Degree of Peri-Prosthetic Aortic Regurgitation: An Independent Predictor of Long-Term Mortality Following Transcatheter Aortic Valve Replacement

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Abstract

Background: Transcatheter aortic valve implantation (TAVI) has recently emerged as a promising alternative to surgical aortic valve replacement (AVR) in those patients whose surgical risk profile prevents them from undergoing an open-heart procedure. However, TAVI is not without drawbacks and potential complications. Peri-prosthetic aortic regurgitation (periAR) is a known complication of TAVI. Furthermore, moderate and severe periAR have previously been identified as independent risk factors for short- and midterm mortality following TAVI. Currently, there is very little information regarding long-term mortality in the presence of periAR following TAVI.

Method: An exhaustive search of available medical literature was conducted by searching Medline-OVID, CINAHL, Web of Science, and MDConsult using the terms: long-term outcomes, transcatheter aortic valve implantation, and aortic regurgitation. Further, citations from articles were searched for additional pertinent studies. Relevant articles were assessed for quality using GRADE. Articles with primary data regarding long-term outcomes for patients with periAR following TAVI were included.

Results: Two studies met inclusion criteria and were evaluated in this systematic review. One retrospective observational study with 202 patients identified moderate/severe periAR as the strongest independent risk factor of both all-cause and cardiovascular mortality at 1-year. Another retrospective observational study with 146 participants concluded that AR index/or moderate/severe degree of periAR independently predicted 1-year mortality.

Conclusion: Degree of periAR and AR index both independently predict 1-year mortality following TAVI. Assessment of periAR provides additional data that can be used to more accurately determine prognosis following TAV

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A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies
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Biography

Shelby Lidstrom is a native of Washington State. She attended the University of Washington as an undergraduate where earned a double degree in Biology: Physiology and English writing. Following graduation, she moved to Connecticut with her husband while he attended medical school. While there, she worked as an Emergency Department Tech at Yale-New Haven Hospital for three years prior to beginning her Physician Assistant training.
Abstract

**Background:** Transcatheter aortic valve implantation (TAVI) has recently emerged as a promising alternative to surgical aortic valve replacement (AVR) in those patients whose surgical risk profile prevents them from undergoing an open-heart procedure. However, TAVI is not without drawbacks and potential complications. Peri-prosthetic aortic regurgitation (periAR) is a known complication of TAVI. Furthermore, moderate and severe periAR have previously been identified as independent risk factors for short- and midterm mortality following TAVI. Currently, there is very little information regarding long-term mortality in the presence of periAR following TAVI.

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**Results:** Two studies met inclusion criteria and were evaluated in this systematic review. One retrospective observational study with 202 patients identified moderate/severe periAR as the strongest independent risk factor of both all-cause and cardiovascular mortality at 1-year. Another retrospective observational study with 146 participants concluded that AR index <25 and/or moderate/severe degree of periAR independently predicted 1-year mortality.

**Conclusion:** Degree of periAR and AR index both independently predict 1-year mortality following TAVI. Assessment of periAR provides additional data that can be used to more accurately determine prognosis following TAVI.

**Keywords:** long-term outcomes, transcatheter aortic valve implantation, aortic regurgitation
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To my Grandpa: You inspired the topic of this project, but more importantly, you have always been a wonderful role model and inspiration to me. I wish you could be here today, because I know you’d be incredibly proud.
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Table I: Characteristics of Reviewed Studies and Summary of Findings

List of Abbreviations

TAVI…………………………………………… Transcatheter aortic valve implantation
AR......................................................................................................................Aortic Regurgitation
AS..................................................................................................................Aortic Stenosis
AVR....................................................................................................................Aortic Valve Replacement
TEE.................................................................................................................Tran
tesophageal Echocardiogram
CAD......................................................................................................................Coronary Artery Disease
LV......................................................................................................................Left Ventricular
PeriAR.............................................................................................................Peri-
prosthetic aortic regurgitation
CT......................................................................................................................Computed tomography
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BACKGROUND

Symptomatic aortic stenosis (AS) carries a very poor prognosis. On average, survival is not more than two to three years following development of symptoms. Consequently, onset of symptomatic AS is an indication for valve replacement. While no randomized controlled studies have been conducted to date, observational studies have consistently found that corrective surgery in the setting of symptomatic AS is typically followed by improvement of symptoms and decreased mortality when compared with medical management alone.

Surgical aortic valve replacement (AVR) is widely considered the current gold standard for treatment of AS. For those patients considered healthy enough for AVR, overall operative risk is low and the procedure yields substantial relief of symptoms as well as improved overall life expectancy. However, surgical AVR carries increased operative risk for some patients including those with concomitant coronary artery disease (CAD), the elderly, patients considered medically frail, those with severely reduced left ventricular (LV) function, or patients with significant comorbidities such as cerebral and peripheral vascular disease, renal failure, and respiratory dysfunction.

Transcatheter aortic valve implantation (TAVI) was introduced in 2002 as a promising alternative to surgical AVR for those patients considered at high surgical risk, however TAVI has some limitations, particularly because it is a very new procedure.
The PARTNER (Placement of AoRTic TraNscathetER Valve) trial\textsuperscript{8-13} demonstrated that TAVI is associated with similar 30-day and 1-year mortality in high-risk patients when compared with AVR. However, it also identified some clinically important drawbacks, most importantly, risk of moderate and severe peri-prosthetic aortic regurgitation (periAR), which recent studies estimate a prevalence of approximately 15\% to 20\%.\textsuperscript{8-13} In fact, moderate to severe periAR has been identified as an independent risk factor for short and midterm mortality following TAVI.\textsuperscript{9,13-16} Unfortunately, there is currently very little data available regarding long-term (>1 year) outcomes related to post-procedure AR.

**METHODS**

An exhaustive search of available medical literature was conducted by searching Medline-OVID, CINAHL, Web of Science, and MDConsult using the terms: long-term outcomes, transcatheter aortic valve implantation, and aortic regurgitation. Further, citations from articles were searched for additional pertinent studies. Articles with primary data regarding long-term outcomes for patients with periAR following TAVI were included. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) scale.\textsuperscript{17}

**RESULTS**

Initial search results yielded five potential articles for review. Following screening of articles for relevance, two studies\textsuperscript{16,18} met inclusion criteria. Both studies are retrospective observational studies. Three additional studies\textsuperscript{9,14,19} were excluded because they did not directly address long-term outcomes related specifically to periAR.

Gotzmann et al
This retrospective observational study investigated incidence of AR following TAVI with the CoreValve prosthesis (Medtronic CV, Minneapolis, Minnesota) along with its effect on functional status and long-term outcomes. Investigators enrolled 202 consecutive patients with either native aortic stenosis or degenerated aortic bioprosthesis who underwent transfemoral (n=197) or transaxillary (n=4) TAVI. During echocardiographic examination following TAVI, patients were subdivided into two independently analyzed groups based on presence of no/mild or moderate/severe measured post-procedural AR. The primary study end point was all-cause mortality following TAVI. Secondary endpoint was cardiovascular death, which included death from myocardial infarction, stroke, sudden cardiac death, heart failure, fatal prosthesis failure with conversion to open heart surgery, and death from unknown cause. All study participants were followed for a minimum of one year, either during routine ambulatory visits, or via telephone conversations with the physicians of deceased patients.

Individual patient risk for surgical AVR was estimated using the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE). Prior to TAVI the aortic annulus of each patient was measured using either transthoracic or transesophageal echocardiography (TEE). Annulus dimensions were also measured using computed tomography (CT) in 154 of the 202 study participants. Based on pre-procedural measurements of aortic annulus, prosthesis size was determined by consensus of the interventional team. Patients were monitored for intra-procedural AR by supra-aortic angiography. Directly following TAVI, invasive measurements, including end-diastolic pressure, were taken for use during retrospective calculation of aortic regurgitation index.
which is expressed as a ratio of ([diastolic blood pressure minus left ventricular end-diastolic pressure]/system blood pressure). \(^{18}\)

Echocardiographic examinations were preformed within 7 days prior to TAVI, within 5 days following TAVI, at 30 days, at 12 months, then annually thereafter, to monitor for presence of post-procedural AR. Following TAVI, prosthetic AR was graded by echocardiography as mild, moderate, or severe according to Valve Academic Research Consortium (VARC) criteria \(^{21}\). \(^{18}\)

Of the 202 enrolled patients, three died prior to the procedure and two patients were converted to surgery due to severe post-procedure AR. As such, these five patients were not included in data analysis. Baseline characteristics of study patients and post-procedure AR were evaluated for all-cause and cardiovascular mortality in univariate regression analysis. Variables identified as significantly associated with study endpoints were entered in multivariate regression analysis to identify independent predictors of all-cause and cardiovascular mortality. Results are available as hazard ratios (HR) and outcomes were analyzed using Kaplan-Meier survival curves. \(^{18}\)

During post-procedural echocardiography 115 (58\%) patients were identified as having some degree of AR. Aortic regurgitation was considered mild in 83 (43\%), moderate in 24 (12\%), and severe in 4 (2\%) of these patients. Overall, all-cause mortality rates at 30-days and at one-year post-procedure were 9\% and 22\%, respectively. For patients in the moderate/severe AR subgroup 30-day and 1-year mortality rates were markedly higher at 21\% and 57\% respectively as opposed to the no/mild subgroup at 6\% and 16\% respectively. Total follow-up for the study was 535 ± 333 days during which the
primary study endpoint of all-cause mortality was reached by a total of 54 (26%) patients, 16 of which occurred in the first 30 days, while 38 occurred after 30 days. The secondary endpoint of cardiovascular death was reached by a total of 33 (15%) patients; 9 during the first 30 days and 24 after 30 days.¹⁸

Following stepwise multivariable analysis, moderate/severe AR, pre-procedural EuroSCORE, atrial fibrillation, and aortic mean gradient were all identified as independent risk factors for all-cause mortality. Of these independent risk factors, post-procedure AR was found to be the strongest (HR 4.89, confidence interval (CI) 2.793 to 8.557, p <0.001). Moreover, moderate/severe AR was identified as the strongest risk factor both for mortality during the first 30 days post-TAVI (HR 3.83, CI 1.384 to 10.482, p = 0.010) and after 30 days (HR 5.48, CI 2.807 to 10.683, p <0.001).¹⁸

Furthermore, stepwise multivariate analysis identified pre-procedural EuroSCORE, female gender, and moderate/severe AR as independent risk factors for cardiovascular death, with the latter again being the strongest (HR 7.90, 95% CI 3.95 to 15.807, p <0.001). Likewise, moderate/severe AR was the strongest risk factor for cardiovascular mortality in the first 30 days following TAVI (HR 7.90, 95% CI 4.193-21.27, p <0.001) as well as after 30 days (HR 9.44, 95% CI 4.193 to 21.27, p <0.001).¹⁸

This study emphasizes that moderate/severe AR post-TAVI is a primary contributor to long-term all-cause and cardiovascular mortality. It also illustrates the profound impact that degree of post-procedure AR has for overall patient prognosis. Despite similar baseline characteristics, patients with moderate/severe AR had consistently worse outcomes when compared with those who had no/mild AR following
TAVI. This study suggests that post-procedure AR has an important impact on mortality, and therefore should be considered when evaluating a patient’s long-term prognosis following TAVI.\textsuperscript{18}

\textbf{Sinning et al}

In this retrospective observational study\textsuperscript{16} investigators sought to determine implications of AR index on overall survival following TAVI. The study included 146 patients who underwent TAVI with third-generation CoreValve prosthesis (Medtronic, Minneapolis, Minnesota). The primary outcome of this study was all-cause mortality at one year. All enrolled patients were considered at high risk for open-heart surgery: defined as a mean Society of Thoracic Surgeons mortality score of 9.8 ± 7.3\%, or a mean logistic European System for Cardiac Operative Risk Evaluation score of 30.2 ± 18\%.

Prior to TAVI aortic valve annulus was determined via TEE as well as by CT. TAVI was performed with biplane fluoroscopy under local anesthesia and was predominantly guided by angiographic control.\textsuperscript{16}

Patients were assessed by a blinded echocardiographer, who did not attend the TAVI procedure, for occurrence and degree of periAR via immediate post-procedural angiography and transthoracic or TEE up until 3 days following TAVI. Invasive pressure measurements were taken in the left ventricle and ascending aorta simultaneously, immediately following TAVI. Aortic regurgitation index was calculated using the following equation: \[((\text{Diastolic blood pressure-left ventricular end-diastolic blood pressure})/\text{systolic blood pressure})\times 100.\] This calculated AR index from just prior to the end of the TAVI procedure was used for data analysis.\textsuperscript{16}
Investigators minimized the number of false positives and negatives by using a receiver-operating characteristic curve analysis as maximum sum of sensitivity and specificity to establish the cutoff value of AR index as an independent predictor of all-cause mortality at one year. Kaplan-Meier survival curves were then generated to evaluate survival based on the presence of periAR, as well as on the measured AR index. The Association of AR index and severity of periAR with 1-year mortality was determined via multivariate Cox regression analysis.\textsuperscript{16}

At day three following TAVI, 53 (36.3\%) patients had no signs of periAR, 71 (48.6) patients had only mild periAR, 18 (12.3\%) patients had moderate periAR, and 4 (2.7\%) patients had severe periAR. Grading of periAR was defined using VARC criteria.\textsuperscript{21} Patients were then split into no/mild and moderate/severe periAR subgroups for further evaluation.\textsuperscript{16}

Within the first 30 days following TAVI, 10 (6.8\%) patients died, while 39 (26.7\%) died during the 1-year follow-up period. For patients with no/mild periAR the 1-year mortality rate was 20.2\% (25 of 124), whereas the moderate/severe periAR subgroup suffered a much higher mortality rate at 63.6\% (14 of 22). During univariate regression analysis, moderate/severe periAR following TAVI was correlated with increased 1-year mortality (HR 3.9, 95\% CI 2.0 to 7.5, \( p < 0.001 \)). Furthermore, patients with an AR index <25 had markedly increased 1-year mortality when compared to patients with an AR index \( \geq 25\% \) (46.0\% and 16.7\% respectively \( p < 0.001 \)). Multivariate regression analysis revealed that AR index was also an independent predictor of 1-year mortality (HR 2.9, 95\% CI 1.3 to 6.4, \( p = 0.009 \)).\textsuperscript{16}
DISCUSSION

Both studies highlight the impact of periAR on overall long-term prognosis. Gotzmann et al\textsuperscript{18} illustrated that patients with moderate/severe periAR following TAVI have consistently higher 1-year all-cause and cardiovascular mortality rates. Sinning et al\textsuperscript{16} confirmed this finding while also establishing that patients with calculated AR index <25 have a similarly elevated overall mortality rate. Both studies emphasize the value of assessing periAR and/or calculating AR index as a prognostic tool.

Both studies\textsuperscript{16,18} had several similar limitations. Both only addressed the CoreValve prosthesis, thus results may not be applicable to TAVI with other prostheses. Additionally, the quality of both studies\textsuperscript{16,18} is limited by small sample size and monocentric character. Furthermore, investigators from both studies\textsuperscript{16,18} identified the specific limitations of their respective research. Sinning et al\textsuperscript{16} noted that CT has been previously established as the most accurate means by which to determine the correct annulus size, however CT was not used in 23\% of study patients due to renal failure. In these patients annulus size was determined solely via echocardiography. Moreover, Gotzmann et al\textsuperscript{18} acknowledged the limitations of AR index as a prognostic tool in that it relies on left ventricular end diastolic pressure which may fluctuate due to many factors following TAVI, ultimately leading to false positive or negative AR indices. Thus, AR index should be considered of complementary value when assessing periAR and overall prognosis.
CONCLUSION

Aortic regurgitation index and degree of periAR have been identified as strong independent risk factors for long-term mortality following TAVI. Furthermore, patients with moderate to severe periAR consistently have worse outcomes and higher overall mortality rates. Both studies suggest that periAR be considered as an important predictor of general prognosis following TAVI. The overall quality of both studies is moderate based on GRADE criteria, largely because they are both retrospective observational studies. However, because this research involves a surgical procedure a study of higher quality, such as a randomized controlled trial may not be feasible. Nevertheless, further studies are needed to assess possible predictors and/or causes of periAR, and thus how it might be minimized or prevented altogether. As this procedure becomes more common, larger, multicenter studies should be conducted in order to substantiate and further assess the results of the studies\textsuperscript{16,18} evaluated in this review. Given that TAVI has only been in practice since 2008 it is imperative that this procedure continue to be studied and refined as it is an important alternative to AVR.
References


   Accessed October 6, 2011.


Table I. Characteristics of Reviewed Studies and Summary of Findings

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