Valve Thrombosis, Durability and Ongoing Antithrombotic Trials for TAVR

Do-Yoon Kang, MD
University of Ulsan College of Medicine, Heart Institute, Asan Medical Center, Seoul, Korea
The TCTAP 2018 Disclosure

Do-Yoon Kang, MD

I have no financial conflicts of interest to disclose concerning the presentation
# TAVR Device Evolution

## Devices for Transcatheter Aortic Valve Implantation

<table>
<thead>
<tr>
<th>Year</th>
<th>Devices</th>
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### Frame/Deployment

### Valve

### Seal/skirt/cuff

### Access

### Anti Calcification Treatment

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TAVR Trends
National Trend in France, 2007~2015

Central Illustration: Changes in Number, Type, and Mortality Rates of AVRs in France from 2007 to 2015

A: Changes in Number of Aortic Valve Replacements from 2007 to 2015

Estimated Global TAVR Growth

This year > 100,000 and by 2025 almost 300,000!

SOURCE: Credit Suisse TAVI Comment – January 8, 2015. ASP assumption for 2024 and 2025 based on analyst model. Revenue split assumption in 2025 is 45% U.S., 35% EU, 10% Japan, 10% ROW
In 2018, TAVR is a Routine Practice

- 76/M with history of CABG
- Visiting Clinic
- Admission Screening
- TAVR Discharge
- 5 Days

- Conscious Sedation
- No TEE,
- No scar, no pain
- No complication
- Back home at D-2
“Minimalist Approach”
Post TAVR Care in AMC

- Short stay (1 day) in ICU
- Optional temporary pacemaker
- Early mobilization
- Avoid polypharmacy
- Cardiac Rehabilitation Clinic
Medical Treatment After TAVR

- Antithrombotic
- Low-Dose Diuretics
- HTN, DM, Lipid Drugs
Timing of CVA 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

Corevalve  Portico  Sapien  Surgical valve

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

Reduced leaflet motion 106 (11.9%) patients

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

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
Clinical Impact of Leaflet Thrombosis

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

<table>
<thead>
<tr>
<th></th>
<th>Normal leaflet motion (N=784)</th>
<th>Reduced leaflet motion (N=106)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events</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 (4%)</td>
<td>2.91</td>
<td>4 (4%)</td>
<td>2.66</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial</td>
<td>4 (1%)</td>
<td>0.34</td>
<td>1 (1%)</td>
<td>0.67</td>
</tr>
<tr>
<td>infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke / TIAs</td>
<td>27 (3%)</td>
<td>2.36</td>
<td>11 (10%)</td>
<td>7.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All stroke</td>
<td>22 (3%)</td>
<td>1.92</td>
<td>6 (6%)</td>
<td>4.12</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>21 (3%)</td>
<td>1.83</td>
<td>6 (6%)</td>
<td>4.12</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>TIA</td>
<td>7 (1%)</td>
<td>0.60</td>
<td>6 (6%)</td>
<td>4.18</td>
</tr>
</tbody>
</table>

## Current 2017 ACC/AHA Guideline: TAVR

<table>
<thead>
<tr>
<th>Level</th>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>C</td>
<td>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.</td>
</tr>
<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>
</tr>
</tbody>
</table>

### Anticoagulation with a VKA

<table>
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<tr>
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<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>Anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after TAVR in patients at low risk of bleeding (203,210,211).</td>
</tr>
</tbody>
</table>

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...
Ongoing Antithrombotic Trials after TAVR

Omission of Clopidogrel
- POPular TAVI Trial
  - CLOE Trial

NOAC Trial
- GALILEO Trial
- ATLANTIS Trial
- ENVISAGE TAVI-AF Trial
- ADAPT-TAVR Trial
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

**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

**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

**The CLOE Trial – Study Scheme (NHLBI, NIH submission)**
Dangas, Mack, Gelijns, Moskowitz, Parides, Mehran, Marx et al
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

Rivaroxaban 10 mg OD and Aspirin 75-100 mg OD

- Drop of aspirin
- Rivaroxaban 10 mg OD

Clopidogrel 75 mg OD 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

- **Stratum 2**: No indication for OAT
  - R 1:1
  - Apixaban 5mg bid*
  - 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
- 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
Trial Scheme: ADAPT-TAVR Trial

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

*30 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
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 – Medical Tx after TAVR 
Antithrombotic Strategy

• TAVR patients have multiple thrombotic- and bleeding-related comorbidities. Thus, it make optimal antiplatelet and anticoagulant management to be complex.
• Currently, the optimal antithrombotic strategy following TAVR is not entirely clear.
• 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 antithrombotic regimens are ongoing & expanding.
Thank You!!

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