Will FFR-Directed PCI Be Better Than CABG?

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Within the past 12 months, I or my spouse/partner have had a financial interest /arrangement or affiliation with the organization(s) listed below:

**Affiliation/Financial Relationship**

**Grant/ Research Support:**  
St. Jude Medical/Medtronic

**Grant/ Research Support:**  
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Medtronic

**Major Stock Shareholder/Equity Interest:**

**Royalty Income:**

**Ownership/Founder:**

**Salary:**  
NIH-R01 HL093475 (PI)

**Intellectual Property Rights:**

**Other Financial Benefit (minor stock options):**  
HeartFlow
Will FFR-Directed PCI be Better Than CABG?

Yes!

….and No
CABG vs. PCI: ASCERT Registry

~ 189,000 stable patients ≥65 years old treated with either PCI or CABG

**Mortality after propensity matching**

<table>
<thead>
<tr>
<th></th>
<th>30-Day (95% CI)</th>
<th>1-Yr (95% CI)</th>
<th>2-Yr (95% CI)</th>
<th>3-Yr (95% CI)</th>
<th>4-Yr (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality after CABG, %</td>
<td>2.25 (2.09–2.41)</td>
<td>6.24 (5.97–6.50)</td>
<td>8.98 (8.68–9.29)</td>
<td>12.4 (12.0–12.8)</td>
<td>16.4 (15.9–16.9)</td>
</tr>
<tr>
<td>Mortality after PCI, %</td>
<td>1.31 (1.21–1.41)</td>
<td>6.55 (6.35–6.76)</td>
<td>11.3 (11.0–11.6)</td>
<td>15.9 (15.6–16.3)</td>
<td>20.8 (20.4–21.2)</td>
</tr>
<tr>
<td>Relative risk with CABG (95% CI)</td>
<td>1.72 (1.52–1.89)</td>
<td>0.95 (0.90–1.00)</td>
<td>0.79 (0.76–0.83)</td>
<td>0.78 (0.75–0.81)</td>
<td>0.79 (0.76–0.82)</td>
</tr>
</tbody>
</table>

Randomized Trials

Meta-Analysis of 10 randomized CABG vs. PCI trials including >7,000 patients

Death
p=NS

Death or MI
p=NS

Meta-Analysis of CABG vs. PCI Trials

Impact of Diabetes

Meta-Analysis of CABG vs. PCI Trials

Impact of Age

SYNTAX Trial:

- 1800 patients with 3 vessel CAD randomized to PCI with Taxus drug-eluting stents or CABG
  - ~28% diabetic
  - ~33% with LM disease
  - 4.6 stents per patient
  - Average of 86 mm of stent (1/3 with >100 mm)

5 Year Outcomes: All Cause Mortality

5 Year Outcomes: Myocardial Infarction

5 Year Outcomes: Stroke

5 Year Outcomes: MACCE

SYNTAX Score

Similar outcomes with PCI vs CABG with lower SYNTAX score

Lowest Tertile (SYNTAX score ≤ 22)
Worse outcomes with PCI vs CABG with higher SYNTAX score

Intermediate Tertile (SYNTAX score 23-32)

Worse outcomes with PCI vs CABG with higher SYNTAX score

High Tertile (SYNTAX score $\geq 33$)

FREEDOM Trial

- 2005-2010: 1900 diabetics enrolled from 140 international centers
- Mostly first generation drug-eluting stents
- Mean SYNTAX score = 26
- 3.5 lesions stented/patient

# FREEDOM Trial

## Early Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>30 Days after Procedure</th>
<th>12 Months after Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCI</td>
<td>CABG</td>
</tr>
<tr>
<td></td>
<td>number (percent)</td>
<td>number (percent)</td>
</tr>
<tr>
<td>Major adverse cardiovascular and cerebrovascular events</td>
<td>45 (4.8)</td>
<td>47 (5.2)</td>
</tr>
<tr>
<td>Death</td>
<td>8 (0.8)</td>
<td>15 (1.7)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>17 (1.8)</td>
<td>15 (1.7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (0.3)</td>
<td>16 (1.8)</td>
</tr>
<tr>
<td>Repeat revascularization</td>
<td>31 (3.3)</td>
<td>10 (1.1)</td>
</tr>
</tbody>
</table>

# FREEDOM Trial

## Late Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>2 Years after Randomization</th>
<th>5 Years after Randomization</th>
<th>Patients with Event</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCI</td>
<td>CABG</td>
<td>PCI</td>
<td>CABG</td>
</tr>
<tr>
<td><strong>Primary composite†</strong></td>
<td>121 (13.0)</td>
<td>108 (11.9)</td>
<td>200 (26.6)</td>
<td>146 (18.7)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>62 (6.7)</td>
<td>57 (6.3)</td>
<td>114 (16.3)</td>
<td>83 (10.9)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>62 (6.7)</td>
<td>42 (4.7)</td>
<td>98 (13.9)</td>
<td>48 (6.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>14 (1.5)</td>
<td>24 (2.7)</td>
<td>20 (2.4)</td>
<td>37 (5.2)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>9 (0.9)</td>
<td>12 (1.3)</td>
<td>73 (10.9)</td>
<td>52 (6.8)</td>
</tr>
</tbody>
</table>

FREEDOM Trial

Mortality

P = 0.049 by log-rank test
5-Yr event rate: 16.3% vs. 10.9%

No. at Risk
PCI  953  897  845  685  466  243
CABG 947  855  806  655  449  238

What have we learned?

- Older patients, patients with more severe CAD, and diabetics fare better with CABG when compared to angiography-guided PCI with *first* generation drug-eluting stents.
How do we explain this?

Stenting addresses the existing lesion but not future lesions.

How do we explain this?

Stenting addresses the existing lesion but not future lesions.

Bypass grafting addresses the existing lesion and also future culprit lesions.

FAME 3:

**Background**

- Why should we expect a different result with FAME 3?
  - 2nd Generation DES outperform 1st Generation.
  - Fractional Flow Reserve-guided PCI outperforms angiography-guided PCI.
Background:

3 Year Mortality Benefit of 2nd Generation DES (SPIRIT II, III, IV)

Background:

3 Year MI Benefit of 2nd Generation DES

Background:

3 Year Stent Thrombosis Benefit of 2nd Generation DES

- **Everolimus DES**
  - N=3350
  - Early + Late (up to 1 year): 0.39%
  - Very Late (>1 year): 0.35%
  - 1 year HR: HR [95%CI] = 0.39 [0.19, 0.82], p=0.01
  - p=0.003

- **Paclitaxel DES**
  - N=1638
  - Early + Late (up to 1 year): 0.92%
  - Very Late (>1 year): 0.67%
  - 1 year HR: 1.65%

Background:

5 Year Mortality Benefit of 2\textsuperscript{nd} Generation DES (SPIRIT III)

Background:

5 Year TLF Benefit of 2nd Generation DES (SPIRIT III)

**Background:**

*Randomized comparison of two 2\textsuperscript{nd} generation DES (Resolute and Xience stents)*

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**Serruys, et al. NEJM 2010;363:136-46.**
Background:

Randomized comparison of 2nd generation Resolute and Xience stents in the TWENTE trial

**BEST Trial**

880 MVD patients randomized to PCI with everolimus-eluting 2\textsuperscript{nd} generation stent or to CABG

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>PCI</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>438</td>
<td>442</td>
</tr>
<tr>
<td></td>
<td>402</td>
<td>415</td>
</tr>
<tr>
<td></td>
<td>362</td>
<td>377</td>
</tr>
<tr>
<td></td>
<td>305</td>
<td>326</td>
</tr>
<tr>
<td></td>
<td>242</td>
<td>262</td>
</tr>
<tr>
<td></td>
<td>126</td>
<td>145</td>
</tr>
</tbody>
</table>

P=0.04 by log-rank test

BEST Trial

880 MVD patients randomized to PCI with everolimus-eluting 2\textsuperscript{nd} generation stent or to CABG

Death, Myocardial Infarction, Stroke, or Repeat Revascularization

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>PCI</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. at Risk

PCI          | 438      | 389      | 341      | 288      | 229      | 117
CABG         | 442      | 409      | 368      | 317      | 250      | 137

P=0.01 by log-rank test

What else has changed?

**FFR = \( P_d / P_a \)**

*during maximal flow*

\[ P_d / P_a = 60 / 100 \]

\[ FFR = 0.60 \]
FAME Study: One Year Outcomes

1005 patients with 2-3 vessel CAD randomized to angio or FFR-guided PCI

%

Death MI Repeat Revasc Death/MI MACE

Angio-Guided FFR-Guided

Death 3 1.8
MI 8.7 5.7
Repeat 9.5 6.5
Revasc ~35% ↓
~30% ↓
~35% ↓
~35% ↓

~40% ↓
~35% ↓
~30% ↓
~30% ↓

18.3 13.2

p=0.02
p=0.04

FAME Study: Two Year Outcomes

Death/MI was significantly reduced from 12.9% to 8.4% (p=0.02)

Survival Free of MACE

FFR-Guided

Angio-Guided

730 days
4.5%

Functional SYNTAX Score

- Low SS: 167 (34%)
- Medium SS: 167 (34%)
- High SS: 163 (32%)

Without FFR

Functional SYNTAX Score

Reclassifies > 30% of cases

Without FFR

With FFR

Functional SYNTAX Score

Discriminates Risk for Death/MI

P < 0.01

34% of patients

32% of patients

59% of patients

20% of patients

Why FAME 3?

1 year MACE Rates

<table>
<thead>
<tr>
<th>Procedure</th>
<th>SYNTAX</th>
<th>FAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>19.1</td>
<td>18.4</td>
</tr>
<tr>
<td>CABG</td>
<td>11.2</td>
<td>13.2</td>
</tr>
<tr>
<td>PCI - angio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI - FFR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FAME 3:

**Objective**

- The primary objective of the FAME 3 Trial is to demonstrate that FFR-guided PCI with the 2\textsuperscript{nd} generation Resolute DES is non-inferior to CABG in patients with multivessel CAD.
FAME 3:

**Design**

- Multicenter, worldwide, prospective, randomized trial
- Non-inferiority design
- 1500 patients from 50 sites
- Plan for 2 years enrolment and up to 5 year follow-up
Study Flow:

All Comers with 3 V CAD (not involving LM)

Heart team identifies lesions for PCI/CABG and then patient is randomized

FFR-Guided PCI with Resolute DES Stent all lesions with FFR ≤ 0.80 (n=750)

Perform CABG based on coronary angiogram (n=750)

Primary: One Year follow-up for Death, MI, CVA, Revascularization
Key Secondary: Three Year follow-up for Death/MI/CVA

Non-inferior Design

NCT02100722
FAME 3:

**Inclusion Criteria**

- Age ≥ 21 years

- Three vessel CAD, defined as ≥ 50% diameter stenosis by visual estimation in each of the three major epicardial vessels, but not involving left main coronary artery, and amenable to revascularization by both PCI and CABG as determined by the Heart Team

- Willing and able to provide informed, written consent
FAME 3:  

**Key Exclusion Criteria**

- Requirement for other cardiac or non-cardiac surgical procedure (e.g., valve replacement)
- Previous CABG
- Left main disease requiring revascularization
- Cardiogenic shock and/or need for mechanical/pharmacologic hemodynamic support
- Recent STEMI (<5 days)
- Ongoing Non STEMI with biomarkers (e.g., cardiac troponin) still rising
- Known left ventricular ejection fraction <30%
FAME 3:

**Major Endpoints**

- **Primary Endpoint:**
  - One year rate of Death, MI, Stroke and Revascularization

- **Key Secondary Endpoint:**
  - Three year rate of Death, MI and Stroke
FAME 3

**Study Organization**

- Investigator-initiated trial
- Coordinated by Stanford with support of a CRO
- Funded by research grants from Medtronic and St. Jude Medical
- Independent DSMB and CEC
FAME 3 Enrollment Update:

<table>
<thead>
<tr>
<th>Institution</th>
<th>Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catharina Hospital Eindhoven</td>
<td>27</td>
</tr>
<tr>
<td>O. L. Vrouw Ziekenhuis Aalst</td>
<td>11</td>
</tr>
<tr>
<td>Danderydssjukhus</td>
<td>9</td>
</tr>
<tr>
<td>Asan Medical Center Seoul</td>
<td>8</td>
</tr>
<tr>
<td>Vilnius University Hospital SA</td>
<td>7</td>
</tr>
<tr>
<td>Södersjukhuset AB</td>
<td>7</td>
</tr>
<tr>
<td>Sahlgrenska University Hospital</td>
<td>5</td>
</tr>
<tr>
<td>Palo Alto VA</td>
<td>4</td>
</tr>
<tr>
<td>ISALA</td>
<td>2</td>
</tr>
<tr>
<td>Stanford University</td>
<td>2</td>
</tr>
<tr>
<td>Centre Hospitalier de l'Univer</td>
<td>1</td>
</tr>
<tr>
<td>FN Brno, Interni Kardiologicka</td>
<td>1</td>
</tr>
</tbody>
</table>

Total = 84
Conclusion:

- By incorporating FFR-guided PCI and utilizing the 2nd generation Resolute Integrity stent, FAME 3 aims to demonstrate that FFR-guided PCI is non-inferior to CABG in patients with 3-vessel coronary disease not involving the left main coronary artery.
Will FFR-Directed PCI be Better Than CABG?

Yes!

- With current generation DES
- Applying FFR guidance to optimize ischemia reduction and minimize stent complications
- Optimizing medical therapy to reduce plaque progression

...and No

- Complex disease will remain a limitation
- Long-term outcomes in diabetics will be a challenge
- Revascularization will remain higher
Thank You!