STABLE CAD
REVASC OR OMT

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ATHENS
• I have no conflict of interest
Stable coronary syndromes: pathophysiology, diagnostic advances and therapeutic need

Thomas J Ford  heartjnl-2017-311446
Definition of SCAD

• Stable Coronary Artery Disease (CAD), or Stable Ischemic Heart Disease (SIHD), refers to the syndrome of recurrent, transient episodes of chest pain reflecting demand-supply mismatch, that is, angina pectoris.

• Angina is considered to be due to flow-limiting CAD

• Cut-off for obstructive CAD is taken as a stenosis of 70% in a main coronary artery (>2.5 mm) in one angiographic projection, or 50% in two projections, and 50% of the left main coronary artery
The management

• Detection of obstructive epicardial CAD
• Systemic problems ?? (anaemia, aortic stenosis)
• In patients with obstructive epicardial CAD, the treatment involves optimal medical therapy and consideration of myocardial revascularisation with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)
## Classification of angina severity according to the Canadian Cardiovascular Society

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Ordinary activity does not cause angina such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.</td>
</tr>
<tr>
<td>Class II</td>
<td>Slight limitation of ordinary activity. Angina on walking or climbing stairs rapidly, walking or stair climbing after meals, or in cold, wind or under emotional stress, or only during the first few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.</td>
</tr>
<tr>
<td>Class III</td>
<td>Marked limitation of ordinary physical activity. Angina on walking one to two blocks(^a) on the level or one flight of stairs in normal conditions and at a normal pace.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Inability to carry on any physical activity without discomfort, angina syndrome may be present at rest.</td>
</tr>
</tbody>
</table>

\(^a\)Equivalent to 100–200 m.

This slide corresponds to Table 5 in the full text.
# Main features of SCAD

## Pathogenesis
Stable anatomical atherosclerotic and/or functional alterations of epicardial vessels and/or microcirculation

## Natural history
Stable symptomatic or asymptomatic phases which may be interrupted by ACS

## Mechanisms of myocardial ischaemia
- Fixed or dynamic stenoses of epicardial coronary arteries
- Microvascular dysfunction
- Focal or diffuse epicardial coronary spasm

The above mechanisms may overlap in the same patient and change over time

## Clinical presentations
- **Effort induced angina** caused by:
  - epicardial stenoses
  - microvascular dysfunction
  - vasoconstriction at the site of dynamic stenosis
  - combination of the above

- **Rest angina** caused by:
  - Vasospasm (focal or diffuse):
    - epicardial focal
    - epicardial diffuse
    - microvascular
    - combination of the above

- **Asymptomatic**:
  - because of lack of ischaemia and/or of LV dysfunction
  - despite ischaemia and/or LV dysfunction

## Ischaemic cardiomyopathy

ACS = acute coronary syndrome; LV = left ventricular; SCAD = stable coronary artery disease.

This slide corresponds to Table 3 in the full text.
• 1/3 of pts no Obstructive CAD

• US Registry 398798 pts
39.2% no evidence of epicardial CAD
Patel et al New Engl J Med 2010
The indications for revascularization in patients with SCAD who receive guideline-recommended medical treatment are the persistence of symptoms despite medical treatment and/or the improvement of prognosis.
# Indications for revascularization in patients with stable angina or silent ischaemia

<table>
<thead>
<tr>
<th>Extent of CAD (anatomical and/or functional)</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For prognosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main disease with stenosis &gt;50%.&lt;sup&gt;c&lt;/sup&gt;</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Proximal LAD stenosis &gt;50%.&lt;sup&gt;c&lt;/sup&gt; 62,68,70,72</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Two- or three-vessel disease with stenosis &gt;50% with impaired LV function (LVEF &lt;35%).&lt;sup&gt;c&lt;/sup&gt; 61,62,68,70,73–83</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Large area of ischaemia detected by functional testing (&gt;10% LV) or abnormal invasive FFR.&lt;sup&gt;d&lt;/sup&gt; 24,59,84–90</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Single remaining patent coronary artery with stenosis &gt;50%.&lt;sup&gt;c&lt;/sup&gt;</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td><strong>For symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemodynamically significant coronary stenosis&lt;sup&gt;c&lt;/sup&gt; in the presence of limiting angina or angina equivalent, with insufficient response to optimized medical therapy.&lt;sup&gt;e&lt;/sup&gt; 2463,91–97</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>
Observational study: Revascularization was associated with lower risk of cardiac death only in those with >10% ischemia on perfusion

\[ N = 10,627 \]
\[ 146 \text{ Cardiac deaths} \]
\[ 492 \text{ ACS} \]
PCI vs. Medicine (Pre-OMT Era)

Meta-analysis of 11 randomized trials; N = 2950

<table>
<thead>
<tr>
<th></th>
<th>Favors PCI</th>
<th>Favors Medical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>Cardiac death or MI</td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>CABG</td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>PCI</td>
<td></td>
<td>0.34</td>
</tr>
</tbody>
</table>

Risk ratio (95% CI)
STRATEGY TRIALS OF REVASC IN STABLE CAD: OMT ERA

• COURAGE
• BARI 2D
• FAME 2
PCI Did Not Reduce Death or MI in SIHD Patients

Optimal Medical Therapy (OMT)

PCI + OMT

Hazard ratio: 1.05
95% CI (0.87-1.27)
P = 0.62

33% PCI rate in OMT; 21% repeat PCI in PCI group

PCI Did Not Reduce Death or MI in SIHD Patients

- **Mainly Bare Metal Stents**

Hazard ratio: 1.05

95% CI (0.87-1.27)

P = 0.62

33% PCI rate in OMT; 21% repeat PCI in PCI group
35,539 Patients assessed

3,071 (8.6%) met eligibility criteria

32,468 patients were excluded

8,677 Did not meet inclusion criteria
5,155 Had undocumented ischemia
3,961 Did not meet protocol for vessels
6,554 Were excluded for logistic reasons
18,360 Had one or more exclusions
4,513 Had undergone recent (<6 mo) revascularization
4,939 Had an inadequate ejection fraction
2,987 Had a contraindication to PCI
2,542 Had a serious coexisting illness
1,285 Had concomitant valvular disease
1,203 Had class IV angina
1,071 Had a failure of medical therapy
947 Had left main stenosis >50%
722 Had only PCI restenosis (no new lesions)
528 Had complications after MI
BARI 2D: Prompt revascularization did not improve survival in diabetic patients with SIHD

BARI 2D

Med group – revasc 19% year 1, 42% by year 5
BARI 2D: Prompt revascularization did not improve survival in diabetic patients with SIHD

Only 35% with DES (1st Gen)

Med group – revasc 19% year 1, 42% by year 5
Low risk patients included
Referral bias by randomizing after cath
Revascularization procedures not optimal
(little DES, no FFR, no CABG in COURAGE)
Times have changed!!!!

What’s changed?
What’s Changed Since BARI 2D and COURAGE?

• Better Stents
• Better Pharmacotherapy
• More judicious use of PCI for ischemia-producing lesions (FFR) but with focus on completeness of revascularization
• PCI optimization (Intravascular imaging)
Drug Eluting Stents

<table>
<thead>
<tr>
<th>Stent Type</th>
<th>Strut Thickness</th>
<th>Polymer Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYPHER®</td>
<td>140 µm</td>
<td>13.7 µm</td>
</tr>
<tr>
<td>TAXUS® Liberté</td>
<td>97 µm</td>
<td>17.8 µm</td>
</tr>
<tr>
<td>ENDEAVOR</td>
<td>91 µm</td>
<td>4.8 µm</td>
</tr>
<tr>
<td>XIENCE V</td>
<td>81 µm</td>
<td>7.8 µm</td>
</tr>
</tbody>
</table>
DES Polymer Changes

1st Gen
- Non uniform polymer coating
- Webbing and bonding
- Delamination

2nd Gen
- Uniform polymer coating
- No webbing and bonding
- No delamination
Inflammation

Rabbit double-injury iliac artery model at 28 days follow-up

- **XIENCE**
  - N=16
  - Inflammatory Cells/strut (N): 7

- **Resolute™**
  - N=16
  - Inflammatory Cells/strut (N): 15

- **BMS***
  - N=16
  - Inflammatory Cells/strut (N): 17

**P-values:**
- P = 0.0005
- P = 0.0001
“Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis”

Windecker S et al
BMJ 2014;348:g3859.

100 trials in 93,553 patients with 262,090 patient years of follow-up
Five-Year Outcomes with PCI Guided by Fractional Flow Reserve

Stable CAD patients scheduled for 1, 2 or 3 vessel DES-PCI (n = 1220)

Randomized Trial

- FFR in all target lesions
  - At least 1 stenosis with FFR ≤ 0.80 (n=888)
    - Randomization 1:1
      - PCI + MT
      - MT
      - 73%
      - 27%

Registry

- When all FFR > 0.80 (n=332)
  - MT
  - 50% randomly assigned to FU

Follow-up after 1, 6 months, 1, 2, 3, 4, and 5 years
Five-Year Outcomes with PCI Guided by Fractional Flow Reserve


FAME 2

447 vs 441 patients

Combined end point (Death, MI, urgent revasc)
Primary endpoint
(All cause death, MI, or urgent revascularisation)

PCI vs. Medical Therapy: HR 0.46 (95% CI 0.34-0.63) P<0.001
PCI vs. Registry: HR 0.88 (95% CI 0.55-1.39) P=0.57
Medical Therapy vs. Registry: HR 1.91 (95% CI 1.25-2.91) P=0.003
Benefit is mainly reduction in urgent revasc

Death

MI

Urgent revasc
5-Year Outcomes With PCI Guided by FFR – FAME 2 Trial
888 Patients

Primary Endpoint (Death) MI, Urgent Revascularization

- Hazard ratio, 0.46 (95% CI, 0.34–0.63)
- P < 0.001

Death from any Cause

- Hazard ratio, 0.98 (95% CI, 0.55–1.75)

Myocardial Infarction

- Hazard ratio, 0.66 (95% CI, 0.43–1.00)

Urgent Revascularization

- Hazard ratio, 0.27 (95% CI, 0.18–0.41)

Crossover – at 5 yrs 51% assigned to medical therapy had PCI

Xapanteris: NEJM, 2018
Conclusions

The 5-year results of the FAME 2 trial confirm the importance of an FFR-based selection for PCI of both patients and lesions:

• **When $\text{FFR} > 0.80$,** outcome is favorable with medical therapy

• **When $\text{FFR} \leq 0.80$,** PCI with DES provides sustained benefits in:
  1. the need for urgent revascularisation
  2. the rate of spontaneous myocardial infarctions
  3. symptomatic relief
  4. without late catch-up phenomenon
Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial

Rasha Al-Lamee, David Thompson, Hakim-Moulay Debbi, Sayan Sen, Kare Tang, John Davies, Thomas Keeble, Michael Mielewiczik, Raffi Kaprielian, Iqbal S Malik, Sukhjinder S Nijjer, Ricardo Petraco, Christopher Cook, Yousif Ahmad, James Howard, Christopher Baker, Andrew Sharp, Robert Gerber, Suneel Talwar, Ravi Assomull, Jamil Mayet, Roland Wensel, David Collier, Matthew Shun-Shin, Simon A Thom, Justin E Davies, Daniel P Francis, on behalf of the ORBITA investigators

www.thelancet.com Published online November 2, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32714-9
PCI in Stable Angina (ORBITA): A Double Blind Randomized Controlled Trial

- 200 pts (300 planned)
- Stable angina/angina equivalent after 6 weeks of therapy (CCS I-II - 62%; No ischemia - 30%)
- Severe (≥70%) single vessel stenoses
- Sham procedure vs PCI

Duration of follow-up 6 weeks

Change in Exercise Time (1º Outcome) from Baseline

- PCI: 28.4
- Sham: 11.6

P=0.20

Al-Lamee; Lancet. 2017
Trial design

MEDICAL OPTIMIZATION PHASE
- Enrolment assessment
  - CCS SAQ EQ-5D-5L
- Pre-randomization assessment
  - CCS SAQ EQ-5D-5L
- Exercise test Stress echo
- Blinded procedure
  - Research angiogram: iFR, FFR Sedation

BLINDED FOLLOW UP PHASE
- Randomization
  - PCI
  - Placebo
- Follow-up Assessment
  - CCS SAQ EQ-5D-5L
- Exercise test Stress echo

Six weeks
Primary endpoint result

Change in total exercise time

<table>
<thead>
<tr>
<th>Change in Exercise Time (seconds)</th>
<th>PCI</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28.4 (SD 86.3) p=0.001</td>
<td>11.8 (SD 93.3) p=0.235</td>
</tr>
</tbody>
</table>

+16.6 sec (-8.9 to 42.0) p=0.200

Error bars are standard errors of the mean.
## Secondary endpoint results

### CCS class improved in both groups

<table>
<thead>
<tr>
<th>CCS class at enrolment</th>
<th>CCS class at pre-randomization</th>
<th>CCS class at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCS IV</strong></td>
<td><strong>CCS III</strong></td>
<td><strong>CCS II</strong></td>
</tr>
<tr>
<td>37%</td>
<td>40%</td>
<td>24%</td>
</tr>
<tr>
<td><strong>CCS III</strong></td>
<td><strong>CCS II</strong></td>
<td><strong>CCS I</strong></td>
</tr>
<tr>
<td>61%</td>
<td>53%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>CCS II</strong></td>
<td><strong>CCS I</strong></td>
<td><strong>CCS 0</strong></td>
</tr>
<tr>
<td>2%</td>
<td>9%</td>
<td>14%</td>
</tr>
</tbody>
</table>

**PCI**  
- CCS IV: 37%  
- CCS III: 61%  
- CCS II: 14%

**Placebo**  
- CCS IV: 40%  
- CCS III: 57%  
- CCS II: 11%

### Follow-up

- PCI: 0%  
- Placebo: 12%
Secondary Outcomes – ORBITA Trial

Change in Seattle Angina Questionnaire (SAQ)

- PCI: 7.4, Sham: 5.6, P = 0.42

Change in SAQ – Angina Frequency

- PCI: 14.0, Sham: 9.6, P = 0.26

Change in Duke Treadmill Score

- PCI: 1.2, Sham: 0.1, P = 0.104

Peak Stress Wall Motion Score

- PCI: P < 0.0011, Sham: 0.0, P = 0.1
Orbita: The reasonable conclusion

ement showed no difference between groups. This first placebo-controlled trial of PCI for stable angina suggests that the common clinical observation of symptomatic improvement from PCI might well contain a large placebo component. Placebo-controlled efficacy data

The editorial!

Last nail in the coffin for PCI in stable angina?

Interventional cardiology began in Switzerland in 1977, when Andreas Gruentzig performed the first successful percutaneous transluminal coronary angioplasty (PTCA) on a 38-year-old man with angina and a focal proximal stenosis of the left anterior descending coronary artery. Despite numerous subsequent randomised trials and meta-analyses of these trials, which have shown no reduction in death or myocardial infarction, the use of percutaneous coronary intervention (PCI) has grown exponentially. Cardiovascular Data Registry showed that less than half of patients undergoing PCI were receiving optimal medical therapy, with no increase following the publication of COURAGE.1 None importantly, despite the known placebo power of invasive procedures, until now, there had not been a blinded clinical trial of PCI in its entire 40 year history.1

In a landmark new study in The Lancet, the investigators of the Objective Randomised Blinded Investigation with optimal medical Therapy of
• Small study
• Single vessel disease
• Patients had a good exercise capacity to begin with
• Interaction with investigational team x3 /week
• 25% Class 0-1 angina : need for PCI?
• 33% normal FFR or iFR
Primary endpoint result

Change in total exercise time

<table>
<thead>
<tr>
<th>Group</th>
<th>Change in Exercise Time (seconds)</th>
<th>Standard Deviation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>+16.6 (-8.9 to 42.0)</td>
<td>86.3</td>
<td>0.200</td>
</tr>
<tr>
<td>Placebo</td>
<td>-11.8 (-93.3)</td>
<td>93.3</td>
<td>0.235</td>
</tr>
</tbody>
</table>

Even with baseline group differences, 2X number of patients enrolled would have resulted in “significance.”

Error bars are standard errors of the mean.
ORBITA Continues to Surprise: 85% of Sham Arm Opted for PCI When Trial Ended

A discussion here at SCAI tackled lingering ORBITA issues, with experts finally grasping a detail the PI says she’s been emphasizing from the outset.
30% of patients with baseline angina were made angina free by PCI

VS

15% of patients with baseline angina were made angina free by OMT

Stents had 2x the anti-anginal impact!  \( p=0.107 \)
30% of patients with baseline angina were made angina free by PCI

15% of patients with baseline angina were made angina free by OMT

Stents had 2x the anti-anginal impact! \( p=0.107 \)
PCI effect on total exercise time was 20.7 secs (-4.0 - +45.4) \( P = 0.1 \)

No relationship to FFR or iFR

PCI improved stress echocardiography score by 1.07 segment units (0.70 - 1.44) \( P < 0.0001 \)

Effect increased with \( \downarrow \) FFR (\( P < 0.00001 \)) and with \( \downarrow \) iFR (\( P < 0.00001 \))

Freedom from Angina at Follow-up

Effect on Angina Score

No change in angina frequency (\( P = 0.072 \))
CABG vs. PCI
<table>
<thead>
<tr>
<th>Stent type and year of publication</th>
<th>Study</th>
<th>N</th>
<th>Baseline characteristics</th>
<th>Primary endpoint*</th>
<th>Secondary endpoints*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age (y)</td>
<td>Women (%)</td>
<td>Diabetes (%)</td>
</tr>
<tr>
<td>DES</td>
<td>PES 2009</td>
<td>SYNTAX</td>
<td>1800</td>
<td>65</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>SES 2011</td>
<td>Baudriao</td>
<td>201</td>
<td>68</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>SES 2011</td>
<td>PRECOMBAT</td>
<td>600</td>
<td>62</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>EES 2015</td>
<td>BEST</td>
<td>880</td>
<td>64</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>BES 2016</td>
<td>NOBLE</td>
<td>1201</td>
<td>66</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>EES 2016</td>
<td>EXCEL</td>
<td>1905</td>
<td>66</td>
<td>24</td>
</tr>
</tbody>
</table>

Age and EF are reported as means.

**P < 0.05.

DES = drug-eluting stents; BEST = Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease; DES = drug-eluting stents; EES = everolimus-eluting stents; EF = ejection fraction; EXCEL = Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; LM = left main coronary artery disease; PS = myocardial infarction; MV = multivessel coronary artery disease; NOBLE = Nordic-Baltic-Brithish Left Main Revascularisation Study; PES = paclitaxel-eluting stents; PRECOMBAT = Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; Revasc = revascularization; SES = sirolimus-eluting stents; SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TVR = target vessel revascularization; Y = years.

*Results are reported as percutaneous coronary intervention vs. coronary artery bypass grafting.

**Non-inferiority met.

***Non-procedural PS (exclusion of periprocedural MI).
Study flowchart: PCI procedure

Patient included in the SYNTAX II study

- iFR in all intended to treat stenoses

iFR < 0.86

- FFR ≤ 0.80
  - Stenosis treated with SYNERGY™ EES
  - IVUS optimization

iFR 0.86 – 0.93

FFR

iFR > 0.93

- FFR > 0.80
  - Stenosis not treated

- FFR ≤ 0.80
  - Stenosis not treated

Optimal medical therapy with strict LDL control (≤ 1.8mmol/L)
Impact of intracoronary physiology on PCI

Lesion treatment after iFR/FFR interrogation (n=1177)

- PCI deferred: 31%
- PCI performed: 69%

Lesions treated per patient (n) in SYNTAX II and SYNTAX I

<table>
<thead>
<tr>
<th></th>
<th>SYNTAX II</th>
<th>SYNTAX I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions</td>
<td>2.64</td>
<td>4.02</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cases of three-vessel PCI (%) in SYNTAX II and SYNTAX I

<table>
<thead>
<tr>
<th></th>
<th>SYNTAX II</th>
<th>SYNTAX I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>37.2%</td>
<td>83.3%</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

WWW.HCS.GR

70 YEARS OF CARDIOLOGY (HSC)
PANHellenic Congress of Cardiology
Treatment of chronic total occlusions (CTO)

CTO PCI procedural success rate in SYNTAX II: 87%

- Success: n=94
- Failed: n=14

CTO revascularisation in SYNTAX II and SYNTAX I

- SYNTAX II: 87%
- SYNTAX I: 53%

p<0.0001
Post-implantation IVUS led to further optimisation of the stented lesion in 30.2%.
Primary endpoint: MACCE

HR 0.58 (95% CI 0.39-0.85), p=0.006

Number at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>SYNTAX I PCI</th>
<th>SYNTAX II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>315</td>
<td>450</td>
</tr>
<tr>
<td>Patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>298</td>
<td>441</td>
</tr>
<tr>
<td>20</td>
<td>288</td>
<td>437</td>
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<td>30</td>
<td>280</td>
<td>433</td>
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<td>90</td>
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<td>120</td>
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</tr>
<tr>
<td>360</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Exploratory End-Point: MACCE PCI vs. CABG

HR 0.91 (95% CI 0.59-1.41), p=0.684
P <0.001 for non-inferiority*

11.2%
10.6%

*Non-inferiority margin of 5% with a one-sided alpha of 5%
MACCE SYNTAX II and SYNTAX I PCI / CABG

![Graph showing the comparison between SYNTAX I PCI, SYNTAX II, and SYNTAX I CABG over days with patient percentage values and patient counts for each category.]

SYNTAX II: 450, 441, 437, 433, 429, 427, 421, 417, 411, 405, 404, 400, 398
SYNTAX I CABG: 334, 313, 304, 295, 293, 291, 289, 288, 287, 279, 278, 277, 277
Conclusions (I)

- In patients with 3VD the use of the **SYNTAX-II strategy** was associated with improved clinical outcomes at one year, compared to matched patients treated percutaneously in the original SYNTAX-I trial.

- The one-year exploratory comparison between SYNTAX II and matched CABG patients from the original SYNTAX-I trial suggests non-inferiority of PCI when the **SYNTAX-II strategy** is followed.
Conclusions (II)

- Compared to SYNTAX I, contemporary state-of-art PCI in SYNTAX II led to significantly fewer lesions treated with PCI, and significantly higher success rates in CTO revascularisation.

- One-year outcomes of patients with SYNTAX score >22, treated with PCI using the SYNTAX score II risk stratification, were similar to those observed in patients with low anatomical risk (SYNTAX score ≤22).
TOTAL REVASC

- CTO TRIALS ???
- DECISION CTO
- EXPLORE
- SHINE CTO

- Residual Syntax score > 8
- ↑ Mortality 5 yrs
Study Design

2905 pts with unprotected left main disease

SYNTAX score ≤32
Consensus agreement of eligibility and equipoise by heart team

Yes
(N=1905)

No
(N=1000)
Enrollment registry

Stratified by diabetes, SYNTAX score and center

PCI (Xience EES)  
(N=948)

CABG  
(N=957)

Follow-up: 1 month, 6 months, 1 year, annually through 5 years
Primary endpoint: D/MI/CVA at median 3-yr FU, minimum 2-yr FU
Primary Endpoint
Death, Stroke or MI at 3 Years

Death, stroke or MI (%)

- CABG (n=957)
- PCI (n=948)

Months

No. at Risk:
PCI
CABG
948
957
896
857
875
821
857
807
957
793
836
712
700

Diff [upper 97.5% CL] = 0.5% [3.8%]

P_{NI} = 0.01

HR [95%CI] = 1.02 [95% CI: 0.80, 1.28]
P_{Sup} = 0.90

## Adjudicated Outcomes at 30 Days

<table>
<thead>
<tr>
<th>Event Description</th>
<th>PCI (n=948)</th>
<th>CABG (n=957)</th>
<th>Hazard Ratio [95%CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, stroke or MI</td>
<td>4.9%</td>
<td>7.9%</td>
<td>0.61 [0.42, 0.88]</td>
<td>0.008</td>
</tr>
<tr>
<td>- Death</td>
<td>1.0%</td>
<td>1.1%</td>
<td>0.90 [0.37, 2.22]</td>
<td>0.82</td>
</tr>
<tr>
<td>- Stroke</td>
<td>0.6%</td>
<td>1.3%</td>
<td>0.50 [0.19, 1.33]</td>
<td>0.15</td>
</tr>
<tr>
<td>- MI</td>
<td>3.9%</td>
<td>6.2%</td>
<td>0.63 [0.42, 0.95]</td>
<td>0.02</td>
</tr>
<tr>
<td>- Peri-procedural</td>
<td>3.6%</td>
<td>5.9%</td>
<td>0.61 [0.40, 0.93]</td>
<td>0.02</td>
</tr>
<tr>
<td>- Spontaneous</td>
<td>0.3%</td>
<td>0.3%</td>
<td>1.00 [0.20, 4.95]</td>
<td>1.00</td>
</tr>
<tr>
<td>- STEMI</td>
<td>0.7%</td>
<td>2.3%</td>
<td>0.32 [0.14, 0.74]</td>
<td>0.005</td>
</tr>
<tr>
<td>- Non-STEMI</td>
<td>3.2%</td>
<td>3.9%</td>
<td>0.82 [0.50, 1.32]</td>
<td>0.41</td>
</tr>
<tr>
<td>Death, stroke, MI or IDR</td>
<td>4.9%</td>
<td>8.4%</td>
<td>0.57 [0.40, 0.82]</td>
<td>0.002</td>
</tr>
<tr>
<td>- Ischemia-driven revascular (IDR)</td>
<td>0.6%</td>
<td>1.4%</td>
<td>0.46 [0.18, 1.21]</td>
<td>0.11</td>
</tr>
<tr>
<td>Definite stent thrombosis or symptomatic graft occlusion</td>
<td>0.3%</td>
<td>1.2%</td>
<td>0.27 [0.08, 0.97]</td>
<td>0.03</td>
</tr>
<tr>
<td>Peri-procedural MAE*†</td>
<td>8.1%</td>
<td>23.0%</td>
<td>0.35 [0.28, 0.45]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Death†, stroke†, MI†, IDR†. TIMI major/minor bleeding, transfusion ≥2 units, major arrhythmia (SVT requiring cardioversion, VT or VF requiring treatment, or bradycardia requiring temp or perm PM), surgical or radiologic procedure, renal failure (SCr increased by ≥0.5 mg/dL from baseline or need for dialysis), sternal wound dehiscence, infection requiring antibiotics, prolonged intubation (>48 hours), or post-pericardiotomy syndrome; †Adjudicated; other MAE components non-adjudicated.

## Adjudicated Outcomes at 3 Years (i)

<table>
<thead>
<tr>
<th>Event</th>
<th>PCI (n=948)</th>
<th>CABG (n=957)</th>
<th>HR [95%CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, stroke or MI (1° endpoint)</td>
<td>15.2%</td>
<td>14.7%</td>
<td>1.02 [0.80, 1.28]</td>
<td>0.90</td>
</tr>
<tr>
<td>- Death</td>
<td>8.0%</td>
<td>5.8%</td>
<td>1.36 [0.96, 1.93]</td>
<td>0.08</td>
</tr>
<tr>
<td>- Definite cardiovascular</td>
<td>3.7%</td>
<td>3.3%</td>
<td>1.13 [0.69, 1.84]</td>
<td>0.64</td>
</tr>
<tr>
<td>- Definite non-cardiovascular</td>
<td>3.8%</td>
<td>2.2%</td>
<td>1.68 [0.97, 2.93]</td>
<td>0.06</td>
</tr>
<tr>
<td>- Undetermined cause</td>
<td>0.7%</td>
<td>0.5%</td>
<td>1.48 [0.42, 5.26]</td>
<td>0.54</td>
</tr>
<tr>
<td>- Stroke</td>
<td>2.3%</td>
<td>3.1%</td>
<td>0.74 [0.42, 1.31]</td>
<td>0.30</td>
</tr>
<tr>
<td>- MI</td>
<td>8.0%</td>
<td>8.4%</td>
<td>0.94 [0.68, 1.29]</td>
<td>0.69</td>
</tr>
<tr>
<td>Death, stroke, MI or IDR</td>
<td>22.8%</td>
<td>18.9%</td>
<td>1.20 [0.98, 1.46]</td>
<td>0.08</td>
</tr>
<tr>
<td>- Ischemia-driven revasc (IDR)</td>
<td>12.5%</td>
<td>7.4%</td>
<td>1.72 [1.27, 2.32]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Definite stent thrombosis or symptomatic graft occlusion</td>
<td>0.8%</td>
<td>5.3%</td>
<td>0.14 [0.06, 0.31]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>EXCEL</th>
<th>NOBLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1905</td>
<td>1201</td>
</tr>
<tr>
<td>Number of centers</td>
<td>126</td>
<td>36</td>
</tr>
<tr>
<td>Number of countries</td>
<td>17 (US, EU, SA, Asia Pacific, Middle East)</td>
<td>7 (UK, Scandinavia)</td>
</tr>
<tr>
<td>SYNTAX score inclusion</td>
<td>≤32</td>
<td>No restriction</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>D, MI or stroke</td>
<td>D, MI, stroke or revasc</td>
</tr>
<tr>
<td>- Included peri-procedural MI</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Stent</td>
<td>Xience</td>
<td>Biomatrix</td>
</tr>
<tr>
<td>- 3-year definite ST rate</td>
<td>0.8%</td>
<td>3%</td>
</tr>
<tr>
<td>- Def ST &lt; symptomatic graft occlusion</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Stroke: PCI vs CABG</td>
<td>Less with PCI</td>
<td>More with PCI!</td>
</tr>
<tr>
<td>Worse PCI prognosis with higher SYNTAX score</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Noble Primary endpoint: 5 YEAR MACCE

PCI did not show non-inferiority and CABG was superior to PCI

HR 1.48 (1.11–1.96); p=0.0066

28% vs. 18%
Mortality

Myocardial Infarction

HR 1.08, 0.67–1.74; p=0.84

PCI

CABG

Non-procedural myocardial infarction (%)

HR 2.87, 1.40–5.89; p=0.0040

Number at risk

PCI

CABG

Lancet 2016 Dec 3;388(10061):2743-2752
Repeat revascularization

HR 1.50, 1.04–2.17, p=0.0304

Number at risk

<table>
<thead>
<tr>
<th>PCI</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>592</td>
<td>592</td>
</tr>
<tr>
<td>540</td>
<td>544</td>
</tr>
<tr>
<td>448</td>
<td>446</td>
</tr>
<tr>
<td>324</td>
<td>323</td>
</tr>
<tr>
<td>236</td>
<td>222</td>
</tr>
<tr>
<td>134</td>
<td>132</td>
</tr>
</tbody>
</table>

Lancet 2016 Dec 3;388(10061):2743-2752

Stroke

HR 2.20, 0.91–5.36, p=0.08

Analysis time (years)

Stroke (%)
# Updated Meta-analysis of LM DES Trials

6 RCTs, 4,686 pts, longest FU (median 39 mos)
(EXCEL, NOBLE, SYNTAX, PRECOMBAT, Boudriot et al, Le MANS)

30-day event rates: PCI vs. CABG

<table>
<thead>
<tr>
<th>Events at 30 days</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>0.63 (0.31-1.28)</td>
<td>0.16</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0.61 (0.30-1.21)</td>
<td>0.11</td>
</tr>
<tr>
<td>MI</td>
<td>0.70 (0.48-1.02)</td>
<td>0.08</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.36 (0.16-0.82)</td>
<td>0.007</td>
</tr>
<tr>
<td>Revascularization</td>
<td>0.66 (0.37-1.19)</td>
<td>0.16</td>
</tr>
<tr>
<td>All-cause death or MI</td>
<td>0.69 (0.49-0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>All-cause death, MI or stroke</td>
<td>0.62 (0.45-0.86)</td>
<td>0.004</td>
</tr>
<tr>
<td>All-cause death, MI, stroke or revasc</td>
<td>0.56 (0.41-0.76)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
# Updated Meta-analysis of LM DES Trials

6 RCTs, 4,686 pts, longest FU (median 39 mos)  
(EXCEL, NOBLE, SYNTAX, PRECOMBAT, Boudriot et al, Le MANS)

## Long-term event rates: PCI vs. CABG

<table>
<thead>
<tr>
<th>Events at long-term follow-up</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>0.99 (0.76-1.30)</td>
<td>0.74</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>1.01 (0.72-1.42)</td>
<td>0.83</td>
</tr>
<tr>
<td>MI</td>
<td>1.33 (0.84-2.11)</td>
<td>0.11</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.71 (0.34-1.49)</td>
<td>0.31</td>
</tr>
<tr>
<td>Revascularization</td>
<td>1.74 (1.47-2.07)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All-cause death or MI</td>
<td>1.11 (0.86-1.44)</td>
<td>0.26</td>
</tr>
<tr>
<td>All-cause death, MI or stroke</td>
<td>1.06 (0.82-1.37)</td>
<td>0.39</td>
</tr>
<tr>
<td>All-cause death, MI, stroke or revasc</td>
<td>1.27 (1.12-1.45)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Individual-patient-data Analysis from 11 PCI vs. CABG Trials
11,518 randomized pts; 4,478 (38.9%) with left main ds.
All-cause Mortality (all patients)

Mortality (%) vs. Follow-up (Years)

Number at risk:
- CABG (LM): 2245, 2086, 1903, 932, 804, 406
- PCI (LM): 2233, 2120, 1946, 978, 849, 478
- CABG (MVD): 3520, 3274, 3091, 2829, 2495, 1856
- PCI (MVD): 3520, 3338, 3155, 2875, 2533, 1928

Mean follow-up of 3.8 ± 1.4 years

HR 1.07 (95% CI 0.87-1.33) P=0.52
HR 1.28 (95% CI 1.09-1.49) P=0.002
Individual-patient-data Analysis from 11 PCI vs. CABG Trials
11,518 randomized pts; 4,478 (38.9%) with left main ds.

Stroke (all patients)

HR 0.77 (95% CI 0.61-0.97)
P = 0.03

Mean follow-up 3.8 ± 1.4 years

PCI (n=5753)
CABG (n=5765)

3.2%
2.6%

No. at risk
CABG 5765
PCI 5753
5421
5545
5282
5415
5138
5265
4901
5044
4550
4653
3677
3788
3446
3554
3213
3320
2957
3038
2202
2360
Individual-patient-data Analysis from 11 PCI vs. CABG Trials
11,518 randomized pts; 4,478 (38.9%) with left main ds.

Stroke (all patients)

- 0-30 days
  - HR 0.33 (95% CI 0.20-0.53)
  - P<0.001

- 31-1825 days
  - HR 1.05 (95% CI 0.80-1.38)
  - P=0.72

Mean follow-up 3.8 ± 1.4 years

No. at risk
CABG 5765
PCI 5753

Head SJ et al. Submitted.
LM Revascularization with Low/Int SS
CABG vs. PCI with Contemporary DES

- **Mortality:** Similar with PCI and CABG
- **Stroke:** Lower with PCI compared to CABG
- **MI:** Lower with PCI in the peri-procedural period; higher with PCI during long-term FU – similar through 5 years
- **Short-term morbidity:** Substantially less with PCI
- **Revascularization:** Less with CABG than PCI (~5%)

PCI with contemporary DES (especially Xience, as proven in EXCEL) may be considered an acceptable or even preferred revascularization modality for selected pts with LMCAD, a decision which should be made after heart team discussion, taking into account each patient’s individual circumstances and preferences.
Recommendation for the type of revascularization in patients with stable coronary artery disease with suitable coronary anatomy for both procedures and low predicted surgical mortality

<table>
<thead>
<tr>
<th>Recommendations according to extent of CAD</th>
<th>CABG</th>
<th>PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-vessel CAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without proximal LAD stenosis</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>With proximal LAD stenosis</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Two-vessel CAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without proximal LAD stenosis</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>With proximal LAD stenosis</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Left main CAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main disease with low SYNTAX score (0 - 22)</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Left main disease with intermediate SYNTAX score (23 - 32)</td>
<td>I</td>
<td>IIa</td>
</tr>
<tr>
<td>Left main disease with high SYNTAX score (≥33)</td>
<td>I</td>
<td>III</td>
</tr>
<tr>
<td>Three-vessel CAD without diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three-vessel disease with low SYNTAX score (0 - 22)</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Three-vessel disease with intermediate or high SYNTAX score (≥22)</td>
<td>I</td>
<td>III</td>
</tr>
<tr>
<td>Three-vessel CAD with diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three-vessel disease with low SYNTAX score 0 – 22</td>
<td>I</td>
<td>IIb</td>
</tr>
<tr>
<td>Three-vessel disease with intermediate or high SYNTAX score (≥22)</td>
<td>I</td>
<td>III</td>
</tr>
</tbody>
</table>
PCI

FAVOURS PCI

Clinical characteristics
Presence of severe co-morbidity (not adequately reflected by scores)
Advanced age/frailty/reduced life expectancy
Restricted mobility and conditions that affect the rehabilitation process

Anatomical and technical aspects
MVD with SYNTAX score 0-22
Anatomy likely resulting in incomplete revascularization with CABG due to poor quality or missing conduits
Severe chest deformation or scoliosis
Sequela of chest radiation
Porcelain aorta

CABG

Clinical characteristics
Left internal thoracic artery to left anterior descending
Right internal thoracic artery or radial artery
Sequential anastomosis to obtuse marginal 1 and 3

Anatomical and technical aspects
MVD with SYNTAX score ≤23
Anatomy likely resulting in incomplete revascularization with PCI
Severely calcified coronary artery lesions limiting lesion expansion

Need for concomitant interventions
Ascending aortic pathology with indication for surgery
Concomitant cardiac surgery
**ISCHEMIA: Design**

**Stable Patient**  
Moderate or Severe Ischemia*

**Blinded CCTA**

Core lab anatomy eligible?  
**no**  
Late screen failure

**yes**  
RANDOMIZE

**INVASIVE Strategy**  
OMT³ + Cath +  
Optimal Revascularization

**CONSERVATIVE Strategy**  
OMT³ alone  
Cath reserved for OMT failures

---

**Average 4 Years of Follow-up**  
Primary Endpoint: Composite of CV Death and MI

---

1. CCTA may not be performed in participants with eGFR <60 mL/min
2. Exclude participants with LM disease or no obstructive disease
3. OMT=optimal medical therapy

*Stable patient with moderate or severe ischemia.*
ΚΩΝΣΤΑΝΤΙΝΟΣ ΛΟΥΤΣΙΔΗΣ
1956-2018