Bypass Angioplasty
Revascularization Investigation
2 Diabetes (BARI 2D)
BARI 2D Dedication

Katherine M. Detre, MD, DrPH
1926 - 2006
BARI 2D

BACKGROUND
NIDDK Fact Sheet

- 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 to 4 times higher than rates among adults without diabetes.
Bypass Angioplasty Revascularization (BARI)

- Compared Percutaneous Transluminal Coronary Angioplasty (PTCA) with Coronary Artery Bypass Graft Surgery (CABG)
- Patients with symptomatic multi-vessel coronary disease requiring revascularization
- Recruitment in 1988-1991
- Unsuspected finding in patients with diabetes
BARI 10-Year Survival
Stratified by Diabetes Status

No Diabetes CABG vs PTCA: $p = 0.50$
Diabetes CABG vs PTCA: $p = 0.012$

- ND CABG 78.2%
- ND PTCA 76.8%
- D CABG 57.1%
- D PTCA 44.1%
# Five-year Cardiac Mortality Rates from BARI

<table>
<thead>
<tr>
<th></th>
<th>PTCA</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>No diabetes</td>
<td>4.8%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20.6%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>
Cardiology Treatment Questions

- Outcomes after revascularization are poorer in patients with diabetes compared to those without diabetes.

- Should revascularization be undertaken earlier in the coronary disease process for patients with diabetes?

- Medical therapy has improved dramatically since prior randomized trials of medical therapy vs revascularization.

- Is medical therapy an acceptable alternative to patients with diabetes and mild symptoms?
Glycemic Treatment Questions

- Insulin resistance is an independent risk factor for Cardiovascular Disease (CVD).
- Does lowering insulin resistance lower CVD risk?
- Hyperinsulinemia has been implicated in the pathogenesis of atherosclerosis.
- Does circulating insulin influence CVD risk?
BARI 2D

DESIGN
BARI 2D Clinical Trial

Compare treatment strategies for patients with:

- Type 2 diabetes mellitus
- Documented coronary artery disease (1+ significant lesion) suitable for elective revascularization
- Documented ischemia
BARI 2D: Inclusion Criteria

- Type 2 diabetes mellitus
- Age ≥ 25 years
- CAD (at least one stenosis ≥ 50%) suitable for revascularization
- Documented ischemia
  
  **Objective:**
  
  exercise or pharmacological stress test (ECG perfusion or wall motion criteria)
  
  Doppler or pressure wire

  **Subjective:**
  
  typical angina plus ≥ 70% coronary stenosis

- Able to adhere to glycemic control and risk factor modification
- Informed written consent
BARI 2D: Exclusion Criteria

- Definite need for revascularization (cardiologist’s opinion)
- Prior CABG or PCI within the past 12 months
- Planned intervention in bypass grafts if assigned to revascularization
- Class III or IV Congestive Heart Failure
- Creatinine > 2.0 mg/dl
- HbA1c > 13.0%
- Need for major vascular surgery concomitant with revascularization
- Left main disease ≥ 50%
- Non-cardiac illness expected to limit survival
Exclusion Criteria (cont’d)

- Hepatic disease (ALT >2X ULN)
- Fasting Triglycerides > 1000 mg/dl in the presence of moderate glycemic control (HbA1c < 9.0%)
- Current alcohol abuse
- Chronic steroid use judged to interfere w/control of diabetes
- Pregnancy, known, suspected, or planned in next 5 yr
- Geographically inaccessible
- Enrolled in a competing randomized trial
- Unable to understand or cooperate with protocol requirements
BARI 2D Goals

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

Compare
Prompt revascularization versus delayed or no revascularization.

Insulin sensitizing strategy versus an insulin providing strategy for glycemic management with target HbA1c < 7.0%.
BARI 2D Primary and Principal Secondary Endpoints

- All-cause mortality
- Major cardiovascular events: Composite of Death / Myocardial Infarction / Stroke
- Average follow-up time 5.3 years
BARI 2D Secondary Endpoints

- Cardiac mortality, MI (Q-wave and/or non-Q-wave), stroke
- PAI-1, t-PA antigen
- Left ventricular function, extent of ischemia
- Cost and cost-effectiveness
- Quality of life, employment
- Angina, subsequent revascularization
Revascularization Decision

Before randomization, Cardiologist selected revascularization method based on clinical and angiographic factors

Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Graft Surgery (CABG)
### BARI 2D Randomization: 2 x 2 Factorial Design

#### Ischemia Control Strategy

<table>
<thead>
<tr>
<th>Glucose Control Strategy</th>
<th>Insulin Provision</th>
<th>Insulin Sensitization</th>
<th>Prompt Revasc</th>
<th>Medical</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>592</td>
<td>593</td>
<td>1185</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>584</td>
<td>599</td>
<td>1183</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1176</td>
<td>1192</td>
<td>2368</td>
</tr>
</tbody>
</table>
BARI 2D Clinic Visits

After initial meeting with diabetologist:

- Monthly visits to diabetologist during first 6 months, with additional nurse coordinator contact as needed
- Quarterly visits thereafter
- Clinical treatment of patients
- Extensive data collection at each visit (e.g., medications, risk factors, complications)
Event Classification

An independent Mortality and Morbidity Classification Committee (MMCC) adjudicated the primary endpoint data. They classified the cause of all deaths and verified all strokes.

The BARI 2D Core ECG Laboratory classified all suspected myocardial infarctions.
Monitored Risk Factors

BARI 2D Management Centers actively monitored and provided feedback to clinical sites regarding site performance and individual patient risk factor control:

- HbA1c
- Severe hypoglycemia
- Lipids
- Blood pressure
- Body Mass Index and Physical Activity
Pre-specified Subgroups Defined by Baseline Data

- Intended Method of Revascularization
- Prior Revascularization
- Receiving Insulin
- HbA1c
- Left Ventricular Function
- Creatinine
- Race

Other important factors to consider:

Number of Diseased Vessels, Body Mass Index, Microalbuminuria, Duration of Diabetes, Blood Pressure, LDL-Cholesterol, Sex, and Age
Statistical Analysis Design

- Intention-to-treat principle for randomized treatment comparisons.
- All-cause mortality and Death / Myocardial Infarction / Stroke estimated using Kaplan Meier curves and compared with log rank statistics.
- Each hypothesis is two-sided with alpha-level = 0.05.
- Randomized treatment comparisons within pre-specified subgroups (e.g. by intended method of revascularization) use alpha-level = 0.01.
Sample Size and Power

In 2005, follow-up was extended so that average patient follow-up would be 5.2 years.

Assuming:
- Overall 5-year mortality and death / myocardial infarction (MI) / stroke rates 11.9% and 21% respectively.
- 5% patients eventually lost to follow-up.

> 85% power to detect a 30% reduction in mortality (14.0% vs 9.8%).

> 95% power to detect a 25% reduction in death/MI/stroke (24.0% vs 18.0%).
BARI 2D Time Line

Recruitment Begins: Jan 1, 2001
Recruitment Complete: March 31, 2005
Follow-up Ends: Nov 30, 2008
BARI 2D

BASELINE
Randomized Patients by Region

- United States: N=1499, 63%
- Brazil: N=356, 15%
- Canada: N=353, 15%
- Mexico: N=85, 4%
- Europe: N=75, 3%

N=2368 Randomized Patients
Demographic and Clinical History
(N=2368 Randomized Patients)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Mean)</strong></td>
<td>62.4 yr</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>30%</td>
</tr>
<tr>
<td><strong>Ethnic/Racial Minority</strong></td>
<td>34%</td>
</tr>
<tr>
<td><strong>Myocardial Infarction Hx</strong></td>
<td>32%</td>
</tr>
<tr>
<td><strong>Congestive Heart Failure Hx</strong></td>
<td>7%</td>
</tr>
<tr>
<td><strong>History of Stroke or TIA</strong></td>
<td>10%</td>
</tr>
<tr>
<td><strong>Peripheral Artery Disease</strong></td>
<td>24%</td>
</tr>
</tbody>
</table>
## Cardiac Clinical Characteristics
*(N=2368 Randomized Patients)*

<table>
<thead>
<tr>
<th>Angina Status*</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No angina nor anginal equivalents</td>
<td>18.0%</td>
</tr>
<tr>
<td>Anginal equivalents (no angina)</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%</td>
</tr>
<tr>
<td>Prior Stent</td>
<td>13%</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>6%</td>
</tr>
</tbody>
</table>

* Angina status at baseline differs significantly between Rev and Med groups
## Angiographic Characteristics

(N=2368 Randomized Patients)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diseased Coronary Vessels:</strong></td>
<td></td>
</tr>
<tr>
<td>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>44 ± 24</td>
</tr>
<tr>
<td>(Mean ± SD)</td>
<td></td>
</tr>
<tr>
<td><strong>Proximal LAD (&gt;50% stenosis)</strong></td>
<td>13%</td>
</tr>
<tr>
<td><strong>Total Occlusion (at least one)</strong></td>
<td>41%</td>
</tr>
<tr>
<td><strong>Abnormal LV Function (&lt;50%)</strong></td>
<td>17%</td>
</tr>
</tbody>
</table>
# Diabetes Clinical History

(N=2368 Randomized Patients)

<table>
<thead>
<tr>
<th>Duration of Diabetes (mean)</th>
<th>10.4 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 Months</td>
<td>8%</td>
</tr>
<tr>
<td>6 months to 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>HbA1c % (mean)</th>
<th>7.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receiving Insulin</td>
<td>28%</td>
</tr>
<tr>
<td>Micro or Macro-albuminuria</td>
<td>33%</td>
</tr>
<tr>
<td>(ACR&gt;30)</td>
<td></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 > 7.0%: 60%
- Total Cholesterol ≥ 200: 19%
- LDL Cholesterol ≥100: 40%
- HDL Cholesterol low: 73%
- Blood Pressure > 130/80mm Hg: 52%
- BMI ≥30: 56%
- Current Smoker: 13%
### Baseline Characteristics By Randomization Stratum

<table>
<thead>
<tr>
<th></th>
<th>PCI Intended N=1605</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%</td>
<td>76%</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>29%</td>
<td>13%</td>
</tr>
<tr>
<td>Proximal LAD</td>
<td>10%</td>
<td>19%</td>
</tr>
<tr>
<td>LVEF &lt; 50</td>
<td>18%</td>
<td>18%</td>
</tr>
<tr>
<td>3 Vessel Disease</td>
<td>20%</td>
<td>52%</td>
</tr>
<tr>
<td>Total Occlusions, 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>
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%
BARI 2D
TREATMENT IMPLEMENTED

Risk factor control

Diabetes

Cardiac
Risk Factor Control

Percent of Patients

- LDL < 100: Baseline 60, Year 3 83
- BP≤130/80: Baseline 48, Year 3 71
- No Smoking: Baseline 78, Year 3 89

Legend: 
- Baseline
- Year 3
## Risk Factor Measures

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Three Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rev</td>
<td>Med</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>96</td>
<td>81</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>Systolic Blood</td>
<td>132</td>
<td>126</td>
</tr>
<tr>
<td>Pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic Blood</td>
<td>75</td>
<td>70</td>
</tr>
<tr>
<td>Pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.7</td>
<td>32.0</td>
</tr>
</tbody>
</table>

* Differences between IS and IP groups significant (p<0.05) for HDL and BMI at 3 years
Drug Use by 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>Baseline</td>
<td>62</td>
<td>36</td>
</tr>
<tr>
<td>Year 1</td>
<td>75</td>
<td>36</td>
</tr>
<tr>
<td>Year 3</td>
<td>88</td>
<td>43</td>
</tr>
<tr>
<td>Year 5</td>
<td>80</td>
<td>54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>IS Drugs</th>
<th>IP Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>60</td>
<td>12</td>
</tr>
<tr>
<td>Year 1</td>
<td>76</td>
<td>12</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>
</tr>
</tbody>
</table>
# Diabetes Medication Use

<table>
<thead>
<tr>
<th>Medication</th>
<th>Baseline</th>
<th>Three Year</th>
<th>IS</th>
<th>IP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>54%</td>
<td>75%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>19%</td>
<td>62%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>12%</td>
<td>55%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>53%</td>
<td>18%</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>28%</td>
<td>28%</td>
<td>61%</td>
<td></td>
</tr>
</tbody>
</table>
HbA1c Mean Over Time

<table>
<thead>
<tr>
<th>Year</th>
<th>Insulin Providing</th>
<th>Insulin Sensitizing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>7.8</td>
<td>7.8</td>
</tr>
<tr>
<td>Year 1</td>
<td>7.3</td>
<td>7.3</td>
</tr>
<tr>
<td>Year 2</td>
<td>7.3</td>
<td>7.4</td>
</tr>
<tr>
<td>Year 3</td>
<td>7.4</td>
<td>7.5</td>
</tr>
<tr>
<td>Year 4</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Year 5</td>
<td>7.2</td>
<td>7.2</td>
</tr>
</tbody>
</table>
Cumulative Rate of First Revascularization

Event Rate vs. Years Since Randomization

- **Prompt Revascularization**
  - 0% at 0 years
  - 3% at 1 year
  - 13% at 2 years
  - 19% at 3 years
  - 28% at 4 years
  - 33% at 5 years
  - 79% at 95% confidence

- **Intensive Medical**
  - 0% at 0 years
  - 3% at 1 year
  - 19% at 2 years
  - 28% at 3 years
  - 33% at 4 years
  - 38% at 5 years
  - 42% at 97% confidence
# Cardiovascular Medication Use

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Three Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Revascularization</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>73%</td>
<td>84%</td>
</tr>
<tr>
<td>ACE / ARB</td>
<td>77%</td>
<td>91%</td>
</tr>
<tr>
<td>Statin</td>
<td>75%</td>
<td>95%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>88%</td>
<td>94%</td>
</tr>
</tbody>
</table>
BARI 2D

PRIMARY

FIVE-YEAR RESULTS
Prompt Revascularization vs Medical Therapy

**All-cause Mortality**
- 88.3% Rev
- 87.8% Med

**Death / MI / Stroke**
- 77.2% Rev
- 75.9% Med

Survival
- 100%
- 90%
- 80%
- 70%
- 60%
- 50%
- 40%
- 30%
- 20%
- 10%
- 0%

Event Free
- 100%
- 90%
- 80%
- 70%
- 60%
- 50%
- 40%
- 30%
- 20%
- 10%
- 0%

Years Since Randomization
- 0
- 1
- 2
- 3
- 4
- 5

p = 0.97

Promt Revascularization
- Red Line

Intensive Medical
- Yellow Line

p = 0.70

Promt Revascularization
- Red Line

Intensive Medical
- Yellow Line
Insulin Sensitization versus Insulin Provision

All-cause Mortality

Survival

Years Since Randomization

Death / MI / Stroke

Event Free

Years Since Randomization

p = 0.89

p = 0.13

88.2% IS

77.7% IS

87.9% IP

75.4% IP

Insulin Sensitization

Insulin Provision

Insulin Sensitization

Insulin Provision
Freedom from Death / MI / Stroke
Among Medical Assigned Patients

PCI Stratum – Medical Patients
78.9%

CABG Stratum – Medical Patients
69.5%

0% 20% 40% 60% 80% 100%
0 1 2 3 4 5

CABG-MED  PCI-MED
PCI Intended Revascularization Stratum (Lower Risk Patients)

All-cause Mortality

- 89.8% Med
- 89.2% Rev

p = 0.48

Years Since Randomization

Death / MI / Stroke

- p = 0.15
- 78.9% Med
- 77.0% Rev

Years Since Randomization
CABG Intended Revascularization Stratum (Higher Risk Patients)

**All-cause Mortality**
- 86.4% Rev
- 83.6% Med
- p = 0.33

**Death / MI / Stroke**
- 77.6% Rev
- 69.5% Med
- p = 0.01
Five-Year Clinical Event Rates
CABG Intended Revascularization Stratum
N=763

** p < 0.01
Major Cardiovascular Events

PCI Intended Stratum

CABG Intended Stratum

p = 0.30

p = 0.021

MED-IS
REV-IS
MED-IP
REV-IP

REV-IS
# Adverse Event Rates by Glycemic Randomized Treatment Assignment

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>IS N=1154</th>
<th>IP N=1156</th>
<th>P-value</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 (CHF)</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>History of CHF *</td>
<td>67.2%</td>
<td>63.5%</td>
<td>0.65</td>
</tr>
<tr>
<td>No history 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>

* N=141 patients had a history of CHF and N=2035 had no history of CHF
BARI 2D

RECAP AND IMPLICATIONS
Five-Year Major Cardiovascular Event Rates Difference by BARI 2D Randomized Treatment Groups

-20 \hspace{1cm} -10 \hspace{1cm} 0 \hspace{1cm} 10 \hspace{1cm} 20

All Patients

PCI Stratum

CABG Stratum

Med Better \hspace{2cm} Rev Better

All Patients

IP Better \hspace{2cm} IS Better

1.3 \hspace{2cm} 95\% CI

-1.9 \hspace{2cm} 99\% CI

8.1 \hspace{2cm} 99\% CI

2.3 \hspace{2cm} 95\% CI
BARI 2D in the Context of Current Clinical Practice

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

Categories of appropriateness criteria:
- Inappropriate
- Uncertain
- Appropriate (but not mandated)

ACCF/SCAI/STS/AATS/AHA/ASNC Circulation 119: 1330-1352, 2009

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.
BARI 2D in the Context of Current Clinical Practice

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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IS</td>
<td>IP</td>
</tr>
<tr>
<td>Metformin</td>
<td>54</td>
<td>75</td>
<td>10</td>
</tr>
<tr>
<td>TZDs</td>
<td>19</td>
<td>62</td>
<td>4</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>53</td>
<td>18</td>
<td>52</td>
</tr>
<tr>
<td>Insulin</td>
<td>28</td>
<td>28</td>
<td>62</td>
</tr>
</tbody>
</table>

*Data courtesy Medco and ADA  
Based on 3,213,000 prescriptions
BARI 2D in the Context of Recent Trials

COURAGE Trial:
- Our PCI results are consistent with the results from COURAGE.
- The majority of participants in COURAGE did not have diabetes.
- COURAGE did not study CABG.
BARI 2D in the Context of 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 HbA1c of < 7.0%.

TZD (Rosiglitazone) Therapy:

BARI 2D assessed therapeutic strategies rather than any specific drug.

No MI/Mortality differences were seen for the IS group in which over 60% were using TZDs, predominately rosiglitazone.

These results are thus consistent with RECORD.
BARI 2D: Cardiology Implications

In patients with both Type 2 diabetes and stable CAD with documented ischemia:

- Those with extensive multi-vessel CAD should be considered for CABG.

- Those with less extensive CAD could be managed safely with intensive medical therapy until revascularization is clinically mandated.
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.
BARI 2D
Diabetes Management Implications

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 was 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.
# 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>Baseline Weight (Kg)</td>
<td>89.6±19.5</td>
<td>89.6±19.8</td>
</tr>
<tr>
<td>3 yr Weight (Kg)</td>
<td>89.9±21.1</td>
<td>91.7±20.7</td>
</tr>
<tr>
<td>Gain (Kg)</td>
<td>0.3±8.6</td>
<td>2.1±7.4</td>
</tr>
<tr>
<td>Baseline Waist Circumference (cm)</td>
<td>108.0±14.4</td>
<td>107.6±13.7</td>
</tr>
<tr>
<td>3 year Waist Circumference (cm)</td>
<td>107.7±15.4</td>
<td>109.1±14.2</td>
</tr>
<tr>
<td>Change (cm)</td>
<td>-0.1±9.1</td>
<td>+1.9±8.4</td>
</tr>
<tr>
<td>1+ Severe Hypoglycemia Episode during trial (%)</td>
<td>5.9</td>
<td>9.2</td>
</tr>
</tbody>
</table>
SUMMARY AND CONCLUSIONS
Summary of BARI 2D Design

What BARI 2D is NOT:
- A test of PCI versus CABG.
- A test of individual diabetes drugs or a test of different HbA1c targets.

What BARI 2D is:
- A comparison of STRATEGIES for myocardial ischemia.
- A comparison of STRATEGIES for glycemic control.
Summary of Treatment Implementation

- Excellent risk factor control
- Randomized treatment strategies effectively implemented for:
  - Prompt revascularization versus delayed/no revascularization
  - Insulin sensitization versus insulin provision
BARI 2D Primary Conclusions

Similar mortality and major cardiovascular event rates, overall for:

- Prompt revascularization versus delayed or no revascularization
- Insulin sensitization versus insulin provision
BARI 2D Primary Conclusions

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.
Final Recommendation from BARI 2D

Therapeutic decisions regarding management of CAD and glycemia in Type 2 diabetes should be made jointly by the patient’s cardiologist, diabetologist and/or primary care physician.
BARI 2D

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).
BARI 2D Sponsors

BARI 2D received major funding from:
  GlaxoSmithKline

BARI 2D received funding from:
  Bristol-Myers Squibb Medical Imaging, Inc.
  Astellas Pharma US, Inc.
  Merck & Co., Inc.
  Abbott Laboratories, Inc.
  Pfizer, Inc.

BARI 2D received medications and supplies from:
  Abbott Laboratories Ltd., MediSense Products
  Bayer Diagnostics
  Becton, Dickinson and Company
  J. R. Carlson Laboratories, Inc.
  Centocor, Inc.
  Eli Lilly and Company
  LipoScience, Inc.
  Merck Sante
  Novartis Pharmaceuticals Corporation
  Novo Nordisk, Inc.
# BARI 2D

## Coordinating Center:

Epidemiology Data Center at the University of Pittsburgh, Graduate School of Public Health

## Core Laboratories:

<table>
<thead>
<tr>
<th>Angiographic</th>
<th>Stanford University</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemistry/Genetics</td>
<td>University of Minnesota</td>
</tr>
<tr>
<td>ECG</td>
<td>St. Louis University</td>
</tr>
<tr>
<td>Economics</td>
<td>Stanford University</td>
</tr>
<tr>
<td>Fibrinolysis</td>
<td>University of Vermont</td>
</tr>
<tr>
<td>Nuclear</td>
<td>Univ. of Alabama, Birmingham</td>
</tr>
</tbody>
</table>
BARI 2D Sites

**University of Sao Paulo Heart Institute
**Toronto General Hospital/University Health Network
**Texas Health Science @ San Antonio/South Texas
*Mayo Clinic-Rochester
*Mexican Institute of Social Security
*University Hospitals of Cleveland/CASE Medical School
*Memphis VA Medical Center/University of Tennessee
*Montreal Heart Institute/Hotel-Dieu-CHUM
*Albert Einstein College of Medicine/Montefiore
*Fuqua Heart Center/Piedmont Hospital
*University of Alabama @ Birmingham
*Northwestern University Medical Center
*Na Homolce Hospital
*Ottawa Heart Institute/Ottawa Hospital-Riverside Campus
*New York Medical College/Westchester Medical Center
*Emory University
*Washington Hospital Center /Georgetown University
*Quebec Heart Institute/Laval Hospital
*University of British Columbia/Vancouver Hospital
NYU School of Medicine
Lahey Clinic Medical Center
University of Virginia
University of Minnesota
StLuke's/Roosevelt Hospital Center
University of Florida

StLouis University
University of Texas @ Houston
Kaiser-Permanente Medical Center
Henry Ford Heart & Vascular Institute
Boston Medical Center
Fletcher Allen Health Care
Jim Moran Heart & Vascular Institute
Baylor College of Medicine
Duke University
University of Maryland Hospital
University of Chicago Medical Center
University of Pittsburgh Medical Center
Washington University/Barnes Jewish Hospital
Mount Sinai Medical Center
Mid America Heart Institute
University of Michigan
Johns Hopkins Bayview Medical Center
Brown University/Rhode Island Hospital
Houston VA Medical Center
New York Hospital Queens
Wilhelminen Hospital
St Joseph Mercy Hospital/Michigan Heart PC
Ohio State University Medical Center
Mayo Clinic-Scottsdale

** ≥ 100 participants
* ≥ 50 and < 100 participants
North America - 1937 participants (USA: 1499 participants, Canada: 353 participants, Mexico: 85 participants)
South America - 356 participants (Brazil: 356)
Europe - 75 participants (Czech Republic: 65, Austria: 10)