

## Supplementary Online Content

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

**eTable 1.** *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Diagnoses Codes to Identify Patients With Heart Failure (HF), Stroke, and Myocardial Infarction (MI)*

| Condition or procedure | ICD-9-CM Codes   |
|------------------------|--|
| Heart Failure          | 398.x, 402.x1, 404.x1, 404.x3, 428.x                       |
| Stroke                 | 433.x1, 434.x1, 997.02, 436, 437.1, 437.9, 430, 431, 432.x |
| MI                     | 410.x0, 410.x1   |

**eTable 2.** Postprocedural and In-Hospital Outcomes in Patients With Off-Label and On-Label TAVR Use

| Variable  | Off-Label Use<br>(N=2272) | On-Label Use<br>(N=21575) | P-value |
|---|---------------------------|---------------------------|---------|
| In-hospital death (%)                               | 143 (6.3)                 | 1011 (4.7)                | <0.001  |
| Myocardial Infarction (%)                           | 12 (0.5)                  | 115 (0.5)                 | 0.98    |
| Transient Ischemic Attack (%)                       | 12 (0.5)                  | 49 (0.2)                  | 0.007   |
| Ischemic Stroke (%)                                 | 43 (1.9)                  | 418 (1.9)                 | 0.89    |
| VARC Major Bleeding Event (%)                       | 134 (5.9)                 | 1514 (7.0)                | 0.06    |
| Major Vascular Access Site Complication (%)         | 10 (0.4)                  | 161 (0.7)                 | 0.1     |
| Cardiac Arrest (%)                                  | 149 (6.6)                 | 1035 (4.8)                | <0.001  |
| Permanent pacemaker (%)                             | 115 (5.1)                 | 1217 (5.6)                | 0.26    |
| Device Migration (%)                                | 4 (0.2)                   | 77 (0.4)                  | 0.16    |
| Aortic Valve Reintervention (%)                     | 12 (0.5)                  | 70 (0.3)                  | 0.11    |
| Unplanned Other Cardiac Surgery or Intervention (%) | 47 (2.1)                  | 429 (2.0)                 | 0.78    |
| Incident Renal Failure (%)                          | 227 (10.0)                | 1964 (9.1)                | 0.13    |
| <b>Post procedure valvular parameters</b>           |                           |                           |         |
| Residual Aortic Stenosis* (%)                       | 134 (7.7)                 | 1047 (6.1)                | 0.01    |
| AV Area* cm <sup>2</sup> , Median (IQR)             | 1.7 (1.3-2.1)             | 1.7 (1.4-2.1)             | 0.26    |
| AV Peak Doppler Velocity* (m/s), Median (IQR)       | 2.1 (1.8-2.5)             | 2 (1.7-2.4)               | 0.06    |
| AV Mean Gradient* (mm Hg), Median (IQR)             | 10 (7-13)                 | 9 (7-13)                  | 0.007   |
| Severe mitral regurgitation* (%)                    | 162 (9.3)                 | 144 (0.8)                 | <0.001  |
| Severe aortic regurgitation* (%)                    | 15 (0.9)                  | 40 (0.2)                  | <0.001  |
| Moderate/Severe Perivalvular leak** (%)             | 138 (12.4)                | 799 (7.6)                 | <0.001  |

\*Assessed in patients who had a post-procedure echocardiogram.

\*\* Assessed in patients with aortic regurgitation.

**eTable 3.** Comparison of Baseline Characteristics Between Patients With CMS-Linked Data Available Versus Patients Without CMS-Linked Data Available

| Variable                           | Patients with CMS-linked data<br>(N=15397) | Patient without CMS-linked data<br>(N=8450) | P-value |
|------------------------------------|--|---|---------|
| Age, Median (IQR), y               | 84 (79-88)                                 | 82 (75-87)                                  | <0.0001 |
| Male                               | 7643 (49.6)                                | 4328 (51.2)                                 | 0.02    |
| Race                               |  |   | <0.0001 |
| White                              | 14664 (95.2)                               | 7737 (91.6)                                 |         |
| Black/African American             | 445 (2.9)                                  | 443 (5.2)                                   |         |
| Insurance Payor                    |  |   | <0.0001 |
| Private                            | 9376 (60.9)                                | 5704 (67.5)                                 |         |
| Public                             | 6021 (39.1)                                | 2674 (31.6)                                 |         |
| Prior PCI                          | 5505 (35.8)                                | 2976 (35.2)                                 | 0.37    |
| Prior CABG                         | 4808 (31.2)                                | 2708 (32.1)                                 | 0.18    |
| Prior Aortic Valve Procedure       | 2431 (15.8)                                | 1433 (17.0)                                 | 0.02    |
| Surgical AV repair or replacement* | 269 (11.1)                                 | 248 (17.3)                                  | <0.0001 |
| Balloon aortic valvuloplasty*      | 2151 (88.5)                                | 1182 (82.5)                                 | <0.0001 |
| TAVR*                              | 38 (1.6)                                   | 22 (1.5)                                    | 0.96    |
| Prior Stroke                       | 1868 (12.1)                                | 1049 (12.4)                                 | 0.53    |
| Prior CEA/CAS                      | 1166 (9.0)                                 | 624 (8.8)                                   | 0.65    |
| Porcelain aorta                    | 974 (6.3)                                  | 681 (8.1)                                   | <0.0001 |
| Peripheral Arterial Disease        | 4865 (31.6)                                | 2654 (31.4)                                 | 0.74    |
| Current/Recent Smoker              | 690 (4.5)                                  | 563 (6.7)                                   | <0.0001 |
| Hypertension                       | 13735 (89.2)                               | 7471 (88.4)                                 | 0.07    |
| Diabetes Mellitus                  | 5410 (35.1)                                | 3445 (40.8)                                 | <0.0001 |
| Dialysis                           | 593 (3.9)                                  | 383 (4.5)                                   | 0.01    |
| Chronic Lung Disease - Severe      | 2055 (13.4)                                | 1203 (14.2)                                 | 0.06    |
| Prior MI                           | 3818 (24.8)                                | 2189 (25.9)                                 | 0.06    |

|  |                |                |         |
|--|----------------|----------------|---------|
| NYHA Class III/IV within 2 weeks   | 12488 (81.1)   | 6945 (82.2)    | 0.005   |
| Cardiogenic Shock w/in 24 Hours  | 69 (0.5)       | 49 (0.6)       | 0.17    |
| Atrial Fibrillation/Flutter  | 6455 (41.9)    | 3271 (38.7)    | <0.0001 |
| % Predicted Mortality (STS AV Replacement Mortality Model), Median (IQR) | 7.0 (4.7-10.6) | 6.4 (4.2-10.0) | <0.0001 |
| Creatinine > 2 mg/dL   | 1365 (8.9)     | 820 (9.7)      | 0.03    |
| LVEF < 30%   | 1047 (6.8)     | 639 (7.6)      | 0.02    |
| Degenerative AV Disease  | 14566 (94.6)   | 7829 (92.7)    | <0.0001 |
| AV Mean Gradient (mm Hg) - Median (IQR)                                  | 43 (36-52)     | 43 (36-52)     | 0.32    |
| Elective Procedure Status  | 13910 (90.3)   | 7575 (89.6)    | 0.06    |
| Femoral Access Site  | 9266 (60.2)    | 5065 (59.9)    | 0.71    |
| Device Success   | 14351 (93.2)   | 7809 (92.4)    | 0.0006  |
|  |                |                |         |
| <b>Hospital Characteristics</b>  |                |                |         |
| Hospital Location  |                |                | <0.0001 |
| Urban  | 11229 (72.9)   | 6414 (75.9)    |         |
| Suburban   | 3399 (22.1)    | 1730 (20.5)    |         |
| Rural  | 769 (5.0)      | 306 (3.6)      |         |
| Hospital Type  |                |                | <0.0001 |
| Private/Community  | 10032 (65.2)   | 5508 (65.2)    |         |
| University   | 5151 (33.5)    | 2886 (34.2)    |         |
| Government   | 214 (1.4)      | 56 (0.7)       |         |
| Teaching Hospital  | 11137 (72.3)   | 6252 (74.0)    | 0.006   |
| TAVR Volume, Median (IQR)  | 107 (70-170)   | 110 (69-170)   | 0.42    |

\* Assessed in patients with prior aortic valve procedure.

**eTable 4.** Cumulative Incidence of 30-Day and 1-Year Adverse Cardiovascular Outcomes in Patients With Off-Label and On-Label TAVR Use

| Outcome       | Off-Label Use |                  | On-Label Use  |                  | p-value |
|---------------|---------------|------------------|---------------|------------------|---------|
|               | No. of Events | Rate, % (95% CI) | No. of Events | Rate, % (95% CI) |         |
| 30 Day        |               |                  |               |                  |         |
| Mortality     | 119           | 8.5 (7.1-10.1)   | 855           | 6.1 (5.7-6.5)    | <0.001  |
| Heart Failure | 81            | 5.8 (4.7-7.1)    | 606           | 4.3 (4.0-4.7)    | 0.01    |
| Stroke        | 27            | 1.9 (1.3-2.8)    | 353           | 2.5 (2.3-2.8)    | 0.17    |
| MI            | 14            | 1.0 (0.6-1.7)    | 105           | 0.8 (0.6-0.9)    | 0.31    |
| 1 Year        |               |                  |               |                  |         |
| Mortality     | 315           | 25.6 (23.2-28.3) | 2549          | 22.1 (21.3-22.9) | 0.001   |
| Heart Failure | 203           | 16.2 (14.2-18.4) | 1718          | 14.4 (13.8-15.1) | 0.07    |
| Stroke        | 41            | 3.1 (2.3-4.2)    | 520           | 4.1 (3.8-4.5)    | 0.10    |
| MI            | 29            | 2.5 (1.7-3.6)    | 245           | 2.2 (1.9-2.5)    | 0.54    |

**eTable 5.** Unadjusted Cumulative Adverse Cardiovascular Outcomes of Individual Off-Label Indications

| Outcome                        | Off-Label Indications  |                        |                          |                          |                                   |
|--------------------------------|------------------------|------------------------|--------------------------|--------------------------|-----------------------------------|
|                                | Only Severe MR (n=855) | Only Severe AR (n=736) | Only Bicuspid AV (n=384) | Only Moderate AS (n=155) | ≥ 2 off-label indications (n=139) |
| In-hospital                    |                        |                        |                          |                          |                                   |
| Death, (%)                     | 75 (8.8)               | 41 (5.6)               | 15 (3.9)                 | 5 (3.2)                  | 7 (5.0)                           |
| Ischemic Stroke, (%)           | 14 (1.6)               | 15 (2.1)               | 8 (2.1)                  | 5 (3.2)                  | 1 (0.7)                           |
| VARC Major Bleeding Event, (%) | 60 (7.2)               | 44 (6.2)               | 18 (4.8)                 | 8 (5.2)                  | 4 (3.0)                           |
| Cardiac Arrest, (%)            | 77 (9.0)               | 38 (5.2)               | 20 (5.2)                 | 6 (3.9)                  | 8 (5.8)                           |
| Permanent pacemaker, (%)       | 41 (4.8)               | 32 (4.4)               | 26 (6.8)                 | 9 (5.8)                  | 7 (5.1)                           |
| Incident Renal Failure, (%)    | 90 (10.8)              | 70 (9.8)               | 31 (8.2)                 | 16 (10.3)                | 20 (15.0)                         |
| 30 Day*                        |                        |                        |                          |                          |                                   |
| Mortality, (%)                 | 63 (11.0)              | 35 (7.8)               | 11 (5.6)                 | 5 (4.8)                  | 5 (6.3)                           |
| Heart Failure, (%)             | 40 (7.0)               | 23 (5.1)               | 6 (3.1)                  | 8 (7.7)                  | 4 (5.1)                           |
| Stroke, (%)                    | 9 (1.6)                | 7 (1.6)                | 5 (2.6)                  | 5 (4.8)                  | 1 (1.3)                           |
| MI, (%)                        | 8 (1.4)                | 4 (0.9)                | 2 (1.0)                  | 0 (0.0)                  | 0 (0.0)                           |
| 1 Year*                        |                        |                        |                          |                          |                                   |
| Mortality, (%)                 | 152 (29.3)             | 94 (23.7)              | 37 (23.9)                | 16 (19.4)                | 16 (22.0)                         |
| Heart Failure, (%)             | 108 (20.7)             | 57 (13.9)              | 12 (7.4)                 | 18 (20.4)                | 8 (11.3)                          |
| Stroke, (%)                    | 17 (3.2)               | 9 (2.1)                | 6 (3.1)                  | 6 (6.3)                  | 3 (4.5)                           |
| MI, (%)                        | 11 (2.1)               | 11 (3.0)               | 3 (1.6)                  | 3 (5.1)                  | 1 (1.3)                           |

\*30-day and 1-year outcomes were assessed in a CMS-linked subset (only severe MR: n=573; only severe AI: n=449; only bicuspid AV: n=196; only moderate AS: n=104; ≥ 2 off-label indications: n=79).

**eTable 6.** Association of Off-Label TAVR Use and Composite Adverse Cardiovascular Outcomes (Death, Heart Failure, MI, and Stroke) by Hospital Tertiles

|                          |                | Unadjusted            |         |                 | Adjusted*             |         |                 |
|--------------------------|----------------|-----------------------|---------|-----------------|-----------------------|---------|-----------------|
| Outcome                  | Level          | Hazard Ratio (95% CI) | p-value | Overall p-value | Hazard Ratio (95% CI) | p-value | Overall p-value |
| 30-Day Composite Outcome | Medium vs. Low | 1.12 (0.97, 1.28)     | 0.12    | 0.10            | 1.08 (0.90, 1.30)     | 0.41    | 0.29            |
|                          | High vs. Low   | 1.16 (1.01, 1.34)     | 0.03    |                 | 1.16 (0.96, 1.40)     | 0.12    |                 |
| 1-Year Composite Outcome | Medium vs. Low | 1.03 (0.94, 1.13)     | 0.55    | 0.62            | 0.94 (0.83, 1.06)     | 0.30    | 0.55            |
|                          | High vs. Low   | 1.05 (0.95, 1.15)     | 0.32    |                 | 0.98 (0.87, 1.11)     | 0.77    |                 |

\*Adjusted for age, sex, body surface area, left ventricular ejection fraction, hemoglobin, platelet count, number of days from 11/1/2011 until procedure date, race, dialysis, left main stenosis  $\geq 50\%$ , proximal LAD stenosis  $\geq 70\%$ , prior MI, endocarditis, prior stroke or TIA, carotid stenosis, PAD, tobacco abuse, diabetes, NYHA class IV, atrial fibrillation/flutter, conduction defect, severe chronic lung disease, home oxygen, hostile chest, porcelain aorta, access site (femoral vs. other), prior PCI, prior CABG, prior cardiac operations (2+ vs. 1 vs. 0), prior aortic valve procedure, prior non-aortic valve procedure, aortic stenosis etiology (degenerative vs. other), valve morphology (tricuspid vs. other), tricuspid regurgitation (moderate/severe vs. other), acuity (elective vs. urgent vs. shock or inotropes or assist device vs. emergency or salvage or cardiac arrest)



**eFigure.** Quarterly Trend in Off-Label TAVR Use

