EVOLVE Short DAPT: A Single Arm Study of 3-Month DAPT in Patients at High Bleeding Risk Treated with a Bioabsorbable Polymer-Based Everolimus-Eluting Stent

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I, Ajay J. Kirtane, have the following potential conflicts of interest to report:

Institutional funding to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific Corporation, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical
Background

- International guidelines\(^1,\)\(^2\) recommend extended durations of DAPT in patients undergoing PCI with DES
  - Initial recommendations to extend DAPT based upon observational analyses and concern for late ST with earlier generation DES a decade ago
  - Extended DAPT is associated with higher bleeding rates, despite lower rates of MI and ST, and a net neutral to negative effect upon mortality\(^3\)

- SYNERGY is a thin-strut everolimus-eluting stent with an ultrathin abluminal bioabsorbable polymer coating designed to facilitate healing
  - Drug release and polymer degradation in ≤4 months\(^4\)
  - SYNERGY demonstrated low ST rates (≤0.7%) through 5 years in normal bleeding risk patients on standard DAPT duration\(^5,\)\(^6\)
  - Optimized platform to test shorter durations of DAPT

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EVOLVE Short DAPT Study Design

Prospective, multicenter, single-arm study powered to define safety of 3-month DAPT in high bleeding risk (HBR) patients treated with SYNERGY

Co-Primary endpoints: Death/MI and ARC definite/probable ST between 3-15 months
Secondary endpoint: BARC 2/3/5 bleeding between 3-15 months (patients not on chronic anticoagulation)

†Subjects free from stroke, MI, revascularization and ST between 0-3 months eligible to discontinue; Mauri et al. AHJ 2018
EVOLVE Short DAPT – Analysis Population

Age:
- ≤55 years: 2.8%
- 56-65 years: 10.0%
- 66-74 years: 16.7%
- ≥75 years: 70.5%

75.7 ± 8.5 years

Gender:
- Female: 34%
- Male: 66%

BMI:
- Height: 170.0 ± 10.9 cm
- Weight: 83.5 ± 20.6 kg

- 2.8% 10.0%
- 16.7% 70.5%

2.8% 10.0%

<table>
<thead>
<tr>
<th>HBR patients with SYNERGY stent implanted</th>
<th>N=1487</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 75 yrs, and, risk of major bleeding associated with &gt;3m DAPT outweighs the benefit</td>
<td>67.5% (1003)</td>
</tr>
<tr>
<td>Need for chronic or lifelong anticoagulation therapy</td>
<td>30.6% (455)</td>
</tr>
<tr>
<td>History of major bleeding (GUSTO severe/life threatening/moderate) within 12m of index procedure</td>
<td>2.7% (40)</td>
</tr>
<tr>
<td>History of stroke (ischemic or hemorrhagic)</td>
<td>13.4% (200)</td>
</tr>
<tr>
<td>Renal insufficiency (creatinine ≥ 2.0 mg/dl) or failure (dialysis dependent)</td>
<td>9.1% (136)</td>
</tr>
<tr>
<td>Platelet count ≤ 100,000/μL</td>
<td>2.0% (29)</td>
</tr>
</tbody>
</table>

Subjects met more than one HBR criteria: 22.9%

# of HBR criteria met/subject: 1.3 ± 0.5
Clinical Outcomes between 3-15 Months

Analysis Population (N=1457)

Event rate, %

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Event Rate</th>
<th>Denominator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/MI</td>
<td>5.8%</td>
<td>67</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2.1%</td>
<td>40</td>
</tr>
<tr>
<td>Non-cardiac death</td>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td>Def/Prob ST</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td>BARC 2/3/5 bleeding*</td>
<td>7.1%</td>
<td>3</td>
</tr>
</tbody>
</table>

Binary rates; denominator includes patients with sufficient f/u or having a CEC event; *Non-hierarchical
Co-Primary Endpoint: Adjusted Death/MI between 3-15 months with 3-Month DAPT Compared to Historical Control

*One-sided 97.5% Upper Confidence Bound (Z-test);

Worst-case scenario analysis: site-reported MI in control group between 0-12m assumed within 0-3m if not CEC adjudicated

Patients with respective event or sufficient follow-up included in the denominator
Co-Primary Endpoint: ARC Definite/Probable ST between 3-15 months

3-15 M Def/Prob ST, %

P<0.0001

Performance goal 1.0%

0.3

0.5%

1-sided 97.5% UCB*

SYNERGY 3-month DAPT
N=1397

Patients with respective event or sufficient follow-up included in the denominator

*One-sided 97.5% Upper Confidence Bound (Exact test)
## Secondary Endpoint: Adjusted BARC 2,3,5 Bleeding Between 3-15 Months

<table>
<thead>
<tr>
<th></th>
<th>12-Month DAPT (N=947)</th>
<th>3-Month DAPT (N=974)</th>
<th>Difference [95% CI]</th>
<th>Superiority Test P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARC 2,3,5 Bleeding</td>
<td>4.17%</td>
<td>6.26%</td>
<td>2.10% [-0.10%, 4.29%]</td>
<td>0.98</td>
</tr>
<tr>
<td>Type 2</td>
<td>2.12%</td>
<td>3.64%</td>
<td>1.52% [-0.16%, 3.19%]</td>
<td>-</td>
</tr>
<tr>
<td>Type 3</td>
<td>2.32%</td>
<td>2.67%</td>
<td>0.35% [-1.17%, 1.87%]</td>
<td>-</td>
</tr>
<tr>
<td>Type 5</td>
<td>0.00%</td>
<td>0.27%</td>
<td>0.27% [-0.05%, 0.60%]</td>
<td>-</td>
</tr>
</tbody>
</table>

 Patients with respective event or sufficient follow-up included in the denominator

Worst-case scenario analysis: site-reported non-death events in control arm between 0-12m assumed within 0-3m if not CEC adjudicated
Limitations

• Data applies to enrolled patients meeting inclusion/exclusion criteria
  o Restricted lesion complexity in patients without myocardial infarction

• Non-randomized design
  o A randomized BMS comparator group would have been extremely challenging to enroll within the US (no FDA-approved short-duration DES)
  o Potential for unmeasured confounding despite multivariable adjustment
  o Differential underreporting of outcomes
    o Non-adjudicated events between 0-12m in the control group led to a conservative “worst-case scenario analysis” where these events were assumed to occur between 0-3m and were therefore censored
Conclusions

• EVOLVE Short DAPT was designed to evaluate the safety of DAPT discontinuation at 3 months in HBR subjects treated with SYNERGY
  o Bleeding risk was significant, and key subgroups (age≥75 with risk/benefit favoring shorter DAPT, need for anticoagulation) were well-represented

• The study met both co-primary endpoints despite incomplete event adjudication in the control group, with favorable rates of ischemic outcomes from 3-15 months after discontinuation of P2Y12 inhibitor
  o Death/MI (adjusted): 5.6%; Definite/probable ST: 0.3%; MI: 1.9%

• These data support the use of SYNERGY with a 3-month duration of DAPT in HBR patients