

# **A Pilot Study of Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves: A Randomized Controlled Trial**

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## **Introduction**

A recent study published in the *New England Journal of Medicine* identified reduced aortic-valve leaflet motion in patients with bioprosthetic aortic valves. Based upon the observation that this finding resolved with therapeutic anticoagulation, the authors suggested that reduced leaflet motion may be attributable to subclinical leaflet thrombosis. The incidence of reduced leaflet motion varied from 7.4% after surgical aortic valve replacement (SAVR) to 43% after transcatheter aortic valve replacement (TAVR). Altered leaflet motion was detected with both 4-dimensional contrast-enhanced cardiac multidetector computed tomography (MDCT) and transesophageal echocardiography (TEE), but could not be identified on transthoracic echocardiography (TTE). The clinical significance of this finding is uncertain.

The true incidence of this finding and the impact of periprocedural anticoagulation on leaflet motion are unknown. In addition, our review of available MDCT scans from the NEJM article raises questions concerning the validity of reduced leaflet motion after SAVR. Therefore, we propose a prospective, randomized pilot study in patients undergoing SAVR and TAVR to 1) Estimate the incidence of reduced leaflet motion and 2) Assess the impact of perioperative anticoagulation on the incidence of reduced leaflet motion. Data from this pilot study will enable us to determine the feasibility of a larger randomized controlled clinical trial to investigate the phenomenon of reduced leaflet motion/subclinical valve thrombosis and, possibly, its clinical importance.

## **Background and Significance**

Aortic valve replacement prolongs survival in patients with severe aortic valve disease. Over the last decade, there has been a gradual shift to bioprosthetic valves in the surgical arena. TAVR involves implantation of bioprostheses, making bioprosthetic aortic valve replacement the most common overall treatment for severe aortic valve disease.

The need for periprocedural warfarin after bioprosthetic aortic valve replacement is uncertain. While some centers treat patients with warfarin for 6 to 12 weeks after bioprosthetic SAVR, others (including the Cleveland Clinic), employ a strategy of aspirin alone. A recent Scandinavian registry-based study suggests that short-term warfarin may improve outcomes after SAVR, but there are no large, prospective studies that validate this strategy.

Anticoagulants are also used to treat TAVR postoperatively. Typically patients will be on aspirin and clopidogrel for 12 weeks before switching them to aspirin alone. Patients who are on warfarin for atrial fibrillation may be treated with warfarin and clopidogrel for 3 months, while others are treated with aspirin and warfarin. No substantial research has shown one treatment to be more effective than the other.

The observation of reduced leaflet motion after SAVR and TAVR with the possibility of subclinical valve leaflet thrombosis has reignited the debate over periprocedural anticoagulation. The authors of the recent NEJM study point out that we need “better characterization of this observation ...to determine its frequency and evaluate its clinical effect.” The purpose of this pilot trial is to determine the frequency of reduced leaflet motion after SAVR and TAVR and to determine whether perioperative anticoagulation with warfarin impacts this frequency.

### **Study Design**

**Methods:** This will be a pilot prospective randomized controlled trial.

**Sample:** The study will enroll 50 adult patients scheduled to undergo SAVR and 50 adult patients scheduled to undergo TAVR.

### ***Inclusion Criteria***

Scheduled for SAVR or TAVR with or without the following concomitant procedures:

- Tricuspid valve surgery
- PFO closure
- ASD closure
- MV repair
- Myectomy

Age  $\geq$  18 years

Able and willing to give informed consent

Able and willing to return for follow up

### ***Exclusion Criteria***

Contraindications to warfarin, Plavix or aspirin

Pre-existing medical indication for warfarin, Plavix or aspirin

History of previous coronary artery stenting

Requirement for concomitant coronary artery bypass grafting or mitral valve replacement

Contraindications to contrast-enhanced MDCT including anaphylactic iodine allergy,

History of atrial fibrillation

Renal dysfunction (GFR < 60 ml/min).

### ***Research Procedures***

#### **Screening**

Patients scheduled for SAVR or TAVR will be identified by nurse practice managers and their records examined to determine eligibility. Potential subjects will be contacted by a research nurse, who will determine the presence of Inclusion/Exclusion Criteria. Subjects who satisfy Inclusion/Exclusion Criteria will be approached for informed consent. Those who give informed consent will be enrolled.

Review of medical records will be done to obtain medical history.

## **Intra-op Aortic Valve Procedure**

### **Randomization and Anticoagulation/Antiplatelet Regimen**

After induction of anesthesia, a computer program will be used to randomize patients to one of the treatment groups below, according to their scheduled procedure:

#### ***SAVR***

Warfarin group (n=25)

Warfarin treatment for 12 weeks with a target INR of 2-3

Warfarin treatment to begin on postoperative day 1-3 according to the patient's clinical status

When warfarin treatment is discontinued, patients will be treated according to standard of care (aspirin 81 mg/day) indefinitely

Aspirin group (n=25)

Aspirin (81 mg/day) to begin within 1-3 postoperative days according to the patient's clinical status and continue indefinitely per standard of care.

#### ***TAVR***

Warfarin group (n=25)

Begin Warfarin and Aspirin (81 mg/day) treatment within 1-3 days postop for 12 weeks with a target INR of 2-3

At 12 weeks, study treatment will end and patients will be treated according to standard of care (aspirin 81 mg/day) indefinitely

Aspirin group (n=25)

Begin aspirin (81 mg/day) and clopidogrel (75 mg/day) in periprocedural period and continue for 12 weeks

At 12 weeks, study treatment will end and patients will be treated according to standard of care (aspirin 81 mg/day) indefinitely

A transesophageal echo (TEE) will be performed prior to implant. Patients will undergo SAVR or TAVR according to standard clinical protocol.

#### **Follow up**

Patients will be seen at 4-6 weeks postoperatively for the following procedures:

- TTE
- 4D MDCT scan
- Review of medical history

At 6 months (+/- 7days), 9 months (+/- 7days) and 12 months (+/- 7days) post operatively, patients will be contacted by phone to assess for change in medications, assessment of bleeding, stroke, TIA or MI signs and symptoms, and to obtain any INR results and imaging tests if done.

## **Imaging**

### **Baseline intraoperative TEE**

Periprocedural TEE will be performed to confirm normal bioprosthetic aortic valve function and establish a “valve footprint”. This will include standard 2D, spectral Doppler, color Doppler, full volume 3D and live 3D acquisitions. In addition, baseline aortic valve gradients will be recorded.

### **Transthoracic echocardiography (4-6 weeks post-procedure)**

All patients will undergo a clinically indicated comprehensive TTE. Along with standard chamber dimension assessment, we will record LV outflow tract diameter in a standard fashion on parasternal long-axis view. Pulsed-wave and continuous-wave Doppler will be used to record velocities across the LV outflow tract (LVOT) and AV, respectively. AV will be examined from multiple windows including apical, suprasternal and right parasternal to obtain the peak AV velocity and the mean AV gradient. Additionally, dimensionless index will be calculated using the ratio of velocity time integral of LVOT obtained on pulse wave velocity divided by velocity time integral across aortic valve on continuous wave Doppler. AVA will be calculated using the continuity equation. In addition, attempts will be made to visualize AV leaflets and assess mobility as described below in “leaflet motion analysis”.

### **Contrast enhanced 4D MDCT**

All subjects will be scanned on standard MDCT scanners (Definition Dual Source/Definition Flash, Siemens Medical Solutions, Erlangen, Germany; or Brilliance 256-slice, Philips Medical Systems, Best, The Netherlands) after administration of iodinated contrast (80-100 mL of Ultravist 370) at 4-5 mL/s followed by 30-50 mL of normal saline. Bolus tracking technique using a region of interest in ascending aorta will be used, and scanning (from the carina to the mid left ventricle) will be performed initiated in the craniocaudal direction during a single inspiratory breath-hold. Spiral data will be acquired with retrospective electrocardiogram gating using the following parameters: gantry rotation time=270-330 ms; beam collimation ranging from 128 x 0.6 mm to 32 x 0.6mm; tube voltage=100-120 kVp; tube current adjusted per patient weight; and beam pitch of 0.2-0.5. Electrocardiogram-based tube current modulation will be used for all patients, with maximum current turned on between 30-70 % phases of the cardiac cycle (hence maintaining image quality during the systolic phases). 4-dimensional images will be reconstructed during 10 phases of the cardiac cycle with a section thickness of 0.75 mm. Radiation in the study sample will typically be < 12 mSEV.

### **Leaflet motion analysis**

Based upon the 4D MDCT data, we will attempt to measure leaflet tip thickness. In addition, leaflet motion will be judged as normal, mildly reduced (<50% reduction in motion), moderately reduced (50 to 70% reduction), severely reduced (>70% reduction), or immobile (lack of motion of at least one valve leaflet). For the purposes of analysis, leaflet motion will be considered reduced if it is moderately reduced, severely reduced, or immobile. The 4D CT scans will be interpreted by a reviewer who is blinded to the anticoagulation/antiplatelet regimen for the patient.

### **Crossovers**

Patients who are randomized to an aspirin group and who develop a new indication for periprocedural anticoagulation (e.g. perioperative atrial fibrillation) will be crossed over into the warfarin group. Patients who are randomized to a warfarin group who develop contraindications to warfarin will be crossed over to the aspirin group. Patients who are randomized to an aspirin group who develop overt leaflet thrombosis, as detected by clinical standard of care imaging may be treated with warfarin at the discretion of the treating physician. However, the physicians will be blinded to the results of the 4D MDCT scan till the completion of the study.

### **Funding**

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### **Adverse Events and Independent Medical Safety Officer**

Adverse events will be reported directly to the IRB.

An Unanticipated Problem Involving Risks to Participants or **Others** is any event that (1) is unforeseen, (2) caused harm or placed a person at increased risk of harm, and (3) is related to the research procedures.

An Adverse Event (AE) defined for this pilot study is any untoward or unfavorable medical occurrence related to structural valve deterioration, bleeding, stroke, TIA or MI.

A Serious Adverse Event (SAE) is any adverse experience that results in any of the following outcomes:

- ☐ death
- ☐ a life-threatening experience
- ☐ inpatient hospitalization or prolongation of existing hospitalization
- ☐ a persistent or significant disability/incapacity
- ☐ a congenital anomaly/birth defect
- ☐ Important medical events that may not result in death, be life-threatening, or

require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The independent Medical Safety Officer will routinely review all deaths, SAEs, adverse events and imaging. The medical safety officer will be separate and independent from clinical staff or anyone responsible for patient care.

### **Statistical Analysis**

A statistician will analyze using the following: Standard descriptive analysis will be performed. Continuous variables will be compared using t-testing or analysis of variance. Categorical variables will be compared using Chi-square. Outcomes will be compared in 2 groups using standard survival analysis. Predictors of 30-day outcomes will be determined using logistic regression analysis. All analysis will be done by standard software (SPSS and SAS). A p-value <0.05 will be considered significant.