Sex Differences in Mortality and 90-day Readmission Rates after Transcatheter aortic valve replacement (TAVR): A Nationwide Analysis from the United States.

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Abstract

Aim: To assess gender differences in in-hospital mortality and 90-day readmission rates among patients undergoing Transcatheter aortic valve replacement (TAVR) in the United States.

Methods and Results: Hospitalizations for TAVR were retrospectively identified in the National readmissions database (NRD) from 2012-2017. Gender based differences in in-hospital mortality and 90-day readmissions were explored using multivariable logistic regression models. During the study period, an estimated 171,361 hospitalizations for TAVR were identified, including 79,722 (46.5%) procedures in women and 91,639 (53.5%) in men. Unadjusted in-hospital mortality and 90-day all-cause readmissions were significantly higher for women compared to men (2.7% vs. 2.3%, $p = .002$; 25.1% vs. 24.1%; $p = .012$ respectively). After adjusting for baseline characteristics, women had 13% greater adjusted odds of in-hospital mortality (aOR: 1.13, 95% CI: 1.02-1.26, $p = .017$), and 9% greater adjusted odds of 90-day readmission compared to men (aOR: 1.09, 95% CI: 1.05-1.14, $p < .001$). During the study period, there was a steady decrease in hospital mortality (5.3% in 2012 to 1.6% in 2017; ptrend < .001) and 90-day (29.9% in 2012 to 21.7% in 2017; ptrend < .001) readmission rate in both genders.

Conclusion: In-hospital mortality and readmission rates for TAVR hospitalizations have decreased over time across both genders. Despite these improvements, women undergoing TAVR continue to have a modestly higher in-hospital mortality, and 90-day readmission rates compared to men. Given the expanding indications and use of TAVR, further research is necessary to identify the reasons for this persistent gap and design appropriate interventions.

Introduction

Severe symptomatic aortic stenosis is associated with high mortality, and aortic valve replacement (surgical or transcatheter) improves both symptoms and survival. The US Food and Drug Administration (US FDA) initially approved Transcatheter aortic valve replacement (TAVR) in 2011 for patients with prohibitive surgical risk. [1, 2] Over the last decade, TAVR has emerged as an effective alternative treatment to surgical aortic valve replacement (SAVR) and the indications for TAVR have expanded to include high risk, intermediate risk and even select older patients with low predicted surgical risk. [3, 4, 5, 6] Given the longer life expectancy in women compared to men, and the increased prevalence of aortic stenosis with older age, the need for aortic valve intervention will continue to increase in women. Prior studies have demonstrated increased risk of vascular and procedural complications after TAVR [7, 8, 10] in women, compared to men, though these do not seem to impact long-term survival. [7, 8, 9] These early procedural complications can lead to prolonged hospital stay, unplanned readmissions, and adversely impact patients' quality of life, and health care costs. [11] Among all Medicare beneficiaries discharged from the hospital, approximately a fifth are readmitted within 30 days and a third are readmitted within 90 days accounting for an estimated $17 billion in potentially avoidable expenditures. [12] In patients undergoing TAVR, prior studies have demonstrated a 30-day readmission rate ranging from 16-18%. However, there is limited data on 90-day readmissions following TAVR which is likely to be more meaningful to healthcare systems as value-based health care evolves into a 90-day episode-based payment model. [11, 13, 14] Furthermore, there is limited data assessing the trends in gender differences in readmission rates and in-hospital mortality in patients undergoing TAVR. Herein, we assessed the in-hospital mortality and 90-day readmissions in women undergoing TAVR as well as the trends in gender related differences using a large administrative database.

Methods

Data Source

In this study, we used data from the National Readmission Database (NRD) from years 2012-2017. NRD is part of the Healthcare Cost and Utilization Project (HCUP) family of databases sponsored by the Agency for Healthcare Research and Quality (AHRQ). [15] NRD is the largest publicly available administrative database that includes index hospitalizations and their readmissions in the United States. [15] The hospitalizations included in the NRD are drawn from the HCUP and include all discharges within the State Inpatient Databases (SID)—excluding discharges in which the patient was aged 0 to 14, missing patient linkage numbers, and hospitals that have 50% of hospitalizations meeting the previous two exclusion criteria. The NRD is constructed from 28 geographically dispersed States with reliable, verified patient linkage numbers that can be used to track patients across hospitals within a State—after exclusions mentioned above, the NRD accounts for 59.7% of US resident population and 58.7% of all US hospitalizations. [15] NRD comprises various data components including patient demographics (e.g., sex, age, median household income quartile, and urban/rural location), variables that assist national inpatient estimates (stratum used for weighing, discharge weight), payment sources (e.g., Medicare, Medicaid, private insurance, self-pay), and hospital costs, and variables to facilitate readmission analysis (verified patient linkage number, length of stay, identification of transfers, same-day stays and timing between admissions of the same patient). Data provided by the NRD is completely de-identified to protect the privacy and thereby it was deemed exempted from the institutional review board approval.

Cohort Identification

We identified index hospitalizations that included a TAVR procedure using International Classification of Diseases, Ninth Edition, Clinical Modification procedure codes (ICD-9-CM) 35.05, 35.06, [11] and International Classification of Diseases, Tenth Edition, Clinical Modification procedure codes (ICD-10-CM) 02RF3xx [16] in which the patient was at least 18 years of age (see Supplemental Table S1 for ICD-9/10 codes). For each hospitalization, we extracted patient demographic characteristics that included biological sex, age, and primary payer (Medicare, private, other) as well as patient clinical characteristics that included heart failure, acute myocardial infarction (MI), coronary arterial disease, atrial fibrillation, sick sinus syndrome, history of Transient ischemic attack (TIA) or stroke, hypertension, diabetes mellitus, prior revascularization, prior cardiac surgery, chronic renal failure, hemodialysis, liver disease, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, tobacco use, malnutrition. Chronic renal failure is defined as a comorbidity that includes chronic kidney disease stages I to V including end stage renal disease without any renal replacement therapy. Current or previous history of tobacco use/dependance was reported. The Elixhauser Comorbidity score is obtained by categorizing patient co-morbidities based on the ICD diagnosis codes found in the administrative data. [17] We used the 29 Elixhauser comorbidities to calculate the AHRQ score for in-hospital mortality and readmission. [17] The Elixhauser Comorbidity score is well validated measure of comorbidity used frequently in administrative databases and has been previously utilized in studies assessing in hospital mortality, in hospital complications and readmissions following TAVR. [11, 18, 19] We extracted hospital characteristics that included teaching status (metropolitan nonteaching, metropolitan teaching, non-metropolitan) and bed size (small, medium, large). When evaluating readmissions, we excluded hospitalizations in which the patient died during the index hospitalization as well as any discharge that occurred after September 30th of each calendar year as the NRD follows patients within a single calendar year and does not capture readmissions across calendar years. Therefore, to enable a full 90-day follow-up for all discharges, we only used data from January 1st to September 30th of each year for the analysis on 90-day readmissions (Figure 1).

Outcomes

Primary outcomes included rates of TAVR procedure, in-hospital mortality during the index hospitalization, and 90-day readmission rates. The TAVR rate is presented as hospitalizations that included TAVR per 100,000 US female or male population, calculated by multiplying by 100,000 the quotient of the weighted frequency of hospitalizations that included TAVR by biological sex within a given year and mid-year US adult population estimates for females and males. [20] Secondary outcomes included length of stay and inflation-adjusted total hospital cost in 2017 US dollars [21] of the index hospitalization, cause specific 90-day readmissions defined by All Patients Refined Diagnosis Related Groups (APR-DRG) at readmission and mortality at readmission.

Statistical Analysis

All demographic and clinical characteristics were stratified by biological sex. Continuous variables are presented as mean ± standard error and compared using a linear regression model, whereas categorical variables are presented as percent and compared using the Rao-Scott chi-square test. Trend analyses were conducted using orthogonal polynomial contrasts with functional forms (e.g., linear, quadratic) evaluated as dictated by the data. Confidence intervals for continuous outcomes are based on log-normal regression models, whereas Wilson confidence intervals are provided for percentages. Separate multivariable logistic regression models were estimated for in-hospital death and all-cause 90-day readmission that included discharge year, primary payer, facility location/teaching status, facility bed size, Elixhauser readmission score, coronary arterial disease, atrial fibrillation, hemodialysis, acute myocardial infarction, obstructive sleep apnea, tobacco use, and malnutrition. The functional form of continuous variables was evaluated using restricted cubic splines with knot points at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. [22] Log-normal regression models were estimated for length of stay and total hospital cost. All analyses accounted for the NRD sampling design and were conducted using SAS v. 9.4 with $p < .05$ used to indicate statistical significance. This study was considered not human subjects research by the Creighton University Institutional Review Board (IRBNet ID: 1450745-1).

Results

Index Hospitalization

A total of 89,495 actual TAVR admissions yielding a weighted estimate of 171,452 TAVR hospitalizations were identified between 2012-2017. After excluding 91 hospitalizations pertaining to <18 years of age, our study included a total of 171, 361 inpatient TAVR procedural hospitalizations. Of these, 79,722 (46.5%) procedures were conducted on female patients and 91,639 (53.5%) were conducted on male patients (See study flow in Figure 1). Importantly, 167,495 (97.7%) of these TAVR hospitalizations were in patients ≥60 years of age. (Supplemental Table S2)

Demographic & clinical characteristics:

Females were older in general, and 66% of females undergoing TAVR were ≥ 80 years old compared to 60% of males. Overall, females had lower Elixhauser comorbidity score compared to males for both index hospitalization (6.4 ± 0.2 in females vs 7.4 ± 0.1 in males; $p < .001$), and 90-day readmissions (17.8 ± 0.2 in females vs 19.4 ± 0.2 in males; $p<.001$). Females had significantly lower rates of diabetes mellitus, coronary artery disease, atrial fibrillation, renal failure, tobacco use, and prior history of revascularization, CABG or valve surgery but a higher rate of hypertension. Of the 171, 361 patients, 91% (156,580) had Medicare as their primary insurance payer, and 90% (152, 443) of the procedures were performed in large metropolitan teaching hospitals. Demographic and clinical characteristics stratified by biological sex are provided in Table 1.

TAVR Procedural Trend:

TAVR procedures increased throughout the observation period; year-over-year increase in TAVR procedures became larger across years for both females and males (both linear p trend < .001; Figure 2a). Although there was no overall trend difference between females and males ($p = .107$), the rate of increase in TAVR hospitalizations was significantly higher in males compared to females in 2016 and 2017 (both $p < .05$).

In-hospital Outcomes during index hospitalization:

The overall unadjusted in-hospital mortality rate for hospitalizations that included TAVR was 2.5% (95% CI: 2.4% to 2.6%), which was statistically higher for females compared to males (2.7% vs. 2.3%, odds ratio [OR]: 1.17, 95% CI: 1.06-1.29, $p = .002$). After adjusting for demographic and clinical characteristics, female sex was associated with greater adjusted odds of in-hospital mortality compared to males (adjusted OR [aOR]: 1.13, 95% CI: 1.02-1.26, p = .017; Supplemental Table S3). From 2012 to 2017, there was a statistically significant decrease in the unadjusted mortality rate (5.3% in 2012 to 1.6% in 2017; p trend < .001). This improving trend, was similar for females and males (both p trend < .001; Figure 2b). Overall, length of stay and inflation-adjusted hospital cost were statistically higher for females compared to males (4.4 days vs. 3.9 days and $50,658 vs. $49,492; both p < .001).

90-day Readmissions:

Of the 171,361 index hospitalizations that included TAVR, 50, 581 hospitalizations were excluded as shown in Figure 1 due to in-hospital death or discharge after September 30th of each calendar year. A total of 63,354 actual TAVR hospitalizations yielding a weighted estimate of 120,780 TAVR discharges were included in the readmission analysis. Of these, 55,791 (46.2%) included female patients and 64,989 (53.8%) included male patients. (See study flow in Figure 1) The all-cause 90-day readmission rate was an estimated 24.6% (95% CI: 24.1% to 25.1%), which was statistically higher in females compared to males (25.1% vs. 24.1%, OR: 1.05, 95% CI: 1.01-1.10; p = .012). After adjusting for demographic and clinical characteristics, females had greater adjusted odds of 90-day readmission compared to males (aOR: 1.09, 95% CI: 1.05-1.14, p < .001; Supplemental Table S4). From 2012 to 2017, there was a statistically significant decrease in the all-cause 90-day readmission rate (29.9% in 2012 to 21.7% in 2017; p trend < .001). This improving trend was similar for both females and males (both linear p trend < .001; trend difference p = .637; Figure 2c). In a sensitivity analyses that stratified TAVR admissions by the discharge quarters from January-March; April-June; July-September (Q1, Q2, Q3) of each calendar year, the gender differences in mortality and 90-day readmission rate were similar across various quarters (Supplemental Table S5). Finally, etiology specific readmission rates are shown in Table 2. Heart failure was the most frequent cause of 90-day readmission in both females and males. While arrhythmias, gastrointestinal hemorrhage, anemia, ischemic cerebrovascular event, and urinary tract infection were more frequent in females; sepsis was a more frequent cause of 90-day readmission in males. Furthermore, while in hospital mortality at readmission was numerically lower in women, this was not statistically different compared to men (4.2% vs 4.6%; p=0.314)

Discussion

The main findings of our analysis are 1) in-hospital mortality rate for the TAVR hospitalizations is higher in women compared to men; 2) length of stay and total in-hospital costs were significantly higher in women compared to men; 3) 90-day readmissions following TAVR are higher in women compared to men; and 4) between 2012-2017, there has been a steady decrease in hospital mortality and 90-day readmissions following TAVR irrespective of gender. Collectively, these data suggest that women undergoing TAVR continue to have modestly higher in-hospital mortality and 90-day readmission rates despite improvements in outcomes over time in both genders.

To the best of our knowledge, this is the largest analysis assessing gender differences in in-hospital mortality and readmissions in the USA. While there could be an issue of under/overweighting in the NRD dataset, the overall procedure numbers and trends in mortality are consistent with data from the Transcatheter Valve Therapy (TVT) registry for the same time frame. [23] The strength of the NRD database stems from the size of the study sample, diverse geographic and demographic representation reflecting real-world clinical practice. In alignment with prior studies, [10] we noted a consistent increase in rates of TAVR hospitalizations in women and men during the study period. Expanding indications of TAVR, [3, 4, 5, 6] increasing number of centers / operators performing TAVR procedures and patient preference due to increased awareness could be the likely reasons for this upward trend. [23] While there were no overall trend differences, our study found the rate of increase in TAVR hospitalizations was significantly higher in men compared to women during the years 2016 and 2017 (both $p < .05$). Potential reasons for this could be lower access and utilization of TAVR in women compared to men despite the expanded indications. It is known that there are gender disparities in referral to and performance of a number of cardiovascular procedures such as coronary angiography, percutaneous coronary intervention, aortic valve surgery and implantable cardioverter defibrillators with women being referred less often. [24-27] Alternatively, this could be due to increased use of TAVR for intermediate risk patients due to the expanding indications. Men with aortic stenosis are in general younger and constitute a greater proportion of severe aortic stenosis patients < 80 years of age.

In our study, we found higher in-hospital mortality in women compared with men (2.7% vs. 2.3%, $p = .002$), and 13% excess risk of in-hospital mortality among women despite adjusting for baseline differences. In contrast, prior studies have demonstrated conflicting results with some showing excess 30-day mortality while most others demonstrated similar in-hospital and 30-day mortality for women. [7, 28, 29, 30] Notably, most of these studies demonstrate numerically higher mortality in women, albeit statistically non-significant. In the analysis by Chandrasekhar et al. from the TVT registry, [8] the in-hospital mortality in women was 5.6% versus 4.3% in men ($p=0.2996$) and in a NIS (2012-14) study by Doshi et al, [10] the in-hospital mortality in women was 4.5% versus 3.9% in men (p=0.15). In a more recent study by Vlastra et al. [30] on data from the Cerebrovascular EveNts in patients undergoing TranscathetER aortic valve implantation with balloon-expandable valves versus self-expandable valves (CENTER) -collaboration, in-hospital mortality was 5.2% in women compared to 4.6% in men (p=0.14). The directionality of all these studies is consistent and lends support to our finding of a modest excess risk of in-hospital mortality among women undergoing TAVR. A number of potential reasons likely contribute to the higher in-hospital mortality in women including a greater Society of Thoracic Surgery Risk (STS) score, despite a lower prevalence of coronary artery disease or diabetes mellitus, greater use of nonfemoral access, higher rates of vascular and bleeding complications and higher rates of conversion to open surgery for complications, such as annular rupture. [8, 31]

Despite the early increase in mortality, data from randomized studies and registries clearly demonstrate that long term mortality is lower in women. [8, 9, 31] This has been attributed to a lower burden of comorbidity, lower rate of peri-valvular leak (particularly with the older balloon expandable valves), and better adaptive mechanisms in women. [32] Longitudinal data is not available in the NRD dataset and we could not confirm these long-term favorable outcomes in women. Despite this, we observed a consistent improvement in the in-hospital mortality rate during the study period which is consistent with other studies across different patient populations. [33, 34]

In our study, both length of stay (LOS) and inflation-adjusted hospital cost during the index hospitalization were higher in women, as compared with men (4.4 days vs. 3.9 days and $50,658 vs. $49,492; both p < .001). Similar to our findings, previous analysis by Doshi et al. reported modestly high LOS and in-hospital costs in women, as compared with men (8.3 days vs 7.7 days, p = 0.0007 and $52,515 vs $50,789, p = 0.40), from the National Inpatient Sample (NIS) database among those who underwent TAVR between 2012-2014. [10] While this is slightly higher than in our study, our observation years were more recent and a number of potential reasons could explain the decreasing LOS and in-hospital costs in both genders, including increasing utility of local anesthesia, moderate/conscious sedation, and smaller sheath size during TAVR procedure which is associated with reduction in periprocedural complications, intensive care unit stay and mortality. [35, 36] Nevertheless, both LOS and in-hospital costs during the index hospitalization were significantly higher in women, as compared with men, which can be explained by higher rates of peri-procedural complications especially stroke/TIA, bleeding, and vascular complications in women as compared with men. [8, 9, 31]

In our study, all-cause 90-day readmission rates after TAVR were higher in women compared with men (25.1% vs. 24.1%; p = .012). After adjusting for demographic and clinical characteristics, women had greater adjusted odds of 90-day readmission compared to men (adjusted OR: 1.09, 95% CI: 1.05-1.14, p < .001). There is limited data on rates of 90-day readmissions in TAVR patients. Previously, Wang et al. [37] reported a 90-day readmission rate of 27% in ≈ 9000 patients who received TAVR between 2011-2015. While this is slightly higher than in our study, our observation years are more recent, extending through 2017 and consistent with the continually improving trend noted across mortality, and readmissions in our study. In a recent analysis of NRD, Tripati et al. [16] reported a 90-day readmission rate of 22% in ≈ 73,000 patients who underwent TAVR between 2016-2017. This slightly lower rate of readmissions compared to our study is expected as Tripati et al. limited their analyses to the two most recent years. While their study also identified age and comorbidity score to be predictors of readmission, female gender was not found to be a significant predictor in their analysis. We suspect that this could be due the significant difference in sample size between the studies and the relatively smaller difference noted in 2016 which was not sustained in 2017. Our study provides information on trends in readmission rates across a longer time frame and gender specific causes of readmission which are important to formulate gender specific strategies to improve readmission rates.

Despite the modestly higher readmission rates in women, we found consistent improving trend in in-hospital mortality and 90-day readmissions after TAVR in both genders. A number of potential reasons can explain this improving trend including improvements in TAVR techniques, operator experience and efforts such as Bundled Payments for Care Improvement (BPCI) which are designed to implement strategies to reduce expenditure, improve the quality of care for Medicare beneficiaries and mitigate the economic impact of TAVR due to growth in procedural indications. [38] Additionally, The BPCI Advanced, an innovative model of the Centers for Medicare & Medicaid Services (CMS) recently issued policy changes with splitting percutaneous coronary intervention (PCI) bundle from the TAVR bundle, and excluding costs involved with the cardiac rehabilitation from the TAVR. [39] Nevertheless, persistent higher readmissions in women, as identified in this study, indicate the need for close outpatient follow up and other individualized strategies to reduce the readmission rates.

Study Limitations and Strengths:

Several design and data limitations should be considered in the interpretation of our findings. First, this is a retrospective study using the NRD database which is primarily designed for administrative purposes. Hence, coding accuracy can impact our findings and it is likely that complications or cause for readmissions were not accurately captured. Second, detailed procedural characteristics like access type, valve size, delivery device type, valve anatomy, contrast volume used, post procedural medications are unavailable and residual bias is probable despite risk adjustment. Third, given the administrative nature of the database, we were unable to obtain all the needed variables to report the Society of Thoracic Surgeons (STS) risk score and EuroSCORE which are the commonly used measures of mortality and morbidity risk. Fourth, we were unable to incorporate the hospitalizations from October 1st to December 31st of each year which constituted about 29.5% of the hospitalization in the readmission analysis due the lack of 90-day follow-up across calendar years in the NRD. While there is potential for bias due this, we believe that this is unlikely to impact the overall directionality of the findings given the very large size of the study sample, and the fact that this quarter accounted for <1/3rd of the dataset. More importantly, in a sensitivity analyses that stratified the study sample by discharge quarters, we found that the gender differences were consistent across all three quarters in a calendar year for readmission rates and across the four quarters for mortality. Fifth, given our inclusion criteria of age >18 years, there is possibility that some of the hospitalizations included people with congenital AS. However, 98% of our study sample was >60 years of age. Hence, the small minority of young patients are unlikely to influence the findings of our study and our results may not be applicable to these younger patients. Finally, we have reported on the data from 2012 to 2017, and results may be not be completely applicable to the most recent generation of devices. Despite these limitations, NRD database is well validated with stringent data accuracy checks and quality control. Our study has the power to capture mortality differences that are not evident in smaller registries and trials due to it large size. Finally, data is ethnically and geographically diverse, includes a wide variety of centers and operators and likely much more representative of real-world practice and outcomes.

Conclusion:

In our analysis of 171,361 hospitalizations for TAVR between 2012 and 2017, women had modestly higher in-hospital mortality and 90-day readmission rates, as compared with men. However, there was a steady decrease in the in-hospital mortality rate and readmissions for both genders during this period. Despite the modest differences, given the expansion of TAVR to low-risk patients, identifying the reasons and mechanisms for gender differences in outcomes and incorporating gender specific preventive strategies should remain a focus in current and future research.

Supplementary Data:

Online Table S1: International Classification of Diseases-9th Edition-Clinical Modification (ICD-9-CM) and International Classification of Diseases-10th Edition-Clinical Modification (ICD-10-CM) diagnosis and procedure codes

Online Table S2: Adjusted model for in-hospital mortality following TAVR

Online Table S3: Adjusted model for all-cause 90-day readmission following TAVR

Acknowledgements: None

Source of funding: None

Conflict of interest: None declared

Data availability statement: The data underlying this article are available in the article and in its online supplementary material.

References

1. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;**363**:1597-1607.

2. US Food and Drug Administration approved TAVR for inoperable patients. https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100041b.pdf. Accessed March 26, 2020.

3. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;**364**:2187-2198.

4. US Food and Drug Administration approved TAVR for intermediate risk patients. https://www.fda.gov/news-events/press-announcements/fda-expands-use-sapien-3-artificial-heart-valve-high-risk-patients. Accessed March 26, 2020.

5. Kolte D, Vlahakes GJ, Palacios IF, Sakhuja R, Passeri JJ, Inglessis I, Elmariah S. Transcatheter versus surgical aortic valve replacement in low-risk patients. *J Am Coll Cardiol* 2019;**74**:1532-1540.

6. US Food and Drug Administration approved TAVR for low risk patients. https://www.fda.gov/news-events/press-announcements/fda-expands-indication-several-transcatheter-heart-valves-patients-low-risk-death-or-major. Accessed March 26, 2020.

7. O'Connor SA, Morice M, Gilard M, Leon MB, Webb JG, Dvir D, Rodés-Cabau J, Tamburino C, Capodanno D, D'Ascenzo F. Revisiting sex equality with transcatheter aortic valve

replacement outcomes: a collaborative, patient-level meta-analysis of 11,310 patients. *J Am Coll Cardiol* 2015;**66**:221-228.

8. Chandrasekhar J, Dangas G, Yu J, Vemulapalli S, Suchindran S, Vora AN, Baber U, Mehran R. Sex-based differences in outcomes with transcatheter aortic valve therapy: TVT registry from 2011 to 2014. *J Am Coll Cardiol* 2016;**68**:2733-2744.

9. Saad M, Nairooz R, Pothineni NVK, Almomani A, Kovelamudi S, Sardar P, Katz M, Abdel-Wahab M, Bangalore S, Kleiman NS. Long-term outcomes with transcatheter aortic valve replacement in women compared with men: evidence from a meta-analysis. *JACC: Cardiovascular Interventions* 2018;**11**:24-35.

10. Doshi R, Shlofmitz E, Meraj P. Comparison of outcomes and complications of transcatheter aortic valve implantation in women versus men (from the National Inpatient Sample). *Am J Cardiol* 2018;**121**:73-77.

11. Kolte D, Khera S, Sardar MR, Gheewala N, Gupta T, Chatterjee S, Goldsweig A, Aronow WS, Fonarow GC, Bhatt DL. Thirty-day readmissions after transcatheter aortic valve replacement in the United States: insights from the Nationwide Readmissions Database. *Circulation: Cardiovascular Interventions* 2017;**10**:e004472.

12. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med* 2009;**360**:1418-1428.

13. Danielsen SO, Moons P, Sandven I, Leegaard M, Solheim S, Tønnessen T, Lie I. Thirty-day readmissions in surgical and transcatheter aortic valve replacement: a systematic review and meta-analysis. *Int J Cardiol* 2018;**268**:85-91.

14. Koeckert MS, Grossi EA, Vining PF, Abdallah R, Williams MR, Kalkut G, Loulmet DF, Zias EA, Querijero M, Galloway AC. Ninety-day readmissions of bundled valve patients: Implications for healthcare policy. 2019;**31**:32-37.

15. Introduction to the HCUP Nationwide Readmission Database (NRD) 2010-2018. Healthcare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality (AHRQ). https://www.hcup-us.ahrq.gov/db/nation/nrd/Introduction_NRD_2010-2018.pdf. Accessed January 13, 2021.

16. Tripathi B, Nerusu LA, Sawant AC, Atti L, Sharma P, Pershad A. Transcatheter Aortic Valve Implantation Readmissions in the Current Era (from the National Readmission Database). *Am J Cardiol* 2020;**130**:115-122.

17. Moore BJ, White S, Washington R, Coenen N, Elixhauser A. Identifying increased risk of readmission and in-hospital mortality using hospital administrative data. *Med Care* 2017;**55**:698-705.

18. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;**36**:8-27.

19. Nagaraja V, Generaeux P, Cohen M, Suh W, Alasnag M, Potts J, Gunning M, Nolan J, Bagur R, Mamas M. P6029 Impact of elixhauser comorbidity score on the outcomes of transcatheter aortic valve replacement. *Eur Heart J* 2018;**39**:ehy566. P6029.

20. United States Census Bureau. Population and housing unit estimates (Table PEPAGESEX). https://www.census.gov/programs-surveys/popest/data/tables.html. Accessed March 13, 2020.

21. United Stated Bureau of Labor Statistics. CPI Inflation Calculator. https://www.bls.gov/data/inflation_calculator.htm. Accessed March 13, 2020.

22 Steyerberg EW. FRANK E. HARRELL, Jr., Regression Modeling Strategies: With Applications, to Linear Models, Logistic and Ordinal Regression, and Survival Analysis, Heidelberg: Springer. *Biometrics* 2016;**72**:1006-1007

23. Society of Thoracic Surgeons (STS). TAVR Update: New Insights and Perspectives from the U.S. National STS/ACC TVT Registry 2019. https://www.sts.org/sites/default/files/102419%201645.%20Bavaria.%20TVT.pdf. Accessed August, 3, 2020.

24. May T, Skinner K, Unger B, Mooney M, Patel N, Dupont A, McPherson J, McMullan P, Nielsen N, Seder DB. Coronary angiography and intervention in women resuscitated from sudden cardiac death. *Journal of the American Heart Association* 2020;**9**:e015629.

25. Tavris D, Shoaibi A, Chen AY, Uchida T, Roe MT, Chen J. Gender Differences in the Treatment of Non–ST- Segment Elevation Myocardial Infarction. *Clin Cardiol* 2010;**33**:99-103.

26. Hartzell M, Malhotra R, Yared K, Rosenfield HR, Walker JD, Wood MJ. Effect of gender on treatment and outcomes in severe aortic stenosis. *Am J Cardiol* 2011;**107**:1681-1686.

27. Davis DR, Tang AS, Lemery R, Green MS, Gollob MH, Birnie DH. Influence of gender on ICD implantation for primary and secondary prevention of sudden cardiac death. *Europace* 2006;**8**:1054-1056.

28. Conrotto F, D'Ascenzo F, Presbitero P, Humphries KH, Webb JG, O'Connor SA, Morice M, Lefèvre T, Grasso C, Sbarra P. Effect of gender after transcatheter aortic valve implantation: a meta-analysis. *Ann Thorac Surg* 2015;**99**:809-816.

29. Katz M, Carlos Bacelar Nunes Filho, Antonio, Caixeta A, Antonio Carvalho L, Sarmento-Leite R, Alves Lemos Neto P, Eduardo Koenig São Thiago, Luiz, Dias Dourado Oliveira A, Antonio Marino M, Tadeu Tumelero R. Gender- related differences on short- and long- term outcomes of patients undergoing transcatheter aortic valve implantation. *Catheterization and Cardiovascular Interventions* 2017;**89**:429-436.

30. Vlastra W, Chandrasekhar J, Del Blanco BG, Tchétché D, de Brito FS, Barbanti M, Kornowski R, Latib A, D'Onofrio A, Ribichini F. Sex differences in transfemoral transcatheter aortic valve replacement. *J Am Coll Cardiol* 2019;**74**:2758-2767.

31. Kodali S, Williams MR, Doshi D, Hahn RT, Humphries KH, Nkomo VT, Cohen DJ, Douglas PS, Mack M, Xu K. Sex-specific differences at presentation and outcomes among patients undergoing transcatheter aortic valve replacement: a cohort study. *Ann Intern Med* 2016;**164**:377-384.

32. Petrov G, Regitz-Zagrosek V, Lehmkuhl E, Krabatsch T, Dunkel A, Dandel M, Dworatzek E, Mahmoodzadeh S, Schubert C, Becher E. Regression of myocardial hypertrophy after aortic valve replacement: faster in women? *Circulation* 2010;**122**:S23-S28.

33. Mattke S, Schneider S, Orr P, Lakdawalla D, Goldman D. Temporal trends in mortality after transcatheter aortic valve replacement: A systematic review and meta-regression analysis. *Structural Heart* 2020;**4**:16-23.

34. Mentias A, Saad M, Desai MY, Horwitz PA, Rossen JD, Panaich S, Elbadawi A, Qazi A, Sorajja P, Jneid H. Temporal Trends and Clinical Outcomes of Transcatheter Aortic Valve Replacement in Nonagenarians. *Journal of the American Heart Association* 2019;**8**:e013685.

35. Toppen W, Johansen D, Sareh S, Fernandez J, Satou N, Patel KD, Kwon M, Suh W, Aksoy O, Shemin RJ. Improved costs and outcomes with conscious sedation vs general anesthesia in TAVR patients: Time to wake up? *PLoS One* 2017;**12**:e0173777.

36. Grover FL, Vemulapalli S, Carroll JD, Edwards FH, Mack MJ, Thourani VH, Brindis RG, Shahian DM, Ruiz CE, Jacobs JP. 2016 annual report of the Society of Thoracic Surgeons/American College of Cardiology transcatheter valve therapy registry. *J Am Coll Cardiol* 2017;**69**:1215-1230.

37. Wang A, Li Z, Rymer JA, Kosinski AS, Yerokun B, Cox ML, Gulack BC, Sherwood MW, Lopes RD, Inohara T. Relation of Postdischarge Care Fragmentation and Outcomes in Transcatheter Aortic Valve Implantation from the STS/ACC TVT Registry. *Am J Cardiol* 2019;**124**:912-919.

38. Bundled Payments for Care Improvement (BPCI) Initiative. https://innovation.cms.gov/innovation-models/bundled-payments. Accessed September 8th, 2020.

39. CMS Provides BPCI Advanced Guidance on PCI, TAVR and Cardiac Rehab. https://www.acc.org/latest-in-cardiology/articles/2019/10/24/08/42/cms-provides-bpci-advanced-guidance-on-pci-tavr-and-cardiac-rehab. Accessed September 8th, 2020.

Table

Table 1. Demographic and clinical characteristics stratified by biological sex

	Female (*n* = 79,722)	Male (*n* = 91,639)	*p*
Age	81.1 ± 0.1	80.0 ± 0.1	<.001
18-64	4.1	5.4	
65-79	30.1	34.3	<.001
80+	65.8	60.2	
Primary Payer			
Medicare	93.3	89.7	
Private	4.7	6.5	<.001
Other	2.0	3.7	
Facility Location/Teaching Status			
Metropolitan Non-teaching	10.2	10.1	
Metropolitan Teaching	88.8	89.1	0.156
Non-metropolitan	1.0	0.9	
Comorbidities			
Elixhauser Comorbidity Score for In-hospital death	6.4 ± 0.2	7.4 ± 0.1	<.001
Elixhauser Comorbidity Score for Readmission	17.8 ± 0.2	19.4 ± 0.2	<.001
Hypertension	62.4	61.0	0.002
Diabetes	20.7	23.2	<.001
Coronary Arterial Disease	61.8	78.4	<.001

Atrial Fibrillation	40.9	44.2	0.001
Congestive Heart Failure	4.4	4.2	0.197
Cirrhosis	2.4	3.1	<.001
Hemodialysis	3.1	4.2	<.001
Renal Failure	30.1	39.1	<.001
Chronic Obstructive Pulmonary Disease	31.1	31.0	0.889
Acute Myocardial Infarction	2.6	3.2	<.001
Sick Sinus Syndrome	3.3	3.2	0.412
Previous Stroke/Transient Ischemic Attack	11.6	11.7	0.898
Prior revascularization	7.8%	10.2%	<0.001
Prior CABG/Valve surgery	12.7%	30.4%	<0.001
Obstructive Sleep Apnea	10.3	16.6	<.001
Tobacco Use	18.7	31.7	<.001
Malnourished	4.0	3.4	<.001

Note. Data presented as mean ± standard error or percent.

CABG - Coronary artery bypass grafting

Table 2. Disease-specific 90-day readmission rates following TAVR

	Female (n = 55,791)	Male (n = 64,989)	p
All-Cause 90-day Readmission	14,019 (25.1)	15,692 (24.1)	0.012
APR-DRG at Readmission			
Heart Failure	17.7	17.5	0.709
Sepsis	5.2	6.5	0.002
Pacemaker w/o Heart Failure or Shock	3.7	4.1	0.380
Arrhythmia	4.5	3.5	0.003
Gastrointestinal Hemorrhage	2.7	2.5	0.384
Pneumonia	2.3	2.6	0.203
Anemia	2.4	1.7	0.004
Post-operative Infection	1.3	1.2	0.601
Digestive System	1.6	1.7	0.718
Cerebrovascular Accident w/ Infarction	2.4	1.8	0.042
Urinary Tract Infection	2.3	1.4	<.001
Other Complication	1.2	0.9	0.059
PE/Respiratory Failure	1.5	1.2	0.114
Chronic Obstructive Pulmonary Disease	1.9	1.6	0.191
Peripheral Vascular Disease	1.1	1.0	0.694

Note. Denominator for APR-DRG at readmission is the total number of within-sex readmissions.

APR-DRG - All Patients Refined Diagnosis Related Groups

PE – Pulmonary Embolism

TAVR – Transcatheter Aortic Valve Replacement

Figure Legends:

Figure 1. Study flow diagram showing inclusion and exclusion criteria. NRD = National Readmission Database, TAVR = Transcatheter Aortic Valve Replacement.

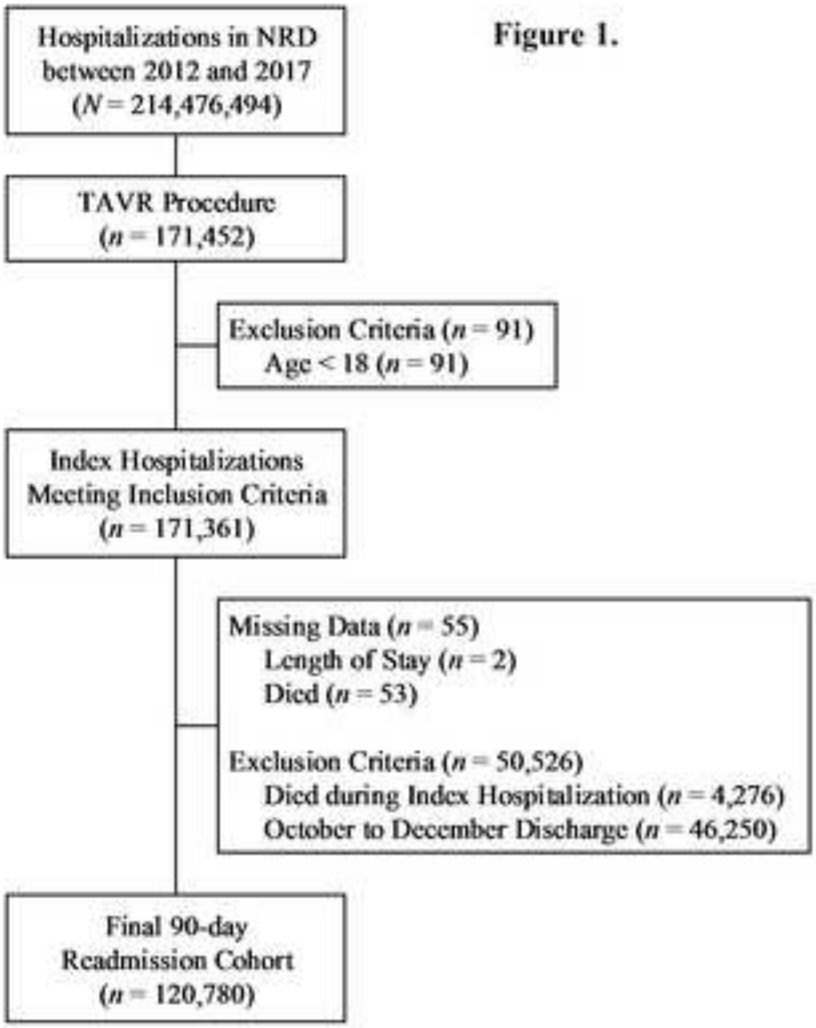
“n” represents weighed estimate.

Actual TAVR hospitalizations of 89,495 yielding a weighted estimate of 171,452.

Figure 2. (a) Trend in hospitalizations that included Transcatheter Aortic Valve Replacement (TAVR) stratified by females or males. Values are presented per 100,000 US adult population within the respective biological sex. (b) Trend in the unadjusted mortality rate after Transcatheter Aortic Valve replacement (TAVR) stratified by females or males. In both figures, error bars represent 95% confidence intervals. (c) Trend in readmission rates for hospitalizations that included Transcatheter Aortic Valve Replacement (TAVR) stratified by females or males for 90-day readmission rate. Error bars represent 95% confidence intervals.

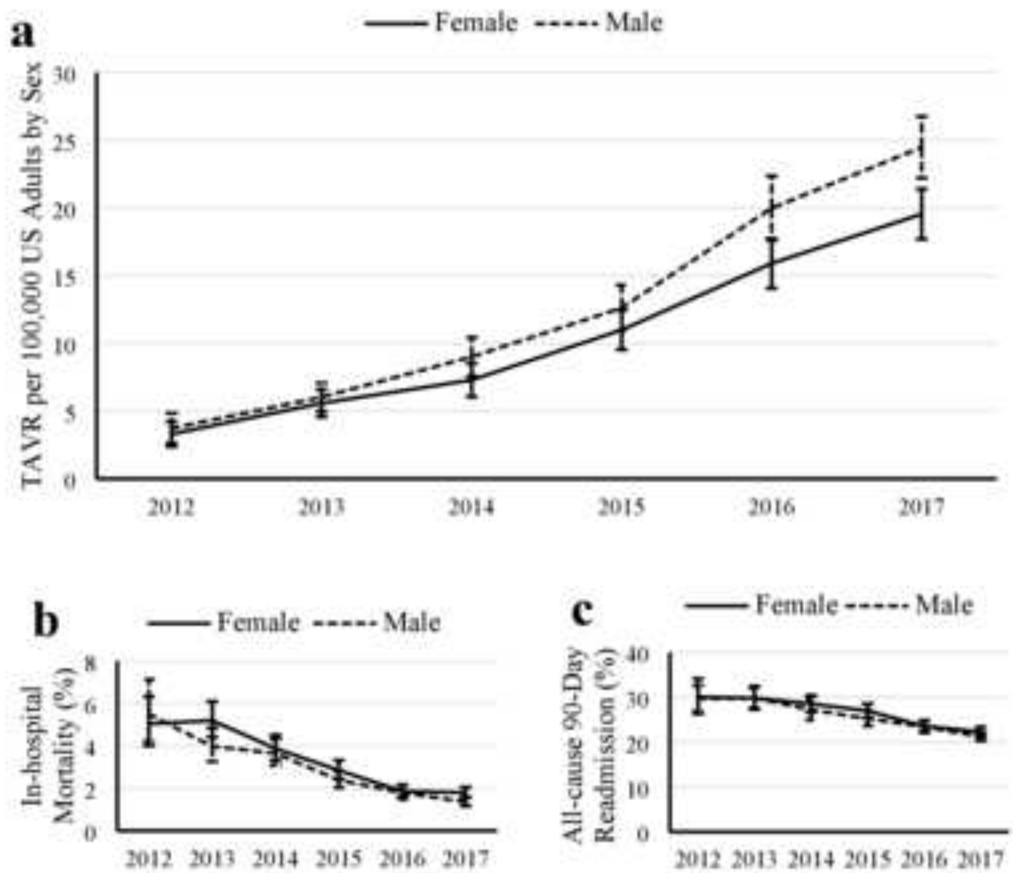
Figure

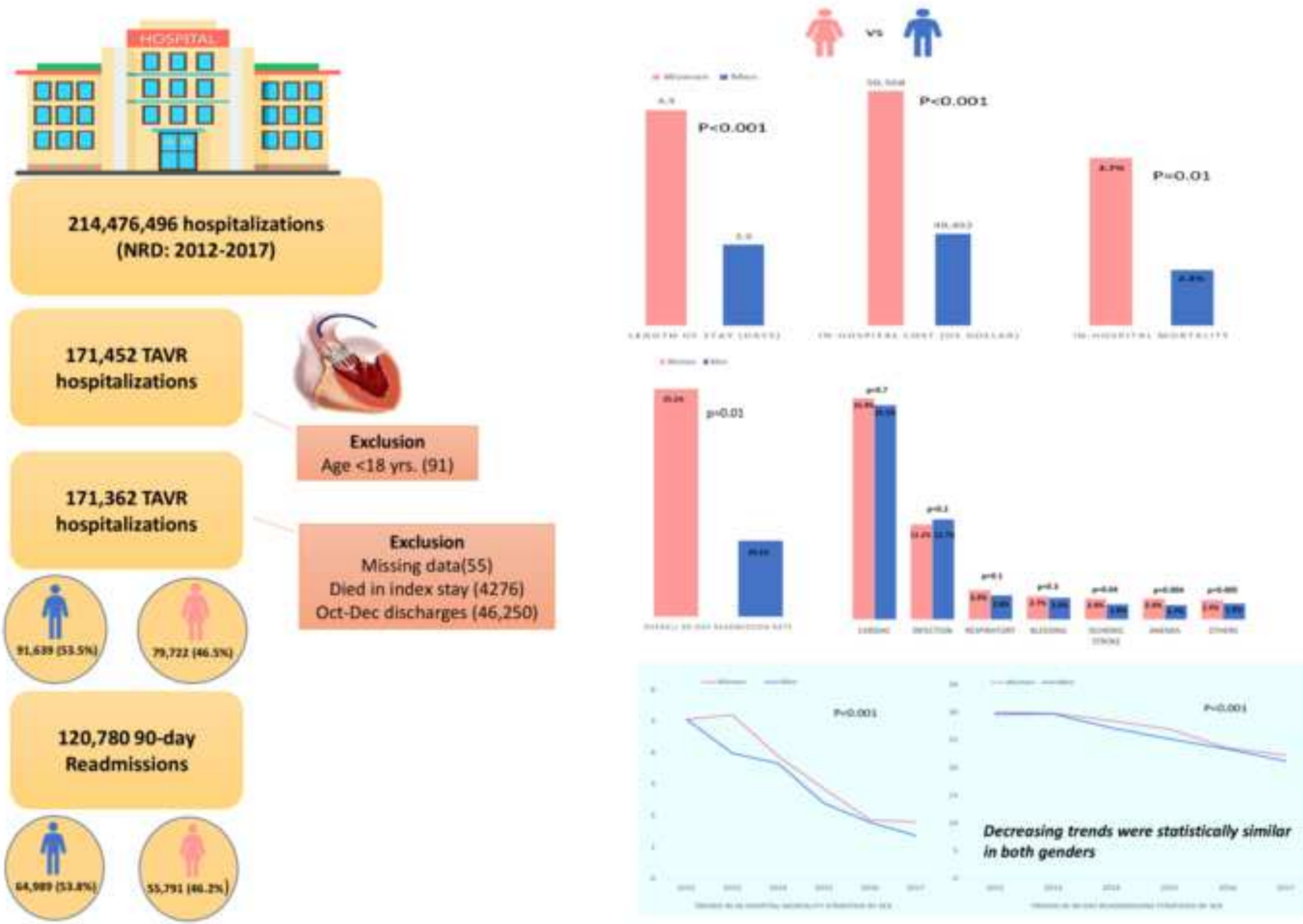
Figure 1.



Figure

Figure 2




HOSPITAL
214,476,496 hospitalizations
(NRD: 2012-2017)
171,452 TAVR hospitalizations
Exclusion
Age <18 yrs. (91)
171,362 TAVR hospitalizations
Exclusion
Missing data(55)
Died in index stay (4276)
Oct-Dec discharges (46,250)
91,639 (53.5%)
79,722 (46.5%)
120,780 90-day Readmissions
64,989 (53.8%)
55,791 (46.2%)
vs
P<0.001
P<0.001
P=0.01
p=0.01
P=0.001
P=0.001
Decreasing trends were statistically similar in both genders