Four-Year Follow-Up of the TYPHOON Study, a Multicenter, Randomized, Single-blind Trial To Assess The Use of the CYPHER® Sirolimus-eluting Stent (SES) in Acute Myocardial Infarction Patients Treated With Balloon Angioplasty

Christian Spaulding

for the TYPHOON Investigators
Potential conflicts of interest

Speaker’s name: Christian Spaulding

X I have the following potential conflicts of interest to report:

- X Research contracts: Cordis, Abbott, Stentys, French Ministry of Health
- ☐ Consulting
- ☐ Employment in industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- X Others: speaker fees: Abbott, Cordis, Lilly, Pfizer and advisory
  boear: Cordis

☐ I do not have any potential conflict of interest
TYPHOON 4 yr FU

Background

- The use of drug-eluting stents (DES) in acute myocardial infarction (AMI) remains controversial.
- Thirteen trials randomizing more than 7,000 patients have been conducted to date comparing DES vs. BMS, however the data has been largely limited to ≤ 2 years.
- Safety data in large-scale registries has provided mixed results with respect to the long-term safety of DES in the setting of AMI.
- Long term follow-up data from randomized trials on the use of DES in AMI is therefore important.
TYPHOON 4 yr FU

Study Design

715 Patients Presenting within 12 hours after Onset of Symptoms of a First AMI Requiring Primary PCI of a Native Coronary Artery

Randomization 1:1

- CYPHER® or CYPHER Select® Sirolimus-eluting Stent (356 patients)
  - 1 withdrew consent post-PCI

- Any Bare-Metal Stent (359 patients)
  - 2 withdrew consent post-PCI

- Sirolimus-eluting Stent (355 patients)

- Any Bare-Metal Stent (357 patients)

Primary Endpoint: Target Vessel Failure at 1 Year

Defined as Composite of Ischemia Driven Target Vessel Revascularization (TVR), recurrent Myocardial Infarction (MI), or Target Vessel–related Cardiac Death

### TYPHOON 4yr FU

#### 48 Participating Centers Across 15 Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>(24)</td>
</tr>
<tr>
<td>Germany</td>
<td>(51)</td>
</tr>
<tr>
<td>France</td>
<td>(337)</td>
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<tr>
<td>Switzerland</td>
<td>(15)</td>
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<tr>
<td>Australia</td>
<td>(11)</td>
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<tr>
<td>United Kingdom</td>
<td>(8)</td>
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<tr>
<td>Spain</td>
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<tr>
<td>France</td>
<td>(337)</td>
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<tr>
<td>Switzerland</td>
<td>(15)</td>
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<td>Austria</td>
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<tr>
<td>United Kingdom</td>
<td>(8)</td>
</tr>
<tr>
<td>Spain</td>
<td>(2)</td>
</tr>
</tbody>
</table>

#### Key Participants
- **Slama, M**: 4
- **Varenne**: 30
- **Teiger, E**: 27
- **Fauvel, JM**: 21
- **Commeau, P**: 32
- **Crochet, PD**: 17
- **Darremont, O**: 2
- **Dibon, O**: 3
- **Fajadet, J**: 14
- **Glatt, B**: 30
- **Py, A**: 14
- **Le Breton, H**: 11
- **Monassier, JP**: 13
- **Morice, MC**: 9
- **Pansieri, M**: 5
- **Valeix, B**: 3
- **Dupouy, P**: 5
- **Bode, C**: 40
- **Nickenig, G**: 9
- **Post, F**: 2
- **Merkely, B**: 40
- **Erglis, A**: 36
- **Rozenman, Y**: 15
- **Krakover, R**: 7
- **Ilia, R**: 3
- **Miller, H**: 5
- **Polonski, L**: 26
- **Farto e Abreu, P**: 10
- **Helder, P**: 15
- **Valdes, M**: 2
Intention-to-Treat Analysis

Clinical Outcomes through 1-Year

Primary Endpoint

MACE: major adverse cardiac events defined as all-cause death, re-MI or TLR.
TLR: target lesion revascularization. TVR: target vessel revascularization.
TVF: target vessel failure defined as ischemia-driven TVR, recurrent MI, or target vessel-related cardiac death
MI: myocardial infarction (all). ST: stent thrombosis (per protocol)
4-Year Extension

• By study design, TYPHOON was closed after 1-year follow-up
• TYPHOON was reopened in 2007 to ascertain 4-year follow-up due to concerns about very late stent thrombosis, especially in high-risk patients such as ST-elevation myocardial infarction
  • Resubmission to ethics committees was necessary
  • Patients were contacted an average of 3 years after inclusion to sign an informed consent for the extension
  • Events were adjudicated by an independent Critical Events Committee using the Academic Research Consortium (ARC)/Dublin definitions
  • Data management and analysis was performed by Cardialysis (Rotterdam, The Netherlands)
### Description of Patient Follow-Up at 4 years

<table>
<thead>
<tr>
<th>CYPHER</th>
<th>Bare Metal</th>
</tr>
</thead>
<tbody>
<tr>
<td>715 Patients enrolled</td>
<td></td>
</tr>
<tr>
<td>3 withdrew consent after procedure</td>
<td></td>
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<tr>
<td>712 patients</td>
<td></td>
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<tr>
<td>355</td>
<td></td>
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<tr>
<td>26 Patients enrolled in centers that refused extension (55)</td>
<td></td>
</tr>
<tr>
<td>35 Status unknown (77)</td>
<td></td>
</tr>
<tr>
<td>36 Alive, no informed consent (68)</td>
<td></td>
</tr>
<tr>
<td>7 Died, no informed consent (11)</td>
<td></td>
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<tr>
<td>251 4-Year Follow-up Completed (501)</td>
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<tr>
<td>“Complete Follow-Up Population” 70% Follow-up</td>
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</tr>
<tr>
<td>250 (71%)</td>
<td></td>
</tr>
<tr>
<td>715 Patients enrolled</td>
<td></td>
</tr>
<tr>
<td>“Survival Status Population” (580) 81% Follow-up</td>
<td></td>
</tr>
<tr>
<td>357</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>250 (70%)</td>
<td></td>
</tr>
</tbody>
</table>
TYPHOON 4 yr FU

Freedom from Target Lesion Revascularization

Kaplan Meier Curves

Years Post Randomization

% of Patients

CYPHER

Bare Metal Stent

95.7%

88.8%

P (log rank) = 0.0009
TYPHOON 4 yr FU

Freedom from Target Lesion Revascularization

Kaplan Meier Curves

% of Patients

Years Post Randomization

CYPHER  Bare Metal Stent

95.7%  92.4%

88.8%  85.1%

P (log rank) = 0.002
TYPHOON 4 yr FU

Freedom from Cardiac Death

**Kaplan Meier Curves**

- **CYPHER** 98.0%
- **Bare Metal** 98.3%

\[ P \text{ (log rank)} = 0.77 \]
TYPHOON 4 yr FU

Freedom from Cardiac Death

Kaplan Meier Curves

- CYPHER 97.6%
- Bare Metal 95.9%

CYPHER 98.0%
Bare Metal 98.3%

P (log rank) = 0.37
TYPHOON 4 yr FU

Freedom from Myocardial Infarction

Kaplan Meier Curves

CYPHER Bare Metal Stent

P (log rank) = 0.26

CYPHER 98.9%
Bare Metal 97.7%
TYPHOON 4 yr FU

Freedom from Myocardial Infarction

Kaplan Meier Curves

- CYPHER: 98.9%
- Bare Metal: 97.7%

- CYPHER: 94.8%
- Bare Metal: 95.6%

P (log rank) = 0.85
Clinical Outcomes at 4 Years

Academic Research Consortium / Dublin-Defined Events

MI: myocardial infarction, TLR: target lesion revascularization, TVR: target vessel revascularisation, Non-hierarchical events
ARC Definite Stent Thrombosis at 4 Years

TYPHOON 4 yr FU

**Early (0 to 30 days)**
- BMS (n=250): 8 (3.2%) Stent Thrombosis
- CYPHER (n=251): 4 (1.6%) Stent Thrombosis

**Very Late (> 1yr)**
- BMS (n=250): 2 (0.8%) Stent Thrombosis
- CYPHER (n=251): 5 (2.0%) Stent Thrombosis

P = 0.82

No late (>30 days to 1 yr) definite stent thrombosis

ARC/Dublin definitions. Hierarchical events
ARC Definite/Probable Stent Thrombosis at 4 Years

TYPHOON 4 yr FU

**BMS (n=250)**
- Early (0 to 30 days): 9 (3.6%)
- Very Late (> 1yr): 3 (1.2%)
- Total: 12 (4.8%)

**CYPHER (n=251)**
- Early (0 to 30 days): 6 (2.4%)
- Very Late (> 1yr): 5 (2.0%)
- Total: 11 (4.4%)

**P = 0.83**

No late (>30 days to 1 yr) definite/probable stent thrombosis

ARC/Dublin definitions. Hierarchical events
Any ARC-Defined Stent Thrombosis (Definite/Probable/Possible) at 4 Years

- Early (0 to 30 d)
- Late (>30 d to 1 yr)
- Very Late (>1 yr)

**BMS (n=250)**
- 9 (3.6%)
- 3 (1.2%)
- 9 (3.6%)
- 21 (8.4%)

**CYPHER (n=251)**
- 6 (2.4%)
- 6 (2.4%)
- 13 (5.2%)

*P = 0.16*

ARC/Dublin definitions. Hierarchical events
<table>
<thead>
<tr>
<th>Variable (%)</th>
<th>CYPHER Stent (n=250)</th>
<th>Bare Metal Stent (n=251)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual Anti-platelet therapy</td>
<td>19.0</td>
<td>15.7</td>
<td>0.40</td>
</tr>
<tr>
<td>Aspirin or Clopidogrel/Ticlopidine</td>
<td>97.7</td>
<td>95.3</td>
<td>0.49</td>
</tr>
<tr>
<td>Aspirin</td>
<td>83.1</td>
<td>85.2</td>
<td>0.53</td>
</tr>
<tr>
<td>Clopidogrel /Ticlopidine</td>
<td>32.6</td>
<td>25.9</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Less than 1% were on Ticlopidine in both groups
## Description of Patient Follow-Up at 4 years

### CYPHER

- **355** patients enrolled
  - 3 withdrew consent after procedure
  - **712** patients alive, no informed consent
- **35** patients enrolled in centers that refused extension (55)
- **36** patients alive, no informed consent (68)
- **26** patients enrolled in centers that refused extension (55)
- **35** patients with status unknown (77)
- **7** died, no informed consent (11)
- **251** (71%) completed follow-up

### Bare Metal

- **357** patients enrolled
  - 70% follow-up
- **35** patients enrolled in centers that refused extension (55)
- **7** died, no informed consent (11)
- **250** (70%) completed follow-up

### Follow-Up Status

- **Complete Follow-Up Population**
  - 70% follow-up
- **Survival Status Population**
  - 81% follow-up
## Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete Follow-Up (n=501)</th>
<th>No Complete Follow-Up (n=211)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (Mean ± SD)</td>
<td>59.2 ± 11.7</td>
<td>59.3 ± 13.2</td>
<td>0.94</td>
</tr>
<tr>
<td>Male (%)</td>
<td>78.6</td>
<td>77.7</td>
<td>0.84</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Diet Only</td>
<td>15.2</td>
<td>19.0</td>
<td>0.22</td>
</tr>
<tr>
<td>- Oral Meds</td>
<td>2.9</td>
<td>1.3</td>
<td>0.34</td>
</tr>
<tr>
<td>- Insulin</td>
<td>10.0</td>
<td>10.2</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>44.5</td>
<td>41.1</td>
<td>0.44</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>45.1</td>
<td>45.3</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous PTCA (%)</td>
<td>4.2</td>
<td>4.3</td>
<td>1.00</td>
</tr>
<tr>
<td>Current Smoking (%)</td>
<td>51.1</td>
<td>59.9</td>
<td>0.04</td>
</tr>
</tbody>
</table>
All-Cause Death

**CYPHER**

- Complete Follow-Up Population: 10/251 (4.0%)
  - Survival Status Population: 17/294 (5.8%)
  - **P = 0.23**

**Bare Metal Stent**

- Complete Follow-Up Population: 16/250 (6.4%)
  - Survival Status Population: 20/286 (7.0%)
  - **P = 0.61**

Sample: 712 patients

TYPHOON 4 yr FU
Conclusions

• The TYPHOON study demonstrated a significant reduction in target vessel failure, target lesion and vessel revascularization at one year in favor of the Cypher stent with no difference in all-cause death, cardiac death, myocardial infarction, and stent thrombosis

• At 4 years these results were maintained

• These findings are reassuring and do not support earlier concerns on the long-term safety and efficacy of the Cypher stent in primary angioplasty for acute myocardial infarction

• The reduction in repeat revascularisation provided by the Cypher stent in acute MI is maintained with no late catch-up. This does not occur at the expense of an increased safety risk during long-term follow-up