Interventional Updates 2016
Matthew Johnson, MD

Dual Antiplatelet Therapy (DAPT)

What is the newest.
Can they ever make up there minds????

What is new in the world of TAVR
New risk

MitraClip getting commercial indication!!!

Mitra what!!!!!
Scope of the Guideline

This document will update six guidelines:

- 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery
- 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention
- 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction
- 2014 ACC/AHA Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes
- 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery
- 2014 ACC/AHA/ASTS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease

Table 1. Applying Class of Recommendation and Level of Evidence

Figure 1. Master Treatment Algorithm for Duration of P2Y12 Inhibitor Therapy in Patients With CAD Treated With DAPT
2016 ACC/AHA Duration of DAPT Guideline Focused Update

Overriding Concepts and Recommendations for DAPT and Duration of Therapy

Specific P2Y₁² Inhibitors

Aspirin Dosing in Patients Treated With DAPT

<table>
<thead>
<tr>
<th>COB</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>a-a</td>
<td>In patients with ACS (STEMI or NSTEMI) treated with DAPT after coronary stent implantation and in patients with NSTEMI-ACS treated with medical therapy alone (without revascularization), it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y₁² inhibitor therapy.</td>
</tr>
<tr>
<td>IIa</td>
<td>a-a</td>
<td>In patients with ACS (STEMI or NSTEMI) treated with DAPT after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel or clopidogrel for maintenance P2Y₁² inhibitor therapy.</td>
</tr>
<tr>
<td>III</td>
<td>a-a</td>
<td>Prasugrel should not be administered to patients with a prior history of stroke or TIA.</td>
</tr>
</tbody>
</table>
Overriding Concepts and Recommendations for DAPT and Duration of Therapy

Aspirin Dosing in Patients Treated With DAPT

**COR LOE Recommendation**

I B-NR In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.

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Aspirin Dosing in Patients Treated With DAPT

<table>
<thead>
<tr>
<th>COI</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B-NR</td>
<td>In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.</td>
</tr>
</tbody>
</table>

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2016 ACC/AHA Duration of DAPT Guideline Focused Update

Percutaneous Coronary Intervention

Duration of DAPT in Patients With SIHD Treated With PCI

Duration of DAPT in Patients With ACS Treated With PCI
**Percutaneous Coronary Intervention**

**Duration of DAPT in Patients With SIHD Treated With PCI**

**COR LOE Recommendations**

I A  In patients with SIHD treated with DAPT after BMS implantation, P2Y₁₂ inhibitor therapy with clopidogrel should be given for a minimum of 1 month.

I B-NR In patients treated with DAPT, the recommended daily dose of aspirin is 81 mg (range, 75 mg to 100 mg).

I B-R In patients with SIHD treated with DAPT after DES implantation, P2Y₁₂ inhibitor therapy with clopidogrel should be given for at least 6 months.

SR indicates systematic review.

**Duration of DAPT in Patients With SIHD Treated With PCI (cont’d)**

**COR LOE Recommendations**

IIb A SR  In patients with SIHD treated with DAPT after BMS or DES implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, repeat revascularization, oral anticoagulant use), continuation of DAPT with clopidogrel for longer than 3 months may be reasonable.

IIb C-LD In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y₁₂ inhibitor therapy after 3 months may be reasonable.
### Duration of DAPT in Patients With ACS Treated With PCI

**COR LOE Recommendations**

<table>
<thead>
<tr>
<th>Level</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I B</td>
<td>R</td>
<td>In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after BMS or DES implantation, P2Y₁₂ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months.</td>
</tr>
<tr>
<td>I B</td>
<td>NR</td>
<td>In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P₂Y₁₂ inhibitor therapy.</td>
</tr>
<tr>
<td>II a</td>
<td>B</td>
<td>In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance P₂Y₁₂ inhibitor therapy.</td>
</tr>
<tr>
<td>II b</td>
<td>A</td>
<td>SR In patients with ACS (NSTE-ACS or STEMI) treated with coronary stent implantation who have tolerated DAPT without a bleeding complication, or develop significant overt bleeding, discontinuation of P₂Y₁₂ inhibitor therapy after 6 months may be reasonable.</td>
</tr>
</tbody>
</table>

### Duration of DAPT in Patients With ACS Treated With PCI (cont’d)

<table>
<thead>
<tr>
<th>Level</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>II b</td>
<td>B</td>
<td>SR Prasugrel should not be administered to patients with a prior history of stroke or TIA.</td>
</tr>
</tbody>
</table>

**Note:** SR indicates systematic review.
In patients treated with DAPT after coronary stent implantation who subsequently undergo CABG, P2Y₁₂ inhibitor therapy should be resumed postoperatively so that DAPT continues until the recommended duration of therapy is completed.

In patients with ACS (NSTE-ACS or STEMI) being treated with DAPT who undergo CABG, P2Y₁₂ inhibitor therapy should be resumed after CABG to complete 12 months of DAPT therapy after ACS.

In patients treated with MAD [a daily aspirin dose of 81 mg (range 75 mg to 100 mg) is recommended.

In patients with SHD, DAPT (with clopidogrel initiated early postoperatively) for 12 month after CABG may be reasonable to improve vein graft patency.
2016 ACC/AHA Duration of DAPT Guideline Focused Update

Stable Ischemic Heart Disease

<table>
<thead>
<tr>
<th>LOE</th>
<th>LBE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>In patients with SIHD treated with DAPT after BMS implantation, P2Y₁₂ inhibitor therapy (clopidogrel) should be given for a minimum of 1 month.</td>
</tr>
<tr>
<td>1</td>
<td>B-NR</td>
<td>In patients with SIHD treated with DAPT after DES implantation, P2Y₁₂ inhibitor therapy (clopidogrel) should be given for at least 6 months.</td>
</tr>
<tr>
<td>1</td>
<td>B-NR</td>
<td>In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.</td>
</tr>
<tr>
<td>2a</td>
<td>A</td>
<td>In patients with SIHD being treated with DAPT for an MI that occurred 6 to 12 months earlier who have tolerated DAPT without a bleeding complication and who are at low bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), further continuation of DAPT may be reasonable.</td>
</tr>
</tbody>
</table>
### Stable Ischemic Heart Disease (cont’d)

<table>
<thead>
<tr>
<th>Level</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb A</td>
<td>SR</td>
<td>In patients with SIHD treated with BMS or DES implantation who have tolerated DAPT without a bleeding complication and are at low bleeding risk (e.g., prior history of vascular surgery or previous bleeding event), continued DAPT with high potency clopidogrel for longer than 1 year is reasonable. If patients treated with BMS or DES are at higher risk for both ischemic and bleeding complications, DAPT may be reasonable.</td>
</tr>
<tr>
<td>IIb B</td>
<td>NR</td>
<td>In patients with SIHD treated with BMS or DES implantation who have tolerated DAPT without a bleeding complication and have a history of ACS, coronary stent implantation, or recent CABG (within 12 months), treatment with DAPT is not beneficial.</td>
</tr>
</tbody>
</table>

**Figure 4. Treatment Algorithm for Duration of P2Y₁₂ Inhibitor Therapy in Patients With SIHD (Without ACS Within the Past Several Years)**

2016 ACC/AHA Duration of DAPT Guideline Focused Update

**Acute Coronary Syndrome**

- Duration of DAPT in Patients With ACS Treated With Medical Therapy Alone
- Duration of DAPT in Patients With STEMI Treated With Fibrinolytic Therapy
- Duration of DAPT in Patients With ACS Treated With PCI
- Duration of DAPT in Patients With ACS Treated With CABG
**Duration of DAPT in Patients With ACS Treated With Medical Therapy Alone**

<table>
<thead>
<tr>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-2</td>
<td>Patients with ACS who are managed with medical therapy alone (without revascularization or fibrinolytic therapy) and treated with DAPT, P2Y₁₂ inhibitor therapy (either clopidogrel or ticagrelor) should be continued for at least 12 months.</td>
</tr>
<tr>
<td>B-NR</td>
<td>Patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.</td>
</tr>
<tr>
<td>1α</td>
<td>Patients with NSTE-ACS who are managed with medical therapy and treated with DAPT, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y₁₂ inhibitor therapy.</td>
</tr>
<tr>
<td>1β</td>
<td>Patients with ACS who are treated with medical therapy alone (without revascularization or fibrinolytic therapy) and who have tolerated DAPT without bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, and antiplatelet use), continuation of DAPT for longer than 12 months may be reasonable.</td>
</tr>
</tbody>
</table>

**Acute Coronary Syndrome (NSTE-ACS and STEMI)**

**Duration of DAPT in Patients With STEMI Treated With Fibrinolytic Therapy**

<table>
<thead>
<tr>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>In patients with STEMI treated with DAPT in conjunction with fibrinolytic therapy, P2Y₁₂ inhibitor therapy (clopidogrel) should be continued for a minimum of 14 days (Level of Evidence: A) and ideally at least 12 months (Level of Evidence: C-EO).</td>
</tr>
<tr>
<td>C-EO</td>
<td>In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.</td>
</tr>
<tr>
<td>1</td>
<td>In patients with STEMI treated with fibrinolytic therapy who have tolerated DAPT without bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, and antiplatelet use), continuation of DAPT for longer than 12 months may be reasonable.</td>
</tr>
</tbody>
</table>
**Acute Coronary Syndrome (NSTEMI and STEMI)**

**Duration of DAPT in Patients With ACS Treated With PCI**

### Recommendations

- **I B-R** In patients with ACS treated with PCI after BMS or DES implantation, P2Y₁₂ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months.

- **I B-NR** In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.

- **IIa B-R** In patients with ACS treated with PCI after coronary stent implantation, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y₁₂ inhibitor therapy.

- **IIa B-R** In patients with ACS treated with PCI after coronary stent implantation, who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance P2Y₁₂ inhibitor therapy.

### Duration of DAPT in Patients With ACS Treated With PCI

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>In patients with ACS treated with PCI after BMS or DES implantation, P2Y₁₂ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months.</td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.</td>
</tr>
<tr>
<td>Ib</td>
<td>B-R</td>
<td>In patients with ACS treated with PCI after coronary stent implantation, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y₁₂ inhibitor therapy.</td>
</tr>
<tr>
<td>Ib</td>
<td>B-R</td>
<td>In patients with ACS treated with PCI after coronary stent implantation, who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance P2Y₁₂ inhibitor therapy.</td>
</tr>
</tbody>
</table>

### Duration of DAPT in Patients With ACS Treated With PCI (cont’d)

<table>
<thead>
<tr>
<th>COR</th>
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<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ib</td>
<td>A II</td>
<td>In patients with ACS treated with PCI after ACS implantation who have tolerated DAPT without bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, or anticoagulant use), continuation of DAPT for longer than 12 months may be reasonable.</td>
</tr>
<tr>
<td>Ib</td>
<td>C-II-D</td>
<td>In patients with ACS treated with PCI after ACS implantation who develop a high-risk of bleeding (e.g., treatment with oral anticoagulant therapy) or are at high risk of severe bleeding complication (e.g., major intracranial surgery), discontinuation of P2Y₁₂ inhibitor therapy after 6 months may be reasonable.</td>
</tr>
<tr>
<td>Ib</td>
<td>B-R</td>
<td>Prasugrel should not be administered to patients with a prior history of stroke or TIA.</td>
</tr>
</tbody>
</table>

**SR** indicates systematic review.
Acute Coronary Syndrome (NSTE-ACS and STEMI)

Duration of DAPT in Patients With ACS Treated With CABG

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 1   | C-LD| In patients with ACS being treated with DAPT who undergo CABG, P2Y12 inhibitor therapy should be resumed after CABG to complete 12 months of DAPT therapy after ACS.

Figure 5. Treatment Algorithm for Duration of P2Y12 Inhibitor Therapy in Patient With Recent ACS (NSTE-ACS or STEMI)
Perioperative Management—Timing of Elective Noncardiac Surgery in Patients Treated With PCI and DAPT

**COR LOE Recommendations**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I B-NR</td>
<td></td>
<td>elective noncardiac surgery should be delayed 30 days after BMS implantation and optimally 6 months after DES implantation.</td>
</tr>
<tr>
<td>I C-EO</td>
<td></td>
<td>In patients treated with DAPT after coronary stent implantation who need urgent surgical procedures that mandate the discontinuation of P2Y&lt;sub&gt;12&lt;/sub&gt; inhibitor therapy, it is recommended that aspirin be continued if possible and the P2Y&lt;sub&gt;12&lt;/sub&gt; platelet receptor inhibitor be restarted as soon as possible after surgery.</td>
</tr>
<tr>
<td>Ii C-EO</td>
<td></td>
<td>When noncardiac surgery is required in patients currently taking a P2Y&lt;sub&gt;12&lt;/sub&gt; inhibitor, a consensus decision among treating physicians as to the relative risks of surgery and discontinuation or continuation of antiplatelet therapy can be useful.</td>
</tr>
<tr>
<td>III: Harm B-NR</td>
<td></td>
<td>Elective noncardiac surgery should not be performed within 30 days after BMS implantation or within 3 months after DES implantation in patients in whom DAPT will need to be discontinued perioperatively.</td>
</tr>
<tr>
<td>III: Harm B-NR</td>
<td></td>
<td>Elective noncardiac surgery should not be performed within 30 days after BMS implantation or within 3 months after DES implantation in patients in whom DAPT will need to be discontinued perioperatively.</td>
</tr>
</tbody>
</table>
Figure 6. Treatment Algorithm for the Timing of Elective Noncardiac Surgery in Patients With Coronary Stents

In summary for DAPT update....

Intensification of antiplatelet therapy, with the addition of a P2Y12 inhibitor to aspirin monotherapy, as well as prolongation of DAPT, necessitates a fundamental tradeoff between decreasing ischemic risk and increasing bleeding risk. Decisions about treatment with and duration of DAPT require a thoughtful assessment of the benefit/risk ratio, integration of study data, and consideration of patient preference.

DAPT

In general, shorter-duration DAPT can be considered for patients at lower ischemic risk with high bleeding risk, whereas longer-duration DAPT may be reasonable for patients at higher ischemic risk with lower bleeding risk.
Prior recommendations for duration of DAPT for patients treated with DES were based on data from “first-generation” DES, which are rarely if ever used in current clinical practice. Compared with first-generation stents, newer-generation stents have an improved safety profile and lower risk of stent thrombosis. Recommendations in this focused update apply to newer-generation stents.

Updated recommendations for duration of DAPT are now similar for patients with NSTE-ACS and STEMI, as both are part of the spectrum of acute coronary syndrome. A Class I recommendation (“should be given”) in most clinical settings is made for at least 6-12 months of DAPT (depending on the setting), and a Class IIb recommendation (“may be reasonable”) is made for prolonged DAPT beyond this initial 6- to 12-month period.

In studies of prolonged DAPT after DES implantation or after MI, duration of therapy was limited to several years (akin to many other studied therapies). Thus, in patients for whom the benefit/risk ratio seemingly favors prolonged therapy, the true optimal duration of therapy is unknown. Recommendations in the document apply specifically to duration of P2Y12 inhibitor therapy in patients with CAD treated with DAPT. Aspirin therapy should almost always be continued indefinitely in patients with CAD.
**DAPT**

Lower daily doses of aspirin, including in patients treated with DAPT, are associated with lower bleeding complications and comparable ischemic protection (56-60) than are higher doses of aspirin. The recommended daily dose of aspirin in patients treated with DAPT is 81 mg (range, 75 mg to 100 mg).

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**TAVR**

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**Background**

- Based on randomized trials with first generation devices, transcatheter aortic valve replacement (TAVR) has been incorporated into the treatment strategy for high-risk and inoperable patients with severe AS.
- Procedural complications remain a concern with TAVR, including stroke, vascular complications, paravalvular leak (PVL) and conduction disturbances.
- Addressing these limitations will support TAVR use in lower risk populations.
Evolution of the Edwards Balloon-Expandable Transcatheter Valves

<table>
<thead>
<tr>
<th>Year</th>
<th>Model</th>
<th>Feature</th>
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<tbody>
<tr>
<td>2002</td>
<td>Cribier</td>
<td>*Sheath compatibility for a 23 mm valve</td>
</tr>
<tr>
<td>2006</td>
<td>SAPIEN</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>SAPIEN XT</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>SAPIEN 3</td>
<td></td>
</tr>
</tbody>
</table>

SAPIEN 3 Transcatheter Heart Valve

**Distinguishing Features**
- Bovine pericardial tissue
- Outer skirt to reduce PVL
- Low frame height
- Enhanced frame geometry for ultra-low delivery profile

SAPIEN 3 Commander Delivery System

**Distinguishing Features**
- Improved coaxial alignment
- Fine control of valve positioning
- Accurate positioning

**SAPIEN 3 Valve Size**

<table>
<thead>
<tr>
<th>Size</th>
<th>26 mm</th>
<th>28 mm</th>
<th>28 mm</th>
<th>30 mm</th>
<th>30 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expandable Sheath</td>
<td>16F</td>
<td>18F</td>
<td>18F</td>
<td>18&quot;</td>
<td>18&quot;</td>
</tr>
<tr>
<td>Minimum Access Vessel Diameter</td>
<td>5.0 mm</td>
<td>5.5 mm</td>
<td>6.0 mm</td>
<td>6.0 mm</td>
<td>6.5 mm</td>
</tr>
</tbody>
</table>
The PARTNER II Program

Purpose

To evaluate the safety and efficacy of the SAPIEN 3 transcatheter heart valve system at 30 days in inoperable, high-risk, and intermediate-risk patients.

The PARTNER II S3 Trial

Study Design

Key Inclusion Criteria

• Risk determined by STS score and heart team:
  - High Risk / Inoperable (S3HR): STS score > 8 or heart team determination
  - Intermediate Risk (S3i): STS score between 4 and 8 or heart team determination

• Severe aortic stenosis determined by echocardiography:
  - Valve area < 0.8 cm² or Valve area index < 0.5 cm²/m² and mean gradient > 40mmHg or peak velocity > 4 m/s
Key Exclusion Criteria

- MI within one month
- Bicuspid aortic valve
- Severe aortic regurgitation
- Prior prosthetic valve in any position
- Untreated significant CAD (S3HR only)
- LVEF < 20%
- Stroke or TIA within 6 months
- Upper GI bleed within 3 months
- Creatinine > 3.0 or dialysis
- Estimated life expectancy < 24 months
- Stroke or TIA within 6 months
- Upper GI bleed within 3 months
- Creatinine > 3.0 or dialysis
- Estimated life expectancy < 24 months
- LVEF < 20%

Study Methodology

- All patients presented on a screening call for approval prior to implant.
- 3D imaging of annulus (CT or 3D TEE) recommended for S3HR and required for majority of S3i with core lab analysis prior to implant.
- All patients evaluated by a neurologist at baseline and at follow-up time points.
- Primary Analysis: As treated patients
- S3HR and S3i combined for echocardiographic analyses (valve implant patients).

Study Flow: S3HR & S3i

30 Day Patient Status

<table>
<thead>
<tr>
<th></th>
<th>S3HR</th>
<th>S3i</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>583</td>
<td>1076</td>
</tr>
<tr>
<td>13 Deaths</td>
<td>n = 570</td>
<td>12 Deaths</td>
</tr>
<tr>
<td>6 Withdrawal</td>
<td>SAPIEN 3</td>
<td>0 Withdrawal</td>
</tr>
<tr>
<td>LTFU</td>
<td></td>
<td>LTFU</td>
</tr>
<tr>
<td>567 / 570 or 99.5% follow-up visits performed at 30 Days</td>
<td></td>
<td>1059 / 1064 or 99.5% follow-up visits performed at 30 Days</td>
</tr>
</tbody>
</table>
Baseline Patient Characteristics
S3HR Patients
Average STS = 8.6% (Median 8.4%)
Average Age = 82.6yrs
N = 583

Baseline Patient Characteristics
S3i Patients
Average STS = 5.3% (Median 5.2%)
Average Age = 81.9yrs
N = 1076

Baseline Patient Characteristics
Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>S3HR (n=583)</th>
<th>S3i (n=1076)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA Class III or IV</td>
<td>90.1%</td>
<td>72.6%</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>33.1%</td>
<td>28.0%</td>
</tr>
<tr>
<td>Previous CVA</td>
<td>11.0%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>35.2%</td>
<td>25.3%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>34.5%</td>
<td>34.1%</td>
</tr>
<tr>
<td>COPD - O2 Dependent</td>
<td>11.7%</td>
<td>5.0%</td>
</tr>
<tr>
<td>CKD - Creat. 2 mg/dL</td>
<td>12.0%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>40.7%</td>
<td>30.6%</td>
</tr>
<tr>
<td>Permanent Pacemaker</td>
<td>18.3%</td>
<td>13.2%</td>
</tr>
<tr>
<td>Frailty</td>
<td>30.9%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>
### Baseline Echocardiography

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>S3HR (n=583)</th>
<th>S3I (n=1076)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV Area - cm² (mean ± SD)</td>
<td>0.67 ± 0.18</td>
<td>0.70 ± 0.17</td>
</tr>
<tr>
<td>Annulus Diam. - cm (mean ± SD)</td>
<td>2.2 ± 0.2</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>AV Gradient - mmHg (mean ± SD)</td>
<td>45.5 ± 14.3</td>
<td>46.3 ± 12.7</td>
</tr>
<tr>
<td>LV Ejection Fraction (%)</td>
<td>56.4 ± 14.8</td>
<td>58.6 ± 13.3</td>
</tr>
<tr>
<td>Mod-Severe MR (%)</td>
<td>3.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

### Procedural Factors

<table>
<thead>
<tr>
<th></th>
<th>S3HR (n=583)</th>
<th>S3I (n=1076)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Dilatation (%)</td>
<td>14.8</td>
<td>11.3</td>
</tr>
<tr>
<td>&gt;1 Valve Implanted (%)</td>
<td>0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Valve Embolization (%)</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>IABP During Procedure (%)</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Cardiopulmonary Bypass (%)</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Conscious Sedation (%)</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Median LOS – Days (Min, Max)</td>
<td>5 (1, 33)</td>
<td>4 (1, 64)</td>
</tr>
</tbody>
</table>

### Mortality and Stroke: S3HR

#### At 30 Days (As Treated Patients)

- **Mortality:**
  - All-Cause: 2.2%
  - Cardiovascular: 1.4%
- **Stroke:**
  - All Stroke: 1.5%
  - Blinding: 0.9%

O:E = 0.26

(STS 8.6%)
Mortality and Stroke: S3i
At 30 Days (As Treated Patients)

O:E = 0.21
(STS 5.3%)

Mortality Stroke

Transfemoral Transapical / Transaortic

Mortality: S3HR & S3i
At 30 Days (As Treated Patients)

All-Cause Mortality at 30 Days
Edwards SAPIEN Valves (As Treated Patients)

PARTNER I and II Trials
Overall and TF Patients
All-Cause Mortality at 30 Days
Edwards SAPIEN Valves (As Treated Patients)

PARTNER I and II Trials
TA/TAo Patients

Strokes
At 30 Days (As Treated Patients)

Events (%)  S3HR  S3HR  S3HR  S3i  S3i  S3i
           Overall (n=583) TF TA/TAo (n=92) Overall (n=1076) TF TA/TAo (n=125)
All          1.54  1.63  1.09    2.60  2.42  4.00
Disabling*   0.86  0.81  1.09    1.02  0.95  1.60
Non-Disabling 0.69  0.61   0     1.58  1.47  2.49
TIA          0.69  0.61  1.09    0.37  0.42   0

* CEC adjudicated or Modified Rankin Score ≥ 2 at 30 days

All Strokes at 30 Days
Edwards SAPIEN Valves

PARTNER I and II Trials

Neurological evaluations (pre- and post)
Other Clinical Events
At 30 Days (As Treated Patients)

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>S3HR Overall (n=583)</th>
<th>S3HR TF (n=491)</th>
<th>S3HR TA/TAo (n=92)</th>
<th>S3i Overall (n=1076)</th>
<th>S3i TF (n=951)</th>
<th>S3i TA/TAo (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Vascular Comp.</td>
<td>5.9</td>
<td>5.3</td>
<td>3.3</td>
<td>5.6</td>
<td>5.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Bleeding - Life Threatening</td>
<td>0.3</td>
<td>0.5</td>
<td>10.9</td>
<td>0.4</td>
<td>4.4</td>
<td>12.9</td>
</tr>
<tr>
<td>Annular Rupture</td>
<td>0.3</td>
<td>0.2</td>
<td>1.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.5</td>
<td>0.4</td>
<td>1.1</td>
<td>0.3</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Coronary Occlusion</td>
<td>0.2</td>
<td>0</td>
<td>1.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Aortic Valve Injury</td>
<td>1.0</td>
<td>0.8</td>
<td>2.2</td>
<td>1.5</td>
<td>0.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Non-Periprosthetic Bleeding</td>
<td>10.0</td>
<td>10.2</td>
<td>12.6</td>
<td>10.1</td>
<td>10.6</td>
<td>7.2</td>
</tr>
<tr>
<td>Coronary Occlusion</td>
<td>1.0</td>
<td>0.8</td>
<td>2.2</td>
<td>0.7</td>
<td>0.8</td>
<td>0</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0.2</td>
<td>0.2</td>
<td>0</td>
<td>0.1</td>
<td>0.1</td>
<td>0</td>
</tr>
</tbody>
</table>

Baseline 30 Days
90% 73% 13% 6%

NYHA Functional Class
At 30 Days (As Treated Patients)

Echo Findings: S3HR & S3i
Aortic Valve Area (Valve Implant Patients)
Paravalvular Leak: S3HR & S3i (Valve Implant Patients)

Moderate/Severe PVL at 30 Days
Edwards SAPIEN Valves

Conclusions (1)

• In high-risk and inoperable patients (S3HR), the SAPIEN 3 TAVR system demonstrated low mortality and stroke and excellent clinical outcomes at 30 days:
  - Mortality: 2.2% (TF 1.6%, TA/TAo 5.4%)
  - Disabling Stroke: 0.9%

• In intermediate-risk patients (S3i), SAPIEN 3 was associated with strikingly low mortality and strokes at 30 days:
  - Mortality: 1.1% (TF 1.1%, TA/TAo 1.6%)
  - Disabling Stroke: 1.0%
Conclusions (2)

- Other important clinical findings with SAPIEN 3 (both S3HR & S3i) include:
  - Major vascular complications: ~5%
  - Annular rupture: ~0.2%
  - Coronary obstruction: ~0.3%
  - New pacemakers: ~10%

- Significant paravalvular regurgitation with SAPIEN 3 (both S3HR & S3) was rare:
  - Severe: 0.1%
  - Moderate: 3.7%

Implications

- The rapid evolution of balloon-expandable TAVR, both procedural developments and technical enhancements, represented in the SAPIEN 3 clinical and echo results, indicates at least parity with the best surgical outcomes in comparable patients.

- **SAPIEN 3 TAVR should now be considered as an alternative to surgery, even in lower risk patients with aortic stenosis.**
Background & Purpose

- Of the 50,000 patients in the United States developing significant mitral regurgitation (MR) each year, up to 60% have functional MR
- Isolated leaflet repair for functional mitral regurgitation (FMR) has not been well characterized
- The purpose of this study is to evaluate the safety and efficacy of isolated leaflet repair using the MitraClip device in patients with FMR.

Edge to Edge & MitraClip Concepts

- Facilitates proper leaflet coaptation
  - Degenerative - Anchor flail and prolapsed leaflets
  - Functional - Coapt tethered leaflets to reduce time and force required to close valve
  - Reduces LV volume overload by reducing MR
- Creates tissue bridge
  - May limit dilatation of annulus
    - Septal-lateral (A-P) dimension
  - Supports durability of repair
- Restrains LV wall
  - Limits LV dilatation

Methods

- Surgical candidates with FMR were treated with the MitraClip device as part of the EVEREST protocols.
- FMR was defined as the presence of MR without demonstrated echocardiographic structural valve defects as assessed by TEE.
- TTE performed to assess MR severity and LV function and dimensions at baseline and at 12 months.
- American Society of Echocardiography criteria were used for systematic Core Laboratory assessment of MR severity and LV function.
Methods: Key Eligibility Criteria

- Age 18 years or older
- Moderate to severe (3+) or severe (4+) MR
  - Symptomatic
  - Asymptomatic with LVEF < 60% or LVESD > 40mm
  - ACC/AHA Guidelines, Circ. 114:450, 2006
- MR originates from A2-P2 malcoaptation
- Candidate for mitral valve surgery
- Transseptal deemed feasible
- Key Exclusions
  - EF < 25% or LVESD > 55 mm
  - Renal insufficiency
  - Endocarditis, rheumatic heart disease

Methods: Anatomic Eligibility

- TEE evidence of FMR:
  - Absence of Degenerative valve disease
  - Presence of leaflet “tethering”
    - Not exceeding 10mm
- Sufficient leaflet tissue available for mechanical coaptation
  - > 2mm “vertical” leaflet tissue available
  - Protocol anatomic exclusions
    - Coaptation depth > 11mm
    - Coaptation length < 2mm
- Absence of severe LV dysfunction
  - Excluding LVIDd > 55mm or EF < 25%
  - Ischemic or non-ischemic etiology

EVEREST Preliminary FMR Cohort

- Initial experience using the MitraClip device in patients with FMR.
- Subset of patients with FMR treated in the EVEREST I Feasibility Study or as roll-ins in the EVEREST II Study.
  - Excludes EVEREST II Randomized patients or EVEREST II High Risk Registry patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVEREST I (Feasibility)</td>
<td>FMR patients</td>
<td>8</td>
</tr>
<tr>
<td>EVEREST II (Pivotal)</td>
<td>Non-randomized FMR patients (excludes high risk patients)</td>
<td>15</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>23</strong></td>
</tr>
</tbody>
</table>

Analysis per EVEREST II definitions
EVEREST MR Reduction Goals

- Eligibility requirement: 3+ or 4+ MR
- Protocol requirement: Reduce MR ≤ 2+
- Procedural goal: Reduce MR ≤ 1+
- Durability goal: Maintain MR reduction ≤ 2+

EVEREST Initial FMR Cohort Clinical Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>FMR N=23</th>
<th>EVEREST Overall N=107</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range)</td>
<td>71 (62-88)</td>
<td>71 (62-88)</td>
</tr>
<tr>
<td>≥ age 65</td>
<td>30%</td>
<td>62%</td>
</tr>
<tr>
<td>Male gender</td>
<td>52%</td>
<td>62%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>48%</td>
<td>21%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>96%</td>
<td>69%</td>
</tr>
<tr>
<td>COPD</td>
<td>22%</td>
<td>12%</td>
</tr>
<tr>
<td>History CHF</td>
<td>87%</td>
<td>56%</td>
</tr>
<tr>
<td>Prior Cardiac Surgery</td>
<td>43%</td>
<td>19%</td>
</tr>
<tr>
<td>Initial formulation</td>
<td>20%</td>
<td>29%</td>
</tr>
<tr>
<td>Median LVEDD</td>
<td>4.3 ± 0.7</td>
<td>3.5 ± 0.8</td>
</tr>
<tr>
<td>NYHA III or IV</td>
<td>83%</td>
<td>46%</td>
</tr>
</tbody>
</table>

EVEREST Initial FMR Cohort Patients with 30 Day Major Adverse Events (N = 23)

<table>
<thead>
<tr>
<th>Freedom from Major Adverse Events</th>
<th>87%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death – Unrelated to Clip</td>
<td>0</td>
</tr>
<tr>
<td>Stroke (&gt;72 hours)</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0</td>
</tr>
<tr>
<td>Re-operation for failed surgery</td>
<td>0</td>
</tr>
<tr>
<td>Non-elective Cardiac Surgery (Pericardial Effusion)</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
</tr>
<tr>
<td>Deep wound infection</td>
<td>0</td>
</tr>
<tr>
<td>Ventilation &gt; 48 hrs</td>
<td>0</td>
</tr>
<tr>
<td>GI complication requiring surgery</td>
<td>0</td>
</tr>
<tr>
<td>Septicemia</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding requiring transfusion ≥ 2 units</td>
<td>2</td>
</tr>
</tbody>
</table>
Acute Procedural Success (APS): Defined as placement of one or more Clips resulting in discharge MR severity of 2+ or less, as determined by Core Lab.

**EVEREST Initial FMR Cohort**

**Efficacy Results through Discharge**

N = 23

**Clip Procedure Attempted**

- No APS
  - No Clip implanted
    - MR > 2+: n=1/23 (4%)
  - Acute Procedural Success:
    - Clip implanted
      - MR < 2+: n=10/23 (43%)
  - No APS
    - Clip implanted
      - MR > 2+: n=5/23 (21%)

MR = 2+ (13%)

**Probability of Event Free Clinical Success**

- 0%
- 20%
- 40%
- 60%
- 80%
- 100%

**Event Free Clinical Success Kaplan-Meier**

**EVEREST Initial FMR Cohort:**

**Freedom From MR > 2+ Kaplan-Meier**

Acute Procedural Success (APS) Patients

**EVEREST Initial FMR Cohort:**

**Event Free Clinical Success Kaplan-Meier**

APS Patients

**Function APS Patients**

Freedom from death, mitral valve surgery, & MR > 2+
EVEREST Initial FMR Cohort
NYHA Class, APS Patients* (matched data, n = 12)

- 75% (9/12) Improved
- 17% (2/12) No Change
- 8% (1/12) Worsened w/o MR > 1+

*N: Excludes patients that went to MV surgery post-Clip prior to 12 months or have not reached 12-month follow-up.

EVEREST Initial FMR Cohort:
Surgery Following Clip Procedure
N = 23

- Surgery After Clip Implanted (n = 3)
  - 2 Repairs
  - 1 Replacement

- Surgery After No Clip (n = 1)
  - 1 Replacement

No Partial Clip Detachments
No Clip Embolizations

EVEREST Initial FMR Cohort
Reverse LV Remodeling
APS Patients* (matched data, n = 12)

LV End Diastolic & Systolic Dimensions

- Diastolic
- Systolic

Baseline 12-Month Baseline 12-Month

- p < 0.04
- p < 0.03

LV End Diastolic & Systolic Volumes

- Diastolic
- Systolic

Baseline 12-Month Baseline 12-Month

- p < 0.006
- p < 0.12

*Excludes patients that went to MV surgery post-Clip prior to 12 months or have not reached 12-month follow-up.
EVEREST Initial FMR Cohort Conclusions

- Percutaneous mitral repair with the MitraClip:
  - Effective in reducing MR with a low MAE rate
  - Significant reverse LV remodeling at 1-year
  - Clinical improvement with 58% of patients NYHA Class I at 1-year
  - 79% freedom from death, surgery for valve dysfunction and MR > 2+ at 1-year
  - Surgical options preserved in majority of patients
  - MitraClip facilitates leaflet coaptation reducing MR in functional patients

Study Limitations

- Very small number of patients
- Non randomized
- Observational study
- Initial experience – early in learning curve

Thank-you