TAVI and Adjunctive Pharmacological Therapy: Current Practice and Future Perspectives

A-Δ. ΜΑΥΡΟΓΙΑΝΝΗ
ΚΑΡΔΙΟΛΟΓΟΣ
ΑΙΜΟΔΥΝΑΜΙΚΟ ΕΡΓΑΣΤΗΡΙΟ
Γ.Ν.Θ. «Γ.ΠΑΠΑΝΙΚΟΛΑΟΥ»
ΘΕΣΣΑΛΟΝΙΚΗ
Disclosure Statement of Financial Interest

none whatsoever…
Prosthesis with CE Mark Approval

EDWARDS SAPIEN THV
EDWARDS SAPIEN XT
SYMETIS ACURATE TA
SJM PORTICO
DIRECT FLOW MEDICAL
BSC LOTUS
EDWARDS SAPIEN 3
MEDTRONIC EVOLUT R
MEDTRONIC COREVALVE
JENAVALVE
MEDTRONIC ENGAGER
SYMETIS ACURATE NEO
TAVI at the Antipodes of the Risk Spectrum: Mortality at 30-days in FDA Approved Studies 2010 - 2015

Pilgrim T., Windecker S.
Transcatheter Aortic Valve Replacement: Lessons Gained From Extreme-Risk Patients.
J Am Coll Cardiol. 2015 Sep 22;66(12):1335-8
The Majority of AS Patients Indicated Per Guidelines Remain Untreated

TAVI Present Guidelines

Indication for AVR

Heart Valve Team

Low Intermediate Surgical Risk

High Surgical Risk

Bridge to TAVR or SAVR for severe symptoms

Predicted post TAVR Survival > 1 year

Prohibitive Surgical Risk

TAVR (II a)

TAVR (I)

Palliative Care

Surgical AVR (I)

BAV (IIa)

Nishimura RA. et al.

Stroke in TAVI

Strotecky S., Windecker S.
Stroke in TAVI

Nombela-Franco L. et al.
What Lies Within?

Van Mieghem NM. et al.
Histopathology of embolic debris captured during transcatheter aortic valve replacement.
Circulation. 2013 Jun 4;127(22):2194-201
TAVI: Rate of Stroke at 30 Days

SOURCE 2012: 2.50%
PARTNER Coh 1. 2011: 4.70%
German Registry 2011: 2.80%
ADVANCE 1 2012: 3.30%
US CORE VALVE 2014: 4.90%
PARTNER II SI3: 1.00%

Petronio SA.
euroPCR 2016
Daneault B. et al.
Stroke associated with surgical and transcatheter treatment of aortic stenosis: a comprehensive review.
TAVI vs SAVR in High-risk Patients
New Onset Atrial Fibrillation

Windecker S.
euroPCR 2015
Comorbidities:
Atrial Fibrillation in TAVI Patients
<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 CABG (%)</td>
<td>25 (14-45)</td>
</tr>
<tr>
<td>Chronic renal failure (%)</td>
<td>35 (20–62)</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>26 (21–30)</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>TA</td>
<td>30 (11–50)</td>
</tr>
<tr>
<td>TF</td>
<td>11 (4–19)</td>
</tr>
<tr>
<td>Porcelain aorta (%)</td>
<td>12 (7-18)</td>
</tr>
<tr>
<td>Frailty (%)</td>
<td>21 (17–25)</td>
</tr>
</tbody>
</table>

Clinical Experience – Published Registries

Patient Characteristics

Mean CHADS2 score ~3
TAVI and Coronary Artery Disease

Gasparato et al. CCI 2013
Wenaweser et al. Eurointervention 2012
67 y/o Male Physician s/p TAVI with 29mm Sapien 3 Valve

Day 1 TTE
Gradient 10 mmHg

4 months post TAVI
Gradient 23 mmHg

Worsening shortness of breath 4 months post-TAVR
Leaflet Thickening/ Restricted Leaflet Motion Noted on 4D VR-CT

Restricted leaflet motion

Hypoattenuating lesions

Leaflet motion restored following anticoagulation with warfarin (INR 2-3)
Repeat CT performed after 3 months
Resolution of symptoms with anticoagulation
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Risk of THV Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0 (0/1) (0.0–97.5)</td>
</tr>
<tr>
<td>Aspirin only</td>
<td>25.0 (4/16) (7.2–52.3)</td>
</tr>
<tr>
<td>Clopidogrel only</td>
<td>12.5 (2/16) (1.5–38.3)</td>
</tr>
<tr>
<td>Aspirin+clopidogrel</td>
<td>9.7 (19/195) (6.0–14.8)</td>
</tr>
<tr>
<td>Warfarin only</td>
<td>7.1 (2/28) (0.9–23.5)</td>
</tr>
<tr>
<td>Warfarin+aspirin</td>
<td>1.0 (1/96) (0.0–5.7)</td>
</tr>
<tr>
<td>Warfarin+clopidogrel</td>
<td>0 (0/41) (0.0–8.6)</td>
</tr>
<tr>
<td>Warfarin+aspirin+clopidogrel</td>
<td>0 (0/6) (0.0–45.9)</td>
</tr>
<tr>
<td>NOAC only</td>
<td>0 (0/5) (0.0–52.2)</td>
</tr>
<tr>
<td>Warfarin, part of post-TAVR antithrombotic</td>
<td>Yes 1.8 (3/171) (0.4–5.0)</td>
</tr>
<tr>
<td>therapy*</td>
<td>No 10.7 (25/234) (7.0–15.4)</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol. 2016 Nov 8;68(19):2059-2069
Transcatheter Aortic Valve Thrombosis: Incidence, Predisposing Factors, and Clinical Implications.
Hansson NC. et al.
TAVI: Risk of Ischaemic and Bleeding Complication

Nijenhuis VJ. et al.
Antithrombotic treatment in patients undergoing transcatheater aortic valve implantation (TAVI).
Thromb Haemost. 2015 Apr;113(4):674-85
Major Late Bleeding: Etiology

142 Major Late Bleedings
(incidence 5.9%)

Généreux P. et al.
Incidence, predictors, and prognostic impact of late bleeding complications after transcatheter aortic valve replacement.
AFIB and MLB after TAVI: Cumulative Risk

Généreux P. et al.
Incidence, predictors, and prognostic impact of late bleeding complications after transcatheter aortic valve replacement.
## Current Recommendations for Anti-Thrombotic Therapy Following Transcatheter Aortic Valve Implantation

<table>
<thead>
<tr>
<th>Long-term anti-thrombotic treatment</th>
<th>Aspirin 81 mg/day indefinitely</th>
<th>Lifelong aspirin 75–100 mg daily (Class IIb; level of evidence: C)</th>
<th>Low-dose aspirin indefinitely</th>
<th>Low-dose aspirin indefinitely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-procedural anti-thrombotic treatment</td>
<td>Aspirin 81 mg/day + clopidogrel 75 mg/day for 3–6 months If warfarin indicated then no clopidogrel</td>
<td>Aspirin 75–100 mg/day + clopidogrel 75 mg/day for 6 months</td>
<td>ASA 80 mg/day + thienopyridine for 1–3 months If oral anticoagulant indicated (AF), avoid triple therapy unless indication exists</td>
<td>Low-dose aspirin + a thienopyridine early after TAVI In patients in AF, a combination of VKA and aspirin or thienopyridine is generally used, but should be weighed against increased risk of bleeding</td>
</tr>
</tbody>
</table>

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b. Circulation 2014;129:e521–e643
c. Can J Cardiol 2012;28:520–5284
d. Eur Heart J 2012;33:2451–2496
Iung B., Rodés-Cabau J.
Do We Really Need DAPT?

Hassell ME. et al.
Antiplatelet therapy following transcatheter aortic valve implantation.
Heart. 2015 Jul;101(14):1118-25
Triple Therapy Following TAVI

Zeymer U et al.
Antithrombotic therapy after transfemoral aortic valve implantation (TAVI). Potential hazard of triple therapy. (Abstract)
Eur Heart J 2011; 32 Suppl:900

- **Death**
  - DAPT: 7.8
  - OAC+single APT: 8.8
  - OAC+DAPT: 10.6

- **Stroke/Embolism**
  - DAPT: 1.3
  - OAC+single APT: 2.5
  - OAC+DAPT: 4

- **Major Bleeding**
  - DAPT: 0.9
  - OAC+single APT: 0.9
  - OAC+DAPT: 2.7

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**Legend**
- Dual antiplatelet (n=993)
- OAC + mono antiplatelet (n=171)
- OAC + dual antiplatelet (n=237)
## Antithrombotic Treatment

<table>
<thead>
<tr>
<th></th>
<th>PARTNER Trial (a)</th>
<th>ACC/STS Recommendations (b)</th>
<th>CCS Statement (c)</th>
</tr>
</thead>
</table>
| **Preprocedural**    | ASA 81 mg  
Clopidogrel 600 mg                            |                                                     |                                            |
| **Periprocedural**   | UFH  
ACT 250 sec  
Reversal with protamine: optional  
Bivalirudin- not allowed | UFH  
ACT 300sec  
Reversal with protamine recommended  
Bivalirudin not mentioned |                                            |
| **Postprocedural**   | ASA 81 mg/ day +  
Clopidogrel 75 mg/ day x 90 d | ASA 81 mg/ day +  
Clopidogrel 75 mg/ day x 3–6 mo. | Indefinite low dose ASA generally recommended +TNP x 1–3 mo. |
|                      | If warfarin indicated (Afib) then no  
clopidogrel                                       | If warfarin indicated (Afib) then no  
clopidogrel                                       | If oral anticoagulant indicated (Afib), avoid triple therapy unless definite indication exists |

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c. J Am Coll Cardiol 2012;59:1200–54
## The Future?

<table>
<thead>
<tr>
<th></th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOACs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban/Rivaroxaban</td>
<td>Rapid onset and predictable anticoagulation</td>
<td>No antidote, &gt; bleeding risk</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Rapid onset and predictable anticoagulation</td>
<td>No experience with antidote in this setting</td>
</tr>
<tr>
<td><strong>New P2Y12 inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Rapid onset, &gt; potency, &lt; interpatient variability</td>
<td>Unknown if &gt; degree of platelet inhibition is useful, contraindicated if prior CVE, &gt; bleeding risk</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Rapid onset, &gt; potency, &lt; interpatient variability</td>
<td>Unknown if &gt; degree of platelet inhibition is useful, BID dose, dyspnoea, &gt; bleeding risk</td>
</tr>
</tbody>
</table>

Rodés-Cabau J. et al.  
Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events.  
<table>
<thead>
<tr>
<th>Trial</th>
<th>ARTE(a)</th>
<th>ATLANTIS(b)</th>
<th>GALILEO(c)</th>
<th>POPular-TAVI(d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
</tr>
<tr>
<td>Planned N</td>
<td>200</td>
<td>1500</td>
<td>1500</td>
<td>1000</td>
</tr>
<tr>
<td>Study regimen</td>
<td>Clopid 3 m ASA 6 m</td>
<td>Apixaban</td>
<td>ASA 3 m + Rivaroxaban 12 m</td>
<td>Aspirin alone / OAC alone</td>
</tr>
<tr>
<td>Control regimen</td>
<td>ASA 6 m</td>
<td>Standard of care (DAPT/SAPT/OAC)</td>
<td>Clopid 3 m + ASA 12 m</td>
<td>Aspirin/OAC + Clopid 3m</td>
</tr>
<tr>
<td>Primary EP</td>
<td>Death, MI, CVA or major bleed @ 1y</td>
<td>Death, MI, stroke, TIA, systemic embolism, intracardiac or bioprosthesis thrombus, DVT, PE, major bleed @ 6m</td>
<td>Death, stroke, MI, valve thrombosis, PE, DVT and systemic embolism @1y</td>
<td>Any bleeding @1y</td>
</tr>
</tbody>
</table>

a.NCT01559298  
b.NCT02664649  
c.NCT02556203  
d.NCT02247128