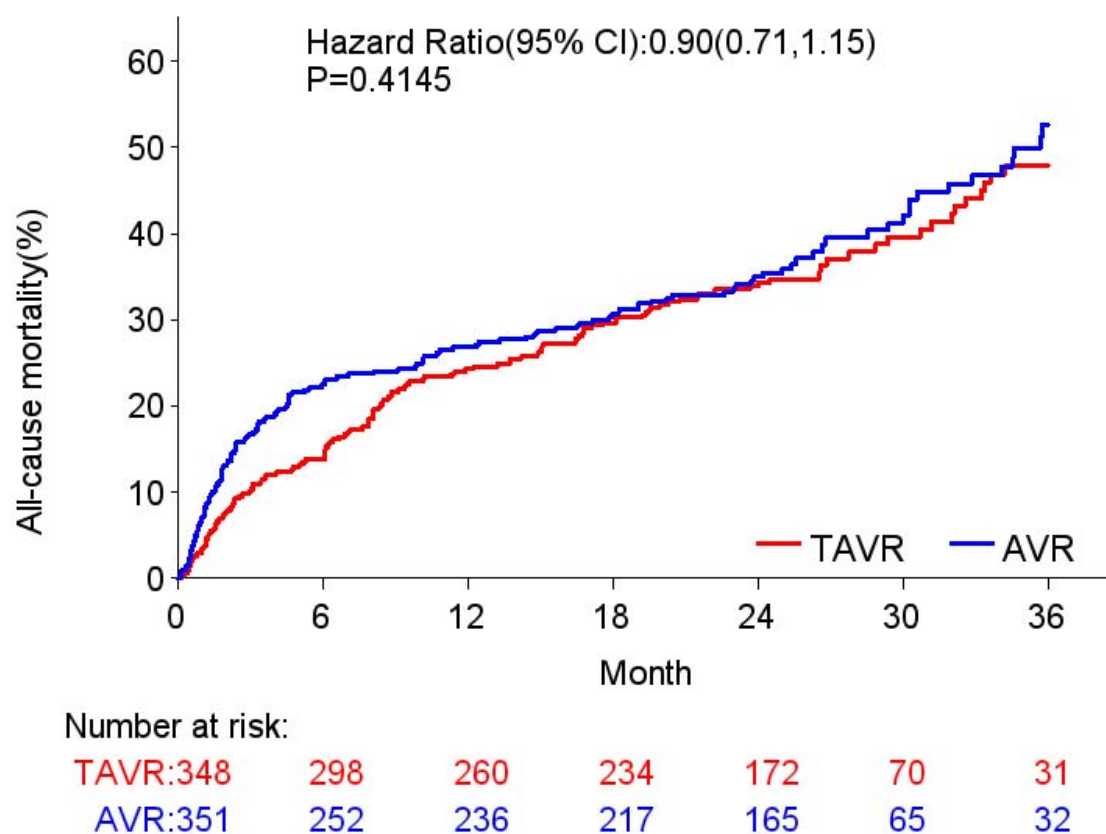




Appendix H. Kaplan Meier Figures at 3 Years

In the body of the Briefing Book, KM plots out to 24 months were provided since the analysis close date was based on the last enrolled patient with 2 years of follow-up. This appendix present all Kaplan Meier estimates out to 3 years since 3 year data have been presented and are in the public domain.

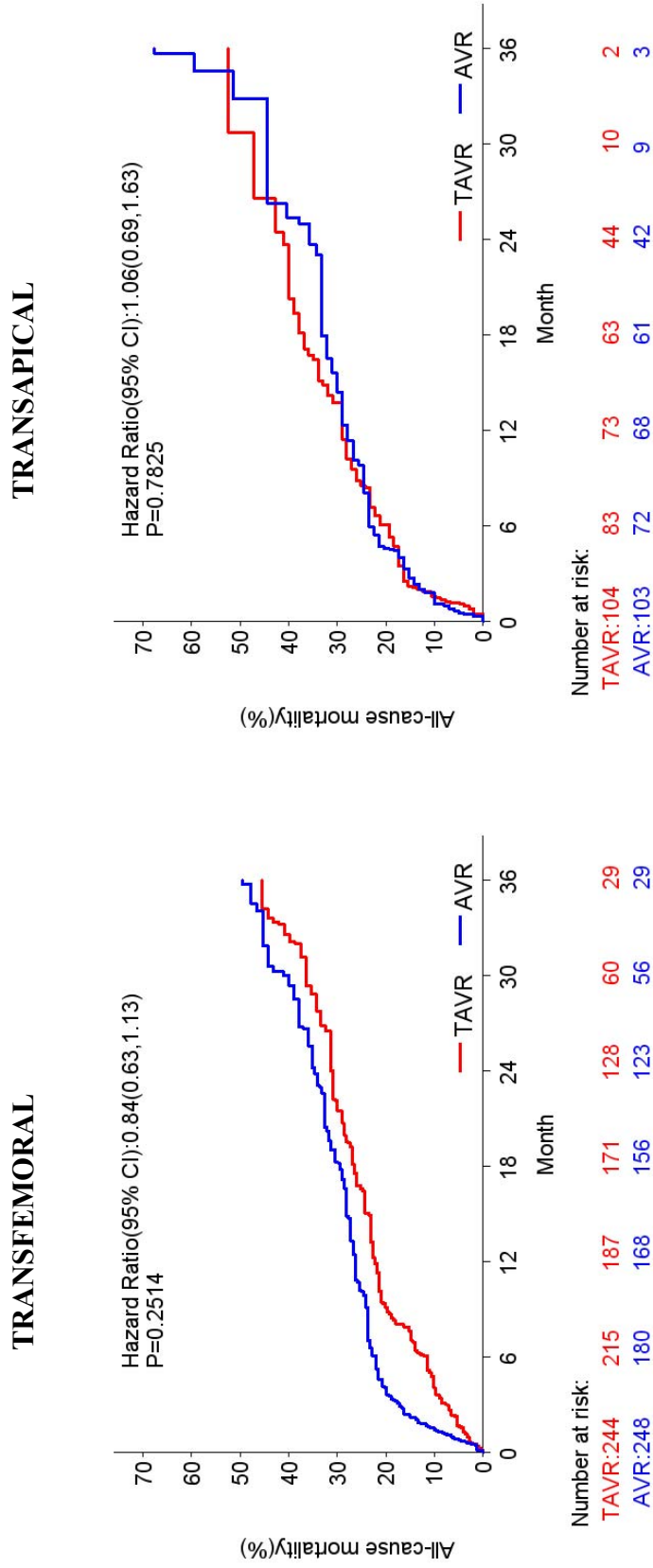
Figure 46. All Cause Mortality at 3 Years - High Risk Cohort in the PARTNER Randomized Study (ITT Population)



Hazard ratio at 3 years; p-value from log-rank test up to 36 months



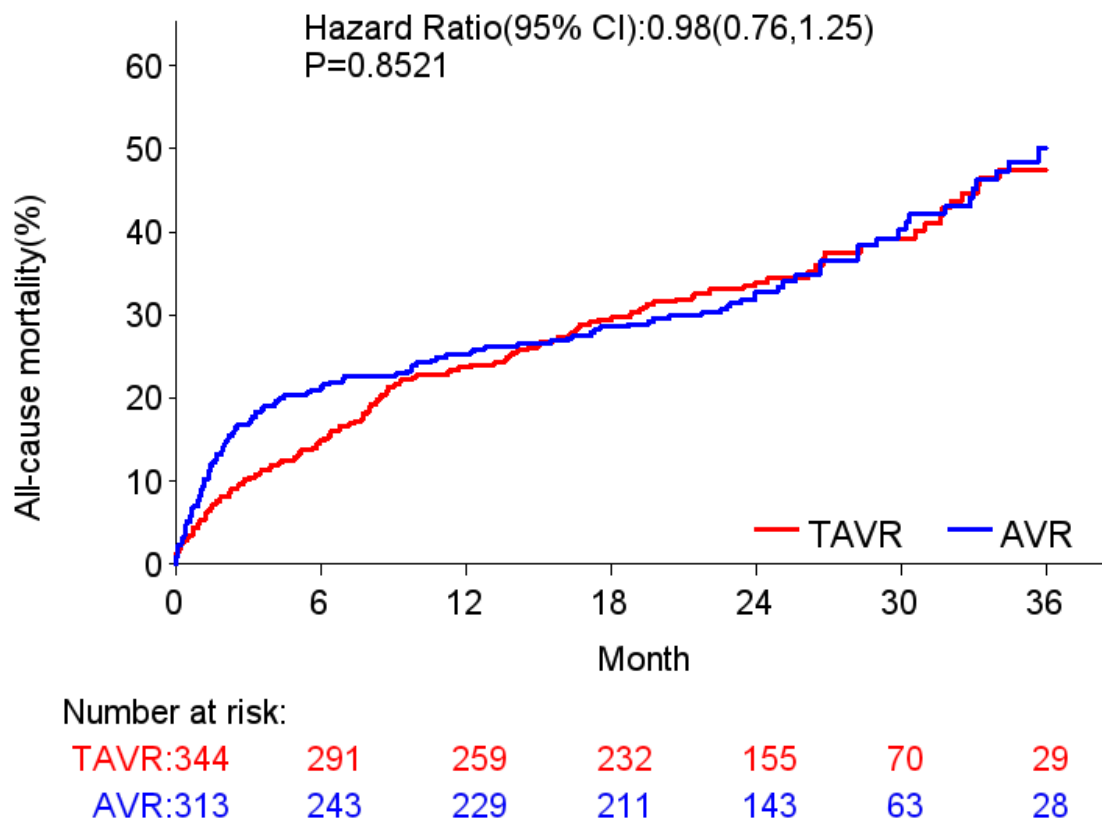
Figure 47. All Cause Mortality by Implant Approach at 3 Years – High Risk Cohort in the PARTNER Randomized Study (ITT Population)



Hazard ratio at 3 years; p-value from log-rank test up to 36 months



Figure 48. All Cause Mortality at 3 Years – High Risk Cohort in the PARTNER Study (AT Population)



Hazard ratio at 3 years; p-value from log-rank test up to 36 months



Figure 49. Myocardial Infarction at 3 Years – High Risk Cohort in the PARTNER Study (ITT Population)

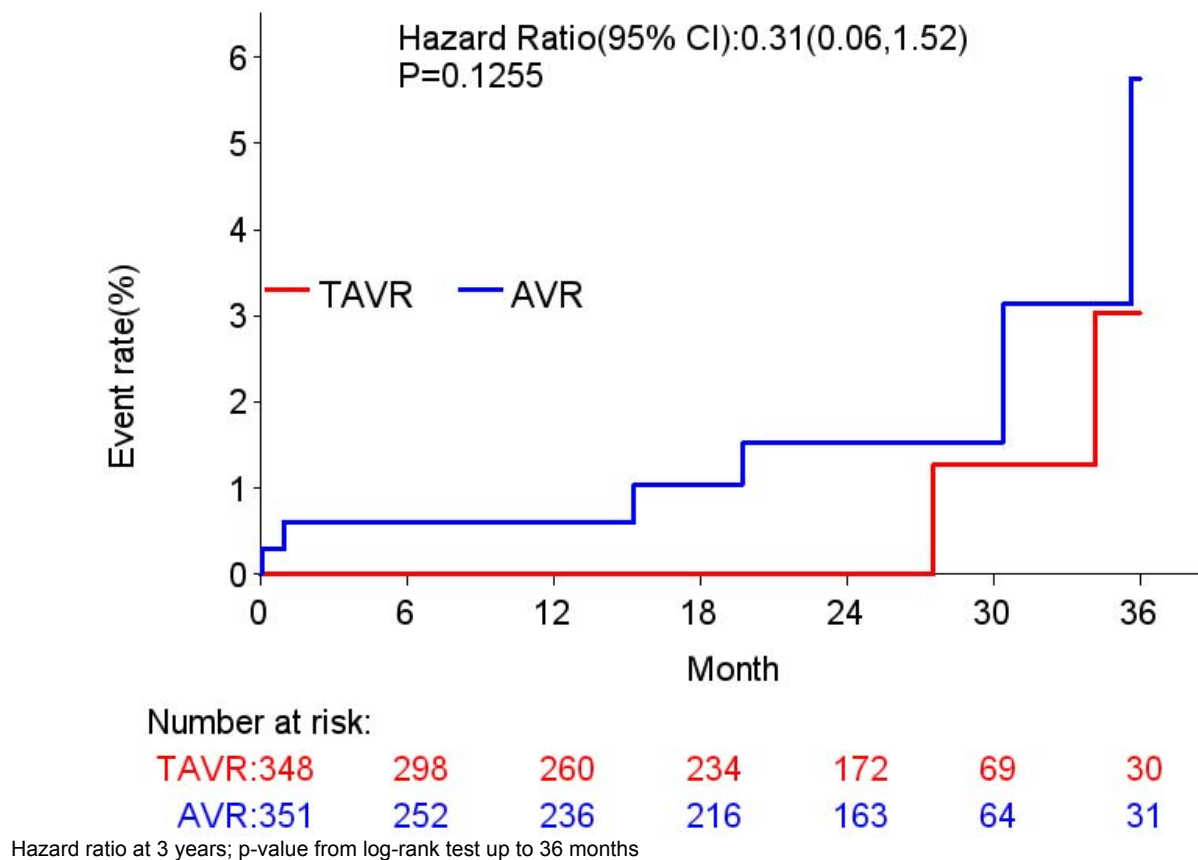




Figure 50. Renal Failure at 3 Years – High Risk Cohort in the PARTNER Study (ITT Population)

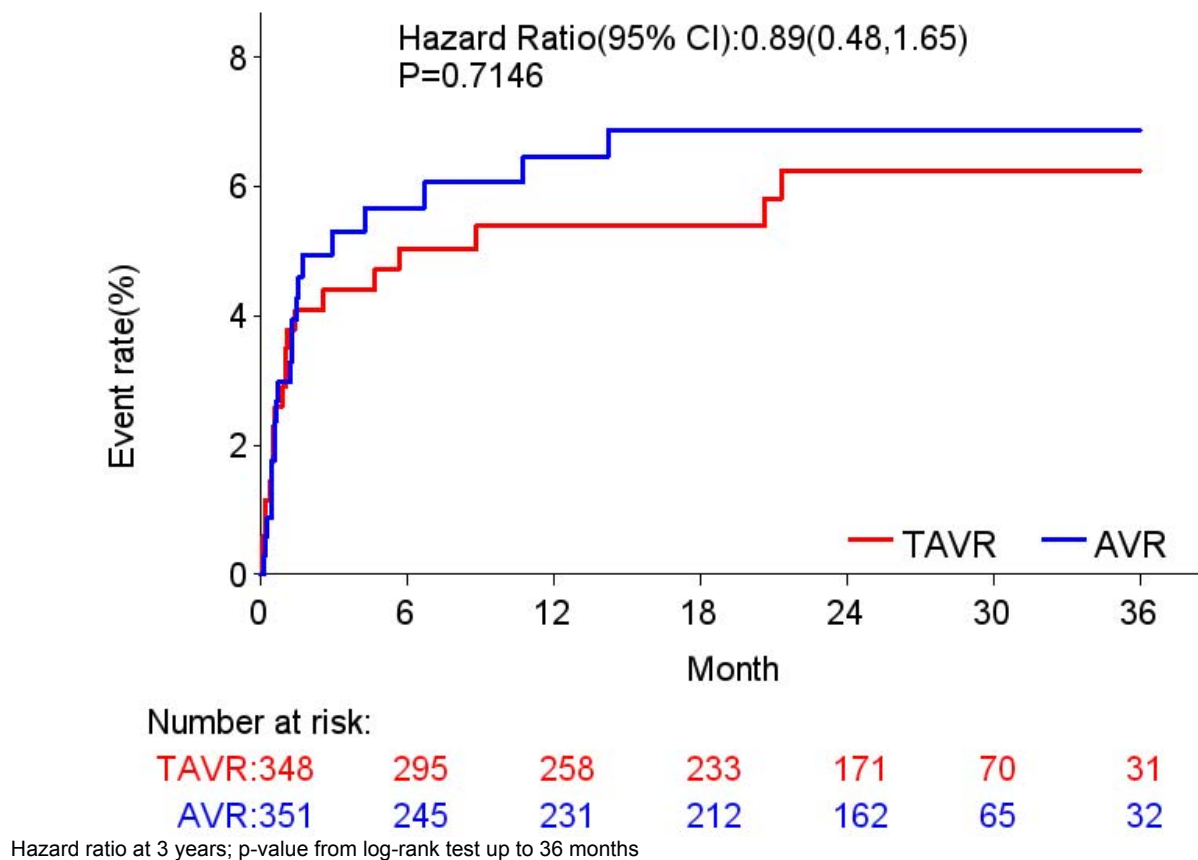
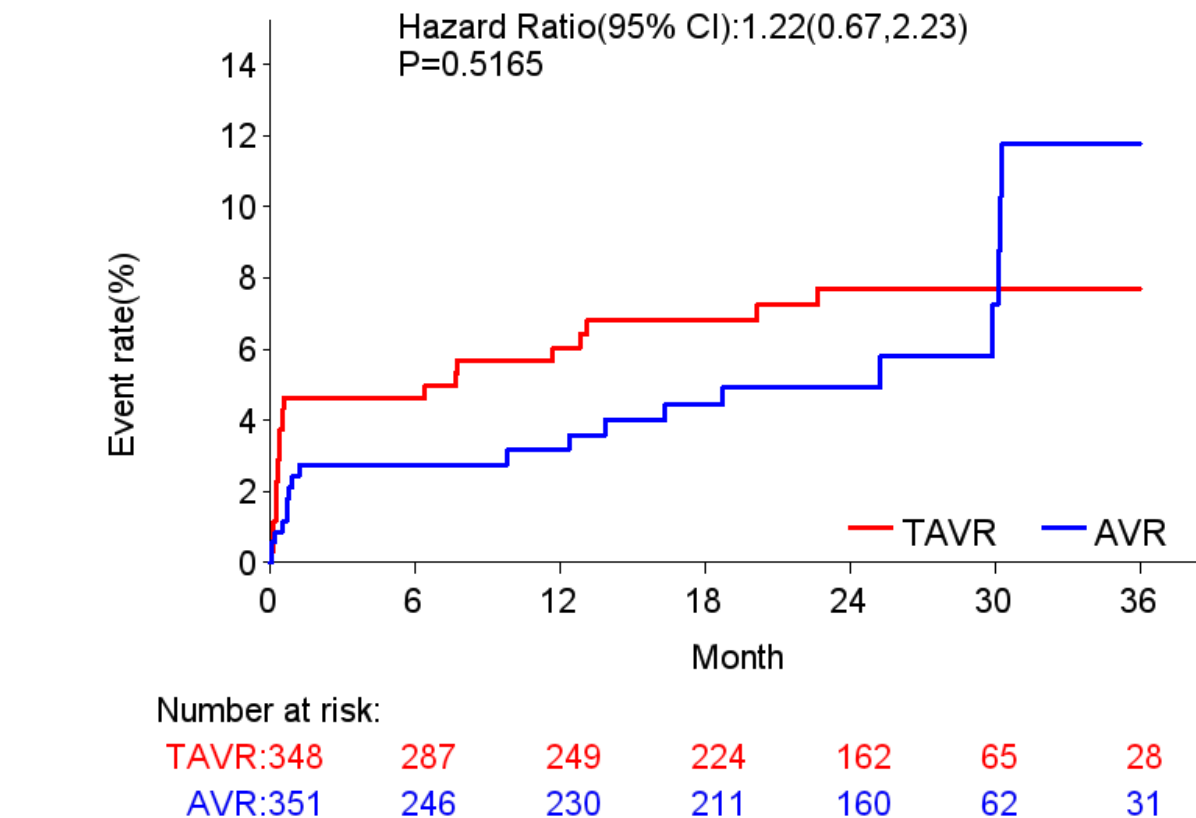




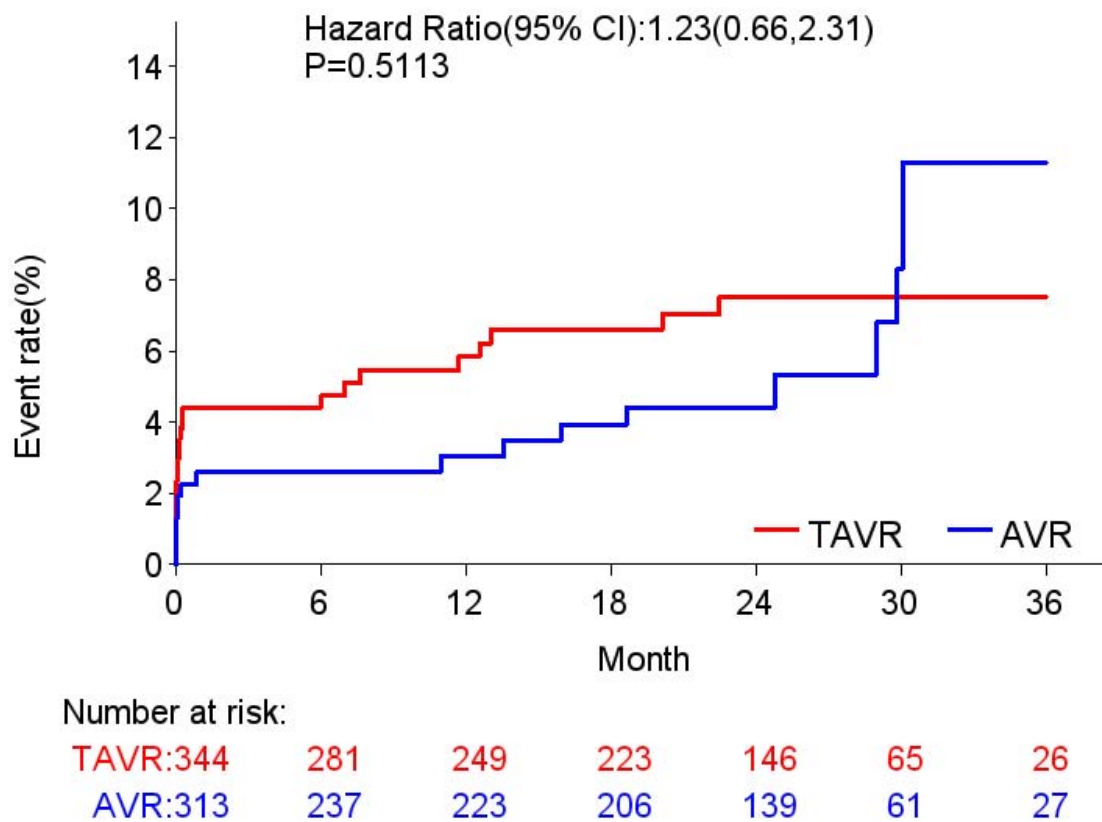
Figure 51. Stroke at 3 Years – High Risk Cohort in the PARTNER Study (ITT Population)



Hazard ratio at 3 years; p-value from log-rank test up to 36 months



Figure 52. Stroke at 3 Years – High Risk Cohort in the PARTNER Study (AT Population)



Hazard ratio at 3 years; p-value from log-rank test up to 36 months



Figure 53. Death or Stroke at 3 Years – High Risk Cohort in the PARTNER Study (AT Population)

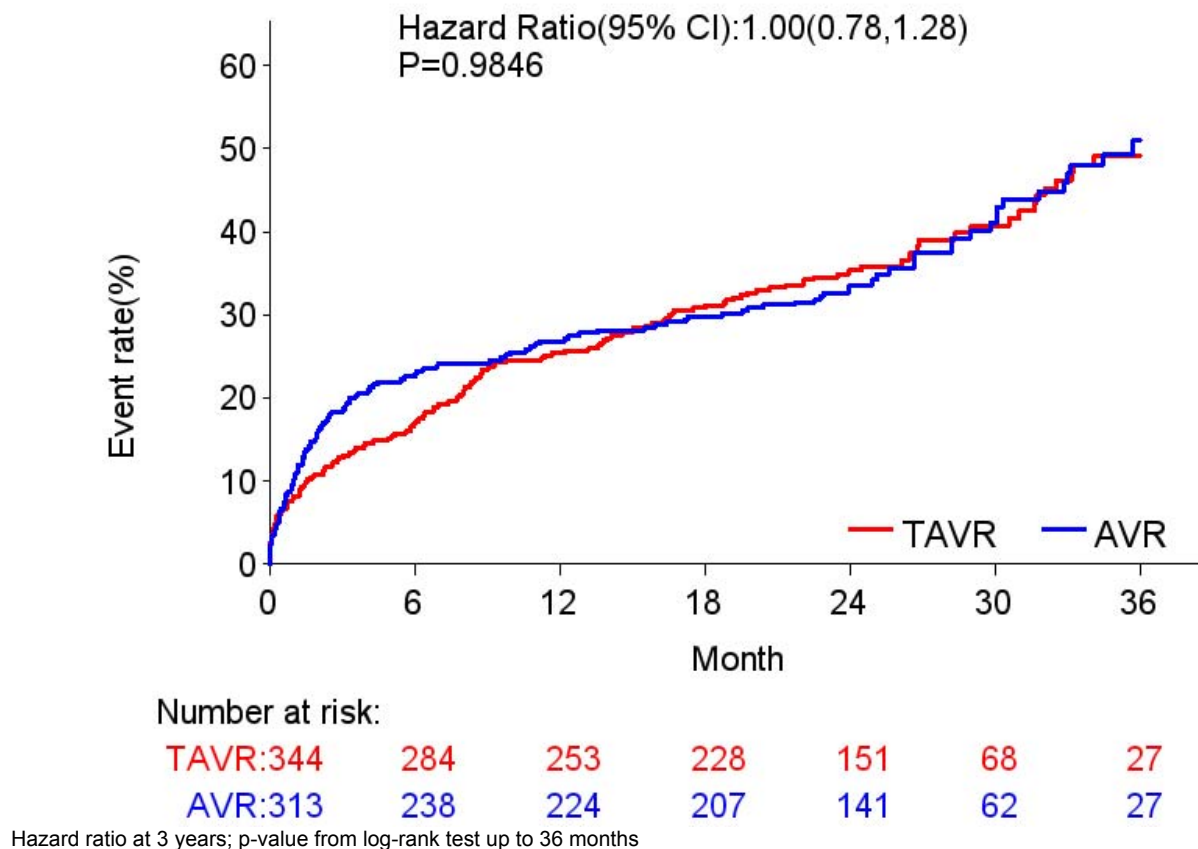




Figure 54. Cardiac Mortality at 3 Years – High Risk Cohort in the PARTNER Study (ITT Population)

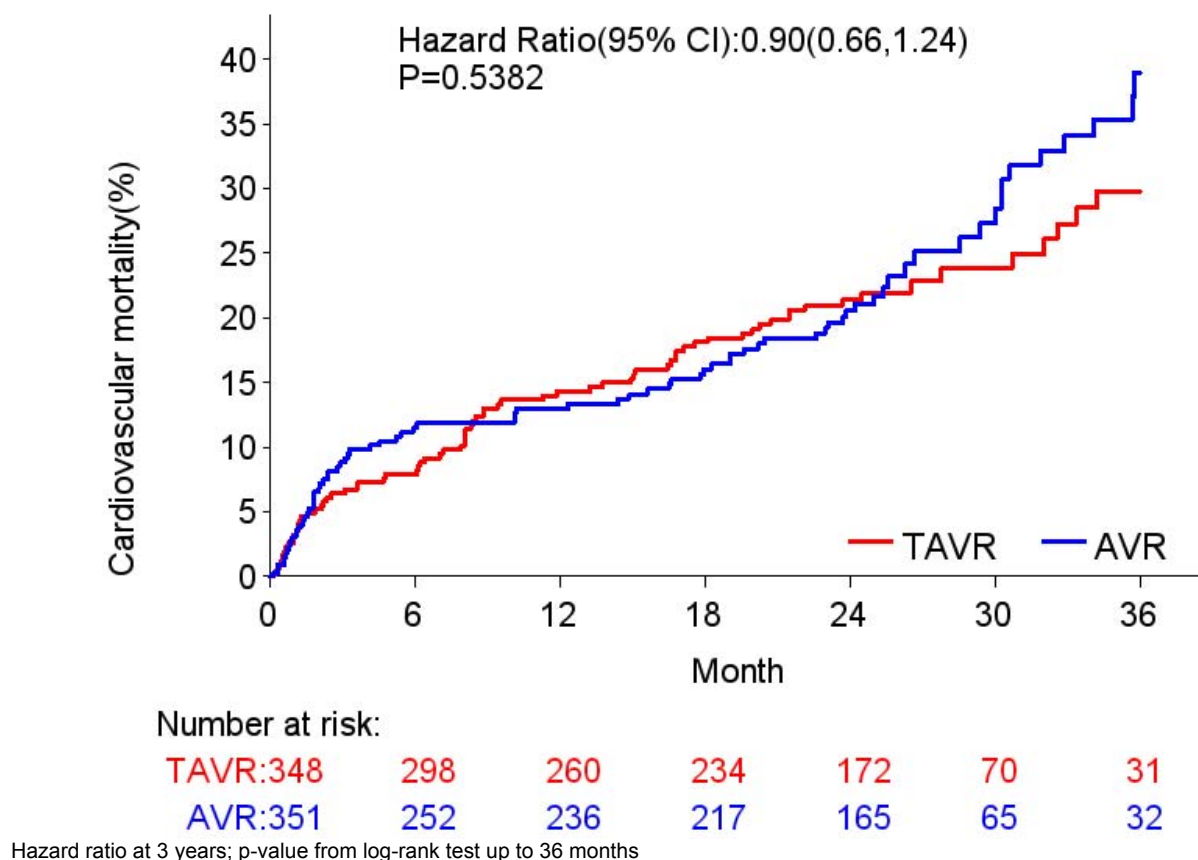
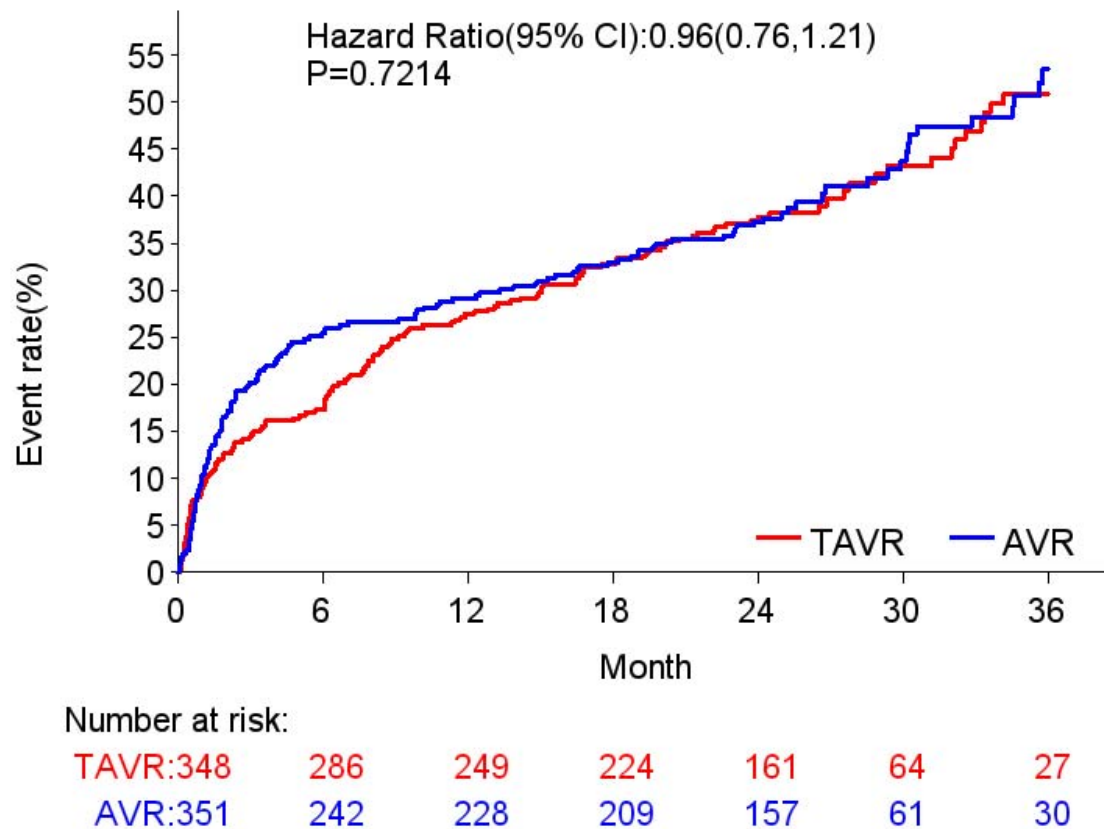




Figure 55. First Occurrence of a MACCE at 3 Years (Per Protocol Definitions) – High Risk Cohort in the PARTNER Study (ITT Population)



Hazard ratio at 3 years; p-value from log-rank test up to 36 months



Appendix I. The Edwards SAPIEN® THV Experience in Inoperable Patients

Introduction

The PARTNER (Placem^ent of AoRTic TraNscathetER Valves) trial identified two cohorts of patients with severe AS: (1) inoperable patients and (2) patients at high risk, for AVR. After stratification by cohort, patients were randomized and studied separately within each cohort. While this Briefing Document focuses on efficacy and safety experience in high-risk patients, this Appendix contains the experience in inoperable patients; 1 year data were previously presented at the Circulatory Systems Panel Meeting on July 20, 2011. Since follow-up of these patients is ongoing, currently 2 year clinical and echocardiographic data are available.

Inclusion and Exclusion Criteria

Eligibility criteria for both cohorts were identical (**Section 6.2**), except for operative risk: patients deemed inoperable had documented evidence that the risk for mortality or serious irreversible morbidity was greater than 50% as determined by the examining cardiac surgeon investigator. Patients were typically deemed inoperable due to prohibitive medical or anatomical conditions (highly compromised respiratory disease, severe immunosuppressive diseases, “true” porcelain aorta, chest wall radiation or deformity, and multiple previous interventions in the presence of advanced multi-system dysfunction). Eligibility for the inoperable arm of the study was confirmed by peer review of two surgical investigators not affiliated with the site. Both had to conclude that the patient met the non-operability criteria.

Study Design and Enrollment

Inoperable patients with severe AS were randomized to TAVR via transfemoral approach or standard care that could include BAV. Patients were enrolled from 18 centers in the US and 4 centers in 2 other countries (Canada and Germany).



Enrollment was initiated in May 2007 and completed in March 2009. Of the 3,105 patients screened for enrollment, 1,057 patients (34%) were randomized; 358 patients (12%) met the criteria for enrollment into the inoperable cohort and 699 patients (23%) met the criteria for enrollment into the high-risk cohort. A total of 179 inoperable patients were randomly assigned to TAVR and 179 inoperable patients were randomly assigned to standard care.

One Year Results

All-cause mortality risk was 49% less for those assigned to TAVR compared to standard care (44.1% vs. 66.5%, respectively; hazard ratio [HR] 0.51; 95% confidence interval [CI] 0.39, 0.68; $P < 0.001$). The risk of the composite end point of death from any cause or repeat hospitalization was 55% less with TAVR as compared with standard care (HR 0.45; 95% CI 0.35, 0.59; $P < 0.0001$) in the intent-to-treat (ITT) population.

All prespecified secondary endpoints also favored TAVR including (1) time to first occurrence of major adverse cardiac and cerebrovascular events (MACCE) within one year, (2) total hospital days through one year, (3) New York Heart Association (NYHA) functional classification at one year and (4) 6-minute walk test at one year.

Sensitivity analyses of patients as they were treated, mortality at one year and cardiovascular mortality all favored TAVR. Mortality at 30 days was increased in the TAVR group. Over the first 30 days after randomization, 9 TAVR patients (5.0%) died vs. 5 standard-care patients (2.8%) in the ITT population. In the as-treated population, 11 TAVR patients (6.3%) died within 30 days of implant vs. 5 standard-care patients (2.8%) who died within 30 days of randomization. The increased mortality was secondary to procedural complications and stroke.

Prespecified adverse events were defined by protocol and adjudicated by a clinical endpoint committee. At 30 days, arterial injury was more likely with TAVR (33.1% compared to 5.0%), as was the risk for stroke (6.7% compared to 1.7%). The safety



experience in inoperable patients treated in feasibility studies was consistent with that observed in PARTNER.

In summary, TAVR in inoperable aortic stenosis patients substantially increases survival compared to standard care. In addition, patient function characterized by quality of life instruments (Kansas City Cardiomyopathy Questionnaire, Short-Form-12, and EQ5D) as well as the 6-minute walk test and NYHA Classification significantly improves at 30 days and 1 year after TAVR versus best medical management including balloon aortic valvuloplasty. TAVR is associated with an increased risk for stroke and procedure-related adverse events such as bleeding and vascular complications. Overall, the benefit from TAVR in inoperable patients with severe aortic stenosis is substantially greater than the risk.

Two Year Outcomes

At 2 years, the incidence of all-cause mortality (Kaplan Meier analysis) was 43.3% for TAVR, and 68.0% for standard care. Over the length of the trial the hazard ratio [HR] for TAVR was 0.56, 95% confidence interval [CI], 0.43-0.74, and log-rank $p < 0.001$. At 2 years, the incidence of cardiac death was 30.2% of TAVR patients compared to 62.4% for standard care (HR for TAVR 0.43, 95%CI 0.31-0.59, $p < 0.001$).

TAVR relative to standard care showed a higher incidence of stroke (13.8% vs. 5.5%, HR for TAVR 2.7, 95% CI 1.2-6.0, $p = 0.012$). The combined rate of death or stroke at 2 years was 46.1% with TAVR compared to 68.0% with standard care (HR for TAVR 0.64, 95% CI 0.49-0.83, $p < 0.001$).

The rate of rehospitalization at 2 years was 33.4% with TAVR and 72.5% with standard care (HR for TAVR 0.39, 95% CI 0.28-0.55, $p < 0.001$).

At 2 years, the rate of significant cardiac symptoms (New York Heart Association class III or IV) was lower for TAVR than standard of care (16.8% vs. 57.5%, $P < 0.001$). Patients in the TAVR group were alive and out of hospital by a significant margin



(median 699 days, interquartile range [IQR] 201-720, for TAVR vs. 355 days, IQR 116-712 for ST, $P=0.002$).

Echocardiographic analysis showed a sustained increase in aortic valve area (AVA) and a decrease in gradients.

A sub-analysis of outcomes according to surgical risk score suggests that the most pronounced benefit of TAVR is attained in patients without extreme co-morbidities (for $STS < 15$, 2 year mortality 38.6% for TAVR vs. 65.8% for ST, HR for TAVR 0.51, 95% CI 0.37-0.71, $p < 0.001$) with diminishing survival benefits in the $STS \geq 15$ STS cohort (2 year mortality 58.3% for ST vs. 74.2% for TAVR, HR for TAVR 0.77, 95% CI 0.46-1.28, $p=0.310$).

In conclusion, in appropriately selected inoperable patients with severe aortic stenosis, TAVR reduced mortality and hospitalizations with an improvement in symptoms and hemodynamics that was sustained at mid-term follow-up.



Appendix J. Second Generation SAPIEN^{XT}

SAPIEN XTTM THV with NovaFlex and Ascendra 2 Delivery Systems

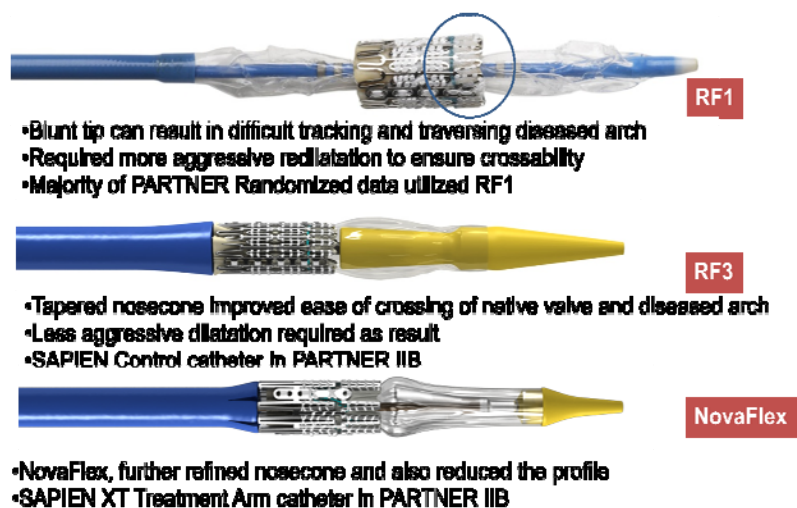
The introduction of the new SAPIEN XT THV and the NovaFlex delivery catheter for trans-femoral cases (as well as the Ascendra 2 system for transapical cases) may provide important technical advantages. The 40% reduction in sheath diameters (for similar valve sizes) (Figure 56) and the softer smooth-transition nosecone in the new delivery catheters (Figure 57) should be less traumatic to the aortic arch and will facilitate easier crossing the native diseased aortic valve. It bears emphasis that iterative generations of lower profile less traumatic catheter tip designs have dramatically improved diseased valve crossing and have reduced catheter manipulation during device positioning which should influence the potential for embolic debris liberation. In the future, the introduction of adjunctive devices which protect the cerebral vasculature by deflecting or filtering embolic debris may also contribute to a reduction in acute stroke events after TAVR.

Figure 56. Comparison of the current and new sheath sizes for placement of a 23mm THV





Figure 57. Comparison of current and new delivery catheters indicating marked differences in tip



Clinical Experience with the SAPIEN XT™ THV, and NovaFlex Delivery System

In 2008, the Edwards SAPIEN XT THV with the NovaFlex delivery system was introduced in European multicenter prospective, non-randomized clinical trials (PREVAIL EU- transfemoral and PREVAIL TA - transapical).

The PREVAIL EU (TF) Study is a comprehensive feasibility study that was designed to assess the safety and effectiveness of the Edwards SAPIEN XT™ valve and delivery systems. The study commenced with early versions of the delivery system (RetroFlex3™, RetroFlex4™) which were modified and then obsoleted for the SAPIEN XT™ platform based on early observations in the study. The PREVAIL EU Study was then expanded and amended to ensure that a meaningful sample of patients were enrolled in order to thoroughly evaluate the final design iteration of 18 French (for 23 mm THV) and 19 French (for 26 mm THV) NovaFlex™ delivery system. The NovaFlex™ delivery system incorporates a novel off-balloon valve crimping procedure enabling the use of a smaller introducer sheath combined with an in-vivo valve-over-balloon alignment maneuver prior to valve crossing and delivery. In total, 213 patients from 11 European hospitals in four countries were enrolled in this study of which 200



patients received a SAPIEN XT valve, 140 of these “as treated” patients were enrolled under the NovaFlex™ protocol amendment.

Similarly, the PREVAIL TA Study is a comprehensive feasibility study also designed to assess the safety and effectiveness of the Edwards SAPIEN XT™ valve and transapical Ascendra delivery systems. The study was initiated with 23 mm and 26 mm valve sizes and was augmented with a new 29 mm valve size in response to user requests for patients with larger native aortic valve annulus diameters. The PREVAIL TA Study was also amended and expanded to thoroughly evaluate the larger 29 mm valve size. In total, 220 patients from 20 European hospitals were enrolled in this study, of which 119 were enrolled under the SAPIEN XT™ 29 mm protocol amendment. A total of 212 patients received a SAPIEN XT valve and are considered “as treated” patients.

Table 100. PREVAIL EU/ TA: Demographics & Outcomes (AT Population)

| | | PREVAIL EU TF/NovaFlex - N = 140 | | PREVAIL TA TA - N = 212 | |
|--------------------------------------|---------------------------|-------------------------------------|--------|----------------------------|--------|
| Enrollment Dates | | 12/2008 – 12/2010 | | 12/2009 - 2/2011 | |
| Demographics | | | | | |
| Mean ± SD Age (years) | | 83.6 ± 5.6 | | 81.2 ± 5.5 | |
| Gender Female (%) | | 67.9 | | 29.2 | |
| Mean EuroSCORE (%) | | 22.4 ± 10.5 | | 24.1 ± 7.3 | |
| STS-Risk Score (%) | | 9.9 ± 7.6 | | 7.7 ± 4.5 | |
| Peripheral Vascular Disease (%) | | 15.5 | | 36.3 | |
| Congestive Heart Failure (%) | | 46.8 | | 63.2 | |
| Procedural Information | | | | | |
| Procedure time (min) | | 93.1 ± 42.6 | | 95.5 ± 31.5 | |
| Fluoroscopy time (min) | | 19.0 ± 8.1 | | 6.9 ± 4.5 | |
| Valve at intended site (%) | | 97.1 | | 98.1 | |
| Conversion to open heart surgery (%) | | 1.4 | | 0.5 | |
| Arterial access diameter (mm) Right | | 8.2 ± 1.5 | | NAP | |
| Arterial access diameter (mm) Left | | 7.7 ± 0.7 | | NAP | |
| End-point | Freedom from Safety Event | Kaplan Meier (%) | | | |
| | | 30 Day | 1 Year | 30 Day | 1 Year |
| Primary | Death | 91.4 | 84.2 | 92.4 | 78.1 |



| | | | | | |
|--------------|--|-------------|-------|-------------|------|
| Secondary | Conduction defect requiring permanent pacemaker | 91.3 | 87.9 | 88.0 | 86.7 |
| | Myocardial infarction | 97.9 | 96.5 | 98.1 | 97.0 |
| | Perivalvular Leak (3+ or 4+) | 98.5 | 96.9 | 98.6 | 96.2 |
| | Reoperation | 97.8 | 96.4 | 99.0 | 97.2 |
| | Stroke – Embolic Origin | 96.3 | 94.1 | 98.1 | 97.3 |
| | Stroke – Unknown Origin | 99.3 | 99.3 | 100.0 | 99.3 |
| | Valve embolization | 100.0 | 100.0 | 99.5 | 99.5 |
| | Vascular Access-Related Compl. | 88.5 | 88.5 | 100.0 | 99.4 |
| | Vascular Access-Related Complication-Thoracic | NAP | NAP | 98.1 | 98.1 |
| | Vascular Access-Related Complication-Ventricular | NAP | NAP | 99.5 | 98.9 |
| | Vascular Complication (Not Access-Related) | 98.5 | 96.9 | 99.1 | 98.3 |
| Data Extract | | 5 July 2011 | | 5 July 2011 | |

Table 101. PREVAIL TA Study: Hemodynamics & NYHA (AT Population)

| | | PREVAIL EU Transfemoral/ NovaFlex N = 140 | PREVAIL TA Transapical (N=207) | |
|------------------------------------|----------|--|-----------------------------------|----------------|
| Hemodynamic Performance | Interval | | All valve sizes N=212 | 29 mm N=119 |
| EOA (cm ²) – mean ± SD | Baseline | 0.7 ± 2 | 0.7 ± 0.2 | 0.8 ± 0.2 |
| | 30 Day | 1.6 ± 0.3 | 1.8 ± 0.4 | 2.0 ± 0.4 |
| | 6 Month | 1.6 ± 0.5 | 1.7 ± 0.6 | 1.9 ± 0.6 |
| Mean Gradient (mmHg) mean ± SD | Baseline | 47.9 ± 16.6 | 40.2 ± 15.7 | 38.5 ± 14.5 |
| | 30 Day | 10.1 ± 3.0 | 9.3 ± 4.5 | 8.1 ± 3.2 |
| | 6 Month | 9.9 ± 3.5 | 9.8 ± 4.9 | 8.6 ± 4.7 |
| PVL >3+ - % | 30 Day | 6.5% | 4.2% | 2.1% |
| | 6 Month | 4.8% | 1.6% | 0.0% |
| NYHA Classification | | | | |
| III & IV | Baseline | 76.4% | 83.5% | 84.0% |
| | 30 Day | 12.9% | 17.9% | 18.5% |
| | 6 Month | 10.0% | 7.6% | 4.2% |
| Data Extract | | 5 July 2011 | 5 July 2011 | |



The combined 30 day freedom from mortality of 92.0% is considered acceptable in the early learning curve, as there were no roll-in patients and procedure success improved over time. No deaths were directly associated with vascular access complications such as dissection, rupture or bleeding.

Modest improvements in vascular access complications were seen in this study, despite enthusiasm by the investigators to attempt 18F sheath introduction into vessels that were small and more diseased than first appreciated. A 3.5% reduction in the incidence of major vascular access complication was seen with the NovaFlex™ when compared to subjects who were treated with the RF3 delivery system.

The PREVAIL TA study demonstrated that the SAPIEN XT stent design iteration to achieve a crimped profile reduction in combination with a larger diameter THV meets the size requirements of the majority of patients that are now being selected for TAVR therapy. The mortality rate of 7.6% at 30 days is significantly lower than those rates seen in earlier transapical cohorts and is similar to that seen in transfemoral patients. Freedom from adverse event rates are also comparable or better than those seen in earlier trials with 98.1% freedom from myocardial infarction, 98.1% freedom from stroke and 100.0% freedom from structural valve deterioration at 30 days.

In both of the PREVAIL trials, the SAPIEN XT THV has demonstrated that all sizes of the SAPIEN XT perform hemodynamically as anticipated with mean effective orifice areas that are progressively larger across the valve sizes and mean gradients that are lower as the valve size increases. The largest EOA and lowest gradients are seen with the 29 mm device. Perivalvular leak continues to be observed, but the incidence of moderate 3+ (2.1%) or severe 4+ leaks (0.0%) requiring a surgical intervention remains low. Valve embolization was reduced in these series and there were no reports of leaflet dysfunction in situations of low cardiac output or low valve placement. This is a positive result of the valve leaflet modification and closed coaptation of the SAPIEN XT. The implantation of a permanent pacemaker post index procedure is higher than what has been reported in earlier studies but still appears to be within the ranges



reported for surgical AVR. The appearance of 3° AV block within the first few days after the replacement of the valve is the primary reason for pacemaker implantation after a TAVR procedure. There does however seem to be less reluctance to implant a pacemaker in patients who experience other arrhythmias that may not be directly related to a transcatheter valve but occur early after the index procedure.

In conclusion, data collected to date in these clinical investigations for the 23 mm, 26 mm and 29 mm SAPIEN XT THV provides objective evidence that: procedural outcomes with the SAPIEN XT™ THV and either the NovaFlex or Ascendra delivery systems are within safe and reasonable ranges for the intended patient population.

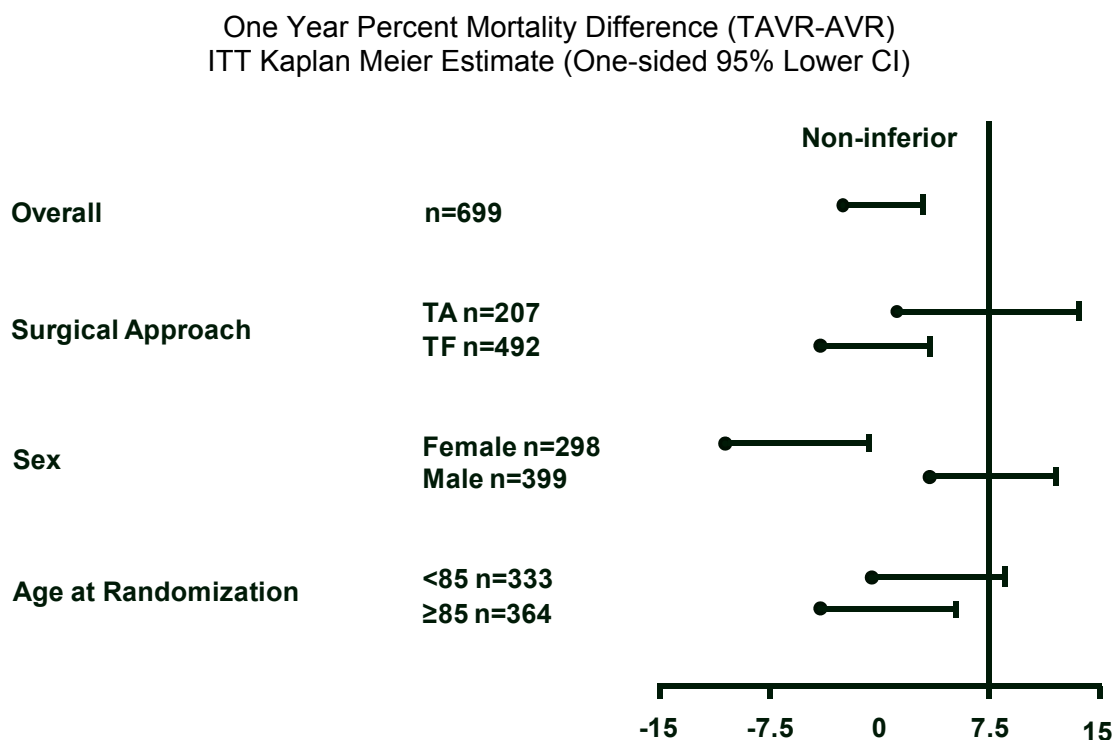
Safety and effectiveness of the Edwards SAPIEN XT THV and NovaFlex delivery system were demonstrated in support of the CE Mark which was conferred in April, 2010.

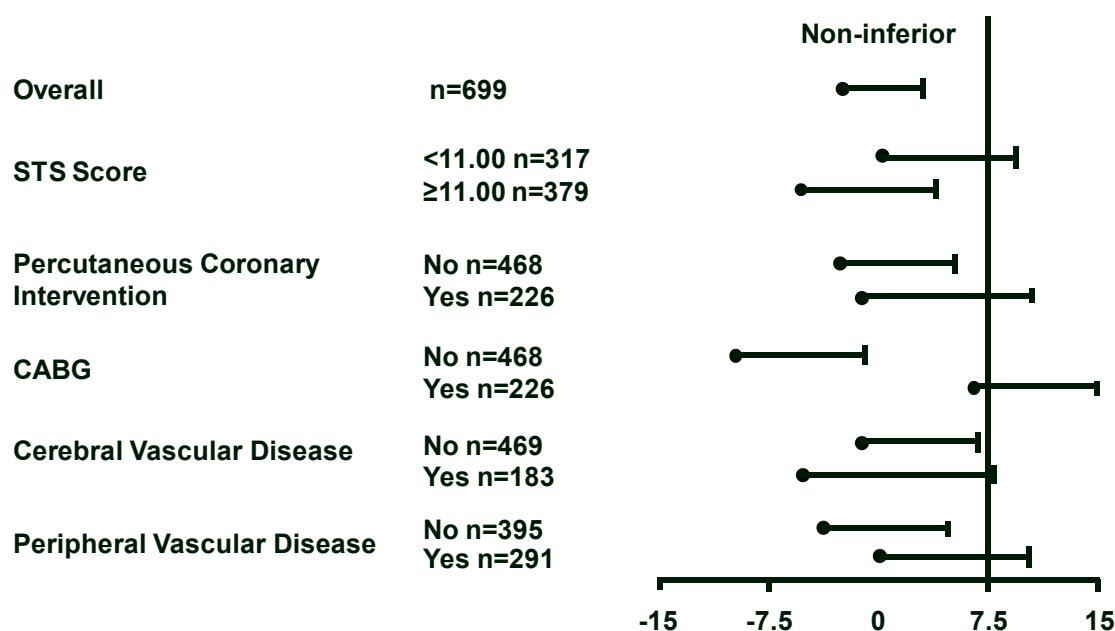


Appendix K. Effect of Patient Demographic and Medical Characteristics on the Primary Endpoint – ITT Population

Eight potential effect modifiers were assessed for their effect on the primary endpoint. Effect modifier analysis assesses consistency of effect across subgroups defined by the factor by estimating the subgroup-specific effects and confidence intervals from a generalized linear model with the factor by arm interaction term included. These estimates and confidence intervals are shown in Figure 58. All point estimates are below the non-inferiority margin of 7.5 percent points.

Figure 58. All Cause Mortality at 1 Year by Various Patient Subgroups - High Risk Cohort in the PARTNER Randomized Study (ITT Population)





Two baseline attributes, sex and prior CABG, were identified as baseline attributes that produced statistical evidence of effect modification. (The criterion for effect modification will be described subsequently.) In addition, three additional baseline attributes, history of atrial fibrillation, history of pulmonary hypertension, and history of cerebral vascular disease, were identified as baseline attributes requiring additional investigation.

In order to assess the relationships between these baseline attributes to outcome, to arm, and among themselves, multiple variable statistical models were used. Proportional Hazard Regression (PHR) of survival time and stratified by surgical approach was used to statistically model. PHR was used because multiple covariates could be modeled simultaneously and the method of analysis for the primary endpoint was not amenable to statistical modeling with covariates. Therefore, the measure of effect is the ratio of the hazard of death in the experimental arm to the hazard of death in the control arm rather than the primary endpoint difference in mortality at one year. Main effect terms are tested for contribution to the statistical model at two-sided 0.05 and interaction terms are tested at 0.10. For reference, the 7.5 point or greater mortality



difference definition of inferiority corresponds approximately to a hazard ratio of 1.3 or greater.

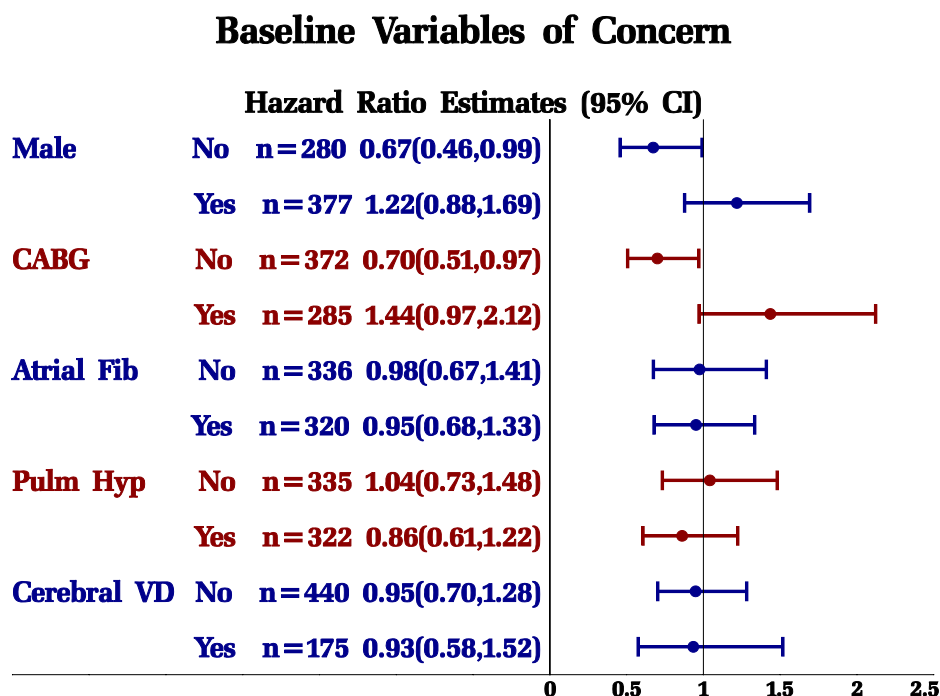
Results for the effect modification models are shown in Table 102 and Figure 59. Figure 59 shows the hazard ratios (and 95% confidence intervals) for each factor group. Sex and CABG have significant effect modification with p-value of 0.0221 and 0.0057, respectively. Males have a hazard ratio estimate above one but the confidence interval includes one. CABG has the same pattern for those with prior CABG. None of the other factors have outcomes that suggest effect modification, and neither pulmonary hypertension nor history of cerebral vascular disease have relationships to survival time, and are therefore not prognostic in isolation. However, history of atrial fibrillation does have a relationship to survival time (main effect p-value is 0.0137) and is therefore prognostic in isolation (it was previously established that it is not an effect modifier). Finally, it is important to note that arm the lack of significance of the arm main effect is consistent with non-inferiority.

Table 102. Baseline Variables Requiring Additional Investigation - High Risk Cohort of the PARTNER Trial

| Factor | Level | Level-specific HR estimate | 95% confidence interval | Model p-value for interaction term | Model without interaction term | |
|---------------------------|--------|----------------------------|-------------------------|------------------------------------|-----------------------------------|--------------------------------------|
| | | | | | Model p-value for arm main effect | Model p-value for factor main effect |
| Sex | Female | 0.673 | 0.457 to 0.992 | 0.0221 | NA | NA |
| | Male | 1.218 | 0.877 to 1.691 | | | |
| CABG | No | 0.700 | 0.506 to 0.970 | 0.0057 | NA | NA |
| | Yes | 1.236 | 0.972 to 2.122 | | | |
| Atrial Fibrillation | No | 0.975 | 0.675 to 1.4090 | 0.9237 | 0.7636 | 0.0137 |
| | Yes | 0.972 | 0.679 to 1.334 | | | |
| Pulmonary Hypertension | No | 1.042 | 0.733 to 1.481 | 0.4532 | 0.6705 | 0.5319 |
| | Yes | 0.862 | 0.607 to 1.224 | | | |
| Cerebral Vascular Disease | No | 0.949 | 0.703 to 1.282 | 0.9569 | 0.6653 | 0.9451 |
| | Yes | 0.935 | 0.576 to 1.517 | | | |



Figure 59. Baseline Variables Requiring Additional Investigation - High Risk Cohort in the PARTNER Randomized Study



These five explanatory variables were modeled simultaneously. Through a series of term removals, including assessing hierarchically up to four-way interactions, the following parsimonious model was found and is shown in Table 103. This parsimonious model does not include sex, pulmonary hypertension, or cerebral vascular disease. The absence of sex is likely due to relationship between sex and CABG, where 19.8% of females had prior CABG as compared to 60.4% of males (Exact $p < 0.001$ testing independence of classification); thus, approximately three times as many males had prior CABG. The contribution of atrial fibrillation to the model as a strong prognostic factor is consistent with the findings from the effect modifier analysis for atrial fibrillation as discussed previously (Table 102). The CABG by arm interaction significance is also consistent with the findings from the effect modifier analysis. Having had a CABG is associated with a poor prognosis.

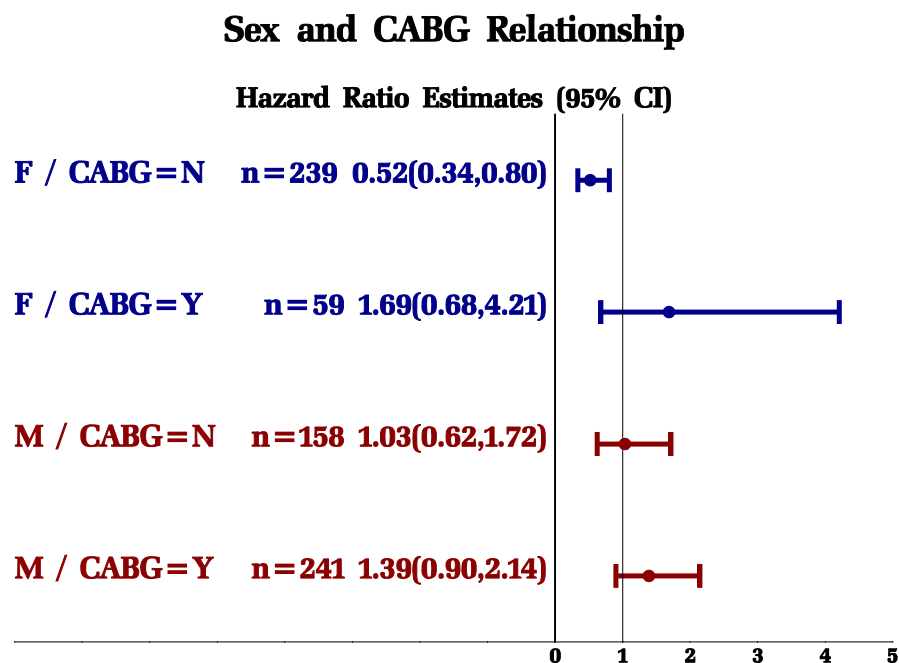


Table 103. Parsimonious Model - High Risk Cohort of the PARTNER Trial

| Covariate | Parameter Estimate | Standard error | P value |
|---------------------|--------------------|----------------|---------|
| Atrial Fibrillation | 0.313 | 0.128 | 0.0142 |
| CABG | -0.514 | 0.192 | 0.0076 |
| Arm | -0.354 | 0.167 | 0.0339 |
| CABG by Arm | 0.737 | 0.261 | 0.0047 |

Further analyses of the relationship between sex, CABG, and arm was performed by estimating the hazard ratios associated with each of the four sex by CABG combinations. These hazard ratio estimates and 95% confidence intervals are shown Figure 60. Having had a CABG conveys a worse outcome for TAVR relative to AVR (hazard ratios greater than one) and this is the case for both sexes. Both sex-specific hazard ratio estimates associated with not having had a prior CABG are close to one or less than one. The hazard ratio estimate for females who had prior CABG is much greater than one, but the confidence interval is wide.

Figure 60. Sex and CABG Relationship - High Risk Cohort in the PARTNER Randomized Study





In conclusion, the modeling and supplemental analysis suggests that sex and baseline CABG status are strongly related and are approximately additive. Being male or prior CABG are both associated with higher estimated hazard ratios than when either (or both) conditions are reversed. There is no evidence that a particular combination of sex or CABG status is synergistically different from the implied additive. Females who had prior CABG had the highest estimated hazard ratio, but the confidence interval is wide (and includes one) because there are a smaller number of patients in this class.