Antithrombotic Rx in the Setting of TAVI

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COI

- Research grants to Mt Sinai:
  - Bayer
  - Daichi Sankyo
  - Claret Medical
  - The Medicines Company

- Consultant (spouse) Janssen, minor level, Claret Medical, minor level

- Stock options (<1%), Claret medical (spouse)
Timing of Cerebrovascular Events after TAVI

Stortecky et al – Circulation 2012; 126:2921-4
Predictors of 30-Day CVEs after TAVI

**UNIVARIATE**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning curve (second half)</td>
<td>0.62 (0.36-1.09)</td>
<td>0.098</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.70 (0.97-2.97)</td>
<td>0.061</td>
</tr>
<tr>
<td>Balloon postdilation</td>
<td>1.95 (1.06-3.58)</td>
<td>0.020</td>
</tr>
<tr>
<td>New-onset atrial fibrillation</td>
<td>2.21 (1.13-4.33)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

**MULTIVARIATE**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning curve (second half)</td>
<td>0.62 (0.35-1.10)</td>
<td>0.105</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.76 (0.97-3.10)</td>
<td>0.055</td>
</tr>
<tr>
<td>Balloon postdilation</td>
<td>1.94 (1.05-3.60)</td>
<td>0.034</td>
</tr>
<tr>
<td>New-onset atrial fibrillation</td>
<td>2.27 (1.15-4.48)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

1061 pts (2/3 Edwards valve; 1/3 CoreValve)

Nombela-Franco et al. Circulation 2012;126:3041-3053
Predictors of Late CVEs (>30-day) after TAVI

**UNIVARIATE**
- Chronic atrial fibrillation
- Peripheral vascular disease
- Cerebrovascular disease
- Anticoagulation treatment at hospital discharge

**MULTIVARIATE**
- Chronic atrial fibrillation
- Peripheral vascular disease
- Cerebrovascular disease
- Anticoagulation treatment at hospital discharge

1061 pts (2/3 Edwards valve; 1/3 CoreValve)

Hazard ratio (95% Confidence Interval)

- Chronic atrial fibrillation: 2.83 (1.45–5.50) p=0.002
- Peripheral vascular disease: 2.19 (1.12–4.27) p=0.022
- Cerebrovascular disease: 2.35 (1.17–4.73) p=0.016
- Anticoagulation treatment at hospital discharge: 2.57 (1.32–5.00) p=0.005
- Chronic atrial fibrillation: 2.84 (1.46–5.53) p=0.002
- Peripheral vascular disease: 2.02 (1.02–3.97) p=0.043
- Cerebrovascular disease: 2.04 (1.01–4.15) p=0.047
- Anticoagulation treatment at hospital discharge: 1.73 (0.78–3.81) p=0.172

Nombela-Franco et al. Circulation 2012;126:3041-3053
# TAVI Experience from Published Registries

## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>82 (50-98)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>44 (24-57)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>28 (23-35)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60 (36-85)</td>
</tr>
<tr>
<td>Prior coronary disease (%)</td>
<td>54 (41-69)</td>
</tr>
<tr>
<td>Prior stroke (%)</td>
<td>9 (7-11)</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>19 (7-35)</td>
</tr>
<tr>
<td>Porcelain aorta (%)</td>
<td>30 (11-50)</td>
</tr>
<tr>
<td>Frailty (%)</td>
<td>11 (4-19)</td>
</tr>
<tr>
<td>Frailty (%)</td>
<td>12 (7-18)</td>
</tr>
<tr>
<td>Frailty (%)</td>
<td>21 (17-25)</td>
</tr>
</tbody>
</table>

Mean CHADS2 score ~ 3 (8.6 per 100 patient/years)
Expression of Tissue Factor in Aortic Valve Leaflets of Varying Status

normal  sclerotic  stenotic

Bioprosthetic Valve Thrombosis Versus Structural Failure: Clinical and Echo Predictors

Multivariate predictors of valve thrombosis:
- Paroxysmal AF (OR: 5.19)
- Persistent AF with subtherapeutic INR (OR: 3.44)
- On VKA with subtherapeutic INR (OR: 7.37)
- 50% increase in gradient within 5 y (OR: 12.7)
- Increased cusp thickness (OR: 12.2)
- Abnormal cusp mobility (OR: 6.94)

J Am Coll Cardiol 2015;66:2285–94
(A) Transesophageal echocardiogram of a case of transcatheter heart valve thrombosis demonstrating the valve stent (long white arrow), thrombus on the stent (short white arrow), and thickened valve leaflets. (B) Post-mortem image of thrombi on the outflow of the stent frame (black arrow).
Reduced leaflet motion was observed in all valve types including surgical bioprostheses.
Volume rendered CT images of bioprosthetic valves
Clinical outcomes in patients with reduced leaflet motion

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.

### Table 3. Clinical Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Normal Leaflet Motion</th>
<th>Reduced Leaflet Motion</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PORTICO IDE study</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 or transient ischemic attack‡</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>Transient ischemic attack</td>
<td>0</td>
<td>0</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Pooled registries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients in group</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 or transient ischemic attack‡</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>Transient ischemic attack</td>
<td>0</td>
<td>3</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*P values calculated using Fisher's exact test.
RESOLVE & SAVORY Registries

752 transcatheter valves: Median time from TAVR to CT 58 ds (IQR 32–236 ds)
138 surgical valves: Median time from SAVR to CT 162 ds (IQR 79–417 ds)
Time from TAVR to CT vs. SAVR to CT: p<0.0001

- In a heterogeneous (yet sizeable) cohort of bioprosthetic aortic valves, the reduced leaflet motion occurred 12%
- Patients undergoing SAVR, compared with TAVR, had lower incidence of reduced leaflet motion (3.6% vs. 12%; p<0.04). However, patients undergoing SAVR were different than TAVR reflecting contemporary practice with lower age and fewer comorbidities.
- Anticoagulation with both warfarin and NOACs and not DAPT which is the widespread standard of care were effective in prevention and treatment of reduced leaflet motion.
- Majority of cases of SLT diagnosed by 4D CT are silent hemodynamically and “missed” by TTE

Makkar et al; Lancet 2017
Anticoagulation and reduced leaflet motion
Anticoagulation vs. antiplatelet therapy

Anticoagulation vs. DAPT: $p<0.0001$
Anticoagulation vs. monoantiplatelet therapy: $p<0.0001$

Makkar et al; Lancet 2017
# Multivariate predictors of reduced leaflet motion

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04 (1.01-1.07)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.98 (0.97-1.00)</td>
<td>0.02</td>
</tr>
<tr>
<td>Surgical vs transcatheter valve</td>
<td>0.33 (0.11-0.96)</td>
<td>0.04</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>0.24 (0.10-0.58)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time to CT</td>
<td>1.00 (0.98-1.02)</td>
<td>0.67</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.62 (0.31-1.23)</td>
<td>0.17</td>
</tr>
<tr>
<td>BMI</td>
<td>0.97 (0.93-1.02)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

All variables with a p-value < 0.20 in univariate model were entered into the multivariate analysis. Time from AVR to CT was forced into the model; despite p-value > 0.20 in univariate analysis.
Impact of initiation of anticoagulation on reduced leaflet motion

- Resolution in 36 out of 36 patients treated with anticoagulation (NOACs, n=12; warfarin, n=24)
- Persistence/progression in 20 out of 22 patients not treated with anticoagulation

P<0.0001

Makkar et al; Lancet 2017
Impact of reduced leaflet motion on valve hemodynamics

Increased mean gradients at the time of CT in patients with reduced leaflet motion

$13.8 \pm 10.0 \text{ mmHg} \text{ vs. } 10.4 \pm 6.3 \text{ mmHg}$,

$p=0.0004$
# Impact of reduced leaflet motion on clinical outcomes

Only non-procedural events (>72 hours post-TAVR/SAVR) included

## No significant difference in strokes; but increased risk of TIAs

<table>
<thead>
<tr>
<th>Non-procedural events</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>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><strong>Strokes/TIAs</strong></td>
<td>20/784 (2.6%)</td>
<td>1.75</td>
<td>8/106 (7.6%)</td>
<td>5.71</td>
</tr>
<tr>
<td>All strokes*</td>
<td>15/784 (1.9%)</td>
<td>1.31</td>
<td>4/106 (3.8%)</td>
<td>2.75</td>
</tr>
<tr>
<td>Ischemic strokes</td>
<td>14/784 (1.8%)</td>
<td>1.22</td>
<td>4/106 (3.8%)</td>
<td>2.75</td>
</tr>
<tr>
<td>TIAs</td>
<td>7/784 (0.9%)</td>
<td>0.60</td>
<td>5/106 (4.7%)</td>
<td>3.48</td>
</tr>
</tbody>
</table>

TIA=Transient ischemic attack

* All strokes include hemorrhagic and ischemic strokes

Makkar et al; Lancet 2017
RESOLVE & SAVORY Registries

- Patients with subclinical leaflet thrombosis (SLT) had a small yet significant increase in transvalvular gradients those without SLT.
- A greater proportion of patients with SLT (15% vs. 1%) had hemodynamically significant increase in gradients (aortic valve gradients>20mmHg and increase in aortic valve gradients>10mmHg).
- While the cumulative death, MI and stroke rates were not significantly different between the 2 groups, SLT had increased rates of TIA alone.
- The imaging findings in this analysis question the current standard of care (dual antiplatelet therapy post-TAVR);
  - DAPT may be considered debatable in the appropriate clinical setting.
  - Further studies should seek if a level of anticoagulation Rx may be more appropriate in certain patients.
- Clinical trials of scheduled CTA imaging and anticoagulation as TAVR moves into lower risk patients and provide evidence on the efficacy of NOACs on bioprosthetic aortic 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.

Makkar et al; Lancet 2017
Bioprosthetic Valve Thrombosis
Time Frame & Diagnostic Approach

### Temporal Classification

<table>
<thead>
<tr>
<th>Time Frame</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUTE</td>
<td>0 to 3 days after TAVR</td>
</tr>
<tr>
<td>SUBACUTE</td>
<td>3 days to 3 months after TAVR</td>
</tr>
<tr>
<td>LATE</td>
<td>3 months to 1 year after TAVR</td>
</tr>
<tr>
<td>VERY LATE</td>
<td>&gt;1 year after TAVR</td>
</tr>
</tbody>
</table>

### Diagnostic Classification

<table>
<thead>
<tr>
<th>Definite Valve Thrombosis</th>
<th>Probable Valve Thrombosis</th>
<th>Possible Valve Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical criteria</strong></td>
<td><strong>Clinical criteria</strong></td>
<td>Clinical criteria</td>
</tr>
<tr>
<td>Regression of new-onset heart failure symptoms after initiation of anticoagulation therapy</td>
<td>Acute- or subacute-onset heart failure symptoms (i.e., progressive dyspnea, peripheral edema, pulmonary rales, jugular turgor)</td>
<td>Unexplained arterial thromboembolic event at any time after TAVR in patients without prior documented cardiogenic source without culprit epicardial or carotid atherosclerosis</td>
</tr>
<tr>
<td>Presence of reduced leaflet motion</td>
<td>Reduced leaflet motion</td>
<td></td>
</tr>
<tr>
<td>Presence of hypointense leaflet thickening</td>
<td>No hypointense leaflet thickening visible</td>
<td></td>
</tr>
<tr>
<td>Echocardiographic criteria</td>
<td>Echocardiographic criteria</td>
<td></td>
</tr>
<tr>
<td>Direct visualization of valve thrombosis</td>
<td>Increase in mean gradient &gt;10 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Regression of elevated mean gradient (&gt;10 mm Hg) after oral anticoagulation therapy</td>
<td>No thrombus visible</td>
<td></td>
</tr>
</tbody>
</table>

### Pathological criteria

- Evidence of device thrombosis at autopsy or via examination of tissue retrieved during cardiac surgery

### Diagnostic Likelihood

- High diagnostic likelihood
- Intermediate diagnostic likelihood
- Low diagnostic likelihood

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Pathological, Clinical, and Imaging Characteristics of Prosthetic Valve Thrombosis Versus Fibrotic Pannus Ingrowth

<table>
<thead>
<tr>
<th>PV Thrombosis</th>
<th>Fibrotic Pannus Ingrowth</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>Platelet aggregation and deposition, thrombin generation and clot formation</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>Shorter time from valve replacement to valve dysfunction (weeks to months)</td>
</tr>
<tr>
<td></td>
<td>Sudden onset of symptoms or subclinical</td>
</tr>
<tr>
<td></td>
<td>More commonly associated with suboptimal anticoagulation</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td>Higher total mass volume and area</td>
</tr>
<tr>
<td></td>
<td>Higher lesion density</td>
</tr>
<tr>
<td></td>
<td>More commonly located on the atrial side for mitral prostheses and on the aortic side for aortic prostheses</td>
</tr>
<tr>
<td></td>
<td>Greater leaflet motion restriction</td>
</tr>
</tbody>
</table>
Mechanisms of Prosthetic Valve Thrombosis

- Surface Factors
  - Incomplete prosthesis endothelialization
  - Leaflet damage
  - Leaflet deterioration
  - Stent fracture
  - Prosthesis malpositioning

- Relative Contribution to Prosthetic Valve Thrombosis

- Hemodynamic Factors
  - Low cardiac output
  - Prosthesis malpositioning
  - Anatomical prosthesis position
  - Prosthetic hemodynamic profile
  - Hyperviscosity

- Hemostatic Factors
  - 1o or 2o hyper-coagulable state
  - Significant tissue injury
  - Heparin-induced thrombocytopenia
  - Suboptimal anticoagulation
  - Platelet reactivity

Potential pathophysiological pathways of prosthetic valve dysfunction leading to thromboembolic events

- Prosthetic Valve Deterioration
- Prosthetic Valve Thrombosis
- Prosthetic Valve Pannus Formation
- Prosthetic Valve Endocarditis

Prosthetic Valve Dysfunction

Subclinical valve dysfunction:
- No clinical symptoms
- Increase in echo gradients
- Valve insufficiency

Clinically overt valve dysfunction:
- New-onset heart failure symptoms
- Severe increase in echo gradients
- Severe valve insufficiency

Cerebrovascular or systemic embolism

Strategies to prevent thrombo-embolic complications during TAVR

Systemic strategies
- Avoid hypotension
- Control hypertension
- Optimise electrolytes
- Optimise antithrombotic therapy - Clopidogrel loading - Anticoagulation with thrombin/Xa inhibitors - Partial reversal of heparin with protamine

Strategies by anatomical location
- Use of selective cerebral embolic protection devices [Claret Montage Device, EMBOL-XI]
- Use of deflection-based cerebral embolic protection devices [Embrella Embolic Deflector, TriGuard Cerebral Protection Device]
- Minimise catheter manipulation and scraping of the aortic arch
- Minimise catheter manipulation and scraping of the ascending aorta
- Development and use of smaller catheters and delivery systems
- Cardioversion of atrial fibrillation
- Left atrial appendage closure
- Chronic oral anticoagulation
- Avoid traumatic crossing of the aortic valve
- Optimisation of preparatory balloon aortic valvuloplasty (timing, balloon size and selection)
- Correct device sizing and implantation technique
- Selective balloon post-dilatation
- Imaging screening for left ventricular thrombus

Giustino & Dangas, Eurointervention 2015; 11 Suppl W:W26-31
Strategies to prevent thrombo-embolic complications after TAVR

# NeuroProtection During TAVR

Clinical Events Meta-Analysis of 5 Randomized Trials

---

### Death or Stroke

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Embolic protection</th>
<th>No embolic protection</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEAN-TAVI</td>
<td>4</td>
<td>50</td>
<td>5</td>
<td>Total</td>
<td>15.9% 0.80 [0.25, 2.81]</td>
</tr>
<tr>
<td>DEFLECT-III</td>
<td>3</td>
<td>46</td>
<td>4</td>
<td>Total</td>
<td>13.7% 0.64 [0.15, 2.67]</td>
</tr>
<tr>
<td>EMBOL-X</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>Total</td>
<td>8.7%   Not estimable</td>
</tr>
<tr>
<td>MISTRAL-C</td>
<td>1</td>
<td>32</td>
<td>6</td>
<td>Total</td>
<td>16.7% 0.17 [0.02, 1.36]</td>
</tr>
<tr>
<td>SENTINEL</td>
<td>16</td>
<td>234</td>
<td>12</td>
<td>Total</td>
<td>51.7% 0.63 [0.31, 1.29]</td>
</tr>
</tbody>
</table>

Total (95% CI): 378 249 100.0% 0.57 [0.33, 0.98]

Heterogeneity: Chi² 1.83, df 3 (P = 0.64), I² 6%
Test for overall effect: Z = 2.01 (P = 0.04)

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### Death

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Embolic protection</th>
<th>No embolic protection</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEAN-TAVI</td>
<td>0</td>
<td>50</td>
<td>1</td>
<td>Total</td>
<td>14.5% 0.33 [0.01, 7.99]</td>
</tr>
<tr>
<td>DEFLECT-III</td>
<td>1</td>
<td>46</td>
<td>2</td>
<td>Total</td>
<td>21.0% 0.42 [0.04, 4.50]</td>
</tr>
<tr>
<td>EMBOL-X</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>Total</td>
<td>8.2%   Not estimable</td>
</tr>
<tr>
<td>MISTRAL-C</td>
<td>1</td>
<td>32</td>
<td>4</td>
<td>Total</td>
<td>38.2% 0.29 [0.03, 2.18]</td>
</tr>
<tr>
<td>SENTINEL</td>
<td>3</td>
<td>334</td>
<td>2</td>
<td>Total</td>
<td>26.3% 0.71 [0.12, 4.20]</td>
</tr>
</tbody>
</table>

Total (95% CI): 378 249 100.0% 0.42 [0.14, 1.26]

Heterogeneity: Chi² 0.56, df 3 (P = 0.91), I² 0%
Test for overall effect: Z = 1.55 (P = 0.12)

---

### Stroke

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Embolic protection</th>
<th>No embolic protection</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEAN-TAVI</td>
<td>4</td>
<td>50</td>
<td>4</td>
<td>Total</td>
<td>16.0% 1.63 [0.36, 3.78]</td>
</tr>
<tr>
<td>DEFLECT-III</td>
<td>2</td>
<td>46</td>
<td>2</td>
<td>Total</td>
<td>9.9% 0.85 [0.12, 5.74]</td>
</tr>
<tr>
<td>EMBOL-X</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>Total</td>
<td>8.0%   Not estimable</td>
</tr>
<tr>
<td>MISTRAL-C</td>
<td>0</td>
<td>32</td>
<td>2</td>
<td>Total</td>
<td>11.1% 0.21 [0.01, 4.13]</td>
</tr>
<tr>
<td>SENTINEL</td>
<td>13</td>
<td>231</td>
<td>10</td>
<td>Total</td>
<td>81.1% 0.62 [0.20, 1.37]</td>
</tr>
</tbody>
</table>

Total (95% CI): 373 248 100.0% 0.66 [0.36, 1.23]

Heterogeneity: Chi² 1.04, df 3 (P = 0.79), I² 11%
overall effect: Z = 1.29 (P = 0.20)
Safety and efficacy of ASA vs. DAPT after TAVR: patient-level pooled analysis of 672 patients

Why Did Dabigatran Not Work in MHVs?

Potential pharmacodynamic explanation for the failure of dabigatran to prevent clotting in patients with MHVs:

By triggering the intrinsic pathway, MHVs induce the generation of thrombin (factor IIa) in concentrations that locally overwhelm those of Dabigatran in its block of thrombin activity.

In contrast, by reducing the levels of fIX, fX, and prothrombin, warfarin attenuates fXa and thrombin generation, thereby preventing local clotting.

GALILEO Trial
Global PIs: G. Dangas, S. Windecker

Study population: Patients with successful TAVR

N=1520

1-7 days post-TAVI

Rivaroxaban 10 mg OD AND ASA 75-100 mg OD

3 months: Drop one antipatelet

Rigor 75 mg OD AND ASA 75-100 mg OD

ASA 75-100 mg OD

Follow-Up Period 30 days

Post-treatment Period

Min 360d Max 730d

Primary Efficacy Endpoint
Composite of Death, Stroke, MI, Symptomatic Valve Thrombosis, Systemic Thromboembolism, Or Major Venous Thromboembolism

Ending in the fall 2017 >1,000 pts randomized (total≈1520)

NCT02556203
The GALILEO Trial
CTA and MRI Substudies

**GALILEO MRI Substudy**
*EARTH*

- N = 180 patients
- Primary endpoint: TLV (mm3) assessed with DW-MRI at 3 months
- Will test superiority of rivaroxaban-based versus clopidogrel-based strategy
- DW-MRI also performed pre-TAVR and post-TAVR (both inpatient) for the 2ary endpoint of periprocedure embolization

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**GALILEO CTA Substudy**

- N = 300 patients; 1 CTA done at 3 months
- Primary endpoint: rate of patients with at least one prosthetic leaflet with > 50% motion reduction as assessed by cardiac 4DCT-scan at 3 months after TAVR
- Will test superiority of rivaroxaban-based versus clopidogrel-based strategy
- Secondary endpoints include leaflet thickening, echocardiographic mean gradient & EOA and NYHA class

NCT02556203
Official substudy title: A randomized comparison of a rivaroxaban-based strategy with an antiplatelet-based strategy following successful TAVR for the prevention of reduced valve leaflet motion as evaluated by four-dimensional, volume-rendered computed tomography (4DCT)

**Objective:** evaluate whether a rivaroxaban-based strategy, following successful TAVR, compared to an antiplatelet-based strategy, is superior in reducing subclinical valve leaflet motion abnormalities – as evaluated by 4DCT imaging at three months following TAVR.

**Short design:** Substudy to GALILEO: Randomized, open-label, active-controlled, multi-center, double-blind, 300 patients

**Indication:** Transcatheter aortic valve replacement (TAVR)

**Phase:** Phase III

**FPFV:** Q1-2016

**LPLV:** Q2-2017
Stratification for substudy 1-7 post-TAVR (or upon hospital discharge if earlier than day 2 post-TAVR)*

EARTH and GALILEO combined flow chart

GALILEO Screening: Patients with successful TAVR

EARTH Visit 0: Screening
EARTH Pre-TAVR: Cerebral MRI scan
EARTH Post-TAVR: Cerebral MRI scan

TAVR

GALILEO: www.clinicaltrials.gov/ct2/show/NCT02556203

DAPT: Clopidogrel 75 mg OD + ASA 75-100 mg

Rivaroxaban 10 mg OD + ASA 75-100 mg

Rivaroxaban 10 mg OD

Follow Up Period 30 days

18 months (12-24 months)

EARTH Post-TAVR: Cerebral MRI scan

EARTH 90d: Cerebral MRI scan

R 1:1

Majority of patients will be on DAPT after TAVR
Gastric protection recommended throughout study

# Majority of patients will be on DAPT after TAVR

GALILEO: www.clinicaltrials.gov/ct2/show/NCT02556203
ATLANTIS trial  PIs: G. Montalescot, JP Collet

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
- Apixaban 5mg bid*

Stratum 2
No indication for OAT
- 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 15-20mL/min or if two of the following criteria: age>80 years, weight>60kg or creatinine>1.5mg/dL (133µMol).
** ENVISAGE-TAVI AF **

**Global PIs:** G. Dangas, N. vanMieghem

**PROBE design:** prospective, randomized, open label, blinded evaluation Edoxaban based regimen vs VKA based regimen in N ≈1400 AF patients (≈ 2500 patient-years)

**TAVI**

w/o severe complications at randomization

between 24 h and 5 days

**Randomize**

**Edoxaban 60 mg/day***

with or w/o antiplatelet therapy (APT)***

**Vitamin K Antagonist**

with or w/o antiplatelet therapy (APT)***

**EDOXABAN DOSE REDUCTION**

30mg if

- CrCL 15- ≤50 ml/min
- BW ≤60 kg*
- P-gp inhibitors per local label*

*no dose reduction in US for AF

**VKA as approved in countries, target INR 2-3**

*** Without other indication for APT: Either no APT or SAPT up to 3 months, i.e., ASA or a P2Y12 inhibitor (preferably clopidogrel).

In PCI: SAPT, i.e., any P2Y12 inhibitor (preferably Clopidogrel) or ASA. DAPT is only allowed post stenting for 1 month after PCI.

With other potential indication for APT: Either no APT or SAPT, i.e., any P2Y12 inhibitor (preferably clopidogrel) or ASA indefinitely.

All APT needs predication by type, dose, & duration (projected last dose)

AF = atrial fibrillation; AP = antiplatelet, APT = antiplatelet therapy; ASA = aspirin; DAPT= dual antiplatelet therapy; Edo = edoxaban; h = hour; INR = international normalized ratio; mo = months, OAC=oral anticoagulant OD=once-daily; P-gp=P-glycoprotein; pts=patients; R=randomization, SAPT=single antiplatelet therapy; TAVI=transcatheter aortic valve implantation; VKA=vitamin K antagonist.
Conclusions

• Many patients undergoing TAVR have multiple thrombotic- and bleeding-related comorbidities that make optimal antiplatelet and anticoagulant management complex.

• Furthermore, the optimal antithrombotic strategy following implantation of any bioprosthetic valve in the aortic position is not entirely clear (SAVR/TAVR/TAVI inclusive).

• Guidelines differ on anticoagulation strategies in TAVR, most without a strong evidence base for their recommendations. Practice variation in the real world is high.
  - Clinical trials on antiplatelet Rx are ongoing & expanding

• Given the focus on stroke following TAVR, and emerging understanding of bioprosthetic leaflet dysfunction in relation to thrombus, antithrombotic therapies are going to play a key role in improving long-term bioprosthetic valve replacement outcomes
  - Clinical trials are ongoing and expanding

• Neuroprotection is clinical investigation & initial approval phase
The evolving concepts of timing, risk factor contributions, and preventive strategies for cerebrovascular events (CVE) in patients undergoing transcatheter aortic valve replacement.
Algorithm for Serial Imaging Follow-Up After Prosthetic Valve Replacement

1. TTE baseline prior to hospital discharge after bioprosthetic valve implantation
   - High risk for bioprosthetic complications?
     - TTE at 1 month
     - Yearly TTE
   - TTE at 3/6 month
     - Yearly TTE
   - Gradient up >50%, thickened cusps, and/or restricted cusp mobility?
     - TEE or CT scan
       - Evidence of thrombosis
         - Continue yearly TTE
       - No evidence of thrombosis
         - TEE or CT scan
         - Treat (see Algorithm Figure 7)
         - Watchful waiting: TTE at 1 month
Suspected Transcatheter Prosthetic Valve Thrombosis

TTE +/- TEE to evaluate hemodynamic severity and detect thrombus

CT scan to evaluate leaflet abnormal mobility

Clinical evaluation

NYHA III - IV

Optimal AC

Valve replacement

Suboptimal or no AC

IV Heparin

Fibrinolysis

Failure

Success

Follow-up with course of AC

Optimal AC

IV Heparin

Fibrinolysis

Failure

Success

Follow-up with course of AC

Suboptimal or no AC

IV Heparin

Success

Follow-up with course of AC

Suboptimal or no AC

IV Heparin

Success

Follow-up with course of AC

Dangas G. et al – JACC 2016