Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study

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Disclosure Statement

I have no personal or financial relationships with commercial interests that pertain to the content presented in this program.
Background: Aortic Stenosis (AS)

• Progressive disease characterized by a spectrum from aortic valve leaflet changes to valve obstruction

• Prevalence
  • 50-59 years old: 0.2%
  • 80-89 years old: 9.8%
  • Overall in adults ≥75 years: 2.8%

• Mortality: >50% at 2 years for patients with symptomatic disease unless aortic-valve replacement is performed promptly

Normal leaflets

Aortic sclerosis

Aortic stenosis

At risk

Disease initiation

Progressive disease

Valve obstruction

Risk genotype
Risk valve morphology
Older age, male sex
Dyslipidemia
Diabetes or metabolic syndrome
Hypertension
Smoking
Renal insufficiency
Increased serum phosphate

Shear stress
Inflammation
Lipid infiltration
Myofibroblast differentiation

Oxidative stress
Increased angiotensin II
Procalcific stimuli
OPG–RANKL
Wnt–LRP

Hydroxyapatite nodules
Cartilage and bone formation

Inflammation
Leaflet calcification
Age
Management of AS

- No medical therapies available to prevent or slow progression of AS

- Aortic valve replacement

<table>
<thead>
<tr>
<th></th>
<th>Surgical aortic valve replacement (SAVR)</th>
<th>Transcatheter aortic valve replacement (TAVR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve type</td>
<td>Mechanical or bioprosthetic</td>
<td>Bioprosthetic</td>
</tr>
</tbody>
</table>
| Place in therapy       | Gold standard for severe AS              | • Non-inferior to SAVR for high surgical risk and intermediate-risk patients
                                           | • Significant survival benefit at 2 years as compared with SAVR |
| Risks vs benefits      | Stroke, respiratory failure, renal failure, significant bleeding, and death | • Minimally invasive
                                           | • Stroke, myocardial infarction, bleeding, vascular injury, and misplacement |

Subclinical Aortic Bioprosthetic Valve Thrombosis

- Rare, potentially devastating complication following SAVR and TAVR

- Various definitions
  - >50% reduction in motion of at least 1 bioprosthetic valve leaflet, as assessed by computed tomography (CT)
  - Hypo-attenuated thickening with or without rigidity in one or more leaflets identified on CT

- Symptomatic, overt thrombosis represents the extreme end of the thrombosis spectrum
  - Likely under-reported (prevalence 0-2%)

- Subclinical leaflet thrombosis with no associated symptoms is more frequent (prevalence 10-15%)
  - May trigger early valve failure and unrecognized cerebral or other thromboembolic events

Recommendations for Prevention of Subclinical Thrombosis
Prior to 2017 Guideline Updates

### SAVR

<table>
<thead>
<tr>
<th>Guideline</th>
<th>0-3 months</th>
<th>&gt;3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012 ESC/EACTS</td>
<td>Aspirin (class IIa) and warfarin (class IIb)</td>
<td>--</td>
</tr>
<tr>
<td>2014 AHA/ACC</td>
<td>Aspirin (class IIa) and warfarin (class IIb)</td>
<td>Aspirin</td>
</tr>
<tr>
<td>2012 ACCP</td>
<td>Aspirin</td>
<td>Aspirin</td>
</tr>
</tbody>
</table>

### TAVR

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014 AHA/ACC</td>
<td>Aspirin and clopidogrel for 6 months followed by life-long aspirin (class IIb)</td>
</tr>
<tr>
<td>2012 ESC/EACTS</td>
<td>--</td>
</tr>
<tr>
<td>2012 Canadian Cardiovascular Society</td>
<td>Aspirin and clopidogrel for 1-3 months</td>
</tr>
<tr>
<td>2012 ACCF/AATS/SCAI/STS</td>
<td>Aspirin and clopidogrel</td>
</tr>
<tr>
<td>2012 ACCP</td>
<td>Aspirin and clopidogrel for 3 months</td>
</tr>
</tbody>
</table>

ACCP, American College of Chest Physicians; AHA/ACC, American Heart Association/American College of Cardiology; ESC/EACTS, European Society of Cardiology/European Association of Cardiothoracic Surgery; ACCF, American College of Cardiology Foundation; AATS, American Association for Thoracic Surgery; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons

Current Research on Subclinical Thrombosis

• PORTICO IDE study (N Engl J Med 2015) found reduced leaflet motion on CT in patients after TAVR
  • Prompted establishment of two registries to evaluate bioprosthetic leaflet function after TAVR or SAVR

• Assessment of Transcatheter and Surgical Bioprosthetic Valve Thrombosis and Its Treatment with Anticoagulation (RESOLVE)

• Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed with Four-Dimensional Computed Tomography (SAVORY)

Limitations of Previous Studies on Subclinical Thrombosis

- Absence of complete clinical follow-up
- No information about differences in prevalence and severity of subclinical leaflet thrombosis between TAVR and SAVR
- No assessment of neurological events
- No information about efficacy of novel oral anticoagulants (NOACs)

Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study

Study Design

Objective

- Report the prevalence of subclinical leaflet thrombosis in surgical and transcatheter aortic valves and the effect of NOACs on subclinical leaflet thrombosis and subsequent valve hemodynamics and clinical outcomes after TAVR or SAVR

Study Design

- Observational prospective registry study

Patient Population

- Patients enrolled in two ongoing single-center registries (RESOLVE and SAVORY)

# Study Population

<table>
<thead>
<tr>
<th><strong>RESOLVE</strong></th>
<th><strong>SAVORY</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cedars-Sinai Medical Center (CA, USA)</td>
<td>• Rigshospitalet (Denmark)</td>
</tr>
<tr>
<td>• 2014-2021</td>
<td>• 2015-2020</td>
</tr>
<tr>
<td>• &gt;18 years old, TAVR or SAVR</td>
<td>• &gt;55 years old, TAVR or SAVR</td>
</tr>
<tr>
<td>• Enrolled before discharge with CT scanning planned post-discharge</td>
<td>• Selected to represent the distribution of different bioprosthetic aortic valves used at the institution</td>
</tr>
<tr>
<td>• TAVR or SAVR patients presenting to clinic for follow-up during study period</td>
<td>• eGFR ≥30 mL/min</td>
</tr>
<tr>
<td>• eGFR ≥30 mL/min</td>
<td></td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate

Methods

RESOLVE

CT and TTE at least 48 hr after TAVR/SAVR
  • If thrombus: warfarin x3 months (INR 2-3)

Repeat imaging after 3 months of warfarin

SAVORY

CT and TTE at 30-180 days after TAVR or SAVR

CT and TTE 120-180 days after 1st follow-up
  • If thrombus: rivaroxaban 20 mg daily

Third CT and TTE follow-up
  • If persistent thrombus: warfarin (INR 2-3)

Fourth CT and TTE follow-up

Methods

• Assessed valve leaflet thickening using CT imaging

• Assessed leaflet motion at maximal leaflet opening during systole
  • Normal
  • Mildly reduced (<50% reduction)
  • Moderately reduced (50-70% reduction)
  • Severely reduced (>70% reduction)
  • Immobile (absence of motion)

• Reduced leaflet motion defined as the presence of at least moderate restriction of leaflet motion
Outcomes

• Primary
  • Frequency of patients with structural/functional abnormalities of bioprosthetic valves
  • Frequency of patients with abnormal aortic valve bioprosthesis leaflet mobility and morphology

• Secondary
  • Percentage of patients with resolution of bioprosthetic valve thrombotic lesions with anticoagulation

• Data collected
  • Mean aortic transvalvular gradients and velocity time integral (VTI) ratio to assess hemodynamics
  • Antiplatelet and antithrombotic therapy
  • Clinical follow-up for death, myocardial infarction (MI), stroke, and transient ischemic attack (TIA)

Statistical Analysis

• Continuous variables
  • Normal distribution: means and standard deviations (SDs), analyzed with two-sample \( t \) tests
  • Non-normal distribution: medians and interquartile ranges (IQRs), analyzed with Mann-Whitney U tests

• Categorical variables
  • Frequencies and percentages, compared with \( X^2 \) or Fisher’s exact tests

• After assessing baseline variables, assessed all variables with a \( p \) value of <0.20 using forward and backward model selection techniques

• Cox regression analysis to calculate hazard ratios and 95% confidence intervals (CIs)
  • Two-sided \( p \) value <0.05 for significance

## Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Normal leaflet motion (n=784)</th>
<th>Reduced leaflet motion (n=106)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean), years</td>
<td>78.9</td>
<td>82.0</td>
<td>0.0009</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>437 (56%)</td>
<td>64 (60%)</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Medical Condition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease (%)</td>
<td>10%</td>
<td>14%</td>
<td>0.22</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>87%</td>
<td>83%</td>
<td>0.30</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>8%</td>
<td>8%</td>
<td>0.88</td>
</tr>
<tr>
<td>Previous TIA (%)</td>
<td>5%</td>
<td>6%</td>
<td>0.63</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>77%</td>
<td>74%</td>
<td>0.49</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>25%</td>
<td>21%</td>
<td>0.38</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>75%</td>
<td>79%</td>
<td>0.37</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>30%</td>
<td>16%</td>
<td>0.003</td>
</tr>
<tr>
<td>Baseline ejection fraction, mean (EF)</td>
<td>57.9</td>
<td>55.5</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Results: Reduced Leaflet Motion

• Reduced leaflet motion detected in 106/890 (12%) of patients
• Median time from aortic valve replacement to CT scanning = 83 days (IQR 33-281)
  • Median time from SAVR to CT = 163 days; from TAVR to CT = 58 days

<table>
<thead>
<tr>
<th></th>
<th>Frequency of reduced leaflet motion (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcatheter valves</td>
<td>101/752 (13%)</td>
</tr>
<tr>
<td>Surgical valves</td>
<td>5/138 (4%)</td>
</tr>
</tbody>
</table>

• Significant predictors of reduced leaflet motion: transcatheter valves, increased age, low EF, and absence of anticoagulation
## Results: Anticoagulation at Time of Index CT

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Normal leaflet motion</th>
<th>Reduced leaflet motion</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation vs no anticoagulation</td>
<td>n=784 216 (28%) 568 (72%)</td>
<td>n=106 8 (8%) 98 (92%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anticoagulation vs DAPT</td>
<td>n=393 216 (55%) 177 (45%)</td>
<td>n=39 8 (21%) 31 (79%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anticoagulation vs monoantiplatelet therapy</td>
<td>n=558 216 (39%) 342 (61%)</td>
<td>n=71 8 (11%) 63 (89%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Warfarin vs no anticoagulation</td>
<td>n=680 112 (16%) 568 (84%)</td>
<td>n=103 5 (5%) 98 (95%)</td>
<td>0.001</td>
</tr>
<tr>
<td>NOACs vs no anticoagulation</td>
<td>n=672 104 (15%) 568 (85%)</td>
<td>n=101 3 (3%) 98 (97%)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Results: Effects of Anticoagulation on Reduced Leaflet Motion

• Among 58 patients with reduced leaflet motion who had follow-up imaging:
  • Restoration of normal leaflet motion in 36/36 (100%) of patients on anticoagulation for 3 months [warfarin 67%, rivaroxaban 33%]
  • Persistent or progressed reduced leaflet motion in 20/22 (91%) of patients in absence of anticoagulation

• After restoration of normal leaflet motion with anticoagulation:
  • Reduced leaflet motion recurred in 4/8 (50%) of patients in whom anticoagulation was discontinued vs 0/15 (0%) of patients who were maintained on anticoagulation (p=0.008)

## Results: Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Normal leaflet motion (n=784)</th>
<th>Reduced leaflet motion (n=106)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4%</td>
<td>4%</td>
<td>0.94</td>
</tr>
<tr>
<td>MI</td>
<td>1%</td>
<td>1%</td>
<td>0.56</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>3%</td>
<td>10%</td>
<td>0.001</td>
</tr>
<tr>
<td>All stroke</td>
<td>3%</td>
<td>6%</td>
<td>0.10</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>3%</td>
<td>6%</td>
<td>0.08</td>
</tr>
<tr>
<td>TIA</td>
<td>1%</td>
<td>6%</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Author’s Conclusions

• Frequency and severity of reduced leaflet motion was lower with SAVR than TAVR
• Anticoagulation with warfarin or NOACs was effective in prevention or treatment of reduced leaflet motion, while DAPT, the standard of care, was not effective
• Mortality and MI were not significantly different in patients with normal vs reduced leaflet motion, while rates of TIA were increased in patients with reduced leaflet motion
• Depending on findings from current randomized trials (GALILEO and ATLANTIS), consideration of a short course of anticoagulation following TAVR might be warranted

Critique

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Largest study to date on the topic of subclinical leaflet thrombosis after TAVR/SAVR</td>
<td>• Observational study</td>
</tr>
<tr>
<td>• First study to assess NOACs for treatment or prevention of subclinical leaflet thrombosis</td>
<td>• Cannot exclude the effect of unmeasured confounders</td>
</tr>
<tr>
<td>• Compares current standard of care to an alternative</td>
<td>• Lack of prospective neurological assessment at follow-up visits</td>
</tr>
<tr>
<td></td>
<td>• Inability to precisely assess time interval between occurrence of subclinical leaflet thrombosis and clinical events</td>
</tr>
<tr>
<td></td>
<td>• Did not assess triple therapy</td>
</tr>
<tr>
<td></td>
<td>• Lack of safety outcomes</td>
</tr>
</tbody>
</table>
Clinical Implications

2017 ACC Expert Consensus Decision Pathway for Transcatheter Aortic Valve Replacement in the Management of Adults with Aortic Stenosis

- Subclinical leaflet thrombus formation may be more common than previously appreciated
- Current standard after TAVR: clopidogrel 75 mg daily for 3-6 months with aspirin 75-100 mg daily lifelong
- VKA therapy may be considered in first 3 months after TAVR in patients at risk for AF or valve thrombosis

2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease

- Anticoagulation with a VKA may be reasonable for at least 3 months after TAVR in patients at low risk of bleeding (IIb, B-NR)

## Future Studies

<table>
<thead>
<tr>
<th></th>
<th>GALILEO</th>
<th>ATLANTIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full title</strong></td>
<td>Global study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement to optimize clinical outcomes</td>
<td>Anti-thrombotic strategy after trans-aortic valve implantation for aortic stenosis</td>
</tr>
<tr>
<td><strong>Timeline</strong></td>
<td>December 2015 – November 2018</td>
<td>August 2016 – April 2019</td>
</tr>
<tr>
<td><strong>Treatment arms</strong></td>
<td>• Rivaroxaban 10 mg daily + ASA 75-100 mg daily for first 90 days</td>
<td>• Apixaban 5 mg BID or 2.5 mg BID</td>
</tr>
<tr>
<td></td>
<td>• ASA 75-100 mg daily + clopidogrel 75 mg daily for first 90 days</td>
<td>• VKA or antiplatelet therapy (standard of care)</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Death or first adjudicated thromboembolic event</td>
<td>Composite of death, MI, stroke, systemic embolism, intracardiac or bioprosthesis thrombus, any episode of DVT or PE, life-threatening or disabling or major bleeding at one year follow-up</td>
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