Final five-year clinical outcomes in the EVOLVE trial: A randomised evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting stent

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Session: Contemporary DES: focus on bioresorbable polymers (part 1)
Date: Thursday, May 19th, 2016
Time: 14:45 – 16:45
Location: Room 343
Disclosures

• Honoraria for speaking/consultancy from Boston Scientific
Bioabsorbable polymer

• Durable polymer coatings of drug-eluting stents have been associated with chronic inflammation and impaired healing.
• Bioabsorbable polymer drug eluting stents may have potential advantages

Reduced polymer load & short-term polymer exposure may:

• Decrease risk of late events including ST and TLR
• Reduce required duration of DAPT and risk if interrupted
The SYNERGY Stent

Platinum Chromium Platform
- 74μm (0.0029in) strut thickness
- Visibility
- Strength
- Flexibility
- Conformability
- Recoil

Everolimus-Eluting
- 100μg/cm²
- 3 month release time
- 45% / 55% mix of drug and polymer

Bioabsorbable Polymer Coating (PLGA)
- Abluminal
- 4μm thick
- 85:15 ratio
- <4 month absorption time

Ultrathin Abluminal Coating

*FESEM image 10K x
The SYNERGY Stent
Synchronous Drug Release & Polymer Absorption

Kinetics of Drug Release and Polymer Absorption
in a Preclinical Porcine Model

PLGA Mass Remaining (%)

Everolimus Released (%)

Time (Days)

0 30 60 90 120

0 25 50 75 100

0 25 50 75 100

Bennett and Dubois. Biologics: Targets and Therapy. 2013; 7: 149-159
Trial Design and Methods

Patients with *de novo* native coronary lesions ≤ 28 mm in length, RVD ≥ 2.25 mm ≤ 3.5, %DS > 50% (excluded LM disease, CTO, AMI or recent MI)

Randomized 1:1:1 at 29 sites (Europe, Australia, New Zealand)

- **PROMUS Element**
  - N = 98
- **SYNERGY**
  - N = 94
- **SYNERGY ½ Dose**
  - N = 99

*Single-blind, noninferiority design*

**Primary Clinical Endpoint:** TLF (TV-CD, TV-MI, or TLR) at 30 days

**Primary Angiographic Endpoint:** In-stent late loss at 6 months

Per protocol patients were treated with clopidogrel, ticlopidine or prasugrel for at least 6 months following the index procedure Meredith et al. *JACC* 2012; 59 (15): 1362-70
*After 1-year follow-up, the prespecified safety analysis patient population, including only those patients treated with a study stent, was analysed. Two SYNERGY patients who did not receive the study stent were not included in the safety analysis.
**EVOLVE Primary Endpoint**

### Late Loss at 6 Months

- **PROMUS Element**: 0.15
- **SYNERGY**: 0.10
- **SYNERGY \( \frac{1}{2} \) Dose**: 0.13

**P** = 0.19*

**P** = 0.56*

### TLF at 30 days

- **PROMUS Element**: 0
- **SYNERGY**: 1.1
- **SYNERGY \( \frac{1}{2} \) Dose**: 3.1

**P** = 0.49*

**P** = 0.25*

Noninferiority was proven because the upper 95.2% confidence bound of the difference in 6-month late loss is <0.20 for both SYNERGY stents (P_{noninferiority} < 0.001)

Intent-to-treat; Mean + Standard Deviation; *P values for superiority comparison

Meredith et al. JACC 2012; 59 (15): 1362-70
### Target Lesion Failure 5-year Follow-up

#### Protocol-required Angiogram

![Graph showing target lesion failure rates over 5 years for SYNERGY vs PE and SYNERGY vs PE ½ dose comparisons.](image)

<table>
<thead>
<tr>
<th>Years</th>
<th>PE</th>
<th>SYNERGY</th>
<th>SYNERGY ½ Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>98</td>
<td>92</td>
<td>99</td>
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<tr>
<td>1</td>
<td>98</td>
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<td>2</td>
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<tr>
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</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>67</td>
<td>61</td>
<td>65</td>
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</tbody>
</table>

**Safety Population; KM Event Rate; log-rank P values**

SYNERGY vs PE: HR 0.77 [0.24, 2.42] \( P = 0.65 \)

SYNERGY vs PE ½: HR 0.74 [0.23, 2.32] \( P = 0.60 \)
## Target Lesion Revascularisation: 5-year Follow-up

### Protocol-required angiogram

<table>
<thead>
<tr>
<th>Numbers at risk</th>
<th>PE</th>
<th>SYNERGY</th>
<th>SYNERGY ½ Dose</th>
</tr>
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<tbody>
<tr>
<td>0 Years</td>
<td>98</td>
<td>92</td>
<td>99</td>
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<tr>
<td>1 Year</td>
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<td>3 Years</td>
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<td>84</td>
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<tr>
<td>4 Years</td>
<td>92</td>
<td>83</td>
<td>91</td>
</tr>
<tr>
<td>5 Years</td>
<td>68</td>
<td>61</td>
<td>67</td>
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</table>

### HR and P values
- **SYNERGY vs PE** HR 0.18 [0.02, 1.47] *P*=0.07
- **SYNERGY vs PE ½** HR 0.17 [0.02, 1.40] *P*=0.06

**TLR (%)**

- **Protocol-required angiogram**
- **6.1%**
- **1.1%**
- **1.0%**

**Safety Population; KM Event Rate; log-rank P values**
Death/MI/TVR
5-year Follow-up

SYNERGY vs PE   HR 0.79 [0.33, 1.89]  P=0.60
SYNERGY vs PE ½ HR 1.28 [0.60, 2.74]  P=0.52

Numbers at risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>98</td>
<td>96</td>
<td>89</td>
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<tr>
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<tr>
<td>SYNERGY ½ Dose</td>
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<td>92</td>
<td>88</td>
<td>85</td>
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</tbody>
</table>

Protocol-required angiogram

Safety Population; KM Event Rate; log-rank P values
5-Year Clinical Outcomes

Number of Events (N)
Safety Population; KM Event Rates; All P values are >0.05
**Primary Endpoint**

**TLF at 1 year**

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>Per Protocol</th>
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</thead>
<tbody>
<tr>
<td>PROMUS Element</td>
<td>6.5%</td>
<td>6.4%</td>
</tr>
<tr>
<td>SYNERGY</td>
<td>6.7%</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

\[ P_{\text{noninferiority}} = 0.0005 \]

\[ P_{\text{noninferiority}} = 0.0003 \]

At 1-year, noninferiority was proven because the one-sided upper 97.5% confidence bound for the difference in TLF is <4.4%

**2-year Outcomes**

**Event Rate (%)**

- **PROMUS Element Plus**
  - TLF: 8.5%
  - Cardiac Death: 1.5%
  - TV-MI: 5.4%
  - TLR: 3.1%

- **SYNERGY**
  - TLF: 9.4%
  - Cardiac Death: 1.0%
  - TV-MI: 5.5%
  - TLR: 4.3%

**Definite/Probable ST**

- Event Rate (%)
  - TLF: 0.8%
  - Cardiac Death: 0.4%

EVOLVE Short DAPT Study Design

Prospective, N=2000, ~100 global sites

Key Inclusion Criteria

Patients considered by the treating physician to be at high risk for bleeding
i) ≥75 years of age and high bleeding risk
ii) long term anticoagulation therapy
iii) history of major bleeding
iv) stroke, or renal insufficiency/failure
(excluded LM disease, ostial lesions, >2 lesions, CTO, SVG, ISR, NSTEMI or STEMI)

P2Y\textsubscript{12} + ASA

ASA Only (for patients eligible for discontinuation of P2Y\textsubscript{12})

Primary Endpoints: Death or MI, ARC def/prob ST
Secondary Endpoint: Rate of major bleeding (GUSTO severe/life-threatening + moderate)

Primary and secondary endpoints evaluated between 3 and 15 months

Propensity adjusted comparison to historical control patients treated with standard DAPT will be performed
Conclusions and Significance

- The final 5-year results of EVOLVE demonstrate no significant differences between groups with respect to TLF, cardiac death or MI
  - Trend toward lower rates of TLR with SYNERGY vs PROMUS Element
  - No definite/probable stent thrombosis in any group at 5 years
- These results support the long-term safety and efficacy of the novel abluminal bioabsorbable polymer SYNERGY everolimus-eluting stent for the treatment of patients with de novo coronary artery disease
- Additional research is needed to evaluate clinical event rates and the potential for dual antiplatelet therapy reduction with this novel stent