# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Makkar RR, Thourani VH, Mack MJ, et al. Five-year outcomes of transcatheter or surgical aortic-valve replacement. N Engl J Med. DOI: 10.1056/NEJMoa1910555

# Table of Contents

## Study Investigators and Key Personnel

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| Site Name | Key Personnel |
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| Site Name | Key Personnel |
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| **The Christ Hospital**<br><br>**Cincinnati, OH** | Principal Investigators: Dean Kereiakes, Thomas Ivey;<br>Co-Investigators: Geoffrey Answini, Donald L Mitts, Ian Sarembock, Robert Gallegos;<br>Echocardiography: Gregory Clarke, Wojciech Mazur, Eugene Chung, Gregory Egnaczyk, John Szawaluk, Terri Stewart Dehner;<br>Site Coordinators: Tracy Darlington |
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| **University of Miami**<br><br>**Miami, FL** | Principal Investigators: Donald Williams, Alan Heldman;<br>Co-Investigators: William Oneill, Pedro Martinez-Clark, Mauricio Cohen, Claudia Martinez, Carlos Alfonso, Roger Carillo, Michael Katsnelson, Sebastian Koch, Bernardo Lopez Sanabria;<br>Echocardiography: Melissa Tracy, Philip Itty, Martin Bilsker;<br>Site Coordinators: Sylvia Morales |
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| **University of Washington**<br><br>**Seattle, WA** | Principal Investigator: Mark Reisman, Edward Verrier;<br>Co-Investigators: Gabriel S. Aldea, Steven Goldberg, Nahush Mokadam, Michael Sang-Hak Kim, Creighton Don, Jack Sun;<br>Echocardiography: Catherine Otto, Rosano Freeman;<br>Site Coordinators: Rebecca Letterer |
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| Site Name | Key Personnel |
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# Appendix A. Inclusion/Exclusion Criteria

### Inclusion Criteria – PARTNER 2

1. Patient had senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient > 40 mmHg or jet velocity greater than 4.0 m/s and an initial aortic valve area (AVA) of $\leq$ 0.8 $cm^2$ or indexed EOA < 0.5 $cm^2/m^2$. Qualifying echo was within 60 days of the date of the procedure.

2. Patient was symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater.

3. The heart team agreed (and verified in the case review process) that valve implantation would likely benefit the patient.

4. The study patient or the study patient's legal representative was informed of the nature of the study, agreed to its provisions and had provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.

5. The study patient agreed to comply with all required post-procedure follow-up visits including annual visits through 5 years and analysis close date visits, which was conducted as a phone follow-up.

### Additional Eligibility Criteria Specific to Cohort A

1. STS $\geq$ 4 or < 4 if the Heart Team determines intermediate-risk patient profile with important comorbidities not represented in the STS risk score algorithm.

2. Heart team (including examining cardiac surgeon) agree on eligibility including assessment that TAVR or AVR is appropriate.

3. Heart team agreed (a priori) on treatment strategy for concomitant coronary disease (if present).

4. Study patient agreed to undergo surgical aortic valve replacement (AVR) if randomized to control treatment.

### Exclusion Criteria

1. Heart Team assessment of inoperability (including examining cardiac surgeon).

2. Evidence of an acute myocardial infarction $\leq$ 1 month (30 days) 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 (WHO definition)].

3. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified.

4. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).

5. Preexisting mechanical or bioprosthetic valve in any position (NR3).

6. Complex coronary artery disease :

    a. Unprotected left main coronary artery

    b. Syntax score > 32 (in the absence of prior revascularization)

7. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease). Implantation of a permanent pacemaker is not excluded.

8. Any patient with a balloon valvuloplasty (BAV) within 30 days of the procedure (unless BAV is a bridge to procedure after a qualifying ECHO).

9. Patients with planned concomitant surgical or transcatheter ablation for Atrial Fibrillation.

10. Leukopenia (WBC < 3000 cell/mL), acute anemia (Hgb < 9 g/dL), Thrombocytopenia (Plt < 50,000 cell/mL).

11. Hypertrophic cardiomyopathy with or without obstruction (HOCM).

12. Severe ventricular dysfunction with LVEF < 20%.

13. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.

14. Active upper GI bleeding within 3 months (90 days) prior to procedure.

15. A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.

16. Native aortic annulus size < 18 mm or > 27 mm as measured by echocardiogram.

17. Clinically (by neurologist) or neuroimaging confirmed stroke or transient ischemic attack (TIA) within 6 months (180 days) of the procedure.

18. Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy at the time of screening.

19. Estimated life expectancy < 24 months (730 days) due to carcinomas, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease.

20. Expectation that patient will not improve despite treatment of aortic stenosis

21. 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, are not considered investigational trials.

22. Active bacterial endocarditis within 6 months (180 days) of procedure.

23. Patient refuses aortic valve replacement surgery.

## Appendix B. Recommended Pharmacotherapy

The recommended antiplatelet regimen was described below. The categories were developed by The PARTNER II Trial Patient and Procedure Management Steering Committee. There are no current validated guidelines in this specific study population, however, the literature was surveyed and used as guidance for the following proposed guidelines. Patients will be assessed by the heart team for Category of Stroke Risk prior to prescribing treatment regimen. The Category will be documented in the discharge case report form. Committee Categories are based on CHAD score for stroke risk.

**NOTE**: The CHAD score only applies to patients in Atrial Fibrillation (AF) and has not been validated in non-AF patient populations; therefore the CHAD score reference was used as one among many guidelines to establish the risk stratification for intensity of anticoagulation regimen.

**Antibiotic Prophylaxis**

Study patients should be prophylactically treated for endocarditis per the recommendations of the American Heart Association.

| | **Surgery** | **TAVR** |
|---|---|---|
| Anti-coagulation regimen - pre procedure | | |
| | Aspirin 81-100 mg QD | Aspirin 81-100 mg QD |
| | • Patients with BMS within one month or drug eluting stent (DES) within 12 months should be continued on Clopidogrel/prasugrel prior to their procedure<br>• Patients in atrial fibrillation on warfarin should be bridged with LMW or UF heparin prior to the procedure<br>• Patients with persistent or paroxysmal atrial fibrillation, not on anticoagulation, will not be required to have a TEE to rule out LA thrombus prior to procedure. If intra-procedural TEE during TAVR reveals thrombus, procedure will be aborted and delayed until patient has been on warfarin or dabigatran for 30 days. In patients in the surgical group with LA clot seen on intraoperative TEE, procedure can proceed per | • Patients with BMS within one month or DES within 12 months should be continued on Clopidogrel/prasugrel prior to their procedure<br>• Patients in atrial fibrillation on warfarin should be bridged with LMW or UF heparin prior to the procedure<br>• Patients with persistent or paroxysmal atrial fibrillation, not on anticoagulation, will not be required to have a TEE to rule out LA thrombus prior to procedure. If intra-procedural TEE during TAVR reveals thrombus, procedure will be aborted and delayed until patient has been on warfarin or dabigatran for 30 days.<br>• In patients under concomitant TAVR/PCI, the following is recommended in addition to ASA<br>• Transfemoral TAVR – Clopidogrel loading with either 300mg or 600mg prior to the procedure<br>• Transapical TAVR – Clopidogrel loading with 300mg just prior to the procedure |
| Anti-coagulation regimen - intraprocedural | | |
| | Heparin will be given to achieve/ maintain ACT>250 sec. | Heparin will be given to achieve/ maintain ACT>250 sec. |
| Anti-coagulation regimen - post procedure | | |
| Category I for Stroke Risk<br>No atrial fibrillation, No recent stents | o ASA 81mg qd<br>o Clopidogrel 75qd started 24 hours post surgery for at least one month if clinically safe and at the discretion of the surgical team. In centers that use warfarin post surgical AVR, Clopidogrel will not be started | o ASA 81mg qd<br>o Clopidogrel 300mg load within 6 hours of procedure (either pre or post)<br>o Clopidogrel 75mg qd for at least one month post procedure |

| | Surgery | TAVR |
|---|---|---|
| Category II for Stroke Risk<br>No atrial fibrillation, recent stents | o ASA 81mg qd<br>o Clopidogrel should not be discontinued prior to surgery if patient had BMS within one month or DES in 12 months<br>o Clopidogrel 75qd started 24 hours post surgery if clinically safe and continued for at least one month post surgical AVR in those with BMS and a total of 12 months for those with DES | o ASA 81mg qd<br>o Clopidogrel 75mg qd should be continued prior to the procedure and after the procedure without interruption for at least one month after BMS and 12 months after DES |
| Category III for Stroke Risk<br>Atrial fibrillation, no recent stents | o ASA 81mg qd<br>o Patients should be started on warfarin or dabigatran 24 hours post AVR if clinically safe and this should be continued for at least one month or indefinitely if possible. If clinically safe, patient's being started on warfarin should be bridged with unfractionated or low molecular weight heparin until INR therapeutic.<br>o If patients are not a candidate for warfarin or dabigatran, Clopidogrel 75mg qd (in addition to ASA 81 mg) can be considered as an alternative | o ASA 81mg qd<br>o Patients should be started on warfarin or dabigatran 24 hours post TAVR if clinically safe and this should be continued for at least one month or indefinitely if possible. If clinically safe, patients started on warfarin should be bridged with unfractionated or low molecular weight heparin until INR therapeutic.<br>o If patients are not a candidate for warfarin or dabigatran, Clopidogrel 75mg qd can be considered as an alternative |
| Category IV for Stroke Risk<br>Atrial fibrillation, recent stents | o ASA 81mg qd<br>o Clopidogrel 75mg qd for at least one month post BMS or 12 months post DES<br>o Patients should be started on warfarin or dabigatran 24 hours post AVR if clinically safe and continued indefinitely. If clinically safe, patients being started on warfarin should be bridged with UF or LMW heparin until INR therapeutic. | o ASA 81mg qd<br>o Clopidogrel 75mg qd for at least one month post BMS or 12 months post DES<br>o Patients should be started on warfarin or dabigatran 24 hours post TAVR if clinically safe and continued indefinitely. If clinically safe, patient's being started on warfarin should be bridged with UF or LMW heparin until INR therapeutic. |
| Antibiotic Prophylaxis | Study patients should be prophylactically treated for endocarditis per the recommendations of the American Heart Association | Study patients should be prophylactically treated for endocarditis per the recommendations of the American Heart Association |

## Appendix C. Clinical Follow-up

For end point analyses, study patients will undergo clinical follow-up at discharge, 30 days, 6 months, 1 and 2 years, and then annually (± 60 days) thereafter for a minimum of 5 years post index procedure. A telephone follow-up will occur at the primary analysis close date; this follow-up must occur on or after that close date (+14 days). In the event that an adverse neurological event is reported by the patient, the patient will be asked to return to the clinic for examination by a neurologist or a neurology fellow. Additional phone follow-ups may be performed as needed to obtain up to date survival information for use in regulatory submissions. For all subjects at all visits, the time clock starts on the date of the implant procedure, whether or not the implant is completed. If the procedure never occurs for a patient, then the 30-day visit will never occur for that patient. If the procedure is not completed, and there is a later implant, the original procedure date still applies for the 30-day visit.

The following data was collected for all study patients at 3 to 5-year follow-up visits.

**Systems:**

- pertinent physical examination
- medications given for cardiovascular effect including anti-platelet/thrombins
- Adverse effect assessment

**Cardiac:**

- CCS status of angina
- NYHA classification
- Chest X-ray examination
- Fluoroscopic imaging implant valve (if required)
- Comprehensive transthoracic echocardiogram (TTE)

**Clinical Laboratory Test:**

- B-type natriuretic peptide (BNP).

**Functional Assessments:**

- Quality of life measurements including Kansas City Cardiomyopathy Questionnaire (KCCQ), EuroQOL (EQ5D) and SF36

**Neurological Assessments**

The clinical follow-up included capturing of all adverse events. These events were recorded on the electric case report forms provided by the database management center.

Every patient should be encouraged to remain in the study until they have completed the protocol required follow-up period. If the patient discontinues prematurely from the study, the reason for discontinuation must be documented. Possible reasons for premature discontinuation may include, but are not limited to the following:

- Withdrawal of consent: Patient decides to withdraw from the study.
- Lost to follow-up: All patients should be encouraged to return to the clinic for evaluation during long term follow-up. Three separate telephone calls should be made to attempt to schedule a follow-up visit or obtain follow-up information. All attempts should be documented in the source documents. If the patient does not respond to the 3 telephone calls then the Investigator will send a certified letter to the study patient. The patient will be considered lost to follow-up if this communication is unsuccessful. Patients who discontinue prematurely will be included in the analysis of results, and will not be replaced.
- Death registries: In the event of a patient withdrawal or lost to follow-up, Edwards may opt to obtain the death certificate, search the Social Security Death Index and/or other death registries to obtain survival information.

## Appendix D. Statistical Methods for Sensitivity Analyses

Multiple Imputation: All the missing echo and KCCQ data are assumed as missing at random as specified in the original study SAP section 3.4.1. Missing echo and KCCQ data at each follow-up time point were imputed using SAS proc MI with the Markov-Chain Monte Carlo method including the following baseline characteristics: Treatment, Age, Gender, STS Risk Score, NYHA class, Diabetes, Renal Insufficiency (Cr greater than or equal to 2 mg/dL), Current Smoker, Body Surface Area, Geographic region (SAP section 3.4.2).

Linear Mixed Models: Least square mean of KCCQ score between treatment groups were calculated at each follow-up time point using linear mixed model with adjustment for treatment group, follow-up visit and interaction between treatment and follow-up visit. The variance-covariance structure is assumed to be AR (1).”

**Table S1. Study endpoint definitions**

| Term | Definition | Reference/ Justification |
|---|---|---|
| **Access Site** | Access site defined as any location (arterial or venous) traversed by a guide-wire, a catheter or a sheath (including the left ventricular (LV) apex and the aorta) | |
| **Annular Dissection** | Disruption or tear of the valve annulus extending to the aorta caused by mechanical injury from over sizing a balloon or the valve device itself. | STS |
| **Aortic Dissection** | 1. Aortic dissection defined as Type A or B dissections that require surgical or percutaneous intervention.<br>2. Stanford Type B or Debakey Type 3 dissections that may be treated medically. | FDA |
| **Aortic Valve Stenosis** | Aortic valve area of less than 0.8 $cm^2$ (or an aortic valve area index of less than 0.5 $cm^2$ per $m^2$) plus either a mean valve gradient of at least 40 mm Hg or a peak velocity of at least 4.0 m per second. | VARC 2 |
| **Bleeding** | Life-threatening or disabling bleeding:<br>• Fatal bleeding OR<br>• Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR<br>• Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR<br>• Overt source of bleeding with drop in haemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units<br>Major bleeding:<br>• Overt bleeding either associated with a drop in the haemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND<br>• Does not meet criteria of life-threatening or disabling bleeding<br>Minor bleeding:<br>• Any bleeding worthy of clinical mention (e.g. access site haematoma) that does not qualify as life-threatening, disabling, or major | VARC 2 |

| Term | Definition | Reference/ Justification |
|---|---|---|
| **Conduction disturbances and arrhythmias** | Data elements to be collected should include:<br>• Baseline conduction abnormalities, paroxysmal or permanent atrial fibrillation (or flutter), and presence of permanent pacemaker<br>• Implant-related new or worsened cardiac conduction disturbance (new or worsened first degree atrioventricular (AV) block, second degree AV block (Mobitz I or Mobitz II), third degree AV block, incomplete right bundle branch block, right bundle branch block, intraventricular conduction delay, left bundle branch block, left anterior fascicular block, or left posterior fascicular block, including block requiring permanent pacemaker implant<br>• Persistent or transient high degree AV block. High grade AV block is persistent if it is present every time the underlying rhythm is checked<br>• New permanent pacemaker implantation, with precision of the indication and number of days post-implant of placement of new permanent pacemaker<br>• New-onset atrial fibrillation (or flutter)<br>Any new arrhythmia resulting in hemodynamic instability or requiring therapy | VARC 2 |
| **Conversion to open surgery** | Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications | VARC 2 |
| **Coronary obstruction** | Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVI procedure | VARC 2 |
| **Death** | Cardiovascular Death<br>• Any one of the following criteria:<br>• Any death due to proximate cardiac disease cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure);<br>• Unwitnessed death and death of unknown cause (includes sudden cardiac death)<br>• All cardiovascular procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure;<br>• Death caused by noncoronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, or other vascular disease.<br>Non-Cardiovascular Death<br>• Death is due primarily to an identifiable non-cardiovascular cause or etiology. Specific diagnoses may include respiratory failure, pneumonia, trauma, suicide, or any other non-cardiovascular defined causes (e.g., liver disease, malignancies etc.) not included in the previous categories. | VARC 2 |
| **Device Embolization** | Device displacement from its initial annular implantation site so that it is no longer in its original position and is either in the left ventricle, aortic root or ascending/descending aorta. | |
| **Device Fracture** | The complete separation of any portion of the frame into two or more parts; as may be determined by radiography, computed tomography or magnetic resonance imaging. | |

| Term | Definition | Reference/ Justification |
|---|---|---|
| **Device Malfunction** | The failure of a device to meet any of its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. | |
| **Device Migration** | Device migration is defined x-ray confirmed movement of the study valve from its initial implantation site such that there is a change in valve orientation within the aortic outflow track resulting in a new ECHO confirmed flow disturbance (pre- and post- filmed documentation). | |
| **Device Success** | • Absence of procedural mortality AND<br>• Correct positioning of a single prosthetic heart valve into the proper anatomical location AND<br>• Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation) | VARC 2 |
| **Device thrombosis** | • Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis | VARC 2 |
| **Embolism** | Free flowing blood clot or lesion material that is located in the systemic or pulmonary circulation.<br><br>Any embolic event that occurs in the absence of infection after the immediate perioperative period (when anesthesia-induced unconsciousness is completely reversed).<br><br>Peripheral embolic event is an operative, autopsy or clinically documented embolus that produces symptoms from complete or partial obstruction or a peripheral (noncerebral) artery. Patients who awaken with a myocardial infarction are excluded. Patients who have a myocardial infarction after the perioperative period are also excluded unless a coronary arterial embolus is shown to be the cause of the infarction by operation, autopsy or clinical investigation. Emboli proven to consist of nonthrombotic material (e.g., atherosclerosis, myxoma) are excluded. | STS |
| **Endocarditis** | Any one of the following:<br>• Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation<br>• Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy | VARC 2 |

| Term | Definition | Reference/ Justification |
|---|---|---|
| **Endocarditis (Operated Valvular Endocarditis)** | Any infection involving an operated valve.<br>The diagnosis of operated valvular endocarditis is based on customary clinical criteria including an appropriate combination of positive blood cultures, clinical signs and histologic confirmation of endocarditis at reoperation or autopsy.<br>Morbidity associated with active infection, such as valve thrombosis, thrombotic embolus, bleeding event or paravalvular leak is included under this category and is not included in other categories of morbidity. | STS<br><br>Suggested reference: Duke Criteria for Infective Endocarditis |
| **Endpoints, VARC Composite Combined Safety at 30 Days** | 1. All- cause mortality<br>2. Stroke (as defined by in the STS/ACC TVT Registry)<br>3. Life-threatening (or disabling) bleeding<br>4. Acute kidney injury - Stage 3 (including renal replacement therapy)<br>5. Peri-procedural MI<br>6. Major vascular complication<br>7. Repeat procedure for valve-related dysfunction (surgical or interventional therapy) | VARC 2<br><br>Stroke as defined in the STS/ACC TVT Registry |
| **Event Free Survival** | Survival from death, stroke, or emergent cardiac surgery during the index procedure hospitalization, plus freedom from death or clinically-driven hospitalization (adjudicated congestive heart failure, myocardial ischemia, or syncope treated by medicine, repeat aortic balloon valvuloplasty, or aortic valve replacement) from index hospital discharge. | |
| **Frailty** | Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence<br>Criteria:<br>• 5 meter walking time<br>• Grip strength<br>• BMI <20 kg/m2 and/or weight loss 5 kg/yr<br>• Serum albumin <3.5 g/dL<br>• Cognitive impairment or dementia | VARC 2 |
| **Hemolysis** | • Plasma Hgb > 40 mg/dl on two consecutive measurements within 24 hours. Laboratory values meeting this criteria should be listed as a major adverse event; or<br>• Clinical diagnosis of hemolysis evidenced by laboratory testing such as serum Hgb, LDH, haptoglobin, bilirubin and/or urine bilirubin levels. | FDA |
| **Highly Compromised Respiratory Disease** | Home oxygen >2L/min, FEV1 <30% predicted, DLCO <15 or as above <30% although <50% if evidence of interstitial lung disease, FEF 25-75 <30% (measure of cough strength, <30%). | |
| **IMA or other critical conduit(s) crossing midline and/or adherent to posterior table of sternum** | A patent IMA graft that is adherent to the sternum such that injuring it during re-operation is likely. A patient may be considered extreme risk if any of the following are present:<br>• The conduit(s) are radiographically indistinguishable from the posterior table of the sternum.<br>• The conduit(s) are radiographically distinguishable from the posterior table of the sternum but lie within 2-3 mm of the posterior table. | VARC 2 |

| Term | Definition | Reference/ Justification |
|---|---|---|
| **Kidney Injury, acute** | Stage 1<br>• Increase in serum creatinine to 150-199% (1.5-1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dL (≥26.4 mmol/L) OR<br>• Urine output <0.5 ml/kg per hour for >6 but <12 hours<br>Stage 2<br>• Increase in serum creatinine to 200-299% (2.0-2.99 × increase compared with baseline) OR<br>• Urine output <0.5 ml/kg per hour for >12 but <24 hours<br>Stage 3<br>• Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) OR<br>• Urine output <0.3 ml/kg per hour for ≥24 hours OR<br>• Anuria for ≥12 hours | VARC 2 |
| **Mitral valve apparatus damage or dysfunction** | Angiographic or echocardiographic evidence of new damage (chordae papillary muscle, or to the leaflet) to the mitral valve apparatus or dysfunction (e.g. restrictions due to the THV) of the mitral valve during or after the TAVI procedure | VARC 2 |
| **Modified Rankin Scale (MRS)** | A commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke.<br><br>DESCRIPTION<br><br>0 No symptoms at all<br>1 No significant disability despite symptoms; able to carry out all usual duties and activities<br>2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance<br>3 Moderate disability; requiring some help, but able to walk without assistance<br>4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance<br>5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention<br>6 Dead | |

| Term | Definition | Reference/ Justification |
|---|---|---|
| **Mortality, all-cause** | Cardiovascular mortality<br>Any of the following criteria:<br>• Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure)<br>• Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease<br>• All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure<br>• All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events<br>• Sudden or unwitnessed death<br>• Death of unknown cause<br>Non-cardiovascular mortality<br>• Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide). | VARC 2 |
| **Myocardial Infarction** | 1. Peri-procedural MI (≤72 h after the index procedure)<br>2. New ischemic symptoms (e.g., chest pain or shortness of breath), or new ischemic signs (e.g., ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND<br>3. Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15x upper reference limit (troponin) or 5x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.<br>4. Spontaneous MI (>72 h after the index procedure)<br>5. Any one of the following criteria:<br>6. Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following:<br>• Symptoms of ischemia<br>• ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]<br>• New pathological Q waves in at least two contiguous leads | VARC 2 |

| Term | Definition | Reference/ Justification |
|---|---|---|
| | • Imaging evidence of new loss of viable myocardium or new wall motion abnormality<br>7. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.<br>8. Pathological findings of an acute myocardial infarction. | |
| **Nonstructural Dysfunction** | An abnormality, which is not intrinsic to the prosthetic valve (i.e. valve is structurally normal) resulting in stenosis or regurgitation.<br>Examples of nonstructural dysfunction include 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.<br>See "paravalvular leak" for additional definitions | STS/AATS |
| **Neurological Event** | Stroke, Cerebral Infarction, Transient Ischemic Attack, Encephalopathy or Intracranial Hemorrhage per specified definitions (see individual definitions and criteria.) | VARC 2 |
| **New York Heart Association Classification (NYHA)** | Class I: Patients with cardiac disease but without resulting limitations of physical activity.<br>Class II: Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.<br>Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation dyspnea, or anginal pain.<br>Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. | New York Heart Association |
| **Paravalvular Leak (See Also "Nonstructural Dysfunction")** | Defined as any evidence of leakage of blood around the prosthesis between the device and the native annulus.<br><br>Primary paravalvular leaks will be stratified by the following:<br><br>All leaks: evidence of moderate to severe paravalvular insufficiency by echocardiography<br>Minor leaks: A paravalvular leak graded < 3+ aortic insufficiency and does not require surgical intervention<br>Major leaks: A paravalvular leak graded ≥ 3+ aortic insufficiency or requires surgical intervention | STS/AATS, FDA |

| Term | Definition | Reference/ Justification |
|---|---|---|
| **Procedure Failure** | Complication(s) arising during implantation of the prosthetic valve such as an inability to properly seat the valve in the annulus, size mismatch between the annulus and the prosthetic valve, or the need for more than one Edwards SAPIEN XT THV (valve in valve), or if a surgical valve is required to correct a paravalvular leak. The reasons for this difficulty may be due to the anatomic configuration of the annulus or a calcific valvular annulus. | |
| **Prosthetic Valve Dysfunction** | **Prosthetic Aortic Valve Stenosis Criteria***<br>**Parameter** / **Normal** / **Possible Stenosis** / **Significant Stenosis**<br>Peak velocity (m/s)† / <3 / 3-4 / >4<br>Mean gradient (mmHg) † / <20 / 20-35 / >35<br>Doppler velocity index / ≥0.30 / 0.25-0.29 / <0.25<br>Effective orifice area ($cm^2$) / >1.2 / 0.8-1.2 / <0.8<br>Contour of the jet velocity through the prosthetic valve / Triangular, early peaking / Triangular to intermediate / Rounded, symmetrical contour<br>Acceleration time (ms) / <80 / 80-100 / >100<br>*In conditions of normal or near normal stroke volume (50-70mL); †These parameters are more affected by flow, including concomitant aortic regurgitation | VARC 2 |
| **Recurrent Hospitalization Re-Hospitalization** | Rehospitalization for symptoms of aortic stenosis and/or complications of the valve procedure<br><br>If the index hospitalization for a patient is greater than 30 days, then hospital day 31 will count as a re-hospitalization for endpoint analysis. | |
| **Reintervention** | Any intervention that repairs, alters or replaces a previously operated valve.<br>Balloon aortic valvuloplasty<br>Surgical aortic valve replacement<br>Valve in valve | STS/AATS |
| **Stroke / Transient Ischemic Attack (TIA)** | Stroke Diagnostic Criteria:<br>Rapid onset of a focal/global neurological deficit with at least one of the following:<br>• Change in level of consciousness<br>• Hemiplegia<br>• Hemiparesis<br>• Numbness or sensory loss affecting one side of the body<br>• Dysphasia/Aphasia<br>• Hemianopia<br>• Amaurosis fugax | VARC 2/CEC |

| Term | Definition | Reference/ Justification |
|---|---|---|
| | • Other new neurological sign(s)/symptom(s) consistent with stroke<br><br>Duration of a focal or global neurological deficit ≥ 24 hours OR < 24 hours if:<br>Therapeutic intervention(s) were performed: (e.g. thrombolytic therapy or intracranial angioplasty); OR<br>• Available neuro-imaging documents a new hemorrhage or infarct;<br>OR<br>• The neurological deficit results in death.<br><br>No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)*<br><br>Confirmation of the diagnosis by at least one of the following#:<br>• Neurology or neurosurgical specialist<br>• Neuro-imaging procedure (at least one of the following):<br>– CT scan<br>– MRI scan<br>– Cerebral angiography<br>Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage).<br><br>* Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuro-imaging studies.<br># If a stroke is reported without evidence of confirmation of the diagnosis by one of these methods, the event may be considered a stroke on the basis of the clinical presentation alone.<br><br>• Transient Ischemic Attack (TIA)<br>• New focal neurological deficit with rapid symptom resolution (usually 1 – 2 hours), always with 24 hours.<br>• Neuroimaging without tissue injury<br>• Disabling" stroke is defined as a mRS score of 2 or more at either at the 30 day or 90 day time period. | |

| Term | Definition | Reference/ Justification |
|---|---|---|
| **Structural Valvular Deterioration (SVD)** | Any change in valve function (a decrease of one NYHA functional class or more) resulting from an intrinsic abnormality of the valve that causes stenosis or regurgitation.<br><br>Structural valve deterioration includes dysfunction or deterioration exclusive of infection or thrombosis as determined by reoperation, autopsy or clinical investigation. The term structural deterioration refers to changes intrinsic to the valve, such as wear, fracture, calcification, leaflet tear, and suture line disruption of components (e.g. leaflets). | STS/AATS |
| **Thrombus (Valve Thrombosis)** | Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis | VARC 2 |
| **Transcatheter Heart Valve in Surgical Valve (THV-SV)** | Implantation of a transcatheter heart valve (THV) in a pre-existing surgical valve (SV). | |
| **Transcatheter Heart Valve in Transcatheter Heart Valve (THV-THV)** | Occurs during the transcatheter heart valve (THV) implantation procedure when an initial THV has not resulted in an appropriately functioning manner requiring an additional THV(s) to be implanted within the originally placed THV. Causes may include, but are not limited to: severe paravalular leak. | VARC 2 |
| **Unplanned use of cardiopulmonary bypass (CPB)** | Unplanned use of CPB for hemodynamic support at any time during the TAVI procedure | VARC 2 |
| **Vascular access site and access-related complications** | Major vascular complications:<br>• Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm OR<br>• Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding, visceral ischemia or neurological impairment OR<br>• Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR<br>• The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment OR<br>• Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR<br>• Surgery for access site-related nerve injury OR<br>• Permanent access site-related nerve injury<br>Minor vascular complications: | VARC 2 |

| Term | Definition | Reference/ Justification |
|---|---|---|
| | • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding, visceral ischemia or neurological impairment OR<br>• Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR<br>• Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR<br>Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)<br>• Percutaneous closure device failure<br>• Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning) | |
| **Valve malpositioning** | Valve migration<br>• After initial correct positioning, the valve prosthesis moves upward or downward, within the aortic annulus from its initial position, with or without consequences<br>Valve embolization<br>• The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus<br>• Ectopic valve deployment<br>• Permanent deployment of the valve prosthesis in a location other than the aortic root | VARC 2 |
| **Ventricular septal perforation** | Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVI procedure | VARC 2 |

**Table S2. Baseline Characteristics for Patients with Complete Follow Up versus Patients with Missing Follow Up**

| | Complete 5-year Follow Up (n = 1751) | Missing 5-year Follow Up (n = 281) |
|---|---|---|
| Age (years) | 81.5 ± 6.73 (1751) | 82.2 ± 6.48 (281) |
| Male | 967/1751 (55.2%) | 141/281 (50.2%) |
| Body mass index | 28.48 ± 6.217 (1751) | 28.30 ± 6.032 (281) |
| STS score | 5.8 ± 1.99 (1750) | 5.9 ± 1.92 (281) |
| NYHA Class III or IV | 1350/1750 (77.1%) | 208/281 (74.0%) |
| Coronary artery disease | 1186/1751 (67.7%) | 193/281 (68.7%) |
| Previous myocardial infarction | 312/1751 (17.8%) | 52/281 (18.5%) |
| Previous coronary artery bypass graft | 436/1751 (24.9%) | 64/281 (22.8%) |
| Previous percutaneous coronary intervention | 479/1751 (27.4%) | 77/281 (27.4%) |
| Prior balloon aortic valvuloplasty | 86/1751 (4.9%) | 15/281 (5.3%) |
| Cerebral vascular disease | 1186/1751 (67.7%) | 193/281 (68.7%) |
| Peripheral vascular disease | 532/1751 (30.4%) | 86/281 (30.6%) |
| Diabetes mellitus | 646/1751 (36.9%) | 84/281 (29.9%) |
| Chronic obstructive pulmonary disease | | |
| Any | 549/1744 (31.5%) | 78/277 (28.2%) |
| Oxygen dependent | 56/1734 (3.2%) | 10/276 (3.6%) |
| Renal insufficiency* | 90/1751 (5.1%) | 14/281 (5.0%) |
| Atrial fibrillation | 583/1751 (33.3%) | 89/281 (31.7%) |
| Permanent pacemaker | 209/1751 (11.9%) | 32/281 (11.4%) |
| Frail condition | | |
| 5-Meter walk-test time >7 sec | 723/1607 (45.0%) | 111/230 (48.3%) |
| Serum albumin < 3.5 g/dl | 257/1716 (15.0%) | 33/223 (14.8%) |
| Liver disease | 43/1751 (2.5%) | 2/281 (0.7%) |
| Aortic valve area, $cm^2$ | 0.7 ± 0.18 (1615) | 0.7 ± 0.23 (235) |
| Mean gradient, mm Hg | 44.7 ± 13.04 (1718) | 45.3 ± 12.50 (251) |
| Left ventricular ejection fraction, % | 55.8 ± 11.32 (1177) | 55.4 ± 11.78 (160) |
| Left ventricular mass index, $g/m^2$ | 120.1 ± 32.26 (1563) | 122.4 ± 32.76 (220) |
| Moderate or severe mitral regurgitation | 271/1573 (17.2%) | 51/220 (23.2%) |

***** Cr ≥ 2 mg/dL

**Table S3. Primary Endpoint with Multiple Imputation**

| Event | TAVR (N=1011) | SAVR (N=1021) | HR 95% CI |
|---|---|---|---|
| All-cause death or Disabling Stroke | 48.7% | 45.6% | 1.06 (0.94, 1.21) |

**Table S4. Clinical Endpoints at 2 and 5 Years* (Transfemoral and Transthoracic Access Cohorts)**

| | At 2 Years | | | At 5 Years | | |
|---|---|---|---|---|---|---|
| | TAVR (N = 775) | Surgery (N = 775) | HR (95% CI) | TAVR (N = 775) | Surgery (N = 775) | HR (95% CI) |
| **Transfemoral-access cohort** | | | | | | |
| Death from any cause or disabling stroke | 128 (16.8) | 149 (20.4) | 0.79 (0.62 to 1.00) | 324 (44.5) | 287 (42.0) | 1.02 (0.87 to 1.20) |
| Death | | | | | | |
| From any cause | 108 (14.2) | 124 (17.2) | 0.80 (0.62 to 1.04) | 310 (42.7) | 273 (40.5) | 1.03 (0.87 to 1.21) |
| From cardiac causes | 67 (9.0) | 78 (11.1) | 0.80 (0.57 to 1.10) | 179 (27.4) | 169 (27.3) | 0.96 (0.78 to 1.19) |
| Not from cardiac causes | 41 (5.7) | 46 (6.9) | 0.81 (0.53 to 1.23) | 131 (21.1) | 104 (18.2) | 1.13 (0.88 to 1.47) |
| Neurologic event | | | | | | |
| Any event | 85 (11.6) | 80 (11.2) | 1.01 (0.74 to 1.37) | 123 (18.7) | 101 (15.6) | 1.14 (0.88 to 1.49) |
| Transient ischemic attack | 27 (3.8) | 15 (2.3) | 1.68 (0.89 to 3.16) | 38 (5.8) | 24 (4.3) | 1.47 (0.88 to 2.45) |
| Any stroke | 62 (8.4) | 67 (9.2) | 0.88 (0.62 to 1.24) | 91 (14.1) | 81 (12.2) | 1.05 (0.78 to 1.42) |
| Disabling stroke | 39 (5.3) | 48 (6.7) | 0.77 (0.50 to 1.17) | 57 (8.7) | 56 (8.3) | 0.95 (0.66 to 1.37) |
| Nondisabling stroke | 24 (3.2) | 21 (2.9) | 1.10 (0.61 to 1.98) | 32 (4.9) | 26 (4.0) | 1.17 (0.70 to 1.97) |
| Rehospitalization | 133 (18.4) | 118 (17.1) | 1.04 (0.81 to 1.34) | 210 (32.0) | 154 (24.1) | 1.26 (1.02 to 1.55) |
| Aortic-valve reintervention | 4 (0.6) | 4 (0.6) | 0.92 (0.23 to 3.67) | 19 (3.7) | 5 (0.9) | 3.48 (1.30 to 9.33) |
| | **TAVR (N=236)** | **Surgery (N=246)** | **HR (95% CI)** | **TAVR (N=236)** | **Surgery (N=246)** | **HR (95% CI)** |
| **Transthoracic-access cohort** | | | | | | |
| Death from any cause or disabling stroke | 64 (27.7) | 53 (23.4) | 1.21 (0.84 to 1.74) | 132 (59.3) | 101 (48.3) | 1.32 (1.02 to 1.71) |
| Death | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| From any cause | 58 (25.1) | 46 (20.7) | 1.26 (0.86 to 1.86) | 126 (56.9) | 97 (47.3) | 1.31 (1.01 to 1.71) |
| From cardiac causes | 30 (13.7) | 27 (12.7) | 1.11 (0.66 to 1.87) | 66 (36.5) | 54 (29.7) | 1.24 (0.86 to 1.77) |
| Not from cardiac causes | 28 (13.2) | 19 (9.2) | 1.47 (0.82 to 2.63) | 60 (32.1) | 43 (24.9) | 1.41 (0.95 to 2.08) |
| Neurologic event | | | | | | |
| Any event | 36 (16.4) | 24 (11.0) | 1.56 (0.93 to 2.62) | 43 (22.4) | 33 (17.2) | 1.36 (0.87 to 2.15) |
| Transient ischemic attack | 7 (3.5) | 6 (3.0) | 1.17 (0.39 to 3.48) | 7 (3.5) | 8 (4.5) | 0.88 (0.32 to 2.43) |
| Any stroke | 29 (12.9) | 18 (7.9) | 1.68 (0.93 to 3.03) | 37 (19.5) | 26 (13.5) | 1.49 (0.90 to 2.46) |
| Disabling stroke | 20 (9.1) | 13 (5.6) | 1.57 (0.78 to 3.16) | 26 (13.6) | 19 (9.7) | 1.40 (0.77 to 2.53) |
| Nondisabling stroke | 9 (3.8) | 6 (3.0) | 1.57 (0.56 to 4.40) | 11 (6.0) | 7 (3.6) | 1.64 (0.64 to 4.23) |
| Rehospitalization | 53 (25.1) | 40 (19.2) | 1.39 (0.92 to 2.09) | 71 (37.8) | 55 (28.9) | 1.36 (0.96 to 1.94) |
| Aortic-valve reintervention | 2 (1.0) | 0 (0) | N/A | 2 (1.0) | 1 (0.6) | 2.00 (0.18 to 22.03) |

Abbreviations: CI, confidence interval.

*Event measures are Kaplan-Meier estimates % (no. of patients with event)

**Table S5. Adjudicated Causes of Death**

| | TAVR | Surgery |
|---|---|---|
| Cardiovascular causes | 245 | 223 |
| Procedure related | 18 | 27 |
| Cardiac disease | 91 | 75 |
| Non-coronary vascular condition such as pulmonary embolism | 4 | 2 |
| Non-coronary vascular condition such as stroke or intracranial hemorrhage | 25 | 18 |
| Unwitnessed and unknown | 107 | 101 |
| Non-cardiovascular causes | 191 | 147 |
| Accidental or trauma | 9 | 8 |
| Gastrointestinal | 8 | 7 |
| Hepatobiliary | 3 | 2 |
| Infectious | 65 | 43 |
| Malignancy | 38 | 29 |
| Hemorrhage | 0 | 6 |
| Neurologic process not related to stroke or intracranial hemorrhage | 11 | 9 |
| Non-cardiovascular surgery or procedure | 1 | 0 |
| Pancreatic | 1 | 1 |
| Pulmonary | 33 | 26 |
| Renal causes | 16 | 11 |
| Suicide | 2 | 0 |
| Systemic inflammatory response syndrome | 0 | 1 |
| Other | 4 | 4 |

**Table S6. Clinical Endpoints at 2 Years and 5 Years* (AT Population)**

| Outcomes | At 2 Years | | | At 5 Years | | |
|---|---|---|---|---|---|---|
| | TAVR (n = 994) | Surgery (n = 944) | HR (95% CI) | TAVR (n = 994) | Surgery (n = 944) | HR (95% CI) |
| Death from any cause or disabling stroke | 186 (18.9%) | 195 (21.0%) | 0.87 (0.71 to 1.07) | 450 (47.7%) | 381 (43.4%) | 1.08 (0.94 to 1.24) |
| Death | | | | | | |
| From any cause | 160 (16.2%) | 165 (17.9%) | 0.89 (0.72 to 1.11) | 430 (45.7%) | 365 (42.0%) | 1.08 (0.94 to 1.25) |
| From cardiac causes | 92 (9.6%) | 100 (11.2%) | 0.85 (0.64 to 1.13) | 240 (29.0%) | 218 (27.6%) | 1.01 (0.84 to 1.22) |
| Not from cardiac causes | 68 (7.3%) | 65 (7.5%) | 0.96 (0.68 to 1.35) | 190 (23.5%) | 147 (19.9%) | 1.19 (0.96 to 1.47) |
| Neurologic event | | | | | | |
| Any event | 121 (12.8%) | 100 (11.2%) | 1.13 (0.87 to 1.47) | 166 (19.6%) | 130 (16.1%) | 1.20 (0.95 to 1.51) |
| Transient ischemic attack | 34 (3.7%) | 21 (2.5%) | 1.51 (0.87 to 2.60) | 45 (5.3%) | 32 (4.4%) | 1.31 (0.83 to 2.06) |
| Any stroke | 91 (9.6%) | 81 (9.0%) | 1.05 (0.78 to 1.41) | 128 (15.4%) | 103 (12.5%) | 1.16 (0.89 to 1.50) |
| Disabling stroke | 59 (6.2%) | 59 (6.5%) | 0.93 (0.65 to 1.33) | 83 (9.9%) | 73 (8.7%) | 1.05 (0.77 to 1.44) |
| Nondisabling stroke | 33 (3.4%) | 25 (2.8%) | 1.24 (0.74 to 2.09) | 43 (5.1%) | 31 (3.8%) | 1.30 (0.82 to 2.07) |
| Rehospitalization | 185 (19.9%) | 158 (18.0%) | 1.09 (0.88 to 1.34) | 280 (33.3%) | 209 (25.6%) | 1.25 (1.05 to 1.50) |
| Death from any cause or rehospitalization | 300 (30.4%) | 278 (30.0%) | 1.00 (0.85 to 1.18) | 553 (57.9%) | 455 (51.1%) | 1.14 (1.01 to 1.29) |
| Death from any cause or any stroke | 217 (22.0%) | 216 (23.2%) | 0.93 (0.77 to 1.12) | 482 (50.9%) | 397 (45.1%) | 1.12 (0.98 to 1.28) |
| Death from any cause, any stroke, or rehospitalization | 340 (34.4%) | 319 (34.3%) | 0.98 (0.84 to 1.15) | 591 (61.7%) | 481 (53.6%) | 1.15 (1.02 to 1.30) |
| Myocardial infarction | 42 (4.6%) | 34 (4.0%) | 1.14 (0.73 to 1.79) | 83 (11.0%) | 59 (8.0%) | 1.29 (0.93 to 1.81) |
| New atrial fibrillation | 111 (11.5%) | 275 (29.5%) | 0.35 (0.28 to 0.43) | 140 (15.8%) | 291 (32.3%) | 0.41 (0.33 to 0.50) |
| New permanent pacemaker implantation | 114 (11.9%) | 97 (10.8%) | 1.11 (0.85 to 1.46) | 138 (15.7%) | 113 (13.5%) | 1.16 (0.90 to 1.48) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Endocarditis | 15 (1.7%) | 13 (1.5%) | 1.06 (0.50 to 2.22) | 30 (3.9%) | 19 (2.5%) | 1.45 (0.82 to 2.58) |
| Aortic-valve reintervention | 6 (0.7%) | 4 (0.5%) | 1.38 (0.39 to 4.90) | 21 (3.2%) | 6 (0.8%) | 3.26 (1.32 to 8.08) |
| Surgical Aortic-valve reintervention | 2 (0.2) | 4 (0.5) | 0.46 (0.08 to 2.53) | 3 (0.3) | 5 (0.6) | 0.55 (0.13 to 2.31) |
| Balloon Aortic Valvuloplasty | 1 (0.1) | 0 (0) | N/A | 1 (0.1) | 0 (0) | N/A |
| Valve-in-valve | 3 (0.3) | 0 (0) | N/A | 17 (2.7) | 1(0.2) | 15.87 (2.11 to 119.14) |

Abbreviations: CI, confidence interval.
*Event rates were calculated with Kaplan-Meier methods.

**Table S7. Clinical Endpoints from 2 Years to 5 Years (ITT Population) ***

| Outcomes | 2 Years to 5 Years | | |
|---|---|---|---|
| | TAVR (n = 1011) | Surgery (n = 1021) | HR (95% CI) |
| Death from any cause or disabling stroke | 278 (36.3%) | 201 (29.5%) | 1.27 (1.06 to 1.53) |
| Death | | | |
| From any cause | 270 (35.2%) | 200 (29.4%) | 1.24 (1.03 to 1.49) |
| From cardiac causes | 148 (21.5%) | 118 (18.5%) | 1.15 (0.91 to 1.47) |
| Not from cardiac causes | 122 (17.5%) | 82 (13.3%) | 1.37 (1.03 to 1.81) |
| Neurologic event | | | |
| Any event | 52 (8.0%) | 35 (5.8%) | 1.37 (0.89 to 2.10) |
| Transient ischemic attack | 14 (2.0%) | 11 (1.8%) | 1.16 (0.53 to 2.56) |
| Any stroke | 39 (6.3%) | 25 (4.2%) | 1.43 (0.87 to 2.37) |
| Disabling stroke | 25 (3.9%) | 16 (2.5%) | 1.43 (0.76 to 2.68) |
| Nondisabling stroke | 10 (1.7%) | 6 (1.0%) | 1.53 (0.56 to 4.22) |
| Rehospitalization | 131 (19.5%) | 76 (12.3%) | 1.62 (1.22 to 2.15) |
| Death from any cause or rehospitalization | 329 (42.8%) | 231 (33.9%) | 1.34 (1.14 to 1.59) |
| Death from any cause or any stroke | 289 (37.7%) | 208 (30.6%) | 1.28 (1.07 to 1.53) |
| Death from any cause, any stroke, or rehospitalization | 346 (45.0%) | 238 (34.9%) | 1.37 (1.16 to 1.62) |
| Myocardial infarction | 48 (7.6%) | 26 (4.1%) | 1.69 (1.05 to 2.73) |
| New atrial fibrillation | 35 (5.3%) | 20 (3.4%) | 1.62 (0.93 to 2.80) |
| New permanent pacemaker implantation | 25 (3.9%) | 16 (2.7%) | 1.44 (0.77 to 2.70) |

| | | | |
|---|---|---|---|
| Endocarditis | 15 (2.2%) | 6 (1.0%) | 2.30 (0.89 to 5.94) |
| Aortic-valve reintervention | 15 (2.5%) | 2 (0.3%) | 6.99 (1.60 to 30.56) |
| Surgical Aortic-valve reintervention | 1 (0.1%) | 1 (0.1%) | 0.90 (0.06 to 14.31) |
| Balloon Aortic Valvuloplasty | 0 (0.0%) | 0 (0.0%) | N/A |
| Valve-in-valve | 14 (2.4%) | 1 (0.2%) | 13.09 (1.72 to 99.51) |

Abbreviations: CI, confidence interval.
*Event rates were calculated with Kaplan-Meier methods.

**Table S8. Restricted Mean Survival/Freedom from Event Time for TAVR and Surgery to 5 Years (ITT Population)**

| Statistic | TAVR (95% CI) | Surgery (95% CI) | Difference (TAVR – Surgery) (95% CI) |
|---|---|---|---|
| Restricted mean survival time (months) | 46.3 (45.1 to 47.5) | 46.6 (45.2 to 47.9) | -0.26 (-2.1 to 1.5) |
| Restricted freedom from event time for death or disabling stroke (months) | 45.0 (43.7 to 46.3) | 44.8 (43.4 to 46.2) | 0.14 (-1.8 to 2.0) |

*Analysis based on Restricted Mean Survival Time (Royston & Parmar), BMC Medical Research Methodology, 204;13-152.*

**Table S9. Rehospitalization Details**

| | TAVR | Surgery | Total |
|---|---|---|---|
| **Hospitalization** | 461 | 312 | 773 |
| **Valve or Procedure related** | 145 | 94 | 239 |
| **Valve Related** | 92 | 31 | 123 |
| **Hospitalization With*** | | | |
| **CHF** | 384 | 240 | 624 |
| **Coronary Ischemia** | 2 | 2 | 4 |
| **Arrhythmia** | 34 | 28 | 62 |
| **Endocarditis** | 16 | 10 | 26 |
| **Syncope** | 9 | 8 | 17 |
| **Pericardial Effusion** | 3 | 1 | 4 |
| **Vascular or Access site related events** | 23 | 17 | 40 |
| **Bleeding** | 11 | 10 | 21 |
| **Stroke/TIA** | 7 | 10 | 17 |
| **AKI** | 9 | 10 | 19 |
| **Others** | | | 35 |
| **Infection** | 5 | 3 | 8 |
| **Plural effusion/ Respiratory Failure** | 1 | 13 | 14 |
| **PVL/AI** | 5 | 1 | 6 |
| **Bleeding** | 1 | 2 | 3 |
| **Pericardial Tamponade** | 1 | 0 | 1 |

*note: categories are not mutually exclusive

**Table S10. Incidence and Case Details for Aortic-Valve Reintervention***

| | TAVR (N=21) | Surgery (N=6) |
|---|---|---|
| Kaplan-Meier Rate (%) | 3.2 | 0.8 |
| Reason for Reintervention | | |
| Valve Stenosis** | 10 (48) | 1 (16.7) |
| Aortic Regurgitation | 11 (52) | 1 (16.7) |
| Paravalvular | 6 (29) | 1 (16.7) |
| Transvalvular | 0 | 0 |
| Combined | 5 (24) | 0 |
| Infection/Endocarditis | 0 | 4 (66.7) |
| Treatment Type | | |
| Percutaneous Intervention | 18 (86) | 0 |
| Valve-in-Valve | 17 (81) | 1 (16.7) |
| Valvuloplasty | 1 (5) | 0 |
| Surgery | 3 (14) | 5 (83.3) |
| In-Hospital Mortality† | 1 (5) | 3 (50) |

*No. of patients (%) unless otherwise specified

** One case included a possible valve thrombosis

†One in-hospital mortality case in the TAVR cohort occurred after valvuloplasty

**Table S11. Echocardiographic Characteristics (Valve Implant Population)**

**A. With Multiple Imputation**

| | TAVR (N= 974) | Surgery (N= 936) |
|---|---|---|
| **Effective Orifice Area, $cm^2$ mean ± SD (n)** | | |
| Baseline | 0.70 ± 0.173 (974) | 0.69 ± 0.203 (936) |
| 30 Days | 1.66 ± 0.430 (945) | 1.46 ± 0.435 (903) |
| 1 Year | 1.56 ± 0.426 (863) | 1.44 ± 0.397 (821) |
| 2 Years | 1.54 ± 0.443 (821) | 1.40 ± 0.424 (776) |
| 3 Years | 1.54 ± 0.436 (730) | 1.37 ± 0.421 (718) |
| 4 Years | 1.49 ± 0.421 (646) | 1.33 ± 0.398 (657) |
| 5 Years | 1.50 ± 0.476 (551) | 1.36 ± 0.437 (576) |
| **Mean Gradient, mmHg mean ± SD (n)** | | |
| Baseline | 44.99 ± 13.329 (974) | 44.68 ± 12.695 (936) |
| 30 Days | 9.68 ± 3.555 (945) | 10.96 ± 4.201 (904) |
| 1 Year | 10.79 ± 4.467 (863) | 11.47 ± 4.355 (821) |
| 2 Years | 10.77 ± 4.621 (821) | 11.64 ± 4.718 (776) |
| 3 Years | 10.89 ± 4.724 (730) | 11.85 ± 4.896 (718) |
| 4 Years | 11.33 ± 5.461 (646) | 11.58 ± 4.936 (657) |
| 5 Years | 11.65 ± 6.409 (551) | 11.11 ± 5.233 (577) |
| **Left Ventricular Ejection Fraction, % mean ± SD (n)** | | |
| Baseline | 55.74 ± 10.985 (974) | 55.57 ± 12.043 (936) |
| 30 Days | 56.42 ± 10.385 (945) | 54.93 ± 10.678 (902) |
| 1 Year | 55.96 ± 11.188 (863) | 57.01 ± 10.450 (822) |
| 2 Years | 54.50 ± 10.979 (820) | 56.59 ± 10.027 (776) |
| 3 Years | 54.33 ± 9.945 (730) | 58.47 ± 9.731 (718) |
| 4 Years | 55.11 ± 10.357 (646) | 57.00 ± 9.372 (657) |
| 5 Years | 55.40 ± 11.032 (551) | 59.19 ± 10.488 (576) |
| **Total Aortic Regurgitation, n/N (%)** | | |
| Baseline | | |
| None or Trace | 473/974 (48.6%) | 436/936 (46.6%) |
| Mild | 390/974 (40.0%) | 386/936 (41.2%) |
| Moderate or Severe | 111/974 (11.4%) | 114/936 (12.2%) |

| | TAVR (N= 974) | Surgery (N= 936) |
|---|---|---|
| 30 Days | | |
| None or Trace | 693/945 (73.3%) | 871/904 (96.3%) |
| Mild | 217/945 (23.0%) | 27/904 (3.0%) |
| Moderate or Severe | 35/945 (3.7%) | 6/904 (0.7%) |
| 2 Years | | |
| None or Trace | 522/821 (63.6%) | 719/776 (92.7%) |
| Mild | 220/821 (26.8%) | 51/776 (6.6%) |
| Moderate or Severe | 79/821 (9.6%) | 6/776 (0.8%) |
| 5 Years | | |
| None or Trace | 349/551 (63.3%) | 520/576 (90.3%) |
| Mild | 163/551 (29.6%) | 48/576 (8.3%) |
| Moderate or Severe | 39/551 (7.1%) | 8/576 (1.4%) |
| **Paravalvular Regurgitation, n/N (%)** | | |
| 30 Days | | |
| None or Trace | 701/945 (74.2%) | 875/904 (96.8%) |
| Mild | 210/945 (22.2%) | 24/904 (2.7%) |
| Moderate or Severe | 34/945 (3.6%) | 5/904 (0.6%) |
| 2 Years | | |
| None or Trace | 544/821 (66.3%) | 746/776 (96.1%) |
| Mild | 207/821 (25.2%) | 27/776 (3.5%) |
| Moderate or Severe | 70/821 (8.5%) | 3/776 (0.4%) |
| 5 Years | | |
| None or Trace | 379/551 (68.8%) | 535/576 (92.9%) |
| Mild | 139/551 (25.2%) | 39/576 (6.8%) |
| Moderate or Severe | 33/551 (6.0%) | 2/576 (0.3%) |

**B. Paired Analyses**

| | TAVR (N= 974) | Surgery (N= 936) |
|---|---|---|
| **Effective Orifice Area, $cm^2$ mean ± SD (n)** | | |
| Baseline | 0.70 ± 0.178 (138) | 0.68 ± 0.179 (139) |
| 30 Days | 1.61 ± 0.406 (138) | 1.49 ± 0.438 (139) |
| 1 Year | 1.56 ± 0.425 (138) | 1.42 ± 0.405 (139) |
| 2 Years | 1.49 ± 0.423 (138) | 1.38 ± 0.441 (139) |
| 3 Years | 1.51 ± 0.450 (138) | 1.37 ± 0.408 (139) |
| 4 Years | 1.48 ± 0.446 (138) | 1.36 ± 0.448 (139) |
| 5 Years | 1.45 ± 0.457 (138) | 1.35 ± 0.413 (139) |
| **Mean Gradient, mmHg mean ± SD (n)** | | |
| Baseline | 45.49 ± 13.312 (235) | 44.84 ± 12.356 (214) |
| 30 Days | 9.89 ± 3.810 (235) | 10.93 ± 4.114 (214) |
| 1 Year | 11.07 ± 4.583 (235) | 11.50 ± 4.129 (214) |
| 2 Years | 11.21 ± 4.930 (235) | 11.98 ± 4.812 (214) |
| 3 Years | 10.91 ± 5.016 (235) | 11.64 ± 4.701 (214) |
| 4 Years | 11.24 ± 5.649 (235) | 11.66 ± 4.965 (214) |
| 5 Years | 11.31 ± 6.624 (235) | 11.04 ± 4.894 (214) |
| **Left Ventricular Ejection Fraction, % mean ± SD (n)** | | |
| Baseline | 56.96 ± 9.517 (65) | 56.81 ± 10.707 (54) |
| 30 Days | 57.42 ± 9.844 (65) | 55.42 ± 11.200 (54) |
| 1 Year | 54.98 ± 10.782 (65) | 57.35 ± 8.289 (54) |
| 2 Years | 56.03 ± 10.155 (65) | 57.46 ± 9.284 (54) |
| 3 Years | 56.83 ± 10.203 (65) | 59.34 ± 6.988 (54) |
| 4 Years | 56.50 ± 10.721 (65) | 60.23 ± 7.089 (54) |
| 5 Years | 55.49 ± 10.205 (65) | 60.18 ± 7.719 (54) |
| **Total Aortic Regurgitation, n/N (%)** | | |
| Baseline | | |
| None or Trace | 101/220 (45.9%) | 99/203 (48.8%) |
| Mild | 87/220 (39.5%) | 86/203 (42.4%) |
| Moderate or Severe | 32/220 (14.5%) | 18/203 (8.9%) |
| 30 Days | | |
| None or Trace | 159/220 (72.3%) | 199/203 (98.0%) |

| | TAVR (N= 974) | Surgery (N= 936) |
|---|---|---|
| Mild | 54/220 (24.5%) | 4/203 (2.0%) |
| Moderate or Severe | 7/220 (3.2%) | 0/203 (0.0%) |
| 2 Years | | |
| None or Trace | 163/220 (74.1%) | 199/203 (98.0%) |
| Mild | 48/220 (21.8%) | 4/203 (2.0%) |
| Moderate or Severe | 9/220 (4.1%) | 0/203 (0.0%) |
| 5 Years | | |
| None or Trace | 118/220 (53.6%) | 181/203 (89.2%) |
| Mild | 84/220 (38.2%) | 20/203 (9.9%) |
| Moderate or Severe | 18/220 (8.2%) | 2/203 (1.0%) |
| **Paravalvular Regurgitation, n/N (%)** | | |
| 30 Days | | |
| None or Trace | 139/190 (73.2%) | 169/172 (98.3%) |
| Mild | 45/190 (23.7%) | 3/172 (1.7%) |
| Moderate or Severe | 6/190 (3.2%) | 0/172 (0.0%) |
| 2 Years | | |
| None or Trace | 122/190 (64.2%) | 169/172 (98.3%) |
| Mild | 48/190 (25.3%) | 3/172 (1.7%) |
| Moderate or Severe | 20/190 (10.5%) | 0/172 (0.0%) |
| 5 Years | | |
| None or Trace | 118/190 (62.1%) | 160/172 (93.0%) |
| Mild | 59/190 (31.1%) | 11/172 (6.4%) |
| Moderate or Severe | 13/190 (6.8%) | 1/172 (0.6%) |

**Table S12. Left Ventricular Size and Function (Valve Implant Population)**

| | TAVR (N= 974) | Surgery (N= 936) |
|---|---|---|
| **LVESD, cm** | | |
| Baseline | 3.22 ± 0.84 (856) | 3.22 ± 0.85 (825) |
| 30 Days | 3.21 ± 0.78 (804) | 3.16 ± 0.78 (723) |
| 30d change from baseline | -0.00 ± 0.52 (744) | -0.08 ± 0.52 (656) |
| 2 Years | 3.26 ± 0.87 (534) | 3.08 ± 0.75 (476) |
| 2y change from baseline | 0.02 ± 0.61 (491) | -0.16 ± 0.67 (428) |
| 5 Years | 3.34 ± 0.87 (288) | 3.15 ± 0.81 (269) |
| 5y change from baseline | 0.11 ± 0.73 (263) | -0.01 ± 0.70 (239) |
| **LVEDD, cm** | | |
| Baseline | 4.57 ± 0.717 (865) | 4.59 ± 0.711 (831) |
| 30 Days | 4.65 ± 0.701 (809) | 4.43 ± 0.669 (729) |
| 30d change from baseline | 0.07 ± 0.457 (753) | -0.18 ± 0.466 (665) |
| 2 Years | 4.58 ± 0.790 (539) | 4.43 ± 0.658 (479) |
| 2y change from baseline | -0.02 ± 0.576 (498) | -0.19 ± 0.591 (436) |
| 5 Years | 4.67 ± 0.784 (291) | 4.46 ± 0.718 (275) |
| 5y change from baseline | 0.06 ± 0.567 (266) | -0.08 ± 0.572 (248) |
| **LVESV, mL** | | |
| Baseline | 46.49 ± 26.421 (641) | 49.51 ± 30.531 (630) |
| 30 Days | 47.40 ± 28.847 (587) | 44.16 ± 25.362 (504) |
| 30d change from baseline | -0.94 ± 13.587 (468) | -5.42 ± 14.994 (403) |
| 2 Years | 49.28 ± 31.577 (364) | 39.96 ± 23.646 (303) |
| 2y change from baseline | -0.64 ± 19.575 (291) | -8.82 ± 22.163 (249) |
| 5 Years | 47.43 ± 32.365 (216) | 36.41 ± 20.337 (178) |
| 5y change from baseline | 1.57 ± 24.305 (163) | -12.76 ± 28.189 (139) |
| **LVEDV, mL** | | |
| Baseline | 102.24 ± 37.07 (642) | 104.88 ± 39.96 (630) |
| 30 Days | 104.99 ± 40.59 (588) | 94.14 ± 34.37 (506) |
| 30d change from baseline | 0.55 ± 20.10 (469) | -11.01 ± 20.40 (405) |
| 2 Years | 103.41 ± 41.96 (364) | 89.13 ± 33.43 (302) |
| 2y change from baseline | -3.01 ± 27.38 (290) | -16.19 ± 28.87 (248) |

| | TAVR (N= 974) | Surgery (N= 936) |
|---|---|---|
| 5 Years | 98.91 ± 43.43 (215) | 84.29 ± 28.49 (178) |
| 5y change from baseline | -4.03 ± 31.60 (161) | -20.54 ± 32.81 (140) |
| **LV Mass index, g/m$^2$** | | |
| Baseline | 119.76 ± 31.52 (865) | 120.62 ± 32.61 (830) |
| 30 Days | 116.76 ± 30.59 (808) | 107.55 ± 29.59 (729) |
| 30d change from baseline | -3.74 ± 20.393 (752) | -13.46 ± 22.906 (664) |
| 2 Years | 109.59 ± 30.67 (538) | 102.86 ± 28.45 (479) |
| 2y change from baseline | -10.06 ± 24.058 (497) | -18.16 ± 25.074 (435) |
| 5 Years | 103.61 ± 30.33 (290) | 95.22 ± 25.93 (274) |
| 5y change from baseline | -13.89 ± 26.555 (266) | -22.59 ± 26.912 (247) |
| **LV Ejection Fraction, %** | | |
| Baseline | 56.37 ± 10.56 (640) | 55.43 ± 11.75 (629) |
| 30 Days | 56.88 ± 10.22 (587) | 55.03 ± 10.99 (504) |
| 30d change from baseline | 0.96 ± 7.13 (467) | -0.29 ± 8.13 (403) |
| 2 Years | 54.83 ± 11.17 (364) | 57.18 ± 9.75 (301) |
| 2y change from baseline | -0.93 ± 9.94 (290) | 0.88 ± 10.06 (247) |
| 5 Years | 54.81 ± 11.13 (214) | 58.40 ± 8.77 (177) |
| 5y change from baseline | -2.78 ± 10.27 (160) | 2.73 ± 11.39 (138) |

Abbreviations: LV, left ventricle; LVESD, left ventricular end systolic diameter; LVEDV, left ventricular end diastolic diameter; LVESV, left ventricular end systolic volume; LVEDV, left ventricular end diastolic volume.
*Data are mean ± SD (n observations).
Note: The number of observations varies based upon whether each particular measurement was evaluable by the echo core lab

**Table S13. New York Heart Association Class (Intention to Treat Population)**

**A. With Multiple Imputation**

| | TAVR (N = 1011) | Surgery (N = 1021) |
|---|---|---|
| **NYHA Class 3 or 4, n/N (%)** | | |
| Baseline | 782/1011 (77.3%) | 777/1021 (76.1%) |
| 30 Days | 101/972 (10.4%) | 142/982 (14.5%) |
| 6 Months | 55/938 (5.9%) | 74/930 (8.0%) |
| 1 Year | 70/888 (7.9%) | 62/899 (6.9%) |
| 2 Years | 77/848 (9.1%) | 56/851 (6.6%) |
| 3 Years | 84/756 (11.1%) | 47/793 (5.9%) |
| 4 Years | 69/670 (10.3%) | 66/732 (9.0%) |
| 5 Years | 53/577 (9.2%) | 49/651 (7.5%) |

**B. Paired Analysis**

| | TAVR (N = 323) | Surgery (N = 280) |
|---|---|---|
| **NYHA Class 3 or 4, n/N (%)** | | |
| Baseline | 234/323 (72.4%) | 76/280 (27.1%) |
| 30 Days | 22/323 (6.8%) | 25/280 (8.9%) |
| 6 Months | 14/323 (4.3%) | 12/280 (4.3%) |
| 1 Year | 14/323 (4.3%) | 1/280 (1.4%) |
| 2 Years | 19/323 (5.9%) | 11/280 (3.9%) |
| 3 Years | 24/323 (7.4%) | 14/280 (5.0%) |
| 4 Years | 25/323 (7.7%) | 17/280 (6.1%) |
| 5 Years | 33/323 (10.2%) | 18/280 (6.4%) |

**Table S14. Kansas City Cardiomyopathy Questionnaire Overall Summary Score (Intention to Treat Population)**

**A. Linear Mixed Effects Model**

| | TAVR (N = 1011) | Surgery (N = 1021) |
|---|---|---|
| **KCCQ-OS, Least Squares Mean ± SD (n)** | | |
| Baseline | 54.9 ± 0.60 (950) | 54.8 ± 0.62 (883) |
| 30 Days | 70.3 ± 0.62 (913) | 59.1 ± 0.67 (792) |
| 1 Year | 75.9 ± 0.66 (797) | 76.5 ± 0.72 (686) |
| 2 Years | 74.2 ± 0.70 (717) | 73.9 ± 0.76 (618) |
| 3 Years | 71.5 ± 0.76 (580) | 72.8 ± 0.82 (505) |
| 4 Years | 72.5 ± 0.85 (470) | 72.1 ± 0.88 (446) |
| 5 Years | 71.3 ± 0.95 (373) | 72.1 ± 1.00 (342) |
| **KCCQ-OS Change from Baseline, Least Squares Mean ± SD (n)** | | |
| 30 Days | 14.5 ± 0.69 (874) | 3.20 ± 0.75 (731) |
| 1 Year | 19.9 ± 0.72 (762) | 20.5 ± 0.78 (634) |
| 2 Years | 18.0 ± 0.75 (683) | 18.0 ± 0.82 (573) |
| 3 Years | 15.2 ± 0.82 (561) | 16.7 ± 0.89 (478) |
| 4 Years | 16.0 ± 0.90 (450) | 15.8 ± 0.95 (419) |
| 5 Years | 14.9 ± 1.02 (359) | 15.9 ± 1.07 (322) |

**B. Paired Analysis**

| | TAVR (N = 290) | Surgery (N = 261) |
|---|---|---|
| **KCCQ-OS Change from Baseline ≥ 20, n/N %** | | |
| 30 Days | 134/290 (46.2%) | 72/261 (27.6%) |
| 1 Year | 161/290 (55.5%) | 135/261 (51.7%) |
| 2 Years | 151/290 (52.1%) | 132/261 (50.6%) |
| 3 Years | 136/290 (46.9%) | 119/261 (45.6%) |
| 4 Years | 140/290 (48.3%) | 123/261 (47.1%) |
| 5 Years | 125/290 (43.1%) | 115/261 (44.1%) |
| **KCCQ-OS Change from Baseline ≥ 10, n/N %** | | |
| 30 Days | 193/290 (66.6%) | 111/261 (42.5%) |
| 1 Year | 213/290 (73.4%) | 186/261 (71.3%) |
| 2 Years | 208/290 (71.7%) | 182/261 (69.7%) |
| 3 Years | 199/290 (68.6%) | 170/261 (65.1%) |
| 4 Years | 186/290 (64.1%) | 163/261 (62.5%) |
| 5 Years | 181/290 (62.4%) | 156/261 (59.8%) |

**Figure S1. Study Flow Chart**

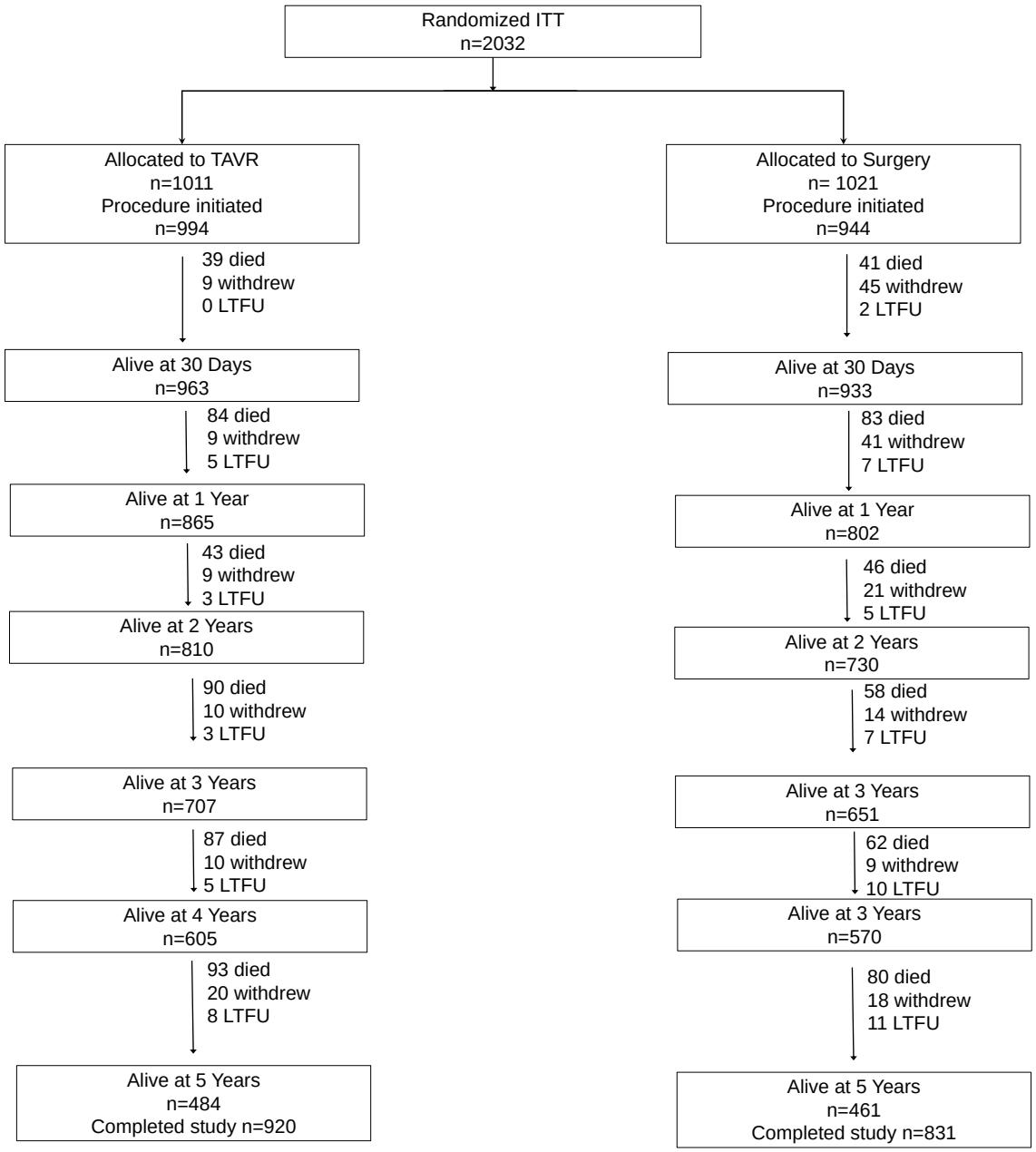
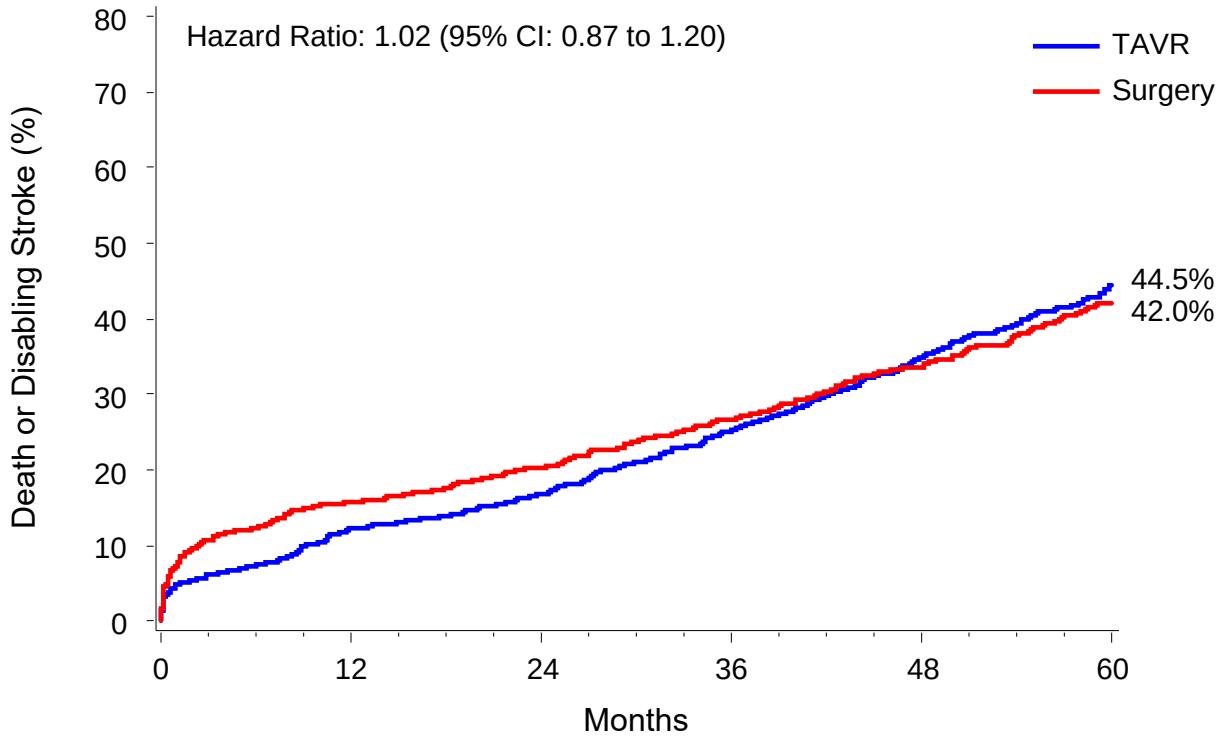


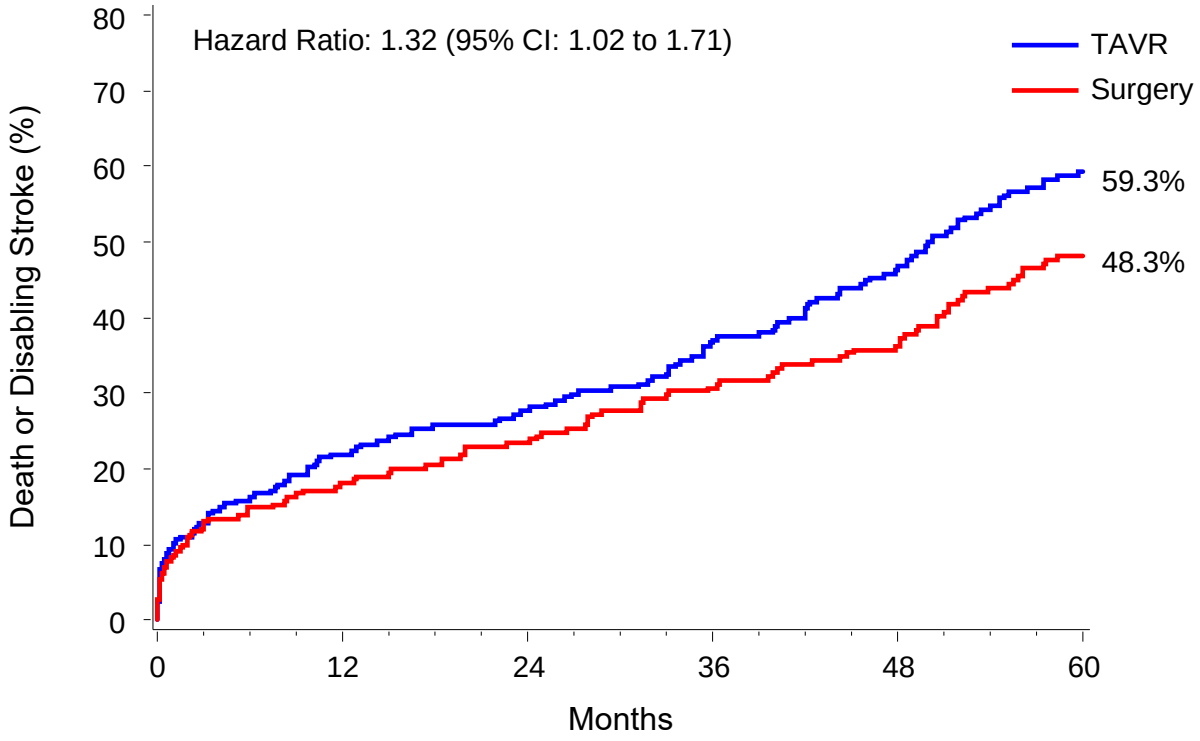
**Figure S2. Time-to-Event Curves for Death or Disabling Stroke stratified by Access**
**A. Transfemoral-access Cohort**




***No. at risk:***

| | | | | | | |
|---|---|---|---|---|---|---|
| TAVR | 775 | 664 | 622 | 548 | 464 | 388 |
| Surgery | 775 | 596 | 547 | 486 | 425 | 347 |

**B. Transthoracic-access Cohort**




***No. at risk:***

| | | | | | | |
|---|---|---|---|---|---|---|
| TAVR | 236 | 179 | 163 | 139 | 117 | 86 |
| Surgery | 246 | 175 | 157 | 139 | 122 | 93 |

**Figure S3. Subgroup Analyses of Death from Any Cause or Disabling Stroke at 5 Years**

| Subgroup | No. of Patients | TAVR | SAVR | Hazard Ratio [95% CI] |
|---|---|---|---|---|
| Overall | 2032 | 460/1011(48.4) | 391/1021(43.9) | 1.09[0.95-1.25] |
| Age | | | | |
| <85 | 1245 | 269/626(45.4) | 229/619(42.0) | 1.07[0.89-1.27] |
| >=85 | 787 | 191/385(53.3) | 162/402(46.7) | 1.13[0.92-1.39] |
| Gender | | | | |
| Female | 924 | 196/463(45.6) | 154/461(38.5) | 1.15[0.93-1.42] |
| Male | 1108 | 264/548(50.7) | 237/560(48.0) | 1.06[0.89-1.26] |
| Body Mass Index | | | | |
| <=25 | 611 | 149/303(51.9) | 132/308(50.9) | 0.95[0.75-1.20] |
| >25 | 1421 | 311/708(46.9) | 259/713(41.0) | 1.15[0.98-1.36] |
| STS Score | | | | |
| <=5 | 897 | 179/469(40.0) | 155/428(40.9) | 0.95[0.76-1.17] |
| >5 | 1134 | 281/542(55.9) | 235/592(45.9) | 1.23[1.03-1.46] |
| Left Ventricular Ejection Fraction | | | | |
| <=55 | 496 | 112/237(51.1) | 110/259(47.0) | 1.03[0.80-1.35] |
| >55 | 841 | 190/426(46.8) | 148/415(40.4) | 1.20[0.97-1.49] |
| Moderate or severe mitral regrugitation | | | | |
| No | 1471 | 333/748(47.0) | 279/723(42.6) | 1.08[0.92-1.26] |
| Yes | 322 | 78/151(55.8) | 75/171(51.5) | 1.09[0.79-1.49] |
| Previous CABG | | | | |
| No | 1532 | 368/772(50.7) | 292/760(44.0) | 1.15[0.98-1.34] |
| Yes | 500 | 92/239(41.0) | 99/261(43.3) | 0.91[0.68-1.20] |
| Peripheral Vascular Disease | | | | |
| No | 1414 | 330/729(48.5) | 256/685(42.3) | 1.13[0.96-1.33] |
| Yes | 618 | 130/282(48.1) | 135/336(47.2) | 1.02[0.80-1.29] |
| 5-meter walk test | | | | |
| <=7 sec | 1003 | 217/520(44.3) | 179/483(40.8) | 1.03[0.85-1.26] |
| >7 sec | 834 | 208/416(52.7) | 167/418(45.7) | 1.18[0.96-1.44] |
| Access Route | | | | |
| Transfemoral | 1550 | 328/775(45.1) | 289/775(42.4) | 1.03[0.88-1.20] |
| Transthoracic | 482 | 132/236(59.3) | 102/246(48.8) | 1.31[1.01-1.69] |

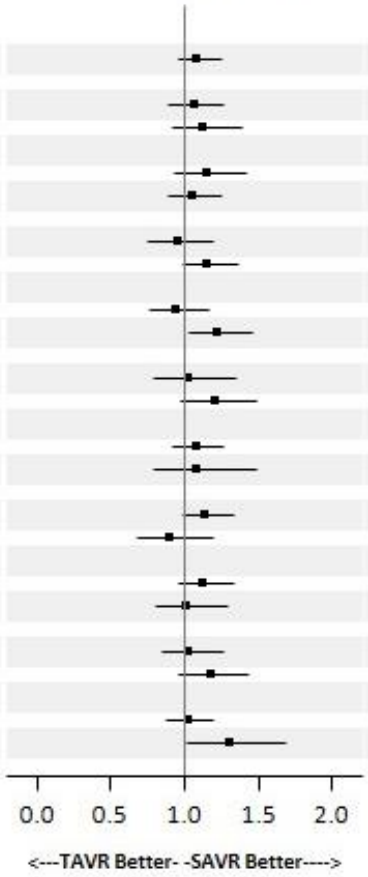
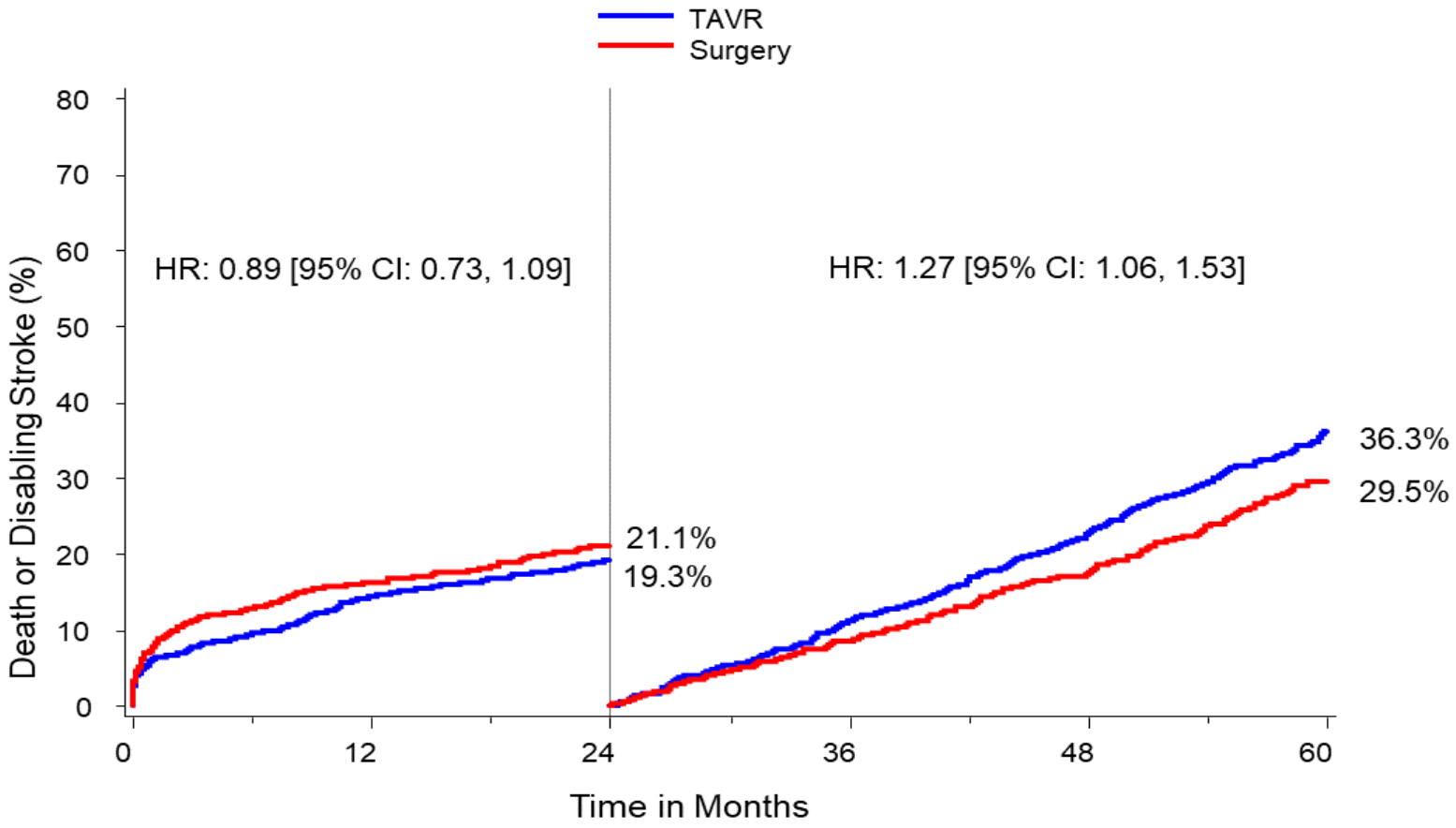


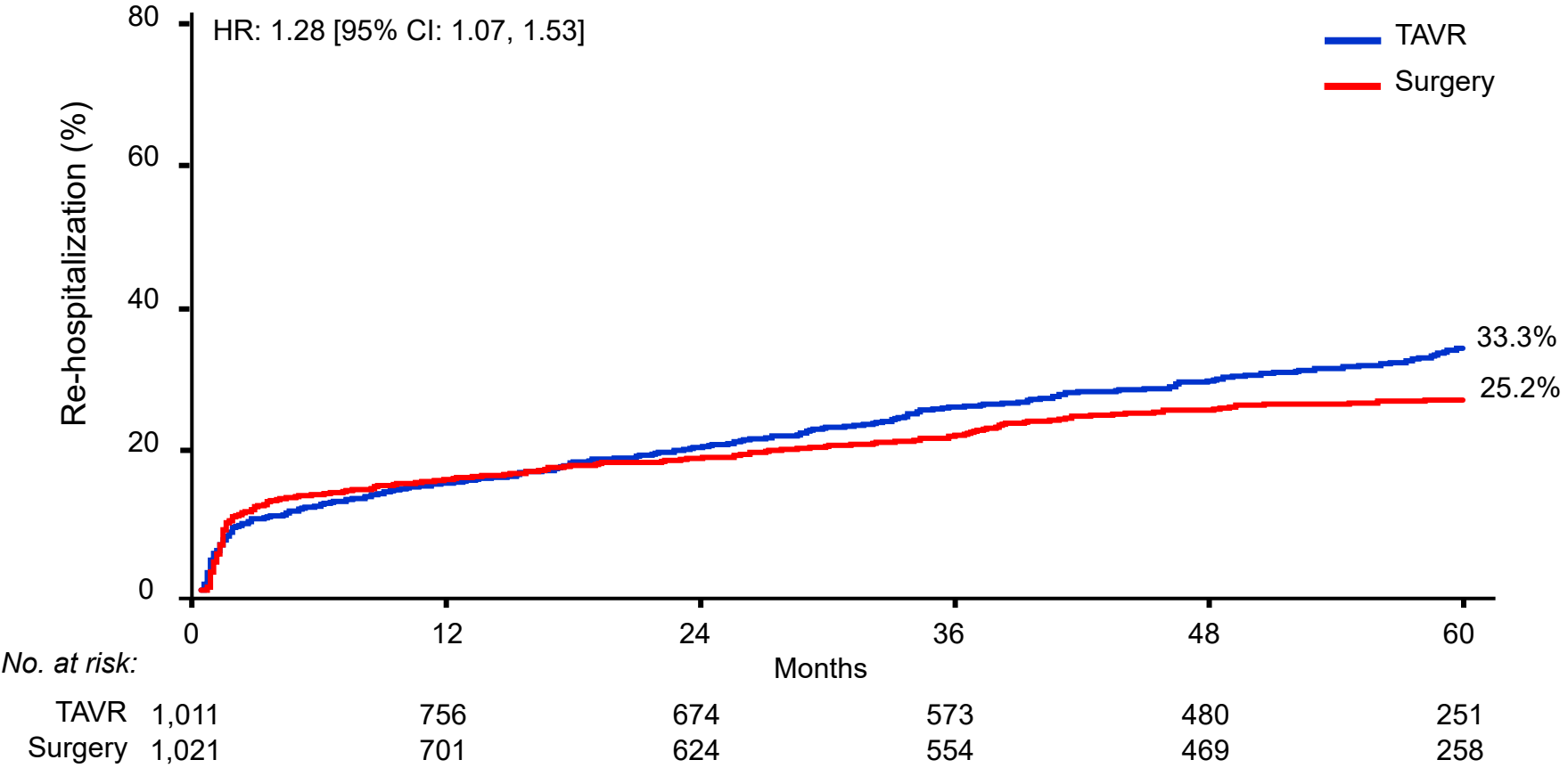
**Figure S4. 2-Year Landmark Analysis for Death or Disabling Stroke (ITT Population)**




*Number at Risk*

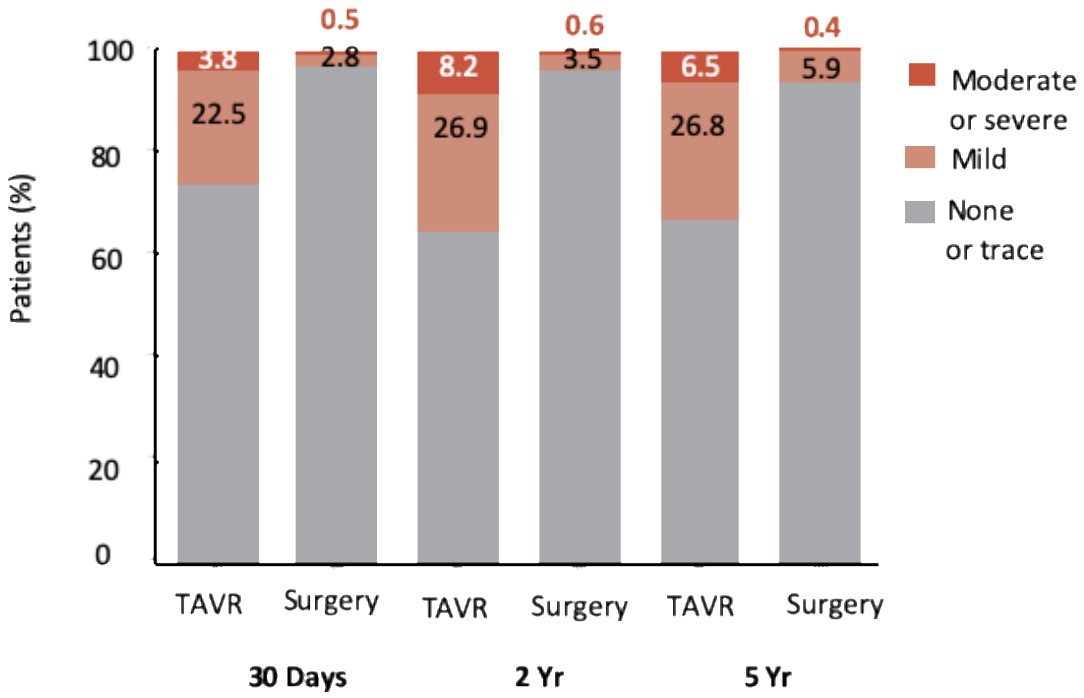
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| TAVR | 1,011 | 901 | 843 | 813 | 810 | 761 | 705 | 654 | 599 | 524 | 314 |
| Surgery | 1,021 | 812 | 771 | 738 | 730 | 680 | 647 | 603 | 563 | 496 | 300 |

**Figure S5. Time-To-Event Curves for Rehospitalization* (ITT Population)**




* Re-hospitalization = procedure or valve-related (including heart failure)

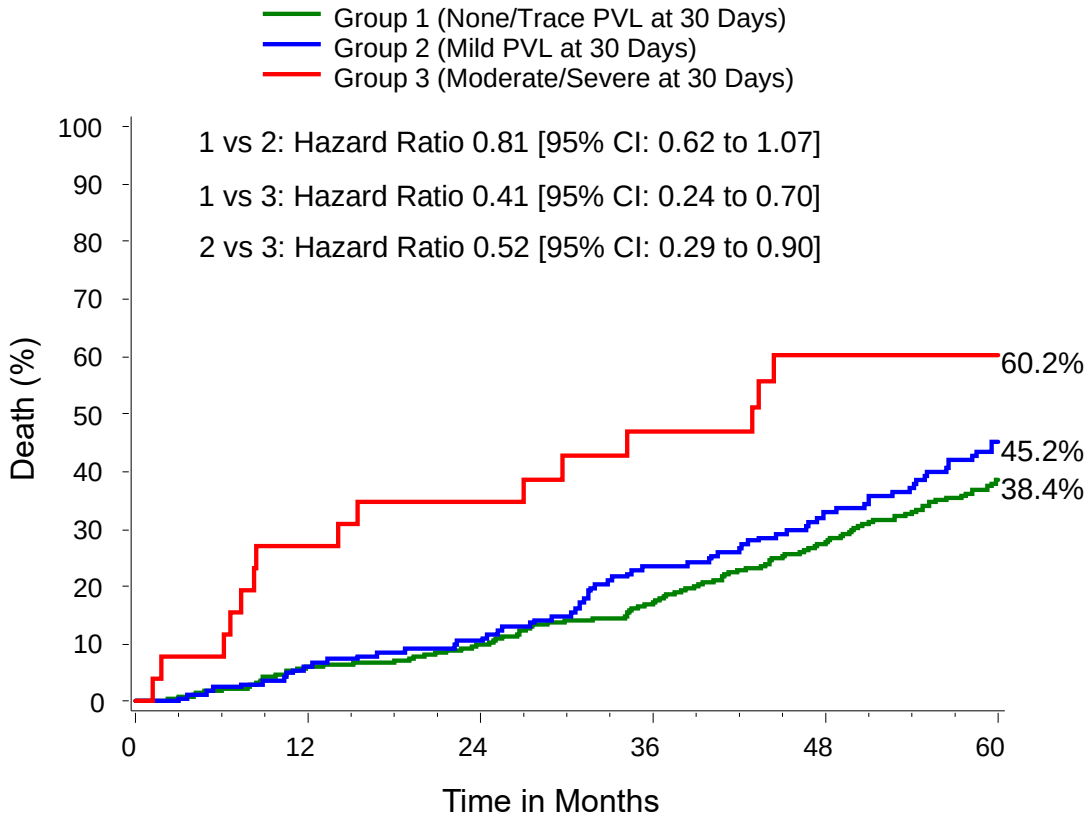
**Figure S6. Paravalvular Aortic Regurgitation After the Procedure Among Patients with Available Echocardiogram**




***No. of Patients with Echocardiographic Findings:***

| | | | |
|---|---|---|---|
| TAVR | 872 | 609 | 310 |
| Surgery | 757 | 516 | 272 |

**Figure S7. Impact of Paravalvular Aortic Regurgitation on Death from Any Cause in the Transfemoral Cohort (Valve Implant Population)**

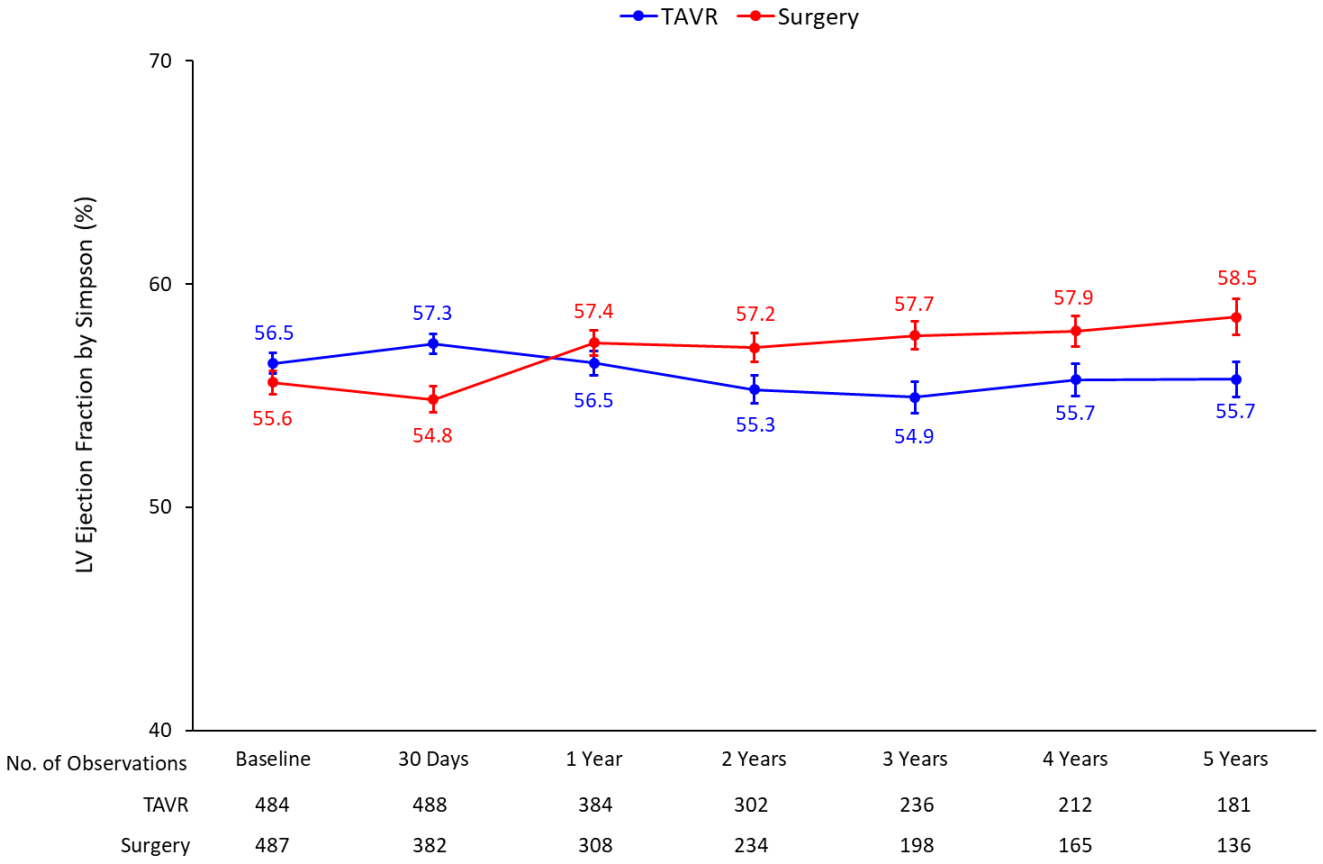



*Number at risk:*

| | | | | | | |
|---|---|---|---|---|---|---|
| Group 1 | 494 | 461 | 437 | 392 | 335 | 176 |
| Group 2 | 163 | 151 | 144 | 121 | 103 | 53 |
| Group 3 | 26 | 19 | 16 | 13 | 9 | 5 |

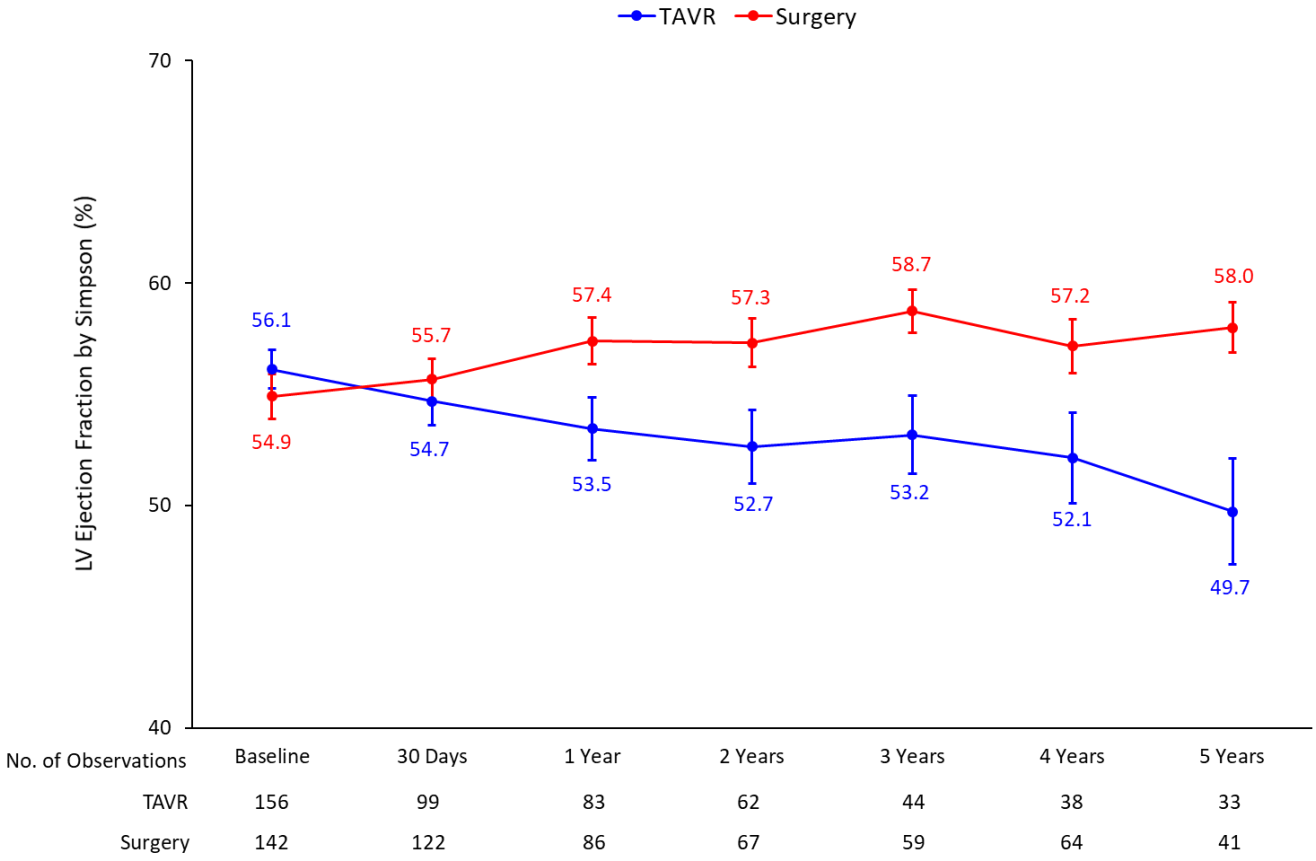
**Figure S8. Left Ventricular Ejection Fraction***

**A. Transfemoral Cohort**




| No. of Observations | Baseline | 30 Days | 1 Year | 2 Years | 3 Years | 4 Years | 5 Years |
|---|---|---|---|---|---|---|---|
| TAVR | 484 | 488 | 384 | 302 | 236 | 212 | 181 |
| Surgery | 487 | 382 | 308 | 234 | 198 | 165 | 136 |

## B. Transthoracic Cohort

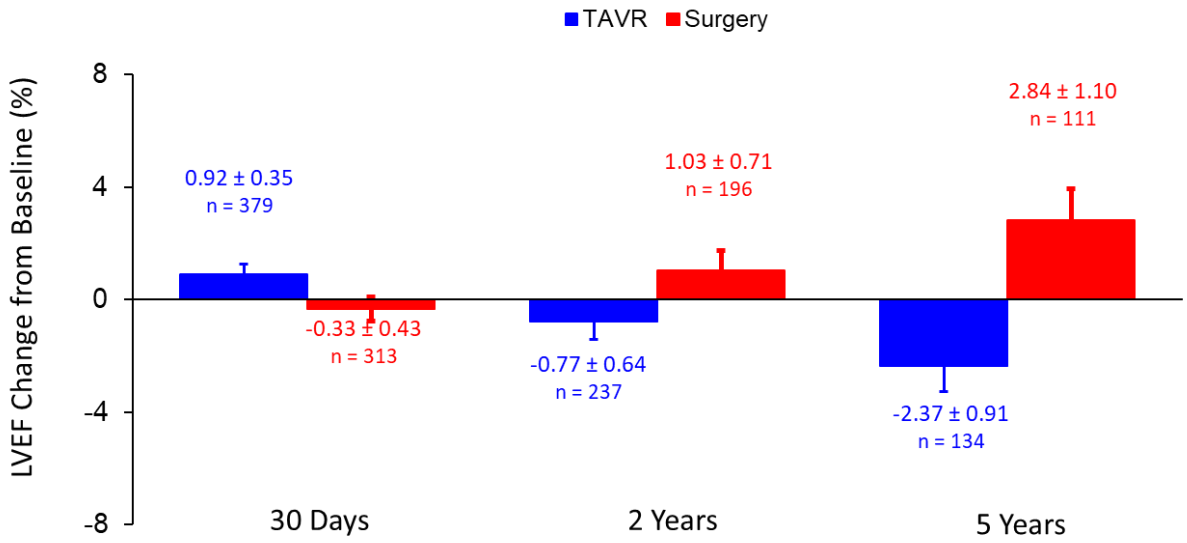



| No. of Observations | Baseline | 30 Days | 1 Year | 2 Years | 3 Years | 4 Years | 5 Years |
|---|---|---|---|---|---|---|---|
| TAVR | 156 | 99 | 83 | 62 | 44 | 38 | 33 |
| Surgery | 142 | 122 | 86 | 67 | 59 | 64 | 41 |

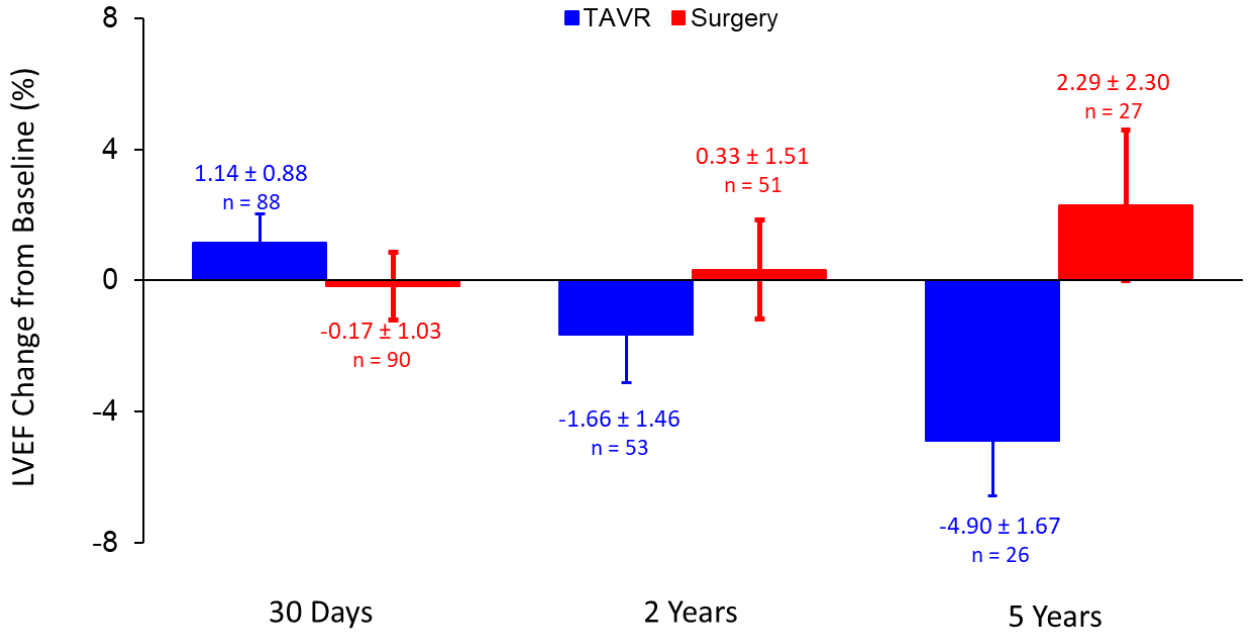
*Simpson's biplane method; Data presented are mean ± SE

**Figure S9. Left Ventricular Ejection Fraction* Change from Baseline**

**A. Transfemoral Cohort**

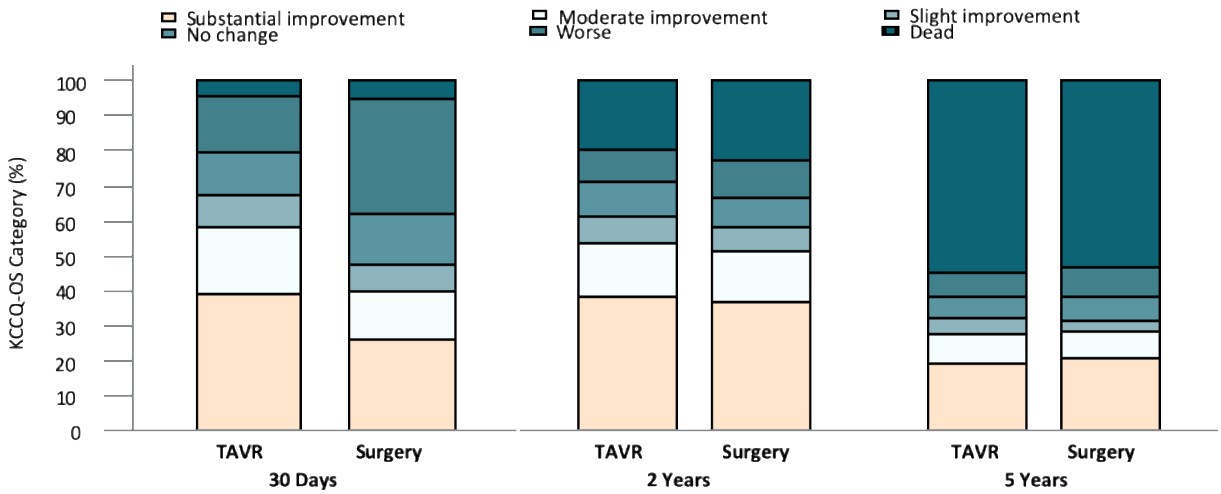



**B. Transthoracic Cohort**




*Simpson's biplane method; Data presented are mean ± SE

**Figure S10. Ordinal Analysis of Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OS)**




Proportions of patients according to survival status and changes in KCCQ overall summary scores are shown from baseline to 5 years. Changes of KCCQ overall summary score were defined as worse (decrease from baseline >5 points), no change (change between -5 and <5 points), mildly improved (increase between 5 and <10 points), moderately improved (increase between 10 and <20 points), and substantially improved (increase ≥20 points).