TAVR 2018
Concepts of Pharmacological Therapy

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COI statement

- Research Grants to Mount Sinai
  - Bayer
  - Daichi-Sankyo
- Advisory Board
  - Sanofi-Aventis (spouse)
- Speaker honoraria
  - Bayer
  - Janssen
Timing of Cerebrovascular Events after TAVI

Stortecky et al. – Circulation 2012; 126:2921-4
### 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>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

Mechanisms of Prosthetic Valve Thrombosis

Bioprosthetic Aortic Valve Dfxn

- ↦ in mean gradient (MG) ≥ 10 mmHg or new MG ≥ 20mmHg
- Rate approximately 4.5% after TAVR (clinically driven)
  - 11-15% Imaging driven as per other registries

Del Trigo et al, J Am Coll Cardiol 2016;67:644
Results from:

- **4832 pts undergoing bioprosthetic AVR in the PARTNER 2 trials and registries**
- **TAVR (n=3889)**
- **SAVR (n=943)**
**Anti-thrombotics After TAVR/TAVI**

<table>
<thead>
<tr>
<th>Bioprosthesis</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DAPT should be considered for the first 3–6 months after TAVR/TAVI, followed by lifelong SAPT in patients who do not need OAC for other reasons.</strong></td>
<td>IIA</td>
<td>C</td>
</tr>
</tbody>
</table>

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<tbody>
<tr>
<td>Anticoagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SAPT may be considered after TAVR/TAVI in the case of high bleeding risk.</strong></td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td><strong>OAC may be considered for the first 3 months after surgical implantation of an aortic bioprosthesis.</strong></td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

*Baumgartner et al., Eur Heart J 2017;38:2739*
Thirty-day outcomes of DAPT versus Aspirin after TAVR

Meta-analysis of 421 patients from 3 RCTs

Three trials on DAPT versus aspirin after TAVR in non-OAC patients are actually available
- ARTE follows 2 previous
- Stabile E et al 2014
- Ussia GP et al 2011

The pooled results of the 3 trials now cumulatively suggest no benefit of DAPT in reducing 30-day stroke and a trend toward an increase in major or life-threatening bleeding over
Design

- Randomized, open-label trial
  - 9 centers in Canada

- Inclusion criteria:
  - TAVR with Edward Sapiens (XT / 3)

- Exclusion criteria:
  - indication for chronic oral anticoagulation
  - DES within one-year of TAVR

- Randomization the day before TAVR
  - Aspirin 80-100mg q.d.
  - Aspirin (80-100mg q.d.) + Clopidogrel 75mg q.d. for 3 month
    - Clopidogrel initiated within 24h before TAVR if transfemoral approach and within 24h after TAVR if other vascular approach

- Primary composite endpoint:
  - Death, MI, ischemic stroke/TIA or major or life-threatening VARC 2 bleeding
  - Within 3 months of TAVR

ARTE Results

Major/life-threatening bleeding

Deafth

Primary composite endpoint

Ischemic stroke/TIA
A multicenter evaluation comprising 621 patients with AF undergoing TAVR

Groups Monotherapy (MT) with VKA (n=101) or multiple antithrombotic therapy (MAT) with VKA plus 1 or 2 antiplatelet agents (aspirin or clopidogrel; n = 520).

<table>
<thead>
<tr>
<th></th>
<th>VKA Group (n = 101)</th>
<th>MAT Group (n = 520)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, any cause*</td>
<td>5 (5.0)</td>
<td>22 (4.2)</td>
<td>0.79</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (4)</td>
<td>19 (3.6)</td>
<td>0.76</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0)</td>
<td>12 (2.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>Major vascular complication</td>
<td>7 (7.0)</td>
<td>57 (10.9)</td>
<td>0.36</td>
</tr>
<tr>
<td>Major bleeding or LTB</td>
<td>6 (5.9)</td>
<td>77 (14.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>17 (16.8)</td>
<td>93 (17.9)</td>
<td>0.89</td>
</tr>
<tr>
<td>Pacemaker implantation</td>
<td>9 (8.9)</td>
<td>72 (13.8)</td>
<td>0.20</td>
</tr>
</tbody>
</table>
Kaplan-Meier Estimates at 1-Year Follow-Up for combined NACE: stroke, MI, or bleeding
France-TAVI registry: KM Estimates per OAC

Unadjusted HR = 1.50 (95% CI: 1.35-1.66)

<table>
<thead>
<tr>
<th>No OAC</th>
<th>7632</th>
<th>5282</th>
<th>3393</th>
<th>2123</th>
<th>1154</th>
<th>472</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAC</td>
<td>3835</td>
<td>2641</td>
<td>1635</td>
<td>1003</td>
<td>519</td>
<td>223</td>
<td>0</td>
</tr>
</tbody>
</table>
Aim of the study:

(1) performed a structured survey to determine if there is consensus among clinicians regarding antiplatelet therapy after TAVI;

(2) performed a systematic review of all suitable studies (randomized controlled trials and registries) to determine if aspirin monotherapy can be used instead of DAPT.

Variance weighted least squared metaregression was then performed to determine the relationship of antiplatelet therapy and adverse events.

Ahmad Y et al Open Heart. 2018 Jan 26;5(1):e000748
Results of structured survey of 45 centers

A. Basis of antithrombotic regimen post-TAVI

- Personal preference: 42.2%
- Local institutional policy: 44.5%
- Guidelines: 13.3%

B. Pre-TAVI antiplatelet loading regimen

- Aspirin alone: 40%
- Clopidogrel alone: 6.6%
- Aspirin and clopidogrel: 24.4%
- No loading: 29.9%

C. Antiplatelet strategy post-TAVI

- Aspirin alone: 17.8%
- 1 month DAPT: 4.4%
- 3 months DAPT: 46.7%
- 6 months DAPT: 22.2%
- 12 months DAPT: 2.2%
- Unspecified: 6.7%
Studies of Different Antithrombotic Strategies After TAVR

**Studies of antiplatelet strategies**
- **ARTE (NCT01559298)**: ASA vs. DAPT
- **POPular TAVI (NCT02247128)**: ASA vs. DAPT
- **CLOE (Announced)**: ASA vs. DAPT
- **AVATAR (NCT02735902)**: ASA+VKA vs. no VKA
- **POPular TAVI (NCT02247128)**: Clopidogrel+VKA vs. VKA
- **CLOE (Announced)**: Clopidogrel+VKA vs. VKA

**Studies of antiplatelet versus anticoagulant strategies**
- **AUREA (NCT01642134)**: DAPT vs. VKA
- **GALILEO (NCT02556203)**: Rivaroxaban + ASA vs. DAPT
- **ATLANTIS (NCT02664649)**: Apixaban vs. Aspirin or DAPT

**Studies of anticoagulant strategies**
- **ATLANTIS (NCT02664649)**: Apixaban vs. VKA
- **ENVISAGE TAVI (NCT02943785)**: Edoxaban* vs. VKA*
Global PIs G Dangas and S Windecker

Official study title: Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes

Primary Efficacy Endpoint
Composite: Death-Stroke-MI-Symptomatic Valve Thrombosis-Systemic Thromboembolism-Major VTE

Population: Patients with successful TAVR*

1–7 days post-TAVR and before hospital discharge

DSMB rec. Aug 2018
Ended f/u in Sept 2018
(total ~1,650 pts)

*110 sites in Europe and N. America (15 countries); gastroprophylaxis recommended throughout study
Brain MRI, 4D CT substudy combined flow chart

- **EARTH Visit 0: Screening**
- **EARTH Pre-TAVR: Cerebral MRI scan + assessment neurocognitive function**
- **EARTH Post-TAVR: Cerebral MRI scan + assessment neurocognitive function**
- **GALILEO Screening:** Patients with successful TAVR
- **TAVR**
- **GALILEO 4D Screening**
- **GALILEO 4D 90d:** 4D-computed tomography
- **GALILEO 90d:** Cerebral MRI scan + assessment neurocognitive function
- **R**

- **Stratification for substudy**
- **DAPT:** Clopidogrel 75 mg OD + ASA 75–100 mg
- **Rivaroxaban 10 mg OD + ASA 75–100 mg**
- **ASA 75–100 mg**
- **Follow-up period 30 days**
- **18 months (12–24 months)**

- **EARTH 90d:** Drop one antiplatelet
- **Rivaroxaban 10 mg OD**

- **https://clinicaltrials.gov/ct2/show/NCT02833948**
- **https://clinicaltrials.gov/ct2/show/NCT02758964**
- **https://clinicaltrials.gov/ct2/show/NCT02556203**
ATLANTIS trial: Current Status ~1000 pts
PIs: JP Collet, G. Montalescot

**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 5 mg bid* vs. standard of care antiplatelet therapy
  - **Stratum 2**: No indication for OAT
    - Apixaban 5 mg bid* vs. standard of care VKA therapy

**Primary endpoint** 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.

*N2.5 mg bid if creatinine clearance 15-29 mL/min or if two of the following criteria: age ≥80 years, weight ≤60 kg or creatinine ≥1.5 mg/dL (133 μMol).*
**ENVISAGE Trial – Current Status ~500 pts**

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

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**Successful TAVR n=1400**

**Patients With an Indication to Chronic Oral Anticoagulation**

- RANDOMIZE 1:1
  - 1-7 Days after the procedure
  - Background Tx: Single Antiplatelet Therapy as per treating MD discretion (*Stratification Variable*)

- **Warfarin (target INR 2-3)**
- **EDOXABAN 60mg po daily**
  - Adjustment to 30mg for low eGFR etc

- Minimum duration of randomized therapy 12 months

- **CLINICAL FOLLOW-UP: 1, 6, 12 Months**

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**Secondary Endpoints**

- All-cause Death, MI, Stroke or TIA, VARC-2 Life-threatening (LT) bleeding and Major bleeding

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**Primary Safety Endpoint:**

**Major Bleeding**

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**Primary Endpoint - NACE**

- [Composite of Death, MI, Stroke, TIA, systemic thromboembolism or VARC-2 Life-threatening (LT) or Major bleeding]

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**Ancillary Studies**

- Cost-Effectiveness
- QoL substudy
Successful TAVR in the STS/SCC TVT Registry n=4,000

Control Arm [No-Clopidogrel]
Stratum 1: Aspirin (81 mg qD)
Stratum 2: Warfarin (INR 2–3) or a NoAC

Treatment Arm [ +Clopidogrel ]
Stratum 1: Clopidogrel (75 mg qD) + Aspirin (81 mg qD)
Stratum 2: Clopidogrel (75 mg qD) + Warfarin (INR 2–3) or a NoAC

1:1 Randomization

Minimum duration of randomized therapy 6 months

CLINIC FOLLOW-UP: 1, 6, 12 Months

Primary Efficacy Endpoint (6 Months)
Composite of Death, Stroke, MI, Valve Thrombosis or Systemic Thromboembolism

Primary Safety Endpoint
Major / Life-Threatening VARC-2 Bleeding

Ancillary Studies
- Cost-Effectiveness
- QoL
- Frailty
- CTA Leaflet Substudy
- MRI Brain Substudy

Secondary Endpoints
- Single Component of the Primary Efficacy and Safety Endpoints at 6 and 12 months
- Net Adverse Clinical Events: the composite of the primary efficacy or safety endpoint.
- Bleeding endpoint as per the TIMI and ISTH definitions

The CLOE Trial – Study Scheme (NHLBI, NIH submission)
PIs: G. Dangas, M. Mack
The evolving concepts of timing, risk factor contributions, and preventive strategies for cerebrovascular events (CVE) in patients undergoing transcatheter aortic valve replacement.
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.

• Guidelines vary on anticoagulation strategies in TAVR, most without a strong evidence base for their recommendations. **Practice variation in the real world is very high.**

• Given the focus on stroke & bleeding following TAVR, antithrombotic therapies, in particular in patients with atrial fibrillation, are going to play a key role in improving long-term TAVR outcomes and **trials will define risk/benefit.**