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Association between Heart Valve Replacement Surgery and the Incidence of Alzheimer's Disease and Related Dementias (ADRDs) in Patients with Severe Aortic Stenosis: Exploratory Results from a Medicare Claims Analysis

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Abstract

While certain vascular diseases have been established as risk factors for Alzheimer's disease and related dementias (ADRDs), one specific type, heart valve disease, has been suspected but understudied. Exploratory analyses were run to understand whether heart valve replacement surgery might be associated with ADRDs. This was conducted in patients with severe aortic stenosis (AS) using propensity score matching and administrative claims data. Compared to medically managed, surgical aortic valve replacement may be associated with delayed ADRD onset (HR 0.82; $p < 0.00$). The transaortic valve replacement era may be associated with a modest delay in ADRD onset (HR 0.95; $p < 0.00$). Future research should consider newer and more rigorously validated methods for identifying severe AS in administrative claims data, utilize alternative data sources such as registry data or electronic medical record (EMR) data that are rich in AS and ADRD variables, and consider collection of ADRD-related data in prospective observational studies.

Keywords: heart valve disease, dementia
JEL Classification: I10

Introduction

In terms of etiology, scientists do not fully understand the causes of dementia and Alzheimer's disease and related disorders (ADRD), but believe it to be a combination of age-related changes to the brain, along with genetic, environmental, and lifestyle factors.[1] While certain vascular diseases have been established as risk factors,[2] one specific type, heart valve disease, has been suspected but understudied. Studies using autopsy data have reported significant aortic and mitral valve disease in AD subjects, compared to non-demented control groups.[3] Clinical studies have also shown the presence of brain infarcts to be associated aortic valve calcification, which is supportive of the association between valve disease and the risk of stroke and cognitive decline.[4-6] One small study of Medicare patients found that compared with

controls, patients with AD were more likely to have valve thickening, aortic valve regurgitation, left ventricular wall motion abnormalities, and other symptoms of heart valve disease.[7]

Given this suspected relationship between heart valve disease and dementia, it is of great interest to study whether heart valve surgeries are associated with slower cognitive decline and/or delayed onset of ADRDs. There are two key heart valve surgeries currently available. Traditionally, surgical aortic valve replacement (SAVR), which has been in use since 1960, has been the treatment of choice for severe aortic stenosis (AS).[8] During an open-heart SAVR procedure, a physician makes an incision in the chest to access the heart, removes the diseased aortic valve, and replaces it with a new valve. In late 2011, a minimally invasive alternative was approved – transcatheter aortic valve replacement (TAVR), in which a catheter is inserted into the leg or chest and is guided to the heart, to perform the valve replacement.[9] While there is a lack of research on the effects of SAVR on cognitive outcomes, there exists a small literature on the cognitive effects of TAVR. A meta-analysis by Khan et al., 2018 looked at 18 studies involving patients with severe AS who underwent TAVR, and found no overall change in cognitive performance at 3 or 6 months after treatment, or over the long term (12 to 34 months).[10] However, these studies emphasized a short-term horizon, and age-matched controls were rarely included in the reviewed studies. A second meta-analysis by Gu et al., 2020 reviewed 6 studies on TAVR patients, in which the longest study horizon was 2 years, and found that a majority of patients did not experience cognitive impairment at any time within 2 years.[11] They did note possible cognitive improvement in patients with impaired baseline cognition. A third meta-analysis by Oldham et al., 2018 evaluated 12 studies of heart valve surgeries (aortic, mitral, and mixed; essentially, surgeries other than just TAVR), in which the longest horizon was 6

months.[12] This meta-analysis concluded that decline after surgery that was later restored within 6 months.

The aforementioned meta-analyses were based on observational studies which collected information on objective measures of cognition before and at different time points after TAVR. Overall, these studies emphasized the perioperative and short-term cognitive outcomes from treatment, with a large majority of studies utilizing a horizon less than a year long – only a handful of studies examined cognitive outcomes beyond one year. Studies rarely included age-matched controls and consisted of small sample sizes. A commentary published by Talbot-Hamon et al., 2017 underscored these concerns.[13] Moreover, none of the prior literature has evaluated the association between traditional SAVR and cognitive outcomes.

Given the uncertainty revolving the long-term impact of heart valve replacement surgeries on ADRD outcomes, we propose a survival analysis using Medicare data that studies the association between heart valve replacement surgeries and time-to-ADRD diagnosis. This analysis studies whether SAVR is associated with delayed onset of ADRD diagnosis, and studies whether the introduction of TAVR was associated with delayed onset of ADRD diagnosis. This analysis uses a longer time horizon than existing studies, incorporates age-matched controls, and draws from a much larger dataset. It is our hope that this study helps shed light on the association between heart valve surgeries and time-to-ADRD diagnosis in patients with severe AS.

Methods

Overview

Our study seeks to understand the association between aortic valve surgeries, such as SAVR and TAVR, and the development of ADRDs in patients with severe AS. We use Medicare administrative claims data to algorithmically identify patients with severe AS,[14] and use a

survival analysis framework – involving Cox proportional hazard models – that accounts for right-censoring in the data to understand the relationship between aortic valve surgeries and time-to-ADRD diagnosis. The University of Southern California Institutional Review Board (IRB) deemed this study exempt from review.

Data Source and Study Population

Analyses were conducted on a cohort derived from the 20% Medicare administrative claims data who were enrolled as fee-for-service beneficiaries. The data spanned from 2002 through 2016 and included inpatient, outpatient, skilled nursing facilities, home health agency, and carrier claims, as well as the Medicare beneficiary summary file and chronic conditions files.

We identify all patients with severe AS from 2004 through 2013 based on a validated Medicare claims-based algorithm by Clark et al., 2012.[14] This algorithm defines severe AS based on an inpatient claim for heart failure or balloon aortic valvuloplasty (BAVP), as well as a claim for AS (either in the inpatient, outpatient, skilled nursing facility, home health agency, or carrier files) within 2 years. This algorithm has been previously validated through chart review using echocardiographic and cardiac catheterization data to assess the severity of AS.[14] We use the earliest of this event as our index, and follow patients forward in time to identify earliest date of ADRD onset. We also require patients have at least 2 years of continuous Part A and Part B enrollment prior to index, and exclude those with a diagnosis for ADRD prior to index. Using this sample, we apply additional criteria, described below, to obtain our cohort for studying SAVR versus MM, and our cohort for studying the TAVR versus pre-TAVR era (**Table 1.1**).

SAVR vs. MM

When comparing SAVR versus MM, we analyze patients with an index between 2004 and 2010, which are the calendar years before the availability of TAVR. TAVR was approved in the fall of 2011. We exclude patients undergoing coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI) in the 6 months post-index. We also exclude patients that died within 6 months post-index, as this is the period used to identify treatment exposure. Patients with onset of ADRD prior to index are also excluded. Finally, patients who receive SAVR within 6 months post-index are defined as SAVR patients, while those who do not are defined as MM patients.

TAVR Era vs. Pre-TAVR Era

When comparing the TAVR era versus pre-TAVR era, we compare the full universe of SAVR + MM patients in the 3 calendar years before the availability of TAVR (2008, 2009, 2010), versus the full universe of TAVR + SAVR + MM patients in the three calendar years following (2011, 2012, 2013). In this cohort, we also exclude patients with onset of ADRD prior to index.

Outcome Measure and Covariates

The date of earliest diagnosis for ADRD was provided by the Medicare chronic conditions file. Our statistical models accounted for covariates such as age at index, male sex, race, EuroSCORE (surgery-related mortality risk), as well as Elixhauser Index, and components of the EuroSCORE [European System for Cardiac Operative Risk Evaluation] that did not overlap with the components of the Elixhauser Index – in specific, active endocarditis, unstable angina, extracardiac arteriopathy, cardiac surgery, and myocardial infarction.

Statistical Analysis

SAVR vs. MM

In our SAVR vs. MM analysis, we compare time-to-ADRD diagnosis between severe AS patients who undergo SAVR and severe AS patients who are MM, using Cox PH models. To address confounding, we employ propensity score matching as SAVR surgery patients tend to be healthier and younger than MM patients. We utilize a propensity score-based method to help match our dataset's treatment group to control group. To estimate the propensity score, we predict the likelihood of treatment using the covariates described above via a logistic model. We match treatment to non-treatment subjects based on 1-to-1 nearest neighbor approach with no replacement, using a caliper of 0.0001. In addition to this main analysis, we also conduct a sensitivity scenario where we subset our study sample for lower surgical risk patients using the EuroSCORE. High surgical risk has been defined as having a EuroSCORE of 20% or higher, and we explored a subset of patients with a EuroSCORE of 10% or lower.[14] Furthermore, we conduct falsification tests which evaluate outcomes that SAVR is not expected to impact. Falsification endpoints include time-to-diagnosis of tumor with or without metastasis, osteoporosis, diabetes, and rheumatoid arthritis or osteoarthritis.

TAVR Era vs. Pre-TAVR Era

In our TAVR era vs. pre-TAVR era analysis, we study the association between TAVR's introduction and time-to-ADRD diagnosis in severe AS patients. By doing so, we aim to shed light on whether TAVR's arrival coincided with changes in the incidence of ADRD among severe AS patients. Since TAVR was approved in fall 2011 for high-risk AS patients (i.e., systematically sicker) who are not suitable for SAVR, a direct comparison of TAVR and SAVR

may suffer from substantial confounding by unobserved variation in health status. Comparing SAVR + MM patients in the pre-TAVR era, versus TAVR + SAVR + MM patients in the TAVR era allows us to avoid this selection bias issue, since we will be looking at the universe of severe AS patients at both times. Essentially, this study design exploits the introduction of TAVR as a "natural experiment" identification strategy. This design will help eludicate the incremental benefit of TAVR. Although this study design will help remove our key confounding problem, we acknowledge that it will dilute the treatment effect of TAVR. A similar study design was employed recently to study survival of severe AS patients in the TAVR versus pre-TAVR era.[15] To test the robustness of this analysis, we ran sensitivity analyses where we varied the cut-off year from 2011 to 2010, 2009, 2008, 2007, and 2006 to investigate whether our treatment effects were due to the arrival of TAVR. These alternative cut-offs were chosen because they were the years leading up to the arrival of TAVR. This analysis was also motivated by a potential secular effect – the incidence of dementia has declined every decade for the past thirty years in the US[16] – and we wished to examine whether our findings were driven by the arrival of TAVR or this secular pattern. We also investigate this secular effect by including calendar year fixed effects in our main Cox PH models.

Results

Patient Populations

We identified a total of 193,154 patients with severe, symptomatic AS in the Medicare 20% administrative claims data from 2004 through 2013 (**Table 1.1**). Of these, 185,505 (96.0%) were continuously enrolled in Part A and B in the 2 years pre-index. In parallel, additional criteria were applied to obtain our SAVR vs. MM cohort, and our TAVR era vs. pre-TAVR cohort.

SAVR vs. MM

To obtain our SAVR vs. MM cohort, we required patients have an index date prior to 2011, no claim for CABG or PCI in the 6 months post-index, no death within 6 months post-index, and no diagnosis for ADRD pre-index. This resulted in a remaining 68,384 (35.4%) of patients, of which 8,460 (12.4%) underwent SAVR within 6 months post-index and thus were eligible for propensity score matching. The propensity-score matched cohort comparing SAVR and MM patients included 8,298 SAVR patients and 8,298 MM patients, with a mean age of 76.6 years, 53.9% male, and a mean Elixhauser Index of 40.0. Baseline characteristics were well-balanced across the two treatment groups (**Table 1.2**).

TAVR Era vs. Pre-TAVR Era

To obtain our TAVR era vs. pre-TAVR era cohort, we required patients have an index date from 2008 through 2013, which is the 3 calendar years before and after the approval of TAVR, and have no diagnosis for ADRDs pre-index. This resulted in a remaining 79,745 (41.3%) of patients. Of these, 38,622 (48.3%) were identified in the TAVR era and 41,123 (51.6%) were identified in the pre-TAVR era, with a mean age of 78.7, 48.2% male, a mean Elixhauser Index of 42.5, and a mean EuroScore of 21.6. These baseline characteristics were balanced between the two treatment groups (**Table 1.4**). In the TAVR era, 12.8% and 6.5% of severe AS patients underwent SAVR and TAVR, respectively, within 6 months post-index (**Table 1.4**). In the pre-TAVR era, 12.6% and 0% underwent SAVR and TAVR, respectively, within 6 months post-index (**Table 1.4**).

Clinical Outcomes

SAVR vs. MM

Cox PH models demonstrate that, compared to MM, SAVR is associated with a significantly lower risk in the development of ADRDs (hazard ratio [HR], 0.818; $p < 0.000$) (**Figure 1.1 and Table 1.3**). We notice that the benefits of SAVR bow outward – in such a way, that SAVR offers a protective effect in earlier periods up until 9.23 years after index, at which point the risk then converges with MM. As such, while median time-to-ADRD diagnosis was not statistically significant (9.58 vs. 8.73 years; $p = 0.060$), it was near significant, since at the 48th percentile of time-to-ADRD diagnosis, time-to-ADRD diagnosis was significantly longer in SAVR patients (9.23 vs. 8.28 years; $p = 0.044$). When looking at the 25th percentile of time-to-ADRD diagnosis, time-to-ADRD diagnosis was also significantly longer in SAVR patients (4.88 vs. 3.45 years; $p < 0.000$). When we further adjust for covariates in the Cox PH model, SAVR was associated with a lower risk compared to MM (HR, 0.771; $p < 0.000$) than when without additional adjustment (**Table 1.3**).

We also examine a sensitivity scenario and a perform series of falsification tests. We examine a sensitivity scenario where we subset to patients with a EuroSCORE of 10% or less, which reflects patients with lower surgical risk (**Figure 1.2A**). In this subset, SAVR continues to be associated with a significantly lower risk in the development of ADRDs (HR, 0.779; $p < 0.000$) (**Appendix Table 1.2**). We examined this sensitivity scenario since patients who undergo SAVR tend to be healthier with less surgical risk. Falsification tests were also performed to understand whether outcomes not causally effected by SAVR were affected (**Figures 1.2B-1.2E**). In these falsification tests, multivariate Cox PH models show that SAVR is not significantly associated with greater risk than MM, in the development of tumors with or without

metastasis (HR, 1.051; p = 0.363), osteoporosis (HR, 0.973; p = 0.660), diabetes (HR, 1.046; p = 0.399), or rheumatoid arthritis or osteoporosis (HR, 0.983; p = 0.722) (**Appendix Table 1.2**).

TAVR Era vs. Pre-TAVR Era

We also compare time to development of ADRDs in severe AS patients in the TAVR era vs. pre-TAVR era (**Figure 1.3**). Cox PH models demonstrate that compared to the pre-TAVR era, the TAVR era was associated with a modest reduced risk in the development of ADRD (HR, 0.945; p < 0.000) (**Figure 1.3 & Table 1.5**). Due to insufficient follow-up in the TAVR era, differences in median survival could not be reported. In earlier years since index, we see that there is a significant delay in time-to-ADRD diagnosis in the TAVR era, compared to the pre-TAVR era. However, this reduction in hazard diminishes over time. As such, we observe that at the 31st percentile of time-to-ADRD diagnosis, time-to-ADRD diagnosis was significant longer in the TAVR era than pre-TAVR era (4.04 vs. 3.81 years; p = 0.011), although this is not the case afterward. When we further adjust for covariates in the Cox PH model, the TAVR era was associated with a lower risk compared to MM (HR, 0.927; p < 0.000) than when without additional adjustment (**Table 1.3**).

Discussion

In this study, we find evidence that aortic valve surgeries may help delay the onset of ADRDs. While the median time-to-ADRD diagnosis may not be significantly different between aortic valve replacement surgery and MM, as shown in our work, we find a protective effect in the earlier years after surgery, which diminishes over time. Our work expands beyond prior literature by using a much longer follow-up, greater sample size, and matched controls. It is also

the first study to investigate the association between aortic valve replacement surgeries and ADRD using Medicare administrative claims data.

Prior research has focused on the perioperative or short-term effects of TAVR on cognition, rather than the long-term effects. A recent meta-analysis of cognitive outcomes after TAVR was conducted by Khan et al., 2018.[10] This meta-analysis of 18 studies consisted of 1,065 participants in total, with 15 of the studies utilizing a follow-up of 6 months or less. Many of these studies were single-arm observational studies, and rarely utilized age-matched controls.

While studies in meta-analyses such as Khan et al., 2018 studied TAVR, we were unable to identify studies in the literature that examined the association between SAVR and cognition. Although TAVR usage has risen rapidly since its approval in late 2011, SAVR is still a common procedure for severe AS and offers a similar surgical function by replacing the defective aortic valve. Our TAVR era vs. pre-TAVR era analysis found that increased TAVR uptake, holding SAVR uptake stable, delayed onset of ADRDs. This finding would be worthy of further exploration using additional sources of data. And while prior work has compared TAVR and SAVR in terms of overall survival,[15] future studies may also want to evaluate TAVR and SAVR in terms of their long-term cognitive trajectory through a variety of other data types).

Given the rapidly aging US population, in which older adults 85+ represent the fastest-growing segment of the population,[16] and the greater incidence of dementia that comes with older age,[17] it is important to understand the mechanisms that give rise to these diseases for better prevention and/or management. Although there is some evidence that patients with AD experience greater heart valve disease and valve abnormalities, the impact of vascular diseases such as heart valve disease on cognitive outcomes has largely been understudied.[3,7] Our research

indicates that there may be a link, and highlights the value of better understanding the role of heart valve disease – as well as vascular disease in general – on cognitive outcomes.

Our work has several limitations. First, the analysis of this study is limited by the availability of variables in Medicare claims data. While AS can be identified in claims data using diagnosis and procedural codes, severity of AS is not readily identifiable. As such, we utilized a validated Medicare claims-based algorithm to identify severe AS.[14] However, while this is a limitation, a benefit of using the Medicare claims dataset is its greater volume of patients and its more comprehensive longitudinal account of the patient experience. An EMR dataset may not offer the longitudinal record needed to properly assess time-to-ADRD diagnosis, and a registry dataset may be limited by sample size. This is the first observational study of its type to be performed at this scale, and we hope it informs future work using other types of data resources. Second, as we chose to use the ADRD onset date provided in the Medicare chronic conditions file, we perform an aggregate analysis of the different types of ADRDs and do not assess by subtypes, or severity level (i.e., mild cognitive impairment, mild AD, moderate AD). Subtype or severity may be more identifiable using survey-centered data. Given challenges in identifying earlier stage ADRDs in administrative claims data, we believe our findings likely represent a disease state that is more developed, rather than an early disease state. Third, we acknowledge that we cannot control for all aspects of patient health status. As such, we take actions to account for confounding. Since patients undergoing SAVR are more likely to be healthier and younger, we conduct propensity score matching in our SAVR vs. MM analysis. We understand that propensity score matching cannot account for confounding on unobservables, and are aware that this will remain a limitation; however, we perform a series of falsification tests to inspect the internal validity of our framework. Furthermore, we perform a supportive analysis comparing the

TAVR vs. pre-TAVR era to further explore the association between aortic valve replacement surgery and the reduced risk of ADRDs. This supportive analysis helps address selection biases since it compares to the universe of severe AS patients in the TAVR and pre-TAVR era, in which the key difference is the percent using an AVR. While this design provides a solution to unobserved confounding, it dilutes the effect of TAVR, which is a limitation of this approach.

Conclusions

In this study, we find supportive evidence that aortic valve replacement surgeries may delay the onset of ADRDs. In patients with severe AS, SAVR is associated with a protective effect and reduces the risk of ADRDs in the earlier years post-index. However, over time this reduction in risk diminishes and the median time-to-ADRD diagnosis is not significantly different between the SAVR and MM treatment groups. We also observe a modest delay in the onset of ADRDs in the TAVR era, compared to the pre-TAVR era. These findings suggest there may be an association between heart valve disease and ADRDs, and encourage further investigation using alternative data sources.

Table 1.1. Patient Selection – Identifying Patients with Severe Aortic Stenosis for Study Cohorts

Main Inclusion/Exclusion Criteria	**N**
Inpatient claim with principal diagnosis of HF or a claim for BAVP in 2004 through 2013, AND a claim for AS diagnosis 2 years pre-index. The earliest event for this serves as the index date	N = 193,154 (100%)
Exclude if patient was not continuously enrolled in Part A & Part B in the 2 years pre-index	N = 185,505 (96.0%)

Additional Inclusion/Exclusion Criteria for SAVR vs. Medically Managed Cohort	**N**
Exclude if patient's index date prior to 2011, which is the TAVR era	N = 131,784 (68.2%)
Exclude if patient had a claim for CABG in the 6 months post-index	N = 128,300 (66.4%)
Exclude if patient had a claim for PCI in the 6 months post-index	N = 127,000 (65.8%)
Exclude if patient died in the 6 months post-index	N = 84,229 (43.6%)
Exclude if patient had a diagnosis for ADRD pre-index	N = 68,384 (35.4%)
Define patients not undergoing SAVR within 6 months post-index as MM subjects	N = 59,924 (87.6%)
Define patients undergoing SAVR within 6 months post-index as SAVR subjects	N = 8,460 (12.4%)

Additional Inclusion/Exclusion Criteria for TAVR vs. Pre-TAVR Era Cohort	**N**
Exclude if patient's index date year is not within 2008 through 2013, which is the 3 calendar years before and after the approval year of TAVR	N = 106,702 (55.2%)
Exclude if patient had a claim for ADRD diagnosis pre-index	N = 79,745 (41.3%)
Define as pre-TAVR era patient if patient's index date was before 2008	N = 41,123 (51.6%)
Define as TAVR era subject if patient's index date was in 2008 or later	N = 38,622 (48.4%)

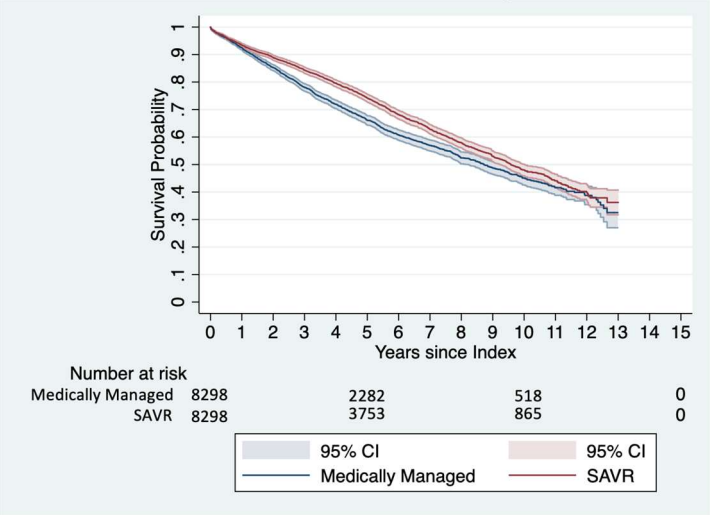
Note: HF = heart failure. BAVP = balloon aortic valvuloplasty. AS = aortic stenosis. CABG = coronary artery bypass surgery. PCI = percutaneous coronary intervention. SAVR = surgical aortic valve replacement. TAVR = transcatheter valve replacement. MM = medically managed.

Table 1.2. SAVR vs. Medically Managed – Propensity Score Matched Baseline Characteristics Table

		Matched Sample (N = 16,596)		
Baseline Characteristic	**Unmatched/Matched**	**SAVR (N = 8,298)**	**MM (N = 8,298)**	**P-Value**
Age at Index (Years)	Unmatched	76.3	79.5	0.000
	Matched	76.6	76.6	0.802
Male (%)	Unmatched	53.6%	43.8%	0.000
	Matched	53.0%	54.8%	0.095
Race (White) (%)	Unmatched	90.8%	85.0%	0.000
	Matched	90.8%	91.1%	0.542
Race (Black) (%)	Unmatched	6.1%	10.6%	0.000
	Matched	6.1%	6.0%	0.897
Race (Other) (%)	Unmatched	3.0%	4.2%	0.000
	Matched	3.0%	2.8%	0.426
Elixhauser Index	Unmatched	39.6	43.9	0.000
	Matched	39.7	40.2	0.207
Active Endocarditis (%)	Unmatched	3.7%	1.4%	0.000
	Matched	2.4%	1.6%	0.007
Unstable Angina (%)	Unmatched	20.6%	21.3%	0.222
	Matched	20.6%	20.3%	0.646
Extracardiac Arteriopathy (%)	Unmatched	5.2%	7.4%	0.000
	Matched	5.3%	5.7%	0.417
Cardiac Surgery (%)	Unmatched	47.8%	31.2%	0.000
	Matched	46.6%	48.0%	0.174
Myocardial Infarction (%)	Unmatched	18.8%	21.4%	0.000
	Matched	18.9%	19.3%	0.565

Note: SAVR = surgical aortic valve replacement. MM = medically managed.

Figure 1.1. SAVR vs. Medically Managed – Propensity Score Matched Unadjusted Kaplan-Meier Curve for Time-to-ADRD Diagnosis



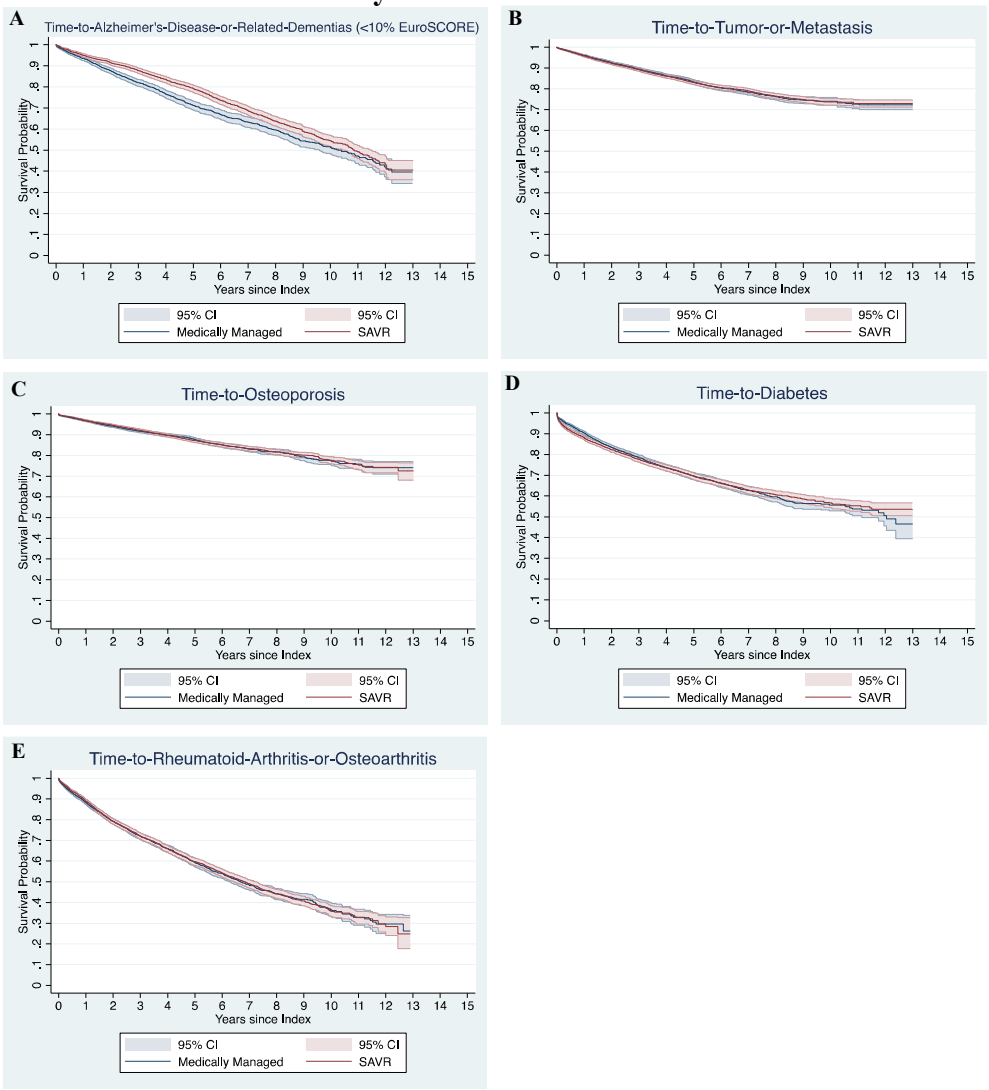
Note: SAVR = surgical aortic valve replacement. MM = medically managed. ADRD = Alzheimer's disease and related disorders.

Table 1.3. SAVR vs. Medically Managed – Propensity Score Matched Cox Proportional Hazard Model Results for Time-to-ADRD Diagnosis

	Model 1 Time-to-ADRD (N = 16,596)		Model 2 Time-to-ADRD (N = 16,596)	
Predictor	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**
SAVR (vs. MM)	0.818	0.000	0.771	0.000
Age at Index (Years)	---	---	1.067	0.000
Male	---	---	0.879	0.000
Race (Ref = White)				
Black	---	---	1.221	0.003
Other	---	---	1.034	0.706
Elixhauser Index	---	---	1.011	0.000
Active Endocarditis	---	---	0.983	0.870
Unstable Angina	---	---	1.007	0.854
Extracardiac Arteriopathy	---	---	1.193	0.051
Cardiac Surgery	---	---	0.942	0.062
Myocardial Infarction	---	---	0.933	0.105
Index Year (Ref = 2004)				
2005	---	---	0.961	0.443
2006	---	---	0.987	0.801
2007	---	---	0.943	0.278
2008	---	---	0.903	0.076
2009	---	---	0.968	0.569
2010	---	---	0.990	0.870

Note: SAVR = surgical aortic valve replacement. MM = medically managed. ADRD = Alzheimer's disease and related disorders.

Figure 1.2. SAVR vs. Medically Managed – Propensity Score Matched Unadjusted Kaplan-Meier Curves for Sensitivity Scenario and Falsification Outcomes



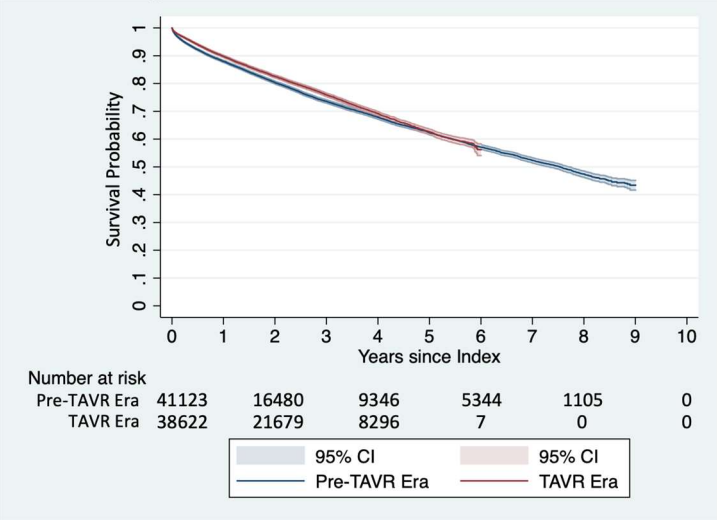
Note: EuroSCORE = European System for Cardiac Operative Risk Evaluation. SAVR = surgical aortic valve replacement. MM = medically managed.

Table 1.4. TAVR vs. Pre-TAVR Era – Baseline Demographic and Clinical Characteristics

Characteristic	Pre-TAVR Era (N = 41,123)	TAVR Era (N = 38,622)	P-Value
Age at Index (Years)	78.6	78.8	0.085
Male (%)	48.0%	48.4%	0.099
Race			0.663
White (%)	87.0%	86.9%	---
Black (%)	8.9%	8.8%	---
Other (%)	4.2%	4.3%	---
Elixhauser Index	42.3	42.8	0.079
EuroSCORE Score	21.4	21.9	0.064
Active Endocarditis (%)	1.8%	2.0%	0.089
Unstable Angina (%)	15.4%	14.9%	0.051
Extracardiac Arteriopathy (%)	6.7%	6.1%	0.071
Cardiac Surgery (%)	30.8%	30.2%	0.102
Myocardial Infarction (%)	22.1%	21.8%	0.390
AVR Surgery (%)			0.000
SAVR	12.6%	12.8%	---
TAVR	0.0%	6.5%	---
MM	87.4%	80.7%	---

Note: TAVR = transcatheter aortic valve replacement. SAVR = surgical aortic valve replacement. AVR = aortic valve replacement. MM = medically managed. EuroSCORE = European System for Cardiac Operative Risk Evaluation.

Figure 1.3. TAVR vs. Pre-TAVR Era – Unadjusted Kaplan-Meier Curve for Time-to-ADRD Diagnosis



Note: TAVR = transcatheter aortic valve replacement. ADRD = Alzheimer's disease and related disorders.

Table 1.5. TAVR vs. Pre-TAVR Era – Cox Proportional Hazard Results for Time-to-ADRD Diagnosis

	Model 1 Time-to-ADRD (N = 79,745)		Model 2 Time-to-ADRD (N = 79,745)	
Predictor	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**
TAVR Era (vs. Pre-TAVR Era)	0.945	0.000	0.927	0.000
Age at Index (Years)	---	---	1.061	0.000
Male	---	---	0.937	0.000
Race (Ref = White)				
Black	---	---	1.276	0.000
Other	---	---	1.036	0.401
Elixhauser Index	---	---	1.010	0.000
Active Endocarditis	---	---	1.027	0.699
Unstable Angina	---	---	0.991	0.706
Extracardiac Arteriopathy	---	---	1.245	0.058
Cardiac Surgery	---	---	0.917	0.070
Myocardial Infarction	---	---	1.009	0.970
Index Year (Ref = 2008)				
2009	---	---	1.011	0.681
2010	---	---	1.006	0.812
2011	---	---	1.049	0.153
2012	---	---	1.005	0.895
2013	---	---	1.060	0.335

Note: TAVR = transcatheter aortic valve replacement. ADRD = Alzheimer's disease and related disorders.

Appendix Table 1.1A. SAVR vs. Medically Managed – Propensity Score Matched Baseline Characteristics Table for Sensitivity Scenario and Falsification Outcomes

		Model 1 Time-to-ADRD Among EuroSCORE < 0.10 (N = 8,432)			Model 2 Time-to-Tumor-or-Metastasis (N = 14,746)			Model 3 Time-to-Osteoporosis (N = 15,342)		
Baseline Characteristic	**Unmatched/ Matched**	**SAVR**	**MM**	**P-Value**	**SAVR**	**MM**	**P-Value**	**SAVR**	**MM**	**P-Value**
Age at Index (Years)	Unmatched	74.0	76.5	0.000	76.2	80.3	0.000	76.0	79.5	0.000
	Matched	74.4	74.5	0.705	76.6	76.6	0.952	76.3	76.4	0.704
Male	Unmatched	56.8%	47.1%	0.000	50.7%	39.0%	0.000	60.1%	50.4%	0.000
	Matched	56.1%	55.8%	0.824	50.0%	50.9%	0.386	59.7%	61.0%	0.184
Race (White)	Unmatched	89.2%	82.5%	0.000	90.5%	84.6%	0.000	90.3%	83.3%	0.000
	Matched	89.0%	89.4%	0.656	90.5%	91.3%	0.175	90.1%	90.5%	0.589
Race (Black)	Unmatched	7.2%	13.0%	0.000	6.4%	10.8%	0.000	6.8%	12.3%	0.000
	Matched	7.4%	7.4%	1.000	6.4%	5.9%	0.368	6.9%	6.3%	0.229
Race (Other)	Unmatched	3.5%	4.3%	0.038	3.0%	4.4%	0.000	2.9%	4.2%	0.000
	Matched	3.5%	3.1%	0.441	3.0%	2.7%	0.363	2.9%	3.2%	0.455
Elixhauser Index	Unmatched	34.1	39.7	0.000	38.1	42.8	0.000	40.7	45.7	0.000
	Matched	34.4	33.8	0.343	38.2	38.7	0.335	40.8	40.9	0.886
Active Endocarditis	Unmatched	1.3%	0.4%	0.000	3.8%	1.2%	0.000	4.1%	1.4%	0.000
	Matched	0.8%	0.6%	0.316	2.7%	2.3%	0.268	2.9%	2.2%	0.037
Unstable Angina	Unmatched	9.8%	9.7%	0.873	20.9%	20.8%	0.860	21.1%	21.3%	0.701
	Matched	9.9%	9.6%	0.709	21.0%	22.2%	0.180	21.2%	21.2%	0.979
Extracardiac Arteriopathy	Unmatched	1.7%	2.9%	0.003	5.8%	8.6%	0.000	5.9%	8.6%	0.000
	Matched	1.8%	1.6%	0.519	5.9%	6.3%	0.416	6.0%	6.4%	0.452
Cardiac Surgery	Unmatched	22.4%	12.2%	0.000	48.4%	29.3%	0.000	49.4%	31.8%	0.000
	Matched	21.1%	20.3%	0.433	47.4%	48.3%	0.386	48.4%	49.3%	0.394
Myocardial Infarction	Unmatched	9.1%	9.3%	0.687	19.0%	21.7%	0.000	19.9%	22.4%	0.000
	Matched	9.0%	8.5%	0.494	19.2%	19.5%	0.742	20.0%	19.5%	0.611

Note: EuroSCORE = European System for Cardiac Operative Risk Evaluation. SAVR = surgical aortic valve replacement. MM = medically managed. ADRD = Alzheimer's disease and related disorders.

Appendix Table 1.1B. SAVR vs. Medically Managed – Propensity Score Matched Baseline Characteristics Table for Sensitivity Scenario and Falsification Outcomes

		Model 4 Time-to-Diabetes (N = 8,404)			Model 5 Time-to-Rheumatoid-Arthritis-or-Osteoarthritis (N = 7,958)		
Baseline Characteristic	**Unmatched/ Matched**	**SAVR**	**MM**	**P-Value**	**SAVR**	**MM**	**P-Value**
Age at Index (Years)	Unmatched	77.3	82.5	0.000	75.0	78.6	0.000
	Matched	78.2	78.4	0.451	75.6	76.0	0.111
Male	Unmatched	53.5%	41.0%	0.000	58.9%	52.0%	0.000
	Matched	52.5%	53.9%	0.346	58.4%	60.5%	0.138
Race (White)	Unmatched	92.7%	89.3%	0.000	90.5%	84.1%	0.000
	Matched	92.9%	92.7%	0.741	90.3%	91.7%	0.081
Race (Black)	Unmatched	5.1%	7.8%	0.000	6.6%	11.3%	0.000
	Matched	5.0%	5.5%	0.443	6.7%	5.7%	0.155
Race (Other)	Unmatched	2.2%	2.7%	0.138	2.9%	4.4%	0.000
	Matched	2.0%	1.8%	0.532	2.9%	2.5%	0.334
Elixhauser Index	Unmatched	33.2	37.3	0.000	38.6	43.3	0.000
	Matched	33.3	33.3	0.965	38.7	38.5	0.733
Active Endocarditis	Unmatched	3.6%	1.2%	0.000	4.3%	1.4%	0.000
	Matched	2.4%	1.7%	0.087	2.3%	2.0%	0.494
Unstable Angina	Unmatched	17.0%	17.0%	0.960	20.2%	19.5%	0.365
	Matched	17.1%	17.1%	1.000	19.8%	20.4%	0.618
Extracardiac Arteriopathy	Unmatched	5.2%	7.0%	0.000	5.1%	8.1%	0.000
	Matched	5.4%	5.2%	0.751	5.2%	5.1%	0.897
Cardiac Surgery	Unmatched	44.8%	25.2%	0.000	47.1%	32.2%	0.000
	Matched	43.0%	45.1%	0.136	45.5%	46.4%	0.509
Myocardial Infarction	Unmatched	16.7%	18.3%	0.040	20.8%	22.6%	0.036
	Matched	16.8%	17.1%	0.761	20.9%	20.9%	0.972

Note: EuroSCORE = European System for Cardiac Operative Risk Evaluation. SAVR = surgical aortic valve replacement. MM = medically managed. ADRD = Alzheimer's disease and related disorders.

Appendix Table 1.2. SAVR vs. Medically Managed – Propensity Score Matched Cox Proportional Hazard Model Results for Sensitivity Scenario and Falsification Outcomes

	Model 1 Time-to-ADRD Among EuroSCORE < 0.10 (N = 8,432)		Model 2 Time-to-Tumor-or-Metastasis (N = 14,746)		Model 3 Time-to-Osteoporosis) (N = 15,342)		Model 4 Time-to-Diabetes (N = 8,404)		Model 5 Time-to-Rheumatoid-Arthritis-or-Osteoarthritis (N = 7,958)	
Predictor	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**
SAVR (vs. MM)	0.779	0.000	1.051	0.363	0.973	0.660	1.046	0.399	0.983	0.722
Age at Index (Years)	1.070	0.000	1.008	0.003	1.026	0.000	0.989	0.000	1.014	0.000
Male	0.860	0.000	1.438	0.000	0.322	0.000	1.137	0.004	0.792	0.000
Race (Ref = White)										
Black	1.229	0.008	1.034	0.721	0.600	0.000	1.352	0.001	1.095	0.257
Other	0.769	0.019	0.715	0.019	1.299	0.050	1.277	0.049	0.817	0.098
Elixhauser Index	1.012	0.000	1.006	0.000	1.005	0.000	1.005	0.000	1.005	0.000
Active Endocarditis	0.989	0.954	1.06	0.712	1.093	0.590	0.816	0.207	0.827	0.183
Unstable Angina	0.980	0.713	1.042	0.477	0.967	0.624	1.215	0.001	1.119	0.026
Extracardiac Arteriopathy	0.976	0.832	0.880	0.198	0.964	0.749	0.933	0.494	1.109	0.242
Cardiac Surgery	0.956	0.236	0.995	0.918	0.982	0.732	0.929	0.125	0.990	0.810
Myocardial Infarction	0.980	0.739	0.915	0.150	0.879	0.072	1.093	0.142	0.890	0.031
Index Year (Ref = 2004)										
2005	1.020	0.748	1.013	0.855	0.927	0.400	1.013	0.866	0.834	0.007
2006	1.029	0.637	0.875	0.084	0.985	0.864	1.063	0.421	0.886	0.071
2007	0.990	0.869	0.840	0.027	1.006	0.944	1.005	0.947	0.897	0.115
2008	0.973	0.685	0.789	0.004	0.982	0.850	1.027	0.744	0.902	0.147
2009	1.026	0.716	0.787	0.006	1.008	0.932	0.990	0.907	0.976	0.760
2010	0.973	0.707	0.720	0.000	0.972	0.771	0.904	0.250	0.985	0.844

Note: EuroSCORE = European System for Cardiac Operative Risk Evaluation. SAVR = surgical aortic valve replacement. MM = medically managed. ADRD = Alzheimer's disease and related disorders.

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