Optimal Antithrombotic Therapy After TAVR and Ongoing Clinical Trials

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Conflict of Interest Statement

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

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<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<tr>
<td>Consulting Fees/Honoraria</td>
<td>Edwards LifeSciences</td>
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<td>Medtronic Inc</td>
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<td>Consulting Fees/Honoraria</td>
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Medical Treatment After TAVR
- Antithrombotic
- Low-Dose Diuretics
- HTN, DM, Lipid Drugs
Timing of CerebroCVA Events after TAVI

Stortecky et al – Circulation 2012; 126:2921-4
4D-CT after TAVR

Normal leaflets

Thickened leaflets with thrombus

Subclinical Leaflet Thrombosis after TAVR

Evidence of Reduced Leaflet Motion in Multiple Prosthesis Types

Subclinical Leaflet Thrombosis in SVR and TAVR: 2 Observational Registry

657 patients underwent CTs in the RESOLVE registry, Cedars-Sinai Medical Center, Los Angeles

274 patients underwent CTs in the SAVORY registry, Rigshospitalet, Copenhagen

931 patients undergoing CTs

890 patients with interpretable CT
RESOLVE registry: 626 patients
SAVORY registry: 264 patients
Median time from AVR to CT 83 days (IQR 32–281 days)

752 TAVR
Median time from TAVR to CT 58 days (IQR 32–236 days)

138 SAVR
Median time from SAVR to CT 162 days (IQR 79–417 days)

Time from TAVR to CT vs. SAVR to CT: p<0.0001

Prevalence of reduced leaflet motion

- **TAVR**: 13.4% (101 out of 752) patients
- **SAVR**: 3.6% (5 out of 138) patients

**TAVR vs. SAVR**: p=0.001

Analysis of Antithrombotic Regimen

Anticoagulation vs. antiplatelet therapy

Anticoagulation vs. DAPT: $p<0.0001$

Anticoagulation vs. monoantiplatelet therapy: $p<0.0001$

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 in 20 out of 22 patients not treated with anticoagulation
  - \(P<0.0001\)
Anticoagulation vs. DAPT

<table>
<thead>
<tr>
<th>Anticoagulation/Thromboprophylaxis</th>
<th>Index CT</th>
<th>Follow-up CT</th>
</tr>
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<tbody>
<tr>
<td>DAPT continued after index CT</td>
<td><img src="path" alt="Index CT" /></td>
<td><img src="path" alt="Follow-up CT" /></td>
</tr>
<tr>
<td>Warfarin initiated after index CT</td>
<td><img src="path" alt="Index CT" /></td>
<td><img src="path" alt="Follow-up CT" /></td>
</tr>
<tr>
<td>Rivaroxaban initiated after index CT</td>
<td><img src="path" alt="Index CT" /></td>
<td><img src="path" alt="Follow-up CT" /></td>
</tr>
<tr>
<td>Apixaban initiated after index CT</td>
<td><img src="path" alt="Index CT" /></td>
<td><img src="path" alt="Follow-up CT" /></td>
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- **Progression of reduced leaflet motion**: Index CT shows reduced leaflet motion, while follow-up CT shows progression.
- **Resolution of reduced leaflet motion**: Index CT shows reduced leaflet motion, while follow-up CT shows resolution.

Legend:
- DAPT: Direct Oral Anticoagulants
- Index CT: Initial computed tomography
- Follow-up CT: Follow-up computed tomography

Note: Images depict examples of anticoagulation and thromboprophylaxis outcomes.
Clinical Impact of Leaflet Thrombosis

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

<table>
<thead>
<tr>
<th>Non-procedural events</th>
<th>Normal leaflet motion (N=784)</th>
<th>Reduced leaflet motion (N=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td></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>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4/784 (0.5%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Strokes/TIs</td>
<td>20/784 (2.6%)</td>
<td>1.75</td>
</tr>
<tr>
<td>All strokes*</td>
<td>15/784 (1.9%)</td>
<td>1.31</td>
</tr>
<tr>
<td>Ischemic strokes</td>
<td>14/784 (1.8%)</td>
<td>1.22</td>
</tr>
<tr>
<td>TIAs</td>
<td>7/784 (0.9%)</td>
<td>0.60</td>
</tr>
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# Current 2017 ACC/AHA Guideline: TAVR

<table>
<thead>
<tr>
<th>IIib</th>
<th>C</th>
<th>Clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100 mg daily.</th>
<th>2014 recommendation remains current.</th>
</tr>
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<tbody>
<tr>
<td>III: Harm</td>
<td>B</td>
<td>Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical valve prostheses (200,212,213).</td>
<td>2014 recommendation remains current.</td>
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</table>

**NEW:** Studies have shown that valve thrombosis may develop in patients after TAVR, as assessed by multidetector computerized tomographic scanning. This valve thrombosis occurs in patients who received antiplatelet therapy alone but not in patients who were treated with VKA.

See Online Data Supplement 6.

Several studies have demonstrated the occurrence of prosthetic valve thrombosis after TAVR, as assessed by multidetector computerized tomography, which shows reduced leaflet motion and hypo-attenuating opacities. The incidence of this finding has varied from 7% to 40%, depending on whether the patients are from a clinical trial or registry and whether some patients received anticoagulation with VKA (203,210,211). Up to 18% of patients with a thrombus formation developed clinically overt obstructive
Antithrombotic Trials After TAVR

Omission of Clopidogrel
- ARTE Trial
- POPular TAVI Trial
- CLOE Trial

NOAC Trial
- GALILEO Trial
- ATLANTIS Trial
- ENVISAGE TAVI-AF Trial
- ADAPT-TAVR Trial
ARTE Trial - Study Design

Prospective, randomized, open label, multicenter study

Patients randomized (the day prior to the TAVR procedure)

Aspirin 80-100mg/d
- Start at least 24hrs before TAVR
- Continued for at least 6 months

Aspirin 80-100mg/d + Clopidogrel 75mg/d

Clopidogrel treatment
- Initial dose of 300 mg followed by 75 mg/d

Transfemoral approach
- Start within 24hrs before TAVR
- Continued for 3 months

Transapical/Transaortic/Transcarotid approach
- Start within 24hrs after TAVR
- Continued for 3 months

Clinical visit/phone contact at 1-3- and 12-month follow-up
ARTE Trial - Results

Flowchart of the Study Population

222 Patients undergoing TAVR randomized

111 Randomized to receive aspirin + clopidogrel
110 Received intervention as randomized
1 Did not receive the allocated treatment (clopidogrel never started)

3-month follow-up
0 Lost to follow-up
111 included in primary analysis

111 Randomized to receive aspirin
109 Received intervention as randomized
2 Did not receive the allocated treatment (clopidogrel prescribed by the physician responsible for the patient)

3-month follow-up
0 Lost to follow-up
111 included in primary analysis
Kaplan-Meier Curves (Combined Endpoint)

- Aspirin + Clopidogrel
- Aspirin

Log-rank p=0.067
Kaplan-Meier Curves (Ischemic, Bleeding Events)

**Major or life-threatening bleeding**
- Aspirin + Clopidogrel
- Aspirin

**Stroke or TIA**
- Aspirin + Clopidogrel
- Aspirin

**Myocardial infarction (MI)**
- Aspirin + Clopidogrel
- Aspirin

**Death**
- Aspirin + Clopidogrel
- Aspirin
Ongoing Trials: Popular-TAVI

To test if monotherapy with aspirin or OAC vs additional clopidogrel after TAVI reduces bleeding with a favorable net-clinical benefit.
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
Antithrombotic Trials After TAVR

Omission of Clopidogrel
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- POPular TAVI Trial
- CLOE Trial

NOAC Trial
- GALILEO Trial
- ATLANTIS Trial
- ENVISAGE TAVI-AF Trial
- ADAPT-TAVR Trial
Ongoing Trials: GALILEO

GALILEO (Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement (TAVR) to optimize clinical outcomes will compare rivaroxaban-based)

1520 patients after successful TAVI procedure

R 1:1

Rivaroxaban 10 mg OD and Aspirin 75-100 mg OD

Drop of aspirin

Rivaroxaban 10 mg OD

Clopidogrel 75 mg OD and Aspirin 75-100 mg OD

Drop of clopi

Aspirin 75-100 mg OD

Primary end-point is death, MI, stroke, non-CNS systemic emboli, symptomatic valve thrombosis, deep vein thrombosis or pulmonary embolism, major bleedings over 720 days of treatment exposure.
Ongoing Trials: ATLANTIS

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
  - **R 1:1**
  - **VKA**
  - **Apixaban 5mg bid***

- **Stratum 2**: No indication for OAT
  - **R 1:1**
  - **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 15-29mL/min or if two of the following criteria: age≥80 years, weight≤60kg or creatinine≥1.5mg/dL (133μMol).*
Ongoing Trials

: ENVISAGE TAVI-AF

ENVISAGE TAVI AF -- Study Design

Prospective, randomized, open-label, blinded evaluation of edoxaban vs VKA in approximately 1400 patients with AF indicated for chronic OAC after successful TAVI (~2500 patient-y)

TAVI without severe complications at randomization

R 1:1

24 h to 5 d

Edoxaban 60 mg daily
with or without antiplatelet therapy

Time to first dose of OAC ≤ 24 h post randomization
Minimum 12-mo treatment event driven
(≥ 6 mo for last patients enrolled)

VKA
with or without antiplatelet therapy

clinicaltrials.gov: NCT02943785; Van Mieghem NM, et al. Am Heart J. (Submitted)
ADAPT-TAVR Trial

Anticoagulant versus Dual Antiplatelet Therapy for Preventing Leaflet Thrombosis and Cerebral Embolization After Transcatheter Aortic Valve Replacement

Seung-Jung Park (Trial Chair) / Duk-Woo Park (Trial Co-chair)
Heart Institute, Asan Medical Center,
University of Ulsan College of Medicine, Seoul, Korea
What is ADAPT-TAVR trial?

• A multi-center, multi-national randomized, open-label, active-treatment, controlled trial.

• To compare the efficacy of NOAC (edoxaban) vs. DAPT (aspirin and clopidogrel) for prevention of leaflet thrombosis (4-D volume-rendered cardiac CT) and cerebral embolization (brain DW-MRI imaging) in patients without an absolute indication for chronic OAC after successful TAVR.
Anticoagulant versus Dual Antiplatelet Therapy for Preventing Leaflet Thrombosis After Transcatheter Aortic Valve Replacement

ADAPT-TAVR Trial

220 patients after successful TAVR procedure

Stratified randomization by (1) device type and (2) participating site

NOAC:
Edoxaban 60 mg once daily* (N=110)

DAPT:
ASA + Clopidogrel (N=110)

Co-Primary endpoint:
1. Incidence of leaflet thrombosis on Cardiac CT scan at 6 months
2. Number of new lesion on brain DW-MRI at 6 months relative to post-TAVR

*N30 mg once daily if moderate or severe renal impairment (creatinine clearance 15 – 50 mL/min), low body weight ≤60kg, or concomitant use of P-glycoprotein inhibitors (cyclosporin, dronedarone, erythromycin, ketoconazole).
Study endpoints

Primary

The primary study end points were pre-defined; Incidence of leaflet thrombosis on 4-dimensional, volume-rendered cardiac CT imaging at 6 months
Study endpoints

Secondary

• Number of new lesions on brain DW-MRI scans at 6 months relative to immediate post-TAVR
• Death (all-cause, cardiovascular, or non-cardiovascular mortality)
• MI
• Stroke or TIA (disabling or non-disabling)
• Bleeding event (life-threatening or disabling, major bleeding, or minor bleeding)
• Echocardiographic parameter (the mean transaortic valve PG and velocity time integral ratio at baseline and 6-month follow-up).
• New lesion volume on MRI scans
• Neurological and neurocognitive function

*All clinical endpoints are adjudicated according to the VARC-2 definition and the NeuroARC definition
Inclusion criteria

1. Aged ≥19 years with successful TAVR procedure
2. Either native valve or valve-in-valve with any approved/marketed device

* A successful TAVR is defined as device success according to the VARC-2 criteria:
Exclusion criteria

1. Any AF with an indication for chronic OAC.
2. An ongoing indication for OAC or any other indication for continued treatment with any OAC
3. Any ongoing indication for DAPT (recent ACS or PCI within 12 months)
4. Planned coronary or vascular intervention or major surgery
5. Clinically significant bleeding patients or patients with increased bleeding risk due to underlying conditions
6. Clinically overt stroke within the last 3 months
Cardiac CT imaging

• For all patients enrolled in this trial, CT (four-dimensional, volume-rendered) will be performed at 6 months (± 1 month) after TAVR to confirm the
1. presence of the leaflet thrombosis of THV
2. quantitative assessment of leaflet motion

• Leaflet motion; defined as normal, mildly reduced (<50% reduction), moderately reduced (50 to 70% reduction), severely reduced (>70% reduction), or immobile (lack of motion in at least one valve leaflet) in at least one valve leaflet
Brain MRI imaging

- For all patients enrolled in this trial, diffusion-weighted (DW) brain MRI using a 3-T scanner will be performed at 1-7 days (baseline) and 6 months (follow-up).

- Follow-up MRI imaging will be matched with immediate post-TAVR scans, and subtraction analyses are performed to identify new lesions in the entire brain. MRI outcomes included calculation of number and volume of new DWIs (postprocedure – 6 months) by subtraction of the existing baseline lesions in the whole brain.
Dedicated Imaging Core Laboratory

Imaging endpoints in clinical trials

Asan Image Metrics - AIM

"임상시험에서 영상 프로토콜 설계부터 활용 및 분석까지
통합적인 자문 및 영상지원 서비스를 통해
효율적이고 신속 정확한 임상시험이 진행되도록 지원합니다."
Neurological and Neurocognitive function assessment

• All study subjects will undergo detailed neurologic and cognitive assessment at 1-7 days (baseline) and 6 months (follow-up).

• Neurologic assessments included standard clinical scales (the National Institutes of Health Stroke Scale [NIHSS] and the modified Rankin Scale [mRS]), and cognitive assessments included the Montreal Cognitive Assessment (MoCA).
Summary – Antithrombotic Strategy after TAVR

- TAVR patients have multiple thrombotic- and bleeding-related comorbidities. Thus, it make optimal antiplatelet and anticoagulant management to be complex.
- Currently, optimal antithrombotic strategy following TAVR is still debating.
- Guidelines differ on anticoagulation strategies in TAVR, without a strong evidence base for their recommendations.
- Practice variation in the real world is substantially high.
- Clinical trials on different antithrombotic regimens are ongoing & expanding.
Thank You !!

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