The Zotarolimus-eluting Endeavor sprint stent in Uncertain DES candidates (ZEUS)

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On behalf of the ZEUS Investigators
Background

Drug-eluting stents (DES) reduce restenosis rates and consequently the risk of target vessel failure as compared to bare metal stents (BMS).

However, first generation devices have raised safety concerns due to an higher incidence of stent thrombosis.

In order to restore safety to a level comparable to that shown after BMS implantation, a prolonged course of dual antiplatelet therapy (DAPT) has been therefore recommended after DES.
DAPT duration and DES

- RCTs comparing DES vs BMS have so far mandated *longer* DAPT regimen after DES as compared to BMS or a similarly *prolonged* course of DAPT in BMS patients (control group) so to match the extended course of therapy after DES.

- No study has so far disentangled the effects of DES vs BMS from those offered by long-term DAPT.

- No study has allowed for the shortest possible DAPT duration, i.e. 30 days, after DES, which is the accepted minimum Tx duration after BMS.
As a consequence, the use of DES instead of BMS remains controversial in selected patient/lesion subsets:

- **Pts at high bleeding risk**
  - *in whom long-term DAPT poses safety concerns*

- **Pts at high thrombosis risk**
  - *whose risk for coronary events may be higher after DES*

- **Pts at low risk for in-stent restenosis**
  - *the need for prolonged DAPT and the long-term risk for adverse events after DES implantation may outweigh their benefit in terms of low re-intervention rates*
Zotarolimus-eluting Endeavor Sprint: hydrophilic polymer-based second-generation device with unique drug fast-release profile

- **Drug Elution Kinetics**
  - E-ZES: 100% eluted at 14 days
  - Other 1 or 2 gen DES

- **Zotarolimus in Arterial Tissue (in Stent)**
  - No detectable drug in arterial tissue beyond 28 days

- **Graphs**
  - Drug release vs. days
  - Zotarolimus concentration vs. days

References:
- Eurolnterv.2007;3:50-53
Study Design

Am Heart J. 2013 Nov;166(5):831-8

Urgent or emergent coronary stenting in pts fulfilling ≥1 of the below:

**High Bleeding Risk**
- Need for OACs
- Previous Relevant Bleeding
- Age > 80 y/o
- Bleeding diathesis
- Known Anemia (Hb<10 gr/dl)
- Need for CCS or NSAID

**High Thrombotic Risk**
- Intolerance to ASA
- Intolerance to any P2Y\textsubscript{12}
- Planned surgery w/in 1 year
- Cancer-life expectancy >1 Y
- Pro-thrombotic diathesis

**Low Restenosis Risk**
- Planned stent ≥3.0 mm, apart from LMCA and SVG intervention or for ISR lesions

Rx: 1:1, Sx: inclusion criteria

1,606 pts, 20 sites in Italy, Switzerland, Portugal and Hungary from June 2011 to September 2012

**Endeavor Sprint**
- Zotarolimus-eluting Stent

**Thin-strut**
- Bare Metal Stent

Primary Endpoint: Death, Myocardial Infarction or Target Vessel Revascularization at 12 months
Study Design

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**Endeavor Sprint**
Zotarolimus-eluting Stent

**Thin-strut**
Bare Metal Stent

**Personalised DAPT duration**, i.e. modelled according to the patient clinical risk profile and **not** by stent type
Study Design

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**DAPT:**
- **None if ASA/P2Y\textsubscript{12} intol.**
- **Up to surgery** if planned
- **≥6 mos** in others

**DAPT:**
- Stable CAD **30 days**
- ACS ≥ **6 mos**
Ferrara—Sponsor and study site with an unrestricted grant from Medtronic.

Clinical Event Committee
- P. Vranckx, Chair
- S. Curello
- G. Guardigli

Data Management and Monitoring
- Medical Trial Analysis
- Eustrategy Research Coordination

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Pavia—M. Ferlini
Lisbon—H. M. Gabriel
Milano—F. Airoldi
Savigliano—A. Dellavalle
Bergamo—G. Musumeci
Ravenna—M. Acquilina
## Key baseline or angiographic features of the study population \( (N=1,606) \)

<table>
<thead>
<tr>
<th>Feature</th>
<th>BMS ( (N=804) )</th>
<th>E-ZES ( (N=802) )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (IQR)</strong></td>
<td>74 (64-81)</td>
<td>74 (64-81)</td>
</tr>
<tr>
<td><strong>Females (%)</strong></td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td><strong>Diabetes (%)</strong></td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td><strong>Prior MI/PCI/CABG (%)</strong></td>
<td>24/19/7</td>
<td>24/19/7</td>
</tr>
<tr>
<td><strong>Mild to Severe CKD (%)</strong></td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td><strong>ACS/STEMI (%)</strong></td>
<td>63/19</td>
<td>63/19</td>
</tr>
<tr>
<td><strong>MVD (%)</strong></td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td><strong>LAD/LMCA treated (%)</strong></td>
<td>51/5</td>
<td>53/5</td>
</tr>
<tr>
<td><strong>≥1 B2/C treated lesion (%)</strong></td>
<td>73</td>
<td>73</td>
</tr>
</tbody>
</table>

MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; CKD: chronic kidney dysfunction; Lad: left anterior descending, LMCA: left main coronary artery; ACS: acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction
Study Population

High Bleeding Risk 828 (52%)

Low Restenosis Risk -Stable- 337 (21%)
- Stable - 199 (12%)
- Unstable - 140 (9%)

High Thrombosis Risk 285 (17%)
- Unstable - 173 (11%)

Low Restenosis Risk -Unstable- 604 (38%)
- Unstable - 29 (2%)
- Stable - 22 (1%)
- Stable - 71 (4%)
- Stable - 14 (1%)
- Stable - 107 (7%)

Study Population
**ZEUS:** Truly high risk patient population

*Event rates at 1 year across stent trials*

≈30% of the screened patient population

<table>
<thead>
<tr>
<th>Event</th>
<th>Death</th>
<th>CV Death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ZEUS</strong></td>
<td>11.3</td>
<td>8</td>
</tr>
<tr>
<td><strong>RESOLUTE AC</strong></td>
<td>2.1</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>LEADERS</strong></td>
<td>3.3</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>SPIRIT IV</strong></td>
<td>1.1</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>SIRIUS</strong></td>
<td>1.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Duration of DAPT* in stent groups (ITT)

*: to first planned permanent discontinuation

- **E-ZES**
  - Median: 31 days (IQR: 30-180)
  - 77.3% cumulative frequency at 180 days

- **BMS**
  - Median: 33 days (IQR: 30-180)
  - 62.5% cumulative frequency at 180 days

- **37.5% on DAPT** at 2 Months
- **24.7% on DAPT** at 6 Months
Major Adverse Cardiovascular events

primary endpoint

HR: 0.76 (0.61-0.95), P=0.011

2 pts, one in each group, were lost to follow-up after hospital discharge
Target Vessel Revascularization

HR: 0.53 (0.37-0.75) P<0.001

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>BMS</th>
<th>E-ZES</th>
</tr>
</thead>
<tbody>
<tr>
<td>804</td>
<td>759</td>
<td>721</td>
</tr>
<tr>
<td>694</td>
<td>675</td>
<td>672</td>
</tr>
<tr>
<td>657</td>
<td>657</td>
<td>657</td>
</tr>
<tr>
<td>636</td>
<td>645</td>
<td>645</td>
</tr>
</tbody>
</table>

BMS 10.7%
E-ZES 5.9%
Myocardial infarction

HR: 0.35 (0.22-0.56), P<0.001

BMS: 8.1%
E-ZES: 2.9%

No. at Risk
BMS: 804 757 730 709 695 684 675 666
E-ZES: 802 762 750 733 726 713 698 684
An application of the Classification System from the Universal MI Definition

![Bar chart showing the application of the Classification System from the Universal MI Definition. The chart compares Type 1, Type 2, Type 3, Type 4a, and Type 4b with E-ZES and BMS. The P-values for each type are as follows: Type 1 (E-ZES: 0.001, BMS: 0.009), Type 2 (E-ZES: 0.11), Type 3 (E-ZES: 0.13), Type 4a (E-ZES: 1, BMS: 0.4), Type 4b (E-ZES: 0.9, BMS: 2.5).]
Definite or Probable Stent Thrombosis

No. at Risk

BMS  804  763  739  723  712  701  692  685
E-ZES  802  767  758  741  733  721  713  708

HR: 0.48 (0.27-0.88), P=0.019
Bleeding events in the two groups

BARC scale

E-ZES
BMS

P=N.S. for all comparisons
### Subgroup Analysis for the Primary Endpoint

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HAZARD RATIO (95% CI)</th>
<th>No. of patients</th>
<th>HAZARD RATIO (95% CI)</th>
<th>P-VALUES Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.76 (0.61-0.95)</td>
<td>1,606</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.85 (0.65-1.10)</td>
<td>1,133</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Female</td>
<td>0.58 (0.38-0.88)</td>
<td>473</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 75 yr</td>
<td>0.82 (0.62-1.10)</td>
<td>741</td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>≤ 75 yr</td>
<td>0.68 (0.48-0.96)</td>
<td>865</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.80 (0.54-1.19)</td>
<td>420</td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>No diabetes</td>
<td>0.74 (0.56-0.96)</td>
<td>1,186</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable coronary disease</td>
<td>0.97 (0.63-1.49)</td>
<td>590</td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>Unstable coronary disease</td>
<td>0.69 (0.53-0.89)</td>
<td>1,016</td>
<td></td>
<td></td>
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<tr>
<td>Protocol mandated no or up to 30 day DAPT</td>
<td>0.75 (0.58-0.96)</td>
<td>1,077</td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>Protocol mandated &gt; 30 day DAPT</td>
<td>0.78 (0.49-1.23)</td>
<td>529</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High bleeding risk criteria yes</td>
<td>0.74 (0.50-1.09)</td>
<td>828</td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>High bleeding risk criteria no</td>
<td>0.74 (0.57-0.97)</td>
<td>778</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High thrombotic risk criteria yes</td>
<td>1.02 (0.64-1.64)</td>
<td>285</td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>High thrombotic risk criteria no</td>
<td>0.70 (0.54-0.90)</td>
<td>1,321</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low restenosis risk criteria yes</td>
<td>0.67 (0.48-0.93)</td>
<td>941</td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>Low restenosis risk criteria no</td>
<td>0.85 (0.63-1.15)</td>
<td>665</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

- In patients at high bleeding, thrombotic or low restenosis risk, E-ZES implantation followed by a personalized duration of DAPT, including no or a 30-day course of therapy, resulted in a lower risk of major adverse cardiovascular events as compared to BMS.

- Our study suggests that E-ZES may become the new gold standard coronary device in pts who cannot or refuse to tolerate (long-term) DAPT.