Milestone for Left Main PCI: Upcoming EXCEL Trial

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The Cardiovascular Research Foundation
SYNTAX Eligible Patients

De novo disease (n=1800)

Left Main Disease (isolated, +1, +2 or +3 vessels) N=705

Limited Exclusion Criteria
- Previous interventions
- Acute MI with CPK>2x
- Concomitant cardiac surgery

3 Vessel Disease (revasc all 3 vascular territories) N=1095

Primary endpoint = death/MI/stroke/repeat revasc at 1 year

Serruys PW et al. NEJM 2009;360:961–72
MACCE to 1 Year (primary endpoint) (All-cause death, stroke, MI, any repeat revascularization)

ITT population

- CABG (N=897)
- TAXUS (N=903)

Cumulative Event Rate (%) vs. Months Since Allocation

$P=0.0015^*$

Serruys PW et al. NEJM 2009;360:961–72
SYNTAX: 2 Year Outcomes in the LM Subgroup (N=705)

- Death/CVA/MI: CABG 11.8%, TAXUS 10.2%, P=0.48
- Revasc: CABG 10.4%, TAXUS 17.3%, P=0.01
- MACCE: CABG 19.3%, TAXUS 22.9%, P=0.27
MACCE to 2 Years by SYNTAX Score Tercile

Left Main SYNTAX Score ≥33

<table>
<thead>
<tr>
<th></th>
<th>CABG (N=149)</th>
<th>PCI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4.1%</td>
<td>10.4%</td>
<td>0.04</td>
</tr>
<tr>
<td>CVA</td>
<td>4.2%</td>
<td>0.8%</td>
<td>0.08</td>
</tr>
<tr>
<td>MI</td>
<td>6.1%</td>
<td>8.4%</td>
<td>0.48</td>
</tr>
<tr>
<td>Death, CVA or MI</td>
<td>11.5%</td>
<td>15.6%</td>
<td>0.32</td>
</tr>
<tr>
<td>Revasc.</td>
<td>9.2%</td>
<td>21.8%</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Site-reported data; ITT population

Cumulative KM Event Rate ± 1.5 SE; log-rank P value
MACCE to 2 Years by SYNTAX Score Tercile Left Main SYNTAX Scores 0–32

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<th>PCI</th>
<th>P–value</th>
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<tbody>
<tr>
<td>Death</td>
<td>7.9%</td>
<td>2.7%</td>
<td>0.02</td>
</tr>
<tr>
<td>CVA</td>
<td>3.3%</td>
<td>0.9%</td>
<td>0.09</td>
</tr>
<tr>
<td>MI</td>
<td>2.6%</td>
<td>3.8%</td>
<td>0.59</td>
</tr>
<tr>
<td>Death, CVA or MI</td>
<td>12.1%</td>
<td>6.9%</td>
<td>0.06</td>
</tr>
<tr>
<td>Revasc.</td>
<td>11.4%</td>
<td>14.3%</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Left Main

Cumulative Event Rate (%)

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

Site-reported Data; ITT population
Stenting of the LMCA as an alternative to CABG may be considered in pts with anatomic conditions that are associated with a low risk of PCI procedural complications and clinical conditions that predict an increased risk of adverse surgical outcomes.

IIb = “may or might be considered; may or might be reasonable; usefulness/effectiveness is unknown/unclear/uncertain or not well established”
What Would an Informative Trial of Left Main DES vs. CABG Look Like?

- It wouldn’t be an all-comers trial!
  - Exclude pts who clearly should go to CABG, e.g. high SYNTAX scores

- Optimize PCI technique
  - Pre-specify when/how to use IVUS, staged procedures, RX of distal bifurcation, no routine angio FU, etc.
  - Use the best stent and adjunctive pharmacology

- Optimize CABG technique
  - Minimize waiting time to CABG, maximize pan-arterial revascularization, adjunctive pharmacology, etc.

- Use a meaningful 1º endpoint: Death, CVA or MI

- ~2500 randomized pts
**EXCEL: Study Design**

**4000 pts with left main disease**

- SYNTAX score ≤32
- Consensus agreement by heart team

**Yes**
- $(N=2500)$
- PCI and CABG registries
  (limited in-hosp data)

**No**
- $(N=1500)$

- PCI (Xience Prime)
  - $(N=1250)$
- CABG
  - $(N=1250)$

**Clinical follow-up:** 30 days, 6 months, yearly through 5 years
**EXCEL: Inclusion Criteria**

- Clinical and anatomic eligibility for both PCI and CABG by heart team consensus
- Silent ischemia, stable angina, unstable angina or recent MI
- Significant LM ds. by heart team consensus
  - Angiographic DS ≥70%, or
  - Angiographic DS ≥50% to <70% with
    - a markedly positive noninvasive study, and/or
    - IVUS MLA <6.0 mm², and/or
    - FFR <0.80
Of all the coronary segments, the LMCA has the greatest angiographic variability.

Comparison in DS% assessment from the core lab (QCA) vs the clinical site (CASS Study).

*area of the square is proportional to the number of cases

Fisher et al. Cathet Cardiovasc Diagn 1982;8:565-75
Which of these LMCA lesions are significant and therefore should be treated? And which are not??

LMCA IVUS usually shows either insignificant or critical disease.
1-Year FU of 122 pts with moderate LM disease

Independent predictors of MACE @11.7 months: DM (p=0.004), untreated lesion >50% (p=0.037), and IVUS MLD (p=0.005)

Abizaid et al. JACC 1999;34:707-15
IVUS determinants of LMCA FFR <0.75

MLA <6.0 mm² (or MLD <3.0 mm) is the suggested criterion for significant LMCA stenosis. Jasti et al. Circulation 2004;110:2831-6
FFR Guidance for Left Main Treatment

FFR was performed in 213 pts with angiographically borderline (DS 30% - 70%) LM lesions

- FFR ≥0.80 ⇒ medical Rx (n=138);
- FFR <0.80 ⇒ CABG (n=75)

Correlation between angiography and FFR in unprotected left main disease

FFR Guidance for Left Main Treatment

FFR was performed in 213 pts with angiographically borderline (DS 30% - 70%) LM lesions.

FFR ≥0.80 ⇒ medical Rx (n=138); FFR <0.80 ⇒ CABG (n=75)

\[ p=0.48 \]

\[ p=0.50 \]
Why not revascularize pts with borderline LM lesions in the absence of ischemia?≤

FFR was performed in 525 lesions in 153 pts before bypass. Baseline FFR was ≤0.75 in 337 (64%) and >0.75 in 168 (36%).

Repeat angiography was performed at 1-year. Graft closure at 1-year according to baseline native cor FFR:

<table>
<thead>
<tr>
<th>Graft closure (%)</th>
<th>FFR ≤0.75</th>
<th>FFR &gt;0.75</th>
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</thead>
<tbody>
<tr>
<td>All grafts</td>
<td>8.9</td>
<td>21.4</td>
</tr>
<tr>
<td>Vein grafts</td>
<td>5.9</td>
<td>20.0</td>
</tr>
<tr>
<td>Arterial grafts</td>
<td>13.7</td>
<td>21.9</td>
</tr>
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</table>

P<0.01

1-yr LIMA patency 93.8%
1-yr radial patency 71.0%
EXCEL: IVUS is recommended over FFR for invasive evaluation of intermediate LM ds.

- Possible False Negative FFR
- Possible False Positive FFR

LCX
LAD
EXCEL: Clinical Exclusion Criteria

• Prior PCI within 1 year, or prior LM PCI anytime
• Prior CABG anytime
• Need for any cardiac surgery other than CABG
• Additional surgery required within 1 year
• Unable to tolerate, obtain or comply with dual antiplatelet therapy for 1 year
• Non cardiac co-morbidities with life expectancy < 3 years
• Clinical equipoise not present
EXCEL: Angiographic Exclusion Criteria

• Left main DS <50% (visually assessed)
• SYNTAX score ≥33
• Left main RVD <2.25 mm or >4.5 mm
**EXCEL: Use of XIENCE Prime**

- Enhanced stent
- New SDS
  - More flexible and deliverable
  - Shorter balloon tapers
  - Higher RBP
XIENCE Prime for LM Ds: LeMaX Pilot

174 pts with ULM ds. were treated with XIENCE Prime at 4 French centers between 12/07 and 5/09
- All-comers, except STEMI and shock excluded
- Mean age 69, 42% NSTEMI, 46% 3VD, mean 2.1 lsns/pt
- Mean SYNTAX score 25.1, 81% distal bifurcation

One-year MACE (in 122 eligible pts)

- MACCE: 14.7%
  - N=5
  - 2 cardiac
  - 3 non-cardiac

- Death: 4.1%

- MI: 2.5%

- Stroke: 1.6%

- Revasc: 11.4%
  - N=2
  - 1 subacute (d4), LM

- Stent thrombosis: 1.6%

Salvatella N. AHA 2009
174 pts with ULM ds. were treated with XIENCE Prime
- Mean SYNTAX score $25.1 \pm 10.1$

$\text{N}=122$

1-year MACCE
Low Score – 10.0%
Int. Score – 11.6%
High Score – 27.6%

$p$ Log Rank <0.0001
**EXCEL: Endpoints**

- **Primary endpoint**: Death, MI, or stroke at median follow-up of 3 years

- **Major secondary endpoint**: Death, MI, stroke or unplanned revascularization at median follow-up of 3 years

  - **Power analysis**: Both endpoints are powered for sequential noninferiority and superiority testing

- **Quality of life and cost-effectiveness assessments**: At regular intervals
**EXCEL: Organization (i)**

Academically driven study; 50% interventionalists, 50% cardiac surgeons

- **Principal Investigators:**
  - **Interventional:** Patrick W. Serruys, Gregg W. Stone
  - **Surgical:** A. Pieter Kappetein, Joseph F. Sabik

- **Executive Operations Committee:**
  - 4 principal investigators, Peter-Paul Kint, Martin B. Leon, Alexandra Lansky, Roxana Mehran, Marie-Angèle Morel, Chuck Simonton, David Taggart, Lynn Vandertie, Gerrit-Anne van Es, Jessie Coe, Poornima Sood, Ali Akavand, Krishnankutty Sudhir, Thomas Engels

- **Optimal Therapy Committee Chairs**
  - **PCI:** Martin B. Leon
  - **Surgery:** David Taggart
  - **Medical:** Bernard Gersh
EXCEL: Organization (ii)

• Countries and Country Leaders (PCI and CABG)
  - United States: David Kandzari and John Puskas
  - Europe (10): Marie-Claude Morice and David Taggart
  - Brazil: Alex Abizaid and Luis Carlos Bento Sousa
  - Argentina: Jorge Belardi and Daniel Navia
  - Canada: Erick Schampaert and Marc Ruel
  - S. Korea: Seung-Jung Park and Jay-Won Lee

• Statistical Committee
  - Stuart Pocock, Chair

• Data Safety and Monitoring Board
  - Lars Wallentin, Chair

• Academic Research Organizations
  - Cardiovascular Research Foundation and Cardialysis

• Sponsor: Abbott Vascular
EXCEL: Status

• After 12 months of preparation the protocol is finalized
• The site selection process is underway
• FDA meetings and global regulatory submissions are being prepared
• First patient enrolled: 3rd Quarter 2010