Supplementary Appendix

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

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Supplementary Appendix

TVTR RPA
Relationship between Annual Hospital Volume and Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement (TAVR)

Summary Report

September 1, 2018

Statement of Intent

- To examine the relationship between annual hospital TAVR volume and 30-day outcomes of patients undergoing transfemoral TAVR in the United States

Data Source

- TVT registry data from January 2015 through December 2017

Study Population

- **Overall population – N = 105200 / 554 sites**
    - Inclusion criteria:
        - **113662** patients at **555** sites undergoing TAVR procedures (#6600 = Yes) between 2015 and 2017
    - Exclusion criteria:
        - **0** patients enrolled in research study (#3030 = Yes)
        - **8050** patients with prior SAVR/TAVR, valve-in-valve procedure, or failed bioprosthetic valve (#4080 = Yes or #4090 = Yes or #6065 = Yes or #6060 = Failed Bioprosthetic valve)
        - **412** patients with TAVR procedure done for primary AI (#6060 = Primary AI)
    - Subgroups by access site (#6200)
        - **Transfemoral – N = 96256 / 554 sites**
            - 91.8% of the overall population with non-missing status on access site
            - Population of interest for the volume-outcome analysis
        - **Non-transfemoral – N = 8544 / 485 sites**
            - Transapical/Transaortic – N = 4666
            - Axillary/Subclavian – N = 3053
            - Other (transiliac/transeptal/transcarotid/other) – N = 825

- **Population A for sensitivity analysis – N =**
    - Exclude (from the overall population) ___ TAVRs performed within the first six months of initiation for each site
    - Analysis will be performed among **transfemoral population – N = 92553 / 521 sites**
- **Population B for sensitivity analysis – N =**

- Exclude (from the overall population) ___ TAVRs performed within the first year of initiation for each site
- Analysis will be performed among **transfemoral population – N = 88592 / 488 sites**

Main variable of interest

- **Annual hospital TAVR volume**
  - Annual TAVR volume will be determined for each hospital over the period of 2015-2017 among the overall population. It will be estimated by annualizing (multiplying by 12) the monthly volume which will be calculated as the total number of TAVRs performed at the site during 2015-2017 divided by the number of months between the first and last cases at that site.
  - Annual hospital TAVR volume will be analyzed both as a continuous variable and as a categorical variable (with categories determined based on quartiles).

Outcomes

- **Primary outcome**
  - 30-day mortality (including in-hospital mortality)

- **Secondary outcomes**
  - 30-day stroke (E011 or E012 or E013)
  - 30-day moderate/severe paravalvular leak (PVL) (#10225 = Moderate or Severe)
    - Use post-procedural PVL (#8106) instead when #10225 is missing
  - 30-day major vascular complications or major bleeding, defined as a composite of the following endpoints:
    - 30-day major vascular access site complication (E041)
    - 30-day VARC major or life-threatening or disabling bleeding
  - 30-day AKI (III):
    1. change in creatinine >= 300% or
    2. post-procedure creatinine >= 4 with change in creatinine >= 0.5 or
    3. 30 day new requirement for dialysis
  - Composite events of the above (mortality/stroke/PVL/major vascular or bleeding/AKI III).

Objectives and Analyses

Objective 1:

- To compare patient baseline characteristics across quartiles of annual hospital TAVR volume among transfemoral population

Analysis:

- Annual hospital TAVR volume will be sorted in descending order and plotted on the Y axis against hospitals on the X axis.

- Patient baseline characteristics will be presented for each quartile of the annual hospital TAVR volume (**Table 1**). Continuous variables will be summarized as medians with the 1st and 3rd quartiles (Q1 and Q3) and compared across the hospital quartiles using the Kruskal-Wallis test. Categorical variables will be summarized as counts with percentages and compared using the Pearson chi-square test. The tests do not assume an ordinal relationship across the hospital quartiles.

Objective 2:

- To compare procedural characteristics across quartiles of annual hospital TAVR volume among transfemoral population

Analysis:

- Procedural characteristics will be presented for each quartile of the annual hospital TAVR volume. Continuous variables will be summarized as medians with Q1 and Q3 and compared across the hospital quartiles using the Kruskal-Wallis test. Categorical variables will be summarized as counts with percentages and compared using the Pearson chi-square test.

Objective 3:

- To compare the observed 30-day outcomes across quartiles of annual hospital TAVR volume among transfemoral population

Analysis:

- Observed 30-day outcomes will be presented for each quartile of the annual hospital TAVR volume. Outcomes will be summarized as the numbers of events with rates and compared across the hospital quartiles using the Pearson chi-square test.

Objective 4:

- To examine the relationship between annual hospital TAVR volume as a continuous variable and 30-day outcomes among transfemoral population

Analysis:

- Unadjusted association between annual hospital TAVR volume and 30-day outcomes will be assessed using mixed effects logistic regression models. Restricted cubic splines (RCS) will be used to examine the potentially nonlinear relationship between hospital volume and outcomes. A 3-level (patient-operator-hospital) hierarchical structure will be used by including hospital-specific and operator-specific random intercepts to account for inter-hospital variability and inter-operator variability nested within hospitals. The results will be presented using RCS curves with volume on the X axis and predicted probability of the outcome on the Y axis.

- Adjusted association between annual hospital TAVR volume and 30-day outcomes will be examined using the following steps:

First, determine if there are any interactions between hospital volume and the following covariates:

1. Year of procedure (2017 vs. 2015-2016)
2. Operator reason for TAVR (inoperable/high risk vs. intermediate/low risk)

Interactions will be tested individually for the two covariates using ordinary logistic regression models. Interaction effects that are found to be significant will be included in the final outcome models; otherwise only main effects of the above covariates will be included.

Then, assess the adjusted association between hospital volume and outcomes using mixed effects logistic regression models with the 3-level hierarchical structure. In addition to the interaction effects (if significant) and main effects of the above covariates, the adjusted models will include the following covariates:

1. Age
2. Sex
3. Race (non-Hispanic white vs. other)
4. Sex-specific BSA
5. LVEF
6. Hemoglobin
7. Platelet count
8. GFR
9. Dialysis
10. Left main stenosis ≥ 50%
11. Proximal LAD ≥ 70%
12. Prior MI
13. Endocarditis
14. Prior stroke or TIA
15. Carotid stenosis
16. Prior PAD
17. Current/recent smoker
18. Diabetes
19. NYHA class IV
20. Atrial fibrillation/flutter
21. Conduction defect
22. Severe chronic lung disease
23. Home oxygen
24. Hostile chest
25. Porcelain aorta
26. Previous pacemaker
27. Previous ICD
28. Prior PCI
29. Prior CABG
30. Prior cardiac operations (2+ vs. 1 vs. 0)
31. Prior aortic valve procedure
32. Prior non-aortic valve procedure

33. Aortic etiology (degenerative vs. other)
34. Valve morphology (tricuspid vs. other)
35. Moderate/severe aortic regurgitation
36. Moderate/severe mitral regurgitation
37. Moderate/severe tricuspid regurgitation
38. Acuity of TAVR (elective vs. urgent vs. shock or inotropes or assist device vs. emergency or salvage or cardiac arrest)
39. Operator volume
    - Defined as the total number of TAVR procedures performed by the operator (identified by NPI number).
    - Two operators are documented for each procedure, so each operator will be assigned a case regardless of which position (A or B) they are listed.
    - The higher volume between the two operators for each procedure will be used in the model.

Missing data for the above covariates will be imputed to the median of continuous variables or to the mode of categorical variables.
The results will be presented using RCS curves with volume on the X axis and predicted probability of the outcome on the Y axis. The predicted probability of the outcome will be estimated for an "average" patient, i.e., at the medians or modes of the covariates.

- If the mixed models fail to converge, an alternative modeling approach will be adopted:
  First, combine all the covariates into a single risk score before constructing the mixed models. The risk score for each outcome will be derived as the predicted log odds of the outcome from an ordinary logistic regression model that includes all the covariates. Then, add the risk score as a single covariate into the mixed models. If any interaction effects are found significant, the corresponding covariates will be excluded from the construction of risk score and be directly included in the mixed models.

Objective 5:

- To examine the relationship between quartiles of annual hospital TAVR volume and 30-day outcomes among the transfemoral population

Analysis:

- Unadjusted association between quartile of annual hospital TAVR volume and 30-day outcomes will be assessed using mixed effects logistic regression models with the 3-level hierarchical structure. The results will be presented as odds ratios (ORs) with 95% confidence intervals (CIs) using Quartile 4 as the reference group.
- Adjusted association between quartiles of hospital volume and outcomes will be examined using the same approach as described above. Interaction effects of volume with procedure year and heart team reason for TAVR will be included in the final models if they are determined to be significant. The results will be presented as odds ratios (ORs) with 95% confidence intervals (CIs) using Quartile 4 as the reference group.

Objective 6:

- To perform a sensitivity analysis by excluding TAVR procedures performed within the first 6 and 12 months of initiation for each site

Analysis:

- As a sensitivity analysis, TAVR procedures performed within the first 6 months of initiation within each site will be excluded from the overall population. The analyses described above will be repeated among transfemoral patients. The results will be presented using RCS curves with volume on the X axis and predicted probability of the outcome on the Y axis.
- As a sensitivity analysis, TAVR procedures performed within the first 1 year of initiation within each site will be excluded from the overall population. The analyses described above will be repeated among transfemoral patients. The results will be presented using RCS curves with volume on the X axis and predicted probability of the outcome on the Y axis

Supplementary Methods

Composite Outcome: a composite endpoint as well as the individual components of 30-day endpoints known to be associated with 1-year mortality and quality of life,[1] consisting of stroke, moderate/severe paravalvular leak, major vascular access site complication or valve academic research consortium major or life-threatening or disabling bleeding, and acute kidney injury according to VARC 2 definitions and the TVT data dictionary were analyzed.

[1]Arnold SV, Baron SJ, McAndrew TC, et al. Impact of Short-Term Complications on Mortality and Quality of Life after TAVR. JACC Cardiovasc Interv 2018;in press.

Missing covariates in the hierarchical models were less than 1% for all data elements except the following:

Number of previous cardiac surgeries – 1.01%
Left main stenosis ≥50% – 1.02%
Proximal LAD ≥70% - 1.07%
Non-Hispanic white – 1.90%
Acuity of procedure – 2.28%
Carotid stenosis – 20.80%**.**

Missing model covariate data was handled by single imputation.

Missing outcome data was handled by inverse probability weighting. Specifically, we constructed a multivariable logistic regression model among patients eligible for 30-day follow-up to determine the probability of having the outcome of interest. Covariates for this model included covariates listed in Appendix C and the volume spline variables. Stabilized weights were derived as the inverse of the probability of observing the outcome multiplied by the proportion of non-missing outcome. This process was done separately for each of the outcomes of interest. Subsequently, hierarchical models were fit with stabilized weights for patients with non-missing outcomes. The distribution of the stabilized weights used in the hospital TF volume–mortality model is provided below:

Quantiles (Definition 5)	
Level	**Quantile**
100% Max	1.648988
99%	1.130479
95%	1.067243
90%	1.043485
75% Q3	1.015149
50% Median	0.995650
25% Q1	0.974539
10%	0.959763
5%	0.955619
1%	0.950586
0% Min	0.940559

Weights before stabilization for the hospital TF volume–mortality model ranged from1.02-1.80. No truncation of weights was implemented.

Appendix A: Site-reported hospital characteristics

1. Hospital region was as defined by U.S Census Region:
   Northeast: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, and Pennsylvania

   Midwest: Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota

   South: Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Washington D.C., West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, and Texas

   West: Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, Alaska, California, Hawaii, Oregon, and Washington

2. Teaching hospital was defined as the facility having a medical school teaching program such as a fellowship, internship, or residency program with teaching rotations including cardiac patients

3. Hospital Reported Rurality:
   a. Urban locations are defined as being within a city
   b. suburban as being the area outlying a city
   c. and rural as being in the country

4. Certified Beds: a "certified" bed is a bed in a health care facility approved by authorities for use by patients on a permanent basis, and which a governing body deems to have sufficient staffing to support its unqualified use.

5. Patient Risk for Surgical Aortic Valve Replacement:
   a. Inoperable / extreme risk was hospital defined as "technically inoperable, comorbid or deconditioned patient"
   b. High risk was defined as >/= 10% risk of 30-day mortality,
   c. Intermediate risk was defined as 4-9% risk of 30-day mortality,
   d. Low risk was defined as <4% risk of 30-day mortality as per standardized TVT definitions.

Appendix B: Spline coefficients and variance components

1. Spline coefficients and variance components (with 95% CI) from hospital TF volume–mortality models

	Unadjusted Estimate (95% CI)	Adjusted Estimate (95% CI)
Conditional estimates for spline coefficients		
Volume spline variable 1 (annvolume)	-0.0026 (-0.0066 to 0.0014)	-0.0030 (-0.0070 to 0.0011)
Volume spline variable 2 (annvolume1)	-0.0001 (-0.0284 to 0.0282)	0.0059 (-0.0229 to 0.0346)
Volume spline variable 3 (annvolume2)	0.0057 (-0.0494 to 0.0607)	-0.0070 (-0.0629 to 0.0489)
Marginal estimates for spline coefficients		
Volume spline variable 1 (annvolume)	-0.0025 (-0.0063 to 0.0013)	-0.0028 (-0.0067 to 0.0011)
Volume spline variable 2 (annvolume1)	-0.0001 (-0.0269 to 0.0267)	0.0056 (-0.0218 to 0.0329)
Volume spline variable 3 (annvolume2)	0.0054 (-0.0468 to 0.0575)	-0.0067 (-0.0598 to 0.0465)
Variance components		
Between-hospital variance component	0.0263 (0.0086 to 0.3434)	0.0379 (0.0158 to 0.1805)
Between-operator A variance component	0.0368 (0.0128 to 0.3528)	0.0206 (0.0046 to 5.2257)
Between-operator B variance component	0.0437 (0.0178 to 0.2239)	0.0410 (0.0158 to 0.2586)

Note: we have used the 5th, 35th, 65th, and 95th of the annualized hospital volume as the 4 knots for the restricted cubic splines. These knots were not prespecified, however, we used the default knots provided by the SAS macro and did not change them based upon the data. Specifically, the volume spline variables are defined as follows:

annvolume is the linear term of annualized hospital volume

annvolume1=max((annvolume-33)/((259 -

33)**.666666666666),0)**3+((131-33)*max((annvolume-259)/((259 -
33)**.666666666666),0)**3

-(259-33)*max((annvolume-131)/((259 - 33)**.666666666666),0)**3)/(259-131)

annvolume2=max((annvolume-74)/((259 -

33)**.666666666666),0)**3+((131-74)*max((annvolume-259)/((259 -
33)**.666666666666),0)**3

-(259-74)*max((annvolume-131)/((259 - 33)**.666666666666),0)**3)/(259-131)

Appendix C: Covariates for model adjustment

1. Age
2. Sex
3. Race (non-Hispanic white vs. other)
4. Sex-specific BSA
5. LVEF
6. Hemoglobin
7. Platelet count
8. GFR
9. Dialysis
10. Left main stenosis ≥ 50%
11. Proximal LAD ≥ 70%
12. Prior MI
13. Endocarditis
14. Prior stroke or TIA
15. Carotid stenosis
16. Prior PAD
17. Current/recent smoker
18. Diabetes
19. NYHA class IV
20. Atrial fibrillation/flutter
21. Conduction defect
22. Severe chronic lung disease
23. Home oxygen
24. Hostile chest
25. Porcelain aorta
26. Previous pacemaker
27. Previous ICD
28. Prior PCI
29. Prior CABG
30. Prior cardiac operations (2+ vs. 1 vs. 0)
31. Prior aortic valve procedure
32. Prior non-aortic valve procedure
33. Aortic etiology (degenerative vs. other)
34. Valve morphology (tricuspid vs. other)
35. Moderate/severe aortic regurgitation
36. Moderate/severe mitral regurgitation
37. Moderate/severe tricuspid regurgitation
38. Acuity of TAVR (elective vs. urgent vs. shock or inotropes or assist device vs. emergency or salvage or cardiac arrest)
39. Operator case number
    - Defined as the sequence number of a case among all of the TAVR procedures performed by an operator (identified by NPI number).
    - Two operators are documented for each procedure, so each operator will be assigned a case regardless of which position (A or B) they are listed.
    - The higher case sequence number between the two operators for each procedure will be used in the model.

Table S1. Unadjusted outcomes by hospital annualized volume quartiles of transfemoral TAVR

	Overall Missingness N (%)	Overall (N=96,256)	Quartile 1 140 Hospitals Vol. 5-36 (N=6827 TAVRs)	Quartile 2 138 Hospitals Vol. 37-54 (N=13,753 TAVRs)	Quartile 3 137 Hospitals Vol. 55-85 (N=22,799 TAVRs)	Quartile 4 139 Hospitals Vol. 86-371 (N=52,877 TAVRs)
In-hospital outcomes						
Mortality	1 (0.0)	1643 (1.7)	139 (2.0)	265 (1.9)	400 (1.8)	839 (1.6)
Vascular complication						
Unplanned vascular surgery or intervention	12 (0.0)	3133 (3.3)	176 (2.6)	398 (2.9)	774 (3.4)	1785 (3.4)
Retroperitoneal bleeding	12 (0.0)	473 (0.5)	34 (0.5)	76 (0.6)	101 (0.4)	262 (0.5)
Vascular access site complication requiring treatment	12 (0.0)	3945 (4.1)	272 (4.0)	533 (3.9)	992 (4.4)	2148 (4.1)
Bleeding complication						
VARC major bleeding	1453 (1.5)	3796 (4.0)	330 (4.9)	571 (4.2)	941 (4.2)	1954 (3.8)
VARC life-threatening or disabling bleeding	1453 (1.5)	2024 (2.1)	179 (2.6)	323 (2.4)	502 (2.2)	1020 (2.0)
Other outcomes						
PVL	8096 (9.4)	1604 (1.9)	99 (1.6)	228 (1.9)	373 (1.8)	904 (1.9)
In-hospital TIA	12 (0.0)	177 (0.2)	15 (0.2)	19 (0.1)	41 (0.2)	102 (0.2)
Unplanned cardiac surgery	12 (0.0)	1405 (1.5)	83 (1.2)	195 (1.4)	339 (1.5)	788 (1.5)
Any in-hospital valve complication	12 (0.0)	672 (0.7)	56 (0.8)	88 (0.6)	162 (0.7)	366 (0.7)
Discharge location	15 (0.0)					

Home		79,315 (83.8)	5607 (83.8)	11,219 (83.2)	18,789 (83.9)	43,700 (84.0)
Extended care/TCU/rehab		10,911 (11.5)	805 (12.0)	1646 (12.2)	2551 (11.4)	5909 (11.4)
Other acute care hospital		379 (0.4)	26 (0.4)	41 (0.3)	132 (0.6)	180 (0.3)
Nursing home		3563 (3.8)	214 (3.2)	522 (3.9)	829 (3.7)	1998 (3.8)
Hospice		190 (0.2)	11 (0.2)	24 (0.2)	53 (0.2)	102 (0.2)
Other		15 (0.0)		3 (0.0)		12 (0.0)
Procedure aborted	105 (0.1)	431 (0.4)	43 (0.6)	76 (0.6)	89 (0.4)	223 (0.4)
Conversion to open-heart surgery	147 (0.2)	466 (0.5)	44 (0.6)	75 (0.5)	125 (0.5)	222 (0.4)
Contrast volume, median (IQR), mL	2783 (2.9)	100.0 (65.0, 140.0)	105.0 (70.0, 150.0)	107.0 (75.0, 150.0)	105.0 (71.0, 150.0)	90.0 (60.0, 130.0)
Fluoroscopy time, median (IQR), min	2752 (2.9)	16.8 (12.4, 22.9)	18.1 (13.9, 24.2)	17.3 (13.1, 23.4)	17.6 (13.1, 23.9)	16.0 (11.7, 22.0)
Cumulative air kerma, median (IQR), mGy	18998 (19.7)	826.0 (468.0, 1391.0)	930.0 (535.0, 1564.0)	877.0 (480.0, 1494.0)	859.0 (498.0, 1475.0)	790.0 (446.0, 1312.0)
30-day outcomes						
Mortality (30-day + in-hospital)		2646 (2.7)	213 (3.1)	432 (3.1)	658 (2.9)	1343 (2.5)
Missing		7858 (8.2)	645 (9.5)	972 (7.1)	1682 (7.4)	4559 (8.6)
Stroke		2093 (2.2)	153 (2.2)	303 (2.2)	524 (2.3)	1113 (2.1)
Missing		8092 (8.4)	673 (9.9)	1012 (7.4)	1710 (7.5)	4697 (8.9)

VARC major or life-threatening or disabling bleeding event	5727 (5.9)	514 (7.5)	903 (6.6)	1400 (6.1)	2910 (5.5)
Missing	9159 (9.5)	700 (10.3)	1183 (8.6)	1850 (8.1)	5426 (10.3)
AKI stage III	3208 (3.3)	235 (3.4)	453 (3.3)	702 (3.1)	1818 (3.4)
Missing	1440 (1.5)	70 (1.0)	144 (1.0)	194 (0.9)	1032 (2.0)
Moderate/severe PVL	2630 (2.7)	169 (2.5)	340 (2.5)	639 (2.8)	1482 (2.8)
Missing	6444 (6.7)	469 (6.9)	944 (6.9)	1254 (5.5)	3777 (7.1)
Composite	13,916 (14.5)	1084 (15.9)	2064 (15.0)	3343 (14.7)	7425 (14.0)
Missing	12773 (13.3)	917 (13.4)	1702 (12.4)	2493 (10.9)	7661 (14.5)

Data presented as no. (%), unless otherwise indicated.
AKI indicates acute kidney injury; IQR, interquartile range; PVL, paravalvular leak; TAVR, transcatheter aortic valve replacement; TCU, transitional care unit; TIA, transient ischemic attack; VARC, Valve Academic Research Consortium.

Table S2. Adjusted outcome rates and odds ratios by volume quartile

Adjusted association (based on marginal estimates) between annualized hospital TF volume quartiles and 30-day outcomes in overall cohort

	Adjusted Rate (95% CI)	Adjusted OR (95% CI)
30-Day Mortality		
Quartile 1	3.19% (2.78%-3.67%)	1.21 (1.03-1.41)
Quartile 2	3.14% (2.84%-3.48%)	1.19 (1.05-1.34)
Quartile 3	2.93% (2.69%-3.20%)	1.10 (0.99-1.23)
Quartile 4 (reference)	2.66% (2.48%-2.85%)	
30-Day Composite		
Quartile 1	18.01% (16.65%-19.46%)	1.10 (0.98-1.23)
Quartile 2	17.39% (16.28%-18.55%)	1.05 (0.95-1.17)
Quartile 3	16.46% (15.48%-17.48%)	0.99 (0.89-1.09)
Quartile 4 (reference)	16.65% (15.75%-17.58%)	
30-Day VARC Bleeding		
Quartile 1	10.03% (8.99%-11.18%)	1.25 (1.08-1.45)
Quartile 2	9.12% (8.31%-10.01%)	1.12 (0.98-1.28)
Quartile 3	8.69% (7.96%-9.47%)	1.06 (0.94-1.21)
Quartile 4 (reference)	8.21% (7.58%-8.89%)	

Adjusted association (based on marginal estimates) between annualized hospital TF volume quartiles and 30-day mortality in sensitivity analysis

	Adjusted Rate (95% CI)	Adjusted OR (95% CI)
6-Month		
Quartile 1	3.19% (2.77%-3.68%)	1.22 (1.04-1.43)
Quartile 2	3.05% (2.75%-3.39%)	1.17 (1.03-1.32)
Quartile 3	2.87% (2.63%-3.13%)	1.09 (0.98-1.22)
Quartile 4 (reference)	2.63% (2.45%-2.82%)	
12-Month		
Quartile 1	3.10% (2.68%-3.58%)	1.19 (1.01-1.40)
Quartile 2	3.03% (2.71%-3.37%)	1.16 (1.02-1.32)
Quartile 3	2.89% (2.64%-3.17%)	1.11 (0.99-1.24)
Quartile 4 (reference)	2.61% (2.43%-2.81%)	

Adjusted association (based on marginal estimates) between annualized operator TF volume quartiles and 30-day mortality

	Adjusted Rate (95% CI)	Adjusted OR (95% CI)
30-Day Mortality		
Quartile 1	3.54% (2.59%-4.84%)	1.26 (0.91-1.75)
Quartile 2	3.46% (3.04%-3.93%)	1.23 (1.06-1.41)
Quartile 3	2.86% (2.61%-3.13%)	1.01 (0.91-1.12)
Quartile 4 (reference)	2.84% (2.68%-3.01%)	

Adjusted association (based on marginal estimates) between annualized hospital non-TF volume quartiles and 30-day mortality

	Adjusted Rate (95% CI)	Adjusted OR (95% CI)
30-Day Mortality		
Quartile 1	10.13% (7.76%-13.11%)	1.65 (1.20-2.27)
Quartile 2	8.55% (7.27%-10.03%)	1.37 (1.10-1.70)
Quartile 3	7.50% (6.31%-8.90%)	1.19 (0.94-1.49)
Quartile 4 (reference)	6.40% (5.56%-7.35%)	

Figure S1. Study cohort diagram: Blue box is the primary study population; gray box is the secondary study population

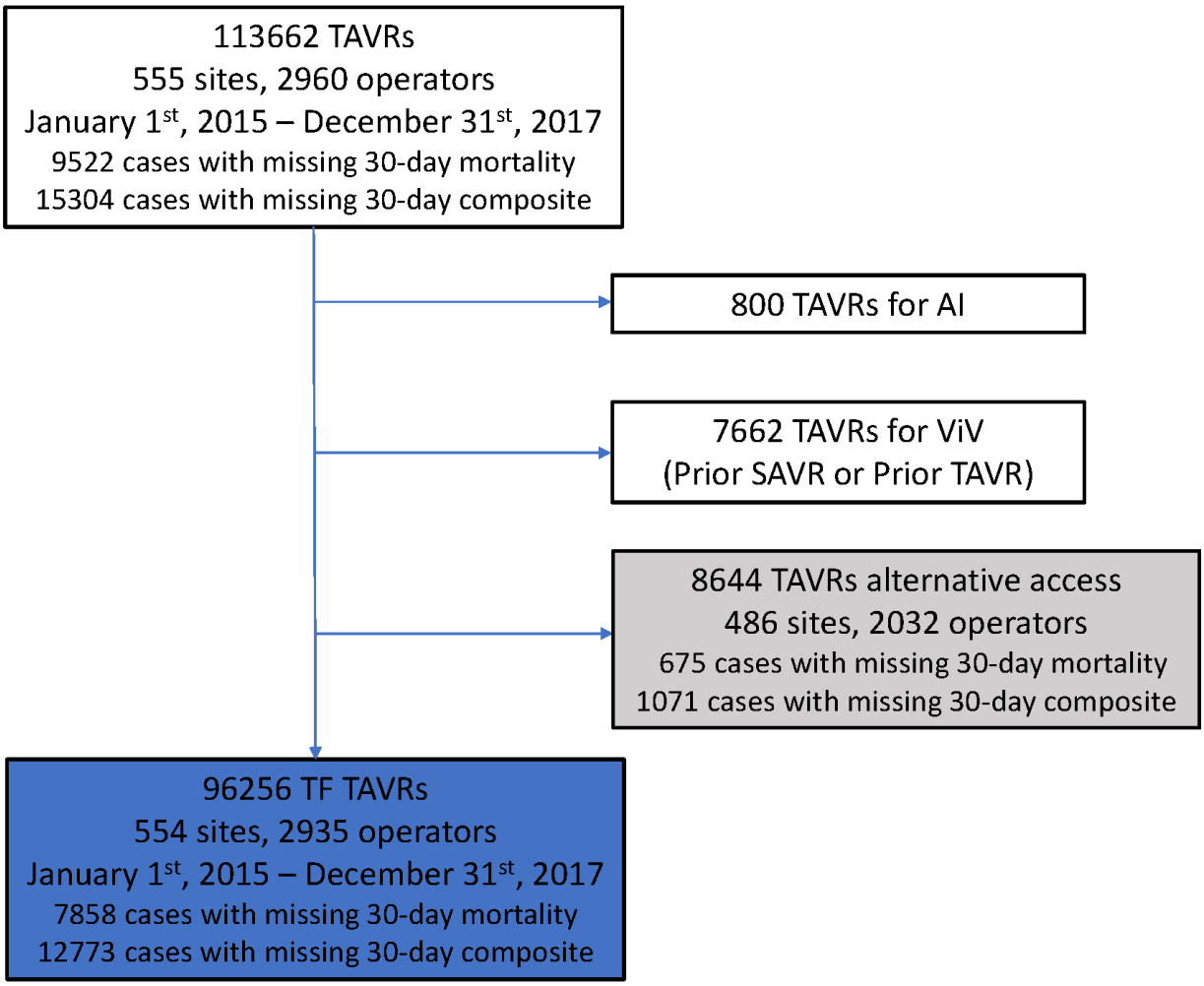
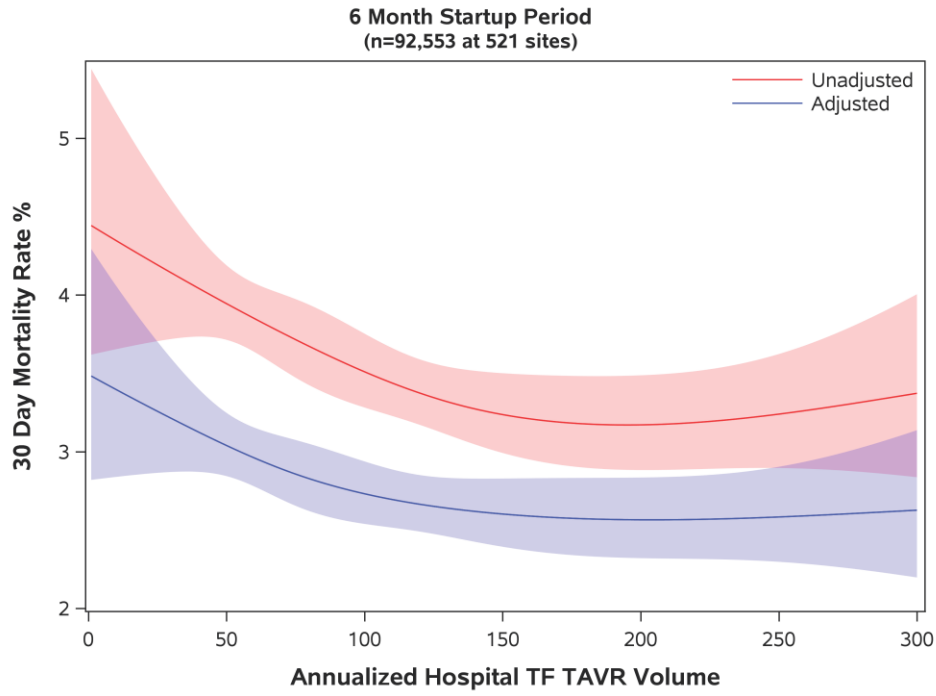


Figure S2. Hospital start-up sensitivity analysis for transfemoral TAVR (red curve for unadjusted relationship and blue curve for adjusted relationship): **(A)** Volume–mortality relationship after excluding all procedures in the first 6 months after a hospital's initial transfemoral TAVR; **(B)** Relative risk reduction of mortality (after excluding all procedures in the first 6 months after a hospital's initial transfemoral TAVR.



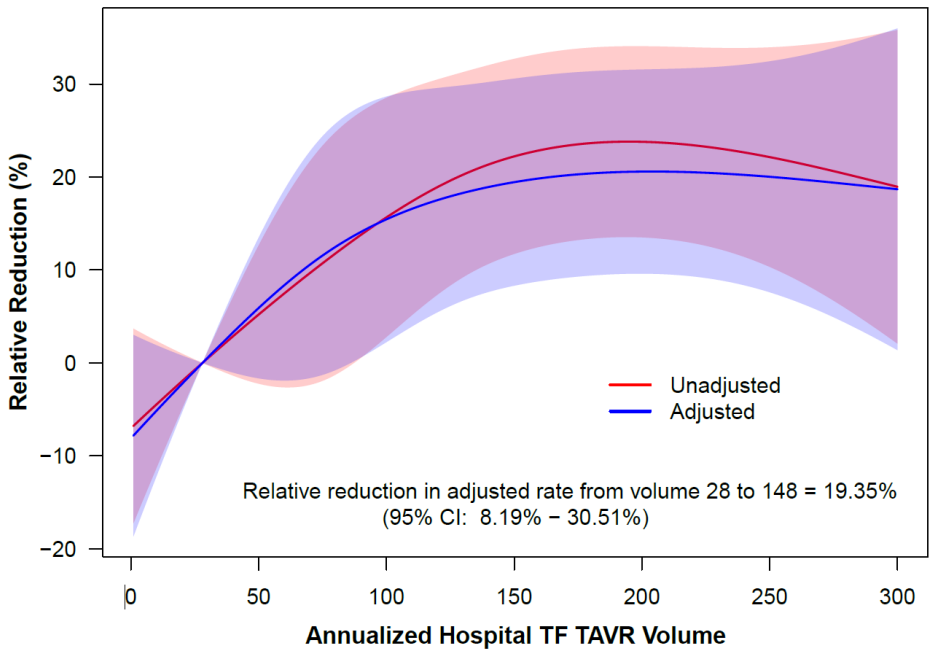
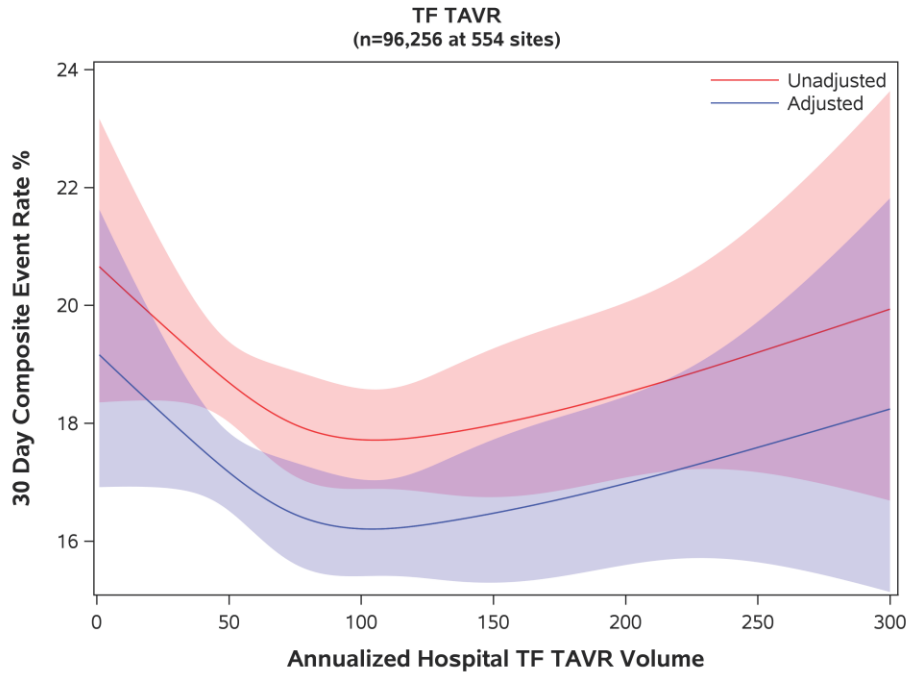


Figure S3. Transfemoral TAVR Volume–Composite relationship (red curve for unadjusted relationship and blue curve for adjusted relationship): **(A)** Volume–composite relationship in all hospitals completing at least 1 transfemoral TAVR from 2015–2017; **(B)** Relative risk reduction of the composite endpoint in all hospitals completing at least 1 transfemoral TAVR from 2015–2017.



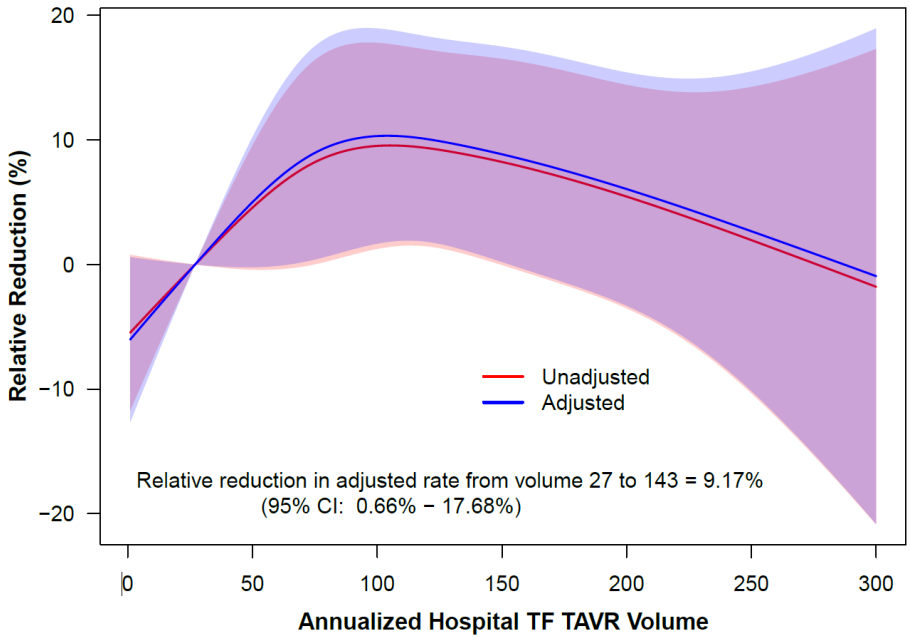


Figure S4. Transfemoral TAVR Volume–Outcomes relationship of the non-fatal components of the composite endpoint: **(A)** Stroke; **(B)** Moderate / Severe PVL; **(C)** Major Vascular / Bleeding; **(D)** Stage 3 AKI.

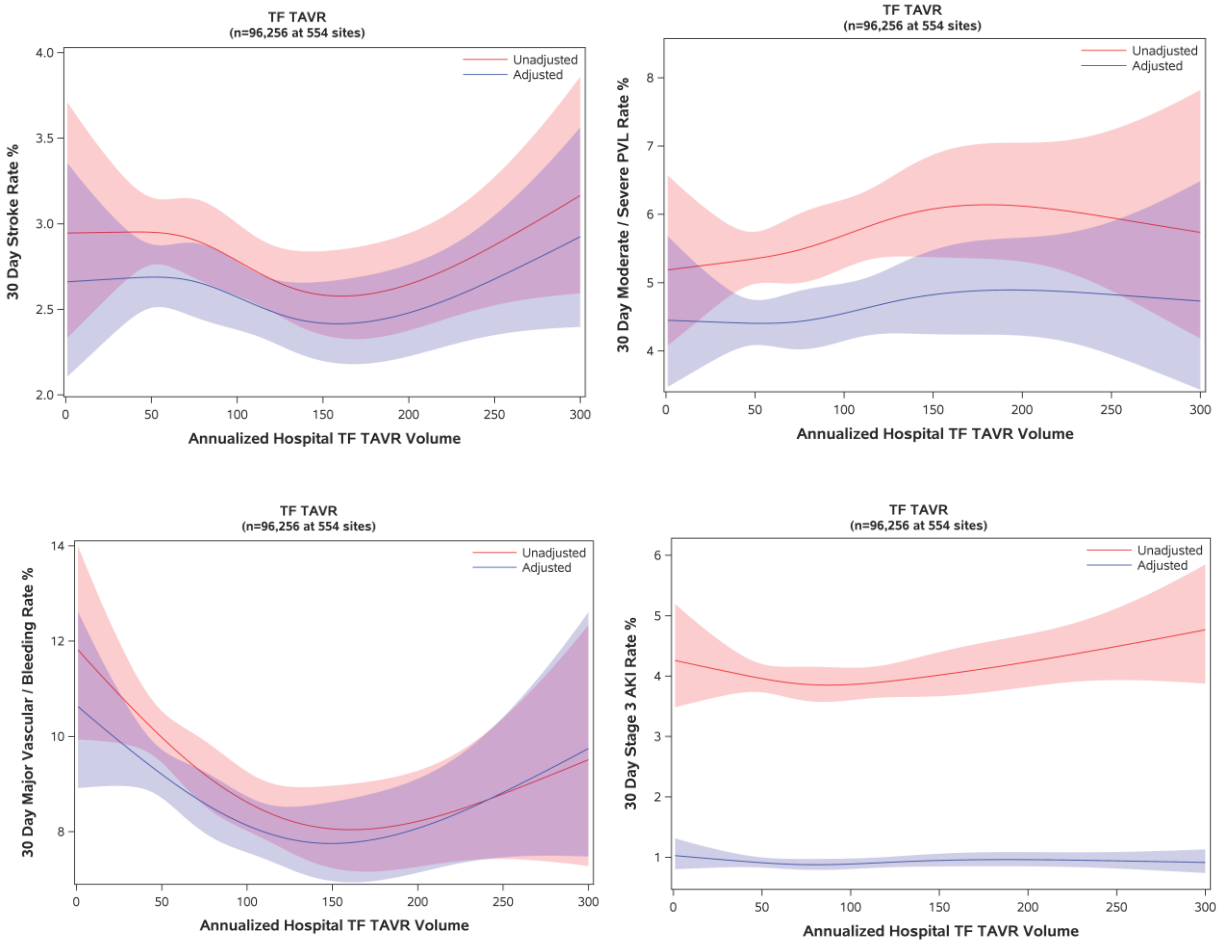


Figure S5. Histogram of annualized non-transfemoral TAVR volume

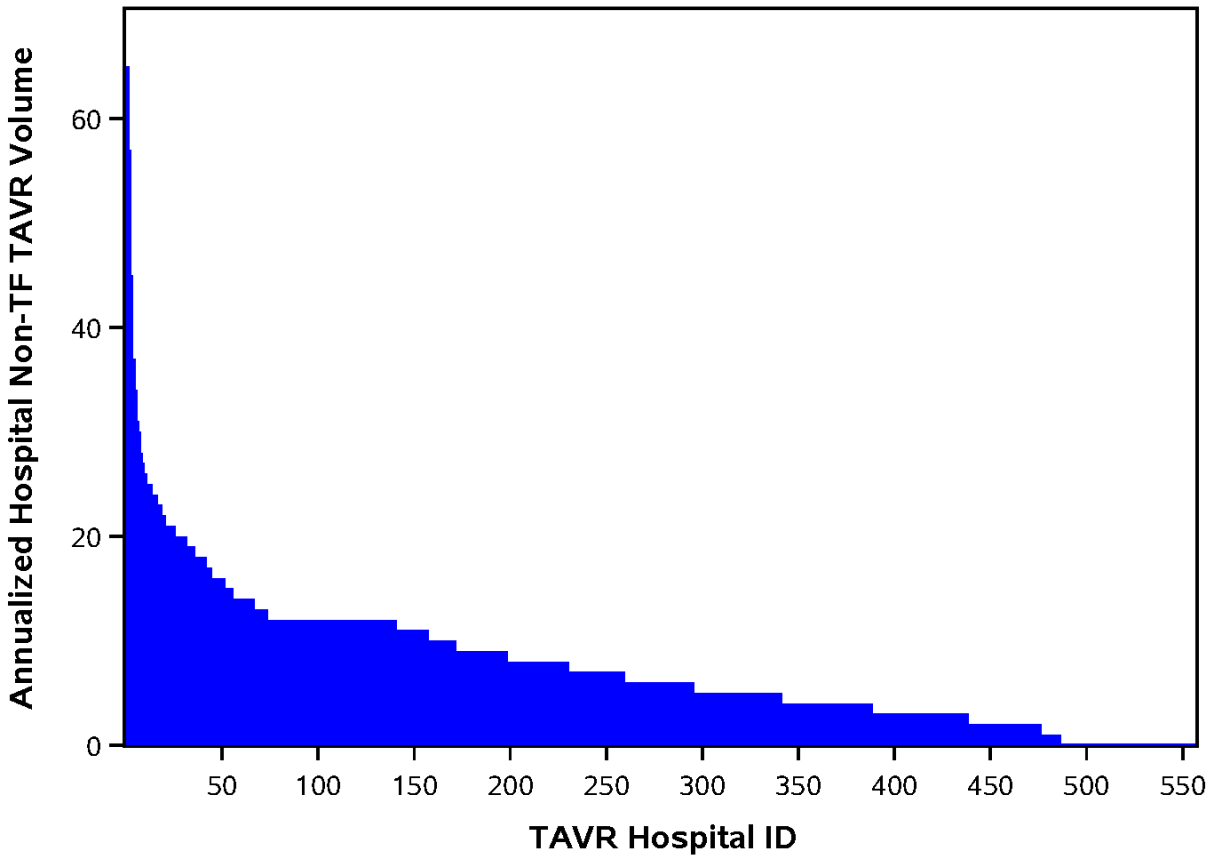


Figure S6. Volume–Mortality relationship in non-transfemoral access (red Curves are unadjusted and blue curves are adjusted): **(A)** Volume–mortality relationship in non-transfemoral TAVR; **(B)** Relative risk reduction of mortality in non-transfemoral TAVR as compared with a hospital with an annual TAVR volume of 2 in all hospitals completing at least 1 TAVR from 2015–2017.