Coronary Revascularization in Diabetic Patients

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Disclosure

Consulting: Many pharmaceutical companies

Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor tax deduction is received.
Not surprisingly, diabetics have worse outcomes with coronary artery disease.
Long Term Mortality after MI in Diabetics

Overall Log-rank P<0.001

Cumulative mortality (%)

Years

Diabetic
Non-Diabetic

Diabetes Care 35:2043–2047, 2012
CABG and Diabetes: 30 Day Outcomes

Society of Thoracic Surgeons Database - 1997

Diabetes-Insulin (n=105,123)
Diabetes Oral (n=25,003)
No Diabetes (n=16,660)

Mortality: 4.6%, 3.2%, 2.7%
Stroke: 2.4%, 2.3%, 1.4%
Renal Failure: 7.1%, 4.3%, 2.9%
Infection: 9.4%, 6.9%, 5.2%
Sepsis: 1.9%, 1.1%, 0.9%

Diabetes in the Early Interventional (PTCA) Era: Rates of Angiographic Restenosis in the 1990’s

Diabetes

No Diabetes

Carrozza (n=220)

Diabetes: 55.0%

No Diabetes: 20.0%

Elezi (n=3554)

Diabetes: 37.5%

No Diabetes: 28.3%

p <0.001

p = 0.001


5 Year Mortality: Diabetes vs. No Diabetes

3220 Patients (1984-1990) Suitable for CABG or PTCA

Adjusted $c^2$ for Diabetes = 43.6, $p <0.0001$

Despite Technical Advances, Diabetics Continue to Have Worse Outcomes for both CABG and Contemporary Stenting
Long-Term Outcomes of Older Diabetic Patients After Percutaneous Coronary Stenting in the United States

A Report From the National Cardiovascular Data Registry, 2004 to 2008

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Hitinder S. Gurm, MD,§ J. Matthew Brennan, MD,† Kevin J. Anstrom, PhD,† David Dai, PhD,†
Eric L. Eisenstein, DBA,† Eric D. Peterson, MD, MPH,† John C. Messenger, MD,∥
Pamela S. Douglas, MD†

Alabaster and Birmingham, Alabama; Durham, North Carolina; Chicago, Illinois; Ann Arbor, Michigan; and Aurora, Colorado

Objectives
The purpose of this study was to characterize long-term outcomes of percutaneous coronary intervention (PCI) in elderly diabetic patients in routine practice.

Background
Although drug-eluting stent (DES) implantation in diabetic patients is common practice, pivotal randomized trials enrolled <2,500 diabetic patients, most of whom were <65 years of age.

Methods
Data from 405,679 patients ≥65 years old (33% had diabetes mellitus, of whom 9.8% had insulin-treated diabetes mellitus [ITDM], and 23.3% had noninsulin-treated diabetes mellitus [NITDM]) undergoing PCI from 2004 to 2008 at 946 U.S. hospitals were linked with Medicare inpatient claims data.

Results
Over 18.4 months median follow-up (25th to 75th percentile: 8.0 to 30.8 months), ITDM/NITDM were associated with significantly increased adjusted hazards of death (hazard ratio [HR]: 1.91 [95% confidence interval (CI):}
Diabetes vs. No Diabetes by Stent Type and Insulin
Given the Worse Outcomes with Revascularization in Diabetic Patients, What Approach is Best: CABG or PCI?
The New England Journal of Medicine

VOLUME 335  JULY 25, 1996  NUMBER 4

COMPARISON OF CORONARY BYPASS SURGERY WITH ANGIOPLASTY IN PATIENTS WITH MULTIVESSEL DISEASE

THE BYPASS ANGIOPLASTY REVASCULARIZATION INVESTIGATION (BARI) INVESTIGATORS*

Hints from the BARI 2D Trial

ABSTRACT

Background  Coronary-artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) are alternative methods of revascularization in patients with coronary artery disease. We tested the hypothesis that in selected patients with multivessel disease suitable for treatment with either procedure, an initial strategy of PTCA does not result

CORONARY-artery bypass grafting (CABG), introduced in 1968,1 results in longer survival and a better quality of life in specific subgroups of patients with multivessel coronary artery disease than does an initial strategy of medical therapy.2-6 Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) in 1977, the use of this less invasive procedure for...
BARI Study Features (Enrolled 1988-91)

• NIH sponsored randomized controlled trial (n=1829) comparing balloon angioplasty with CABG.

• Subgroup of 353 patients (19%) with treated diabetes (insulin or oral agents)

• Patients followed for an average of 5.4 years for repeat revascularization and survival.

• Study performed at 18 centers in US and Canada, results reported in 1996
Survival PCI vs. CABG: Diabetics vs. Non-diabetics

- Non-Diabetics: 80.6%
- Diabetes PCI: 65.5%
- Diabetes CABG: 80.6%

Patients with treated diabetes, $P = 0.003$
All other patients, $P = 0.73$
BARI: Time to Repeat Revascularization

All 1829 randomized patients

PTCA group: 54%
CABG group: 8%

P < 0.001

Years after Randomization

First Subsequent Revascularization (%)
Criticisms of BARI from Interventional Cardiologists

- Interventions consisted of only balloon angioplasty, not more contemporary revascularization approaches such as stenting.
- Not specifically designed to study diabetics. The results in patients with diabetes represented a non-prespecified subgroup.
- A new trial need in the contemporary stent era comparing PCI vs. CABG
Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease

Patrick W. Serruys, M.D., Ph.D., Marie-Claude Morice, M.D., A. Pieter Kappetein, M.D., Ph.D., Antonio Colombo, M.D., David R. Holmes, M.D., Michael J. Mack, M.D., Elisabeth Ståhle, M.D., Ted E. Feldman, M.D., Marcel van den Brand, M.D., Eric J. Bass, B.A., Nic Van Dyck, R.N., Katrin Leadley, M.D., Keith D. Dawkins, M.D., and Friedrich W. Mohr, M.D., Ph.D., for the SYNTAX Investigators*

ABSTRACT

BACKGROUND

Percutaneous coronary intervention (PCI) involving drug-eluting stents is increasingly used to treat complex coronary artery disease, although coronary-artery bypass grafting (CABG) has been the treatment of choice historically. Our trial compared...
Syntax Primary Composite Endpoint: All Patients

Death, Stroke, MI or Coronary Revascularization

**P = 0.002**

![Graph showing cumulative rate (%) over months since randomization for CABG and PCI.](image-url)
## Syntax: Outcomes in Diabetics and Non Diabetics

<table>
<thead>
<tr>
<th></th>
<th>Non-Diabetics (n=1348)</th>
<th>Diabetics (n=452)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CABG (676)</td>
<td>PCI (672)</td>
<td>P value</td>
<td>HR and 95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, MI, stroke, or revascularization</td>
<td>26.3%</td>
<td>34.1%</td>
<td>0.002</td>
<td>1.37 (1.13,1.68)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>4.9%</td>
<td>7.7%</td>
<td>0.035</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat revascularization</td>
<td>13.4%</td>
<td>22.8%</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CABG (221)</td>
<td>PCI (231)</td>
<td>P value</td>
<td>HR and 95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, MI, stroke, or revascularization</td>
<td>29.0%</td>
<td>46.5%</td>
<td>0.001</td>
<td>1.81 (1.31,2.48)</td>
<td></td>
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<tr>
<td>Cardiac Death</td>
<td>6.5%</td>
<td>12.7%</td>
<td>0.034</td>
<td></td>
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<tr>
<td>Repeat revascularization</td>
<td>14.6%</td>
<td>35.3%</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Criticisms of Syntax from Interventional Cardiologists

- Not specifically designed to study diabetics.
- The results in patients with diabetes represented a non-prespecified subgroup.
- Suggestion: More trials needed.
A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease

The BARI 2D Study Group*

ABSTRACT

BACKGROUND
Optimal treatment for patients with both type 2 diabetes mellitus and stable ischemic heart disease has not been established.

METHODS
We randomly assigned 2368 patients with both type 2 diabetes and heart disease to undergo either prompt revascularization with intensive medical therapy or intensive medical therapy alone.
PCI: Revascularization vs. Medical Therapy

P = 0.15
CABG: Revascularization vs. Medical Therapy

Event-free Survival (%) vs. Years since Randomization

- Revascularization: 77.6%
- Medical therapy: 69.5%

P = 0.01
Criticisms of BARI-2D from Interventionalists

• Although specifically designed to study diabetics, PCI and CABG compared with medical therapy, not with each other.

• Study was not designed to directly compare PCI and CABG.
Randomized Comparison of Percutaneous Coronary Intervention With Coronary Artery Bypass Grafting in Diabetic Patients
1-Year Results of the CARDia (Coronary Artery Revascularization in Diabetes) Trial

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Ayesha C. Qureshi, MBBS,* Jeremy Butts, MBBS,† Mark de Belder, MD,§ Andreas Baumbach, MS,||
Gianni Angelini, MD, MCh,‖ Adam de Belder, MBBS, MD,¶ Keith G. Oldroyd, MBChB, MD,#
Marcus Flather, MBBS,†** Michael Roughton, MSc,** Petros Nihoyannopoulos, MD,†
Jens Peder Bagger, MBBS, DSc,† Kenneth Morgan, MBChB, BSc,† Kevin J. Beatt, MBBS, PhD‡‡
London, Norwich, Middlesbrough, Bristol, and Brighton, England; and Glasgow, Scotland

Objectives
The purpose of this study was to compare the safety and efficacy of percutaneous coronary intervention (PCI) with stenting against coronary artery bypass grafting (CABG) in patients with diabetes and symptomatic multivessel coronary artery disease.

Background
CABG is the established method of revascularization in patients with diabetes and multivessel coronary disease, but with advances in PCI, there is uncertainty whether CABG remains the preferred method of revascularization.

Methods
The primary outcome was a composite of all-cause mortality, myocardial infarction (MI), and stroke, and the main secondary outcome included the addition of repeat revascularization to the primary outcome events. A total of 510 diabetic patients with multivessel or complex single-vessel coronary disease from 24 centers were...
CARDia: Study Design Features

• 510 patients at 24 centers in the UK with diabetes and significant CAD suitable for either PCI or CABG

• Stable angina or non-ST elevation MI or ACS

• Primary outcome: Composite of death, non-fatal myocardial infarction, non-fatal stroke.

• Enrolled beginning in 2002, median follow up 5.1 years with final visit in 2012

• Median of 3.6 stents, 69% drug eluting
<table>
<thead>
<tr>
<th></th>
<th>CABG</th>
<th>PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.6</td>
<td>64.3</td>
</tr>
<tr>
<td>Male</td>
<td>77.9%</td>
<td>70.7%</td>
</tr>
<tr>
<td>Years with diabetes</td>
<td>10.4</td>
<td>10.1</td>
</tr>
<tr>
<td>Type 1</td>
<td>5.3%</td>
<td>2.8%</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.9%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Ethnicity White</td>
<td>72.4%</td>
<td>67.1%</td>
</tr>
<tr>
<td>South Asian</td>
<td>20.1%</td>
<td>25.9%</td>
</tr>
<tr>
<td>3 vessel disease</td>
<td>58.7%</td>
<td>64.8%</td>
</tr>
</tbody>
</table>
CARDia: Primary Endpoint (Death, Stroke, MI)

- CABG: 10.5%
- PCI: 13.0%

HR for CABG = 1.25 (0.75-2.09)

P = 0.39

Upper CI < 1.3 required for non-inferiority
CARDIA Results: PCI vs. CABG in Diabetics

Primary non-inferiority analysis for composite outcome

Death, MI, Stroke
CABG 20.5% vs PCI 26.6%
+5.9% (-2 to +13%)

Non-Inferiority margin=12%*

Percent difference

PCI better

CABG better

Difference and 95% Confidence Interval in percent
Primary Endpoint Plus Repeat Revascularisation

Death, Non-Fatal MI, Non-Fatal Stroke, Revascularisation

HR for CABG 1.77
P=0.02

Number at risk
CABG 248
PCI 254
214 201
207 189
191 167
181 159
159 124
36 26
<table>
<thead>
<tr>
<th>Event</th>
<th>CABG (248)</th>
<th>PCI (254)</th>
<th>p value</th>
<th>HR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, stroke</td>
<td>20.5%</td>
<td>26.6%</td>
<td>0.11</td>
<td>1.34 (0.94, 1.93)</td>
</tr>
<tr>
<td>Death</td>
<td>12.6%</td>
<td>14%</td>
<td>0.53</td>
<td>1.17 (0.73, 1.87)</td>
</tr>
<tr>
<td>Non fatal MI</td>
<td>6.3%</td>
<td>14%</td>
<td>0.007</td>
<td>2.26 (1.25, 4.08)</td>
</tr>
<tr>
<td>Non fatal stroke</td>
<td>4.3%</td>
<td>3.1%</td>
<td>0.48</td>
<td>0.72 (0.29, 1.79)</td>
</tr>
<tr>
<td>Repeat revascularisation</td>
<td>8.3%</td>
<td>21.9%</td>
<td>&lt;0.001</td>
<td>2.87 (1.74, 4.74)</td>
</tr>
<tr>
<td>Death, MI, stroke, repeat revascularisation</td>
<td>26%</td>
<td>37.5%</td>
<td>0.005</td>
<td>1.56 (1.14, 2.14)</td>
</tr>
</tbody>
</table>
CARDia Conclusions

• Primary outcome does not demonstrate non-inferiority of PCI compared to CABG

• Higher rates of MI and repeat revascularisation in PCI group

• No clear evidence to support routine PCI in patients with diabetes and multivessel disease

• CABG remains the preferred method of revascularisation unless there are clinical features that make PCI clearly preferable.
FREEDOM Trial
Strategies for Multivessel Revascularization in Patients with Diabetes

Michael E. Farkouh, M.D., Michael Domanski, M.D., Lynn A. Sleeper, Sc.D., Flora S. Siami, M.P.H.,
George Dangas, M.D., Ph.D., Michael Mack, M.D., May Yang, M.P.H., David J. Cohen, M.D.,
Yves Rosenberg, M.D., M.P.H., Scott D. Solomon, M.D., Akshay S. Desai, M.D., M.P.H.,
Bernard J. Gersh, M.B., Ch.B., D.Phil., Elizabeth A. Magnuson, Sc.D., Alexandra Lansky, M.D.,
Robin Boineau, M.D., Jesse Weinberger, M.D., Krishnan Ramanathan, M.B., Ch.B., J. Eduardo Sousa, M.D., Ph.D.,
Jamie Rankin, M.D., Balram Bhargava, M.D., John Buse, M.D., Whady Hueb, M.D., Ph.D., Craig R. Smith, M.D.,
Victoria Muratov, M.D., M.P.H., Sameer Bansilal, M.D., Spencer King III, M.D., Michel Bertrand, M.D.,
and Valentin Fuster, M.D., Ph.D., for the FREEDOM Trial Investigators*

ABSTRACT

BACKGROUND
Freedom Study Design

Eligibility: DM patients with multivessel CAD eligible for either stent or surgery

Randomized 1:1

Drug-eluting stent  CABG

All concomitant medications known to be beneficial encouraged, including: clopidogrel, ACE Inhibitors or ARBs, β-blockers, statins
FREEDOM Trial Design

- Superiority trial of 7 years (median 3.8 years) in 1900 patients (953 drug eluting stent vs. 947 CABG)

- Primary outcomes: Composite of all-cause mortality, non-fatal MI or non-fatal stroke

- Secondary outcomes: Death, MI, stroke, repeat revascularization at 1 year. Survival at 1, 2, and 3 years. Components at 30 days post-procedure.

- Original power based target N=2400, power = 85% to detect at least an 18% reduction in 4-year rates ranging from 30-38 %, $\alpha = .05$
Diabetes and Medical Management

• Target Hemoglobin A1C: < 7.0%. Therapy prescribed by diabetologist

• Aggressive, evidence-based medical management:
  – Target LDL-C: < 70 mg/dL
  – Target BP: < 130/80 mm Hg
<table>
<thead>
<tr>
<th></th>
<th>Stent</th>
<th>CABG</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>953</td>
<td>947</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>63.2</td>
<td>63.1</td>
<td>0.78</td>
</tr>
<tr>
<td>Male</td>
<td>73%</td>
<td>70%</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI</td>
<td>29.7</td>
<td>29.8</td>
<td>0.08</td>
</tr>
<tr>
<td>Duration of Diabetes (years)</td>
<td>10.1</td>
<td>10.3</td>
<td>0.49</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.8</td>
<td>7.8</td>
<td>0.86</td>
</tr>
<tr>
<td>Prior MI</td>
<td>26%</td>
<td>25%</td>
<td>0.56</td>
</tr>
</tbody>
</table>
FREEDOM Primary Endpoint: Death, Stroke or MI

- Stent
- CABG

Logrank $P = 0.005$

Death, MI or Stroke (%)

Years Post Randomization

26.6%
18.7%
Post-Procedural Myocardial Infarction

Myocardial infarction Incidence (%)

Years Post Randomization

Logrank P < 0.0001

- Stent
- CABG

13.9%

6.0%
FREEDOM: All Cause Mortality

Mortality Rate (%)

Logrank $p = 0.049$

5 Year Event Rates: 16.3% vs. 10.9%
FREEDOM: Incidence of Post-Procedural Stroke

**Severely Disabling**

<table>
<thead>
<tr>
<th>Scale</th>
<th>CABG</th>
<th>PCI/DES</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH &gt; 4</td>
<td>55%</td>
<td>27%</td>
</tr>
<tr>
<td>Rankin &gt; 1</td>
<td>70%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Logrank p = 0.034

Stroke Rate (%)

Years Post Randomization
FREEDOM: Need for Repeat Revascularization

Revascularization Rate (%) vs Years Post Randomization

- PCI/DES
- CABG

Logrank p < 0.0001

13.0% at 12 years
5.0% at 12 years

Years Post Randomization
Expanded MACE (Adds Repeat Revascularization)

Logrank p = 0.004
Mortality in Type 1 Diabetics: PCI vs. CABG

Swedish Registry
1195 deaths
Unadjusted HR = 1.86 (1.64-2.11)
Adjusted HR = 1.14 (0.99-1.32)

J Am Coll Cardiol 2017;70:1441–51
Summary and Conclusions

• Outcomes for patients with ischemic heart disease diabetes less favorable than non-diabetics for both PCI and CABG.

• CABG results in significantly better outcomes compared with PCI in diabetics with multivessel CAD, although stroke was slightly increased.

• Improvements in stent technology have not eliminated the advantage of CABG.

• CABG surgery is the preferred method of revascularization for patients with diabetes and multi-vessel CAD.
Diabetes vs. No Diabetes by Stent Type and Insulin

Myocardial Infarction

Mortality

Days from Procedure

- DES (No DM)
- DES (No insulin)
- DES (insulin)
- BMS (No DM)
- BMS (No insulin)
- BMS (insulin)
Diabetes vs. No Diabetes by Stent Type

Myocardial Infarction

Days from procedure

Any MI

No DM DES — NITDM DES — ITDM DES
No DM BMS — NITDM BMS — ITDM BMS
NCDR Registry: Risk of Adverse Outcomes in Older Diabetics (n=405,679)
An Invasive or Conservative Strategy in Patients With Diabetes Mellitus and Non-ST-Segment Elevation Acute Coronary Syndromes

A Collaborative Meta-Analysis of Randomized Trials

Michelle L. O’Donoghue, MD, MPH,* Ajay Vaidya, MD, MPH,† Rizwan Afsal, MSc,‡ Joakim Alfredsson, MD, PhD,§ William E. Boden, MD,∥ Eugene Braunwald, MD,* Christopher P. Cannon, MD,* Tim C. Clayton, MSc,¶ Robbert J. de Winter, MD, PhD,# Keith A. A. Fox, MB ChB,** Bo Lagerqvist, MD, PhD,†† Peter A. McCullough, MD, MPH,‡‡ Sabina A. Murphy, MPH,* Rudolf Spacek, MD, PhD, §§ Eva Swahn, MD, PhD,§ Fons Windhausen, MD,# Marc S. Sabatine, MD, MPH*

Boston, Massachusetts; San Francisco, California; Hamilton, Ontario, Canada; Linköping and Uppsala, Sweden; Albany, New York; London and Edinburgh, United Kingdom; Amsterdam, the Netherlands; Novi, Michigan; and Prague, Czech Republic

Objectives

The purpose of this study was to conduct a meta-analysis to examine an invasive or conservative strategy in diabetic versus nondiabetic patients.

Background

Diabetic patients are at increased risk of cardiovascular events after an acute coronary syndrome, yet it remains…
Early Invasive Strategies Superior after MI

Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI IIIB</td>
<td>0.99 (0.65-1.52)</td>
</tr>
<tr>
<td>MATE</td>
<td>1.33 (0.62-2.87)</td>
</tr>
<tr>
<td>VANQWISH</td>
<td>0.96 (0.71-1.30)</td>
</tr>
<tr>
<td>FRISC II</td>
<td>0.65 (0.46-0.91)</td>
</tr>
<tr>
<td>TACTICS-TIMI 18</td>
<td>0.77 (0.58-1.01)</td>
</tr>
<tr>
<td>RITA 3</td>
<td>0.76 (0.49-1.20)</td>
</tr>
<tr>
<td>VINO</td>
<td>0.33 (0.08-1.45)</td>
</tr>
<tr>
<td>ICTUS</td>
<td>1.09 (0.69-1.74)</td>
</tr>
<tr>
<td>OASIS 5 Substudy</td>
<td>1.62 (0.71-3.71)</td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td><strong>0.87 (0.73-1.03)</strong></td>
</tr>
</tbody>
</table>

Death, MI or Rehospitalization with ACS

J Am Coll Cardiol
2012;60:106–11
Diabetics Have Worse Outcomes after CABG or Balloon Angioplasty

Evidence emerged in the 1980’s and 90’s early after development of revascularization techniques
CABG Management

• The use of an internal mammary artery (IMA) to the left anterior descending (LAD) was strongly recommended in all patients

• The surgical approach - conventional CABG with cardio-pulmonary bypass and cardioplegic arrest or off-pump CABG with beating heart - was left to the individual surgeon’s judgement
Interventional Stent Procedure

• Prior to PCI: Clinical suitability of each lesion – left main was an absolute exclusion

• Certified operator - PCI within 14 days of randomization

• Drug eluting stent for all lesions

• ASA 325 mg + Clopidogrel, unfractionated heparin or bivalirudin, abciximab at initial PCI.

• ASA 81-100 mg + Clopidogrel. 75 mg/day for 1-year
Diabetes and PCI: Modern Stents

Outcome Drug Eluting Stents: Zotarolimus Global Program

![Graph showing cumulative incidence of cardiac death/TVMI over time for different patient groups.]
FREEDOM Trial Main Results

AHA 2012
November 4, 2012
Los Angeles, CA

Valentin Fuster, MD PhD

Supported by NHLBI U01 grant #01HLO71988
This work is solely the responsibility of the authors
Revascularization in Diabetes

BARI 2D Substudy

Framingham RS: AHJ 139-272, 2000

Framingham RS: AHJ 139-272, 2000

Brooks M., et al, Circulation;126:2115-2124

SGE; 1012-2, 51
**Freedom Design**

**Eligibility:** DM patients with MV-CAD eligible for stent or surgery

**Exclude:** Patients with acute STEMI

Randomized 1:1

MV-Stenting with Drug-eluting stent

CABG with or without CPB

*All concomitant Meds shown to be beneficial were encouraged, including: Clopidogrel, ACE Inhibitors, ARBs, β-blockers, Statins*
FREEDOM Trial Design

- **Design:** superiority trial of 7 years (minimum 2 yrs, median 3.8 yrs)
- **Sample size:** N=1900 (953 PCI / DES vs. 947 CABG; 131 ctrs)
- **Primary Outcomes:** composite of earliest occurring of:
  - All cause mortality, non-fatal MI and non-fatal stroke
- **Secondary outcomes:**
  - MACCE (Death, MI, Stroke, Repeat Revasc.) at 1 Year Survival at 1, 2, and 3 Years
  - MACCE components at 30 Days Post-Procedure
  - Cost-Effectiveness
  - Quality of Life at 30 Days, 6 Months, 1, 2 & 3 Years
- **Original Power:** Target N=2400, Power ≥ 85% to detect at least an 18% reduction from 4-year rates ranging from 30-38 %, $\alpha = .05$
FREEDOM Inclusion Criteria

- **Diabetes Mellitus (Type 1 or Type 2):** according to the American Diabetes Association.

- **Angiographically:** confirmed multivessel CAD, with severe (≥ 70%) lesions in at least two major epicardial vessels.

- **Indication for revascularization:** based upon symptoms of angina and/or objective evidence of myocardial ischemia.
Diabetes and Medical Management

- Target Hemoglobin A1C: < 7.0%
  - Therapy prescribed by MD / Diabetologist
  - Recommended ACCORD Protocol
- Target LDL-C: < 70 mg/dL
- Target BP: < 130/80 mm Hg
CABG Management

- The use of an internal mammary artery (IMA) to the left anterior descending (LAD) was strongly recommended in all patients.

- The surgical approach - conventional CABG with cardiopulmonary bypass and cardioplegic arrest or off-pump CABG with beating heart - was left to the individual surgeon’s judgement.
Interventional – Pre-Stent Process

• **Prior to PCI:** Clinical suitability of each lesion
  - *left main was an absolute exclusion -
  Certified operator
  PCI within 14 days of randomization

• **DES:** For all lesions
  Only one type for any given FREEDOM patient

• **Antithr:** Oral ASA 325 mg + Clopid. ≥ 300 mg load, Unfractionated Heparin or Bivalirudin, Abciximab on the initial PCI
  ASA 81-100 mg + Clopid. 75 mg/day 1-yr
Myocardial Infarction Definition

Within 30 days of the revascularization procedure:

– New Q waves: in at least 2 or more contiguous leads and CK elevation >2x normal or with elevation of CK-MB

After the first 30 days, presence of the following:

– Troponin: typical rise and gradual fall of or
– CK-MB: more rapid rise and fall of to detect necrosis with
– At least one of the following:
  – Symptoms: Ischemic or atypical symptoms of ischemia;
  – Q waves: pathological development on the ECG;
  – Ischemia (STE or STD): ECG changes, indicative
  – Coronary artery intervention: e.g., coronary PCI
  – Pathologic findings: acute MI
Stroke Definition

• A definitive evaluation for stroke was conducted in both treatment arms at baseline, 30 days and 12 months after the assigned treatment.

• A focal neurological deficit of central origin lasting >72 hours.
32,966 Patients were screened for eligibility

3,309 were eligible (10%)

1,409 did not consent

953 Randomized to PCI/DES*
- 5 underwent CABG
- 3 withdrew prior to procedure
- 3 died prior to procedure
- 3 underwent neither PCI/DES or CABG
- 16 withdrew post-procedure
- 43 were lost to follow-up

1,900 consented (57%)

947 Randomized to CABG
- 18 underwent PCI/DES
- 26 withdrew prior to procedure
- 3 died prior to procedure
- 7 underwent neither PCI/DES or CABG
- 36 withdrew post-procedure
- 51 were lost to follow-up

953 and 947 included ITT analysis using all available follow-up time post-randomization
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PCI/DES</th>
<th>CABG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>953</td>
<td>947</td>
<td></td>
</tr>
<tr>
<td>Age at randomization – yr</td>
<td>63.2 ± 8.9</td>
<td>63.1 ± 9.2</td>
<td>0.78</td>
</tr>
<tr>
<td>Male sex</td>
<td>73%</td>
<td>70%</td>
<td>0.08</td>
</tr>
<tr>
<td>Body mass index – gm/m²</td>
<td>29.7 ± 5.4</td>
<td>29.8 ± 5.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Duration of diabetes – yrs</td>
<td>10.1 ± 8.9</td>
<td>10.31 ± 9.0</td>
<td>0.49</td>
</tr>
<tr>
<td>Hemoglobin A1c - %</td>
<td>7.8 ± 1.7</td>
<td>7.8 ± 1.7</td>
<td>0.86</td>
</tr>
<tr>
<td>Current smoker</td>
<td>15%</td>
<td>17%</td>
<td>0.31</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>26%</td>
<td>25%</td>
<td>0.56</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>4%</td>
<td>3%</td>
<td>0.31</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>85%</td>
<td>85%</td>
<td>0.75</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>26%</td>
<td>28%</td>
<td>0.25</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>84%</td>
<td>83%</td>
<td>0.66</td>
</tr>
</tbody>
</table>
### Baseline Characteristics By Treatment Assignment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PCI/DES</th>
<th>CABG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL cholesterol – mg/dL</td>
<td>38.9 ± 10.9</td>
<td>39.4 ± 11.4</td>
<td>0.34</td>
</tr>
<tr>
<td>Angina</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>68%</td>
<td>71%</td>
<td>0.25</td>
</tr>
<tr>
<td>Unstable</td>
<td>32%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>LV Ejection Fraction (&lt; 30%)</td>
<td>0.8%</td>
<td>0.3%</td>
<td>0.28</td>
</tr>
<tr>
<td>LV Ejection Fraction (&lt; 40%)</td>
<td>3%</td>
<td>2%</td>
<td>0.07</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>27 ± 2.4</td>
<td>2.8 ± 2.5</td>
<td>0.52</td>
</tr>
<tr>
<td>[Median (IQR)]</td>
<td>[1.9 (1.3, 3.1)]</td>
<td>[2.0(1.3, 3.3)]</td>
<td></td>
</tr>
<tr>
<td>SYNTAX score</td>
<td>26.2 ± 8.4</td>
<td>26.1 ± 8.8</td>
<td>0.77</td>
</tr>
<tr>
<td>No. of lesions</td>
<td>5.7 ± 2.2</td>
<td>5.7 ± 2.2</td>
<td>0.33</td>
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<tr>
<td>Chronic total occlusion</td>
<td>6%</td>
<td>6%</td>
<td>0.99</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>22%</td>
<td>21%</td>
<td>0.06</td>
</tr>
</tbody>
</table>
# Cardiac Medications By Treatment Assignment

<table>
<thead>
<tr>
<th>Medications</th>
<th>Baseline</th>
<th>Discharge</th>
<th>1 yr</th>
<th>2 yrs</th>
<th>5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>1900</td>
<td>1867</td>
<td>1651</td>
<td>1483</td>
<td>410</td>
</tr>
<tr>
<td><strong>Aspirin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI/DES</td>
<td>91%</td>
<td>99%</td>
<td>97%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>CABG</td>
<td>90%</td>
<td>88%</td>
<td>94%</td>
<td>95%</td>
<td>93%</td>
</tr>
<tr>
<td><strong>Thienopyridine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI/DES</td>
<td>28%</td>
<td>98%</td>
<td>89%</td>
<td>59%</td>
<td>42%</td>
</tr>
<tr>
<td>CABG</td>
<td>22%</td>
<td>25%</td>
<td>63%</td>
<td>23%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>Statin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI/DES</td>
<td>82%</td>
<td>88%</td>
<td>90%</td>
<td>91%</td>
<td>89%</td>
</tr>
<tr>
<td>CABG</td>
<td>83%</td>
<td>89%</td>
<td>89%</td>
<td>90%</td>
<td>91%</td>
</tr>
</tbody>
</table>

SGE; 1112-3, 13
## Cardiac Medications By Treatment Assignment

<table>
<thead>
<tr>
<th>Medications</th>
<th>Baseline</th>
<th>Discharge</th>
<th>1 yr</th>
<th>2 yrs</th>
<th>5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta blocker</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PCI/DES</td>
<td>76%</td>
<td>84%</td>
<td>82%</td>
<td>83%</td>
<td>80%</td>
</tr>
<tr>
<td>CABG</td>
<td>75%</td>
<td>83%</td>
<td>82%</td>
<td>83%</td>
<td>79%</td>
</tr>
<tr>
<td><strong>ACE inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI/DES</td>
<td>64%</td>
<td>74%</td>
<td>72%</td>
<td>67%</td>
<td>64%</td>
</tr>
<tr>
<td>CABG</td>
<td>64%</td>
<td>68%</td>
<td>70%</td>
<td>67%</td>
<td>64%</td>
</tr>
<tr>
<td><strong>ARB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI/DES</td>
<td>16%</td>
<td>22%</td>
<td>26%</td>
<td>32%</td>
<td>37%</td>
</tr>
<tr>
<td>CABG</td>
<td>16%</td>
<td>16%</td>
<td>25%</td>
<td>29%</td>
<td>32%</td>
</tr>
</tbody>
</table>
Primary Outcome – Death / Stroke / MI

Death / Stroke / MI, (%)

Logrank p=0.005

5 Year Event Rates: 26.6% vs. 18.7%

Years Post Randomization

PCI/DES N=953 848 788 625 416 219 40
CABG N=943 814 758 613 422 221 44

SGE; 1112-3, 15
Myocardial Infarction

Myocardial Infarction, (%)

Logrank p < 0.0001

PCI/DES
CABG

Years Post Randomization

PCI/DES  N=953  853  798  636  422  220
CABG    N=947  824  772  629  432  229

SGE; 1112-3, 16
All-Cause Mortality

![Graph showing All-Cause Mortality over 5 years post randomization for PCI/DES and CABG.]

**Logrank p = 0.049**

5 Year Event Rates: 16.3% vs. 10.9%

<table>
<thead>
<tr>
<th>Years Post Randomization</th>
<th>PCI/DES N=953</th>
<th>CABG N=947</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>897</td>
<td>855</td>
</tr>
<tr>
<td>1</td>
<td>845</td>
<td>806</td>
</tr>
<tr>
<td>2</td>
<td>685</td>
<td>655</td>
</tr>
<tr>
<td>3</td>
<td>466</td>
<td>449</td>
</tr>
<tr>
<td>4</td>
<td>243</td>
<td>238</td>
</tr>
</tbody>
</table>

SGE; 1112-3, 17
Stroke

**Logrank p = 0.034**

<table>
<thead>
<tr>
<th>Years Post Randomization</th>
<th>PCI/DES</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>N=953</td>
<td>891</td>
</tr>
<tr>
<td>1</td>
<td>833</td>
<td>791</td>
</tr>
<tr>
<td>2</td>
<td>673</td>
<td>640</td>
</tr>
<tr>
<td>3</td>
<td>460</td>
<td>439</td>
</tr>
<tr>
<td>4</td>
<td>241</td>
<td></td>
</tr>
</tbody>
</table>

**Severely Disabling**

<table>
<thead>
<tr>
<th>Scale</th>
<th>CABG</th>
<th>PCI/DES</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH &gt; 4</td>
<td>55%</td>
<td>27%</td>
</tr>
<tr>
<td>Rankin &gt; 1</td>
<td>70%</td>
<td>60%</td>
</tr>
</tbody>
</table>

PCI/DES vs. CABG - SGE; 1112-3, 18
Repeat Revascularization

PCI/DES vs. CABG

Logrank p < 0.0001

PCI/DES N=944
CABG N=911

SGE; 1112-3, 19
MACCE
(Death, Stroke, MI, Repeat Revascularization)

Log rank $p=0.004$

PCI/DES
N=944
873
842
803
773

CABG
N=911
825
805
794
773

SGE; 1112-3, 20
FREEDOM Subgroup Analyses

All Subjects: 1900
- SYNTAX < 22: 669
- SYNTAX 23-32: 844
- SYNTAX ≥ 33: 374
- Males: 1356
- Females: 544
- Caucasian: 1452
- African-American: 119
- 2 Vessel Disease: 314
- 3 Vessel Disease: 1573
- LVEF < 40%: 32
- LVEF > 40%: 1259
- No LAD involved: 151
- LAD involved: 1737
- Hx stroke: 65
- No Hx stroke: 1835
- Renal insuff.: 129
- No Renal insuff.: 1771
- HbA1c < 7%: 630
- HbA1c > 7%: 1119
- N. American Site: 770
- Non-N. American: 1130

5 Year Rate (%)
- PCI/DES CABG: 27 19
  - Worse CABG: 23 17
  - PCI/DES Worse: 27 18
  - Treatment x Subgroup Interaction: 31 23
  - PCI/DES CABG: 27 18
  - PCI/DES CABG: 26 21
  - PCI/DES CABG: 27 19
  - PCI/DES CABG: 24 16
  - PCI/DES CABG: 27 20
  - PCI/DES CABG: 22 11
  - PCI/DES CABG: 62 31
  - PCI/DES CABG: 23 18
  - PCI/DES CABG: 23 18
  - PCI/DES CABG: 27 19
  - PCI/DES CABG: 59 35
  - PCI/DES CABG: 25 18
  - PCI/DES CABG: 44 37
  - PCI/DES CABG: 25 17
  - PCI/DES CABG: 23 16
  - PCI/DES CABG: 28 20
  - PCI/DES CABG: 28 16
  - PCI/DES CABG: 25 21

Hazard Ratio for Death/Stroke/MI
Conclusion

• In patients with diabetes and advanced coronary disease CABG was of significant benefit as compared to PCI. MI and all cause mortality were independently decreased, while stroke was slightly increased.

• There was no significant interaction between the treatment effect of CABG on the primary endpoint according to SYNTAX score or any other prespecified subgroup.

• CABG surgery is the preferred method of revascularization for patients with diabetes & multi-vessel CAD.
Limitations of the Trial

• On a long term disease, this is a relatively short term study – 7 years, with a minimum of 2 years and a median of 3.8 years.

• Longer term follow up of FREEDOM will lead to better understanding of the comparative benefit by CABG, specifically on mortality
Background

- Trial planned in early 2000s
- 1996: BARI diabetic subset (353 patients) showed that at 5 years PCI had double the mortality of CABG
- No randomised comparison of CABG and PCI in diabetics
- CARDia compared PCI with CABG in diabetics with multivessel (or complex LAD) disease.
- Plan to randomise 600 with sample size based on ARTS and EPI trial meta-analysis
- Non inferiority design
CARDia Investigators

- **Chief Investigators**: Akhil Kapur, Kevin Beatt, Roger Hall,
- **Steering Committee**: Roger Hall, Akhil Kapur, Kevin Beatt, Marcus Flather, Iqbal Malik, Petros Nihoyannopoulos, Keith Oldroyd, Andreas Baumbach, Gianni Angelini, Mark de Belder, Adam de Belder
- **DSMB**: Desmond Julian, Tom Treasure, Adrian Banning
- **Coordinating Centre and Data management**: Clinical Trials and Evaluation Unit, Royal Brompton Hospital, London
- **Statisticians**: Winston Banya and Michael Roughton
- **CEC**: Andrew Archbold, Doug Fraser, Iqbal Malik, Ayesha Qureshi, Kevin Fox, Mark Gunning, Marcus Flather, Simon Corbett, Simon Kennon, Roger Hall
- **Funding**: Supported by major grants from Hammersmith Hospitals special trustees, Eli Lilly, Cordis, BMS/Sanofi.
- **Further support from**: Boston Scientific, Medtronic, Guidant and Jomed
# CARDia: 24 Participating Centres

<table>
<thead>
<tr>
<th>Centre</th>
<th>Principal Investigator</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammersmith Hospital, London</td>
<td>Kevin Beatt, Punit Ramrakha</td>
<td>84</td>
</tr>
<tr>
<td>St Mary’s Hospital, London</td>
<td>Iqbal Malik</td>
<td>62</td>
</tr>
<tr>
<td>London Chest Hospital</td>
<td>Martin Rothman, Akhil Kapur, Anthony Mathur</td>
<td>52</td>
</tr>
<tr>
<td>St James Hospital, Dublin</td>
<td>Peter Crean</td>
<td>42</td>
</tr>
<tr>
<td>Royal Sussex County, Brighton</td>
<td>Steve Holmberg, Adam de Belder</td>
<td>34</td>
</tr>
<tr>
<td>Bristol Royal Infirmary</td>
<td>Andreas Baumbach, Gianni Angelini</td>
<td>33</td>
</tr>
<tr>
<td>James Cook University Hosp, Middlesboro</td>
<td>Mark de Belder</td>
<td>32</td>
</tr>
<tr>
<td>Western Infirmary, Glasgow</td>
<td>Keith Oldroyd</td>
<td>30</td>
</tr>
<tr>
<td>King’s College Hospital</td>
<td>Martyn Thomas, Phillip McCarthy</td>
<td>27</td>
</tr>
<tr>
<td>Manchester Royal infirmary</td>
<td>Farzin Fath-Ordoubadi, Nick Curzen</td>
<td>19</td>
</tr>
<tr>
<td>Hairmyres Hospital</td>
<td>Keith Oldroyd, Barry Vallance</td>
<td>13</td>
</tr>
<tr>
<td>St Thomas’ Hospital</td>
<td>Simon Redwood, Graham Venn</td>
<td>12</td>
</tr>
</tbody>
</table>
## CARDia Participating Centres/ 2

<table>
<thead>
<tr>
<th>Centre</th>
<th>Principal Investigator</th>
<th>Patients recruited</th>
</tr>
</thead>
<tbody>
<tr>
<td>City Hospital, Birmingham</td>
<td>Teri Millane</td>
<td>12</td>
</tr>
<tr>
<td>Royal Victoria, Blackpool</td>
<td>David Roberts, Anoop Chauhan</td>
<td>11</td>
</tr>
<tr>
<td>Beaumont, Dublin</td>
<td>David Foley</td>
<td>11</td>
</tr>
<tr>
<td>St Bartholomew’s Hospital, London</td>
<td>Richard Schilling, Akhil Kapur</td>
<td>10</td>
</tr>
<tr>
<td>Papworth Hospital, Cambridge</td>
<td>Peter Schofield</td>
<td>8</td>
</tr>
<tr>
<td>Royal Brompton Hospital</td>
<td>Carlo di Mario</td>
<td>4</td>
</tr>
<tr>
<td>North Staffs, Stoke</td>
<td>Mark Gunning</td>
<td>4</td>
</tr>
<tr>
<td>City Hospital, Nottingham</td>
<td>Kamran Baig, Rob Henderson</td>
<td>3</td>
</tr>
<tr>
<td>CTC, Liverpool</td>
<td>Rod Stables</td>
<td>3</td>
</tr>
<tr>
<td>Northern General, Sheffield</td>
<td>Ever Grech</td>
<td>2</td>
</tr>
<tr>
<td>Harefield Hospital</td>
<td>Charles Ilsley, Mark Mason</td>
<td>1</td>
</tr>
<tr>
<td>Mayday, Surrey</td>
<td>Kevin Beatt</td>
<td>1</td>
</tr>
</tbody>
</table>
Inclusion Criteria

- Age 18-80
- Significant coronary artery disease suitable for PCI or CABG
  - Proximal/Complex LAD
  - 2 or 3 Vessel disease
- Diabetes mellitus
- Stable angina or Non ST elevation-ACS
Main Exclusion Criteria

• Age >80 years
• Previous CABG or PCI
• Left main stem disease
• Cardiogenic shock
• Recent ST elevation myocardial infarction
Endpoints:
Primary outcome: **Composite of death, myocardial infarction, stroke ... (time to first event)**
Secondary outcome: **rate of repeat revascularisation**

Definitions:
- **Death**: All cause mortality
- **Myocardial infarction**:
  - First 7 days post revascularisation one or more of following –
    - CK or CKMB >3x ULN, Tn (T or I ) >1, ECG new Q waves
  - After first 7 days need at least 2 of i) raised enzymes (CK/CKMB >x2 ULN or Troponin Tor I >1), ii) new Q waves on ECG, iii) ischaemic symptoms
- **Stroke**: Neurological signs/symptoms that persist for more than 24 hrs with a neurological imaging study that does not indicate a different aetiology

**Analysis**: Non inferiority, upper bound of 95% CI not to exceed 12% (~80% power with 500 patients and 27% event rate)
CARDia Patient flow Chart

510 Pts randomised

CABG
- 254 patients
  - 6 withdrew consent (no further data) *
  - 14 crossed over to PCI
  - 5 yr follow up
  - 248 records available
  - 204 alive, included and followed up
  - 33 deaths
  - 7 lost to follow up
  - 4 further withdrawals

PCI
- 256 patients
  - 2 withdrew consent (no further data)*
  - 1 crossed over to CABG
  - 31% BMS, 69% DES
  - 5 year follow
  - 254 records available
  - 198 alive, included and followed up
  - 41 deaths
  - 11 lost to follow up
  - 4 further withdrawals

* Not included in subsequent analysis
# Main Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>CABG</th>
<th>PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number in group</td>
<td></td>
<td>254</td>
<td>256</td>
</tr>
<tr>
<td>Age</td>
<td>Years</td>
<td>63.6</td>
<td>64.3</td>
</tr>
<tr>
<td>Male</td>
<td>%</td>
<td>77.9</td>
<td>70.7</td>
</tr>
<tr>
<td>Years with diabetes</td>
<td>Years</td>
<td>10.4</td>
<td>10.1</td>
</tr>
<tr>
<td>Type 1</td>
<td>%</td>
<td>5.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Hba1c</td>
<td>%</td>
<td>7.9</td>
<td>7.9</td>
</tr>
<tr>
<td>BMI</td>
<td>kg/m²</td>
<td>29.4</td>
<td>29.2</td>
</tr>
<tr>
<td>Creatinine</td>
<td>µmol/l</td>
<td>107.0</td>
<td>104.2</td>
</tr>
<tr>
<td>Ethnicity White</td>
<td>%</td>
<td>72.4</td>
<td>67.1</td>
</tr>
<tr>
<td>South Asian</td>
<td></td>
<td>20.1</td>
<td>25.9</td>
</tr>
<tr>
<td>Acute admission</td>
<td>%</td>
<td>23.6</td>
<td>21.5</td>
</tr>
<tr>
<td>3 vessel disease</td>
<td>%</td>
<td>58.7</td>
<td>64.8</td>
</tr>
</tbody>
</table>
Results

• 510 patients enrolled (1st patient enrolled Jan 2002, final Follow up April 2012)

• Median follow up 5.1 years inter-quartile range 3.8 to 5.4 years

• Mean vessels/ patient revascularised in CABG group = 2.9 (94% received LIMA grafts)

• Mean number of stents/ patient in PCI group = 3.6 (69% drug eluting stents)
Primary Analysis for Non Inferiority

Non Inferiority margin = 12%*

*Non inferiority method based on PARTNER Trial NEJM 2011;364:2187-98.

Death, MI, Stroke
CABG 20.5% vs PCI 26.6%
+5.9% (-2 to +13%)

Difference and 95% Confidence Interval in %

 PCI better
CABG better

Non-Inferiority margin = 12%*
Adjudicated events post randomisation

<table>
<thead>
<tr>
<th>Event</th>
<th>CABG (248)</th>
<th>PCI (254)</th>
<th>p value</th>
<th>HR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, stroke (primary outcome) (n)</td>
<td>20.5% (52)</td>
<td>26.6% (68)</td>
<td>0.11</td>
<td>1.34 (0.94,1.93)</td>
</tr>
<tr>
<td>Death</td>
<td>12.6 % (32)</td>
<td>14% (37)</td>
<td>0.53</td>
<td>1.17 (0.73,1.87)</td>
</tr>
<tr>
<td>Non fatal MI</td>
<td>6.3% (16)</td>
<td>14% (36)</td>
<td>0.007</td>
<td>2.26 (1.25,4.08)</td>
</tr>
<tr>
<td>Non fatal stroke</td>
<td>4.3% (11)</td>
<td>3.1% (8)</td>
<td>0.48</td>
<td>0.72 (0.29,1.79)</td>
</tr>
<tr>
<td>Repeat revascularisation</td>
<td>8.3% (23)</td>
<td>21.9% (57)</td>
<td>&lt;0.001</td>
<td>2.87 (1.74, 4.74)</td>
</tr>
<tr>
<td>Death, MI, stroke, repeat revasc</td>
<td>26% (66)</td>
<td>37.5% (96)</td>
<td>0.005</td>
<td>1.56 (1.14, 2.14)</td>
</tr>
</tbody>
</table>
All Cause Mortality up to 6 Yrs

![Graph showing All Cause Mortality](image)

- **Death**
  - 1.00
  - 0.75
  - 0.50
  - 0.25
  - 0.00

- **Time since Randomization (Years)**
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6

- **Number at risk**
  - CABG 248: 234, 231, 221, 213, 191, 43
  - PCI 254: 241, 236, 221, 211, 179, 37

- **p=0.52**
Primary Endpoint up to 6 Yrs

![Graph showing the comparison of Death, MI, Stroke and Death, Non-Fatal MI, Non-Fatal Stroke between CABG and PCI. The graph demonstrates a trend where CABG has a lower risk compared to PCI. The number of patients at risk over time is also provided.](image)

- **Death, MI, Stroke**
  - CABG
  - PCI

- **Death, Non-Fatal MI, Non-Fatal Stroke**
  - CABG
  - PCI

Number at risk:
- CABG 248
- PCI 254

Time since Randomization (Years)
0 1 2 3 4 5 6

Number at risk:
216 213 200 192 174 38
216 208 192 182 148 28

**p=0.11**
Primary Composite Endpoint
Plus Repeat Revascularisation to 6 Yrs

Death, Non-Fatal MI, Non-Fatal Stroke, Revasc

CABG

PCI

$\text{p}=0.0048$

Number at risk
CABG 248 214 207 191 181 159 36
PCI 254 201 189 167 159 124 26

SGE; 0912-12, 15
• Primary outcome does not demonstrate non-inferiority of PCI compared to CABG

• Conventional analysis does not show a statistical difference in primary outcome but study underpowered for this comparison

• Higher rates of MI and repeat revascularisation in PCI group

• No clear evidence to support routine PCI in patients with diabetes and multivessel disease
• Previous reports of much higher mortality for PCI at 5 yrs not confirmed and mortality very similar for two treatments

• Clinical message
  – CABG remains the preferred method of revascularisation unless there are clinical features that make PCI clearly preferable.
  – In such a patient it is reasonable for PCI to be performed after appropriate consultation with colleagues (including surgeons) and also the patient
Trial of Everolimus-Eluting Stents or Bypass Surgery for Coronary Disease

Seung-Jung Park, M.D., Ph.D., Jung-Min Ahn, M.D., Young-Hak Kim, M.D., Duk-Woo Park, M.D., Sung-Chee Yun, Ph.D., Jong-Young Lee, M.D., Soo-Jin Kang, M.D., Seung-Whan Lee, M.D., Cheol Whan Lee, M.D., Seung-Wook Park, M.D., Suk Jung Choo, M.D., Cheol Hyun Chung, M.D., Jae Won Lee, M.D., David J. Cohen, M.D., Alan C. Yeung, M.D., Seung Ho Hur, M.D., Ki Bae Seung, M.D., Tae Hoon Ahn, M.D., Hyuck Moon Kwon, M.D., Do-Sun Lim, M.D., Seung-Woon Rha, M.D., Myung-Ho Jeong, M.D., Bong-Ki Lee, M.D., Damras Tresukosol, M.D., Guo Sheng Fu, M.D., and Tiong Kiam Ong, M.D. for the BEST Trial Investigators
BEST: CAGB vs. EES

• 880 CAD pts
  – RCT
  – 40% diabetics
  – 77% 3VD
  – Mean SYNTAX = 24
  – 84% EuroSCORE < 6
  – Median 4.6 y f/u

• CABG pts
  – 2 +/- 1 arterial grafts
  – 64% off-pump

• PCI pts
  – 3.4 stents/85 mm

King, et al., Emory University
Subgroup analysis of the primary endpoint.

Hazard ratios and 95% confidence intervals are shown for the primary composite end point of death, myocardial infarction or TVR in subgroups of patients assigned to undergo PCI or CABG.

# BEST

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>PCI</th>
<th>CABG</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34/177 (19.2)</td>
<td>17/186 (9.1)</td>
<td>2.24 (1.25–4.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>No</td>
<td>33/261 (12.6)</td>
<td>30/256 (11.7)</td>
<td>1.07 (0.65–1.76)</td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40/228 (17.5)</td>
<td>33/238 (13.9)</td>
<td>1.30 (0.82–2.06)</td>
<td>0.35</td>
</tr>
<tr>
<td>No</td>
<td>27/210 (12.9)</td>
<td>24/204 (11.8)</td>
<td>1.89 (0.99–3.60)</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40%</td>
<td>7/17 (41.2)</td>
<td>4/17 (23.5)</td>
<td>1.79 (0.51–6.21)</td>
<td>0.65</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>60/421 (14.3)</td>
<td>43/425 (10.1)</td>
<td>1.43 (0.97–2.12)</td>
<td></td>
</tr>
<tr>
<td>No. of diseased vessels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>56/330 (17.0)</td>
<td>42/349 (12.0)</td>
<td>1.45 (0.97–2.17)</td>
<td>0.65</td>
</tr>
<tr>
<td>2</td>
<td>11/108 (10.2)</td>
<td>5/93 (5.4)</td>
<td>1.89 (0.66–5.43)</td>
<td></td>
</tr>
<tr>
<td>SYNTAX score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥33</td>
<td>13/66 (19.7)</td>
<td>10/79 (12.7)</td>
<td>1.59 (0.70–3.62)</td>
<td>0.25</td>
</tr>
<tr>
<td>23–32</td>
<td>30/187 (16.0)</td>
<td>14/177 (7.9)</td>
<td>2.14 (1.13–4.03)</td>
<td></td>
</tr>
<tr>
<td>≤22</td>
<td>24/185 (13.0)</td>
<td>23/186 (12.4)</td>
<td>1.04 (0.59–1.84)</td>
<td></td>
</tr>
<tr>
<td>EuroSCORE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥6</td>
<td>12/51 (23.5)</td>
<td>11/59 (18.6)</td>
<td>1.25 (0.55–2.84)</td>
<td>0.65</td>
</tr>
<tr>
<td>&lt;6</td>
<td>55/387 (14.2)</td>
<td>36/383 (9.4)</td>
<td>1.55 (1.02–2.35)</td>
<td></td>
</tr>
</tbody>
</table>

King, et al., Emory University

More “new lesion” revascularization in PCI (6.5% vs 2.4%; p = 0.01)


King, et al., Emory University
Mortality Follow PCI or CABG:

HR 1.04 (0.93-1.17)  
P = 0.50
BARI 2D Trial - Diabetes and CAD

Stable CAD

Cardiac Events with Revascularization vs Medical Rx

C  Freedom from Major Cardiovascular Events in PCI Stratum

D  Freedom from Major Cardiovascular Events in CABG Stratum

Diabetes and PCI

Long-Term Outcome After PCI in Patients > 65 Yrs Old
Bare Metal (BMS) vs Drug Eluting (DES) Stents
National Cardiovascular Data Registry, 2004 to 2008

Hillegass et al. JACC 2012;60:2280
Diabetes and PCI

Long-Term Outcome After PCI in Patients > 65 Yrs Old
National Cardiovascular Data Registry, 2004 to 2008

Hillegass et al. JACC 2012;60:2280
Diabetes and PCI
Outcome After Drug Eluting Stents
RESOLUTE Zotarolimus Stent Global Clinical Program

Silber et al. JACC Intervention 2013;6:357.
Diabetes and PCI

Coronary Lesion Complexity and Outcome After DES

18 Pooled Randomized Trials of DES
Diabetes in 3467 of 18,441 Patients (18.8%)

- DM is a risk factor for repeat revascularization only for complex lesions
- Pts with DM remain at higher risk for Death or MI

Kedhi et al. JACC 2014;63:2111
### Meta-Analysis: RCTs of Invasive vs Conservative Strategy in NSTE-ACS

**Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Event Rates (n/N)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI III</td>
<td>Invasive: 42.9% (24/55)</td>
<td>Conservative: 43.1% (25/58)</td>
</tr>
<tr>
<td>MATE</td>
<td>Invasive: 50.0% (6/12)</td>
<td>Conservative: 37.5% (9/24)</td>
</tr>
<tr>
<td>VANQWISH</td>
<td>Invasive: 40.0% (46/115)</td>
<td>Conservative: 41.6% (52/125)</td>
</tr>
<tr>
<td>FRISC II</td>
<td>Invasive: 27.1% (38/141)</td>
<td>Conservative: 41.6% (50/124)</td>
</tr>
<tr>
<td>TACTICS-TIMI 18</td>
<td>Invasive: 21.7% (60/281)</td>
<td>Conservative: 28.3% (85/600)</td>
</tr>
<tr>
<td>RITA 3</td>
<td>Invasive: 20.8% (27/133)</td>
<td>Conservative: 27.2% (31/114)</td>
</tr>
<tr>
<td>VINO</td>
<td>Invasive: 11.8% (2/17)</td>
<td>Conservative: 35.7% (5/14)</td>
</tr>
<tr>
<td>ICTXS</td>
<td>Invasive: 31.4% (27/86)</td>
<td>Conservative: 29.3% (23/80)</td>
</tr>
<tr>
<td>OASIS 5 Substudy</td>
<td>Invasive: 42.1% (8/19)</td>
<td>Conservative: 25.9% (7/27)</td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td>Invasive: 27.7% (247/892)</td>
<td>Conservative: 33.4% (293/876)</td>
</tr>
</tbody>
</table>

**No Diabetes**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Event Rates (n/N)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI III</td>
<td>Invasive: 30.7% (105/342)</td>
<td>Conservative: 35.6% (116/329)</td>
</tr>
<tr>
<td>MATE</td>
<td>Invasive: 21.2% (21/99)</td>
<td>Conservative: 19.7% (13/66)</td>
</tr>
<tr>
<td>VANQWISH</td>
<td>Invasive: 29.2% (103/345)</td>
<td>Conservative: 22.8% (79/333)</td>
</tr>
<tr>
<td>FRISC II</td>
<td>Invasive: 15.5% (157/949)</td>
<td>Conservative: 27.5% (269/969)</td>
</tr>
<tr>
<td>TACTICS-TIMI 18</td>
<td>Invasive: 14.0% (117/831)</td>
<td>Conservative: 16.9% (133/800)</td>
</tr>
<tr>
<td>RITA 3</td>
<td>Invasive: 12.4% (95/765)</td>
<td>Conservative: 17.5% (140/801)</td>
</tr>
<tr>
<td>VINO</td>
<td>Invasive: 6.4% (347)</td>
<td>Conservative: 26.4% (14/53)</td>
</tr>
<tr>
<td>ICTXS</td>
<td>Invasive: 21.2% (119/519)</td>
<td>Conservative: 20.0% (103/515)</td>
</tr>
<tr>
<td>OASIS 5 Substudy</td>
<td>Invasive: 17.8% (13/73)</td>
<td>Conservative: 15.4% (10/65)</td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td>Invasive: 18.3% (722/3940)</td>
<td>Conservative: 22.2% (894/398)</td>
</tr>
</tbody>
</table>
TACTICS

Outcome with Diabetes

Death, MI, Rehosp for ACS - 6 Months (%)

<table>
<thead>
<tr>
<th></th>
<th>Conservative</th>
<th>Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic (n = 613)</td>
<td>27.7</td>
<td>20.1</td>
</tr>
<tr>
<td>Non-Diabetic (n = 1607)</td>
<td>16.4</td>
<td>14.2</td>
</tr>
</tbody>
</table>

Cannon CP et al. NEJM 2001;344:1879.
Abciximab and Diabetes

EPIC, EPILOG, EPISTENT - 1 Year Mortality

Non-Diabetic (N = 5072)
Diabetic (N = 1462)

<table>
<thead>
<tr>
<th>Mortality (%)</th>
<th>Non-Diabetic</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 1850)</td>
<td>2.6%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Abciximab (n = 3222)</td>
<td>1.9%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

# Antiplatelet Therapy and Diabetes

ADP P2Y$_{12}$ Inhibitor Trials in ACS

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary endpoint</th>
<th>n</th>
<th>Standard treatment: % of events</th>
<th>Active treatment: % of events</th>
<th>P-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE</td>
<td>1-year CV death, nonfatal MI or stroke</td>
<td>No DM:9,722, DM:2,840</td>
<td>9.9%</td>
<td>7.9%</td>
<td>0.31</td>
</tr>
<tr>
<td>PCI CLARITY</td>
<td>30-day CV death, recurrent MI or stroke</td>
<td>No DM:1,555, DM:282</td>
<td>5.3%</td>
<td>2.9%</td>
<td>0.93</td>
</tr>
<tr>
<td>TRITON-TIMI 38</td>
<td>15-month CV death, nonfatal MI or nonfatal stroke</td>
<td>No DM:10,462, DM:3,146</td>
<td>10.6%</td>
<td>9.2%</td>
<td>0.09</td>
</tr>
<tr>
<td>PLATO</td>
<td>1-year CV death, MI or stroke</td>
<td>No DM:13,951, DM:4,662</td>
<td>10.2%</td>
<td>8.4%</td>
<td>0.49</td>
</tr>
</tbody>
</table>

CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; MI, myocardial infarction; STEMI, ST-segment elevation MI.

Antiplatelet Therapy and Diabetes

Prasugrel in ACS

Ischemic Composite

Major Bleeding

Antiplatelet Therapy and Diabetes

Ticagrelor vs Prasugrel – Platelet Inhibition

Alexopoulos et al. Dia Care 2013;36:2211.

Bivalirudin and Diabetes
HORIZONS Trial – STEMI Patients
Bivalirudin vs Heparin + GP IIb/IIIa Inhibition

Witzenbichler et al.  JACC Intervention 2011;4:760.
HEAT-PPCI Trial

Bivalirudin vs Heparin in STEMI

MACE

# Diabetes and CABG

## Linkage with Chronic Kidney Disease (CKD)

**BARI Registry and Trial:** $N = 3805$ Pts

<table>
<thead>
<tr>
<th>Event</th>
<th>CKD (%)</th>
<th>No CKD (%)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emboli</td>
<td>4.4</td>
<td>0.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Shock</td>
<td>4.4</td>
<td>0.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Death</td>
<td>6.7</td>
<td>0.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Death/QMI</td>
<td>11.0</td>
<td>3.0</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

## 7-Year Mortality (%)

<table>
<thead>
<tr>
<th>7-Year Mortality (%)</th>
<th>CKD</th>
<th>No CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>67</td>
<td>28</td>
</tr>
<tr>
<td>No Diabetes</td>
<td>39</td>
<td>12</td>
</tr>
</tbody>
</table>

Szczech LA et al. *Circulation Online 2002.*
Diabetes and CABG

Mortality Protection Post Q-MI: BARI Registry and Trial

3603 Patients - PTCA or CABG

Diabetes - 641 pt
- 20% death
- 8% QMI

No Diabetes - 2962 pt
- 8% death
- 4% QMI

No CABG - 352 pt
- 25% death
- QMI - 23 pt
- 80% death

CABG - 289 pt
- 18% death
- QMI - 27 pt
- 17% death

No CABG - 1739 pt
- 8% death
- QMI - 69 pt
- 30% death

CABG - 1223 pt
- 7% death
- QMI - 67 pt
- 27% death

BARI Trial

Mortality and Diabetes

**All-Cause Mortality (%)**

- CABG: 34.7%
- PTCA: 19.1%

- All Diabetes: 10.3%
- All Others: 9.5%

**Cardiac Mortality (%)**

- IMA: 20.6%
- SVG Only: 18.2%
- PTCA: 4.6%
- All Others: 5.4% and 4.8%

*p = 0.0003*

*p < 0.005*

ARTS Trial - 1 Year Outcome

Diabetics

Non-Diabetics

CABG and Diabetes

Society of Thoracic Surgeons Database - 1997
434 Institutions: 146,786 Patients

30 Day Outcome (%)

- No DM (n = 105,123)
- DM - Oral Meds (n = 25,003)
- DM - Insulin (n = 16,660)

<table>
<thead>
<tr>
<th>Condition</th>
<th>No DM</th>
<th>DM - Oral Meds</th>
<th>DM - Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>2.7%</td>
<td>3.2%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.4%</td>
<td>2.3%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>2.9%</td>
<td>4.3%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Infection</td>
<td>5.2%</td>
<td>6.9%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.9%</td>
<td>1.1%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Diabetes and Balloon Angioplasty

NHLBI Registry
1985-86


Emory
1980-90


Mortality - 9 yrs (%)

<table>
<thead>
<tr>
<th>Non-Diabetic (n=1833)</th>
<th>Diabetic (n=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.9</td>
<td>35.9</td>
</tr>
</tbody>
</table>

Mortality - 5 yrs (%)

<table>
<thead>
<tr>
<th>Non-Diabetic (n=9300)</th>
<th>Diabetic (n=1133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>12</td>
</tr>
</tbody>
</table>
Diabetes and Balloon Angioplasty
Late Repeat Revascularization

Event Rate (%)

Diabetes and Balloon Angioplasty

Late Mortality

Mortality (%)

- **NHLBI (9 yrs)**
  - Non-Diabetic: 17.9%
  - Diabetic: 35.9%

- **Emory (5 yrs)**
  - Non-Diabetic: 7.0%
  - Diabetic: 12.0%

- **BARI (5 yrs)**
  - Non-Diabetic: 9.5%
  - Diabetic: 34.7%
Diabetes and Balloon Angioplasty
Impact of Occlusive Restenosis
604 Diabetic Patients

Diabetes and Stenting

Angiographic Restenosis

% of Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-Diabetic</th>
<th>Diabetic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrozza</td>
<td>20.0</td>
<td>55.0</td>
<td>0.001</td>
</tr>
<tr>
<td>(n=220 pts)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Belle</td>
<td>27.0</td>
<td>25.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=300 pts)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elezi</td>
<td>28.3</td>
<td>37.5</td>
<td></td>
</tr>
<tr>
<td>(n=3554 pts)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diabetes and Stenting

Late Mortality

Mortality - 1 Yr (%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-Diabetic</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHC(^1)</td>
<td>1.6</td>
<td>2.5</td>
</tr>
<tr>
<td>EPISTENT(^2)</td>
<td>1.9</td>
<td>4.1</td>
</tr>
<tr>
<td>ESPRIT(^3)</td>
<td>1.5</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Diabetes and Revascularization

Duke University: 1984-1990

3220 Patients (24% Diabetic) with 2- or 3-Vessel CAD Suitable for CABG or PTCA


Adjusted $\chi^2$ for Diabetes = 43.6, $p < 0.0001$
Diabetes and Coronary Brachytherapy

GAMMA-1: Ir-192 γ Radiation for In-Stent Restenosis
Angiographic Outcome at 6 Months

Diabetic

Non-Diabetic

% of Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=29)</th>
<th>Ir-192 (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restenosis In-Stent</td>
<td>25</td>
<td>66</td>
</tr>
<tr>
<td>p</td>
<td>p&lt;0.002</td>
<td>p&lt;0.002</td>
</tr>
<tr>
<td>Restenosis In-Lesion</td>
<td>36</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.002</td>
<td>p&lt;0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=84)</th>
<th>Ir-192 (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restenosis In-Stent</td>
<td>20.0</td>
<td>43.0</td>
</tr>
<tr>
<td>p</td>
<td>0.004</td>
<td>0.06</td>
</tr>
<tr>
<td>Restenosis In-Lesion</td>
<td>31.0</td>
<td>47.0</td>
</tr>
</tbody>
</table>

Diabetes and Coronary Brachytherapy

GAMMA-1: Ir-192 γ Radiation for In-Stent Restenosis Clinical Outcome at 9 Months

TVR - 9 Months (%)

- Diabetic: Placebo 45, Ir-92 12 (p = 0.002)
- Non-Diabetic: Placebo 18, Ir-92 19

1-Year Costs ($)

- Diabetic: Placebo 36,469, Ir-92 28,153
- Non-Diabetic: Placebo 22,270, Ir-92 25,532

Diabetes and Coronary Brachytherapy

Washington Hospital Center
749 Patients with ISR Rx'd in Trials or Registries


Diabetes and No Diabetes

Restenosis

- Diabetes: 63.8%
  - Placebo: 48.1%
  - Radiation: 15.7%
- No Diabetes: 48.4%
  - Placebo: 37.7%
  - Radiation: 10.7%

Target Vessel Revasc

- Diabetes: 70.6%
  - Placebo: 47.7%
  - Radiation: 22.9%
- No Diabetes: 56.0%
  - Placebo: 27.8%
  - Radiation: 28.2%

All p <0.05