SYNTAX Five-year Results: Left Main Cohort

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Background

- The SYNTAX trial assessed the optimum revascularisation treatment for patients with de-novo LM or 3VD (or both), by randomly assigning patients to either PCI with a first-generation PES or CABG.

- For the primary endpoint of MACCE at 1 year, PCI did not meet the goal of non-inferiority compared with CABG.

- In the observational hypothesis-generating analysis of patients with LM disease, PCI had safety and efficacy outcomes comparable to CABG at 1 year.
SYNTAX Trial Design

62 EU Sites + 23 US Sites

Heart Team (surgeon & interventional cardiologist)

Amenable for both treatment options
Amenable for only one treatment approach

Stratification: LM and Diabetes

Randomized Arms
N=1800

CABG n=897
3VD n=549 (66.3%)
LM n=348 (33.7%)

TAXUS* n=903
3VD n=546 (65.4%)
LM n=357 (34.6%)

Two Registry Arms
N=1275

CABG n=1077

PCI n=198

*TAXUS Express
Conclusions

- Applying the all-comers design did not result in inclusion of all consecutive patients, as only half of the target population was enrolled.
- This design included more patients than observed in classical RCTs.
- AC-RCT participants and non-participants were different in terms of baseline characteristics and outcome.
Patient Disposition to 5 Years

**LM Subset Intent-to-Treat**

<table>
<thead>
<tr>
<th>CABG</th>
<th>Enrollment</th>
<th>1 Year Follow-up</th>
<th>2 Year Follow-up</th>
<th>3 Year Follow-up</th>
<th>4 Year Follow-up</th>
<th>5 Year Final Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=348</td>
<td>N=705</td>
<td>CABG 96.6%</td>
<td>CABG 92.0%</td>
<td>CABG 95.1%</td>
<td>CABG 93.4%</td>
<td>CABG 92.5%</td>
</tr>
<tr>
<td>n=336</td>
<td></td>
<td>PCI 99.4%</td>
<td>PCI 97.1%</td>
<td>PCI 98.6%</td>
<td>PCI 97.8%</td>
<td>PCI 96.9%</td>
</tr>
<tr>
<td>n=331</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=502</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=325</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=322</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PCI*  
n=357  
n=355  
n=533  
n=352  
n=349  
n=346  

*TAXUS Express*
Heterogeneity in the Left Main Group

Left Main Isolated: n=91 (13%)
Left Main + 1VD: n=138 (20%)
Left Main + 2VD: n=218 (31%)
Left Main + 3VD: n=258 (37%)

Site-reported data
### Patient Characteristics

**LM Subset**

<table>
<thead>
<tr>
<th></th>
<th>CABG N=348</th>
<th>TAXUS N=357</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*, mean ± SD (y)</td>
<td>65.6 ± 10.1</td>
<td>65.4 ± 9.8</td>
<td>0.78</td>
</tr>
<tr>
<td>Medically treated diabetes*, %</td>
<td>22.4</td>
<td>21.8</td>
<td>0.86</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>27.7 ± 5.0</td>
<td>28.2 ± 4.9</td>
<td>0.24</td>
</tr>
<tr>
<td>Additive euroSCORE*, mean ± SD</td>
<td>3.9 ± 2.9</td>
<td>3.9 ± 2.8</td>
<td>0.91</td>
</tr>
<tr>
<td>Total Parsonnet score*, mean ± SD</td>
<td>9.1 ± 7.4</td>
<td>8.9 ± 7.8</td>
<td>0.77</td>
</tr>
<tr>
<td>Total SYNTAX Score, mean ± SD</td>
<td>26.7 ± 11.5</td>
<td>28.1 ± 12.4</td>
<td>0.13</td>
</tr>
<tr>
<td>No. lesions, mean ± SD</td>
<td>3.2 ± 1.9</td>
<td>3.3 ± 1.8</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Core laboratory reported unless *Site-reported*
All-Cause Death to 5 Years
Left Main Subset

**CABG (N=348)**
- Before 1 year*: 4.5% vs 4.2% \( P=0.88 \)
- 1-2 years*: 1.9% vs 1.5% \( P=0.68 \)
- 2-3 years*: 2.3% vs 1.8% \( P=0.67 \)
- 3-4 years*: 3.0% vs 4.3% \( P=0.39 \)
- 4-5 years*: 4.2% vs 1.6% \( P=0.06 \)

**TAXUS (N=357)**

\( P=0.53 \)

Cumulative Event Rate (%)

Months Since Allocation

Cumulative KM Event Rate ± 1.5 SE; log-rank \( P \) value; *Binary rates

ITT population

SYNTAX 3VD 5-year Outcomes • TCT 2012 • Serruys • 23 October 2012 • Slide 8
Cardiac Death to 5 Years
Left Main Subset

Cumulative Event Rate (%)

- **CABG (N=348)**
  - Before 1 year*: 2.4% vs 3.9%
    - $P=0.24$
  - 1–2 years*: 0.9% vs 0.6%
    - $P=0.68$
  - 2–3 years*: 1.3% vs 1.2%
    - $P=1.00$
  - 3–4 years*: 1.3% vs 2.5%
    - $P=0.31$
  - 4–5 years*: 1.7% vs 0.6%
    - $P=0.27$

- **TAXUS (N=357)**

$P=0.46$

Cumulative KM Event Rate ± 1.5 SE; log–rank $P$ value; *Binary rates

ITT population

SYNTAX 3VD 5-year Outcomes - TCT 2012 - Serruys - 23 October 2012 - Slide 9
Myocardial Infarction to 5 Years
Left Main Subset

- **CABG** (N=348)
- **TAXUS** (N=357)

### Cumulative Event Rate (%)

- **Before 1 year**
  - CABG: 4.2%
  - TAXUS: 4.2%
  - *P = 0.97*

- **1–2 years**
  - CABG: 0.0%
  - TAXUS: 1.2%
  - *P = 0.12*

- **2–3 years**
  - CABG: 0.0%
  - TAXUS: 1.5%
  - *P = 0.06*

- **3–4 years**
  - CABG: 0.7%
  - TAXUS: 0.3%
  - *P = 0.61*

- **4–5 years**
  - CABG: 0%
  - TAXUS: 1.0%
  - *P = 0.25*

### Cumulative KM Event Rate ± 1.5 SE; log-rank P value; *Binary rates*

- **Months Since Allocation**
  - 0: CABG 0.4%, TAXUS 0.2%
  - 12: CABG 0.6%, TAXUS 1.0%
  - 24: CABG 1.2%, TAXUS 1.7%
  - 36: CABG 1.8%, TAXUS 2.3%
  - 48: CABG 2.4%, TAXUS 2.9%
  - 60: CABG 3.0%, TAXUS 3.5%

**ITT population**
CVA to 5 Years
Left Main Subset

<table>
<thead>
<tr>
<th></th>
<th>CABG (N=348)</th>
<th>TAXUS (N=357)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 1 year*</td>
<td>2.7% vs 0.3%</td>
<td>P=0.009</td>
</tr>
<tr>
<td>1–2 years*</td>
<td>0.9% vs 0.6%</td>
<td>P=0.68</td>
</tr>
<tr>
<td>2–3 years*</td>
<td>0.3% vs 0.3%</td>
<td>P=1.00</td>
</tr>
<tr>
<td>3–4 years*</td>
<td>0.3% vs 0.3%</td>
<td>P=1.00</td>
</tr>
<tr>
<td>4–5 years*</td>
<td>0% vs 0%</td>
<td>P=Undefined</td>
</tr>
</tbody>
</table>

P=0.03

Cumulative KM Event Rate ± 1.5 SE; log-rank P value; *Binary rates
ITT population
All-Cause Death/CVA/MI to 5 Years
*Left Main Subset*

CABG (N=348) vs TAXUS (N=357)

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>CABG Event Rate (%)</th>
<th>TAXUS Event Rate (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 1 year</td>
<td>9.2% vs 7.0%</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>1–2 years</td>
<td>2.8% vs 3.2%</td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>2–3 years</td>
<td>2.6% vs 3.0%</td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>3–4 years</td>
<td>3.7% vs 4.9%</td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>4–5 years</td>
<td>4.2% vs 2.3%</td>
<td></td>
<td>0.18</td>
</tr>
</tbody>
</table>

P = 0.57

Cumulative KM Event Rate ± 1.5 SE; log-rank P-value; *Binary rates

ITT population
MACCE to 5 Years
Left Main Subset

Before 1 year*: 13.7% vs 15.8%  
P = 0.44

1–2 years*: 7.5% vs 10.3%  
P = 0.22

2–3 years*: 5.2% vs 5.7%  
P = 0.78

3–4 years*: 6.4% vs 8.3%  
P = 0.35

4–5 years*: 5.9% vs 5.5%  
P = 0.82

Cumulative Event Rate (%)  
P = 0.12

Cumulative KM Event Rate ± 1.5 SE; log-rank P value; *Binary rates

SYNTAX 3VD 5-year Outcomes • TCT 2012 • Serruys • 23 October 2012 • Slide 14
Symptomatic Graft Occlusion & Stent Thrombosis to 5 Years

LM Subset

\[
P = 0.70
\]

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Patients (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>4.4</td>
<td>14</td>
</tr>
<tr>
<td>PCI</td>
<td>5.1</td>
<td>17</td>
</tr>
</tbody>
</table>

Post-procedure; ITT population
SYNTAX: Definite/Probable ARC Stent Thrombosis to 5 Years *(Per Patient)*

~3% ST rate within 30 days, and then ~1-2%/yr thereafter

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Rate (%)</th>
<th>Days Post-procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ≤1d</td>
<td>0.3</td>
<td>366-730d</td>
</tr>
<tr>
<td>Subacute 2-30d</td>
<td>2.6</td>
<td>731-1095d</td>
</tr>
<tr>
<td>Late 31-365d</td>
<td>1.7</td>
<td>1096-1460d</td>
</tr>
<tr>
<td>Very Late</td>
<td>1.3</td>
<td>1461-1825d</td>
</tr>
<tr>
<td>Total 5 year</td>
<td>10.4</td>
<td></td>
</tr>
</tbody>
</table>

Rate was ~ same in the LM and 3VD cohorts, and roughly independent of Syntax Score

Serruys PW. TCT2012
MACCE to 5 Years
Left Main Subsets

<table>
<thead>
<tr>
<th>Subset</th>
<th>CABG</th>
<th>TAXUS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM all (n=705)</td>
<td>31.0</td>
<td>33.2</td>
<td>0.12</td>
</tr>
<tr>
<td>LM only (n=91)</td>
<td>23.5</td>
<td>14.3</td>
<td>0.30</td>
</tr>
<tr>
<td>LM+1VD (n=138)</td>
<td>32.9</td>
<td>30.1</td>
<td>0.67</td>
</tr>
<tr>
<td>LM+2VD (n=218)</td>
<td>34.5</td>
<td>40.9</td>
<td>0.24</td>
</tr>
<tr>
<td>LM+3VD (n=258)</td>
<td>29.9</td>
<td>44.0</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Cumulative KM Event Rate; log-rank P-value

ITT population

SYNTAX 3VD 5-year Outcomes - TCT 2012 - Smurray - 23 October 2012 - Slide 16
MACCE to 5 Years by SYNTAX Score Tercile

**LM Subset Low Scores 0–22**

- **CABG (N=104)**
- **TAXUS (N=118)**

**LM Disease**

- Cumulative KM Event Rate ± 1.5 SE; log-rank \( P \) value
- Months Since Allocation
- Cumulative Event Rate (%)
- \( P=0.74 \)
- 31.5%
- 30.4%

<table>
<thead>
<tr>
<th>Event</th>
<th>CABG</th>
<th>PCI</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>11.3%</td>
<td>7.0%</td>
<td>0.28</td>
</tr>
<tr>
<td>CVA</td>
<td>4.1%</td>
<td>1.8%</td>
<td>0.28</td>
</tr>
<tr>
<td>MI</td>
<td>3.1%</td>
<td>6.2%</td>
<td>0.32</td>
</tr>
<tr>
<td>Death, CVA or MI</td>
<td>15.2%</td>
<td>13.9%</td>
<td>0.71</td>
</tr>
<tr>
<td>Revasc.</td>
<td>20.3%</td>
<td>23.0%</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Site-reported Data; ITT population
MACCE to 5 Years by SYNTAX Score Tercile

LM Subset Intermediate Scores 23–32

<table>
<thead>
<tr>
<th>Event</th>
<th>CABG</th>
<th>PCI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>19.3%</td>
<td>8.9%</td>
<td>0.04</td>
</tr>
<tr>
<td>CVA</td>
<td>3.6%</td>
<td>1.0%</td>
<td>0.23</td>
</tr>
<tr>
<td>MI</td>
<td>4.6%</td>
<td>6.0%</td>
<td>0.71</td>
</tr>
<tr>
<td>Death, CVA or MI</td>
<td>24.9%</td>
<td>15.7%</td>
<td>0.11</td>
</tr>
<tr>
<td>Revasc.</td>
<td>16.6%</td>
<td>22.2%</td>
<td>0.40</td>
</tr>
</tbody>
</table>

LM Disease

P=0.88

Cumulative KM Event Rate ± 1.5 SE; log-rank P value

Site-reported Data; ITT population
### MACCE to 5 Years by SYNTAX Score Tercile

*Low to Intermediate Scores (0–32)*

#### LM Disease

<table>
<thead>
<tr>
<th>Event Type</th>
<th>CABG</th>
<th>PCI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>15.1%</td>
<td>7.9%</td>
<td>0.02</td>
</tr>
<tr>
<td>CVA</td>
<td>3.9%</td>
<td>1.4%</td>
<td>0.11</td>
</tr>
<tr>
<td>MI</td>
<td>3.8%</td>
<td>6.1%</td>
<td>0.33</td>
</tr>
<tr>
<td>Death, CVA or MI</td>
<td>19.8%</td>
<td>14.8%</td>
<td>0.16</td>
</tr>
<tr>
<td>Revasc.</td>
<td>18.6%</td>
<td>22.6%</td>
<td>0.36</td>
</tr>
</tbody>
</table>

MACCE to 5 Years by SYNTAX Score Tercile

LM Subset High Scores ≥33

<table>
<thead>
<tr>
<th>Event</th>
<th>CABG</th>
<th>PCI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>14.1%</td>
<td>20.9%</td>
<td>0.11</td>
</tr>
<tr>
<td>CVA</td>
<td>4.9%</td>
<td>1.6%</td>
<td>0.13</td>
</tr>
<tr>
<td>MI</td>
<td>6.1%</td>
<td>11.7%</td>
<td>0.13</td>
</tr>
<tr>
<td>Death, CVA or MI</td>
<td>22.1%</td>
<td>26.1%</td>
<td>0.40</td>
</tr>
<tr>
<td>Revasc.</td>
<td>11.6%</td>
<td>34.1%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cumulative KM Event Rate ± 1.5 SE; log-rank P value

Site-reported Data; ITT population
Summary

Left Main Subset

- At 5 years, overall MACCE in the PCI group was comparable with CABG (31.0% CABG vs 36.9% PCI)
- Similar overall safety outcomes (Death/CVA/MI) between CABG and PCI at 5 years (20.8% CABG vs 19.0% PCI)
- There was a higher rate of revascularization in the PCI group (15.5% CABG vs 26.7% PCI), driven primarily by patients with high baseline SYNTAX scores
- A higher rate of CVA in the CABG group (4.3% CABG vs 1.5% PCI) was driven mostly by periprocedural events, with no difference between groups after 1 year
- PCI outcomes are excellent relative to CABG in LM isolated and LM+1VD
SYNTAX (2009-2013): Which Legacy?

**1-Year Outcomes**

Ferrarotto Hospital
University of Catania

**5-Year Outcomes**

Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial

Legacy #1 - Risk models for Complex PCI

Angiographic
- Residual SYNTAX Score
- CABG SYNTAX score
- Plaque Compos SYNTAX score
- MI SYNTAX score

Clinical
- ACE F CrCl
- MI SYNTAX score
- Logistic EuroSCORE
- Logistic EuroSCORE II
- Plaque Compos SYNTAX score

Combined
- Additive CSS
- Logistic CSS
- Additive EuroScore
- Logistic EuroSCORE
- Logistic EuroSCORE II

Functional
- Functional SYNTAX score
- Non Invasive FSS
- GRC
- SYNTAX score II

Adapted from Capodanno D, Eur Heart J 2012;33:3008-10
Legacy #2 – SYNTAX Advanced Our understanding on how to improve the outcomes of LM PCI

- Use best in class DES
  - Thienopyridine pre-loading
  - Statin pre-loading
  - Bivalirudin anticoagulation
- Optimal pharmacotherapy
- IVUS/FFR to assess the intermediate LM lesion
- FFR to avoid unnecessary stenting, but also to ensure complete ischemic revascularization
- IVUS guided LM stenting
  - 1- vs 2-stent techniques
  - Debulking
  - Hemodynamic support
  - Staging
  - Routine angiographic FU

Ferrarotto Hospital
University of Catania
Legacy #3 – From the Ashes of the SYNTAX, a New Trial: The EXCEL

~ 3600 patients with left main disease

SYNTAX score $\leq 32$
Consensus agreement by the Heart Team

Yes
N $\sim 2600$

Xience
CABG

Clinicaltrials.gov id NCT01205776
Legacy #4 - The Heart Team Approach

The rationale for Heart Team decision-making for patients with stable complex coronary artery disease

Stuart J. Head¹, Sanjay Kaul², Michael J. Mack³, Patrick W. Serruys¹, David P. Taggart⁴, David R. Holmes Jr⁵, Martin B. Leon⁶,⁷, Jean Marco⁸, Ad J.J.C. Bogers¹, and A. Pieter Kappetein¹*

The Heart Team of Cardiovascular Care

David R. Holmes, Jr, MD,* Jeffrey B. Rich, MD,† William A. Zoghbi, MD,‡ Michael J. Mack, MD,§

• Initially introduced in revascularization trials to select patients for randomization. The Coronary Heart Team consists of a clinical/non-invasive cardiologist, an interventional cardiologist, and a cardiac surgeon. Other physicians with specific expertise can be added if necessary.
• The Heart Team has recently become a class 1C recommendation in European and American guidelines on myocardial revascularization

Head SJ, et al. Eur Heart J 2013 In press
5-Year from SYNTAX… key messages

For patients with left main disease

- Revascularization with PCI has comparable safety and efficacy outcomes to CABG

- Although formally unproved at this stage, PCI seems a reasonable treatment alternative in this patient population, in particular, when the SYNTAX Score is low (≤22) or intermediate (23-32)

Legacies from SYNTAX include evolving concepts in trial design and decision making for LM PCI