ANTICOAGULATION IN SPECIFIC POPULATIONS: BIOLOGICAL HEART VALVES, TAVI

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WHAT DO THESE GENTLEMEN HAVE IN COMMON?

Foreign Minister of Germany
1974-1992

US Secretary of State
1973-1977

TAVI 2012

TAVI 2014
Left-sided valvular heart disease

Nkomo VT et al., Lancet 2006
### 15 Years of TAVI (2002 – 2017)

**Prosthesis with CE – Mark Approval**

<table>
<thead>
<tr>
<th>Year</th>
<th>Device</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>Edwards Sapien THV</td>
<td>TF, TA</td>
</tr>
<tr>
<td>2007</td>
<td>Edwards Sapien XT</td>
<td>TF, TA</td>
</tr>
<tr>
<td>2011</td>
<td>Symetis Acurate TA</td>
<td>TF, TA</td>
</tr>
<tr>
<td>2012</td>
<td>SJM Portico</td>
<td>BF</td>
</tr>
<tr>
<td>2013</td>
<td>Direct Flow Medical</td>
<td>TF</td>
</tr>
<tr>
<td>2014</td>
<td>BSC Lotus</td>
<td>TF</td>
</tr>
<tr>
<td>2015</td>
<td>Edwards Sapien 3</td>
<td>TF, TA</td>
</tr>
<tr>
<td>2017</td>
<td>Medtronic Evolut R</td>
<td>TF</td>
</tr>
<tr>
<td>2017</td>
<td>Medtronic CoreValve</td>
<td>TF, TS, DA</td>
</tr>
<tr>
<td>2017</td>
<td>JenaValve</td>
<td>TF</td>
</tr>
<tr>
<td>2017</td>
<td>Medtronic Engager</td>
<td>TF</td>
</tr>
<tr>
<td>2017</td>
<td>Symetis Acurate Neo</td>
<td>TF</td>
</tr>
<tr>
<td>2017</td>
<td>Lotus Edge</td>
<td>TF</td>
</tr>
</tbody>
</table>
Global TAVI Adoption

- **2012**: 32,000
- **2013**: 41,000
- **2014**: 56,000
- **2015**: 71,000
- **2016**: 83,000

World: 330,000

4-fold increase

*Source: Credit Suisse TAVI Comment - January 8, 2015*
# TAVI vs SAVR: Meta-Analysis Of 4 Randomized Trials


**All-cause Mortality at 2 years**

(N = 3,806)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Trials</th>
<th>τ²</th>
<th>HR (95% CI)</th>
<th>P-inter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Access route</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfemoral</td>
<td>4</td>
<td>&lt;0.001</td>
<td>0.80 (0.69, 0.93)</td>
<td>0.024</td>
</tr>
<tr>
<td>Transthoracic</td>
<td>2</td>
<td>&lt;0.001</td>
<td>1.17 (0.88, 1.56)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>6</td>
<td></td>
<td>0.87 (0.76-0.99), P=0.038</td>
<td></td>
</tr>
</tbody>
</table>
## TAVI vs. SAVR
### Peri-Procedural Adverse Events

**Siontis et al, *Eur Heart J* 2016 Dec 14;37(47):3503-3512**

**4 RCTs (N = 3,806)**

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>SAVR</th>
<th>HR (95% CI)</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New-onset AF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARTNER 1A</td>
<td>42/348</td>
<td>60/351</td>
<td>0.71 (0.49, 1.02)</td>
<td>54%</td>
</tr>
<tr>
<td>US CoreValve</td>
<td>71/390</td>
<td>121/357</td>
<td>0.54 (0.42, 0.69)</td>
<td></td>
</tr>
<tr>
<td>NOTION</td>
<td>32/145</td>
<td>80/135</td>
<td>0.28 (0.18, 0.43)</td>
<td></td>
</tr>
<tr>
<td>PARTNER 2A</td>
<td>110/1011</td>
<td>273/1021</td>
<td>0.41 (0.33, 0.50)</td>
<td></td>
</tr>
<tr>
<td>Overall (Heterogeneity $\tau^2 = 0.076, P = 0.004$)</td>
<td></td>
<td></td>
<td>0.46 (0.34, 0.63) &lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

| **Major bleeding** |          |          |             |        |
| PARTNER 1A       | 60/348   | 95/351   | 0.64 (0.48, 0.85) | 43%    |
| US CoreValve     | 123/390  | 135/357  | 0.83 (0.68, 1.02) |        |
| NOTION           | 16/142   | 28/134   | 0.54 (0.31, 0.95) |        |
| PARTNER 2A       | 169/1011 | 471/1021 | 0.36 (0.31, 0.42) |        |
| Overall (Heterogeneity $\tau^2 = 0.212, P < 0.001$) |  |          | 0.57 (0.35, 0.92) 0.020 |

| **Kidney injury** |          |          |             |        |
| PARTNER 1A       | 20/348   | 21/351   | 0.96 (0.53, 1.74) | 39%    |
| US CoreValve     | 24/390   | 54/357   | 0.41 (0.26, 0.64) |        |
| NOTION           | 2/145    | 3/135    | 0.61 (0.10, 3.70) |        |
| PARTNER 2A       | 36/1011  | 57/1021  | 0.64 (0.42, 0.96) |        |
| Overall (Heterogeneity $\tau^2 = 0.064, P = 0.155$) |  |          | 0.61 (0.41, 0.90) 0.013 |
ANTICOAGULATION: BIOLOGICAL HEART VALVES

CURRENT STATUS OF TAVI

FUTURE PERSPECTIVES

ANTICOAGULANTS AND SURGICAL HEART VALVES

STROKE

THROMBOSIS OF TRANSCATHETER HEART VALVES

STROKE FUTURE PERSPECTIVES
SURGICAL HEART VALVES

BIOLOGICAL

Xenografts

Stented  Stentless

Porcine

St. Jude Medical
Toronto SPV

Medtronic
Freestyle

Caged ball valve

Tilting disc valve

Single leaflet valve

Bi-leaflet valve

Porcine or bovine valve

MECHANICAL

Medtronic Hancock II
Medtronic Mosaic
St. Jude Medical Biocor

Carpentier-Edwards Magna Ease
Sorin group Mitroflow
St. Jude Medical Trifecta

Pericardial

Sorin group Pericarbon Freedom
Medtronic 3f Enable
**Pathology of Bioprosthetic Valves Thrombosis**

- Thrombi on the nonflow surface of the valve

- Thrombus and Subvalvular Pannus


**Prevalence, Timing and Predictors**

Mayo Clinic matched case–control study
Between 1997 and 2013, 397 consecutive explanted bioprostheses

BPVT occurred earlier than structural deterioration, after a median of 24 months and regardless of position

<table>
<thead>
<tr>
<th>BPV Explanted (n)</th>
<th>BPVT (n)</th>
<th>BPVT Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic</td>
<td>265</td>
<td>29</td>
</tr>
<tr>
<td>Mitral</td>
<td>71</td>
<td>9</td>
</tr>
<tr>
<td>Tricuspid</td>
<td>58</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>397</strong></td>
<td><strong>46</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BPV Explanted (n)</th>
<th>Estimated BPVT Incidence* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic</td>
<td>3,843</td>
</tr>
<tr>
<td>Mitral</td>
<td>1,395</td>
</tr>
<tr>
<td>Tricuspid</td>
<td>722</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>218</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6,178</strong></td>
</tr>
</tbody>
</table>

- **Prevalence 11.6%**
- **Incidence 0.74%**
- **Predictors**
  - AF, ↑gradient, ↑cusp thickness, subtherapeutic INR

**Recommendations for Anticoagulant Therapy**

### BIOLOGICAL

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulation is recommended lifelong for patients with bioprostheses who have other indication for anticoagulation</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Oral anticoagulation should be considered for the first three months after implantation of a mitral- or tricuspid bioprosthesis</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Oral anticoagulation may be considered for the first three months after implantation of an aortic bioprosthesis</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Low-dose aspirin should be considered for the first three months after implantation of an aortic bioprosthesis</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin 75 mg to 100 mg per day is reasonable in all patients with a bioprosthetic aortic or mitral valve</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Anticoagulation with a VKA to achieve an INR of 2.5 is reasonable for at least 3 months and for as long as 6 months after surgical bioprosthetic MVR or AVR in patients at low risk of bleeding</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

Nishimura et al. Circulation. 2017 Mar 15
**Duration of Anticoagulant Therapy**

4,075 patients who had bioprosthetic AVR in the Danish National Patient Registry

For every 23 (95% CI, 14-54) patients not being treated with warfarin, 1 patient died from cardiovascular cause.
## Recommendations for Anticoagulant Therapy

### Mechanical

**Vahanian et al.**
*European Heart Journal 2012*

- **Oral anticoagulation is recommended lifelong for all patients with a mechanical prosthesis.**
- **Oral anticoagulation is recommended lifelong for patients with bioprostheses who have other indications for anticoagulation.**
- **The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis and concomitant atherosclerotic disease.**
- **The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis after thromboembolism despite adequate INR.**

**Nishimura et al.**
*Circulation. 2017*

- **Anticoagulation with a VKA and INR monitoring is recommended in patients with a mechanical prosthetic valve (178-183).**
- **Anticoagulation with a VKA to achieve an INR of 2.5 is recommended for patients with a mechanical bileaflet or current-generation single-tilting disc AVR and no risk factors for thromboembolism (178,184-186).**
- **Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical AVR and additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an older-generation mechanical AVR (such as ball-in-cage) (178).**
- **Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical MVR (178,187,188).**
- **Aspirin 75 mg to 100 mg daily is recommended in addition to anticoagulation with a VKA in patients with a mechanical valve prosthesis (178,189,190).**
The Re-ALIGN Trial

Dabigatran vs. warfarin (2:1) after aortic- or mitral-valve replacement

Prematurely interrupted after the enrollment of 252 patients because of an excess of thromboembolic and bleeding events among patients in the dabigatran group
Attenuates thrombin generation by reducing functional levels of fIX, fX, and fII

Inhibits thrombin in a 1:1 manner

Anticoagulation: Biological Heart Valves

Current Status of TAVI

Future Perspectives

Anticoagulants and Surgical Heart Valves

Stroke

Thrombosis of Transcatheter Heart Valves
DURABILITY OF TRANSCATHETER HEART VALVES
PARTNER 1A
MACK MJ ET AL. LANCET 2015

5-Years Follow-up

Mean valve area (cm²)

Mean gradient (mm Hg)
MECHANISMS OF BIOPROSTHETIC VALVE THROMBOSIS

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

Hemostatic Factors
- Hyper-coagulable state*
- Significant tissue injury
- Heparin-induced thrombocytopenia
- Suboptimal anticoagulation†
- Platelet reactivity

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

Relative Contribution to Prosthetic Valve Thrombosis

†Suboptimal anticoagulation is not equivalent to complete resistance to anticoagulant medications.
ANATOMIC LOCATION AND BIOPROSTHETIC VALVE THROMBOSIS

≈ 20 times more frequent than with the mitral valve

Right-sided heart valves
- clotting pathway > platelet pathway

TRICUSPID VALVE
1. Hemodynamic factors
   - Slow venous blood flow (especially if concomitant pulmonary hypertension with low RV output).
2. Hemostatic factors
   - Hypercoagulability
   - Tissue injury
3. Surface factors
   - Incomplete prosthesis endothelialization.
   - Prosthesis malpositioning

PULMONIC VALVE
1. Hemodynamic factors
   - Slow venous blood flow (especially if concomitant pulmonary hypertension with low RV output).
2. Hemostatic factors
   - Hypercoagulability
3. Surface factors
   - Valve frame fracture

Left-sided heart valves
- platelet pathway > clotting pathway

AORTIC VALVE
1. Surface factors
   - Incomplete prosthesis endothelialization.
   - Prosthesis malpositioning
2. Hemostatic factors
   - Tissue injury
   - Prosthesis malpositioning
3. Hemodynamic factors
   - Local blood flow turbulences
   - Incomplete apposition

MITRAL VALVE
1. Hemodynamic factors
   - Relatively slow blood flow in case of AF, atrial dilation or low LV output.
   - Local blood flow turbulences
   - Incomplete apposition
2. Hemostatic factors
   - Tissue injury
3. Surface factors
   - Incomplete prosthesis endothelialization.
   - Prosthesis malpositioning
   - Leaflet injury

≈ 2-3 times more frequent than with the aortic valve

## Clinical Spectrum of Prosthetic Valve Thrombosis

<table>
<thead>
<tr>
<th>Clinically Apparent</th>
<th>Subclinical</th>
<th>Silent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve dysfunction</td>
<td>Hypoattenuating opacities</td>
<td>Silent Brain Infarction</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>Reduced leaflet motion</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Subclinical Leaflet Thrombosis in Bioprosthetic Valves


- **Incidence**: 17 of 132 patients (13%)
- **Reduced incidence with oral anticoagulation** (0% vs 29%, *p*=0.04)
  - Restoration of leaflet motion in all 11 patients who received oral anticoagulation
- **Higher incidence of stroke/TIA in patients with leaflet motion abnormality** (18% vs 1%, *p*=0.007)

**Hypoattenuating Opacities**

**Reduced Leaflet Motion**
**Subclinical Leaflet Thrombosis in Bioprosthetic Valves**

Chakravarty et al. Lancet 2017

- 890 patients with interpretable CT scans were included (RESOLVE registry, n=626; SAVOR Registry, n=264)
- Incidence: **12%**: 4% after SAVR and **13%** after TAVR (p<0.001)
SUBCLINICAL LEAFLET THROMBOSIS IN BIOPROSTHETIC VALVES

Chakravarty et al. Lancet 2017

Mean aortic gradient > 20mmHg

Increase in gradients > 10mmHg

Mean aortic gradient > 20mmHg AND Increase in gradients > 10mmHg
SUBCLINICAL LEAFLET THROMBOSIS IN BIOPROSTHETIC VALVES
Chakravarty et al. Lancet 2017

Anticoagulation vs. no anticoagulation: \( p<0.0001 \)
NOACs vs. no anticoagulation: \( p=0.0002 \)
Warfarin vs. no anticoagulation: \( p=0.001 \)
NOACs vs. warfarin: \( p=0.72 \)
ANTICOAGULATION: BIOLOGICAL HEART VALVES

- Current Status of TAVI
- Anticoagulants and Surgical Heart Valves
- Stroke
- Thrombosis of Transcatheter Heart Valves
- Future Perspectives
TAVI and Cerebrovascular Events

Stortecky, Windecker. *Circulation* 2012;126:2921-4
**Effect of Cerebrovascular Events on Mortality**


**ADVANCE (N=1,015)**

**Stroke**

**Stroke or TIA**

![Graphs showing freedom from all-cause mortality over time](image)
EMBOLECTIC PROTECTION DEVICES AND SAVR

Randomized (n=383)

- Embol-X (n=133)
- Shared Control (n=132)
- CardioGard (n=118)

Percent of Embol-X Patients with at Least One Particle of a Given Size
- ≥ 0.15 mm: 99%
- ≥ 0.5 mm: 88%
- ≥ 1 mm: 61%
- ≥ 2 mm: 16%

Percent of CardioGard Patients with at Least One Particle of a Given Size
- ≥ 0.15 mm: 68%
- ≥ 0.5 mm: 43%
- ≥ 1 mm: 14%
- ≥ 2 mm: 2%

Mack M. ACC 2017
**Embolic Protection Devices and SAVR**

**Primary Endpoint**

**Freedom From Clinical or Radiographic CNS infarction**

<table>
<thead>
<tr>
<th>Device</th>
<th>% of Patients w/ No Infarcts</th>
<th>OR of CNS Infarct: 1.06 (95% CI: 0.60,1.87)</th>
<th>P = 0.84</th>
</tr>
</thead>
<tbody>
<tr>
<td>CardioGard</td>
<td>32.7 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>34.8 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embol-X</td>
<td>27.1 %</td>
<td>OR of CNS Infarct: 1.40 (95% CI: 0.81,2.40)</td>
<td>P = 0.22</td>
</tr>
<tr>
<td>Control</td>
<td>34.8 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*OR and P-value based on analysis of imputed data; bar chart based on observed data*

**Stroke**

- **≤7 Days**
  - CardioGard: 5.1%
  - Control: 5.8%
  - Embol-X: 8.3%
  - Control: 6.1%
  
- **≤3 Days**
  - CardioGard: 3.4%
  - Control: 5%
  - Embol-X: 6%
  - Control: 5.3%

P values:
- P=0.61
- P=0.49
- P=0.77
- P=.99

Mack M. ACC 2017
Embolic Protection Devices and TAVI

PROTAVI-C
Rodés-Cabau et al. JACC Cardiovasc Interv. 2014
41 patients
- Average volume of ischemic lesion

CLEAN-TAVI
Haussig et al. JAMA 2016
100 patients
- Frequency of ischemic cerebral lesions

DEFLECT III Trial
Lansky et al. European Heart Journal 2015
85 patients
- New ischemic brain lesions and neurologic deficits
- Cognitive function

SENTINEL
Kapadia et al. JACC 2017
363 patients
- No significant reduction of lesion volume on MRI
Late Thromboembolic Events After TAVI

Subacute Embolization

Atrial fibrillation

AS/AF common risk factors (e.g., age, hypertension)

AS comorbidities
- Obesity
- Obstructive sleep apnea
- Increased pericardial fat

Atrial fibrosis

Systemic inflammatory response
- Atrial oxidative stress
- Slow atrial conduction
  - Refractoriness
  - Early afterdepolarization
  - Endo-epicardial dissociation

Atrial autonomic remodelling
- Genetic polymorphisms

AORTIC VALVE STENOSIS

LV hypertrophy

TAVI PROCEDURE

LV dysfunction
- Heart failure
- Volume overload
  - ↑ LV filling pressures
- ↑ LA pressures

Ballon valvuloplasty
- Hemodynamic instability
- Procedural complications

Re-entry / ectopic activity
- Atrial strain/dilatation
- Atrial fibrosis

NEW-ONSET AF

Tarantini et al. European Heart Journal (2016) 0, 1–12
Baseline AFib in TAVI Candidates

<table>
<thead>
<tr>
<th>Location</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian</td>
<td>34</td>
</tr>
<tr>
<td>European</td>
<td>29</td>
</tr>
<tr>
<td>Italian</td>
<td>16</td>
</tr>
<tr>
<td>Belgian</td>
<td>30</td>
</tr>
<tr>
<td>PARTNER B</td>
<td>33</td>
</tr>
<tr>
<td>PARTNER A</td>
<td>41</td>
</tr>
<tr>
<td>FRANCE II</td>
<td>27</td>
</tr>
<tr>
<td>Motloch et al.</td>
<td>32</td>
</tr>
<tr>
<td>Amat-Santos et al.</td>
<td>29</td>
</tr>
<tr>
<td>Nuis et al.</td>
<td>30</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>33</td>
</tr>
<tr>
<td>SOURCE XT</td>
<td>25</td>
</tr>
<tr>
<td>CoreValve Extreme</td>
<td>47</td>
</tr>
<tr>
<td>CoreValve High Risk</td>
<td>41</td>
</tr>
<tr>
<td>UK TAVI</td>
<td>27</td>
</tr>
<tr>
<td>Swiss</td>
<td>34</td>
</tr>
</tbody>
</table>

1-Rodes-Cabau et al, JACC 2010
2-Piazza et al, EuroInterv 2008
3-Tamburino et al, Circulation, 2011
4- Bosmans et al, Inter Cardiovasc and Thor Surg, 2011
5-Leon et al, NEJM 2010
6-Smith et al, NEJM 2011
7-Gillard et al, NEJM 2012
8-Motloch et al, Ann Thorac Surg 2011
9-Amat-Santos et al, JACC 2012
10-Nuis et al, Am J Cardiol 2012
11-Linke et al, TVT 2012
12-Wendler et al, EuroPCR 2012
13-Popma et al, JACC 2014
14-Adams et al, NEJM 2014
15-Ludman, Circulation 2015
16-Stortecky, Circ Cardiovit Interv 2013


**NEW ONSET ATRIAL FIBRILLATION**

**PARTNER 1A**

<table>
<thead>
<tr>
<th></th>
<th>30 Days</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEW ONSET AFIB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TAVI</strong></td>
<td>8,6</td>
<td>16</td>
</tr>
<tr>
<td><strong>SAVR</strong></td>
<td>12,1</td>
<td>17,1</td>
</tr>
</tbody>
</table>

**CoreValve High-Risk**

<table>
<thead>
<tr>
<th></th>
<th>30 Days</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEW ONSET OR WORSENING AFIB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TAVI</strong></td>
<td>11,7</td>
<td>30,5</td>
</tr>
<tr>
<td><strong>SAVR</strong></td>
<td>15,9</td>
<td>32,7</td>
</tr>
</tbody>
</table>
### SUBCLINICAL LEAFLET THROMBOSIS IN BIOPROSTHETIC VALVES

Chakravarty et al. *Lancet* 2017

<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><strong>All events</strong></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></td>
<td></td>
<td></td>
<td></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><strong>All strokes</strong></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
ANTICOAGULATION: BIOLOGICAL HEART VALVES

ANTICOAGULANTS AND SURGICAL HEART VALVES

CURRENT STATUS OF TAVI

STROKE

THROMBOSIS OF TRANSCATHETER HEART VALVES

FUTURE PERSPECTIVES
**CURRENT RECOMMENDATIONS FOR MANAGEMENT OF ANTIPLATELET THERAPY AFTER TAVI**

<table>
<thead>
<tr>
<th>ESC&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ACC/AHA&lt;sup&gt;2&lt;/sup&gt;</th>
<th>ACCP CONSENSUS&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose aspirin and a thienopyridine early after the procedure followed by aspirin or a thienopyridine alone</td>
<td>Clopidogrel 75 mg plus aspirin 75–100 mg for 6 months followed by aspirin 75–100 mg daily alone (Class IIb)</td>
<td>Aspirin 50–100 mg plus clopidogrel 75 mg/dl for the first 3 months (Grade 2C) followed by aspirin lifelong</td>
</tr>
</tbody>
</table>

<sup>1</sup>Eur Heart J 2012;33:2451–96; <sup>2</sup>Circulation 2014;129:e521–643; <sup>3</sup>Chest 2012;141:e576S–600S
Study Hypothesis: Monotherapy with Aspirin or OAC monotherapy is safer (non-procedure-related bleeding) than the addition of clopidogrel for 3 months.

Recruitment began in February 2014, and the trial will continue until a total of 1,000 patients (684 expected in cohort A and 316 in cohort B) are included and followed up for 1 year.
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).
**Design overview**

**Study population:**
Patients with successful TAVR*

**Key Excl. criteria:**
Ongoing indication for DAPT or anticoagulation, previous ischemic stroke, active peptic ulcer or upper GI bleeding, previous ICH, or severe renal insufficiency

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- **Rivaroxaban 10 mg OD** + ASA 75–100 mg
- **ASA 75–100 mg**
- **Rivaroxaban 10 mg OD**

**Follow Up Period**
- 30 days
- 18 months (12–24 months)

*~110 sites in Europe & North America (15 countries); # Majority of patients will be on DAPT after TAVR gastric protection recommended throughout study. ASA=Acetylsalicylic acid; DAPT=Dual antiplatelet therapy; GI=Gastrointestinal; ICH=Intracranial haemorrhage; OD=Once daily; TAVR=Transcatheter aortic valve replacement.

Treatment after new onset of AF (NOAF)

15% of patients develop NOAF after randomisation

1. Randomised to rivaroxaban
   - Switch to 20 mg OD
   - Switch to 15 mg OD for moderate renal impairment*

2. Randomised to clopidogrel
   - Switch to VKA (target INR: 2–3)

• Follow-up until end of study
  – Included in primary efficacy analysis (ITT)
  – Censoring in secondary analysis

* i.e. CrCl=30–49 mL/min.
CrCl=Creatinine clearance; INR=International normalised ratio; ITT=Intention to treat; NOAF=New onset atrial fibrillation; OD=Once daily; VKA=Vitamin K antagonist. Unpublished data.
The GALILEO trial: Study design

Global study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement to optimize clinical outcomes.

**Objective**
To assess a rivaroxaban-based anticoagulation regimen following successful TAVR balancing ischaemic and bleeding outcome measures.

**PI**=Principal investigator; TAVR=Transcatheter aortic valve replacement.

- Stephan Windecker, PI, George Dangas, PI
- Roxana Mehran, Marco Valgimigli
- Pascal Vranckx, Robert Welsh

Conclusions

- Severe aortic stenosis is associated with increased thrombogenicity;
- Increased thrombogenicity may explain in part the risk of CVEs, systemic thromboembolism and valve thrombosis observed in SAVR and TAVR patients;
- The use of dual antiplatelet therapy is currently empirical and may be not optimal in targeting mechanisms of thrombus formation;
- Oral anticoagulation may represent a valid alternative and its use is supported by indirect proof of effectiveness;
- Ongoing randomized trials will improve current limited knowledge on optimal antithrombotic treatment after TAVI.
Henry Kissinger, 92, the former secretary of state, has had the procedure (TAVI). “I was getting out of breath more easily, and my cardiologist said something had to happen,” he said in a telephone interview. “He said I would be in a wheelchair if I didn’t have it, and my survival rate in a year would be only 50–50.” “I am more energetic, people tell me I look better, and I feel much less tired,” Mr. Kissinger said. He described the procedure as easier and less debilitating than the open-heart bypass surgery he had previously. “There’s no comparison.”