Subclinical Thrombosis of Bioprosthetic Aortic Valves: Is It Clinically Relevant?

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Disclosures

- Consultant and proctor for Edwards LifeSciences
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
Leaflet thickening and restricted leaflet motion noted on 4D VR-CT

Restricted leaflet motion

Hypoattenuating lesions
Leaflet motion restored following anticoagulation with warfarin (INR 2-3)

Repeat CT performed after 3 months

Resolution of symptoms with anticoagulation
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
Case 2
85 y/o male s/p TAVR with 23mm Sapien 3 valve

Mean gradient 12mmHg

Trivial PVL
Cardiac CT done 1 month post-TAVR
Mildly reduced leaflet motion, minimal thrombus with mildly increased leaflet thickness

Mildly reduced leaflet motion

Mild hypoattenuating opacity

Mean gradient 14mmHg
Patient transferred to Cedars-Sinai 9 months later for altered mental status

Multiple embolic acute and subacute strokes noted on MRI brain

Aortic valve gradients elevated on echo

30-day echo
Mean gradient 14mmHg

Echo now
Mean gradient 23mmHg

<table>
<thead>
<tr>
<th>Max PG</th>
<th>41 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PG</td>
<td>23 mmHg</td>
</tr>
<tr>
<td>VTI</td>
<td>53.5 cm</td>
</tr>
<tr>
<td>AVA (VTI)</td>
<td>0.56 cm²</td>
</tr>
<tr>
<td>AVA (Vmax)</td>
<td>0.48 cm²</td>
</tr>
</tbody>
</table>
Patient transferred to Cedars-Sinai 9 months later for altered mental status

Extensive thrombus on the aortic valve, with severely reduced leaflet motion

Patient started on anticoagulation with rivaroxaban 10mg daily; repeat imaging pending
Case 3
71 y/o female s/p TAVR with 29mm Sapien 3 valve

Mean gradient 9mmHg

- AV VTI
- Vmax: 209 cm/s
- Vmean: 135 cm/s
- Max PG: 18 mmHg
- Mean PG: 9 mmHg
- VTI: 42.6 cm

- AV VR: 0.49
- AVA (VTI): 1.67 cm²
- AVA (Vmax): 1.55 cm²
- AVA(VTI)/BSA: 0.83
Patient admitted 2 weeks later at an outside hospital with stroke
No significant change in gradients

Day 1 echo
Mean gradient 9mmHg

3 week echo
Mean gradient 8mmHg
CT aortic valve revealed significant thrombus and reduced leaflet motion

Patient admitted a day later to an outside hospital with stroke
Case 4
65 y/o male s/p ViV with 23mm Sapien 3 valve

Mean gradient 13mmHg

Trivial PVL
Patient complaining of worsening shortness of breath on post-TAVR Day 2

Repeat TTE revealed rise in gradients from 12mmHg to 37mmHg

**Day 1 echo**
Mean gradient 13mmHg

**Day 2 echo**
Mean gradient 37mmHg
CT performed to rule out valve thrombus

Extensive thrombus on the aortic valve, with severely reduced leaflet motion

Patient started on anticoagulation with rivaroxaban 10mg daily; repeat TTE 1 month later revealed decrease in gradients, repeat CT to be done in 3 months

Severely reduced leaflet motion

Hypoattenuating opacities on 2 leaflets

Mean AV gradients decreased from 37mmHg to 23mmHg
Case 5
Valve Thrombus can occur despite normal gradients and anticoagulation
83 y/o female s/p TAVR with 26mm Evolut valve

Patient enrolled in RESOLVE registry
Cardiac CT performed at 1 month post-TAVR

Patient already on warfarin, INR 2.5

Severely reduced leaflet motion

Hypoattenuating lesions
Normal valve gradients despite reduced leaflet motion

Day 1 TTE
Mean gradient 7mmHg

1 month TTE
Gradient 5mmHg
Resolution of thrombus and restoration of normal leaflet motion in 3 months
Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study

Tarun Chakravarty, Lars Søndergaard, John Friedman, Ole De Backer, Daniel Berman, Klaus F Kofoed, Hasan Jilaihawi, Takahiro Shiota, Yigal Abramowitz, Troels H Jørgensen, Tanya Rami, Sharjeel Israr, Gregory Fontana, Martina de Knecht, Andreas Fuchs, Patrick Lyden, Alfredo Trento, Deepak L Bhatt, Martin B Leon, Raj R Makkar, on behalf of the RESOLVE and SAVORY Investigators*

Evidence before this study
We searched MEDLINE on Feb 1, 2017, for articles published in English, with the search terms “bioprosthesis valve thrombosis”, “transcatheter aortic valve thrombosis”, “subclinical leaflet thrombosis”, “hypoattenuating leaflet thickening”, and “TAVR thrombosis”. Although symptomatic thrombosis represents the extreme end of the spectrum of bioprosthesis aortic valve thrombosis and is probably under-reported (prevalence of 1–2%), subclinical leaflet thrombosis with no associated symptoms is more frequent (prevalence of 10–15%) than is symptomatic bioprosthesis aortic valve thrombosis. Reduced leaflet motion detected with high-resolution CT in bioprosthetic aortic valves has been attributed to subclinical leaflet thrombosis in previously reported series. The published series have several limitations, including absence of complete clinical follow-up, no core laboratory assessment of transthoracic echocardiograms, no information about differences in the prevalence and severity of subclinical leaflet thrombosis between transcatheter and surgical valves, no adjudication of neurological events, and no information about the efficacy of novel oral anticoagulants (NOACs).

Added value of this study
We report, to our knowledge, the largest study to date of 931 patients who had CT scans done after surgical or transcatheter aortic valve replacement (TAVR) to assess reduced leaflet motion and its effect on clinical outcomes. This study is the first, to our knowledge, to report differences in subclinical leaflet thrombosis between surgical and transcatheter aortic valves. Findings from this study are also the first, to our knowledge, to show the potential efficacy of NOACs in the prevention and treatment of subclinical leaflet thrombosis in bioprosthetic aortic valves. The frequency and severity of subclinical leaflet thrombosis was lower in surgical than in transcatheter aortic valves. Patients with reduced leaflet motion had a small, but significant, increase in valve gradients. Anticoagulation was better than dual antiplatelet therapy (DAPT; standard of care for patients after TAVR) or monoantiplatelet therapy in the prevention and treatment of subclinical leaflet thrombosis; both NOACs and warfarin were effective. We also observed increased rates of neurological events, including transient ischaemic attacks and strokes or transient ischaemic attacks associated with reduced leaflet motion, although the rates of strokes were not significantly different.

Implications of all the available evidence
Our findings question the guidelines recommending DAPT after TAVR and raise the issue of whether or not warfarin or NOACs are more appropriate in certain patients than is DAPT. The risk-benefit profile of anticoagulation will be established in future clinical trials. Despite excellent outcomes after TAVR with the new-generation valves, room might exist for further improvement in outcomes through an understanding of the predictors of reduced leaflet motion and consideration of a short course of anticoagulation if findings from ongoing randomised trials substantiate these existing findings.

Chakravarty T. et al. Lancet 2017
Reduced leaflet motion in multiple valve types

931 patients post TAVR CT
Prevalence of reduced leaflet motion
Transcatheter vs. surgical bioprosthetic aortic valves: $p=0.001$

Reduced leaflet motion was present in 106 (11.9%) patients

Transcatheter valves
13.4% (101 out of 752)

Surgical valves
3.6% (5 out of 138)
Anticoagulation and reduced leaflet motion

Anticoagulation vs. no anticoagulation

- Anticoagulation vs. no anticoagulation: $p<0.0001$
- NOACs vs. no anticoagulation: $p=0.0002$
- Warfarin vs. no anticoagulation: $p=0.001$
- NOACs vs. warfarin: $p=0.72$

<table>
<thead>
<tr>
<th>Group</th>
<th>Prevalence</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation</td>
<td>8/224 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>NOACs</td>
<td>3/107 (2.8%)</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>5/117 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>No anticoagulation</td>
<td>98/666 (14.7%)</td>
<td></td>
</tr>
</tbody>
</table>
## Anticoagulation vs. DAPT

<table>
<thead>
<tr>
<th>Anticoagulation</th>
<th>DAPT continued after index CT</th>
<th>Index CT</th>
<th>Follow-up CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
</tr>
</tbody>
</table>

- **DAPT continued after index CT**: Shows progression of reduced leaflet motion from index CT to follow-up CT.
- **Warfarin initiated after index CT**: Shows resolution of reduced leaflet motion from index CT to follow-up CT.
- **Rivaroxaban initiated after index CT**: Shows resolution of reduced leaflet motion from index CT to follow-up CT.
- **Apixaban initiated after index CT**: Shows resolution of reduced leaflet motion from index CT to follow-up CT.

*Notes:*
- Index CT: Initial CT scan.
- Follow-up CT: CT scan taken after treatment initiation.
Anticoagulation vs. DAPT

<table>
<thead>
<tr>
<th>DAPT continued after index CT</th>
</tr>
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<tbody>
<tr>
<td>Warfarin initiated after index CT</td>
</tr>
<tr>
<td>Rivaroxaban initiated after index CT</td>
</tr>
<tr>
<td>Apixaban initiated after index CT</td>
</tr>
</tbody>
</table>

Index CT

Follow-up CT

- Progression
- Resolution
- Resolution
- Resolution
Recurrence of reduced leaflet motion following discontinuation of anticoagulation

Baseline
Reduced leaflet motion

s/p Xarelto 10mg
Normal leaflet motion

Six months following discontinuation of Xarelto
Reduced leaflet motion

Reduced leaflet motion recurred in majority in whom anticoagulation was discontinued
Increased gradients in patients with reduced leaflet motion

Mean aortic gradient > 20mmHg

Increase in gradients > 10mmHg

Mean aortic gradient > 20mmHg AND Increase in gradients > 10mmHg

Normal leaflet motion

Reduced leaflet motion

Prevalence

P=0.0002

15/96 (16%)

P<0.0001

13/88 (15%)

P<0.0001

12/88 (14%)

40/714 (6%)

9/632 (1%)

7/632 (1%)
# Impact of reduced leaflet motion on clinical outcomes

All clinical events post-TA VR/SA VR included

No significant difference in strokes; but increased risk of TIAs and strokes/TIAs

<table>
<thead>
<tr>
<th></th>
<th>Normal leaflet motion (N=784)</th>
<th>Reduced leaflet motion (N=106)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N (%)</td>
<td>Rate per 100 person-years</td>
<td>n/N (%)</td>
<td>Rate per 100 person-years</td>
</tr>
<tr>
<td>All events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>34/784 (4.3%)</td>
<td>2.91</td>
<td>4/106 (3.8%)</td>
<td>2.66</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4/784 (0.5%)</td>
<td>0.34</td>
<td>1/106 (0.9%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Strokes/TIAs</td>
<td>27/784 (3.4%)</td>
<td>2.36</td>
<td>11/106 (10.4%)</td>
<td>7.85</td>
</tr>
<tr>
<td>All strokes*</td>
<td>22/784 (2.8%)</td>
<td>1.92</td>
<td>6/106 (5.7%)</td>
<td>4.12</td>
</tr>
<tr>
<td>Ischemic strokes</td>
<td>21/784 (2.7%)</td>
<td>1.83</td>
<td>6/106 (5.7%)</td>
<td>4.12</td>
</tr>
<tr>
<td>TIAs</td>
<td>7/784 (0.9%)</td>
<td>0.60</td>
<td>6/106 (5.7%)</td>
<td>4.18</td>
</tr>
</tbody>
</table>

TIA=Transient ischemic attack
* All strokes include hemorrhagic and ischemic strokes
405 patients with Sapien-XT or Sapien 3 valve undergoing MDCT

Echocardiograms performed 1-3 months and 12 months post-TAVR

THV thrombosis noted in 28/405 (7%) of patients

Risk of THV thrombosis was lower in patients on warfarin, compared to those not on warfarin

1.8% vs. 10.7%

RR 6.09, 95% CI 1.86-19.84
## Impact of subclinical leaflet thrombosis on valve hemodynamics and clinical outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Incidence</th>
<th>Valve hemodynamics</th>
<th>Clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pache et al. EHJ 2015</td>
<td>156</td>
<td>10.3%</td>
<td>Small, but significant increase in gradients (11.6±3.4 vs. 14.9±5.3 mmHg, P=0.026)</td>
<td>No strokes/TIAs</td>
</tr>
<tr>
<td>Hansson et al. Clin Cardiology 2016</td>
<td>405</td>
<td>7%</td>
<td>Small, but significant increase in gradients (8±3 vs 10±7, p=0.003)</td>
<td>Increased, but <strong>not statistically significant</strong>, stroke rates (3% vs 12%, p=0.15)</td>
</tr>
<tr>
<td>Makkar et al. NEJM 2015</td>
<td>187</td>
<td>13% in registries, 40% in Portico IDE</td>
<td>NA</td>
<td>Stroke/TIAs: Portico IDE (0% vs 9%, p=0.14) Registries (0.8% vs 17.6%, p=0.007)</td>
</tr>
<tr>
<td>Chakravarty et a. Lancet 2017</td>
<td>931</td>
<td>12%</td>
<td>Small, but significant increase in gradients (10.4±6.3 vs 13.8±10, p=0.0004)</td>
<td>Increased rates of TIAs (0.6 vs 4.18 TIAs per 100 person-years, p=0.0005)</td>
</tr>
</tbody>
</table>
4D-CT in 75 transcatheter and 30 surgical valves in SAVORY
84 patients undergoing 2 consecutive 4D-CTs, without change in pharmacotherapy between the 2 scans, included in the analysis
HALT in 32 patients (38%) and HAM in 17 patients (20%)

<table>
<thead>
<tr>
<th>HALT/HAM at first CT</th>
<th>HALT/HAM at second CT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HALT−/HAM−</td>
<td>53</td>
<td>64</td>
</tr>
<tr>
<td>HALT+/HAM−</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>HALT+/HAM+</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>85</td>
</tr>
</tbody>
</table>

HALT and HAM were dynamic, showing progression in 13 (15.5%) and regression in 9 (10.7%) of patients
4D-CT in 75 transcatheter and 30 surgical valves in SAVORY

84 patients undergoing 2 consecutive 4D-CTs, without change in pharmacotherapy between the 2 scans, included in the analysis

HALT in 32 patients (38%) and HAM in 17 patients (20%)

The only multivariate predictor of progression was lack of anticoagulation between the 2 scans

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with progression (mean ± SD or %)</th>
<th>Patients without progression (mean ± SD or %)</th>
<th>Univariable model</th>
<th>Multivariable model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 13)</td>
<td>(n = 71)</td>
<td>Odds ratio (95% CI)</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>77.8 ± 7.2</td>
<td>78.6 ± 8.1</td>
<td>0.99 (0.92, 1.06)</td>
<td>1.01 (0.92, 1.11)</td>
</tr>
<tr>
<td>Female gender</td>
<td>76.9%</td>
<td>50.7%</td>
<td>3.24 (0.82, 12.77)</td>
<td>3.09 (0.69, 13.86)</td>
</tr>
<tr>
<td>First CT: mean interval after</td>
<td>176 ± 115</td>
<td>133 ± 158</td>
<td>4.83 (1.22, 19.07)</td>
<td>2.20 (0.51, 9.57)</td>
</tr>
<tr>
<td>implantation (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First CT: &gt;3 months after valve</td>
<td>76.9%</td>
<td>40.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>implantation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second CT: mean interval after first</td>
<td>147 ± 45.9</td>
<td>160 ± 45.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>scan (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second CT: &gt;5 months after first CT</td>
<td>38.5%</td>
<td>53.5%</td>
<td>0.54 (0.16, 1.88)</td>
<td>0.41 (0.14, 1.68)</td>
</tr>
<tr>
<td>Medication: in (N)OAC group</td>
<td>0%</td>
<td>33.8%</td>
<td>0.072 (0.004, 1.33)</td>
<td>0.014 (0.0003, 0.76)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7.7%</td>
<td>32.4%</td>
<td>0.17 (0.021, 1.42)</td>
<td>6.77 (0.34, 135.7)</td>
</tr>
</tbody>
</table>
• 47 patients undergoing CT after SAVR with sutureless Perceval valve
• Timing of CT after SAVR: Median 491 days (range 36-1247 days)

HALT found in 18 (38%) of patients
Reduced leaflet motion found in 13 (28%) patients

Dalen M. et al. JAHA 2017
51 patients with leaflet thickening (29 patients treated with anticoagulation and 22 patients treated with DAPT)

Repeat CT obtained in 22 patients on AC and 16 patients on DAPT

Leaflet thickening progressed in 11 of 16 patients undergoing repeat CT

Leaflet thickening regressed in all 22 patients undergoing repeat CT

Single center registry of 642 patients undergoing TAVR

- 305 CoreValve, 281 Sapien and 56 Lotus
- Oral anticoagulation in 261 patients, DAPT in 377 patients
- 0% valve thrombosis in patients on anticoagulation, 4.5% NO anticoagulation

Jose et al. JACC: Cardiovascular Interventions 2017
Very Late Thrombosis of a Transcatheter Aortic Valve-in-Valve

Valve thrombosis 4 years post-TAVR
Mayo Clinic experience

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
Which valve is less likely to be durable after 5 years?
Facts..

- Asymptomatic Valve leaflet thrombosis leading to reduced motion occurs not infrequently (15%)

- Subclinical leaflet thrombosis is likely associated with increased neurologic events

- Subclinical leaflet thrombosis may lead to early hemodynamic degeneration in some patients

- Clinically relevant valve thrombosis may occur about 5% of times in patients not on anticoagulation

- Anticoagulation, not DAPT, reduces valve thrombosis
Clinical implications

• The imaging findings in our and other analyses question the current standard of care (dual antiplatelet therapy post-TAVR); thus DAPT can be considered dispensable in the appropriate clinical setting. These findings raise the issue if anticoagulation is more appropriate in certain patients.

• These data call for clinical trials of routine CT imaging and anticoagulation as TAVR moves into lower risk patients and for the first time provide evidence on the efficacy of NOACs on bioprosthetic valve thrombosis.

• In the appropriate clinical setting such as TIAs, stroke, new onset heart failure; or even small increase in gradients post-procedure should lead to vigilance and CT imaging.

• The reduced leaflet motion observed on CT secondary to leaflet thrombosis and increase in gradients may provide insights into one of the preventable mechanisms of structural valve deterioration.
Fact..

- Anticoagulation will reduce subclinical and clinical valve thrombosis

Hypothesis..

- *Routine* Anticoagulation in *all* will improve clinical outcomes since it comes with a risk of bleeding
Not looking for subclinical leaflet thrombosis with CT imaging will not solve the problem of subclinical leaflet thrombosis.

To solve these issues we must look at them in 4D!
Despite excellent clinical outcomes of newer generation valves, these findings can help further optimize adjunctive pharmacotherapy which may result in further improvements.

Lower 3-year death/stroke rates with CoreValve, compared with surgery

<table>
<thead>
<tr>
<th>Months Post-Procedure</th>
<th>All-Cause Mortality or Stroke (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18.2</td>
</tr>
<tr>
<td>12</td>
<td>26.4</td>
</tr>
<tr>
<td>24</td>
<td>37.9</td>
</tr>
<tr>
<td>36</td>
<td>46.7</td>
</tr>
</tbody>
</table>

Log Rank p = 0.006

Deeb M. et al. JACC 2016

Similar 5-year death rates with Edwards-SAPIEN, compared with surgery

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>TAVR group</th>
<th>SAVR group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>348</td>
<td>351</td>
</tr>
<tr>
<td>12</td>
<td>262</td>
<td>236</td>
</tr>
<tr>
<td>24</td>
<td>228</td>
<td>210</td>
</tr>
<tr>
<td>36</td>
<td>191</td>
<td>174</td>
</tr>
<tr>
<td>48</td>
<td>154</td>
<td>131</td>
</tr>
<tr>
<td>60</td>
<td>61</td>
<td>64</td>
</tr>
</tbody>
</table>

HR 1.04, 95% CI 0.86-1.24; p=0.76