Should We Reconsider using Anticoagulation for Biological Tissue Valves
Disclosures

- No Disclosures
Watching grass grow

- Complete with audio
- 1 hour 8 minutes
- 9884 views
Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves


ABSTRACT

BACKGROUND
A finding of reduced aortic-valve leaflet motion was noted on computed tomography (CT) in a patient who had a stroke after transcatheter aortic-valve replacement (TAVR) during an ongoing clinical trial. This finding raised a concern about possible subclinical leaflet thrombosis and prompted further investigation.

METHODS
We analyzed data obtained from 55 patients in a clinical trial of TAVR and from two single-center registries that included 132 patients who were undergoing either TAVR or surgical aortic-valve bioprosthesis implantation. We obtained four-dimensional, volume-rendered CT scans along with data on anticoagulation and clinical outcomes (including strokes and transient ischemic attacks [TIAs]).

RESULTS
Reduced leaflet motion was noted on CT in 22 of 55 patients (40%) in the clinical trial and in 17 of 132 patients (13%) in the two registries. Reduced leaflet motion was detected among patients with multiple bioprosthesis types, including transcatheter and surgical bioprostheses. Therapeutic anticoagulation with warfarin, as compared with dual antiplatelet therapy, was associated with a decreased incidence of reduced leaflet motion (0% and 55%, respectively, P=0.01 in the clinical trial; and 0% and 29%, respectively, P=0.04 in the pooled registries). In patients who were reevaluated with follow-up CT, restoration of leaflet motion was noted in all 11 patients who were receiving anticoagulation and in 1 of 10 patients who were not receiving anticoagulation (P=0.001). There was no significant difference in the incidence of stroke or TIA between patients with reduced leaflet motion and those with normal leaflet motion in the clinical trial (2 of 22 patients and 0 of 33 patients, respectively; P=0.16), although in the pooled registries, a significant difference was detected (3 of 17 patients and 1 of 115 patients, respectively; P=0.007).

CONCLUSIONS
Reduced aortic-valve leaflet motion was shown in patients with bioprosthetic aortic valves. The condition resolved with therapeutic anticoagulation. The effect of this finding on clinical outcomes including stroke needs further investigation.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Makkar at the Department of Interventional Cardiology, Cedars–Sinai Heart Institute, 8700 Beverly Blvd., Los Angeles, CA 90048, or at makkarr@csih.org.

This article was published on October 5, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1509233
Copyright © 2015 Massachusetts Medical Society.
Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

- Originated from the St. Jude PORTICO IDE trial of a new transcatheter aortic valve (TAVR)
  - PORTICO vs. commercially available valve (Sapien XT or CoreValve)
- All pts underwent 4D volume-rendering CT scans at 30 days
  - Protocol to evaluate the stent frame
Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

- One of the pts had a TIA which lead to closer evaluation of the CT of the chest
  - Showed reduced single leaflet motion suggesting subclinical leaflet thrombosis
  - Lead to further patient CT and ECHO review and found not to be an isolated event
- Prompted the development of two physician initiated registries to evaluate bioprosthetic leaflet function after TAVR or SAVR
  - RESOLVE registry
  - SAVORY registry
Clinical Questions

- Questions:
  - How common is reduced leaflet motion after TAVR or SAVR?
  - Does therapeutic anticoagulation reduce the risk of reduced leaflet motion?
Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

- **187 patients underwent TAVR or SAVR**
  - 55 pts from the PORTICO TAVR trial
  - 132 pts from 2 separate registries (TAVR or SAVR)
- **All registry patients underwent CT scanning**
  - TAVR at 30 days
  - SAVR at a median of 87 days
    - Range 7 to 1851
    - 32% at 30 days
    - 55% within 90 days
Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

- **Blinded analysis of all CT scans**
  - Mildly reduced (<50% reduction)
  - Moderately reduced (50-70% reduction)
  - Severely reduced (>70% reduction)
    - Anything greater than moderate = reduced leaflet motion

- **Transthoracic ECHO obtained at the time of the CT scan in all patients**
  - Selective TEE on a subgroup of PORTICO IDE and SAVORY cohorts
Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

- TIA or stroke patients formally evaluated
  - All pts from PORTICO IDE trial and both registries
  - Neuroimaging
  - Neurology evaluation

- Looked at the association of reduced leaflet motion, procedural data and timing of the neurological event

- Data also collected on anticoagulation with warfarin or antiplatelet therapy was collected
Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

- **88 patients in the TAVR PORTICO IDE trial**
  - 65 underwent CT
  - 55 had usable CT scans for analysis

- **137 patients in the registries underwent CT**
  - 132 had usable CT scans for analysis (70 RESOLVE, 62 SAVORY)
    - 105 TAVR
    - 27 SAVR
Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

- Reduced leaflet motion
  - PORTICO trial: 40%
  - Registries: 13%
    - TAVR 14%
    - SAVR 7%

- ECHO data
  - 100% concordance in assessment of leaflet motion between the two imaging methods (TEE and 4D CT)
  - No difference in gradients in those with reduced leaflet motion vs. those with normal leaflet motion
    - Discharge: 9.1 vs. 9.5 mmHg
    - 30 days: 10.5 vs. 9.0 mmHg
    - 6 months: 9.6 vs. 9.5 mmHg
Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

- **Anticoagulation effects on reduced leaflet motion**
- **PORTICO XTE**
  - Warfarin: 0% (0/16)
    - INR < 2.0
  - Subtherapeutic INR or no anticoagulation: 51% (32/61)
  - Dual antiplatelet therapy: 55% (11/20)
- **Registries**
  - Warfarin 0% (0/13)
  - Dual antiplatelet therapy 29% (10/35)
Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

- 21 patients underwent follow up CT
  - 12 of 22 PORTICO IDE
  - 9 of 17 registry patients
- Reduced leaflet motion resolved in all 11 patients started on anticoagulation
- Reduced leaflet motion persisted in 9 of 10 patients who did not start anticoagulation
Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

- **TIA/Stroke**
  - PORTICO trial 9% (2/22)
  - Registries 18% (3/17)
    - Not significant in either group
Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

**Author’s Conclusions**

- Only 5 prior findings of subclinical leaflet thrombosis in TAVR previously reported
- Difficult to draw conclusions based on the small numbers but these 3 cohorts suggest it is not an uncommon phenomenon
- Transthoracic ECHO is ineffective in evaluating subclinical leaflet thrombosis
- Therapeutic anticoagulation in 11 patients resulted in restoration of normal leaflet motion suggesting that reduced leaflet motion is due to thrombosis
- Stroke/TIA data is inconclusive and all occurred within 1 day after TAVR
- Reduced leaflet motion is easily detected by 4D CT. Anticoagulation with Coumadin prevented and treated this phenomenon. More data is necessary.
ACC/AHA 2014 Guidelines
• Risk of ischemic stroke in bioprosthetic AVR patients are highest in the first 90 days
• Anticoagulation is intended to decrease the thromboembolic risk until endothelialization of the valve occurs
• Benefit of anticoagulation must be weighed against the risk of bleeding, especially in patients with low risk for thromboembolism
  ▪ NSR, normal LV function, no history to thromboembolism, no history of hypercoaguable state
ACC/AHA 2014 Guidelines

- **Risk of clinical thromboembolism is 0.7% per year in patients with biological valves in NSR without anticoagulation**
  - Aortic valve: 1.9% per patient-year
  - Mitral valve: 2.4% per patient-year

- **AVR: No difference in aspirin, other antiplatelet agents and full anticoagulation**
  - Prospective study of biological AVR patients in NSR and no other indication for anticoagulation
  - Incidence of thromboembolic events, bleeding, and death was equal
  - No studies for MV repair or replacement

- **Level of Evidence: B**
Small randomized controlled trials have not established benefit for anticoagulation after implantation of a bioprosthetic aortic valve.

Observational registry of 4,075 patients:
- Estimated rate of stroke per 100 person-years:
  - 7.0 not treated with anticoagulation
  - 2.69 treated with anticoagulation
- Estimated cardiovascular rate of death per 100 person-years at 6 months:
  - 6.5 not treated with anticoagulation
  - 2.08 treated with anticoagulation

Anticoagulation for 3-6 months is reasonable following bioprosthetic AVR.

Level of Evidence: B
ACC/AHA 2014 Guidelines

**TAVR**

- Dual antiplatelet therapy for 6 months (Plavix and ASA), followed by ASA alone
- Recommendations based on the research protocol published studies and a single RCT, single-center study of 79 patients
  - No difference in major adverse cardiac or cerebrovascular events (death, MI, stroke, life-threatening bleeding) comparing DAP therapy vs. ASA alone
    - 30 days: 13% versus 15%
    - 6 months: 18% versus 15%
- No studies looking at the use of full anticoagulation
- **Level of Evidence: C**
European Society of Cardiology (ECC) and European Association for CT Surgery (EACTS) Recommendations

**Levels of Evidence**

<table>
<thead>
<tr>
<th>Level of evidence A</th>
<th>Data derived from multiple randomized clinical trials or meta-analyses.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence B</td>
<td>Data derived from a single randomized clinical trial or large non-randomized studies.</td>
</tr>
<tr>
<td>Level of evidence C</td>
<td>Consensus of opinion of the experts and/or small studies, retrospective studies, registries.</td>
</tr>
</tbody>
</table>

**Classes of Recommendations**

<table>
<thead>
<tr>
<th>Classes of recommendations</th>
<th>Definition</th>
<th>Suggested wording to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.</td>
<td>Is recommended/is indicated</td>
</tr>
<tr>
<td>Class II</td>
<td>Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.</td>
<td>Should be considered</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Weight of evidence/opinion is in favour of usefulness/efficacy.</td>
<td>Should be considered</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence/opinion.</td>
<td>May be considered</td>
</tr>
<tr>
<td>Class III</td>
<td>Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.</td>
<td>Is not recommended</td>
</tr>
</tbody>
</table>
European Society of Cardiology (ECC) and European Association for CT Surgery (EACTS) Recommendations

- **Low-dose aspirin should be considered for the first 3 months after implantation of an aortic bioprosthesis**
  - Class IIa recommendation
  - Level of Evidence: C

- **Oral anticoagulation may be considered for the first 3 months after implantation of an aortic bioprosthesis**
  - Class IIb recommendation
  - Level of Evidence: C
Why not anticoagulate all biological tissue valve patients?

  - Northwestern University
  - Warfarin-associated Intracerebral Hemorrhage (WAICH) is increasing in Prevalence in the United States
    - Nationwide Inpatient Sample Database 2005-2008
    - Identified all ICH patients and those specifically on warfarin
    - Univariate and multivariate analysis
Why not anticoagulate all biological tissue valve patients?

- 52,993 pts identified
  - WAICH increased each year (5.8% → 7.3%, P < 0.001)
  - In hospital mortality remained unchanged for WAICH patients (42.1% → 40.0%, P = 0.346)
    - Decreased for non-WAICH patients (29.0% → 25.4%, P < 0.001)
    - Warfarin remained an independent predictor for mortality

- WAICH is increasing in prevalence and associated with a 35% higher mortality than non-WAICH
  - Lead to development of rapid reversal protocols
Rapid Reversal Risks

- **Osaki, et al**
  - A multicenter, prospective, observational study of warfarin-associated intracerebral hemorrhage: The SAMURAI-WAICH study
    - WAICH patients have a higher risk of ongoing bleeding, disability and death, urgent reversal is not employed
    - Thromboembolism may occur with reversal or holding of anticoagulation
    - Sought to evaluate the current status of hemostatic treatments and clinical outcomes in WAICH patients
Rapid Reversal Risks

- Looked at WAICH patients admitted within 3 days of symptoms since onset enrolled in 10 stroke centers
  - Thromboembolic and hemorrhagic complications were followed for 1 year
- 50 WAICH patients identified
  - Warfarin stopped at admission
  - PT/INR normalized in 43 patients (86%)
  - At 1-year follow up (n=47), 11 thromboembolic (23.4%) and 6 (12.8%) hemorrhagic complications were documented
  - Thromboembolic complications were independently associated with unfavorable outcomes
ACC and STS Response
David R Holmes and Michael J Mack

- Study “sets the stage for a robust, multifaceted debate in which clear scientific answers are still lacking”

- Study is very small and underpowered for definitive conclusions, therefore need more data to answer a list of major questions raised by this preliminary study
**Table 1. Questions Raised by the Study by Makkar et al.**

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the true incidence of reduced aortic-valve leaflet motion? Is it device-specific, is it specific to transcatheter aortic-valve replacement (TAVR), or does it occur as frequently with surgical aortic-valve replacement?</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>
</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>
</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>
</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>
</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>
</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>
</tr>
</tbody>
</table>
FDA Response

- **Acknowledge the findings by Makkar et al. including:**
  - Reduced leaflet motion can be reliably detected by advanced CT imaging processing or TEE
  - Reduced leaflet motion and hemodynamic performance were not detected by transthoracic ECHO
    - We have traditionally relied upon for assessing the structural and hemodynamic performance
  - No temporally related changes in patients’ clinical status was observed, consistent with prior low incidence reports of reduced leaflet motion for bioprosthetic aortic valves
FDA Response

- Further studies are needed to determine the true incidence and predictors of reduced leaflet motion and potential risks posed to patients before changing imaging practices and anticoagulation regimens for bioprosthetic aortic valves.

- Benefit-risk profile and durability data gathered over 30 years show reduced symptoms, improved quality of life and that these valves save/prolong lives of appropriately selected patients.
FDA Response

- TAVR has revolutionized the care of patients with severe AS whose risk is deemed too high for SAVR. Newer generation devices have reduced PVL, major vascular complications and neurologic events.

- FDA continues to monitor the reduced leaflet motion reports through reviews of medical device reports, clinical studies and scientific publications, as well as the STS/ACC TAVR Registry
FDA Response

- After careful review of all available data, the FDA believes the benefits continue to outweigh the risks.
  - Findings by advanced imaging CT or TEE is an early signal of unknown significance
  - Need to continue to investigate changes in hemodynamic performance of a valve, occurrence of late stroke/TIAs, myocardial infarction or unexplained heart failure or death with consideration of advanced CT imaging or TEE to guide potential change in treatment options.
Conclusions

- Bioprosthetic aortic valves play a critical role in improving the health and quality of life of many patients with severe aortic valve disease.
- Subclinical leaflet motion abnormalities only reliably detected by advanced 4D CT imaging
  - Transthoracic echo was unreliable
- No identified increased risk to patients were associated with these findings
- Findings are of unknown significance at this time and should continue to follow the outlined ACC/AHA guidelines
Thank You