Early Bioprosthetic Valve Leaflet Thickening: Imaging Observations, Clinical Implications, and Controversies

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Professor, David Geffen School of Medicine at UCLA
Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves


NEJM Oct 2015
Background

A finding of severely reduced leaflet motion noted in 2 patients in the early part of the Portico IDE study.
Study population (n=187)

- *Portico IDE study*
  - 1:1 randomization of high risk patients between Portico and Commercial valve
  - 55 CT scans analyzed at 30 days prospectively (Sapien XT, Portico and CoreValve)

- *RESOLVE* registry (NCT02318342) at Cedars-Sinai Heart Institute
  - Real world registry
  - 70 CT scans at multiple time points after TAVR and SAVR

- *SAVORY* registry (NCT02426307) at Rigshospitalet, Copenhagen
  - Real world registry
  - 62 CT scans at multiple time points after TAVR and SAVR

- Core lab analysis of all CT scans. Echo core lab for Portico IDE.
Results I
Prevalence of possible subclinical leaflet thrombosis
Overall: 21%

• The Portico IDE had reduced leaflet motion present in 22/52 (40·0%) of patients
  ▪ 16/37 (43.2%) Portico, 6/14 (42.9%) Sapien XT and 0/4 (0%) CoreValve

• The registries (RESOLVE and SAVORY) had reduced leaflet motion in 17 of 132 patients (13%).
  ▪ 7/58 (12.1%) Sapien/XT/S3, 2/24 (8.3%) Corevalve, 1/8 Lotus (12.5%), 2/27 SAVR (7.4%)
Volume rendered CT images of bioprosthetic valves

<table>
<thead>
<tr>
<th>Normal leaflets</th>
<th>Thickened leaflets with thrombus</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Systole image" /></td>
<td><img src="image2" alt="Systole image" /></td>
</tr>
<tr>
<td><img src="image3" alt="Diastole image" /></td>
<td><img src="image4" alt="Diastole image" /></td>
</tr>
</tbody>
</table>

Diastole
Reduced leaflet motion was observed in all valve types including surgical bioprostheses.
Results II: Role of TTE

This finding was invariably missed on TTE, which demonstrated normal transvalvular gradients.

Portico IDE gradients in patients with and without reduced leaflet motion.

Day 1 mean gradient = 9 mmHg

Day 30 mean gradient = 9 mmHg
Results III: Role of TEE

There was 100% concordance in the assessment of leaflet motion between TEE and 4D VR-CT in 10 out 22 patients with reduced leaflet motion undergoing TEE.
Results IV: Therapeutic warfarin vs. DAPT: Portico-IDE

Decreased incidence of subclinical leaflet thrombosis

0% vs. 55.0%, p=0.01

0/8
0.0%

55.0%
11/20

Therapeutic warfarin

DAPT
Results IV: Therapeutic warfarin vs. DAPT: Registries
Decreased incidence of subclinical leaflet thrombosis

0% vs. 29.0%, p=0.04

0/13 (0.0%)

29.0%
10/35

Therapeutic warfarin
DAPT
Results V: Natural history of this phenomenon
Anticoagulation was associated with resolution of thrombus and restoration of leaflet motion in 11 out of 11 patients

Reduced leaflet motion on 30-day CT

Patient was started on Warfarin

Resolution of thrombus and restoration of leaflet motion on 7 month follow-up CT
Results V: Natural history of this phenomenon
Persistence of thrombus and reduced leaflet motion in 9 out of 10 patients without therapeutic anticoagulation

Persistent reduced leaflet motion on subtherapeutic warfarin (INR 1.1)
## Results VI: Clinical outcomes – Portico IDE

<table>
<thead>
<tr>
<th></th>
<th>Normal Leaflet Motion</th>
<th>Reduced Leaflet Motion</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PORTICO IDE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients in study</td>
<td>33</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Death†</td>
<td>1</td>
<td>2</td>
<td>0.56</td>
</tr>
<tr>
<td>Myocardial infarction‡</td>
<td>1</td>
<td>1</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Stroke/TIA§</td>
<td>0</td>
<td>2</td>
<td>0.16</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>2</td>
<td>0.16</td>
</tr>
<tr>
<td>TIA</td>
<td>0</td>
<td>0</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

† One patient with normal leaflet motion died 111 days after valve implantation from congestive heart failure. Of the two deaths among patients with reduced leaflet motion, one was the result of a myocardial infarction 147 days after valve implantation and the other was the result of pneumonia 249 days after valve implantation.

‡ The myocardial infarction occurred 1 day after valve implantation and 27 days before computed tomography (CT) in the group with normal leaflet motion and 147 days after valve implantation and 114 days after CT in the group with reduced leaflet motion.

§ In the two patients with stroke, the event occurred 6 hours after TAVR (with CT performed 1 day after TAVR) in one patient and 1 day after TAVR (with CT performed 28 days after TAVR) in the second patient. The first patient had multiple risk factors for stroke, including atrial fibrillation and substantial spontaneous echo contrast in the left atrium on echocardiography during TAVR.
## Results VI: Clinical outcomes – Registries

<table>
<thead>
<tr>
<th>Registries</th>
<th>Normal Leaflet Motion</th>
<th>Reduced Leaflet Motion</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients in study</td>
<td>115</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Stroke/TIA¶</td>
<td>1</td>
<td>3</td>
<td>0.007</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>0</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>TIA</td>
<td>0</td>
<td>3</td>
<td>0.002</td>
</tr>
</tbody>
</table>

¶ In the group with normal leaflet motion, one patient had a stroke 1 day after TAVR (with CT performed 35 days after TAVR). In the group with reduced leaflet motion, three patients had transient ischemic attacks: one that occurred 15 days after TAVR (with CT performed 39 days after TAVR), a second that occurred 239 days after TAVR (with CT performed 24 days after TAVR), and a third that occurred 147 days after TAVR (with CT performed 32 days after TAVR).
Conclusion of NEJM manuscript

In conclusion, reduced aortic-valve leaflet motion occurred in patients with bioprosthetic aortic valves and was easily detected noninvasively by four-dimensional, volume-rendered CT. Therapeutic anticoagulation with warfarin, but not therapy with antiplatelet drugs, prevented and effectively treated this phenomenon. Better characterization of this observation is needed to determine its frequency and evaluate its clinical effect.
Uncertainty and Possible Subclinical Valve Leaflet Thrombosis

David R. Holmes, M.D., and Michael J. Mack, M.D.

Table 1. Questions Raised by the Study by Makkar et al.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the true incidence of reduced aortic-valve leaflet motion? Is it device-specified, is it specific Lu L Transcatheter aortic-valve replacement (TAVR), or does it occur as frequently with surgical aortic-valve replacement?</td>
<td></td>
</tr>
<tr>
<td>Is reduced leaflet motion caused by thrombus formation on the leaflets? If so, is subclinical leaflet thrombosis related to the stent structure or to deployment strategies (e.g., undersizing or oversizing or other patient-specific factors)?</td>
<td></td>
</tr>
<tr>
<td>What does this abnormality mean clinically? How frequent are strokes or transient ischemic attacks in patients with this finding? Should the list of clinical events of potential concern be broadened to include valve durability, central aortic regurgitation, sudden death, or recurrent or unrelenting heart failure?</td>
<td></td>
</tr>
<tr>
<td>What is the natural history of the abnormality? When (and at what intervals) should it be evaluated, and does it play a role in premature structural valve deterioration?</td>
<td></td>
</tr>
<tr>
<td>What treatment strategy should be studied? If anticoagulation is presumed to be the most effective strategy, will adverse outcomes associated with bleeding result in more complications than this abnormality?</td>
<td></td>
</tr>
<tr>
<td>What is the most effective imaging approach for monitoring this abnormality? Is monitoring needed in all patients, and if so, when?</td>
<td></td>
</tr>
<tr>
<td>Does this issue need to be fully resolved before the expansion of Food and Drug Administration approval of TAVR for lower-risk patients?</td>
<td></td>
</tr>
</tbody>
</table>
Reduced Leaflet Motion in Bioprosthetic Aortic Valves - The FDA Perspective

John C. Laschinger, M.D., Changfu Wu, Ph.D., Nicole G. Ibrahim, Ph.D., and Jeffrey E. Shuren, M.D., J.D.

The FDA is mindful of the perceived and real complications associated with routine and possibly unnecessary applications of advanced or invasive imaging and with prolonged anticoagulation, especially in high-risk populations. However, the potential for increased risks of late adverse clinical events related to reduced leaflet motion or thrombosis warrants careful systematic investigation. The absence of evidence of temporally related adverse clinical sequelae of imaging-detected reduced leaflet motion suggests that additional bench and clinical testing can be carried out while normal cardiac care continues under the currently approved indications for transcatheter or surgical placement of bioprosthetic aortic valves.

We at the FDA believe that the available clinical evidence supports the conclusion that these valves remain safe and effective and that findings to date concerning reduced leaflet motion have not changed the overall favorable benefit-risk balance for these valves when they are used for their approved indications. These devices reduce symptoms, improve quality of life, and save and prolong the lives of appropriately selected patients. This view is supported by the favorable observed benefit-risk profile and the durability data obtained over the past 30 years for the currently approved surgically implanted bioprosthetic aortic valves.
Transcatheter heart valve failure: a systematic review

Darren Mylotte\textsuperscript{1,2}, Ali Andalib\textsuperscript{1}, Pascal Thériault-Lauzier\textsuperscript{1}, Magdalena Dorfmeister\textsuperscript{3}, Mina Girgis\textsuperscript{1}, Waleed Alharbi\textsuperscript{1}, Michael Chetrit\textsuperscript{1}, Christos Galatas\textsuperscript{1}, Samuel Mamane\textsuperscript{1}, Igal Sebag\textsuperscript{4}, Jean Buithieu\textsuperscript{1}, Luc Bilodeau\textsuperscript{1}, Benoit de Varennes\textsuperscript{5}, Kevin Lachapelle\textsuperscript{5}, Ruediger Lange\textsuperscript{3}, Giuseppe Martucci\textsuperscript{1}, Renu Virmani\textsuperscript{6}, and Nicolo Piazza\textsuperscript{1,3}\textsuperscript{*}

15 cases of TAVR valve thrombosis reported from 12/02-03/14
14 symptomatic
1 subclinical

Multicenter, multinational registry of patients with TAVR thrombosis
26 out of 4266 patients undergoing TAVR (0.61%)

- Median time to THV thrombosis: 181 days
- Median time to resolution of thrombus with anticoagulation: 39 days

Multicenter, multinational registry of patients with TAVR thrombosis
26 out of 4266 patients undergoing TAVR (0.61%)
Systematic assessment
February 2014 – March 2015

N = 249 with TAVI
SAPIEN 3

n = 156 (60.2%)
Post TAVI CT at day 5

n = 140 (89.8%)
without leaflet thickening

n = 16 (10.2%)
with leaflet thickening

N = 16
Clinically inapparent

treated with phenprocoumon
INR 2.5 – 3.5

n = 11
CT after median of 77 days

n = 11
Regression of leaflet thickening

n = 93 (39.8%)
without post TAVI CT

- 15 renal impairment
- 13 frailty
- 4 death
- 33 patient refusal
- 27 logistic reasons
- 1 poor image quality

n = 5
awaiting follow-up

## Antithrombotic regimens

<table>
<thead>
<tr>
<th>Antithrombotic regime at Implantation</th>
<th>All patients (n=156)</th>
<th>No leaflet thickening (n=140)</th>
<th>Leaflet thickening (n=16)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono-antiplatelet therapy</td>
<td>45 (28.8)</td>
<td>39 (27.8)</td>
<td>6 (37.5)</td>
<td>0.420</td>
</tr>
<tr>
<td>Dual-antiplatelet therapy</td>
<td>111 (71.2)</td>
<td>101 (72.2)</td>
<td>10 (62.5)</td>
<td></td>
</tr>
<tr>
<td>Antithrombotic regime at CTA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono-antiplatelet therapy</td>
<td>17 (10.9)</td>
<td>14 (10.0)</td>
<td>3 (18.8)</td>
<td>0.468</td>
</tr>
<tr>
<td>Dual-antiplatelet therapy</td>
<td>76 (48.7)</td>
<td>70 (50.0)</td>
<td>6 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Mono-antiplatelet therapy + Anticoagulation</td>
<td>63 (40.4)</td>
<td>56 (40.0)</td>
<td>7 (43.7)</td>
<td></td>
</tr>
</tbody>
</table>

Very Early Thrombosis of Sapien 3 Valve

Sapien3 valve thrombosis 3 days post-TAVR

Valve thrombosis

Resolution with anticoagulation

thrombus on aortic valve leaflets

normal valve leaflets - post anticoagulation

Neylon A. et al. JACC: Cardiovascular Interventions 2016
Very Late Thrombosis of a Transcatheter Aortic Valve-in-Valve

Valve thrombosis 4 years post-TAVR
46 cases (12%) of bioprosthetic valve thrombosis out of 397 consecutive explanted bioprosthetic valves

- Valve thrombosis (n=46)
- Matched cases of valve degeneration (n=92)

BPVT referred for surgical intervention occurs significantly earlier than BPV degeneration

Egbe A. et al. JACC 2015
Predictors of valve hemodynamic degeneration after TAVR

1521 patients undergoing TAVR
Valve hemodynamic degeneration = 10mmHg rise in transvalvular gradients

- BMI
- Valve ≤ 23mm
- Valve in valve
- No anticoagulation at discharge

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>(95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>1.08</td>
<td>(1.03-1.13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Valve ≤ 23mm</td>
<td>2.07</td>
<td>(1.14-3.76)</td>
<td>0.016</td>
</tr>
<tr>
<td>Valve in valve</td>
<td>2.32</td>
<td>(1.07-5.04)</td>
<td>0.032</td>
</tr>
<tr>
<td>No anticoagulation at discharge</td>
<td>3.35</td>
<td>(1.57-7.13)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Del Trigo M. et al. JACC 2016
Valve hemodynamic degeneration and clinical outcomes
No significant increase in mortality or stroke

Mortality

[Graph showing cumulative mortality over months with Log rank: p=0.915]

Stroke

[Graph showing stroke rates over months with Log rank: p=0.969]
Association of warfarin therapy with clinical events after bioprosthetic AVR: Danish Registry

4075 patients undergoing bioprosthetic AVR in the Danish Registry

Discontinuation of warfarin treatment within 6 months after bioprosthetic AVR associated with worse outcomes

Merie C. et al. JAMA 2012
Association of warfarin therapy with clinical events after bioprosthetic AVR: Danish Registry

4075 patients undergoing bioprosthetic AVR in the Danish Registry

Discontinuation of warfarin treatment within 6 months after bioprosthetic AVR associated with worse outcomes

Increased strokes

Increased thromboembolic events

Merie C. et al. JAMA 2012
Association of warfarin therapy with clinical events after bioprosthetic AVR: STS database
25,656 patients undergoing bioprosthetic AVR at 797 hospitals in the STS database

Warfarin plus aspirin associated with a reduced risk of death and embolic events, compared to aspirin alone

Brennan M. et al. JACC 2012
Association of warfarin therapy with clinical events after bioprosthetic AVR: STS database

25,656 patients undergoing bioprosthetic AVR at 797 hospitals in the STS database

“The addition of warfarin to aspirin at hospital discharge would be a reasonable treatment option, on the basis of these results, with an expected number needed to avert 1 death of 153 patients and 1 embolic event of 212 patients. The therapeutic benefit observed with the addition of warfarin to aspirin was not without risk in this elderly cohort, and 1 additional bleeding event was observed at 3 months for every 55 patients treated with warfarin”.

Brennan M. et al. JACC 2012
Should we treat Leaflet Thrombosis?

- Should we treat *symptomatic* leaflet thrombosis?
  Definitely YES

- Should we treat *asymptomatic* leaflet thrombosis?
  **Yes**—we treat thrombus in other location why not here, may be too late to find out if it affects valve durability, there is a signal for TIA's

  **No**—there is no definite impact on outcomes yet, risk of bleeding may not be trivial. We need to elucidate this phenomenon better.
Should we routinely do CTs on all patients post TAVR?

• Best done systematically in research protocols with the involvement of imaging experts
• Radiation and contrast use may be an issue
• What would we do with the information in patients who are not candidates for anticoagulation?
• There should be low threshold to image in patients with suspected valve dysfunction, thrombo-embolic events
My perspective

• We started with a finding that we thought was an imaging artifact. We have established that this is a real finding. We have also established with a reasonable, but not unquestionable certainty, that this may be related to leaflet thrombosis.

• There is no conclusive evidence regarding the clinical significance of this finding. This requires longer and larger adequately powered studies.

• In appropriate clinical situations (elevated gradients, worsening heart failure, stroke/TIA, MI and other clinical situations concerning for embolic phenomenon), CT imaging should be performed to rule out leaflet thrombus.
My perspective

• While a case for routine CT scanning in clinical practice cannot be made at this time. This is best studied in registries/research protocols, with the involvement of imaging experts.

• Similarly, routine anticoagulation in all patients post-TAVR cannot be recommended, given the high risk of bleeding in the current TAVR population and the uncertain clinical significance of this finding.

• These findings provide a sound rationale for some of the planned studies with different antithrombotic regimens post-TAVR and question current guidelines of dual antiplatelet therapy. Imaging should be incorporated in some of the planned pharmacologic studies.
GALILEO (Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivaroxaban-based antithrombotic strategy to an aspirin-based strategy after transcatheter aortic valve replacement (TAVR) to optimize clinical outcomes will compare rivaroxaban-based)

1520 patients after successful TAVI procedure

- Rivaroxaban 10 mg OD and Aspirin 75-100mg OD
  - Drop of aspirin
  - Rivaroxaban 10 mg OD

- Clopidogrel 75 mg OD
  - Aspirin 75-100 mg OD
  - Drop of clopi
  - Aspirin 75-100 mg OD

Primary end-point is death, MI, stroke, non-CNS systemic emboli, symptomatic valve thrombosis, deep vein thrombosis or pulmonary embolism, major bleedings over 720 days of treatment exposure.
The GALILEO Trial

CTA and MRI Substudies

GALILEO 4D

- N = 300 patients; 1 CTA done at 3 month
- Primary endpoint: rate of patients with at least one new stentless heart with > 50% mean malposition assessed by cardiac 4D CT at 3 month after TAV
- Secondary endpoint:Includes leaflet thickening, echocardiographic variables, mean gradient, and EOA and function: NYHA status

GALILEO MRI Substudy EARTH

- N = 10 patients
- Primary endpoint: TVV assessed with DI MR at 1 month
- Will be superior to Dresus and sex: echocardiographic variables
- DI MRI also performed at TAV and sex: TAV (both laboratories) for the 2 year endpoint of periprocedure embolization

NCT02556203
ATLANTIS (Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis)

1509 patients after successful TAVI procedure

- Stratum 1: Indication for OAT
  - VKA
- Stratum 2: No indication for OAT
  - Apixaban 5mg bid*
  - DAPT/SAPT

Primary end-point is a composite of death, MI, stroke, systemic emboli, intracardiac or bioprosthesis thrombus, episode of deep vein thrombosis or pulmonary embolism, major bleedings over one year follow-up.

*2.5mg bid if creatinine clearance 15-29mL/min or if two of the following criteria: age≥80 years, weight≤60kg or creatinine≥1,5mg/dL (133µMol).
67 y/o male physician s/p TAVR with 29mm Sapien3 valve

Worsening shortness of breath 4 months post-TAVR
Transvalvular gradients elevated from 10 mmHg to 23 mmHg

Day 1 TTE
Gradient 10mmHg

4 months post-TAVR
Gradient 23mmHg
Leaflet thickening and restricted leaflet motion noted on 4D VR-CT
Leaflet motion restored following anticoagulation with warfarin (INR 2-3)
Repeat CT performed after 3 months

Resolution of symptoms with anticoagulation

Restricted leaflet motion

Normal leaflet motion
Normalized transvavular gradients with anticoagulation (warfarin, INR 2-3)

Repeat TTE performed after 3 months

Resolution of symptoms with anticoagulation

Pre-anticoagulation
Gradient 23mmHg

Post-anticoagulation
Gradient 11mmHg