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Aortic valve replacement among patients with Alzheimer's Disease and related dementias

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Key points

- TAVR diffusion occurred more rapidly in those with ADRD.
- TAVR diffusion was associated with significant declines in 1-year mortality and Medicare institutional care days in those with and without ADRD.

Why does this matter? TAVR diffusion in the ADRD population did not come at the expense of adverse outcomes.

Abstract

Background: Transcatheter aortic valve replacement (TAVR) has made palliation from aortic stenosis more broadly available to populations previously thought to be too high risk for surgery, such as those with Alzheimer's Disease and related dementias (ADRD); however, its safety and effectiveness in this context are uncertain.

Methods: We performed a retrospective cohort study of national Medicare beneficiaries, aged 66 and older with Parts A and B, between 2010 and 2016. Patients undergoing AVR were identified, and follow-up was available through 2017. Multivariable regression was used to measure the independent association between having a diagnosis of ADRD at the time of AVR, stratified by TAVR and surgery, and outcomes (mortality and Medicare institutional days at 1 year after AVR).

Results: The average rate of increase in AVR per year was 17.5 cases per 100,000 ADRD and 8.4 per 100,000 non-ADRD beneficiaries, largely driven by more rapid adoption of TAVR. Adjusted mortality following AVR declined significantly between those treated in 2010 and 2016, from 13.5% (95% CI 10.2-17.7%) to 6.3% (95% CI 5.2-7.6%) and from 13.7% (95% CI 12.7-14.7%) to 6.3% (95% CI 5.8-6.9%) in those with and without ADRD, respectively. The sharpest decline was noted for patients undergoing TAVR between 2011 and 2016, with adjusted mortality declining from 19.9% (95% CI 11.2-32.8%) to 5.2% (95% CI 4.1-6.5%) and from 12.2% (95% CI 9.3-15.8%) to 5.0% (95% CI 4.4-5.6%) in patients with and without ADRD, respectively. Similar declines were evident for Medicare institutional days in the year after AVR in both patient groups.

Conclusions: Rates of AVR in those with ADRD increased during the past decade largely driven by the diffusion of TAVR. The use of TAVR in this vulnerable population did not come at the expense of increasing Medicare institutional days or mortality at 1-year.

Keywords: Alzheimer's Disease, TAVR, Aortic Valve Replacement, Outcomes

Introduction

Innovations in procedural and peri-procedural care (e.g., minimally invasive technology, enhanced recovery pathways) have resulted in procedures that reduce illness and hospitalizations, making them more broadly available. As a means of improving survival and palliation from the symptoms of severe aortic stenosis, such as shortness of breath, chest pain, or syncope, transcatheter aortic valve replacement (**TAVR**) was initially adopted among patients who were deemed too high risk for open surgical valve replacement.[1,2] In this very high risk population, TAVR reduced mortality and hospitalizations while simultaneously enhancing functional status and quality of life.[3] More recent studies have supported broadening eligibility for TAVR to include patients who are suitable for surgical aortic valve replacement (**SAVR**).[4-9] Since the introduction of TAVR in 2011, rates of aortic valve replacement (**AVR**) have more than doubled largely due to diffusion of TAVR.[10] Given enthusiasm for its safety and effectiveness across a wide range of patients, some worry that it may be used in contexts where its palliative effects, and potential for extending life,[11] are less clear.

People with Alzheimer's Disease and related dementias (**ADRD**) are challenging in this context because the risks and benefits of surgery include not only operative risk, but also the risks associated with anesthesia and postoperative delirium that may not be mitigated by less invasive procedures, such as TAVR. Additionally, elective surgery, such as AVR in most circumstances, has a narrower margin of benefit in those with ADRD in whom life expectancy and quality of life is influenced by the underlying dementia itself. One must decide between intervening— and its risks related to anesthesia, surgery and hospitalization—versus medical management—and its

implications for symptoms related to progressive heart failure and associated consequences. Balancing these risks and consequences depends heavily on the procedure itself. On the one hand, use of new technologies, such as TAVR, in those with ADRD improves access to palliative relief from a significant illness. On the other hand, procedures in patients with ADRD can worsen cognitive decline, as evidenced by the high incidence of postoperative delirium in this population,[12-17] or result in high rates of complications, both of which may hasten decline or amplify the underlying dementia.

As the prevalence of ADRD is expected to grow to 13 million people by 2050,[18] patients with the disease will increasingly interact with healthcare systems and face decisions about treatment for competing illnesses. Dissemination of new technologies has the potential to spur utilization in these patients, in whom the calculus for the risks and benefits is less certain. This national study uses national Medicare data to assess the uptake of AVR in the era of TAVR, its safety (30-day mortality, complications and readmissions) and effectiveness (1-year rates of Medicare institutional days and mortality) in those with and without a diagnosis of ADRD.

Methods

Data and study population

A 20% national sample of Medicare claims was used to perform a retrospective cohort study of fee-for-service beneficiaries between January 1, 2010 and December 31, 2016. Patients undergoing AVR were identified using Healthcare Common Procedure Coding System codes in the Carrier file (see supplementary Table S1). Follow-up was available through December 31, 2017. We chose to study AVR because it is a relatively common procedure in older persons. Further, the study period coincided

with the rapid diffusion of TAVR, a less invasive alternative to SAVR, that greatly increased the population eligible for treatment, including those with ADRD. To identify patients with ADRD, an established and validated method, similar to that used by the Chronic Conditions Warehouse, was implemented (diagnosis codes available in supplementary Tables S2 and S3).[19] A study evaluating the performance of this algorithm indicate good specificity, but lack of sensitivity to the earliest stage of the disease (i.e., those with minimal symptoms).[19]

The study included patients age 66 years or older to permit risk adjustment using a 1-year look back. Only those with continuous enrollment in both Medicare Parts A and B from one year before through one year after the procedure were included. Patients participating in Medicare Advantage plans were excluded due to the absence of complete claims.

Outcomes

For all outcomes, the patient was the unit of analysis. Primary outcomes of the study were assessed at 1 year following AVR and included mortality (explicitly available in the Medicare Beneficiary Summary File) and the number of Medicare institutional days post-discharge. Because of the relatively high underlying mortality rate in the ADRD population and the palliative nature of AVR, and TAVR in particular, mortality was modeled as a binary outcome. The latter measure was inclusive of days spent in an acute care hospital (i.e., either as an inpatient or observation stay) or skilled nursing facility. Secondary outcomes, including complications, readmission and mortality, were measured at 30-days post-discharge to determine safety and feasibility of AVR in those

with and without ADRD. Complications were enumerated using the Agency for Healthcare Research and Quality's patient safety indicators.[20]

Analysis

For each year of study, we compared patient characteristics between those with and without ADRD using the Wilcoxon Rank-sum Test and Fisher's Exact Test for continuous and binary data, respectively. Next, we estimated rates of AVR annually among these two populations both overall and by procedure type (i.e., SAVR vs. TAVR and urgent vs. elective). In all cases, the numerator was characterized by the number of eligible patients undergoing the procedure. The denominator was represented by the entitlement eligible Medicare population that did and did not have the procedure, regardless of the presence or absence of aortic stenosis. Logistic regression models were used to adjust the rates for patient age, gender and race.

To examine the independent effect of ADRD, multivariable logistic regression (binary outcomes, such as mortality) and linear (continuous outcomes, such as Medicare institutional days) models were fit separately for all primary and secondary outcomes. All models were adjusted for patient age, race, gender, comorbidity as measured by Hierarchical Condition Categories (**HCCs**), procedure urgency (i.e., elective vs. non-elective as noted in MedPAR), hospital days in the year prior to surgery, having a nursing home stay within 90 days of the procedure and a zip code-level measure of socioeconomic class.[21]

All analyses were carried out using computerized software (SAS 9.4, Cary, NC). All tests were two-sided and the probability of Type 1 error was set at 0.05. The study protocol was judged to be exempt by the institutional review board.

Results

Adjusted rates of AVR increased from 99.6 per 100,000 (95% CI 97.0-102.2) in 2010 to 152.0 per 100,000 in 2016 (95% CI 148.7-155.2). As illustrated in Figure 1a, rates increased more rapidly over this period among those with ADRD (between rate p-value <0.001). The increase in the rate of AVR in patients with and without ADRD was primarily due to the introduction of TAVR (Figure 1b). For instance, in those with ADRD, adjusted rates of SAVR decreased from 49.1 per 100,000 (95% CI 43.5-55.4) in 2010 to 36.8 per 100,000 in 2016 (95% CI 32.9-41.2), while adjusted rates of TAVR increased from 0 in 2010 to 107.8 per 100,000 (95% CI 100.4-115.7) in 2016 (p-value for trend <0.001). Importantly, the adoption of TAVR in those with ADRD was significantly faster than in patients without ADRD (between rate p-value <0.001). As illustrated in Figure 1c, the growth in use of AVR in both patient groups occurred in an elective context.

Supplementary Table S4 compares patient characteristics according to the presence of ADRD for those undergoing AVR over time. Generally, patients with ADRD were older, had higher levels of comorbidity, spent more days in an acute care hospital in the preceding 12-month period, and were more likely to have a nursing home stay within 90 days of the index procedure. Interestingly, those with ADRD were more likely to undergo a non-elective procedure in 2010 (40.0% [95% CI 34.1-46.1%] vs. 29.2% [95% CI 27.9-30.4%]), though this difference ebbed over time and was not statistically different by 2016 (21.5% [95% CI 19.1-24.0%] vs. 20.2% [95% CI 19.3-21.1%]).

During the study period, unadjusted mortality at 1 year following AVR was 17.9% (95% CI 16.9-19.0) and 12.2% (95% CI 11.9-12.5) for those with and without ADRD, respectively. Unadjusted mortality declined between 2010 and 2016 particularly among

those undergoing TAVR (ADRD: from 37.5% (95% CI 21.8-53.2%) to 10.6% (95% CI 8.5-12.8%), non-ADRD: from 23.5% (95% CI 18.3-28.6%) to 8.5% (95% CI 7.6-9.4%), see Supplementary Figure 1). After adjusting for patient differences, mortality at 1 year following AVR by either TAVR or SAVR declined significantly from 13.5% (95% CI 10.2-17.7%) to 6.3% (95% CI 5.2-7.6%) and from 13.7% (95% CI 12.7-14.7%) to 6.3% (95% CI 5.8-6.9%) in those with and without ADRD, respectively. As illustrated in Figure 2a, the sharpest decline was noted for patients undergoing TAVR, with mortality declining from 19.9% (95% CI 11.2-32.8%) to 5.2% (95% CI 4.1-6.5%) and 12.2% (95% CI 9.3-15.8%) to 5.0% (95% CI 4.4-5.6%) between 2011 and 2016, in patients with and without ADRD, respectively.

Decreasing trends in the number of Medicare institutional days in the year following valve replacement for TAVR and SAVR (Figure 2b) were also evident in both patient populations (Figure 2b). Among patients undergoing TAVR without ADRD, days spent in an institution decreased from 18.4 (95% CI 13.2-23.7) to 8.3 (95% CI 6.9-9.7) days between 2011 and 2016. In those with ADRD, the rate initially increased between 2011 and 2012, from 12.5 (95% CI -1.2-26.3) to 25.8 (19.6-32.0) days, but then declined to 15.2 (95% CI 12.2-18.2) days for those treated in 2016. As illustrated in Figure 3, trends in Medicare institutional days after TAVR were largely due to declines in days spent in a skilled nursing facility in both populations.

Among secondary outcomes assessing safety of AVR within 30 days post-discharge, patients with ADRD had a similar risk of complications, readmission and mortality compared with those without ADRD (Table 1). In patients with ADRD, the risk of complications, readmission and mortality within 30 days post-discharge decreased

over time by 58.1% (95% CI 53.7-62.5%), 37.9% (95% CI 34.5-41.3%) and 50.2% (95% CI 48.5-51.8%), respectively. Among patients without ADRD, the risk of complications, readmission and mortality within 30 days post-discharge decreased over time by 50.0% (95% CI 48.8-51.2%), 38.4% (95% CI 37.5-39.3) and 51.2% (95% CI 50.6-51.7%), respectively.

Discussion

Rates of AVR increased significantly between 2010 and 2016, largely due to the rapid dissemination of elective TAVR. Diffusion of TAVR among patients with ADRD outpaced that in those without ADRD such that by 2016, rates of AVR were similar in the two populations. Importantly, growing use of AVR did not compromise safety, as evidenced by decreasing risk of complications, readmissions and mortality within 30 days post-discharge in both the vulnerable ADRD population and those without ADRD. Importantly, TAVR diffusion was associated with significant declines in 1-year mortality and institutional care days. Among those treated with TAVR in 2016, 1-year risk-adjusted mortality rates were 5.2% and 5.0% for those with and without ADRD, respectively.

The development and dissemination of new technology is a major determinant of growth in Medicare spending,[22-24] of which surgical procedures is one important sector.[25] Some new procedures, such as catheter ablation of atrial fibrillation,[26] are aimed at replacing pharmacologic therapy. Others fill a void, treating conditions for which there was no prior therapy (e.g., vertebroplasty and kyphoplasty[27,28]). However, most are designed to replace an established procedure, aimed at achieving comparable effectiveness while lowering the morbidity to patients (e.g., endovascular abdominal

aortic aneurysm repair,[29,30] laparoscopic colectomy[31,32]). In some instances, such as with newer treatment technologies for prostate cancer, diffusion can occur prior to evidence development and in populations that stand little to benefit.[33,34] TAVR has transformed AVR over the past decade, accounting for nearly half all procedures.[35] Aimed at palliating symptoms and improving survival, TAVR provides treatment for a debilitating disease for those who would be at too high risk for SAVR due to competing health risks. Indeed, beyond those at prohibitive risk for surgery, TAVR has been shown to be non-inferior to SAVR for those with low and moderate risk for surgery, suggesting the importance of patient preference and clinical factors, such as the presence of ADRD, when selecting treatment approach.

People with ADRD are emblematic of a population with significant competing health risks, with mortality from the disease approaching 20% at 1 year after diagnosis among enrollees in fee-for-service Medicare.[36] With few effective treatments either to prevent the disease or slow its progression, clinicians are limited to managing established disease and avoiding further negative outcomes at a cost of $200 billion per year.[37] This extraordinary cost arises in part because ADRD complicates the management of comorbid conditions, especially in the hospital setting.[38-41] Postoperative management among those with ADRD is particularly prone to complications and worsening cognition, due to the high incidence of delirium and the use of anesthetics.[14,42-44] This study offers unique insight into the implementation of a new technology, TAVR, in a population in whom the net benefits are unclear. On the one hand, the dissemination of TAVR in ADRD could afford this vulnerable population the benefits of palliation from the symptoms of aortic stenosis that yield improvements in

functional status and quality of life. On the other hand, increasing use of these procedures could result in deteriorating cognition, thereby accelerating a downward spiral, and result in unacceptable rates of mortality and loss of independence. Importantly, this study demonstrated that the real-world implementation of TAVR in the ADRD population was both safe and effective at reducing hospital use as evidenced by the reassuring 30-day and 1-year outcomes. Future studies are warranted to determine the impact on quality of life and cognitive function in this population, particularly given concerns of possible subclinical brain infarcts with TAVR insertion.[45,46]

Our findings that the real-world implementation of AVR in those with ADRD is safe and effective must be interpreted in the context of two limitations. First, both ADRD and aortic stenosis have a wide range of severity, which we are unable to completely account for in Medicare claims. We address this by adjusting for hospitalization days in the preceding 12 months and the use of a nursing home stay within 90 days of the procedure. Further, we perform comprehensive risk adjustment using the Centers for Medicare and Medicaid HCCs. Indeed, we observed that measured comorbidity during dissemination remained relatively stable between 2012 and 2016 in those with (mean HCC score 2.68 vs. 2.73, respectively) and without (mean HCC score 2.14 vs. 2.21, respectively) ADRD. Second, we fully appreciate that indications for TAVR have broadened over the period study from inoperable aortic stenosis[1,2] to those with less severe disease.[4-6] Evolving indications for treatment with TAVR toward less severe aortic stenosis over time (which likely further enriches the SAVR population with the most robust patients) coupled with increasing physician experience with the procedure itself likely contribute to noted improvements in both primary and secondary outcomes.

To some extent, these issues are addressed by our modeling framework that incorporates a fixed effect for year of treatment and our robust approach to risk adjustment. However, as the intent of the study focused on outcomes of implementation within diverse populations (i.e., those with and without ADRD), we view this as a potential strength as it represents real-world outcomes.

Conclusions

This study demonstrates that rates of AVR have increased dramatically among those with ADRD during the past decade and are largely driven by the diffusion of TAVR. By 2016, rates of AVR were similar for those with and without ADRD. Importantly, broader implementation of AVR in patients with ADRD did not come at the expense of increasing Medicare institutional days or mortality at 1-year after the procedure.

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This represents original work and all authors have contributed significantly, as detailed below.

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Author contributions: Drs. Hollenbeck, Bynum and Sen are responsible for the concept and design of the study. Drs. Hollenbeck and Bynum and Mr. Dunn are

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Descriptive title for supplementary material: Cohort identification, characteristics and unadjusted analysis.

Supplementary Table 1: Healthcare Common Procedure Coding System (HCPCS) codes to identify TAVR and SAVR in the Carrier file
Supplementary Table 2. Dementia and cognitive impairment (ICD-9 Codes)
Supplementary Table 3. Dementia and cognitive impairment (ICD-10 Codes)
Supplementary Table 4. Characteristics of patients undergoing AVR in those with and without ADRD
Supplementary Figure S1. Unadjusted mortality in patients with and without Alzheimer's Disease and related dementias (ADRD) undergoing transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR).

Figure Legends

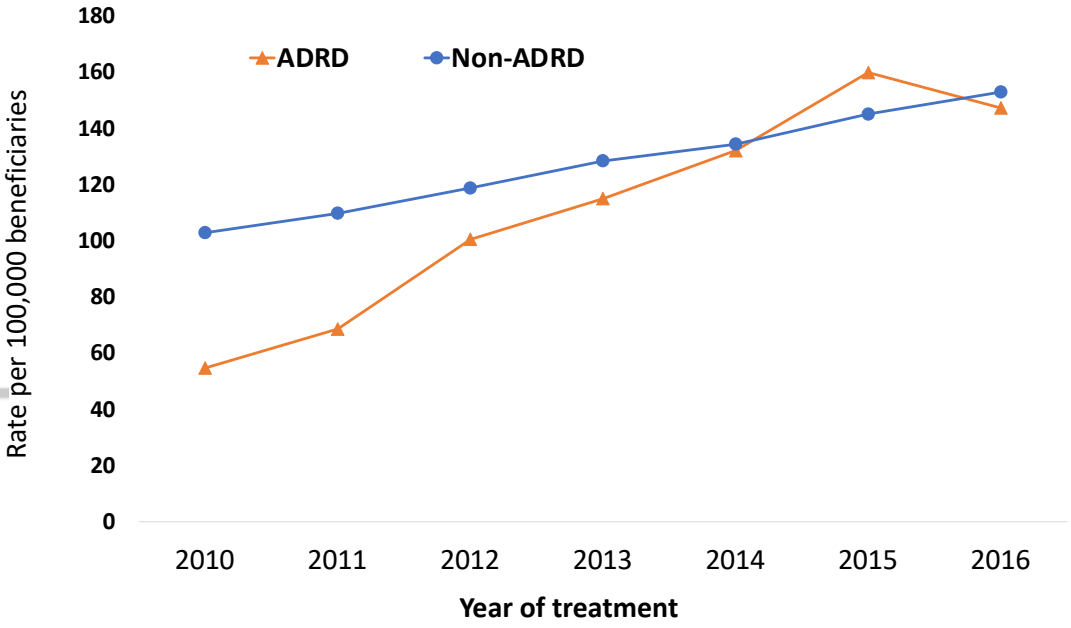
Figure 1. Rates of aortic valve replacement (AVR) adjusted for age, race and gender. **(A)** Overall in those with and without Alzheimer's Disease and related dementias (ADRD). The average rate of change per year was 17.5 cases per 100,000 ADRD beneficiaries and 8.4 per 100,000 non-ADRD, p<0.001 for test between slopes. **(B)** Rates in those with and without ADRD according to approach (transcatheter aortic valve replacement [TAVR] vs. surgical aortic valve replacement [SAVR]). Rates of SAVR declined in both populations over time (p<0.01 for trend over time in those with and without ADRD), while that for TAVR increased (p<0.01 for trend over time in those with and without ADRD). The average annual growth rate was 17.0 per 100,000 ADRD beneficiaries and 10.3 per 100,000 non-ADRD, p<0.001 for test between slopes. **(C)** Rates in those with and without ADRD according to whether the procedure was classified as non-elective. Rates of non-elective surgery were flat in those without ADRD (p=0.31 for trend over time) but increased slightly in patients with ADRD (from 21.9 [95% CI 18.1-26.4] to 30.9 [95% CI 27.2-35.0] per 100,000 beneficiaries). Conversely, rates of elective AVR increased dramatically over time in both populations (p<0.001 for trend over time in those with and without ADRD).

Figure 2. Rates of mortality **(A)** and Medicare institutional days **(B)** in the 1-year after aortic valve replacement (AVR), adjusted for age, race, gender, socioeconomic class, hospital days in 1-year prior to surgery, nursing home days in 90-days prior to surgery, and comorbidities.

Figure 3. Among patients undergoing **(A)** surgical aortic valve replacement (SAVR) and **(B)** transcatheter aortic valve replacement (TAVR), the number of days spent in a

hospital (inclusive of observation stays) and skilled nursing facility (SNF) in the 1-year period after the procedure among those with and without ADRD, adjusted for age, race, gender, socioeconomic class, hospital days in 1-year prior to surgery, nursing home days in 90-days prior to surgery, and comorbidities (NB. data shown for even years). **(A)** In those with Alzheimer's Disease and related dementias (ADRD), hospital and SNF days following SAVR decreased by an average of 0.46 (95% CI 0.22-0.70) and 0.91 (95% CI 0.11-1.72) days per year, respectively. Declines were also evident in those without ADRD (average decrease of 0.24 [95% CI 0.18-0.31] and 0.43 [95% CI 0.21-0.64] days, respectively). **(B)** In those with ADRD, hospital and SNF days following TAVR decreased by an average of 0.56 (95% CI 0.22-0.90) and 1.36 (95% CI 0.21-2.52) days per year, respectively. Declines were also evident in those without ADRD (average decrease of 0.46 [95% CI 0.30-0.62] and 1.55 [95% CI 0.99-2.10] days, respectively).

A



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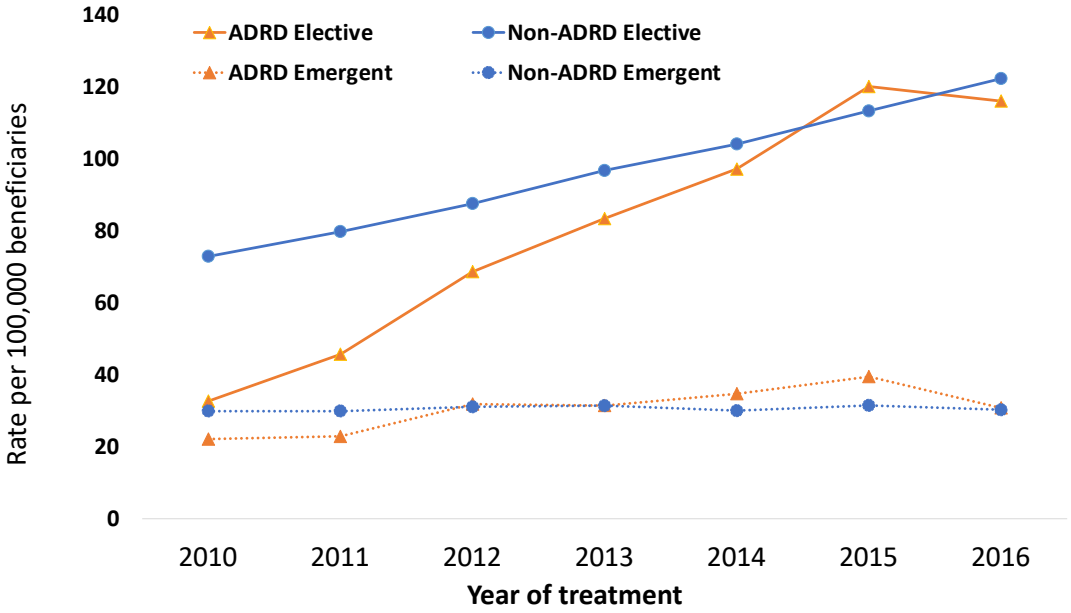

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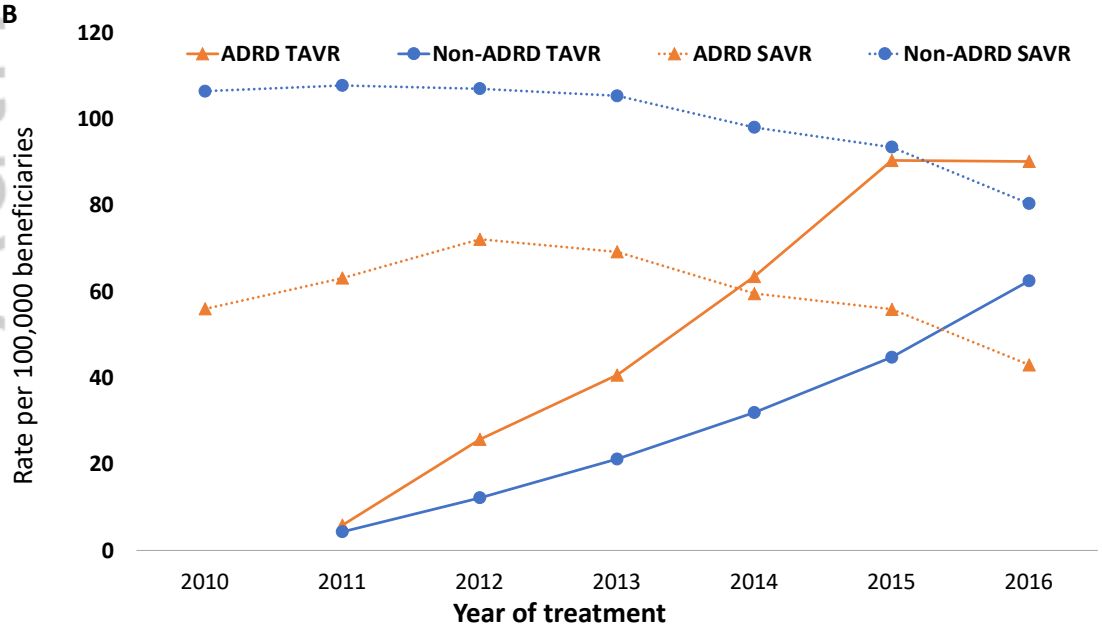

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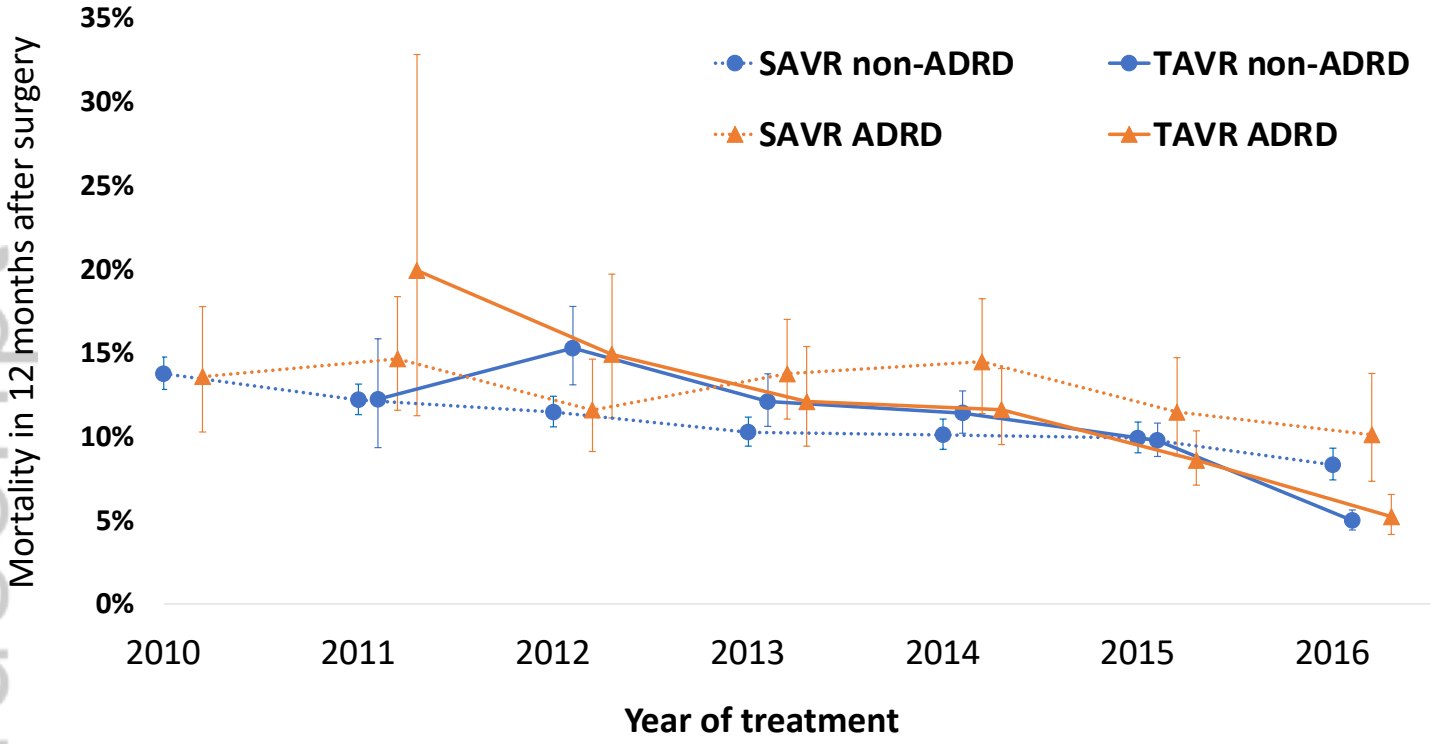

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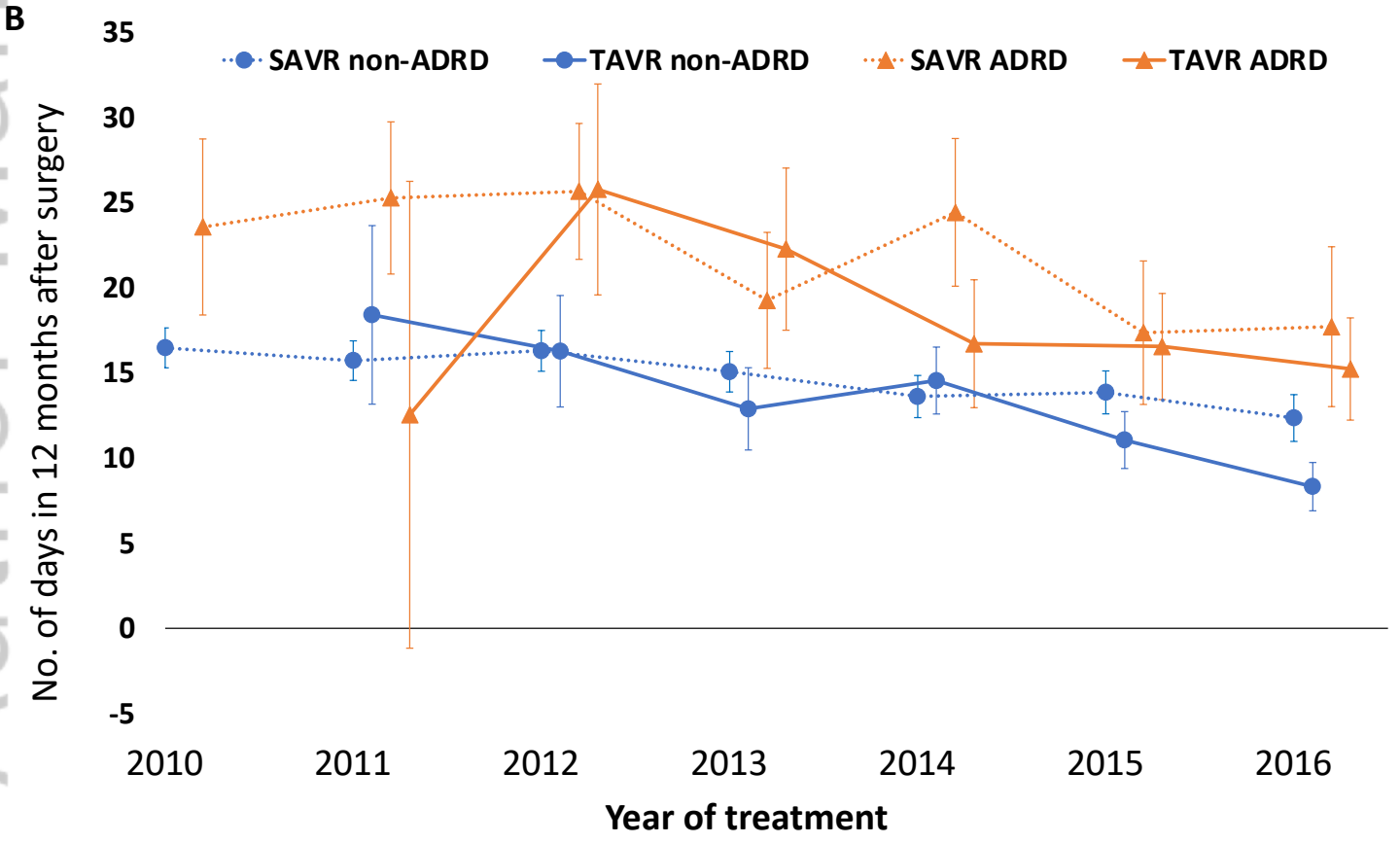

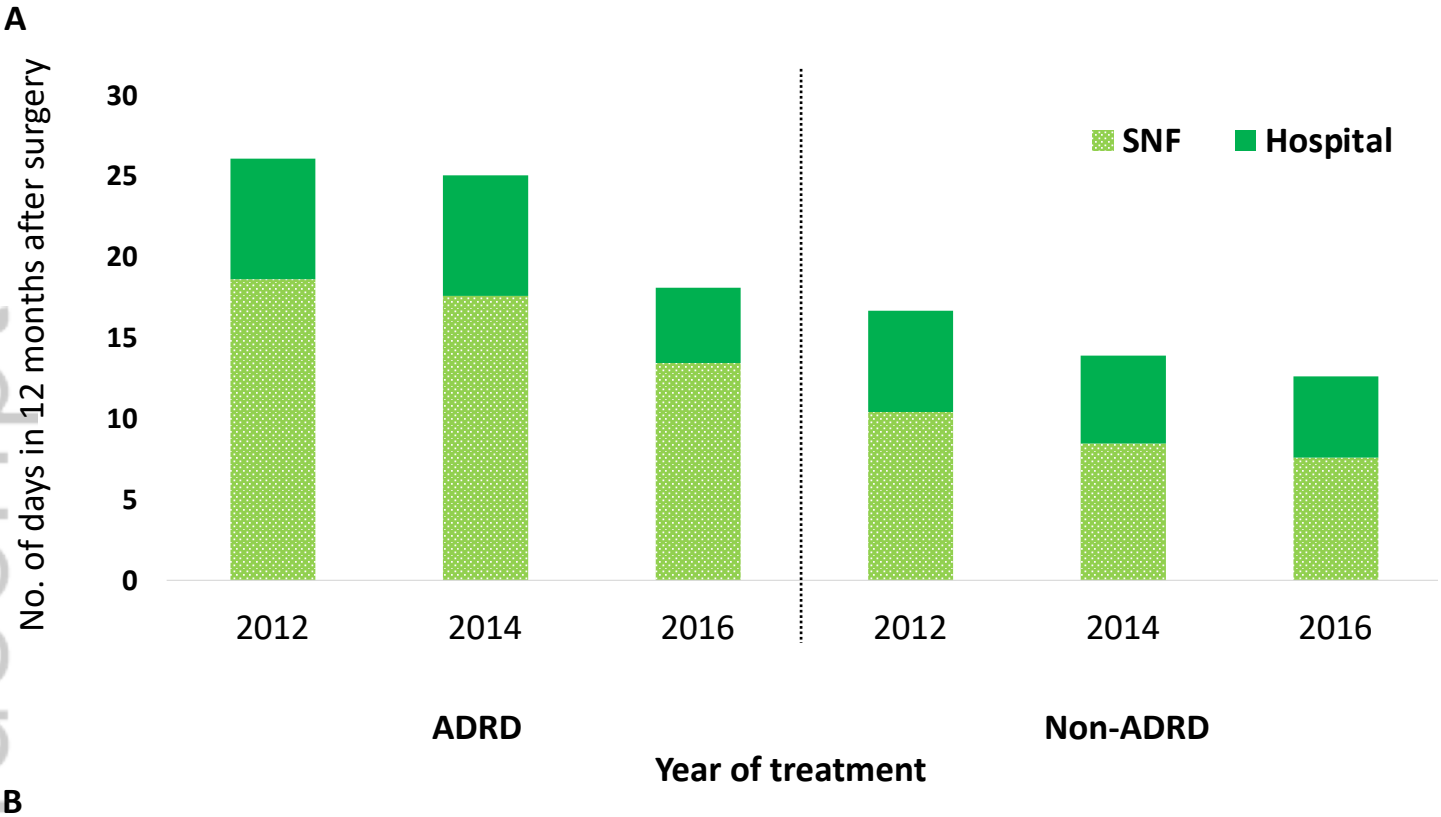

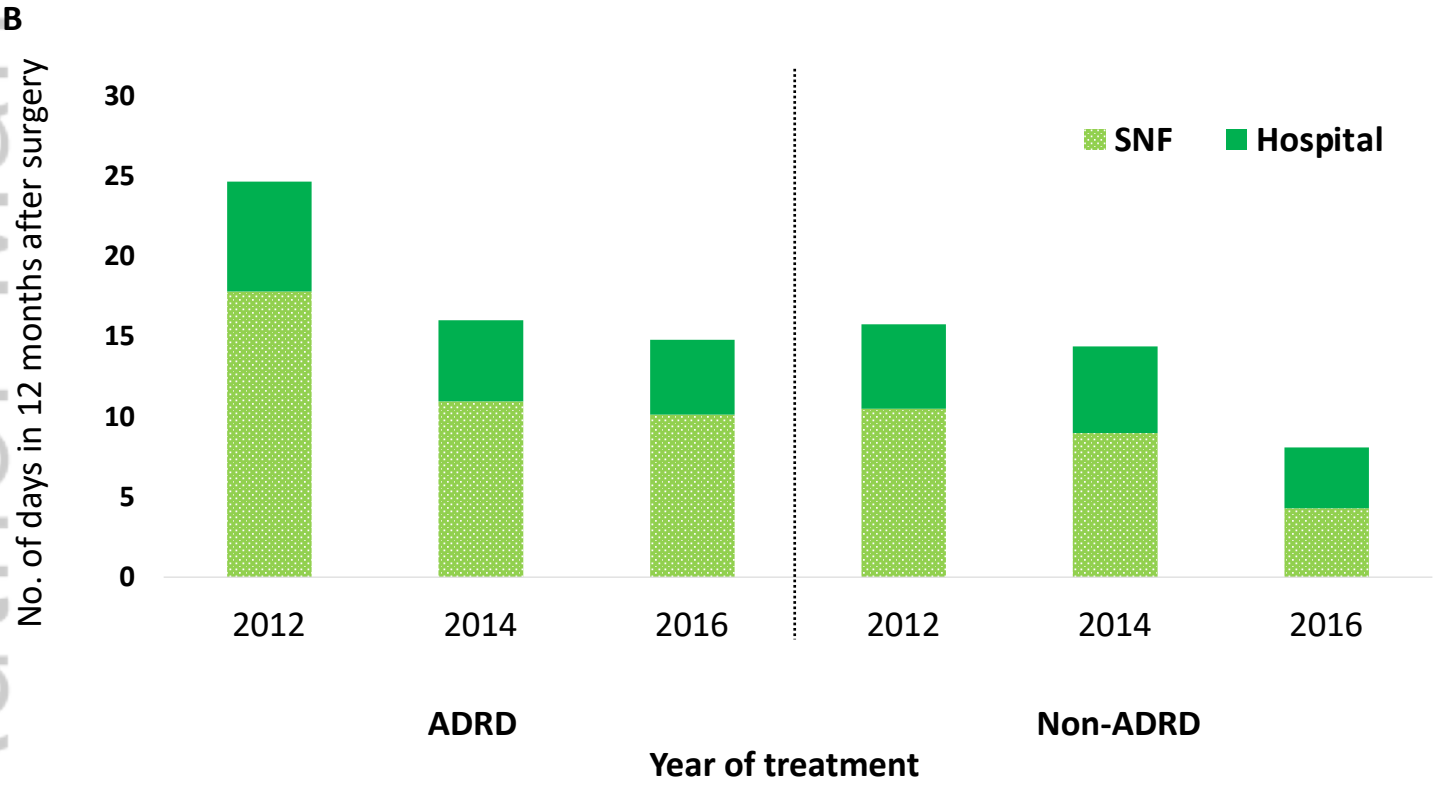

Table 1. Secondary outcomes (complications, readmissions, and mortality) assessed 30 days post-discharge, adjusted for age, race, gender, year, socioeconomic class, hospital days in 1-year prior to surgery, nursing home days in 90-days prior to surgery, and comorbidities.

Outcome	Non-ADRD			ADRD		
	Total	SAVR	TAVR	Total	SAVR	TAVR
Complication % (95% CI)	38.4 (37.9-38.9)	42.5 (41.9-43.1)	27.2 (26.2-28.3)	38.1 (36.6-39.6)	45.7 (43.6-47.8)	26.1 (24.3-28.0)
Readmission, % (95% CI)	16.4 (16.0-16.8)	17.4 (16.9-17.8)	13.6 (12.9-14.3)	17.6 (16.6-18.7)	18.1 (16.7-19.6)	15.9 (14.5-17.4)
Mortality, % (95% CI)	4.8 (4.5-5.0)	5.4 (5.1-5.6)	3.1 (2.8-3.5)	4.7 (4.2-5.2)	5.8 (5.0-6.6)	3.0 (2.5-3.5)