Sub-Clinical Leaflet Thrombosis Post-TAVR

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Disclosures
PVT-Prosthetic Valve Thrombosis

• Prosthetic Valve Thrombosis is reported as rare complication of biological surgical prosthesis

• Transcatheter Prosthetic Valve Thrombosis clinically symptomatic have been reported with all type of valves

• HALT Hypo-Attenuated Leaflet Thickening has been recently described in asymptomatic patient after TAVR, treated with anticoagulation therapy
Prosthetic Valve Thrombosis: definition

• symptoms (dyspnoea, arrhythmia, systemic embolism)
• transthoracic echocardiography:
  – transvalve peak velocity ≥4 m/s
  – Gradient ≥35 mmHg at rest or increase ≥20 mmHg during stress
• Effective orifice area < 0.8 cm²
• TEE is the gold standard for detailed assessment of prosthetic leaflet thickening and motion.
• Meta-analysis of 5837 patients with a porcine aortic valve bioprosthesis reported obstructive thrombosis in 0.03% and thrombo-embolism in 0.9% per 100 patient-years. (Puvimanasinghe JP Circulation 2001;103:1535–1541)

• Single-centre analysis of 1751 patients over 3.4 years of follow-up reported a 2.3% thrombosis rate in patients with a porcine prosthesis (Jander N et al. Int Journal of Cardiology 2015; 199: 90–95)
Early thrombosis risk in patients with biologic valves in the aortic position

Morgan L. Brown, MD, PhD, a Soon J. Park, MD, b Thoralf M. Sundt, MD, b and Hartzell V. Schaff, MD b

FIGURE 1. A, The aortic valve has been explanted, and there is extensive thrombus present in the cusps on the aortic side of the valve. B, The ventricular side of the valve was spared.

FIGURE 2. Porcine valves share a common design feature dictated by attachment of the leaflet to the stent, which is a “rail” that could promote stasis of blood in the belly of the leaflet. Pericardial valves have no rail.
The pathologic events leading to early thrombosis in SAVR starts after surgery

- Platelets are activated as blood starts flowing across the valve with immediate platelet adhesion and aggregation
- Coagulation factors are activated by the prosthetic material (suture material, Dacron sewing ring, struts, and hinge points) and sites of debrided tissue
- The shear stress damages the endocardium
- Turbulent areas on the outflow side of the prosthesis create flow stagnation,
- early thrombus formation is determined by lack of host endothelial cell in-growth and mature platelet fibrin coating on the valvular surface

Colli et al. EJCTS 2008
The highest thrombosis risk in patients with bioprosthetic valves is within 3 months of implantation (before endothelialization occurs) and varies between 0.8% and 4.0%.
Prosthetic Valve Thrombosis in TAVR


• 4266 patients undergoing TAVR in 12 centres.
• Valve thrombosis prevalence 0.61% (26/4266 pts) at 181 days (range 3–375),
• 96% (25/26) of patients were using dual antiplatelet therapy.
• Clinical factors associated with thrombosis were
  – previous stroke (19%),
  – Atrial fibrillation (19%),
  – history of malignancy (12%).
• Dyspnoea in 65%
• Mean transvalve gradient was 40+14 mmHg
• Echocardiographic leaflet thickening /thrombotic apposition in 77% Thrombotic mass in 23%.
• oral anticoagulation dissolved thrombus 23 patients
# Case series in the Literature

## TABLE 1 Case Reports of TAV Thrombosis

<table>
<thead>
<tr>
<th>Case #</th>
<th>First Author (Ref. #)</th>
<th>Age, yrs</th>
<th>Sex</th>
<th>Type of THV</th>
<th>Duration</th>
<th>Symptom</th>
<th>Examination</th>
<th>Antiplatelet Therapy After TAVR</th>
<th>Treatment</th>
<th>Outcome/Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Triggl et al. (15)</td>
<td>84</td>
<td>Female</td>
<td>Edwards Sapien, 23 mm</td>
<td>8 months</td>
<td>Dyspnea</td>
<td>Mean PG: 11 to 53 mm Hg TEE: restricted leafllet mobility</td>
<td>DAPT discontinued after 6 weeks</td>
<td>THV retrieval and SAVR</td>
<td>Thrombus with fibrin organization. Thrombophilia screen: mild protein 5 reduction, positive cold agglutinin</td>
</tr>
<tr>
<td>2</td>
<td>Kefal et al. (16)</td>
<td>78</td>
<td>Male</td>
<td>Edwards Sapien, 26 mm</td>
<td>4 months</td>
<td>NSTEMI, CHF</td>
<td>Mean PG: 15 to 72 mm Hg ICE/TEE: thrombus on leafllets</td>
<td>DAPT, clopidogrel stopped after 1 month</td>
<td>Heparin followed by warfarin</td>
<td>Mean PG decreased to 22 mm Hg Thrombophilia screen: negative</td>
</tr>
<tr>
<td>3</td>
<td>Pergolini et al. (17)</td>
<td>87</td>
<td>Male</td>
<td>Edwards Sapien XT, 29 mm</td>
<td>8 months</td>
<td>Dyspnea</td>
<td>Mean PG: 9 to 50 mm Hg TEE: restricted leafllet mobility with thrombus</td>
<td>DAPT, clopidogrel stopped at 3 months, then restarted after 4 months</td>
<td>Aspirin</td>
<td>Asymptomatic Mean PG decreased to 9 mm Hg</td>
</tr>
<tr>
<td>4</td>
<td>Greason et al. (23)</td>
<td>74</td>
<td>Female</td>
<td>Edwards Sapien, 23 mm</td>
<td>2 weeks</td>
<td>Dyspnea</td>
<td>Mean PG increased to 43 mm Hg Echo: restricted leafllet mobility with thrombus</td>
<td>DAPT</td>
<td>THV retrieval and SAVR</td>
<td>Discharged after long hospitalization. Mean PG decreased to 15 mm Hg Histology: organizing thrombosis</td>
</tr>
<tr>
<td>5</td>
<td>Cota et al. (19)</td>
<td>80</td>
<td>Male</td>
<td>Edwards SAPIEN XT, 23 mm</td>
<td>10 months</td>
<td>Dyspnea</td>
<td>Mean PG increased to 54 mm Hg TEE: suspected thrombotic fusion of two THV leafllets</td>
<td>None</td>
<td>Aspirin</td>
<td>Asymptomatic Mean PG decreased to 13 mm Hg Thrombophilia screen: negative</td>
</tr>
<tr>
<td>6</td>
<td>Cota et al. (19)</td>
<td>81</td>
<td>Male</td>
<td>Edwards Sapien XT, 23 mm, in Carpenter Edwards, 25 mm</td>
<td>4 months</td>
<td>Dyspnea</td>
<td>Mean PG increased to 51 mm Hg TEE: suspected thrombotic fusion of 2 THV leafllets</td>
<td>DAPT</td>
<td>Aspirin</td>
<td>Asymptomatic Mean PG decreased to 9 mm Hg</td>
</tr>
<tr>
<td>7</td>
<td>Cota et al. (19)</td>
<td>74</td>
<td>Female</td>
<td>Edwards Sapien XT, 26 mm</td>
<td>2 months</td>
<td>Dyspnea</td>
<td>Mean PG increased to 44 mm Hg TEE: Suspected thrombotic apposition of THV leafllets</td>
<td>None</td>
<td>Aspirin</td>
<td>Asymptomatic Mean PG decreased to 9 mm Hg</td>
</tr>
<tr>
<td>8</td>
<td>Latib et al. (20)</td>
<td>83</td>
<td>Male</td>
<td>Edwards Sapien XT, 26 mm</td>
<td>6 months</td>
<td>Dyspnea</td>
<td>Mean PG increased to 68 mm Hg TEE: restricted leafllet mobility without thrombus</td>
<td>DAPT</td>
<td>Aspirin</td>
<td>Asymptomatic Mean PG decreased to 11 mm Hg</td>
</tr>
<tr>
<td>9</td>
<td>Latib et al. (20)</td>
<td>81</td>
<td>Male</td>
<td>Edwards Sapien XT</td>
<td>15 months</td>
<td>Dyspnea</td>
<td>Mean PG increased to 65 mm Hg TEE: restricted leafllet mobility without thrombus</td>
<td>DAPT, clopidogrel stopped after 3 months</td>
<td>None</td>
<td>Symptomatic improvement Mean PG decreased to 19 mm Hg</td>
</tr>
<tr>
<td>10</td>
<td>Latib et al. (20)</td>
<td>83</td>
<td>Male</td>
<td>Edwards Sapien XT, 26 mm</td>
<td>24 months</td>
<td>Dyspnea</td>
<td>Mean PG increased to 37 mm Hg</td>
<td>None</td>
<td>Aspirin</td>
<td>Symptomatic improvement Mean PG decreased to 13 mm Hg</td>
</tr>
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<tr>
<td>11</td>
<td>Al-Rashid et al. (22)</td>
<td>72</td>
<td>Male</td>
<td>Edwards Sapien</td>
<td>6 months</td>
<td>Dyspnea</td>
<td>NYHA II to III</td>
<td>Discontinuing DAPT after 4 months</td>
<td>DAPT</td>
<td>Symptomatic improvement</td>
</tr>
<tr>
<td>12</td>
<td>Tay et al. (18)</td>
<td>66</td>
<td>Male</td>
<td>Edwards Sapien, 23 mm</td>
<td>3 days</td>
<td>Cardiac arrest</td>
<td>TEE: thrombus on the THV at post-implantation</td>
<td>DAPT</td>
<td>Heparin continued post-TAVR</td>
<td>Deceased</td>
</tr>
<tr>
<td>13</td>
<td>Tay et al. (18)</td>
<td>77</td>
<td>Female</td>
<td>Edwards Sapien, 26 mm, within MVR</td>
<td>1 month</td>
<td>Dyspnea</td>
<td>TEE: thrombus on edge of THV</td>
<td>DAPT</td>
<td>Anticoagulation</td>
<td>Discharged home</td>
</tr>
<tr>
<td>14</td>
<td>LanceBotti et al. (24)</td>
<td>86</td>
<td>Male</td>
<td>Medtronic CoreValve, 26 mm</td>
<td>12 months</td>
<td>Dyspnea</td>
<td>NYHA I to III</td>
<td>DAPT, clopidogrel stopped at 3 months</td>
<td>THV retrieval and SAVR</td>
<td>Discharged after long hospitalization</td>
</tr>
<tr>
<td>15</td>
<td>Pache et al. (21)</td>
<td>86</td>
<td>Male</td>
<td>Edwards Sapien XT, 29 mm</td>
<td>7 days</td>
<td>NA</td>
<td>CTA: Restricted leaflet mobility with thrombus (incidental)</td>
<td>DAPT</td>
<td>Anticoagulation (warfarin)</td>
<td>Complete disappearance of cusp thrombus</td>
</tr>
<tr>
<td>16</td>
<td>Leetmaa et al. (29)</td>
<td>NA</td>
<td>NA</td>
<td>Edwards Sapien XT, 29 mm</td>
<td>1 month</td>
<td>Bleeding problems</td>
<td>NA</td>
<td>DAPT, started monotherapy after 1 month due to bleeding problems</td>
<td>NA</td>
<td>Deceased on day 106</td>
</tr>
<tr>
<td>17</td>
<td>Leetmaa et al. (29)</td>
<td>NA</td>
<td>NA</td>
<td>Edwards Sapien XT, 29 mm</td>
<td>1 month</td>
<td>Bleeding problems</td>
<td>NA</td>
<td>DAPT, started monotherapy after 1 month due to bleeding problems</td>
<td>NA</td>
<td>Deceased on day 137</td>
</tr>
<tr>
<td>18</td>
<td>Orbach et al. (30)</td>
<td>81</td>
<td>Female</td>
<td>Edwards Sapien, 26 mm</td>
<td>21 months</td>
<td>Heart failure</td>
<td>Mean PG increased to 53 mm Hg</td>
<td>Aspirin</td>
<td>Enoxaparin and warfarin</td>
<td>Symptomatic improvement</td>
</tr>
</tbody>
</table>
Hypo-Attenuated Leaflet Thickening - HALT

“... Evidence of HALT was defined as hypo-attenuated thickening with or without rigidity of one or more leaflets identifiable in at least two different MPR projections and two different reconstruction time intervals...”
Cusp thrombosis after transcatheter aortic valve replacement detected by computed tomography and echocardiography

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An 86-year-old male underwent transcatheter aortic valve replacement (TAVR) for severe aortic stenosis with an Edwards Sapien 29 mm XT valve and percutaneous coronary intervention simultaneously. Periprocedural transoesophageal echocardiography (TOE) showed good positioning and expansion of the prosthesis with only minor paravalvular insufficiency. Routine post-TAVR computed tomography angiography (CTA) performed 7 days after implantation revealed a crescent shaped, hypoattenuating structure adherent to the prosthesis cusp located in the former native left-coronary cusp position (Panels A—C). Rigidity of the cusp was displayed by 4D-cine CT imaging and confirmed by TOE (Panels D and E; Supplementary material online, Videos S1 and S2), suggestive of cusp thrombosis. Despite restricted cusp movement, the mean pressure gradient (9 mmHg) was normal. Post-interventional anticoagulation therapy had consisted of daily aspirin and clopidogrel, while heparin had been paused from Day 4 to 7 post-intervention due to perianal bleeding complications. After restoring coumadin therapy, the patient had received for 3 years due to a history of pulmonary embolism and which had been paused prior to TAVR, 10-week follow-up CTA (Panel F) and TOE showed complete disappearance of the initial finding, underlying the diagnosis of cusp thrombosis. As to our knowledge, this is the first report of a cusp thrombosis of a transcatheter aortic valve detected by computed tomography.
• 156 received CT scan at mean 5 days after TAVR with balloon expandable valve.
• 16 patients (10.3%) showed HALT associated with leaflet rigidity in 50%.
• Clinically asymptomatic
Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves


European Heart Journal
doi:10.1093/eurheartj/ehv526
1. Post-TAVI CTA revealed early HALT in 10% of our patients treated with an SAPIEN 3 THV.

2. HALT was detected in pts under single antiplatelet therapy (13%) and dual-antiplatelet therapy (9%), without significance (P = 0.42).

3. Early HALT was clinically inapparent in all patients.

4. Early HALT was reversible under full anticoagulation with a vitamin K antagonist.
• 55 pts IDE TAVR clinical trial + 132 patients of two single center registries (TAVR or SAVR)
• 4D, volume-rendered CT scans 32 days after TAVR
• Reduced leaflet motion and HALT in 22/55 patients (40%) in the clinical trial and in 17/132 patients (13%) in the registries.
• Mean transvalve gradients in the clinical trial were normal on transthoracic echocardiography.
• In the two registries, reduced leaflet motion was noted in both TAVR (15/105, 14%) and SAVR (2/27, 7%) recipients.
• Higher incidence of CVA in patients with ↓leaflet motion (18% vs. 1%, P 0.007)
• Therapeutic anticoagulation restored normal leaflet motion
Possible Sul in Biof


Diastole

Systole

CoreValve

Edwards XT

Portico

CE Perimount
• **140 pts**, 1–3 months after TAVR using CT – TTE
• HALT was reported in 5 (4%)
• only 1 was symptomatic for heart failure
• Transoesophageal echocardiography revealed restricted cusp motion and/or leaflet thickening in all five patients,
• HALT had resolved completely after 3 months anticoagulation therapy.
• No embolic events were reported.
HALT

After 3 months anticoagulation
Thrombus Formation Following Transcatheter Aortic Valve Replacement

Eduardo De Marchena, MD,* Julian Mesa, MD,* Sydney Pomenti, BS,* Christian Marin y Kall, MD,* Ximena Marincic, BS,* Kazuyuki Yahagi, MD,† Elena Ladich, MD,‡ Robert Kutys, MS,§ Yaar Aga, BS,* Michael Ragosta, MD,‡ Atul Chawla, MD,§ Michael E. Ring, MD,‡ Renu Virmani, MD
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A

Free margin end

Basal end

D

Aortic surface

RCC

Ventricular surface

1000 µm

E

Aortic surface

NCC

Ventricular surface

1000 µm

F

Aortic surface

Th

RCC

Ventricular surface

1000 µm

C

RCC NCC LCC

Aortic view

RCC NCC LCC

Aortic view

LCC

Ventricular surface

1000 µm
“All leaflets from these 3 autopsy cases:
• absence of microinjury or leaflet degeneration
• Aortic surface of the valve leaflets with thrombosis revealed macrophage presence underneath the thrombus.
• Presence of many inflammatory cells within the thrombus, ...it is likely that the valve leaflet was not the culprit.
• There was no indication of excessive lymphocytic infiltrate that would suggest an autoimmune rejection
• What is the clinical relevance of HALT?
• Is there a difference in frequency of HALT or reduced leaflet motion in SAVR vs. TAVR, or among the different transcatheter valves?
• Are rates of TIA/stroke increased in these three recent studies?
• What are the therapeutic consequences of HALT?
• Is routine CT after SAVR/TAVR justified?
What is the clinical relevance of HALT?

• HALT is asymptomatic but could be a very early stage of Prosthetic Valve Thrombosis

• Early detection of HALT can be treated clopidogrel and vit K antagonist therapy prevent evolution toward symptomatic prosthetic valve thrombosis
Is there a difference in frequency of HALT or reduced leaflet motion in SAVR vs. TAVR, or among the different transcatheter valves?

•HALT has been reported in several type of transcatheter aortic valves and in surgical biological valve

•Because the numbers are very small, it is very difficult to say whether a transcatheter valve can develop this phenomenon more often than another
Are rates of TIA/stroke increased in these three recent studies?

• The available data do not demonstrate a direct relationship between CT findings and an increased rate of TIA/stroke,

• Only one series reported CVA when there was a marked leaflet hypomobility.
Is routine CT after SAVR/TAVR justified?

• For clinical use cannot be justified since CT is associated with radiation exposure and use of contrast agents

• The optimal timing of post-procedural imaging is unclear

• CT scan for HALT detection can be performed in selected patients with high suspicion of thrombus stratification
What are the therapeutic consequences of HALT?

• Anticoagulation with vit K antagonist is effective with complete resolution of thrombus stratification

• The routine use of vit K ant. Could increase hemorrhagic risk in the TAVR population particularly in the older frail cohort

• the ACC recommendation should be followed, using anticoagulation in selected patient population
Thank You