Revascularization in Diabetes: New Insights from the BARI 2D Angioplasty Summit 2010 Seoul, Korea

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Presenter Disclosure Information

David R. Holmes, Jr., M.D.

“Revascularization in Diabetes: New Insights from the BARI 2D”

The following relationships exist related to this presentation:

No relationships to disclose
Korea and Diabetes

- Korean National Health and Nutrition Survey
- Cross Sectional Nationally Representation Survey Diabetes and Impaired Fasting Glucose

Korea and Diabetes
Prevalence of Diabetes and Impaired Fasting Glucose (IFG)

Korean Men

Age (years)

% 35 30 25 20 15 10 5 0

Diabetes IFG

Korean Women

Age (years)

% 35 30 25 20 15 10 5 0

Diabetes IFG

Angioplasty not best option for diabetics

By Doug Levy
USA TODAY

Diabetics with heart disease are better off with bypass surgery than angioplasty, the National Heart, Lung and Blood Institute said Thursday.

A study of 1,829 people with blockages in two or more heart
drugs, George Sopko, an NHLBI cardiologist. However, the recommendation only applies to patients with both severe diabetes and two or more blocked coronary arteries.

Such patients who already have had angioplasty should be monitored carefully, he says, "but there's no need to panic."
BARI - 7 Year Survival

Survival-Patients with Treated Diabetes

P = 0.0011

No. of pts
CABG 180 161 100
PTCA 173 139 70

CABG (76.4)
PTCA (55.7)

Detre, JACC 2000
BARI 2D Clinical Trial

Compare treatment strategies for patients with

- Type 2 diabetes mellitus
- Documented CAD suitable for elective revascularization (1 or more significant lesions)
- Documented ischemia
- No prior CABG or PCI within the last 12 months
Cardiologist a priori selected revascularization method based on clinical and angiographic factors

- Percutaneous coronary intervention
- Coronary artery bypass graft surgery
2368 patients with mild to moderate CAD and Type 2 diabetes prior to randomization. Prospective. Randomized. Mean follow-up 5.3 years

- **Primary Endpoint:** Death (from any cause)
- **Secondary Endpoint:** Composite of Death, MI, or Stroke

BARI 2D Study Group, NEJM 2009
## Angiographic Characteristics

**2,368 Randomized Patients**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAD diseased vessels</strong></td>
<td></td>
</tr>
<tr>
<td>0/1</td>
<td>33%</td>
</tr>
<tr>
<td>2</td>
<td>36%</td>
</tr>
<tr>
<td>3</td>
<td>31%</td>
</tr>
<tr>
<td><strong>Myocardial jeopardy</strong></td>
<td></td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td>44±24</td>
</tr>
<tr>
<td><strong>Proximal LAD (&gt;50% stenosis)</strong></td>
<td>13%</td>
</tr>
<tr>
<td><strong>Total occlusion</strong></td>
<td>41%</td>
</tr>
<tr>
<td><strong>Abnormal LV function (&lt;50%)</strong></td>
<td>17%</td>
</tr>
</tbody>
</table>
1593 patients with MVD

CABG: 11% suitable for PCI

PCI: 49% suitable for CABG

BARI 2D

- Selection of CABG rather than PCI
  - Based largely on greater extent, severity and complexity of CAD
  - More likely in patients >65 years
  - Less likely in patients with prior PCI
  - More likely in non U.S. centers
  - Less likely after introduction of DES

Conclusions: The majority of diabetic patients with multivessel disease were selected for PCI rather than CABG. Preference for CABG over PCI was largely based on angiographic features related to the extent, location, and nature of CAD, as well as geographic, demographic, and clinical factors. (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes [BARI 2D]; NCT00006035)
BARI 2D Trial: Primary Endpoint

- The 5-year death rate for the group receiving revascularization plus optimal medical therapy was 13.2% vs. 13.5% in the group receiving optimal medical therapy alone.

- The difference between the two treatment groups did not reach statistical significance.

BARI 2D Study Group, NEJM 2009
Prompt Revascularization vs Medical Therapy

**All-Cause Mortality**
- 88.3% rev
- 87.8% med

**Death/MI/Stroke**
- 77.2% rev
- 75.9% med

- Survival (%)
- Event free (%)

- Years since randomization

P=0.97
P=0.70
The rates of MI, stroke and the combined secondary endpoint of death, MI, and stroke were similar between the group receiving revascularization plus optimal medical therapy vs. the group receiving optimal medical therapy alone.

The difference between the two treatment groups for the combined secondary endpoint of death, MI, and stroke did not reach statistical significance (p=0.70).
PCI Intended Revascularization Stratum
Lower Risk Patients

**All-Cause Mortality**

- Survival (%)
- Years since randomization
- P=0.48
- Prompt revascularization: 89.2% rev
- Intensive medical: 89.8% med

**Death/MI/Stroke**

- Event free (%)
- Years since randomization
- P=0.15
- Prompt revascularization: 78.9% med
- Intensive medical: 77.0% rev
CABG Intended Revascularization Stratum Higher Risk Patients

**All-Cause Mortality**

- **Prompt revascularization**: 86.4% rev
- **Intensive medical**: 83.6% med

*P=0.33*

**Years since randomization**

**Death/MI/Stroke**

- **Prompt revascularization**: 77.6% rev
- **Intensive medical**: 69.5% med

*P=0.01*

**Years since randomization**
Insulin Sensitization vs Insulin Provision

All-Cause Mortality

Survival (%)

Years since randomization

88.2% IS
87.9% IP

P=0.89

Death/MI/Stroke

Event free (%)

Years since randomization

77.7% IS
75.4% IP

P=0.70
**BARI 2D Primary Conclusion**

**Overall similar mortality and CV events**
- Prompt revascularization vs delayed or no revascularization
- Insulin sensitization vs insulin provision

**Among high-risk patients selected for CABG**
- Prompt revascularization reduces major CV events compared with delayed or no revascularization (P=0.01)

**Among lower-risk patients selected for PCI**
- Prompt revascularization and delayed or no revascularization had similar rates for major CV events
Conclusions

• Optimal medical therapy is required for diabetic patients with CAD

• Despite optimal medical therapy, 42% of diabetic patients will still undergo revascularization during 5 years FU

• Revascularization strategies chosen depend in large part on severity and extent of disease

• Clinical decision making still works
We're lining up to patients with Diabetes. Are there issues with that?

Another problem caused by deforestation
There are no facts, only interpretations.

-Friedrich Nietzsche
There are no facts, only interpretations.

-Friedrich Nietzsche

Life is better served without a helping of diabetes.
Revascularization Decision
BARI 2D

Cardiologist a priori selected revascularization method based on clinical and angiographic factors

Percutaneous coronary intervention
or
Coronary artery bypass graft surgery
Death/MI/Stroke Among Medical Assigned Patients

- CABG stratum – medical patients: 30.5%
- PCI stratum – medical patients: 21.1%

Years since randomization
5-Year Clinical Event Rates
CABG Intended Revascularization Stratum
n=763

- **Prompt revascularization**
- **Intensive medical**

<table>
<thead>
<tr>
<th>Event</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>14</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>9</td>
<td>15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Death/MI/stroke</td>
<td>22</td>
<td>31</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

P<0.01
BARI 2D Primary Conclusions

Similar mortality and major cardiovascular events, overall for

• Prompt revascularization vs delayed or no revascularization

• Insulin sensitization vs insulin provision
Among high-risk patients selected for CABG

• Prompt revascularization reduces major cardiovascular events compared with delayed/no revascularization (P=0.01)

Among lower-risk patients selected for PCI

• Prompt revascularization and delayed/no revascularization had similar rates for major cardiovascular events
### 4 Treatment Combinations
#### 5-Year Clinical Event Rates – All Patients (n=2,368)

<table>
<thead>
<tr>
<th></th>
<th>All-cause mortality</th>
<th>Death/MI/stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prompt revasc</td>
<td>Intensive medical</td>
</tr>
<tr>
<td>Insulin sensitization (%)</td>
<td>11.2</td>
<td>12.3</td>
</tr>
<tr>
<td>Insulin provision (%)</td>
<td>12.2</td>
<td>12.0</td>
</tr>
<tr>
<td>Interaction P</td>
<td>0.78</td>
<td></td>
</tr>
</tbody>
</table>
Major Cardiovascular Events

**PCI Intended Stratum**
- MED-IS
- MED-IP
- REV-IS
- REV-IP

P=0.30

**CABG Intended Stratum**

P=0.021
# Adverse Event Rates

**Glycemic Randomized Treatment Assignment**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>IS n=1,154 (%)</th>
<th>IP n=1,156 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>53.3</td>
<td>73.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>5.9</td>
<td>9.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>56.6</td>
<td>51.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>22.6</td>
<td>20.0</td>
<td>0.13</td>
</tr>
<tr>
<td>Hx of CHF*</td>
<td>67.2</td>
<td>63.5</td>
<td>0.65</td>
</tr>
<tr>
<td>No Hx of CHF*</td>
<td>19.4</td>
<td>16.6</td>
<td>0.09</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>7.6</td>
<td>6.9</td>
<td>0.54</td>
</tr>
</tbody>
</table>

*141 pt had a Hx of CHF and 2,035 had no Hx of CHF*
Insulin sensitization appeared to enhance the benefit of revascularization particularly among those selected for CABG.

Insulin sensitization was associated with lower BMI, higher HDL and lower rates of severe hypoglycemia.
5-Year All-Cause Death Rates
Difference Between BARI 2D Randomized Treatment Groups

- All patients: 95% CI, 0.3; 99% CI, 2.8
- PCI stratum: 95% CI, 0.5; 99% CI, -0.6
- CABG stratum: 99% CI, 0.6

Med better vs. Rev better

IP better vs. IS better
5-Year Major Cardiovascular Event Rates
Difference by BARI 2D
Randomized Treatment Groups

<table>
<thead>
<tr>
<th>Stratum</th>
<th>95% CI</th>
<th>99% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1.3</td>
<td>2.3</td>
</tr>
<tr>
<td>PCI stratum</td>
<td></td>
<td>8.1</td>
</tr>
<tr>
<td>CABG stratum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IP better     IS better

-20  -10     0     10    20
• In the United States, 24 million people have diabetes

• At least 65% of people with diabetes die of heart disease or stroke

• Heart disease death rates among people with diabetes are 2-4 times higher than rates among adults without diabetes
• Patients with Type 2 diabetes have an increased risk of suffering a cardiovascular event over non-diabetic patients.

• The success of coronary revascularization in reducing myocardial infarction and death in diabetic patients with chronic stable angina has not been established.

• Similarly, it is unclear if insulin sensitization therapy offers benefits over insulin provision therapy in reducing cardiovascular events.
BARI 2D Primary and Principal Secondary Endpoints

• All-cause mortality

• Major cardiovascular events: composite of death/MI/stroke

• Average follow-up 5.3 years
Coronary angiography was performed in patients with type 2 diabetes referred for evaluation for CAD

2,368 were enrolled

763 were selected for CABG stratum

- 385 were randomly assigned to medical therapy
  - 194 were randomly assigned to insulin provision
  - 191 were randomly assigned to insulin sensitization

- 378 were randomly assigned to revascularization
  - 190 were randomly assigned to insulin provision
  - 188 were randomly assigned to insulin sensitization

1,605 were selected for PCI stratum

- 807 were randomly assigned to medical therapy
  - 399 were randomly assigned to insulin provision
  - 408 were randomly assigned to insulin sensitization

- 798 were randomly assigned to revascularization
  - 402 were randomly assigned to insulin provision
  - 396 were randomly assigned to insulin sensitization

194 were randomly assigned to insulin provision

191 were randomly assigned to insulin sensitization

190 were randomly assigned to insulin provision

188 were randomly assigned to insulin sensitization

399 were randomly assigned to insulin provision

408 were randomly assigned to insulin sensitization

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396 were randomly assigned to insulin sensitization.
The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial is sponsored by the National Heart, Lung and Blood Institute (NHLBI) and receives substantial funding from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
### Demographic and Clinical History
2,368 Randomized Patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean yr)</td>
<td>62.4</td>
</tr>
<tr>
<td>Female (%)</td>
<td>30</td>
</tr>
<tr>
<td>Ethnic/racial minority (%)</td>
<td>34</td>
</tr>
<tr>
<td>Myocardial infarction Hx (%)</td>
<td>32</td>
</tr>
<tr>
<td>Congestive heart failure Hx (%)</td>
<td>7</td>
</tr>
<tr>
<td>Hx of stroke or TIA (%)</td>
<td>10</td>
</tr>
<tr>
<td>Peripheral artery disease (%)</td>
<td>24</td>
</tr>
</tbody>
</table>
## Cardiac Clinical Characteristics

### 2,368 Randomized Patients

<table>
<thead>
<tr>
<th>Angina status</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No angina or anginal equivalents</td>
<td>18.0</td>
</tr>
<tr>
<td>Anginal equivalents</td>
<td>21.4</td>
</tr>
<tr>
<td>Stable angina CCS 1-2</td>
<td>42.5</td>
</tr>
<tr>
<td>Stable angina CCS 3-4</td>
<td>8.6</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>9.5</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>20.0</td>
</tr>
<tr>
<td>Prior stent</td>
<td>13.0</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>6.0</td>
</tr>
</tbody>
</table>
## Diabetes Clinical History
### 2,368 Randomized Patients

<table>
<thead>
<tr>
<th>Duration of diabetes (mean yr)</th>
<th>10.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 months</td>
<td>8%</td>
</tr>
<tr>
<td>6 months-5 years</td>
<td>25%</td>
</tr>
<tr>
<td>5-10 years</td>
<td>24%</td>
</tr>
<tr>
<td>10-20 years</td>
<td>29%</td>
</tr>
<tr>
<td>≥20 years</td>
<td>14%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HbA$_{1c}$ % (mean)</th>
<th>7.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receiving insulin</td>
<td>28%</td>
</tr>
<tr>
<td>Micro or macroalbuminurinuria (ACR &gt;30)</td>
<td>33%</td>
</tr>
<tr>
<td>Neuropathy (MNSI clinical score &gt;2)</td>
<td>50%</td>
</tr>
</tbody>
</table>
Risk Factor Status Among BARI 2D Patients at Baseline

- HbA1c >7%: 60%
- Total cholesterol ≥200: 19%
- LDL cholesterol ≥100: 40%
- HDL cholesterol low: 73%
- BP >130/80 mm Hg: 52%
- BMI ≥30: 56%
- Current smoker: 13%
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Revasc (CABG + OMT or PCI + OMT) (n=1176)</th>
<th>OMT (n=1192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs ± SD)</td>
<td>62.3 ± 8.8</td>
<td>62.4 ± 9.0</td>
</tr>
<tr>
<td>Male (%)</td>
<td>70.4</td>
<td>70.3</td>
</tr>
<tr>
<td>HbA1c (% mean ± SD)</td>
<td>7.6 ± 1.6</td>
<td>7.7 ± 1.6</td>
</tr>
<tr>
<td>Duration of diabetes (yrs mean ± SD)</td>
<td>10.2 ± 8.5</td>
<td>10.7 ± 8.8</td>
</tr>
<tr>
<td>History of MI (%)</td>
<td>31.7</td>
<td>32.4</td>
</tr>
<tr>
<td>History of CHF (%)</td>
<td>7.1</td>
<td>6.2</td>
</tr>
<tr>
<td>Cerebrovascular event (%)</td>
<td>9.5</td>
<td>10.0</td>
</tr>
<tr>
<td>Peripheral artery disease (%)</td>
<td>23.7</td>
<td>23.7</td>
</tr>
<tr>
<td>Prior revascularization (%)</td>
<td>22.9</td>
<td>24.2</td>
</tr>
</tbody>
</table>

BARI 2D Study Group, NEJM 2009
# BARI 2D Trial: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Insulin Sensitization (n=1183)</th>
<th>Insulin Provision (n=1185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs ± SD)</td>
<td>62.3 ± 9.2</td>
<td>62.5 ± 8.7</td>
</tr>
<tr>
<td>Male (%)</td>
<td>70.1</td>
<td>70.6</td>
</tr>
<tr>
<td>HbA1c (% mean ± SD)</td>
<td>7.6 ± 1.6</td>
<td>7.7 ± 1.6</td>
</tr>
<tr>
<td>Duration of diabetes (yrs mean ± SD)</td>
<td>10.1 ± 8.4</td>
<td>10.8 ± 8.9</td>
</tr>
<tr>
<td>History of MI (%)</td>
<td>32.6</td>
<td>31.5</td>
</tr>
<tr>
<td>History of CHF (%)</td>
<td>6.7</td>
<td>6.6</td>
</tr>
<tr>
<td>Cerebrovascular event (%)</td>
<td>9.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Peripheral artery disease (%)</td>
<td>23.9</td>
<td>23.5</td>
</tr>
<tr>
<td>Prior revascularization (%)</td>
<td>23.1</td>
<td>24.1</td>
</tr>
</tbody>
</table>

BARI 2D Study Group, NEJM 2009
The rates of MI, stroke and the combined secondary endpoint of death, MI, and stroke were similar between the group insulin sensitization therapy vs. the group receiving insulin provision therapy.

The difference between the two treatment groups for the combined secondary endpoint of death, MI, and stroke did not reach statistical significance (p=0.13).
BARI 2D Trial: Limitations

• Patients who are at high risk for MI and, therefore, stand to benefit the most from revascularization were excluded from the trial.

• The broad applicability of BARI 2D is limited by the fact that the patient population selected represents only a small subset of patients with diabetes and coronary artery disease.

BARI 2D Study Group, NEJM 2009
SYNTAX Trial
With and Without

N=1800

Non-Diabetic
75%

Diabetic, Med Rx
25%

Insulin
40.3%

Oral Agents
59.7%

Banning AP et al, JACC 55:2010
SYNTAX Trial
With and Without

<table>
<thead>
<tr>
<th></th>
<th>Non-Diabetic n=1348</th>
<th>Diabetic n=452</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>79.9</td>
<td>71.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>27.5</td>
<td>29.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current tobacco</td>
<td>21.7</td>
<td>15.8</td>
<td>&lt;0.006</td>
</tr>
<tr>
<td>CHF</td>
<td>3.7</td>
<td>7.4</td>
<td>0.001</td>
</tr>
<tr>
<td>PVD</td>
<td>8.2</td>
<td>14.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Banning AP et al, JACC 55:2010
## SYNTAX Trial
### With and Without

<table>
<thead>
<tr>
<th></th>
<th>Non-Diabetic n=1348</th>
<th>Diabetic n=452</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lesions</td>
<td>4.3 ± 1.8 (1340)</td>
<td>4.6 ± 1.8 (449)</td>
<td>0.003</td>
</tr>
<tr>
<td>Left main, any</td>
<td>35.9 (480/1338)</td>
<td>29.0 (130/449)</td>
<td>0.007</td>
</tr>
<tr>
<td>Left main only</td>
<td>3.9 (52/1338)</td>
<td>2.2 (10/449)</td>
<td>0.10</td>
</tr>
<tr>
<td>Left main +1 V</td>
<td>5.6 (75/1338)</td>
<td>4.0 (18/449)</td>
<td>0.19</td>
</tr>
<tr>
<td>Left main + 2 V</td>
<td>12.0 (160/1338)</td>
<td>11.1 (50/449)</td>
<td>0.64</td>
</tr>
<tr>
<td>Left main + 3 V</td>
<td>14.4 (193/1338)</td>
<td>11.6 (52/449)</td>
<td>0.13</td>
</tr>
<tr>
<td>3-V disease only</td>
<td>64.1 (858/1338)</td>
<td>71.0 (319/449)</td>
<td>0.007</td>
</tr>
</tbody>
</table>
SYNTAX Trial
Diabetic Patient Outcomes - 1 Year F/U

Death

MI

CVA

Scores 0-22
Scores 23-32
Scores ≥33

Scores 0-22
Scores 23-32
Scores ≥33

Scores 0-22
Scores 23-32
Scores ≥33

P=0.51
P>0.99
P=0.04

P=0.24
P=0.21
P>0.99

P=0.45
P=0.61
P>0.99

Banning AP et al, JACC 55:2010
SYNTAX Trial
Diabetic Patient Outcomes - 1 Year F/U

Death/CVA/MI

- Scores 0-22 (n=136): 13.3\% of pts, 5.4\% CABG
- Scores 23-32 (n=156): 10.4\% of pts, 8.6\% CABG
- Scores ≥33 (n=157): 9.5\% of pts, 14.9\% CABG

MACCE

- Scores 0-22 (n=136): 18.3\% of pts, 20.3\% MACCE
- Scores 23-32 (n=156): 12.9\% of pts, 26.0\% MACCE
- Scores ≥33 (n=157): 12.2\% of pts, 32.4\% MACCE

P-values:
- Death/CVA/MI: P=0.11, P=0.71, P=0.31
- MACCE: P=0.78, P=0.46, P=0.003

Banning AP et al, JACC 55:2010
SYNTAX Trial
Diabetic Patient Outcomes - 1 Year F/U

Revascularization

<table>
<thead>
<tr>
<th>Scores</th>
<th>CABG</th>
<th>PES</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-22</td>
<td>6.7</td>
<td>20.3</td>
<td>0.02</td>
</tr>
<tr>
<td>23-32</td>
<td>7.1</td>
<td>16.9</td>
<td>0.07</td>
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<tr>
<td>≥33</td>
<td>5.4</td>
<td>24.3</td>
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Banning AP et al, JACC 55:2010
## SYNTAX Trial
### With & Without Medically Treated Diabetes
#### 1 Year F/U

<table>
<thead>
<tr>
<th></th>
<th>Medically Treated Diabetes (n=452)</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>CABG n=221</td>
<td>PES n=231</td>
<td>RR (95% CI)</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Composite MACCE</td>
<td>14.2 (29/204)</td>
<td>26.0 (59/227)</td>
<td>1.83 (1.22-2.73)</td>
<td>0.003</td>
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<tr>
<td>Safety Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death/CVA/MI (composite)</td>
<td>10.3 (21/204)</td>
<td>10.1 (23/227)</td>
<td>0.98 (0.56-1.72)</td>
<td>0.96</td>
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<tr>
<td>Death</td>
<td>6.4 (13/204)</td>
<td>8.4 (19/227)</td>
<td>1.31 (0.67-2.59)</td>
<td>0.43</td>
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<tr>
<td>Cardiac death</td>
<td>3.9 (8/204)</td>
<td>7.0 (16/227)</td>
<td>1.80 (0.79-4.11)</td>
<td>0.16</td>
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<tr>
<td>CVA</td>
<td>2.5 (5/204)</td>
<td>0.9 (2/227)</td>
<td>0.36 (0.07-1.83)</td>
<td>0.26</td>
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<tr>
<td>MI</td>
<td>4.4 (9/204)</td>
<td>4.8 (11/227)</td>
<td>1.10 (0.46-2.60)</td>
<td>0.83</td>
<td></td>
</tr>
</tbody>
</table>

Banning AP et al, JACC 55:2010
SYNTAX Trial
Non-Diabetic Patient Outcomes - 1 Year F/U

Death

% of pts

P=0.26
P=0.48
P=0.04

CABG
PES

Scores 0-22 Scores 23-32 Scores ≥33
(n=437) (n=454) (n=449)

2.5 0.9 3.3 2.2 6.1
5/199 2/221 7/214 5/229 13/212

MI

% of pts

P=0.75
P=0.38
P=0.10

CABG
PES

Scores 0-22 Scores 23-32 Scores ≥33
(n=437) (n=454) (n=449)

2.0 2.7 2.8 4.4 3.9 7.5
4/199 6/221 10/229 9/229 16/212

CVA

% of pts

P=0.19
P=0.27
P=0.06

CABG
PES

Scores 0-22 Scores 23-32 Scores ≥33
(n=437) (n=454) (n=449)

2.0 0.5 2.3 0.9 2.2 0.0
4/199 1/221 5/214 2/229 5/229 0/212

Banning AP et al, JACC 55:2010
SYNTAX Trial
Non-Diabetic Patient Outcomes - 1 Year F/U

Death/CVA/MI

CABG  PES

0  20  40  60
% of pts

MACCE

P=0.48  P=0.56  P=0.004

0  20  40  60
% of pts

Banning AP et al, JACC 55:2010
SYNTAX Trial
Non-Diabetic Patient Outcomes - 1 Year F/U

Revascularization

% of pts

<table>
<thead>
<tr>
<th>Scores</th>
<th>CABG</th>
<th>PES</th>
<th>P-value</th>
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</thead>
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<tr>
<td>0-22</td>
<td>7.5</td>
<td>8.6</td>
<td>0.69</td>
</tr>
<tr>
<td>23-32</td>
<td>5.1</td>
<td>10.5</td>
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</tr>
<tr>
<td>≥33</td>
<td>4.8</td>
<td>14.2</td>
<td>&lt;0.001</td>
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</table>

Banning AP et al, JACC 55:2010
### SYNTAX Trial

**With & Without Medically Treated Diabetes**

**1 Year F/U**

<table>
<thead>
<tr>
<th></th>
<th>No Diabetes (n=1,348)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CABG n=676</td>
<td>PES n=672</td>
<td>RR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Composite MACCE</td>
<td>11.8 (76/645)</td>
<td>15.1 (100/664)</td>
<td>1.28 (0.97-1.69)</td>
<td>0.08</td>
</tr>
<tr>
<td>Safety Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death/CVA/MI (composite)</td>
<td>6.8 (44/645)</td>
<td>6.8 (45/664)</td>
<td>0.99 (0.67-1.48)</td>
<td>0.97</td>
</tr>
<tr>
<td>Death</td>
<td>2.6 (17/645)</td>
<td>3.0 (20/664)</td>
<td>1.14 (0.60-2.16)</td>
<td>0.68</td>
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<tr>
<td>Cardiac death</td>
<td>1.6 (10/645)</td>
<td>2.6 (17/664)</td>
<td>1.65 (0.76-3.58)</td>
<td>0.20</td>
</tr>
<tr>
<td>CVA</td>
<td>2.2 (14/645)</td>
<td>0.5 (3/664)</td>
<td>0.21 (0.06-0.72)</td>
<td>0.006</td>
</tr>
<tr>
<td>MI</td>
<td>2.9 (19/645)</td>
<td>4.8 (32/664)</td>
<td>1.64 (0.94-2.86)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Banning AP et al, JACC 55:2010
## SYNTAX Trial
With & Without Medically Treated Diabetes
1 Year F/U

<table>
<thead>
<tr>
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<th>No Diabetes (n=1,348)</th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CABG n=676</td>
<td>PES n=672</td>
<td>RR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Graft occlusion/ST</td>
<td>3.8 (23/601)</td>
<td>3.4 (22/639)</td>
<td>0.90 (0.51-1.60)</td>
<td>0.72</td>
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<tr>
<td>Acute (≤ 1 d)</td>
<td>0.5 (3/664)</td>
<td>0.3 (2/666)</td>
<td>0.66 (0.11-3.96)</td>
<td>0.69</td>
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<tr>
<td>Subacute (2-30 d)</td>
<td>0.5 (3/662)</td>
<td>2.1 (14/665)</td>
<td>4.65 (1.34-16.09)</td>
<td>0.008</td>
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<tr>
<td>Late (31-365 d)</td>
<td>2.6 (17/653)</td>
<td>1.1 (7/654)</td>
<td>0.41 (0.17-0.98)</td>
<td>0.04</td>
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<tr>
<td><strong>Efficacy Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat Revasc</td>
<td>5.7 (37/645)</td>
<td>11.1 (74/664)</td>
<td>1.94 (1.33-2.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI</td>
<td>4.8 (31/645)</td>
<td>9.6 (64/664)</td>
<td>2.01 (1.32-3.04)</td>
<td>&lt;0.001</td>
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<tr>
<td>CABG</td>
<td>1.1 (7/645)</td>
<td>2.4 (16/664)</td>
<td>2.22 (0.92-5.36)</td>
<td>0.07</td>
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</table>

Banning AP et al, JACC 55:2010
<table>
<thead>
<tr>
<th></th>
<th>Medically Treated Diabetes (n=452)</th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CABG n=221</td>
<td>PES n=231</td>
<td>RR (95% CI)</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Graft occlusion/ST</td>
<td>2.2 (4/186)</td>
<td>2.9 (6/209)</td>
<td>1.33 (0.38-4.66)</td>
<td>0.76</td>
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<tr>
<td>Acute (≤ 1 d)</td>
<td>0.0 (0/206)</td>
<td>0.0 (0/230)</td>
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<td>--</td>
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</tr>
<tr>
<td>Subacute (2-30 d)</td>
<td>0.0 (0/206)</td>
<td>1.8 (4/228)</td>
<td>--</td>
<td>0.13</td>
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<tr>
<td>Late (31-365 d)</td>
<td>2.0 (4/201)</td>
<td>0.9 (2/220)</td>
<td>0.46 (0.08-2.47)</td>
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<tr>
<td>Efficacy Outcomes</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Repeat Revasc</td>
<td>6.4 (13/204)</td>
<td>20.3 (46/227)</td>
<td>3.18 (1.77-5.71)</td>
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<td>PCI</td>
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<td>16.7 (38/227)</td>
<td>3.79 (1.88-7.65)</td>
<td>&lt;0.001</td>
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<tr>
<td>CABG</td>
<td>2.0 (4/204)</td>
<td>4.0 (9/227)</td>
<td>2.02 (0.63-6.47)</td>
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## Randomized Clinical Trials of Revasc & DM

<table>
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<tr>
<th></th>
<th>Diabetic Patients</th>
<th>All Diabetic Patients</th>
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<tbody>
<tr>
<td><strong>Randomization</strong></td>
<td>BARI n=353</td>
<td>SYNTAX n=452</td>
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<tr>
<td></td>
<td>PCTA vs CABG</td>
<td>DES vs CABG</td>
</tr>
<tr>
<td><strong>F/U reported</strong></td>
<td>10 yrs</td>
<td>1 yr</td>
</tr>
<tr>
<td><strong>PCI method</strong></td>
<td>PTCA</td>
<td>Taxus DES</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>Multivessel CAD</td>
<td>LMCA, MV CAD</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Death 5 yrs</td>
<td>Death, MI, stroke or revasc 1 yr</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>PTCA: 34.5%</td>
<td>DES: 8.4%</td>
</tr>
<tr>
<td></td>
<td>CABG: 19.4%</td>
<td>CABG: 6.4%</td>
</tr>
<tr>
<td></td>
<td>p=0.002</td>
<td>p=0.43</td>
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</tbody>
</table>

Dauerman HL, JACC 55:2010
<table>
<thead>
<tr>
<th></th>
<th>Diabetic Patients</th>
<th>All Diabetic Patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>BARI n=353</td>
<td>SYNTAX n=452</td>
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<tr>
<td></td>
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<td>BARI 2D n=2368</td>
</tr>
<tr>
<td>Death MI Stroke</td>
<td>Not reported</td>
<td>At 1 yr:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DES: 10.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CABG: 10.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=0.96</td>
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<tr>
<td></td>
<td></td>
<td>At 5 yrs:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All revasc: 22.8%</td>
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<tr>
<td></td>
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<td>Med Rx: 24.1%</td>
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<td>DES: 26.0%</td>
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<tr>
<td></td>
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<td>CABG: 14.2%</td>
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<td></td>
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<td>p=0.003</td>
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<tr>
<td>Death MI Stroke</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Revasc</td>
<td></td>
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</tr>
<tr>
<td>Repeat Revasc</td>
<td>PTCA: 69.9%</td>
<td>DES: 20.3%</td>
</tr>
<tr>
<td></td>
<td>CABG: 11.1% (at 7 yrs)</td>
<td>CABG: 6.4%</td>
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<tr>
<td></td>
<td></td>
<td>p&lt;0.001</td>
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<tr>
<td></td>
<td>42% of Med Rx pts</td>
<td>42% of Med Rx pts</td>
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<tr>
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<td>crossover to</td>
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<tr>
<td></td>
<td>revasc group</td>
<td>revasc group</td>
</tr>
</tbody>
</table>

Dauerman HL, JACC 55:2010
SYNTAX Trial
What Can We Say

• There is still room for good clinical judgment in decision making
Risk Factor Control

- **LDL <100**: Baseline 60%, Year 3 83%
- **BP ≤130/80**: Baseline 48%, Year 3 71%
- **No smoking**: Baseline 78%, Year 3 89%
## Risk Factor Measures

<table>
<thead>
<tr>
<th>Mean</th>
<th>Base-line</th>
<th>3 year</th>
<th></th>
<th></th>
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<tr>
<td></td>
<td></td>
<td>Rev</td>
<td>Med</td>
<td>IS</td>
<td>IP</td>
<td></td>
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<tr>
<td>LDL (mg/dL)</td>
<td>96</td>
<td>81</td>
<td>79</td>
<td>79</td>
<td>80</td>
<td></td>
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<tr>
<td>HDL (mg/dL)</td>
<td>38</td>
<td>41</td>
<td>41</td>
<td>42</td>
<td>40</td>
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<tr>
<td>SBP (mm Hg)</td>
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<td>126</td>
<td>125</td>
<td>125</td>
<td>126</td>
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<tr>
<td>DBP (mm Hg)</td>
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<td>70</td>
<td>70</td>
<td>70</td>
<td>71</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>31.7</td>
<td>32.0</td>
<td>32.2</td>
<td>31.7</td>
<td>32.5</td>
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Drug Use
Randomized Treatment Assignment

**Insulin Sensitization Group**
- IS drugs
- IP drugs

**Insulin Provision Group**
- IS drugs
- IP drugs

<table>
<thead>
<tr>
<th>Year</th>
<th>IS drugs</th>
<th>IP drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>62</td>
<td>75</td>
</tr>
<tr>
<td>Year 1</td>
<td>91</td>
<td>80</td>
</tr>
<tr>
<td>Year 3</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>Year 5</td>
<td>54</td>
<td>88</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>IS drugs</th>
<th>IP drugs</th>
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<tbody>
<tr>
<td>BL</td>
<td>60</td>
<td>90</td>
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<tr>
<td>Year 1</td>
<td>76</td>
<td>91</td>
</tr>
<tr>
<td>Year 3</td>
<td>91</td>
<td>90</td>
</tr>
<tr>
<td>Year 5</td>
<td>92</td>
<td>92</td>
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</table>
# Diabetes Medication Use

<table>
<thead>
<tr>
<th>Medication</th>
<th>Baseline (%)</th>
<th>IS (%)</th>
<th>IP (%)</th>
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<tbody>
<tr>
<td>Metformin</td>
<td>54</td>
<td>75</td>
<td>10</td>
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<tr>
<td>Thiazolidinedione</td>
<td>19</td>
<td>62</td>
<td>4</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>12</td>
<td>55</td>
<td>3</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>53</td>
<td>18</td>
<td>52</td>
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<tr>
<td>Insulin</td>
<td>28</td>
<td>28</td>
<td>61</td>
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</tbody>
</table>

3 year
HbA1c Mean Over Time

HbA$_{1c}$ (\%)

<table>
<thead>
<tr>
<th>Year</th>
<th>HbA$_{1c}$</th>
<th>Year</th>
<th>HbA$_{1c}$</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>7.8</td>
<td>Year 1</td>
<td>6.9</td>
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<tr>
<td>Year 1</td>
<td>7.0</td>
<td>Year 2</td>
<td>6.9</td>
</tr>
<tr>
<td>Year 2</td>
<td>6.9</td>
<td>Year 3</td>
<td>7.1</td>
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<tr>
<td>Year 3</td>
<td>7.5</td>
<td>Year 4</td>
<td>7.5</td>
</tr>
<tr>
<td>Year 4</td>
<td>7.5</td>
<td>Year 5</td>
<td>7.2</td>
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</table>

Insulin providing

Insulin sensitizing

Baseline
# Cardiovascular Medication Use

<table>
<thead>
<tr>
<th>Medication</th>
<th>Baseline (%)</th>
<th>Revasc (%)</th>
<th>Medical (%)</th>
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<tbody>
<tr>
<td>Beta blocker</td>
<td>73</td>
<td>84</td>
<td>88</td>
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<tr>
<td>ACE/ARB</td>
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<td>91</td>
<td>92</td>
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<td>Statin</td>
<td>75</td>
<td>95</td>
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<tr>
<td>Aspirin</td>
<td>88</td>
<td>94</td>
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</tbody>
</table>
Summary

- Excellent risk factor control
- Randomized treatment strategies effectively implemented for
  - Prompt revascularization vs delayed/no revascularization
  - Insulin sensitization vs insulin provision
Bypass Angioplasty
Revascularization Investigation
2 Diabetes (BARI 2D)

5-Year Results

American Diabetes Association Conference
June 7, 2009

Robert Frye, MD
Mayo Clinic – Rochester
BARI 2D Primary and Principal Secondary Endpoints

- All-cause mortality
  Major cardiovascular events
- Composite of death/MI/stroke
- Average follow-up 5.3 years
Coronary angiography was performed in patients with type 2 diabetes referred for evaluation for CAD.

2,368 were enrolled

763 were selected for CABG stratum

- 385 were randomly assigned to medical therapy
  - 194 were randomly assigned to insulin provision
  - 191 were randomly assigned to insulin sensitization

- 378 were randomly assigned to revascularization
  - 190 were randomly assigned to insulin provision
  - 188 were randomly assigned to insulin sensitization

1,605 were selected for PCI stratum

- 807 were randomly assigned to medical therapy
  - 399 were randomly assigned to insulin provision
  - 408 were randomly assigned to insulin sensitization

- 798 were randomly assigned to revascularization
  - 402 were randomly assigned to insulin provision
  - 396 were randomly assigned to insulin sensitization

194 were randomly assigned to insulin provision
191 were randomly assigned to insulin sensitization
190 were randomly assigned to insulin provision
188 were randomly assigned to insulin sensitization
399 were randomly assigned to insulin provision
408 were randomly assigned to insulin sensitization
402 were randomly assigned to insulin provision
396 were randomly assigned to insulin sensitization
## Baseline Characteristics by Randomization Stratum

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PCI intended (n=1,605)</th>
<th>CABG intended (n=763)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean years)</td>
<td>62.0</td>
<td>63.2</td>
</tr>
<tr>
<td>Male (%)</td>
<td>68.0</td>
<td>76.0</td>
</tr>
<tr>
<td>Prior revasc (%)</td>
<td>29.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Proximal LAD (%)</td>
<td>10.0</td>
<td>19.0</td>
</tr>
<tr>
<td>LVEF &lt;50 (%)</td>
<td>18.0</td>
<td>18.0</td>
</tr>
<tr>
<td>3 vessel disease (%)</td>
<td>20.0</td>
<td>52.0</td>
</tr>
<tr>
<td>Total occlusion (mean number)</td>
<td>0.48</td>
<td>0.84</td>
</tr>
<tr>
<td>Myocardial jeopardy (mean %)</td>
<td>37.2</td>
<td>59.7</td>
</tr>
</tbody>
</table>
BARI 2D in the Context of Current Clinical Practice and Recent Trials

How did BARI 2D inclusion criteria fit with current guidelines for appropriateness of revascularization?

Categories of appropriateness criteria

- Inappropriate
- Uncertain
- Appropriate (but not mandated)


BARI 2D participants met uncertain or appropriate criteria for each revascularization stratum

BARI 2D was conducted in the setting of aggressive risk factor management including 95% receiving statin therapy
Does Glycemic Control Explain the Apparent Benefit of Combined CABG and IS Therapy

<table>
<thead>
<tr>
<th></th>
<th>Mean 3-year HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IS</td>
</tr>
<tr>
<td>PCI stratum</td>
<td></td>
</tr>
<tr>
<td>Prompt</td>
<td>6.9 ± 1.1</td>
</tr>
<tr>
<td>Delayed</td>
<td>7.2 ± 1.3</td>
</tr>
<tr>
<td>CABG stratum</td>
<td></td>
</tr>
<tr>
<td>Prompt</td>
<td>6.9 ± 1.1</td>
</tr>
<tr>
<td>Delayed</td>
<td>7.1 ± 1.4</td>
</tr>
</tbody>
</table>

Does any other “on Rx” factor appear to be different in the CABG/IS subgroup? No
BARI 2D
Diabetes Implications

- Overall both insulin sensitizing and insulin providing approaches appear appropriate in BARI 2D eligible patients
- Further analyses will determine whether these strategies differ in other secondary outcomes
However there is suggestive evidence that IS therapy may have a number of potential advantages over IP:

- The benefit of prompt CABG in terms of mortality/CVD events appeared stronger in those receiving IS therapy.
- IS therapy showed a borderline (P=0.06) benefit over IP in those receiving prompt revascularization.
- HbA₁c target value was more frequently achieved in the IS group.
- Severe hypoglycemia was less frequent in the IS group.
- Weight and waist circumference change were less adverse in the IS group.
Can Any Difference Between IS and IP CVD/Death Results be Explained by the Difference in HbA$_{1c}$ Between Them?

<table>
<thead>
<tr>
<th>Study</th>
<th>$\Delta$ HbA$_{1c}$</th>
<th>$\Delta$ CVD outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARI 2D</td>
<td>0.5%</td>
<td>NS</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>0.6%</td>
<td>NS</td>
</tr>
<tr>
<td>ACCORD</td>
<td>1.1%</td>
<td>NS</td>
</tr>
<tr>
<td>VADT</td>
<td>1.6%</td>
<td>NS</td>
</tr>
</tbody>
</table>
Achievement of HbA1c Goals in BARI 2D

![Bar graph showing the percentage of participants achieving different HbA1c goals.](image)
# Weight Gain, Waist Circumference Change and Severe Hypoglycemia by IS/IP Group

<table>
<thead>
<tr>
<th></th>
<th>IS</th>
<th>IP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline weight (kg)</strong></td>
<td>89.6±19.5</td>
<td>89.6±19.8</td>
</tr>
<tr>
<td><strong>3-yr weight (kg)</strong></td>
<td>89.9±21.1</td>
<td>91.7±20.7</td>
</tr>
<tr>
<td><strong>Gain (kg)</strong></td>
<td>0.3±8.6</td>
<td>2.1±7.4</td>
</tr>
<tr>
<td><strong>Baseline waist circumference (cm)</strong></td>
<td>108.0±14.4</td>
<td>107.6±13.7</td>
</tr>
<tr>
<td><strong>3-yr waist circumference (cm)</strong></td>
<td>107.7±15.4</td>
<td>109.1±14.2</td>
</tr>
<tr>
<td><strong>Change (cm)</strong></td>
<td>-0.1±9.1</td>
<td>+1.9±8.4</td>
</tr>
<tr>
<td><strong>1+ severe hypoglycemia episode during trial (%)</strong></td>
<td>5.9</td>
<td>9.2</td>
</tr>
</tbody>
</table>
Adjusted Odds Ratio of CABG Selection Among Multivessel Disease

- Non-US vs US
- Rand after DES available
- Male sex
- Age ≥65 years
- Prior PCI
- Triple vessel disease
- LAD ≥70% stenosis
- Proximal LAD ≥50% stenosis
- Total occlusion
- Class C lesions ≥2

Log scale

PCI preferred
CABG preferred

Log scale
BARI 2D Goals

Setting

• Intensive medical therapy: uniform control of glycemia, dyslipidemia, hypertension, angina, and lifestyle factors

Compare

• Prompt revascularization vs delayed or no revascularization

• Insulin sensitizing strategy vs an insulin providing strategy for glycemic management with target HbA$_1^c$ <7.0%
SYNTAX and Diabetes

• At one year, there is no death penalty associated with multivessel PCI
• At one year, there is no significant difference in death/MI/stroke between CABG and PCI
• The use of DES does not mitigate the adverse effect of diabetes

Jeopardized myocardium (in quartiles) (%)

<table>
<thead>
<tr>
<th>Quartile</th>
<th>US (n=714)</th>
<th>Non-US (n=594)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-38</td>
<td>15 (n=224)</td>
<td>15 (n=105)</td>
</tr>
<tr>
<td>39-52</td>
<td>45 (n=180)</td>
<td>25 (n=151)</td>
</tr>
<tr>
<td>53-70</td>
<td>51 (n=164)</td>
<td>70 (n=166)</td>
</tr>
<tr>
<td>71-100</td>
<td>78 (n=146)</td>
<td>78 (n=172)</td>
</tr>
</tbody>
</table>
Subject: BARI 2D Kim

Background: BU3
Banner/brdr: 0-40-159/BU41
Side title: YW105
• /colhdgs: YW105
Text: WT/BK
Highlight: YO114
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x, y only

PPT shooting instructions
PPT File to Server
(3 images)

Artist: mls
Start Date: 4-12-10

COLOR REFERENCE ONLY
Match: Mayo2bu-2002 (CP1111378)
CARDia Trial

- Multicenter trial of 510 patients with MVD or single vessel complex disease
- Randomization to CABG (254) or PCI (256)
- Primary outcome measure: all cause mortality, MI and stroke
- Secondary outcome measure: all cause mortality, MI, stroke, repeat revascularization
- Noninferiority design

Conclusions: The CARDia (Coronary Artery Revascularization in Diabetes) trial is the first randomized trial of coronary revascularization in diabetic patients, but the 1-year results did not show that PCI is noninferior to CABG. However, the CARDia trial did show that multivessel PCI is feasible in patients with diabetes.
Baseline Clinical Characteristics of CARDia Trial Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n=510</th>
<th>CABG n=254</th>
<th>PCI n=256</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), mean (SD)</td>
<td>510</td>
<td>63.6 (9.1)</td>
<td>64.3 (8.5)</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>509</td>
<td>197 (77.9)</td>
<td>181 (70.7)</td>
</tr>
<tr>
<td>BMI (kg/m(^2)), mean (SD)</td>
<td>486</td>
<td>29.4 (5.3)</td>
<td>29.2 (4.9)</td>
</tr>
<tr>
<td>Admission type, no. (%)</td>
<td>510</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>60 (23.6)</td>
<td>55 (21.5)</td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>194 (76.4)</td>
<td>201 (78.5)</td>
<td></td>
</tr>
<tr>
<td>Diabetes status</td>
<td>510</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1, no. (%)</td>
<td>17 (6.7)</td>
<td>8 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Noninsulin treated, no. (%)</td>
<td>155 (60.9)</td>
<td>168 (65.5)</td>
<td></td>
</tr>
<tr>
<td>Insulin treated, no. (%)</td>
<td>99 (39.1)</td>
<td>88 (36.5)</td>
<td></td>
</tr>
<tr>
<td>Years with diabetes, mean (SD)</td>
<td>477</td>
<td>10.4 (9.6)</td>
<td>10.1 (9.6)</td>
</tr>
</tbody>
</table>

### Baseline Clinical Characteristics of CARDia Trial Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n=510</th>
<th>CABG n=254</th>
<th>PCI n=256</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseased vessels, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>510</td>
<td>149 (59.7)</td>
<td>166 (64.8)</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td></td>
<td>88 (34.7)</td>
<td>72 (28.1)</td>
</tr>
<tr>
<td>Bifurcation</td>
<td></td>
<td>5 (2.0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Proximal LAD</td>
<td></td>
<td>12 (4.7)</td>
<td>16 (6.3)</td>
</tr>
<tr>
<td>Hx of renal impairment, no. (%)</td>
<td>508</td>
<td>10 (4.0)</td>
<td>14 (5.5)</td>
</tr>
<tr>
<td>PVD, no (%)</td>
<td>508</td>
<td>13 (5.2)</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>CVD Hx (stroke or TIA), no. (%)</td>
<td>508</td>
<td>12 (5.6)</td>
<td>8 (3.5)</td>
</tr>
<tr>
<td>EF (%), mean (SD)</td>
<td>256</td>
<td>60.0 (12.7)</td>
<td>59.1 (14.4)</td>
</tr>
</tbody>
</table>

Primary End Point Event-Free Survival
CABG vs PCI

MACCE Event-Free Survival
CABG vs PCI

## Major End Points at 1 Year

<table>
<thead>
<tr>
<th>Adjudicated events post-randomization</th>
<th>CABG (n=248)</th>
<th>PCI (n=254)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Death</td>
<td>8</td>
<td>3.2</td>
<td>8</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>14</td>
<td>5.7</td>
<td>25</td>
</tr>
<tr>
<td>Periprocedural MI</td>
<td>11</td>
<td>4.4</td>
<td>12</td>
</tr>
<tr>
<td>Late MI*</td>
<td>3</td>
<td>1.2</td>
<td>14</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>7</td>
<td>2.8</td>
<td>1</td>
</tr>
<tr>
<td>Composite outcome of d, nonfatal MI, and nonfatal stroke at 1 yr: primary outcome</td>
<td>26</td>
<td>10.5</td>
<td>33</td>
</tr>
<tr>
<td>Further revasc at 1 yr</td>
<td>5</td>
<td>2.0</td>
<td>30</td>
</tr>
<tr>
<td>Composite outcome of d, nonfatal MI, nonfatal stroke, and repeat revasc at 1 yr: secondary outcome</td>
<td>28</td>
<td>11.3</td>
<td>49</td>
</tr>
<tr>
<td>TIMI major bleed</td>
<td>15</td>
<td>6.1</td>
<td>3</td>
</tr>
</tbody>
</table>

*Late MI defined as occurring >7 days after index revasc proc
Forest Plot of Death, Myocardial Infarction and Stroke in Key Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard ratio</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 vessel disease</td>
<td>0.90</td>
<td>(0.36, 2.28)</td>
</tr>
<tr>
<td>3 vessel disease</td>
<td>1.42</td>
<td>(0.76, 2.67)</td>
</tr>
<tr>
<td>BMS group</td>
<td>2.99</td>
<td>(0.97, 9.16)</td>
</tr>
<tr>
<td>DES group</td>
<td>0.93</td>
<td>(0.51, 1.71)</td>
</tr>
<tr>
<td>No insulin</td>
<td>1.02</td>
<td>(0.51, 2.01)</td>
</tr>
<tr>
<td>Insulin treated</td>
<td>1.87</td>
<td>(0.76, 3.67)</td>
</tr>
<tr>
<td>Female</td>
<td>2.13</td>
<td>(0.68, 6.68)</td>
</tr>
<tr>
<td>Male</td>
<td>1.07</td>
<td>(0.59, 1.93)</td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>1.04</td>
<td>(0.49, 2.17)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>1.48</td>
<td>(0.72, 3.05)</td>
</tr>
</tbody>
</table>

Subject: CARDia Trial, Kapur

Background: BU3
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Side title: YW105
\( /colhdgs: \) YW105

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“When 2 elephants fight, it is the grass that gets trampled”

African proverb
Oh,crap! Was that TODAY?
Diabetes Mellitus

• I know what we do but the answers to the questions we ask keep changing
• Screening for ischemia
• Specific treatment regimen: IS vs IP
• Specific IS drug
• Revascularization versus medical therapy
• Specific revascularization strategy
• Adjunctive therapy after PCI
Systematic Review

PCI vs CABG

- 23 randomized clinical trials
- 5,019 patients assigned PCI
- 4,944 patients assigned CABG
- Outcomes of interest:
  - Survival, myocardial infarction, stroke, angina, additional revascularization

# 5-Year Survival in Diabetics

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Surviving patients/all patients</th>
<th>Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCI</td>
<td>CABG</td>
</tr>
<tr>
<td>AWESOME, 2002</td>
<td>8/11</td>
<td>8/12</td>
</tr>
<tr>
<td>BARI, 1997; 1996</td>
<td>45/69</td>
<td>75/93</td>
</tr>
<tr>
<td>EAST, 2000</td>
<td>26/29</td>
<td>27/30</td>
</tr>
<tr>
<td>ERACI II, 2005</td>
<td>35/39</td>
<td>35/39</td>
</tr>
<tr>
<td>MASS II, 2006</td>
<td>47/56</td>
<td>50/59</td>
</tr>
<tr>
<td>RITA, 1998</td>
<td>27/29</td>
<td>25/33</td>
</tr>
<tr>
<td>Overall</td>
<td>188/233</td>
<td>220/266</td>
</tr>
</tbody>
</table>

**Ann Int Med 147:708, 2007**
Systematic Review
PCI vs CABG

Diabetics

• 5-year survival: Higher by 2%
  CABG but 95% bounds – 8.8%, 8.3%

CABG vs PCI
Multivessel CAD

- Pooled individual patient data analysis
- 10 trials
- 7,812 patients
- Median FU 5.9 yrs
- Stratified random effects Cox proportional hazards models for all cause mortality

Mortality in Patients Assigned to Coronary Artery Bypass Graft or Percutaneous Coronary by Diabetes Status

A

<table>
<thead>
<tr>
<th>Patients (no.)</th>
<th>Follow-up (yr)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG no diabetes</td>
<td>0-1</td>
<td>3,263</td>
</tr>
<tr>
<td>CABG diabetes</td>
<td>1-2</td>
<td>3,169</td>
</tr>
<tr>
<td>CABG no diabetes</td>
<td>2-3</td>
<td>3,089</td>
</tr>
<tr>
<td>CABG diabetes</td>
<td>3-4</td>
<td>2,877</td>
</tr>
<tr>
<td>CABG no diabetes</td>
<td>4-5</td>
<td>2,677</td>
</tr>
<tr>
<td>CABG diabetes</td>
<td>5-6</td>
<td>2,267</td>
</tr>
<tr>
<td>CABG no diabetes</td>
<td>6-7</td>
<td>1,592</td>
</tr>
<tr>
<td>CABG diabetes</td>
<td>7-8</td>
<td>1,380</td>
</tr>
<tr>
<td>CABG no diabetes</td>
<td>8-9</td>
<td>1,274</td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Patients (no.)</th>
<th>Follow-up (yr)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI no diabetes</td>
<td>0-1</td>
<td>2,529</td>
</tr>
<tr>
<td>PCI diabetes</td>
<td>1-2</td>
<td>2,457</td>
</tr>
<tr>
<td>PCI no diabetes</td>
<td>2-3</td>
<td>2,382</td>
</tr>
<tr>
<td>PCI diabetes</td>
<td>3-4</td>
<td>2,179</td>
</tr>
<tr>
<td>PCI no diabetes</td>
<td>4-5</td>
<td>1,992</td>
</tr>
<tr>
<td>PCI diabetes</td>
<td>5-6</td>
<td>1,592</td>
</tr>
<tr>
<td>PCI no diabetes</td>
<td>6-7</td>
<td>1,274</td>
</tr>
<tr>
<td>PCI diabetes</td>
<td>7-8</td>
<td>1,380</td>
</tr>
</tbody>
</table>

Tests raise life extension hopes

A drug discovered in the soil of a South Pacific island may help to fight the ageing process, research suggests.

When US scientists treated old mice with rapamycin it extended their expected lifespan by up to 38%.

The findings, published in the journal Nature, raise the prospect of being able to slow down the ageing process in older people.
# CABG vs DES in Patients with Multivessel Disease and Diabetes

<table>
<thead>
<tr>
<th>Name</th>
<th>N (DM pts)</th>
<th>Design</th>
<th>DES Type (%)</th>
<th>Death</th>
<th>Revasc</th>
<th>CVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTS I/II*</td>
<td>255</td>
<td>Reg. MVD</td>
<td>SES 100%</td>
<td>=</td>
<td>DES ↑</td>
<td>DES ↓</td>
</tr>
<tr>
<td>Ben-Gal 06</td>
<td>518</td>
<td>Reg. SVD &amp; MVD</td>
<td>SES 100%</td>
<td>NR</td>
<td>DES ↑</td>
<td>NR</td>
</tr>
<tr>
<td>Briguori 07</td>
<td>218</td>
<td>Reg. SVD &amp; MVD</td>
<td>SES 67, PES 33%</td>
<td>=</td>
<td>DES ↑</td>
<td>=</td>
</tr>
<tr>
<td>Lee 07</td>
<td>205</td>
<td>Reg. MVD</td>
<td>SES 75, PES 11%</td>
<td>=</td>
<td>DES ↑</td>
<td>DES ↓</td>
</tr>
<tr>
<td>Mack 08</td>
<td>1450</td>
<td>Reg. SVD &amp; MVD</td>
<td>DES 73.1%</td>
<td>=</td>
<td>DES ↑</td>
<td>NR</td>
</tr>
<tr>
<td>Park 08</td>
<td>891</td>
<td>Reg. MVD</td>
<td>~SES 80, PES 20%</td>
<td>=</td>
<td>DES ↑</td>
<td>NR</td>
</tr>
<tr>
<td>Yang 08</td>
<td>352</td>
<td>Reg. MVD</td>
<td>SES &amp; PES</td>
<td>=</td>
<td>DES ↑</td>
<td>=</td>
</tr>
<tr>
<td>CARDia</td>
<td>510</td>
<td>RCT SVD &amp; MVD</td>
<td>SES 71, BMS 29%</td>
<td>=</td>
<td>DES ↑</td>
<td>DES ↓</td>
</tr>
<tr>
<td>FREEDOM</td>
<td>1394†</td>
<td>RCT MVD</td>
<td>SES 51, PES 47%</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

*Diabetic patients from ARTS I & II (Macaya, EuroIntervention. 2006;2:69-76)
†As of 22 September 2008; Enrollment ongoing.
Patients with Diabetes in SYNTAX Randomized Cohort, Intent-to-Treat

- Total Randomized: N=1800
- Non-Diabetic, n=1289
  - 'Non-Diabetic' (n=1348)
  - Diet Only, n=59
- All Diabetes: n=511
- Medically Treated: n=452
- CABG: n=221
  - Oral Agents: n=270
    - CABG: n=128
    - TAXUS: n=142
  - Insulin: n=182
    - CABG: n=93
    - TAXUS: n=89
- TAXUS: n=231

12-months
Outcome According to Diabetic Status at 12 Months

Death/CVA/MI

- 'Non-Diabetic' (n=1348): 6.8%
- Diabetic (n=452): 10.3%

MACCE

- 'Non-Diabetic' (n=1348): 11.8%
- Diabetic (n=452): 15.1%

P-values:
- Death/CVA/MI: P=0.97
- MACCE: P=0.08

Serruys, ESC 2008
Death (All-Cause) at 12 Months

Patients (%)

CABG  TAXUS

'Non-Diabetic'  Medically Treated Diabetes

Oral Hypoglycemics

P = 0.72

P = 0.43

P = 0.12

Insulin-Treated

P = 0.01

P < 0.001

Death (All-Cause) at 12 Months

12/645  17/204  19/227

13/664  20/227  8/139

5/87  11/88

P = 0.01

P < 0.001
Death/CVA/MI at 12 Months

- **CABG** vs **TAXUS**
  - 'Non-Diabetic'
    - $P=0.97$
    - $P=0.96$
    - Medically Treated Diabetes
    - $P=0.10$
  - Insulin-Treated
    - $P=0.10$
  - Oral Hypoglycemics
    - $P=0.19$
    - $P=0.16$

Patients (%)

- 6.8
- 6.8
- 10.3
- 10.1
- 12.0
- 7.2
- 8.0
- 14.8

Diabetes

'Non-Diabetic'

Death/CVA/MI at 12 Months
Murder

Parking Ticket
Higher 12-Month MACCE in Diabetics,* Driven by Revasc.

- All Death: CABG (6.4%) vs. TAXUS (8.4%), P=0.43
- MI: CABG (4.4%) vs. TAXUS (4.8%), P=0.83
- CVA: CABG (2.5%) vs. TAXUS (0.9%), P=0.26
- Revasc.: CABG (6.4%) vs. TAXUS (20.3%), P<0.001
- MACCE: CABG (14.2%) vs. TAXUS (26.0%), P=0.003

*Medically treated diabetes
Summary: 12-Month Outcomes

• Patients without Diabetes
  • No significant difference in MACCE in CABG versus TAXUS
  • Increased revascularization in TAXUS
  • Increased stroke with CABG

• Patients with Diabetes
  • Significantly increased MACCE with TAXUS, driven by increased revascularization
  • Significantly increased mortality compared to non-diabetics in both CABG and TAXUS groups

• Revascularization rates in TAXUS are increased in diabetic patients compared to non-diabetics

• In CABG group, revascularization rates are comparable regardless of diabetic status
Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease
Patients with DM and multivesel CAD eligible for PCI or CABG

Randomized 1:1

Contemporary PCI with DES
N=950

Contemporary CABG with or without CPB
N=950

Contemporary background therapy for CAD and diabetes
FREEDOM Recruitment

as of 11/10/09

<table>
<thead>
<tr>
<th>Year</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>17</td>
<td>36</td>
<td>60</td>
<td>130</td>
</tr>
<tr>
<td>2006</td>
<td>240</td>
<td>388</td>
<td>526</td>
<td>644</td>
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<tr>
<td>2007</td>
<td>774</td>
<td>897</td>
<td>1173</td>
<td>1408</td>
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<tr>
<td>2008</td>
<td>1046</td>
<td>1298</td>
<td>1503</td>
<td>1611</td>
</tr>
<tr>
<td>2009</td>
<td>1697</td>
<td>1756</td>
<td>1785</td>
<td>1900</td>
</tr>
<tr>
<td>History of Present Illness</td>
<td>A (N=739)</td>
<td>B (N=734)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable Coronary Heart Disease</td>
<td>67.1%</td>
<td>70.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Coronary Syndrome (ACS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST elevation MI (&gt;72 hrs prior to admission)</td>
<td>32.9%</td>
<td>29.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-ST elevation ACS</td>
<td>19.2%</td>
<td>17.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA CHF Classification (Class III/IV excluded)</td>
<td>80.8%</td>
<td>82.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>74.0%</td>
<td>71.4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## PCI Procedure Summary

<table>
<thead>
<tr>
<th></th>
<th>PCI/DES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staging: % unstaged procedure</strong></td>
<td>66.2%</td>
</tr>
<tr>
<td>% staged procedure</td>
<td>33.8%</td>
</tr>
<tr>
<td>% staged procedures involving &gt;1 hospitalization</td>
<td>71.2%</td>
</tr>
<tr>
<td><strong>Mean total # of lesions attempted across all stages</strong></td>
<td>4.2 ± 1.5</td>
</tr>
<tr>
<td><strong>Mean total # drug-eluting stents placed per patient (across all stages)</strong></td>
<td>4.3 ± 1.8</td>
</tr>
<tr>
<td><strong>Reopro used during index procedure (stage 1 for staged procedures)</strong></td>
<td>49.7%</td>
</tr>
<tr>
<td><strong>Heparin administered</strong></td>
<td>83.9%</td>
</tr>
<tr>
<td><strong>Bivalirudin administered</strong></td>
<td>14.9%</td>
</tr>
<tr>
<td>Reference vessel diameter (mm):</td>
<td>Lesions</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>&lt;2.5</td>
<td>16.4%</td>
</tr>
<tr>
<td>2.5-3.0</td>
<td>49.4%</td>
</tr>
<tr>
<td>3.0-3.5</td>
<td>25.4%</td>
</tr>
<tr>
<td>3.5-4.0</td>
<td>7.8%</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>0.9%</td>
</tr>
<tr>
<td>Chronic total occlusion</td>
<td>4.8%</td>
</tr>
<tr>
<td>Bifurcation lesion</td>
<td>11.6%</td>
</tr>
<tr>
<td>Balloon angioplasty alone</td>
<td>3.6%</td>
</tr>
<tr>
<td>Direct stenting</td>
<td>28.5%</td>
</tr>
<tr>
<td>FREEDOM Trial</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td></td>
</tr>
<tr>
<td>• Effect of PCI (DES) versus CABG on composite of all cause death, non fatal infarction and stroke with a minimum follow up of 2 years</td>
<td></td>
</tr>
<tr>
<td>• Evaluate the need for the secondary endpoint of repeat revascularization between PCI and CABG (N.B. difference from SYNTAX)</td>
<td></td>
</tr>
<tr>
<td>• Study the differences in Quality of Life and Cost Effectiveness between the two strategies</td>
<td></td>
</tr>
<tr>
<td>• Facilitate comparisons between performance of two DES in this patient group</td>
<td></td>
</tr>
<tr>
<td>• It will not tell us whether BARI 2D was right about revascularization versus optimal medical therapy</td>
<td></td>
</tr>
</tbody>
</table>
“In your case, Dave, there’s a choice—elective surgery, outpatient medical therapy, or whatever’s in the box that our lovely Carol is holding.”
PCI vs CABG
MV Disease in Diabetics
Conclusions

Clinical judgment still works
Primary Endpoint: 12-month MACCE Difference Non-inferiority analysis

CABRI (2VD 57%, 3VD 43%): MACCE difference 32%

ARTS I (2VD 66%, 3VD 33%): MACCE difference 14%

SYNTAX (3VD, LM): MACCE difference 5.5%

The criteria for non-inferiority comparison was not met for the primary endpoint, further comparisons for the LM and 3VD subgroups are observational only and hypothesis generating.
Vessel Distribution in LM Population According to Syntax Score Terciles

Low Syntax: 4% LM + 3VD, 11% LM + 2VD, 27% LM + 1VD, 61% LM isolated
Intermediate Syntax: 35% LM + 3VD, 29% LM + 2VD, 59% LM + 1VD, 7% LM isolated
High Syntax: 33% LM + 3VD, 27% LM + 2VD, 66% LM + 1VD, 7% LM isolated

Legend:
- Nondistal
- Distal
- Both
Vessel Distribution in LM Population According to Syntax Score Terciles

Low Syntax
- 0-22
- 4% (Nondistal)
- 35% (Distal)
- 61% (Both)

Intermediate Syntax
- 23-32
- 11% (Nondistal)
- 29% (Distal)
- 59% (Both)

High Syntax
- 33+
- 7% (Nondistal)
- 27% (Distal)
- 66% (Both)
### MACCE to 2 Years by SYNTAX Score

**Tercile Low Scores (0-22)**

<table>
<thead>
<tr>
<th></th>
<th>CABG</th>
<th>PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td>4.9% &gt;</td>
<td>0.9%</td>
</tr>
<tr>
<td><strong>CVA</strong></td>
<td>4.1% &gt;</td>
<td>0.9%</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>2.0% &lt;</td>
<td>3.6%</td>
</tr>
<tr>
<td><strong>Death, CVA or MI</strong></td>
<td>9.9% &gt;</td>
<td>4.5%</td>
</tr>
<tr>
<td><strong>Revasc.</strong></td>
<td>10.1% &gt;</td>
<td>14.7%</td>
</tr>
</tbody>
</table>

**KM Event rate ± 1.5 SE, *chi-square or Fisher exact test**

**LM Subset†**

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

- **P=0.45**

†Patients with isolated LM or LM +1, +2 or +3 vessel disease

Site-reported Data; ITT population
Vessel Distribution in LM Population According to Syntax Score Terciles

- Low Syntax:
  - LM + 3VD: 4%
  - LM + 2VD: 35%
  - LM + 1VD: 61%
  - LM isolated: 0%

- Intermediate Syntax:
  - LM + 3VD: 11%
  - LM + 2VD: 29%
  - LM + 1VD: 59%
  - LM isolated: 0%

- High Syntax:
  - LM + 3VD: 7%
  - LM + 2VD: 27%
  - LM + 1VD: 66%
  - LM isolated: 0%
DIAD Study
Screening in Type 2 Diabetes

• 1,123 patients with type 2 diabetes but no symptoms of CAD

• Random assignment to screening with MPI or not

• Main outcome of cardiac death or non-fatal MI

Young LH et al, JAMA 301:1547-1555, 2009
## DIAD Study

<table>
<thead>
<tr>
<th></th>
<th>No Screening N=562</th>
<th>Screening N=561</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>60.8</td>
<td>60.7</td>
</tr>
<tr>
<td><strong>Duration DM (yrs)</strong></td>
<td>8.9</td>
<td>8.2</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>31.0</td>
<td>31.1</td>
</tr>
<tr>
<td><strong>HAIC</strong></td>
<td>7.0</td>
<td>7.2</td>
</tr>
<tr>
<td><strong>PVD</strong></td>
<td>9.0</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Young LH et al, JAMA 301:1547-1555, 2009
## DIAD Study

<table>
<thead>
<tr>
<th></th>
<th>No Screening N=562</th>
<th>Screening N=561</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral agents</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>Insulin</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Insulin and oral</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Diet</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

Young LH et al, JAMA 301:1547-1555, 2009
Conclusion In this contemporary study population of patients with diabetes, the cardiac event rates were low and were not significantly reduced by MPI screening for myocardial ischemia over 4.8 years.
## Follow-up Events

<table>
<thead>
<tr>
<th>Event</th>
<th>No screening n=562</th>
<th>Screening n=561</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No screening n=562</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Screening n=561</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td><strong>Primary events</strong></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10</td>
<td>1.7</td>
<td>7</td>
<td>1.3</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>7</td>
<td>1.2</td>
<td>8</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Secondary events</strong></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>3</td>
<td>0.5</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7</td>
<td>1.2</td>
<td>7</td>
<td>1.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>5</td>
<td>0.9</td>
<td>10</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Revascularizations</strong></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>PTCA</td>
<td>27</td>
<td>4.8</td>
<td>15</td>
<td>2.7</td>
</tr>
<tr>
<td>CABG surgery</td>
<td>20</td>
<td>3.6</td>
<td>16</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>All cause</td>
<td>15</td>
<td>2.7</td>
<td>18</td>
<td>3.2</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>8</td>
<td>1.4</td>
<td>10</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Young LH et al: JAMA 301(15):1547, 2009

Mean follow-up 4.8 yr
Median follow-up 5.0 yr
Cardiac Events

Cumulative incidence cardiac events

All Participants

Screening
No screening

P=0.73

Young LH et al: JAMA 301(15):1547, 2009
Cardiac Events by Screening Group

Young LH et al: JAMA 301(15):1547, 2009

Cumulative incidence of cardiac events

Screening Group

MPI screening results
- Normal
- Small defect
- Moderate or large defect
- Nonperfusion abnormality
- No screening test

P=0.005

Years

0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00

0 1 2 3 4 5
# Events According to Findings of Screening Myocardial Perfusion Imaging (n=522)

<table>
<thead>
<tr>
<th></th>
<th>Patients with normal imaging (n=409)</th>
<th>Small perfusion defect (n=50)</th>
<th>Moderate or large perfusion defect (n=33)</th>
<th>Nonperfusion abnormality (n=30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Patient (%)</td>
<td>Patient (%)</td>
<td>Patient (%)</td>
<td>Patient (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>78</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Primary events</strong></td>
<td>2.0</td>
<td>2.0</td>
<td>12.1</td>
<td>6.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.7</td>
<td></td>
<td>0</td>
<td>6.7</td>
<td>0.14</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0.5</td>
<td>2.0</td>
<td>12.1</td>
<td>3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary events</strong></td>
<td>3.2</td>
<td>2.0</td>
<td>9.1</td>
<td>13.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0.2</td>
<td></td>
<td>3.0</td>
<td>6.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.2</td>
<td></td>
<td>0</td>
<td>6.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.7</td>
<td>2.0</td>
<td>6.1</td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Revascularizations</strong></td>
<td>3.9</td>
<td>4.0</td>
<td>21.2</td>
<td>20.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PTCA</td>
<td>2.2</td>
<td>2.0</td>
<td>9.1</td>
<td>6.7</td>
<td>0.43</td>
</tr>
<tr>
<td>CABG surgery</td>
<td>1.7</td>
<td>2.0</td>
<td>12.1</td>
<td>13.3</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>All Cause</td>
<td>2.2</td>
<td>4.0</td>
<td>15.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>1.7</td>
<td>2.0</td>
<td>3.0</td>
<td></td>
<td>0.90</td>
</tr>
</tbody>
</table>

Young LH et al: JAMA 301(15):1547, 2009
## Follow-Up

<table>
<thead>
<tr>
<th>Additional cardiac testing</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonprotocol stress test</td>
<td>170</td>
<td>30</td>
<td>118</td>
<td>21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal nonprotocol stress test</td>
<td>45</td>
<td>26</td>
<td>28</td>
<td>24</td>
<td>0.60</td>
</tr>
<tr>
<td>Coronary angiogram &lt;120 d</td>
<td>3</td>
<td>0.5</td>
<td>25</td>
<td>4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Revascularization &lt;120 d</td>
<td>2</td>
<td>0.36</td>
<td>9</td>
<td>1.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Total coronary angiograms</td>
<td>66</td>
<td>12</td>
<td>80</td>
<td>14</td>
<td>0.20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of vessels &gt;70% stenosis</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>22</td>
<td>33</td>
<td>40</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>21</td>
<td>32</td>
<td>11</td>
<td>14</td>
<td>0.05</td>
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<tr>
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Young LH et al: JAMA 301(15):1547, 2009
# Medication Use

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<th>Pharmacological treatment</th>
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Young LH et al: JAMA 301(15):1547, 2009
Subject: DIAD Study, Young

Background: BU3
Banner/brdr: 0-40-159/BU41
Side title: YW105
• /colhdgs: YW105
Text: WT/BK
Highlight: YO114
Subdue: BU31
Footnotes: BU41

Plot/brdr: open/BU41 x, y only

PPT shooting instructions
PPT File to Server
(7 images)

Artist: KK Start Date: 11-10-09

COLOR REFERENCE ONLY
Match: Mayo2bu-2002 (CP1111378)
Problems with Bypass Surgery

- Morbidity of the procedure
- Saphenous vein grafts
- Acceleration of underlying native coronary disease
- Informed consent
## Procedural Stroke Risk

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Procedural stroke</th>
<th>Surviving patients/all patients</th>
<th>Risk difference (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>ARTS, 2001</td>
<td>590/600</td>
<td>592/605</td>
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<tr>
<td>AWESOME, 2001</td>
<td>220/222</td>
<td>229/232</td>
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<tr>
<td>BARI, 1996</td>
<td>913/915</td>
<td>907/914</td>
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<tr>
<td>EAST, 1994</td>
<td>197/198</td>
<td>191/194</td>
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<td>ERACI II, 2001</td>
<td>225/225</td>
<td>223/225</td>
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<tr>
<td>GABI, 1994</td>
<td>182/182</td>
<td>175/177</td>
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<tr>
<td>Drenth et al, 2002</td>
<td>50/51</td>
<td>51/51</td>
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<tr>
<td>Diegeler et al, 2002</td>
<td>110/110</td>
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<td>MASS, 1995</td>
<td>72/72</td>
<td>70/70</td>
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<td>MASS II, 2004</td>
<td>203/205</td>
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<td>Octostent, 2003</td>
<td>138/138</td>
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<td>Cisowski et al, 2002</td>
<td>50/50</td>
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<td>RITA, 1992</td>
<td>509/510</td>
<td>496/501</td>
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<td>Hong et al, 2005</td>
<td>119/119</td>
<td>69/70</td>
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<td>SIMA, 2000</td>
<td>62/63</td>
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<tr>
<td><strong>Overall</strong></td>
<td><strong>3,640/3,660</strong></td>
<td><strong>3,561/3,604</strong></td>
<td><strong>-0.10</strong></td>
</tr>
</tbody>
</table>

More strokes with CABG

More strokes with PCI

“Ha! That finishes it!...I always knew he’d be back one day to get the other one!”
Problems with Bypass Surgery

- Morbidity of the procedure
- Saphenous vein grafts
- Acceleration of underlying native coronary disease
- Informed consent
What Surgeons Do Not Tell You

• I am going to put you to sleep

• I am going to put a small hose into your breathing tube and breathe for you. I will also put a smaller tube somewhat lower for drainage

• I am going to divide your breast bone with a saw and then singe the ends to stop bleeding and then spread open your chest

• I am going to pick up and and then stop your heart
What the Surgeon Does Not Tell You

- I am going to make a long cut in your leg and remove veins
- I am going to do some hookups in your chest
- I am going to then take baling wire to put you back together again
- I am going to wake you up and tell you that everything is GREAT!
“Great”
appears to be a relative term
Who is left?

BRUCE WILLIS

THERE ARE TWO SIDES TO EVERY WAR. AND JOHN SMITH IS ON BOTH OF THEM.

LAST MAN STANDING
3 Vessel & Left Main Disease
Post SYNTAX

CABG – 66%
CABG or PCI – 28%
PCI – 6%
“I hate this place.”
"It was back in '52 that the hits stopped coming."
“More quarters! For God’s sake, more quarters!”
Lesion Severity in Native Vessels before Treatment

Rupprecht HJ et al, Eur Heart J 17:1192-1198, 1996
Lesion Severity in Native Vessels
6 Months after Treatment

P<0.0001
P<0.001
P<0.005
P<0.01

Rupprecht HJ et al, Eur Heart J
17:1192-1198, 1996
The son of Enoch and the father of Lamech (father of Noah), whom he fathered at the age of 187. “And all the days of Methuselah were nine hundred sixty and nine years: and he died in the year of the Great Flood”.
The BARI 2D Study Group
Event Rates at 5 Years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Revasc</th>
<th>Medical Therapy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients (n=1828)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Insulin sensitization (%)</td>
<td>11.1</td>
<td>12.3</td>
<td>0.81</td>
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<tr>
<td>Insulin provision (%)</td>
<td>12.2</td>
<td>12.0</td>
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<tr>
<td>P value</td>
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<td>0.90</td>
<td>0.78</td>
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<tr>
<td><strong>PCI stratum (n=1065)</strong></td>
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<tr>
<td>Insulin sensitization (%)</td>
<td>10.2</td>
<td>10.1</td>
<td>0.67</td>
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<tr>
<td>Insulin provision (%)</td>
<td>11.4</td>
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<td>0.56</td>
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<td>P value</td>
<td>0.79</td>
<td>0.94</td>
<td>0.92</td>
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<tr>
<td><strong>CABG stratum (n=763)</strong></td>
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<tr>
<td>Insulin sensitization (%)</td>
<td>13.4</td>
<td>17.1</td>
<td>0.34</td>
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<tr>
<td>Insulin provision (%)</td>
<td>13.9</td>
<td>15.6</td>
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<tr>
<td>P value</td>
<td>0.83</td>
<td>0.71</td>
<td>0.72</td>
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</table>

NEJM 360:2503, 2009
## The BARI 2D Study Group
### Event Rates at 5 Years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Revasc</th>
<th>Medical Therapy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients (n=1828)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin sensitization (%)</td>
<td>20.3</td>
<td>24.1</td>
<td>0.29</td>
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<tr>
<td>Insulin provision (%)</td>
<td>25.2</td>
<td>24.1</td>
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<tr>
<td>P value</td>
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<td>0.85</td>
<td>0.23</td>
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<tr>
<td><strong>PCI stratum (n=1065)</strong></td>
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<tr>
<td>Insulin sensitization (%)</td>
<td>21.1</td>
<td>20.4</td>
<td>0.36</td>
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<tr>
<td>Insulin provision (%)</td>
<td>24.9</td>
<td>21.7</td>
<td>0.28</td>
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<tr>
<td>P value</td>
<td>0.30</td>
<td>0.51</td>
<td>0.84</td>
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<tr>
<td><strong>CABG stratum (n=763)</strong></td>
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<td>Insulin sensitization (%)</td>
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<td>Insulin provision (%)</td>
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<td>P value</td>
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*NEJM 360:2503, 2009*
The Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial

BARI 2D Trial

Presented at the American Diabetes Association (ADA) Annual Scientific Sessions 2009 in New Orleans
Prior CABG and STEMI
APEX-AMI Trial

- 5745 STEMI patients with planned primary PCI
- 128 (2.2%) had prior CABG
- Evaluate 90 day clinical outcomes
## Prior CABG and STEMI
### APEX-AMI Trial

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No Prior CABG (n=5617)</th>
<th>Prior CABG (n=128)</th>
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<tbody>
<tr>
<td>Age, yrs, median (IQR)</td>
<td>61 (52, 71)</td>
<td>69 (58.3, 76)</td>
<td>&lt;0.001</td>
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<tr>
<td>Female, n (%)</td>
<td>1306 (23.3)</td>
<td>18 (14.1)</td>
<td>0.014</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>2749 (49.0)</td>
<td>90 (70.3)</td>
<td>&lt;0.001</td>
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<tr>
<td>Prior MI, n (%)</td>
<td>612 (10.9)</td>
<td>82 (64.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior PCI, n (%)</td>
<td>881 (9.2)</td>
<td>32 (36.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior CHF, n (%)</td>
<td>187 (3.3)</td>
<td>21 (16.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>DM, n (%)</td>
<td>187 (15.7)</td>
<td>32 (25.0)</td>
<td>0.007</td>
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## Prior CABG and STEMI
### APEX-AMI Trial

<table>
<thead>
<tr>
<th>90-Day Clinical Outcomes, n (%)</th>
<th>No Prior CABG (n=5617)</th>
<th>Prior CABG (n=128)</th>
<th>P</th>
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<tbody>
<tr>
<td>Death</td>
<td>256 (4.6)</td>
<td>15 (11.9)</td>
<td>0.001</td>
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<tr>
<td>CHF</td>
<td>267 (4.8)</td>
<td>8 (6.3)</td>
<td>0.4</td>
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<tr>
<td>Shock</td>
<td>188 (3.3)</td>
<td>8 (6.3)</td>
<td>0.082</td>
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<td>Death/CHF/Shock</td>
<td>565 (10.1)</td>
<td>21 (16.4)</td>
<td>0.019</td>
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Welsh (under review)
# Prior CABG and STEMI
## APEX-AMI Trial

<table>
<thead>
<tr>
<th>Angio &amp; Revasc Characteristics</th>
<th>No Prior CABG (n=5617)</th>
<th>Prior CABG (n=128)</th>
<th>P</th>
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<tbody>
<tr>
<td>Primary PCI, n (%)</td>
<td>5272 (93.9)</td>
<td>101 (78.9)</td>
<td>&lt;0.001</td>
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<tr>
<td>No urg revasc (no urg csurg or primPCI), n (%)</td>
<td>242 (5.0)</td>
<td>24 (18.8)</td>
<td>&lt;0.001</td>
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<td>Post PCI TIMI flow, n (%) in those with primPCI</td>
<td>N=5272</td>
<td>N=101</td>
<td>&lt;0.001</td>
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<td>0/1</td>
<td>110 (2.1)</td>
<td>6 (6.2)</td>
<td>&lt;0.001</td>
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<td>328 (6.3)</td>
<td>11 (11.3)</td>
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<td>4800 (91.6)</td>
<td>80 (82.5)</td>
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</table>

Welsh (under review)
Prior CABG and STEMI
APEX-AMI Trial

Prior CABG patients with STEMI are less likely to undergo acute reperfusion, have worse angiographic outcomes following primary PCI and higher 90-day mortality. These findings are especially applicable when the IRA was a bypass graft.

Welsh (under review)
90-Day Mortality According to Prior CABG

Cumulative mortality (%) vs. Follow-up (days)

- Prior CABG: 11.9%
- No prior CABG: 4.9%

P<0.001
90-Day Death/CHF/Shock According to Prior CABG

Prior CABG
16.4%

No prior CABG
10.1%

P=0.014
Associations Between Prior CABG and 90-Day Clinical Outcomes

<table>
<thead>
<tr>
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<th>HR (95% CI)</th>
<th></th>
<th>HR (95% CI)</th>
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<td><strong>90-day death</strong></td>
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<tr>
<td>Unadjusted</td>
<td>2.71 (1.61-4.57)</td>
<td>Adjusted</td>
<td>1.90 (1.08-3.33)</td>
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<tr>
<td>Adjusted</td>
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<tr>
<td><strong>90-day death/CHF/shock</strong></td>
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<tr>
<td>Unadjusted</td>
<td>1.72 (1.11-2.66)</td>
<td>Adjusted</td>
<td>1.06 (0.66-1.70)</td>
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<tr>
<td>Adjusted</td>
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</tbody>
</table>

Graph showing HR (95% CI) for 90-day death and 90-day death/CHF/shock outcomes.
90-Day Mortality According to Prior CABG – Graft vs Native IRA

- Graft IRA vs no prior CABG: \( P < 0.001 \)
- Native IRA vs no prior CABG: \( P = 0.713 \)
- Graft IRA vs native IRA: \( P = 0.031 \)

Prior CABG
- Graft IRA – 19.0%
- Native IRA – 5.7%
- No prior CABG – 4.6%
90-Day Death/CHF/Shock According to Prior CABG – Graft vs Native IRA

Prior CABG
Graft IRA – 22.2%

Graft IRA vs no prior CAGB: P<0.001
Native IRA vs no prior CAGB: P=0.488
Graft IRA vs native IRA: P=0.171

Prior CABG
Native IRA – 12.7%

No prior CABG
10.1%
## Adjusted Associations Between Prior CABG – Graft vs Native IRA and 90-Day Clinical Outcomes

<table>
<thead>
<tr>
<th>Prior CABG – graft IRA</th>
<th>90-day death</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior CABG (ref)</td>
<td></td>
<td>3.33 (6.30-16.0)</td>
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<tr>
<td>Prior CABG – native IRA</td>
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<td>1.22 (3.84-12.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior CABG – graft IRA</th>
<th>90-day death/CHF/shock</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior CABG (ref)</td>
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<td></td>
</tr>
<tr>
<td>Prior CABG – graft IRA</td>
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<td>0.86 (0.41-1.8)</td>
</tr>
<tr>
<td>Prior CABG – native IRA</td>
<td></td>
<td>1.18 (0.46-3.0)</td>
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</tbody>
</table>
Apex Prior CABG Figures

Background: BU3
Banner/brdr: BU2/BU41
Side title: YW105
• /colhdgs: YW105
Text: WT/BK
Highlight: YO114
Subdue: BU31
Footnotes: BU41

Plot/brdr: open/BU41
x, y only

PPT shooting instructions
PPT File to Server
(6 images)

Artist: DV
Start Date: 7-9-09

COLOR REFERENCE ONLY
Match: Mayo2bu-2002 (CP1111378)
Intended Mode of Revascularization by Number of Diseased Vessels

- **None or single VD (n=791):**
  - Intended CABG: 10%
  - Intended PCI: 90%

- **Double VD (n=849):**
  - Intended CABG: 34%
  - Intended PCI: 66%

- **Triple VD (n=726):**
  - Intended CABG: 55%
  - Intended PCI: 45%
<table>
<thead>
<tr>
<th>Glucose control strategy</th>
<th>Ischemic control strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prompt revasc</td>
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<tr>
<td>Insulin provision</td>
<td>592</td>
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<tr>
<td>Insulin sensitization</td>
<td>584</td>
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### BARI 2D in the Context of Current Clinical Practice and Recent Trials

How does glycemic drug use during BARI 2D (% of patients) compare to general use in USA?

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Year 3</th>
<th>USA* 2008</th>
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<td>IP</td>
<td>Overall</td>
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<td>TZDs</td>
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<td>Sulfonylureas</td>
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<td>Insulin</td>
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<td>28</td>
<td>62</td>
</tr>
</tbody>
</table>

*Data courtesy Medco and ADA
Based on 3,213,000 prescriptions
Our PCI results are consistent with the results from COURAGE, in which the majority of participants did not have diabetes.

COURAGE did not study CABG – further BARI2D analyses will address the effect of PCI on angina.
BARI 2D in the Context of Current Clinical Practice and Recent Trials

Intensive glycemic control trials (ADVANCE, ACCORD and VADT)
- BARI 2D does not address the question of intensive glycemic control as all subjects were treated with a target $A_{1C}$ of <7.0%

TZD (rosiglitazone) therapy
- BARI 2D assessed therapeutic strategies rather than any specific drug
- No safety concerns were seen for the IS group in which over 60% were using TZD’s, predominately rosiglitazone
- These results are thus consistent with RECORD
Effect of Insulin Sensitizing vs Insulin Providing Strategy on Death/Non-Fatal MI or Stroke Among Patients Assigned to Prompt Revascularization

- **Patients suffering event (%)**
  - All revascularization
  - CABG
  - PCI

- **Comparison between IS and IP**
  - IS: P=0.059
  - IP: P=0.066
  - PCI: P=0.30
Do the Results of BARI 2D Suggest Any Changes Should be Made to Current Diabetes Management Practices?

- In general, no, as significant IS vs IP differences were not demonstrated.
- However, adoption of an IS strategy could be considered in those undergoing revascularization and needing improved glycemic control.
Conclusions

• In patients with type 2 diabetes and stable CAD with documented ischemia, mortality does not differ according to either prompt or delayed revascularization strategies or by diabetes management strategies of insulin provision or sensitization.

• In appropriately chosen type 2 diabetic patients, CABG is superior to aggressive medical therapy alone in reducing the combined incidence of death, non-fatal MI and non-fatal stroke.
Therapeutic decisions regarding management of the CAD and glycemia in type 2 diabetes should be made jointly by the patient’s cardiologist, diabetologist and/or primary care physician.
Subject: BARI presentation

Background: BU3
Banner/brdr: BU2/BU41
Side title: YW105
• /colhdgs: YW105
Text: WT/BK
Highlight: YO114
Subdue: BU31
Footnotes: BU41

Plot/brdr: open/BU41
  x, y only

PPT shooting instructions
PPT File to Server
(57 images)

Artist: mls  Start Date: 7-10-09

COLOR REFERENCE ONLY
Match: Mayo2bu-2002 (CP1111378)
PCI vs CABG: New vs Old Technology

Sources: Cordis Database, Morgan Stanley
PCI vs CABG

Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Pt (no.)</th>
<th>F-U (yr)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AWESOME</td>
<td>454</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>MASS-II*</td>
<td>408</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>SOS</td>
<td>988</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>ARTS</td>
<td>1,205</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ERACI-II*</td>
<td>450</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>BARI*</td>
<td>1,829</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>EAST</td>
<td>392</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>CABRI</td>
<td>1,054</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>GABI</td>
<td>359</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ERACI*</td>
<td>127</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>RITA*</td>
<td>1,011</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8,258</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard*/risk ratios

Do repeat revascularization rates = durability?

Mercado et al: J Thoracic Cardiovasc Surg, 2005
## PREVENT 4

<table>
<thead>
<tr>
<th>Type of event</th>
<th>CABG + edifoligide (n=1508)</th>
<th>CABG + placebo (n=1506)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>379</td>
<td>25.1</td>
</tr>
<tr>
<td>Perioperative MI in CABG surgery</td>
<td>145</td>
<td>9.6</td>
</tr>
<tr>
<td>Renal failure</td>
<td>49</td>
<td>3.2</td>
</tr>
<tr>
<td>Bleeding requiring reoperation</td>
<td>40</td>
<td>2.7</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>33</td>
<td>2.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>28</td>
<td>1.9</td>
</tr>
<tr>
<td>Adult respiratory distress syndrome</td>
<td>10</td>
<td>0.7</td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>9</td>
<td>0.6</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>12</td>
<td>0.8</td>
</tr>
</tbody>
</table>
SYNTAX
1-Year Clinical Outcomes

P=0.0015

P=0.98

P=0.37

P=0.11

P=0.003

P<0.001
Drug-Eluting Stents vs. Coronary-Artery Bypass Grafting in Multivessel Coronary Disease

Mortality (after adjustment) 7.3% for DES Vs. 6.0% for CABG
This 1.3% absolute difference (P=0.03) yields a NNT of 77

If we need to do 77 bypasses to save one life, I believe the mortality benefit is clinically meaningless!
This point was completely missed by the lay press
SYNTAX Trial Design

62 EU sites + 23 U.S. sites

Heart team (surgeon & interventionalist)

Amenable for both treatment options
Randomized arms n=1,800
CABG n=897 vs TAXUS n=903
DM 28.5% Non-DM 71.5% DM 28.2% Non-DM 71.8%

Amenable for only 1 treatment approach
2 registry arms n=1,275
CABG n=1,077 PCI n=198

TAXUS® Express® Stent

DM 28.5% Non-DM 71.5% DM 28.2% Non-DM 71.8%
**SYNTAX**

1-Year Clinical Outcomes

Number needed to prevent analysis

Number of CABGs needed to prevent 1 re-PCI = 13

At the cost of almost 4 times as many strokes

Serruys and Mohr: ESC, 2008

*Primary endpoint*
Adverse Events to 12 Months
Left Main Subset

Cumulative event rate (%)

Months since allocation

All Death
P=0.88*

CVA (Stroke)
P=0.009*

Number needed to prevent

Number of CABGs needed to prevent
1 re-PCI = 19

This means 18 of every 19 CABGs were unnecessary!

At the cost of 9 times as many strokes
Safety at 12 Months (Death/CVA/MI)

Left Main Subset

ITT population; presented by Dr. Serruys: TCT 2008

The safety and effectiveness of the TAXUS® Express® Stent System have not been established in the following patient populations: lesions located in the unprotected left main coronary artery or patients with multi-vessel disease.
Revascularizations at 12 Months

Left Main Subset

ITT population; presented by Dr. Serruys: TCT 2008

The safety and effectiveness of the TAXUS® Express® Stent System have not been established in the following patient populations: lesions located in the unprotected left main coronary artery or patients with multi-vessel disease.
Adverse Events to 12 Months

Left Main Subset

Myocardial Infarction

- Cumulative event rate (%)
- Months since allocation

- All Death
  - P=0.04
  - 4.4% - 2.9% = 1.5 abs diff
  - NNT = 67, ie, 67 CABGs to save 1 life

- CVA (Stroke)
  - P=0.09
  - 1.9% - 0.8% = 1.1 abs diff
  - NNP = 91, by 91 CABGs there is 1 extra CVA

- Revascularization
  - P=0.02
  - NNP = 10.7, ie, must do 10.7 CABGs to prevent 1 re-PCI
Generic QOL and Utilities

SF-36 Physical Component Summary

- P<0.001
- P=0.50
- P=0.07

SF-36 Mental Component Summary

- P<0.001
- P=0.23
- P=0.43

EQ-SD Utilities (US)

- PCI
- CABG

- P<0.001
- P=0.16
- P=0.99

Baseline 1 mo 6 mo 12 mo
Total 1-Year Costs

- 1-year follow-up
- Initial hospitalization

$35,991
$39,581

$3,590 (P<0.001)
Higher 12-Month MACCE in Diabetics* Driven by Revascularization

Diabetic patients
Number needed to prevent
Number of CABGs needed to prevent 1 re-PCI = 8

CABG (n=204) vs TAXUS® Express® Stent (n=227)

Event rates in diabetic patients (%)

All death MI CVA Revasc MACCE

P=0.43 P=0.83 P=0.26 P<0.001 P=0.003

P=0.003

All death MI CVA Revasc MACCE

6.4 8.4 2.5 0.9 14.2

Medically treated diabetics; presented by Dr. Dawkins: TCT 2008
The TAXUS® Express® Stent System has not been specifically indicated for patients with diabetes
Death/CVA/MI at 12 Months
Diabetic Subgroups

- Oral Hypoglycemics
  - CABG: 12.0, P=0.19
  - TAXUS®: 7.2, 14/117 vs 10/139
  - P=0.10

- Insulin Treated
  - CABG: 8.0
  - TAXUS®: 14.8
  - P=0.16

Patients (%)

<table>
<thead>
<tr>
<th>Category</th>
<th>Non-diabetics</th>
<th>Medically-treated diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>6.8 (44/645)</td>
<td>10.3 (21/204)</td>
</tr>
<tr>
<td>TAXUS®</td>
<td>6.8</td>
<td>10.1</td>
</tr>
<tr>
<td>P</td>
<td>0.97</td>
<td>0.96</td>
</tr>
<tr>
<td>Oral Hypoglycemics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin Treated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P=0.10
MACCE to 12 Months vs SYNTAX Score™

**CABG (n=897)**
- SYNTAX score ≥22: 14.7%
- SYNTAX score 23-32: 12%
- SYNTAX score ≤33: 10.9%

**P=0.38**

**TAXUS® Express® Stent (n=903)**
- SYNTAX score ≥22: 13.6%
- SYNTAX score 23-32: 16.7%
- SYNTAX score ≤33: 23.4%

**P=0.007**

- **P=0.04**
- **P=0.002**
- **P=0.29**

- **P=0.002**
### MACCE to 12 Months by SYNTAX Score

#### Tertile High Score (33+)

<table>
<thead>
<tr>
<th>Event</th>
<th>CABG</th>
<th>PCI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4.1%</td>
<td>9.7%</td>
<td>0.06</td>
</tr>
<tr>
<td>CVA</td>
<td>3.4%</td>
<td>0.8%</td>
<td>0.22</td>
</tr>
<tr>
<td>MI</td>
<td>6.0%</td>
<td>7.6%</td>
<td>0.65</td>
</tr>
<tr>
<td>Death, CVA or MI</td>
<td>10.8%</td>
<td>14.1%</td>
<td>0.40</td>
</tr>
<tr>
<td>Revasc</td>
<td>4.9%</td>
<td>17.8%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

#### Cumulative event rate (%)

- **LM Subset**
  - P=0.008
  - 25.3%

#### Months since allocation

- CABG (n=150)
- TAXUS (n=135)

- Death, CVA or MI
  - 10.8%
  - 14.1%
  - 0.001
MACCE to 12 Months by SYNTAX Score

Tertile High Score (33+)

<table>
<thead>
<tr>
<th></th>
<th>CABG</th>
<th>PCI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.2%</td>
<td>6.5%</td>
<td>0.02</td>
</tr>
<tr>
<td>CVA</td>
<td>1.2%</td>
<td>0.0%</td>
<td>0.50</td>
</tr>
<tr>
<td>MI</td>
<td>1.9%</td>
<td>6.5%</td>
<td>0.04</td>
</tr>
<tr>
<td>Death, CVA or MI</td>
<td>4.3%</td>
<td>9.7%</td>
<td>0.07</td>
</tr>
<tr>
<td>Revasc</td>
<td>5.1%</td>
<td>16.6%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Cumulative event rate (%)

3VD Subset

P=0.002

CABG (n=166)

TAXUS (n=155)
Subject: Teirstein Presentation

Background: BU3
Banner/brdr: BU2/BU41

Side title: YW105
• /colhdgs: YW105

Text: WT/BK
Highlight: YO114

Subdue: BU31
Footnotes: BU41

Plot/brdr: open/BU41
x, y only

PPT shooting instructions
PPT File to Server
(28 image)

Artist: KK
Start Date: 7-14-09

COLOR REFERENCE ONLY
Match: Mayo2bu-2002 (CP1111378)
58% Average Restenosis Rate in Diabetes Following POBA

- Holmes (1984)
- Vandormael (1987)
- Lambert (1988)
- Quigley (1989)
- Ellis (1989)
- Macdonald (1990)
- Bourassa (1991)
- Weintraub (1993)
- Rabbini (1994)
- Lefevre (1994)
- Van Belle (1997)
- Levine (1997)
- Van Belle (1998)

Restenosis Rate (%)
Restenosis Increased in Diabetes Following BMS Implantation

6-Month Rates

<table>
<thead>
<tr>
<th></th>
<th>No Diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restenosis</td>
<td>28.3%</td>
<td>37.5%</td>
</tr>
<tr>
<td>TV Occlusion</td>
<td>3.4%</td>
<td>5.3%</td>
</tr>
</tbody>
</table>

P<0.001

P=0.04

J Am Coll Cardiol 1998;32:1866-1873
Diabetes Also Increases Mortality After Bare Metal Stenting

Event-Free Survival (%)

- Diabetes: 73.1% (P<0.001)
- No Diabetes: 78.5%

Months After Stent Placement

J Am Coll Cardiol 1998;32:1866-1873
What About Diabetic Patients with 3-Vessel and/or Left Main Disease?

- Current guidelines recommend CABG
- Estimated 34% of patients with Class I indications for CABG receive PCI in the DES era

What is the optimal treatment?

J Am Coll Cardiol 2008;51:172-209
Circulation 2007;116II:795
**BARI - 7 Year Survival**

**Survival-Patients without Treated Diabetes**

- **CABG** (86.4)
- **PTCA** (86.8)

$P = 0.7155$

---

**No. of pts**

- **CABG**: 734, 699, 490
- **PTCA**: 742, 703, 509

Detre, JACC 2000
# Amount of Disease
## BARI vs SYNTAX

<table>
<thead>
<tr>
<th></th>
<th>BARI</th>
<th>SYNTAX</th>
</tr>
</thead>
<tbody>
<tr>
<td>3VD</td>
<td>44%</td>
<td>71%</td>
</tr>
<tr>
<td>LMCA</td>
<td>0</td>
<td>29%</td>
</tr>
<tr>
<td># sig. lesions</td>
<td>3.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Diffuse disease</td>
<td>?</td>
<td>13.4%</td>
</tr>
<tr>
<td>1-yr survival</td>
<td>90%</td>
<td>92%*</td>
</tr>
</tbody>
</table>

*Death/CVA/MI
Medical therapy needs to be optimal, closely followed, specific metrics of treatment objectives
Mortality in Type 2 Diabetes
Multifactorial Intervention

• STENO-2 study randomly assigned 160 patients with type 2 diabetes and micro-albuminuria to conventional therapy or intensive therapy

• Targets:
  • HAIC <6.5%
  • Cholesterol <175
  • Triglycerides <150
  • BP <130/80

• Approach – tight glucose regulation, RAS blockers, ASA, lipid lowering agents

• Primary endpoint all cause mortality at 13.3 yrs

Risk of Death

Cumulative incidence of death (%)

Follow-up (yr)

P=0.02

Numbers at risk

<table>
<thead>
<tr>
<th>Intensive therapy</th>
<th>80</th>
<th>78</th>
<th>75</th>
<th>72</th>
<th>65</th>
<th>62</th>
<th>57</th>
<th>39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional therapy</td>
<td>80</td>
<td>80</td>
<td>77</td>
<td>69</td>
<td>63</td>
<td>51</td>
<td>43</td>
<td>30</td>
</tr>
</tbody>
</table>

Risk of any cardiovascular event

Cumulative incidence of any cardiovascular event (%)

Follow-up (yr)

Numbers at risk

Intensive therapy

Conventional therapy

P<0.001

0 1 2 3 4 5 6 7 8 9 10 11 12 13

0 10 20 30 40 50 60 70 80

80 72 65 61 56 50 47 31

80 70 60 46 38 29 25 14

Risk of Death

- Death from cardiovascular causes
- Stroke
- Myocardial infarction
- CABG
- PCI
- Revascularization
- Amputation

Intensive therapy vs. Conventional therapy

Clinical Implications

- A central approach to optimizing outcome of all diabetic patients is optimal control.
- By optimizing control, we can optimize the results of any revascularization strategy.
BARI 2D

• Multicenter RCT 49 sites
• 2,368 patients with type 2 diabetes and stable CAD
• Randomization to revascularization (CABG or PCI) vs standardized medical therapy
• Primary endpoint – cardiovascular events
What are the outstanding issues?

- Diabetes
- Acute myocardial infarction
- Chronic total occlusion
- LMCA or MVD
- Dual antiplatelet therapy
2368 patients with mild to moderate CAD and Type 2 diabetes prior to randomization. Prospective. Randomized. Mean follow-up 5.3 years

- **Primary Endpoint:** Death (from any cause)
- **Secondary Endpoint:** Composite of Death, MI, or Stroke