TIDES-ACS Trial

Comparison of Titanium-nitride-oxide coated bioactive stent to the Drug (everolimus)-Eluting Stent in Acute Coronary Syndrome

on behalf of the Investigators

Pim A.L. Tonino, MD, PhD
TIDES-ACS Background

- Titanium-nitride-oxide (TNO)-coated bioactive stents based on 316L stainless-steel platform showed non-inferiority to everolimus-eluting stents (EES), for the composite of MACE in patients presenting with ACS.
**BASE-ACS**

MACE at 12 months

![Graph showing the percentage of MACE at 12 months for Titan-2 BAS (n=417) and Xience-V EES (n=410).](image)

- **Titan-2 BAS (n=417)**
  - 30 days: 2.6%
  - 90 days: 3.9%
  - 180 days: 6.8%
  - 270 days: 7.2%
  - 360 days: 9.0%

- **Xience-V EES (n=410)**
  - 30 days: 0.6%
  - 90 days: 0.6%
  - 180 days: 6.8%
  - 270 days: 9.6%
  - 360 days: 9.0%

- Log-Rank \( P = 0.82 \)
- \( P = 0.81 \)
- \( P = 0.89 \)
- \( P = 0.33 \)

**HR (95% CI)** \( 0.94 (0.59-1.50) \)

*Karjalainen, EuroIntervention, 2012*
TIDES-ACS Background

- Titanium-nitride-oxide (TNO)-coated bioactive stents based on 316L stainless-steel platform showed non-inferiority to everolimus-eluting stents (EES), for the composite of MACE in patients presenting with ACS.

- Cobalt-chromium alloy has superior radial strength, compared with 316L stainless-steel, which allows development of stents with ultrathin struts; yet, preserved radial force and radio-opacity.
Titanium-Nitride-Oxide coated BAS

*Ideal stent for ACS?*

- Inhibits Platelet Aggregation
- Minimizes Fibrin Growth
- Minimizes Thrombus Formation
- Reduce Inflammation
- Promotes Endothelial Healing

Windecker et al. Circulation 2001
Titanium-nitride-oxide (TNO)-coated bioactive stents based on 316L stainless-steel platform showed non-inferiority to everolimus-eluting stents (EES), for the composite of MACE in patients presenting with ACS.

Cobalt-chromium alloy has superior radial strength, compared with 316L stainless-steel, which allows development of stents with ultrathin struts; yet, preserved radial force and radio-opacity.

We conducted a randomized non-inferiority trial to compare the safety and efficacy of cobalt-chromium-based TNO-coated stents versus platinum-chromium-based biodegradable-polymer EES in ACS patients.
# TIDES-ACS Devices

<table>
<thead>
<tr>
<th></th>
<th>Cobalt-chromium-based BAS (OPTIMAX™)</th>
<th>Platinum-chromium-based biodegradable-polymer EES (SYNERGY™)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stent Platform</strong></td>
<td>Cobalt-chromium platform</td>
<td>Platinum-chromium platform</td>
</tr>
<tr>
<td></td>
<td>Helicoidal Design</td>
<td>Slotted Tube</td>
</tr>
<tr>
<td></td>
<td>Strut thickness 75 µm</td>
<td>Strut thickness (74-81) µm</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td>---</td>
<td>Everolimus</td>
</tr>
<tr>
<td><strong>Drug Density</strong></td>
<td>---</td>
<td>100 µg/cm²</td>
</tr>
<tr>
<td><strong>Coating</strong></td>
<td>Titanium-Nitride-Oxide</td>
<td>---</td>
</tr>
<tr>
<td><strong>Polymer</strong></td>
<td>---</td>
<td>Abluminal poly (D,L-lactide-co-glycolide) (4 µm)</td>
</tr>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Hexacath, Paris, France</td>
<td>Boston Scientific Corp. MA. USA</td>
</tr>
</tbody>
</table>
Patients presenting with Acute Coronary Syndrome

OPTIMAX-BAS
Titanium-Nitride-Oxide-coated Bioactive Stent
1200 Patients

12 International Sites
Randomisation 2:1

SYNERGY-EES
Everolimus-Eluting Stent with biodegradable polymer
600 Patients

Clinical Follow-up
30d 6mo 12mo 18mo 2yr 3yr 4yr 5yr

Primary Endpoint: MACE (Cardiac death, MI, and TLR) at 12 months

PI P Karjalainen (FIN)
Co-PI K Kervinen (FIN), J van Der Heyden (NED), H Romppanen (FIN), P Tonino (NED)
CEC: J Marco (FRA), A de Belder (UK), R Wiseth (NOR), J Gomez-Hospital (SPA), D Formigli (ITA)

ClinicalTrials.gov: NCT02049229
**Inclusion Criteria:**
- Written informed consent
- Age > 18 years
- Patient with acute coronary syndrome (ACS) requiring PCI
- ACS:
  - Unstable angina
  - Non-ST-elevation myocardial infarction
  - ST-elevation myocardial infarction

**Exclusion Criteria:**
- Prior PCI on target vessel (ISR)
- Unprotected LM disease
- Aorto-ostial lesion
- Contraindication to:
  - aspirin, heparin, clopidogrel
- Life expectancy < 12 months
- Stent length needed > 28 mm
TIDES-ACS
Study Endpoints

Primary Endpoint (non-inferiority)
Composite event rate at 12 months
- Cardiac death
- Myocardial Infarction (MI)
- Ischemia-driven Target Lesion Revascularization (TLR)

Co-Primary Endpoint (superiority)
Composite event rate at 18 months
- Cardiac death
- Myocardial Infarction (MI)
- Major bleeding
TIDES-ACS
Stent Thrombosis

**Academic Research Consortium (ARC) definition:**

(Circulation 2007;115:2344-51)

**Definite:**
- Acute coronary syndrome and angiographic (or autopsy) confirmation of stent thrombosis

**Probable:**
- Any unexplained death within the first 30 days
- Target vessel related acute MI

**Possible:**
- Any unexplained death from 30 days after PCI
Primary Endpoint: **MACE** at 12 months

- Expected MACE rate in SYNERGY EES (control) arm = 8.5%
- Non-inferiority margin (\(\Delta\)) = 3.5% percentage points
- 2-sided type I error (\(\alpha\)) = 0.05
- type II error (\(\beta\)) = 10%

- Enrollment of 1800 patients (2:1 randomization; 1200 in the OPTIMAX arm, and 600 in the SYNERGY arm) would yield 90% power to detect non-inferiority.
TIDES-ACS

Statistical considerations

Co-Primary Superiority Endpoint at 18 months including

* Myocardial Infarction (MI)
* Cardiac Death
* Major Bleeding

- Expected event rate in SYNERGY vs. OPTIMAX; 6.5% vs. 3.5%
  * Sample size needed (α=5%; β=80%), N = 1500
# TIDES-ACS Clinical Sites

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Hospital</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>J Lalmand</td>
<td>C.H.U. de Charleroi, Charleroi, Belgium</td>
<td>50</td>
</tr>
<tr>
<td>P Tonino</td>
<td>Heartcenter Catharina Hospital, Eindhoven, Netherlands</td>
<td>391</td>
</tr>
<tr>
<td>M Laine, M Pentikäinen</td>
<td>Helsinki University Hospital, Helsinki, Finland</td>
<td>27</td>
</tr>
<tr>
<td>J Sia, T Pinola</td>
<td>Kokkola Central Hospital, Kokkola, Finland</td>
<td>82</td>
</tr>
<tr>
<td>H Romppanen, A Perälä</td>
<td>Kuopio University Hospital, Kuopio, Finland</td>
<td>220</td>
</tr>
<tr>
<td>P Frambach</td>
<td>INCCI Luxembourg Hospital, Luxembourg</td>
<td>86</td>
</tr>
<tr>
<td>J van der Heyden</td>
<td>St Antonius Hospital, Nieuwegein, Netherlands</td>
<td>236</td>
</tr>
<tr>
<td>K Kervinen, M Niemelä</td>
<td>Oulu University Hospital, Oulu, Finland</td>
<td>128</td>
</tr>
<tr>
<td>P Karjalainen, W Nammas, J Mikkelsson</td>
<td>Satakunta Central Hospital, Pori, Finland</td>
<td>174</td>
</tr>
<tr>
<td>A Serra</td>
<td>Hospital Sant Pau, Barcelona, Spain</td>
<td>30</td>
</tr>
<tr>
<td>Dr. Vaquerino, M Fuertes</td>
<td>Hospital del Mar, Barcelona, Spain</td>
<td>17</td>
</tr>
<tr>
<td>M Pietilä, J Airaksinen</td>
<td>Turku University Hospital,Turku, Finland</td>
<td>50</td>
</tr>
</tbody>
</table>
## TIDES-ACS Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>OPTIMAX BAS (n=989)</th>
<th>SYNERGY EES (n=502)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.7 ± 11.0</td>
<td>62.6 ± 10.5</td>
<td>0.85</td>
</tr>
<tr>
<td>Male</td>
<td>75.3%</td>
<td>76.3%</td>
<td>0.70</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14.2%</td>
<td>12.5%</td>
<td>0.43</td>
</tr>
<tr>
<td>- Insulin treated</td>
<td>2.3%</td>
<td>3.8%</td>
<td>0.14</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>41.5%</td>
<td>40.2%</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46.8%</td>
<td>43.6%</td>
<td>0.25</td>
</tr>
<tr>
<td>Current smoker</td>
<td>31.2%</td>
<td>35.9%</td>
<td>0.08</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>7.6%</td>
<td>9.0%</td>
<td>0.37</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>7.0%</td>
<td>6.6%</td>
<td>0.83</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>0.6%</td>
<td>1.2%</td>
<td>0.23</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>46.3%</td>
<td>45.0%</td>
<td>0.66</td>
</tr>
<tr>
<td>STEMI</td>
<td>44.9%</td>
<td>47.6%</td>
<td>0.32</td>
</tr>
</tbody>
</table>
# TIDES-ACS Lesion Characteristics

<table>
<thead>
<tr>
<th></th>
<th>OPTIMAX BAS (n=989)</th>
<th>SYNERGY EES (n=502)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lesions treated/patient</td>
<td>1.17 ± 0.44</td>
<td>1.18 ± 0.49</td>
<td>0.83</td>
</tr>
<tr>
<td>2 or 3 vessels treated</td>
<td>36.0%</td>
<td>36.7%</td>
<td>0.75</td>
</tr>
<tr>
<td>RVD(^{a}) (mm)</td>
<td>3.20 ± 0.45</td>
<td>3.21 ± 0.45</td>
<td>0.67</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>14.9 ± 6.5</td>
<td>14.8 ± 5.9</td>
<td>0.81</td>
</tr>
<tr>
<td>Culprit lesion location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Left anterior descendens</td>
<td>45.7%</td>
<td>45.8%</td>
<td>0.86</td>
</tr>
<tr>
<td>- Left circumflex</td>
<td>21.2%</td>
<td>20.0%</td>
<td>0.65</td>
</tr>
<tr>
<td>- Right coronary artery</td>
<td>33.0%</td>
<td>34.1%</td>
<td>0.56</td>
</tr>
<tr>
<td>B2/C type complex lesion</td>
<td>22.5%</td>
<td>21.7%</td>
<td>0.67</td>
</tr>
<tr>
<td>Thrombus in culprit lesion</td>
<td>33.1%</td>
<td>36.7%</td>
<td>0.18</td>
</tr>
</tbody>
</table>

\(^{a}\) Reference vessel diameter
### TIDES-ACS Procedural Data

<table>
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<tr>
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<th>SYNERGY EES (n=502)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial access</td>
<td>75.8%</td>
<td>76.9%</td>
<td>0.65</td>
</tr>
<tr>
<td>No. of stents/culprit lesion</td>
<td>1.13 ± 0.38</td>
<td>1.14 ± 0.37</td>
<td>0.80</td>
</tr>
<tr>
<td>- Stent diameter (mm)</td>
<td>3.22 ± 1.14</td>
<td>3.19 ± 0.43</td>
<td>0.51</td>
</tr>
<tr>
<td>- Stent length (mm)</td>
<td>18.6 ± 4.7</td>
<td>19.0 ± 4.9</td>
<td>0.13</td>
</tr>
<tr>
<td>- Total stent length/lesion (mm)</td>
<td>20.5 ± 7.8</td>
<td>20.6 ± 7.2</td>
<td>0.86</td>
</tr>
<tr>
<td>Post-Dilatation</td>
<td>33.0%</td>
<td>38.0%</td>
<td>0.06</td>
</tr>
<tr>
<td>Stent failure</td>
<td>0.3%</td>
<td>1.0%</td>
<td>0.13</td>
</tr>
</tbody>
</table>
## TIDES-ACS Antiplatelet Agent Utilization

<table>
<thead>
<tr>
<th></th>
<th>OPTIMAX BAS (n=989)</th>
<th>SYNERGY EES (n=502)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- At discharge</td>
<td>99.2%</td>
<td>99.2%</td>
<td>NS</td>
</tr>
<tr>
<td>- At 12 months</td>
<td>94.5%</td>
<td>95.3%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Clopidogrel/Prasugrel/Ticagrelor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- At discharge</td>
<td>99.4%</td>
<td>100%</td>
<td>0.56</td>
</tr>
<tr>
<td>- At 12 months</td>
<td>59.4%</td>
<td>76.7%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Mean duration of DAPT (months)</strong></td>
<td>10.8 ± 2.7</td>
<td>11.1 ± 2.3</td>
<td>0.007</td>
</tr>
</tbody>
</table>
TIDES-ACS
MACE at 12 months

- Cumulative incidence of events (%)

Log-Rank $P = 0.60$

$P = 0.66$

$HR (95\% CI) = 1.12 (0.73-1.72)$

Number at risk
BAS (n=989) 945 917
EES (n=502) 467 454
Primary Endpoint
MACE at 12 Months

- BAS (n=989): 6.3%
- EES (n=502): 7.0%
- Difference: -0.7% (Upper boundary of 1-sided 95% CI)
- -0.7% + 95% CI = 1.7%
- P Value (Non-inferiority) < 0.001

Primary Non-Inferiority Endpoint Met

Zone of Non-inferiority
Pre-specified margin = 3.5%

BAS better
3.5%
EES better

TIDES-ACS
TIDES-ACS MACE at 12 months

Event rate (%)

- Cardiac death
- Myocardial infarction
- Ischemia-driven TLR
- MACE

- OPTIMAX-BAS (989)
- SYNERGY-EES (502)

$$P = 0.004$$
$$P = 0.04$$
$$P = 0.09$$

$$P = 0.66$$

HR (95% CI) = 1.12 (0.73-1.72)
TIDES-ACS other events at 12 months

Event rate (%)

- Definite ST
- Non-cardiac death
- Ischemia-driven TVR (non-TLR)
- Major bleeding

OPTIMAX-BAS (989) vs SYNERGY-EES (502)

- Definite ST: 1.0% vs 2.0%
- Non-cardiac death: 0.4% vs 1.0%
- Ischemia-driven TVR (non-TLR): 1.2% vs 1.0%
- Major bleeding: 1.2% vs 2.0%

P-values:
- P = 0.15
- P = 0.17
- P = 0.80
- P = 0.26
# TIDES-ACS ARC Stent Thrombosis

<table>
<thead>
<tr>
<th></th>
<th>OPTIMAX BAS (n=989)</th>
<th>SYNERGY EES (n=502)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite ST</td>
<td>10 (1.0)</td>
<td>10 (2.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Probable ST</td>
<td>1 (0.1)</td>
<td>4 (0.8)</td>
<td>0.047</td>
</tr>
<tr>
<td>Definite or Probable ST</td>
<td>11 (1.1)</td>
<td>14 (2.8)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
TIDES-ACS
Conclusions

• OPTIMAX-BAS was non-inferior to platinum-chromium-based biodegradable-polymer SYNERGY-EES for the primary composite of safety and efficacy outcome (MACE) at 12-month follow-up.

• Both cardiac death and MI were observed less frequent with OPTIMAX-BAS, whereas ischemia-driven TLR was undertaken more frequent in the OPTIMAX-BAS arm.

• Co-primary, “superiority” endpoint at 18 months (myocardial infarction, cardiac death and major bleeding) will be presented in spring 2018.