Title: PreHabilitation for patients undergoing Transcatheter Aortic Valve Replacement (TAVR PreHab)

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Prinicipal Investigator: James Harvey, MD, MSc

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Background

Degenerative aortic stenosis is the most common form of valvular heart disease in developed countries and its prevalence increases with age. Patients with severe aortic stenosis who develop symptoms and are only treated with medical therapy have a very poor prognosis with survival rates as low as 50% at 2 year and 15% at 5 years.(1) Traditionally patients with severe, symptomatic aortic stenosis are treated with surgical aortic valve replacement (SAVR) which significantly decreases mortality and improves quality of life.(2) Unfortunately, many patients suffering with this are deemed too high risk to undergo SAVR and surgical correction is not offered.(3)

Transcatheter aortic valve replacement (TAVR) has emerged as an alternative therapy to surgery for patients with severe, symptomatic aortic stenosis. In TAVR, a bioprosthetic valve is mounted on a catheter, advanced to the aortic annulus, then expanded and deployed inside the native diseased valve. Multiple randomized-controlled trials have shown TAVR to be superior to medical therapy and equal or superior to SAVR in patients with severe symptomatic aortic stenosis and high to prohibitive predicted surgical risk. (4-7) When compared to SAVR, TAVR also offers shorter hospital length of stay and better quality of life at 30 days.

Patients undergoing TAVR are older and have more comorbidities than patients undergoing surgical aortic valve replacement (SAVR) and thus often have high frailty scores. It has recently been shown that the presence of a high frailty score predicts increased 1-year mortality in patients undergoing TAVR.(8) In addition, it has been shown that patients who undergo TAVR "benefit from rehabilitation despite their older age and comorbidities" and that this helps to maintain their independence.(9)

Study Rationale

Although the effect of pre-procedural physical conditioning on TAVR patients has not been studied, there is significant evidence that pre-procedural physical conditioning, or "prehabilitation," is beneficial to patients undergoing cardiac surgery. Pre-procedural conditioning has been shown to decrease both ICU and hospital length of stay in patients undergoing coronary artery bypass grafting surgery (CABG) as well as improve physical functioning after surgery.(10)(11) Additionally, a recent meta-analysis concluded that pre-procedural conditioning is effective at reducing postoperative complication rates and length of hospital stay after cardiac surgery.(12)

Patients with severe symptomatic aortic stenosis are at high risk for adverse cardiac event or death and they are advised to only perform activities requiring mild exertion. However, monitored exercise testing in these patients has been shown to be safe.(13,14) In addition, current guidelines recommend monitored exercise testing in patients with severe aortic stenosis and absent or equivocal symptoms.(15) As such, the modest exertion required for physical therapy in a monitored environment is predicted to carry a very low risk.

Decreased exercise capacity and high frailty scores have been shown to be a strong determinant of mortality and adverse events in patients with aortic stenosis. However, implementation of a systematic and monitored physical therapy program to improve exercise capacity and modify frailty scores prior to a major intervention such as TAVR has never been performed. Nor have the outcomes of such a monitored program been evaluated.

Objectives

In this pilot study, we aim to identify patients undergoing TAVR who are at elevated risk for adverse clinical events due to decreased exertional capacity and physical deconditioning. We aim to determine if monitored pre-procedural physical therapy is safe in these patients. Lastly, we aim to assess the efficacy of prehabilitation a) to improve physical functioning by the time of TAVR and to sustain benefit through 30 days post-procedure; and b) to determine its effect on post-procedural length-of-stay, clinical outcomes, and quality of life.

As a precursor to a large, definitive randomized clinical trial, this pilot study will examine the components of patient recruitment and retention, assessment of exertional capacity, and program implementation of this intervention with the goal that they will be employed in a larger scale study and possibly to all TAVR programs in the United States. To this end, all components of this study were chosen not only for clinical efficacy, but also for cost effectiveness and ease of implementation into current "real world" TAVR programs.

Primary Efficacy Outcomes

- **Functional exercise capacity – Change in 6 Minute Walk Test (6MWT)**
  Measure: Does prehabilitation improve the subject's functional exercise capacity from first PT assessment to pre-procedure assessment and first PT assessment to one month post-procedure, as measured by the 6MWT?

Secondary Efficacy Outcomes

- **Mobility – Timed Up-and-Go (TUG) test**
  Measure: Does prehabilitation improve the subject's mobility from first PT assessment to pre-procedure assessment and first PT assessment to one month post-procedure, as measured by the TUG test?

- **Balance – Four Square Step Test (FSST)**
  Measure: Does prehabilitation improve the subject's balance from first PT assessment to pre-procedure assessment and first PT assessment to one month post-procedure, as measured by the FSST?

- **Discharge disposition**
  Measure: Does prehabilitation make it less likely that a patient will require a higher level of care at discharge than they required prior to admission (for example, arrive from home and discharged to home)?

- **Length of stay in Intensive Care Unit (hours)**

- **Total hospital length of stay (days)**

- **Change in quality of life**
  Measure: Does Kansas City Cardiomyopathy Questionnaire score change from first PT assessment to one month post-procedure?

- **30-day readmission**
  Measure: Does the subject have a 30-day readmission post-procedure?

Safety Outcomes

- Syncope
- Major adverse cardiac events (MACE)
- Falls and musculoskeletal adverse events
- Adverse events from other complications
- Serious adverse events, including those that require hospitalization

Hypotheses

1. Monitored pre-procedural physical therapy is safe for patients identified as frail who are undergoing transcatheter aortic valve replacement.
2. Monitored pre-procedural physical therapy in patients to undergo transcatheter aortic valve replacement will result in:
   a. An objective improvement in patient physical function from baseline to the time of procedure and 30 days post-procedure.
   b. Decreased length of stay and improved clinical outcomes and quality of life.

Study design

This is a pilot study involving a cohort of seventy subjects randomized to either participate (treatment group) or not participate (control) in a prehabilitation program prior to undergoing a TAVR. After providing informed consent, subjects will be randomized via REDCap™ to a treatment or control group. Thirty five subjects will be randomized to each group. Subject number and randomization will be assigned by REDCap™. All subjects in this pilot study will be followed from the intake assessment through one year post-procedure.

Study population and recruitment methods

The research coordinator will identify potential TAVR patients using clinic schedules and then conduct a chart review to verify that they meet inclusion/exclusion criteria. Patients will be approached by the research coordinator regarding the study. The research coordinator will verbally explain the study and provide time for questions and discussion. The patient will be provided with a written copy of the consent document to read and review. The research coordinator will set up an additional appointment to assess understanding and verify willingness to participate. The patient will then sign the consent if interested in participation.

Inclusion and exclusion criteria:

Inclusion Criteria

- Subject must be ambulatory (with or without an assist device)
- Subject has severe aortic stenosis and is felt an appropriate candidate for TAVR by the Heart Team.

- Subject requires 6.0 seconds or longer to complete a 15ft walk test
- Subject must be able to move between sitting and standing without assistance from another person.
- Subject has adequate iliac and femoral arterial anatomy to allow for TAVR via transfemoral access
- Subject is 18 years of age or greater
- Subject is willing to give consent and participate in the study

Exclusion Criteria

- Subject is incapable of following instructions
- Subject is unable to meet the minimum required physical therapy visits
- Subject has other medical conditions rendering it unsafe, in the opinion of the Principal Investigator and physical therapy staff, to perform a 6 Minute Walk Test or physical therapy conditioning prior to TAVR
- Subject has significant severe un-revascularized epicardial coronary disease.

Role of subjects

Subject Schedule

Subjects in the control arm will undergo all items except the prehabilitation intervention. Subjects in the treatment arm will undergo all items.

Intake Assessment

At this visit, subjects will meet with a member of the Physical Therapy staff who will perform an assessment of the subject's functional exercise capacity, mobility, and balance through the following:

a. 6MWT
b. TUG Test
c. FSST
d. Kansas City Cardiomyopathy Questionnaire

Other information collected by the research coordinator will be demographic information, subject contact information and comorbidities. Subjects will be randomized at the conclusion of the Intake Assessment.

Prehabilitation (treatment group only)

Based on the results of the Intake Assessment, the physical therapist will determine a course of conditioning specific to each subject; however, each subject will receive a minimum of eight visits and a maximum of 12 over the 3 to 5 weeks prior to the surgery date. Date and time of each visit will be collected. Providers will note the following adverse events that occur during conditioning:

a. MACE
b. Syncope, Falls and musculoskeletal adverse events
c. Adverse events from other complications
d. Serious adverse events, including those that require hospitalization

Pre-operative Assessment
The final encounter with the subject pre-operatively will perform the same assessments as performed during the Intake Assessment:

e. 6MWT
f. TUG Test
g. FSST
h. Kansas City Cardiomyopathy Questionnaire

TAVR procedure
Providers will implant the aortic valve and record the following:

i. Type and size of valve used
j. Adverse events during surgery

Discharge assessment
Upon discharge, the subject will be assessed for the following:

k. Discharge disposition
l. Length of stay in ICU (hours) and total hospital (days)
m. Cost of stay (assessed by total charges accrued during hospitalization)

30-day Follow-up Assessment
All subjects' electronic health records (EHR) will be monitored for thirty days from the discharge date for the following:

n. Comorbidities and study comorbidities
o. Inpatient re-admission information
p. Cost of stay (assessed by total charges accrued during a readmission hospitalization)
q. Date and time of visit
r. Syncope
s. MACE
t. Falls and musculoskeletal adverse events
u. Adverse events from other complications
v. Serious adverse events, including those that require hospitalization
w. Mortality

The subject will also perform the following:

x. 6MWT
y. TUG Test
z. FSST
aa. Kansas City Cardiomyopathy Questionnaire

1-year Follow-up Assessment
All subjects' electronic health records (EHR) will be monitored for one year from the discharge date for the following:

a. Inpatient re-admission information
b. Cost of stay (assessed by total charges accrued during hospitalization)
c. Date and time of visit
d. Syncope
e. MACE
f. Falls and musculoskeletal adverse events

g. Adverse events from other complications
h. Serious adverse events, including those that require a readmission hospitalization
i. Mortality

The subject will also perform the following:

j. 6MWT
k. TUG Test
l. FSST
m. Kansas City Cardiomyopathy Questionnaire

Research procedures

Patients who qualify for TAVR will be screened by the research coordinator. The research coordinator will also review provider office visit schedules and maintain close contact with the TAVR program coordinator for potential study subjects. The patient will be screened thoroughly ensuring he/she meets all inclusion and exclusion criteria. Once the possible study patient has been identified then the research coordinator will approach the patient and verbally explain the study to them. Adequate time will be provided for questions and answers. The patient will be provided a written copy of the informed consent and time to read it. Once the patient signs the informed consent, the study procedures may commence. The first visit will be the Intake Assessment where the patient will meet with the physical therapist and research coordinator. This assessment will include the 6MWT, TUG test, FSST, KCCQ, patient demographics, subject contact information, and comorbidities. At the completion of this assessment, the patient can be randomized.

The patients randomized to the treatment arm will then be scheduled to begin the prehabilitation part of the study. Subjects will receive a maximum of 12 therapy visits over the next 3 to 5 weeks prior to the surgery date.

Below is a chart that describes what will occur at each required study visit.

	Intake Assessment	Prehabilitation (Treatment only)	Pre-operative Assessment	TAVR	Discharge Assessment	30-day Follow-up Assessment	1-year Post-operative monitoring
Demographics (MRN, name, date of birth, gender, payor, surgery date, surgery type, etc.)	X						
Subject contact information (preferred method, address, phone/text, e-mail, etc.)	X						
Comorbidities (all diagnoses codes)	X					X	X
Study comorbidities • Current medications • Pre-existing conditions related to reduced exercise capacity, mobility, and/or balance; including physical disabilities unrelated to aortic stenosis	X					X	X

6MWT	X		X			X	X
TUG Test	X		X			X	X
FSST	X		X			X	X
Kansas City Cardiomyopathy Questionnaire	X		X			X	X
Date and time of visit		X	X			X	X
Adverse events • MACE • Syncope • Falls and musculoskeletal adverse events • Adverse events from other complications • Serious adverse events, including those that require hospitalization		X	X*			X	X
Type and size of valve used for TAVR				X			
Adverse events during surgery				X			
Discharge disposition					X		
Length of stay • In ICU (hours) • Total hospital (days)					X		
Cost of stay (assessed by total charges accrued during hospitalization)					X		
Inpatient readmission information						X	X

*This should be assessed in both groups prior to TAVR to see if the control arm experienced similar adverse events independent of prehab therapy.

Data analysis and Data Monitoring

Evaluate primary, secondary and the safety outcomes (as listed in the protocol) by conducting a data integrity check to assure reliability of the data. Once all data inconsistencies are corrected data analysis should occur. The analysis would compare 2 groups: the study group and the control. Based on the objectives, the data will be analyzed using the required statistical tests; categorical variables would be compared using the Fishers Exact test or Chi-square tests and measurement data would be compared using the independent sample t-test or Mann Whitney U test. All analysis will be evaluated using parametric tests unless the data is not normal in which case non-parametric tests will be used.

As needed interim analysis of primary, secondary and safety outcomes by study group (treatment vs. no treatment) will be conducted. If a decision is made to stop the study early, this limitation should be expressed in any project write-up. If at the conclusion of the assessment of the primary outcome (6 minute walk test) there is a significant difference between the study groups ($p<.05$) a Power analysis will be conducted, and if the Power is greater than 80%, a recommendation to conclude the study could be made – if this is done there is risk of making a type II error and should be shared in any project write up.

A Data Safety Monitoring Board (DSMB) will monitor all AEs and SAEs to provide safety oversight. DSMB members will not be involved in the study and have no conflict of interest.

Redcap will be the database that will provide data management through a secure, password protected Electronic Data Capture (EDC) system accessible via the Internet. A unique Patient ID will be assigned for each patient enrolled in the study. All pertinent data will be entered by the study site personnel into the electronic Case Report Forms (eCRFs).

Every reasonable effort should be made to complete data entry within 5 business days of data collection. Data review by Quality will occur remotely as well as during on site monitoring. Data discrepancies will be queried and resolved through the EDC system.

The site Principal Investigator or designee must ensure the accuracy and completeness of the recorded data and then provide his/her electronic signature on the appropriate eCRFs. Changes to data previously submitted to the Sponsor will require a new electronic signature to acknowledge/approve the changes.

Risks and risk management

The primary potential physical risks to patients enrolled in this study appear to be adverse cardiac events including dizziness, syncope, angina pectoris, ventricular tachycardia, or sudden cardiac death. Observation studies report exertional dizziness or syncope in patients with severe aortic stenosis suggesting this is a potential risk for patients in this study. Also, ventricular tachycardia has been reported in early studies of patients with severe aortic stenosis undergoing exercise stress tests however this has not been reported in contemporary studies. Other potential physical risks include falling or pain due to exercise.

To mitigate these risks, all potential participants will undergo a complete history and physical examination by a cardiologist prior to enrollment. Any patient determined to be at high risk for adverse clinical event by the cardiologist will be excluded. Also, all participants will undergo standard TAVR non-invasive and invasive testing; this includes: transthoracic echocardiography, transesophageal echocardiography, right and left heart catheterization, and Computer-Assisted Tomography (CAT scan) of the chest, abdomen, and pelvis. Patients with un-revascularized coronary artery disease will not be enrolled in the study.

In addition, patients who undergo pre-procedural physical therapy will do so under the close supervision of the physical therapist and the Research Registered Nurse. The physical therapist and RN will continually assess the patient, ask how the patient is feeling, and ask if they are experiencing any negative symptoms in accordance with the American College of Sports Medicine (ACSM) guidelines (Table 1). Any participant who experiences any significant negative symptoms or exhibits any significant adverse signs will have his/her current active stopped and will be clinically assessed and observed. If the adverse symptoms have not resolved within 20 minutes, the patient, will undergo immediate clinical evaluation and treatment.

Table 1: Indication to stop therapy and assess and observe patient per ACSM guidelines.

• Onset of angina or angina-like symptoms
• Drop in SBP of ≥ 10 mmHg with an increase in work rate or if SBP decreases below the value obtained in the same position prior to testing
• Excessive rise in BP: systolic pressure > 250 mmHg and/or diastolic pressure > 115 mmHg
• Shortness of breath, wheezing, leg cramps, or claudication
• Signs of poor perfusion: light-headedness, confusion, ataxia, pallor, cyanosis, nausea, or cold and clammy skin
• Failure of HR to increase with increased exercise intensity
• Noticeable change in heart rhythm by palpation or auscultation
• Subject requests to stop

- Physical or verbal manifestations of severe fatigue
- Failure of the testing equipment

Benefits
There are no guaranteed benefits from participation in this study. Information gained from the conduct of this study may be of benefit to future patients with the same medical condition.

Compensation / incentives and research-related costs
Those randomized to the physical therapy arm of the study will receive free physical therapy prior to their TAVR procedure.

Participants will receive $20 for each completed on-site visit to help cover expenses for attending study visits. These expenses include:

- Local travel/parking expenses to and from office visits and tests.

Alternative procedures
The alternative is to not participate in this study. Patients are not required to participate in the study and refusing to do so will not affect the quality of their treatment.

Research materials, records, privacy and confidentiality
All records identifying the patient are kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Patient names will not be supplied to the sponsor. Only the patient number is recorded in the eCRF, and if the patient name appears on any other document (e.g. angiogram or echo), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer are stored in accordance with local data protection laws. As part of the informed consent process, the subjects are informed in writing that representatives of the sponsor, IRB/EC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection is handled in strictest confidence and in accordance with local data protection laws and all applicable Privacy Regulations. If the results of the study are published, patients' identity will remain confidential. The investigator will maintain a list to enable subjects to be identified.

Subject informed consent
The study investigator(s) and research staff will approach patients with severe, aortic stenosis to assess their interest in participating in the study by providing them an overview of the study including the background, risks, benefits and study procedures. The research nurse will provide the patient a copy of the consent for their review. The patient will be given sufficient time to review the consent on their own time. All questions will be answered and all potential patients will have an understanding of the trial prior to signing consent. If patients are interested in participating in the study, the study patient will sign the Institutional Review Board (IRB) approved informed consent form prior to any study specific procedures are performed. All patients consented should be entered into the study's electronic database (EDC).

Intended use of research
It is intended that the results of this research will be submitted as an abstract or oral presentation at a national meeting such as the American College of Cardiology (ACC) Scientific Sessions or the

Transcatheter Technologies (TCT) national meeting. Also, it is planned that the results will be submitted for publication in a peer –review scientific journal.

Delineation of resources required to conduct the study
The resources required to conduct this study include research coordinators and physical therapists. No special software, equipment, processes, or tests are needed to conduct this study.

ADVERSE EVENTS

Adverse Event
An Adverse Event (AE) is any untoward medical occurrence, unintended injury or untoward clinical signs in patients, users or other persons, related to the study.

Adverse events may be volunteered by patients, elicited by the Investigator or designee, or collected via observation by the Investigator. All AEs will be assessed by the Investigator who will determine whether or not the event is related to the study, and whether or not the event meets serious criteria. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE Form of the CRF. Source documents should be collected for each AE. In addition, patients will be instructed to contact the investigator, and/or study coordinator if any significant adverse events occurs between study visits.

Serious Adverse Event

An Adverse Event is considered serious if the event:

1. Leads to death;
2. Leads to a serious deterioration in the health of the study patient that:
    - Results in life-threatening illness or injury;
    - Results in a permanent impairment of a body structure or a body function;
    - Requires inpatient hospitalization or prolongation of existing hospitalization;
    - Results in medical or surgical intervention to prevent permanent impairment to body structure or a body function;
3. Significant medical event.

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