

# **Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D)**



# BARI 2D Dedication



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**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.

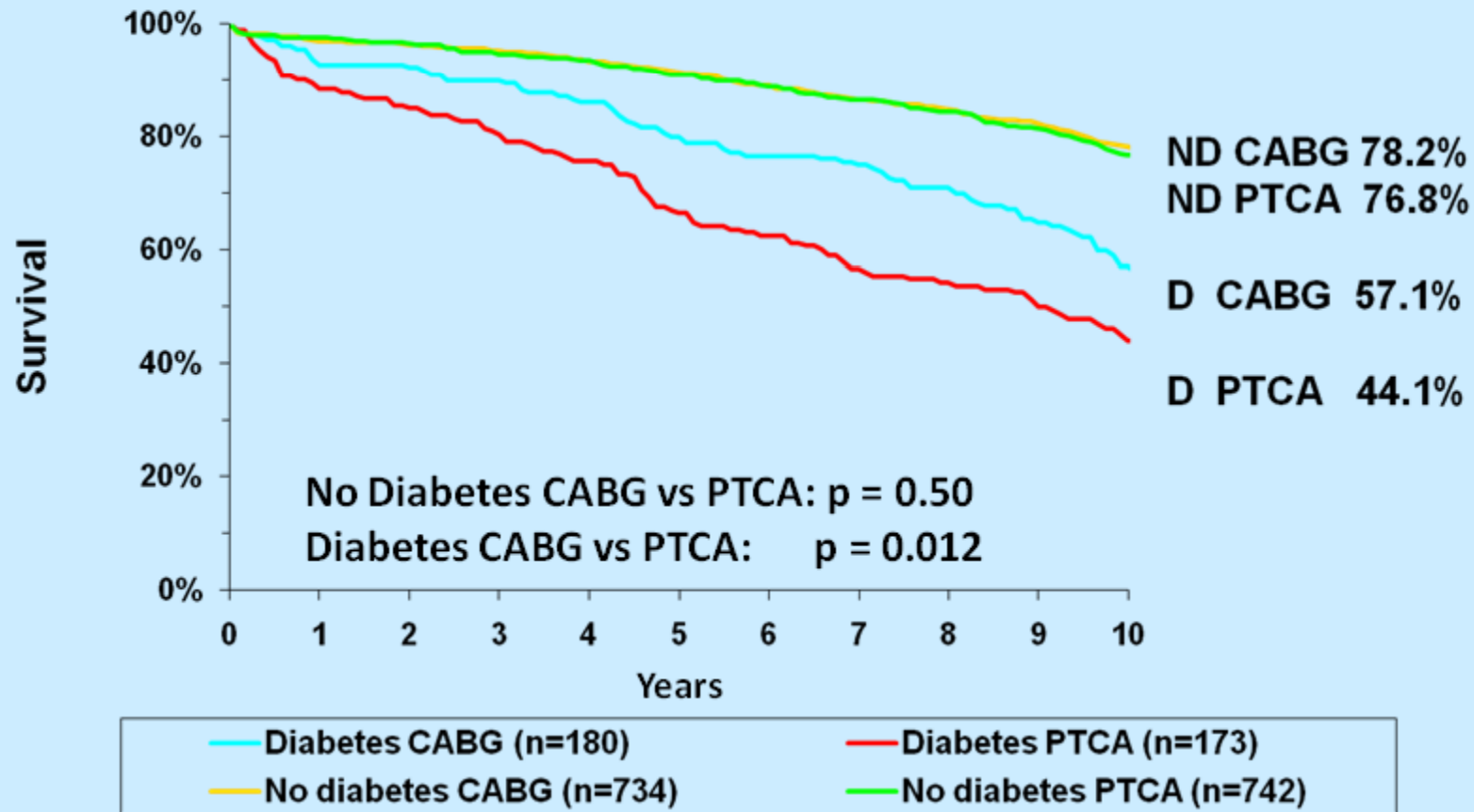


# Bypass Angioplasty Revascularization (BARI)

- 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



# Five-year Cardiac Mortality Rates from BARI

	<b>PTCA</b>	<b>CABG</b>
No diabetes	4.8%	4.7%
Diabetes	<b>20.6%</b>	5.8%



# 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  $\geq$  25 years
- CAD (at least one stenosis  $\geq$  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  $\geq$  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  $\geq 50\%$
- 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

Glucose  
Control  
Strategy

	Ischemia Control Strategy			
	Prompt Revasc		Medical	
	Insulin Provision	592	593	1185
	Insulin Sensitization	584	599	1183
		1176	1192	2368



# 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

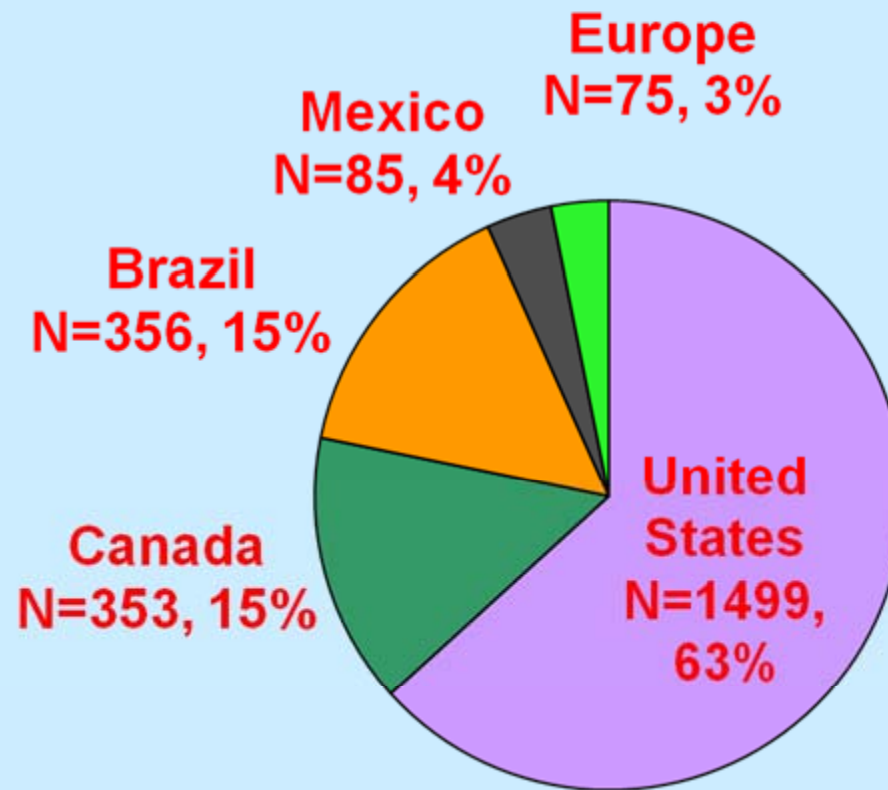


# **BARI 2D**

# **BASELINE**



# Randomized Patients by Region



**N=2368 Randomized Patients**



# Demographic and Clinical History

(N=2368 Randomized Patients)

Age (Mean)	62.4 yr
Female	30%
Ethnic/Racial Minority	34%
Myocardial Infarction Hx	32%
Congestive Heart Failure Hx	7%
History of Stroke or TIA	10%
Peripheral Artery Disease	24%



# Cardiac Clinical Characteristics

(N=2368 Randomized Patients)

Angina Status*	
No angina nor anginal equivalents	18.0%
Anginal equivalents (no angina)	21.4%
Stable angina CCS 1-2	42.5%
Stable angina CCS 3-4	8.6%
Unstable angina	9.5%
Prior PCI	20%
Prior Stent	13%
Prior CABG	6%

\* Angina status at baseline differs significantly between Rev and Med groups



# Angiographic Characteristics

(N=2368 Randomized Patients)

Diseased Coronary Vessels: 1	33%
2	36%
3	31%
Myocardial Jeopardy (Mean $\pm$ SD)	44 $\pm$ 24
Proximal LAD (>50% stenosis)	13%
Total Occlusion (at least one)	41%
Abnormal LV Function (<50%)	17%



# Diabetes Clinical History

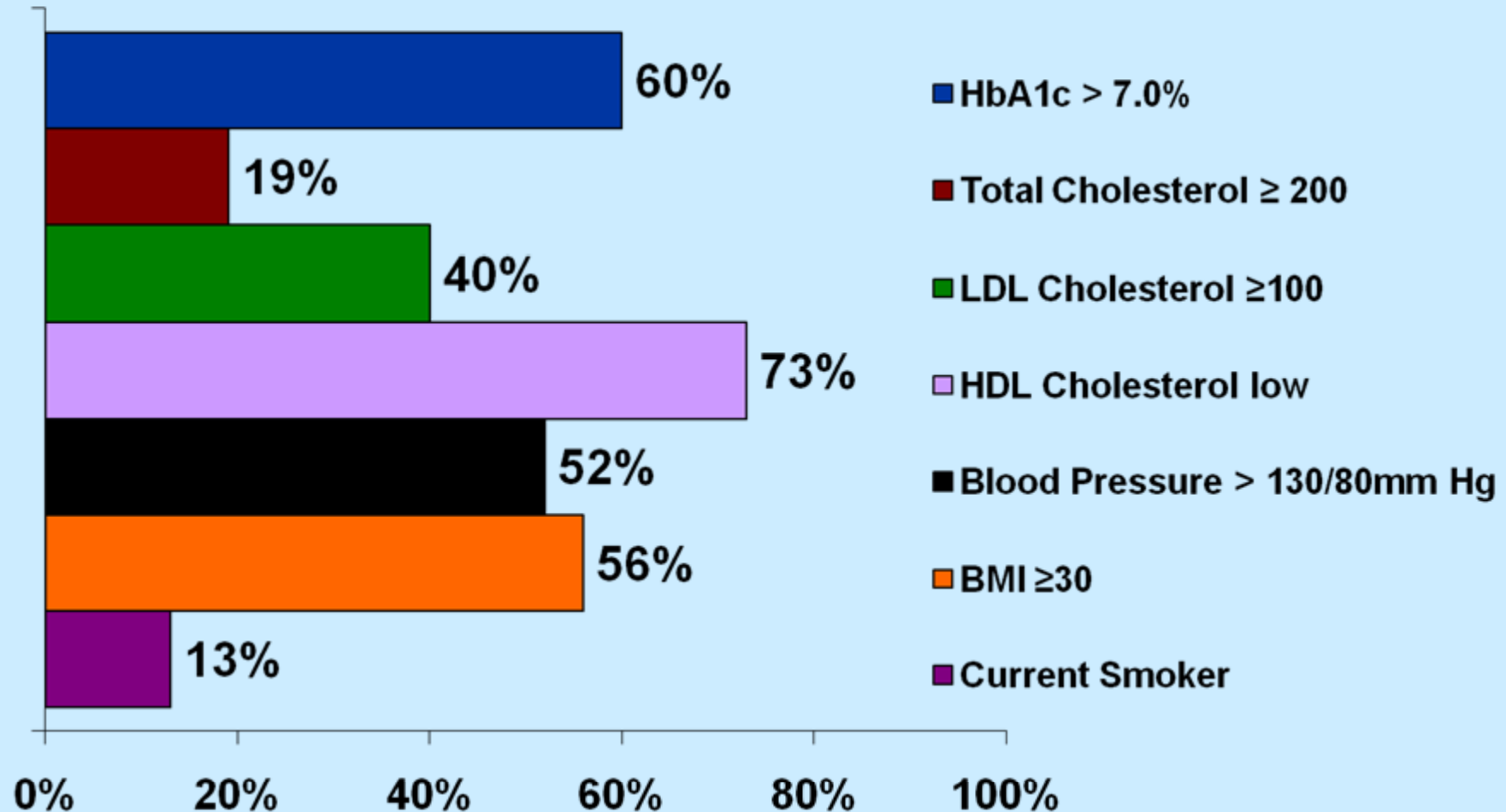
(N=2368 Randomized Patients)

Duration of Diabetes (mean)	10.4 yrs
< 6 Months	8%
6 months to 5 Years	25%
5-10 Years	24%
10-20 Years	29%
≥ 20 Years	14%
HbA1c % (mean)	7.7
Receiving Insulin	28%
Micro or Macro-albuminuria (ACR>30)	33%
Neuropathy (MNSI clinical score > 2)	50%





# Risk Factor Status among BARI 2D Patients at Baseline

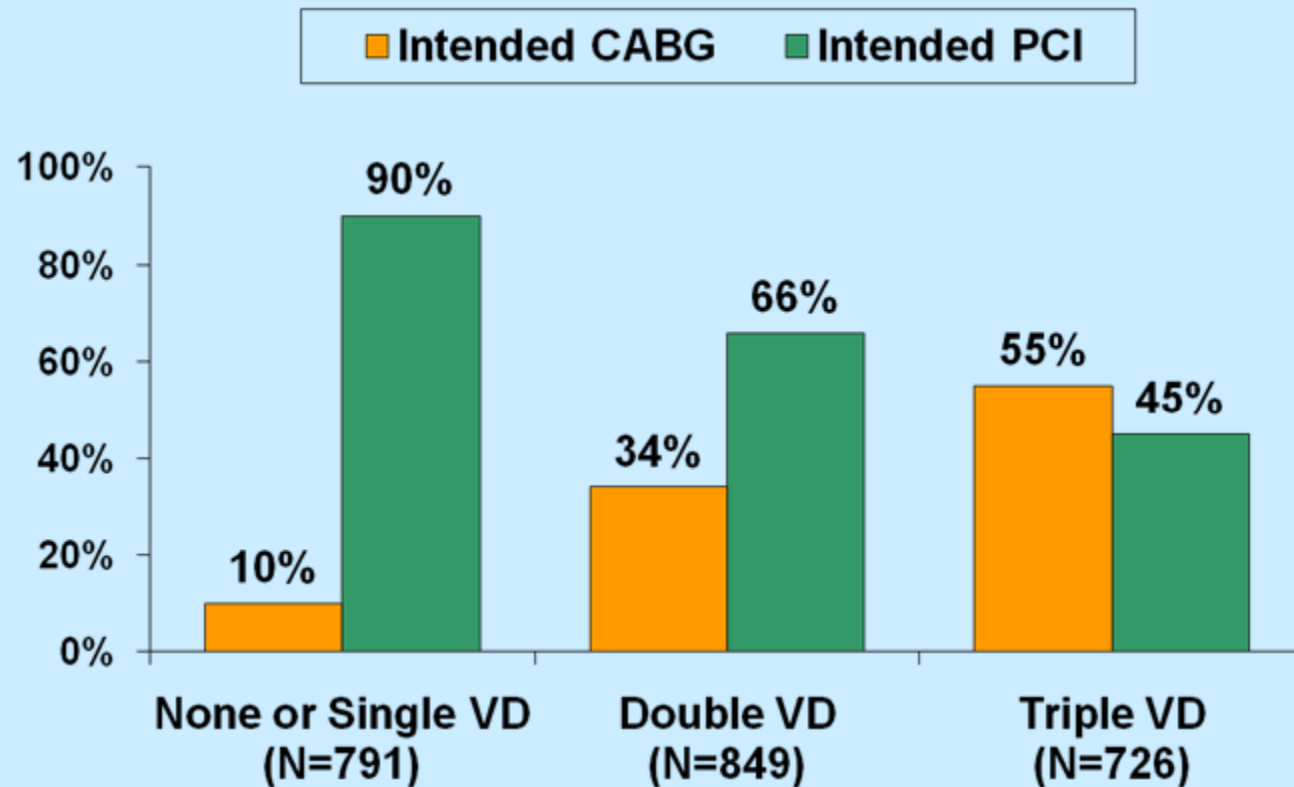


# Baseline Characteristics By Randomization Stratum

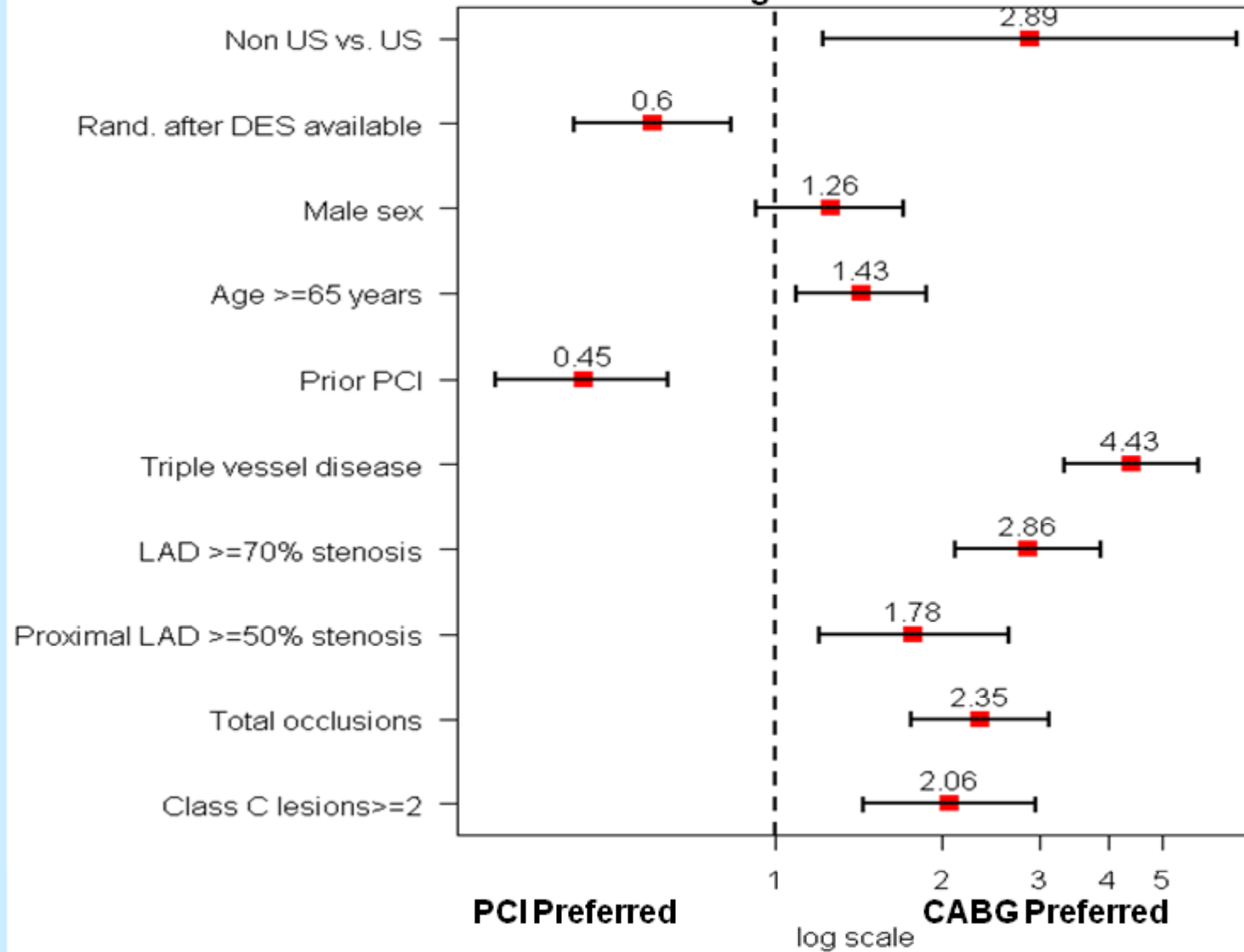
	<i>PCI Intended N=1605</i>	<i>CABG Intended N=763</i>
<b>Age, mean years</b>	62.0	63.2
<b>Male</b>	68%	76%
<b>Prior revascularization</b>	29%	13%
<b>Proximal LAD</b>	10%	19%
<b>LVEF &lt; 50</b>	18%	18%
<b>3 Vessel Disease</b>	20%	52%
<b>Total Occlusions, mean number</b>	0.48	0.84
<b>Myocardial Jeopardy, mean %</b>	37.2	59.7



# Intended Mode of Revascularization by Number of Diseased Vessels



### Adjusted Odds Ratio of CABG Selection Among Multivessel Disease



# **BARI 2D**

## **TREATMENT IMPLEMENTED**

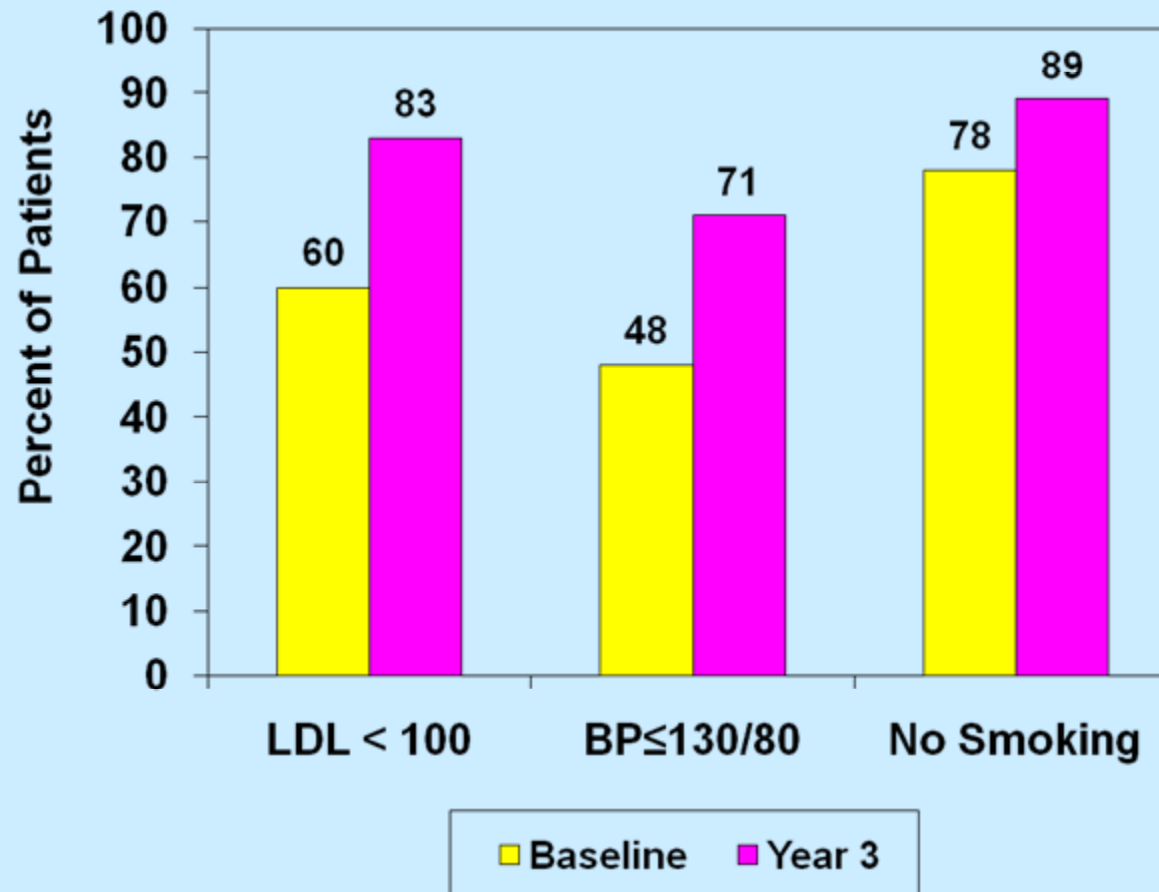
**Risk factor control**

**Diabetes**

**Cardiac**



# Risk Factor Control



# Risk Factor Measures

	Baseline	Three Year			
Mean		Rev	Med	IS	IP
LDL (mg/dl)	96	81	79	79	80
HDL (mg/dl)	38	41	41	<b>42</b>	<b>40</b>
Systolic Blood Pressure (mmHg)	132	126	125	125	126
Diastolic Blood Pressure (mmHg)	75	70	70	70	71
BMI (kg/m <sup>2</sup> )	31.7	32.0	32.2	<b>31.7</b>	<b>32.5</b>

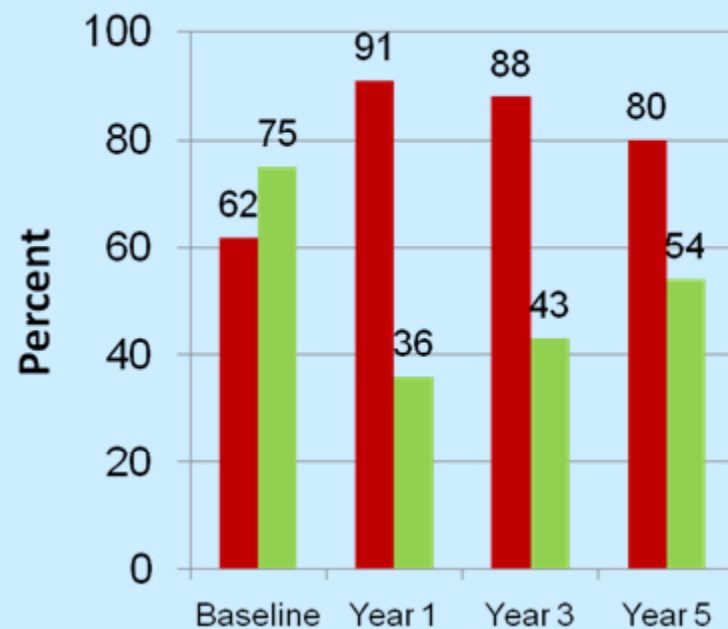
\* Differences between IS and IP groups significant ( $p < 0.05$ ) for HDL and BMI at 3 years



# Drug Use by Randomized Treatment Assignment

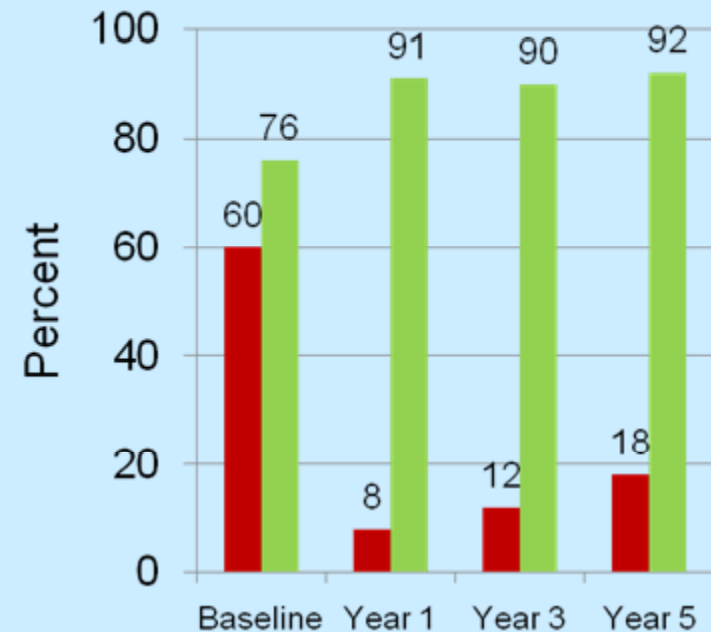
## Insulin Sensitization Group

■ IS Drugs ■ IP Drugs



## Insulin Provision Group

■ IS Drugs ■ IP Drugs



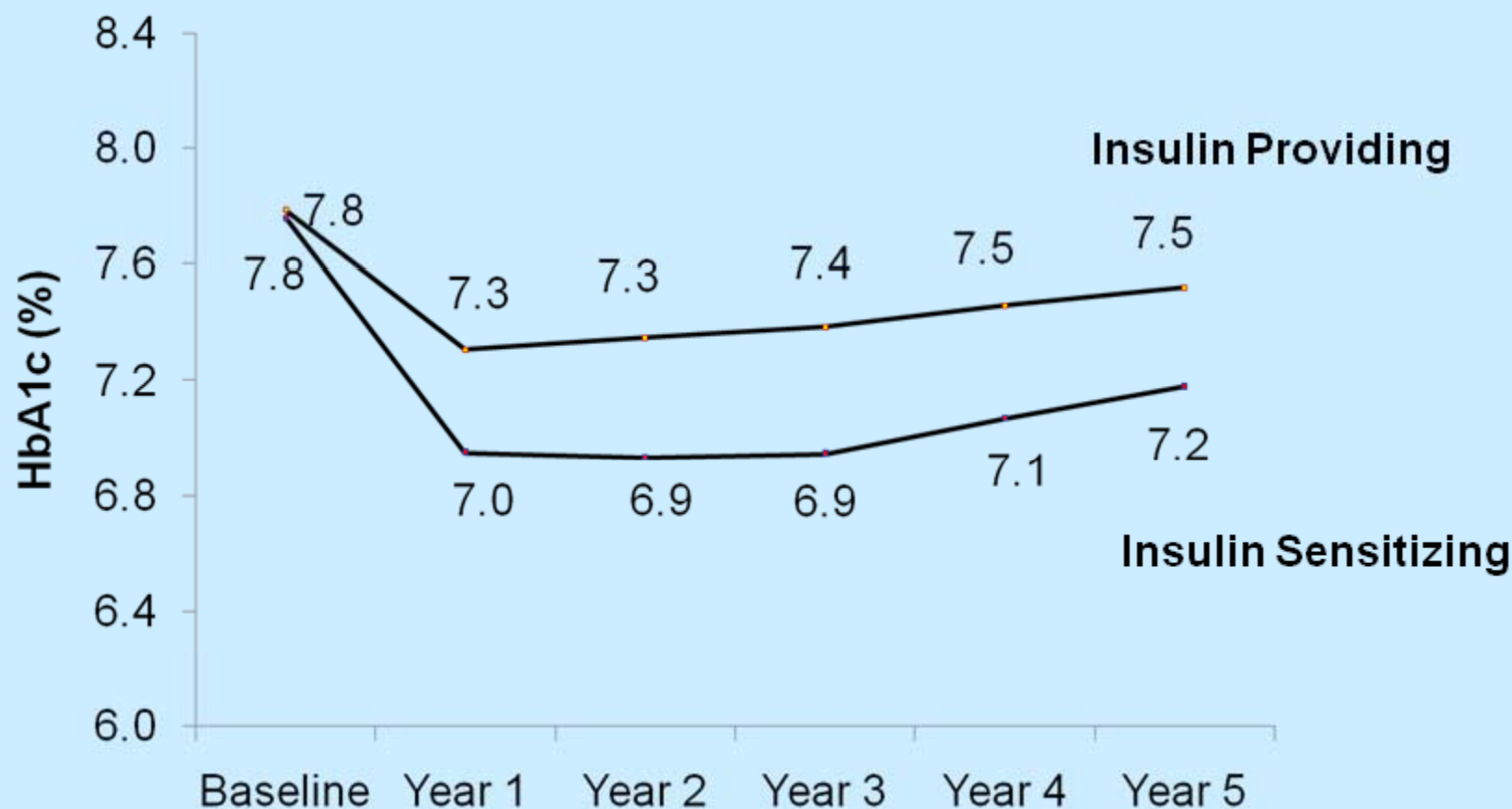


# Diabetes Medication Use

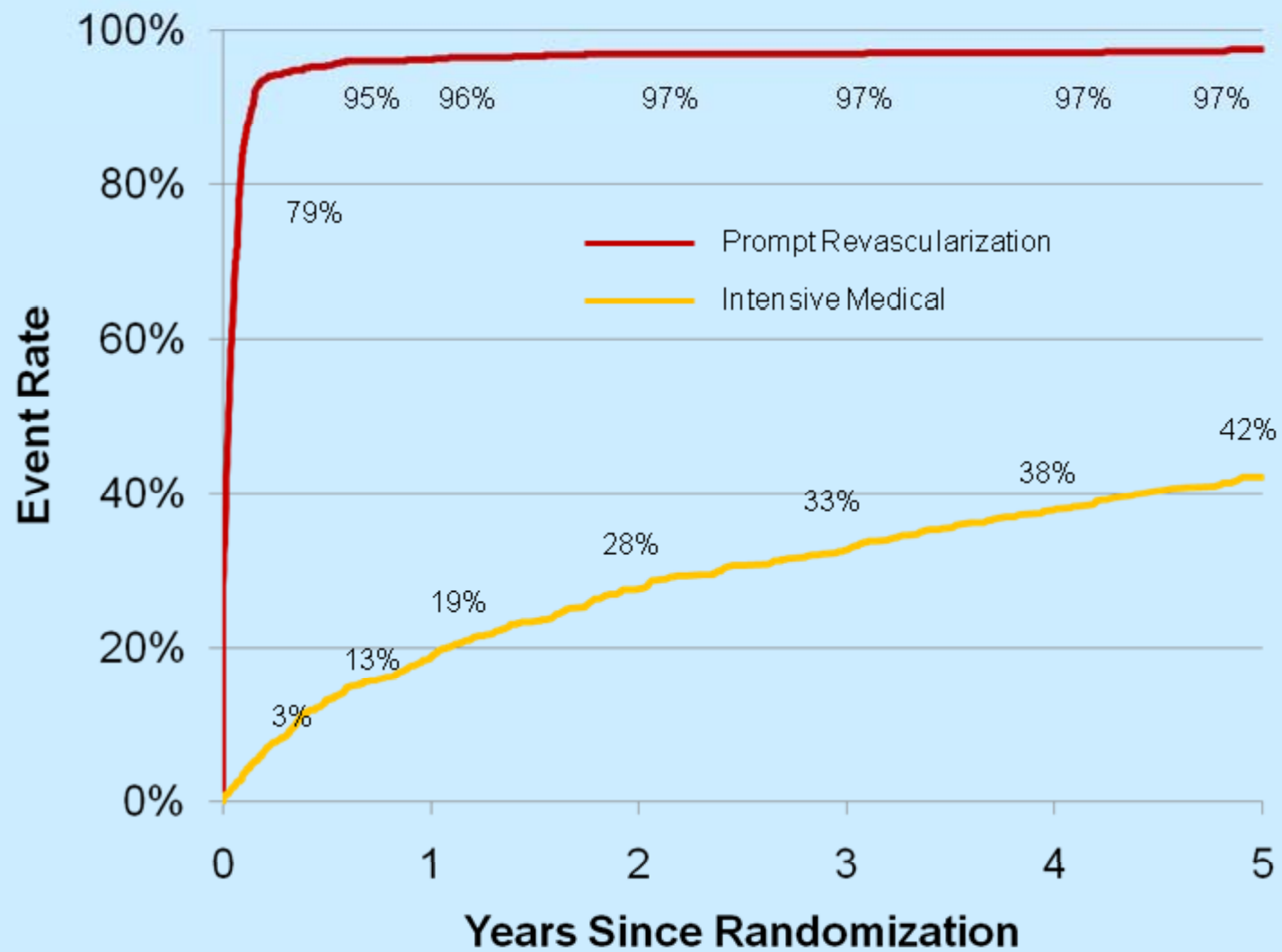
Medication	Baseline	Three Year	
		IS	IP
Metformin	54%	75%	10%
Thiazolidinedione	19%	62%	4%
Rosiglitazone	12%	55%	3%
Sulfonylurea	53%	18%	52%
Insulin	28%	28%	61%



# HbA1c Mean Over Time



# Cumulative Rate of First Revascularization



# Cardiovascular Medication Use

	Baseline	Three Year	
		Revascularization	Medical
Beta Blocker	73%	84%	88%
ACE / ARB	77%	91%	92%
Statin	75%	95%	95%
Aspirin	88%	94%	94%



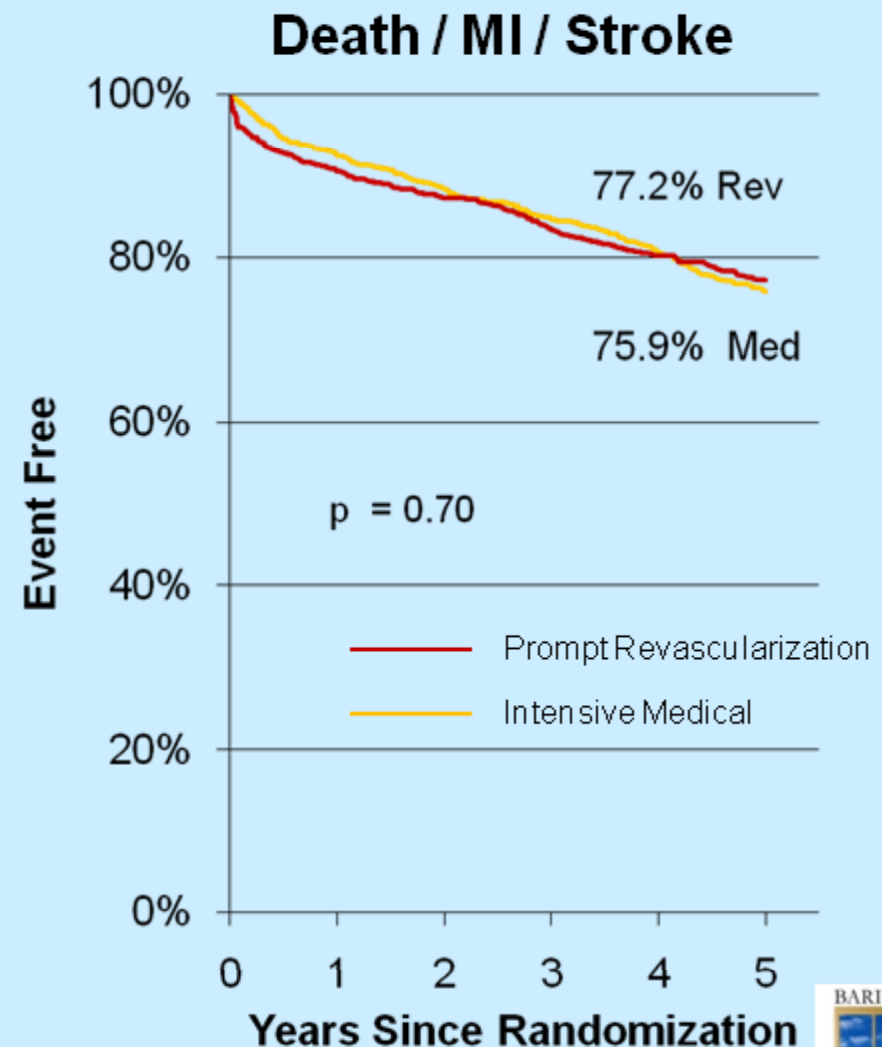
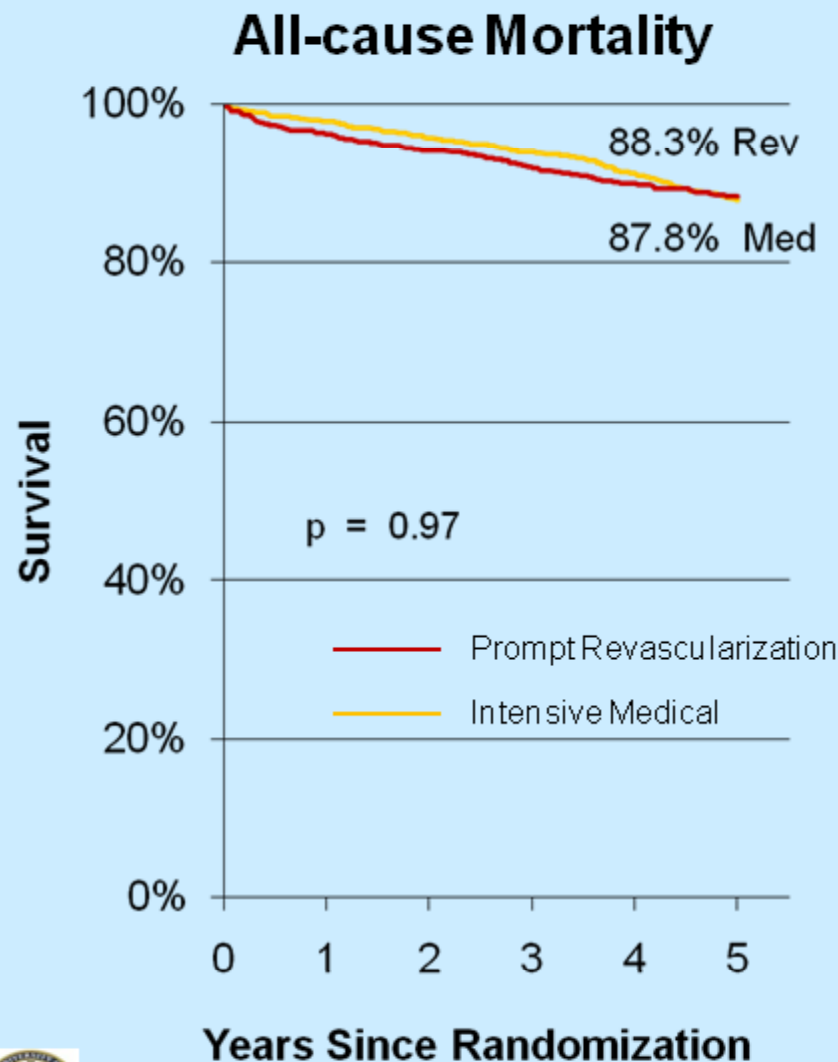
# **BARI 2D**

## **PRIMARY**

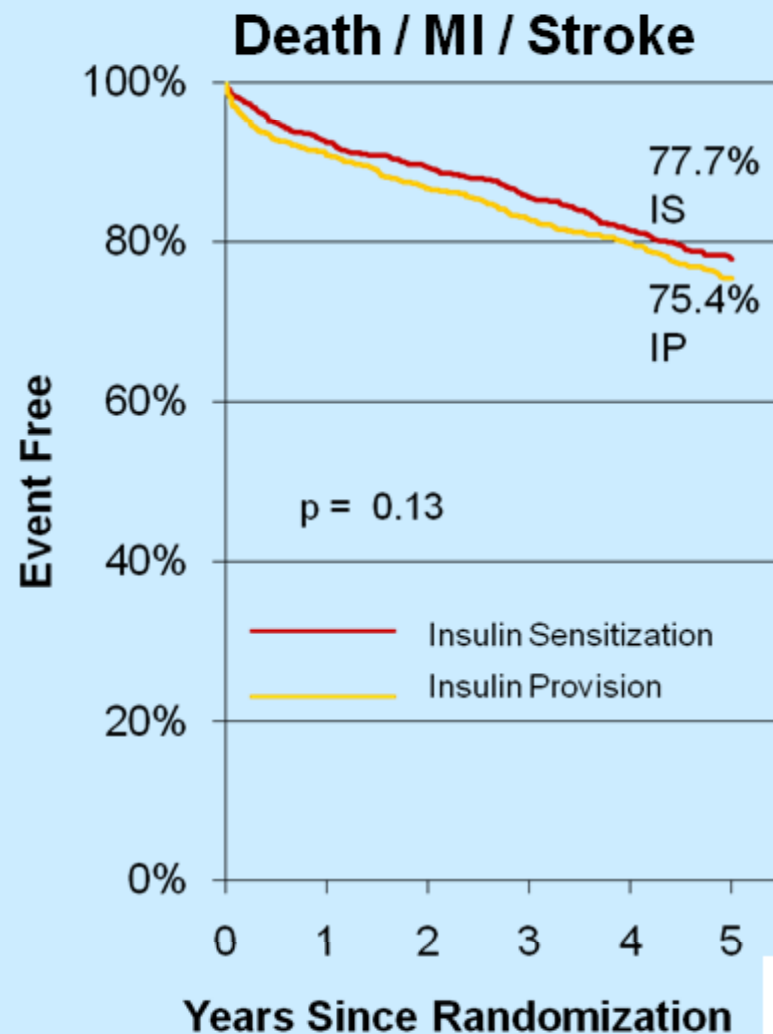
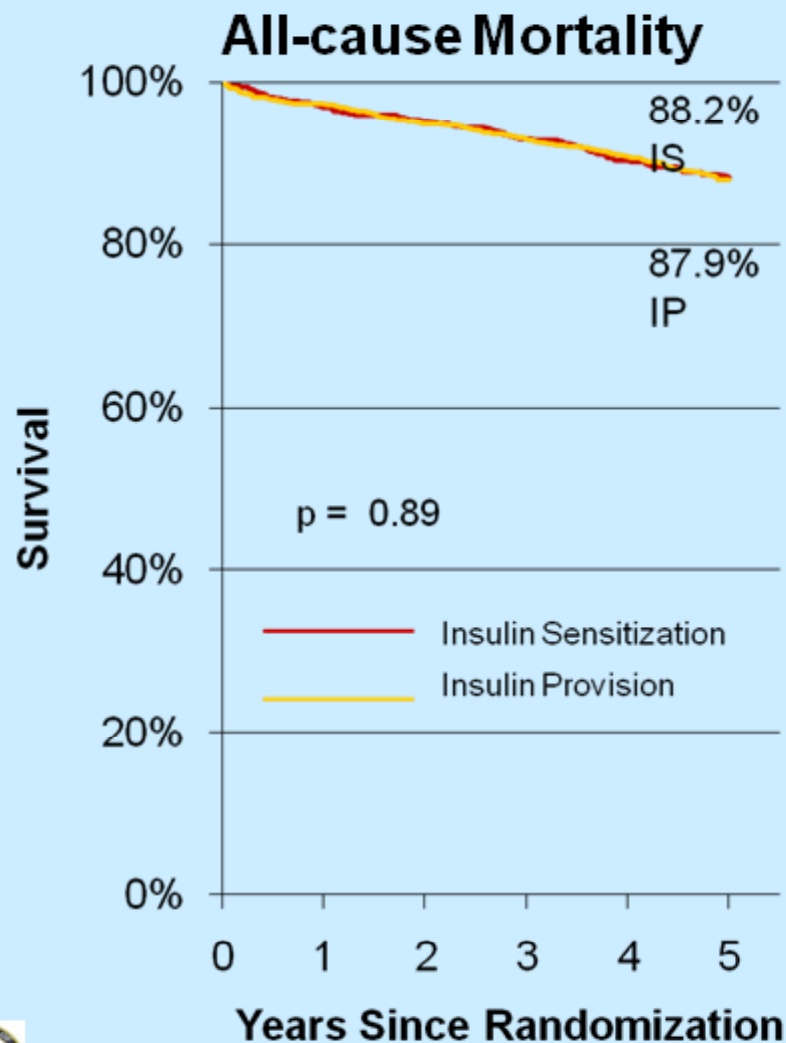
### **FIVE-YEAR RESULTS**



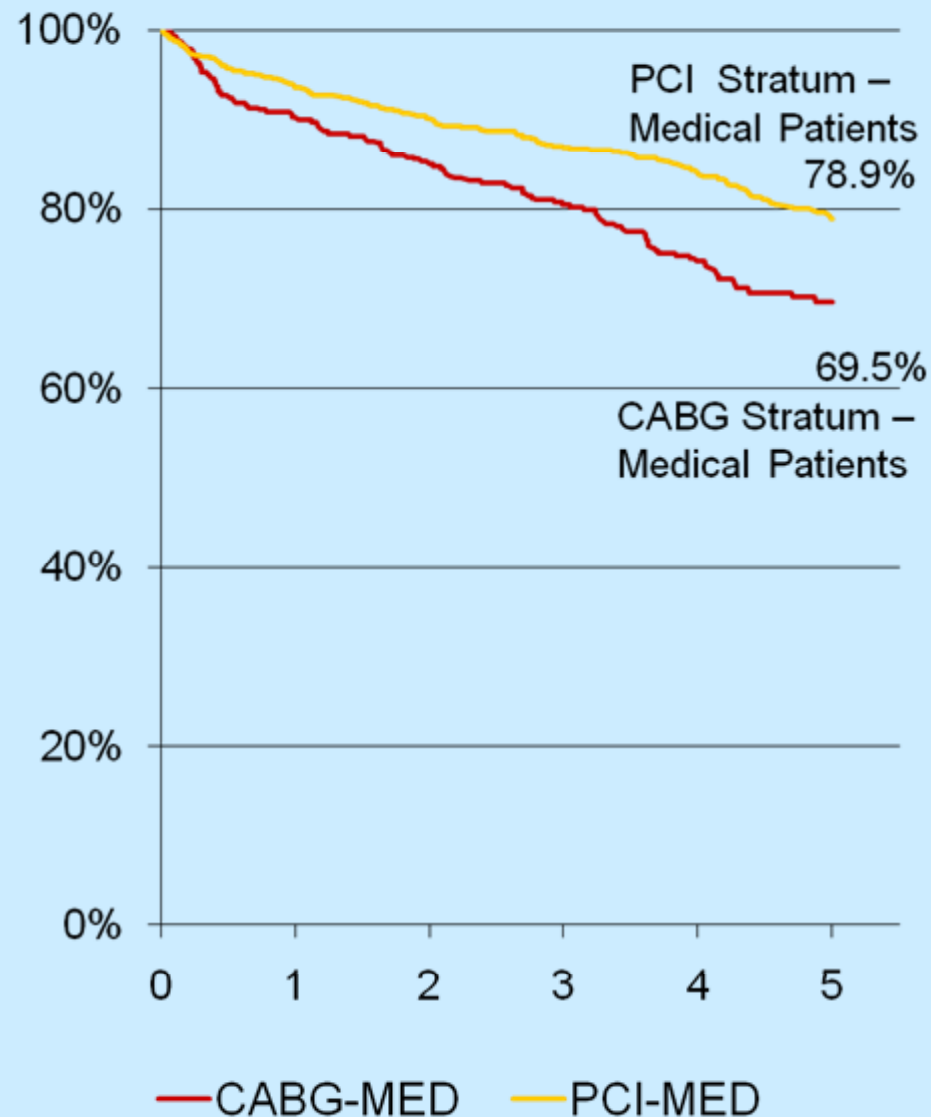
# Prompt Revascularization vs Medical Therapy



# Insulin Sensitization versus Insulin Provision

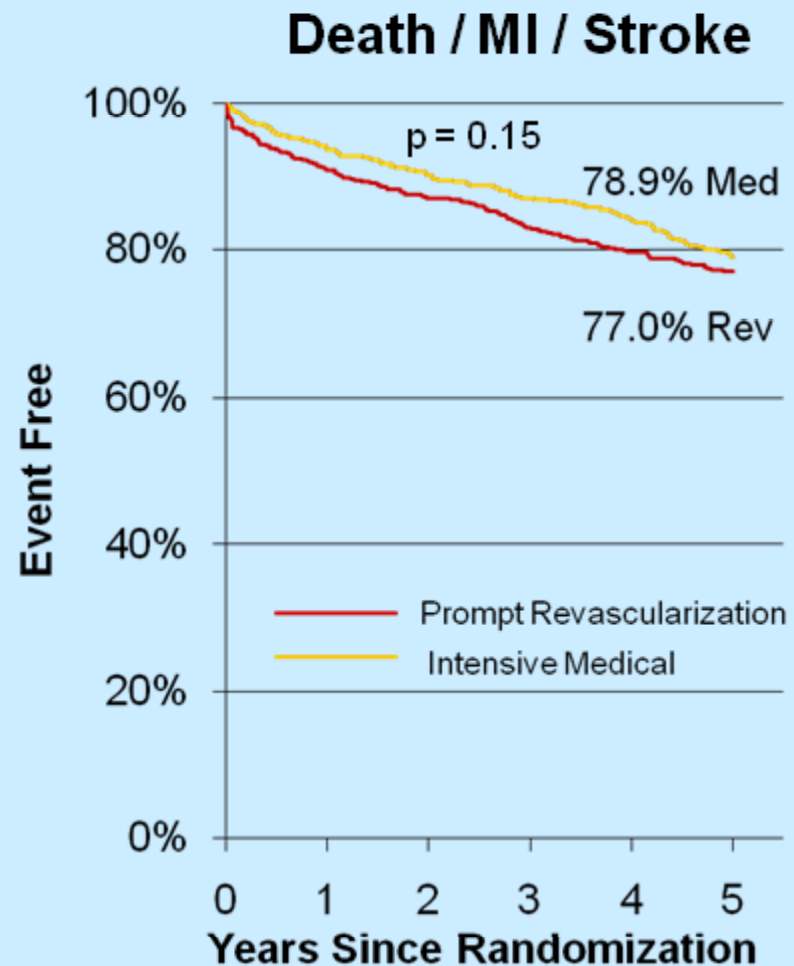
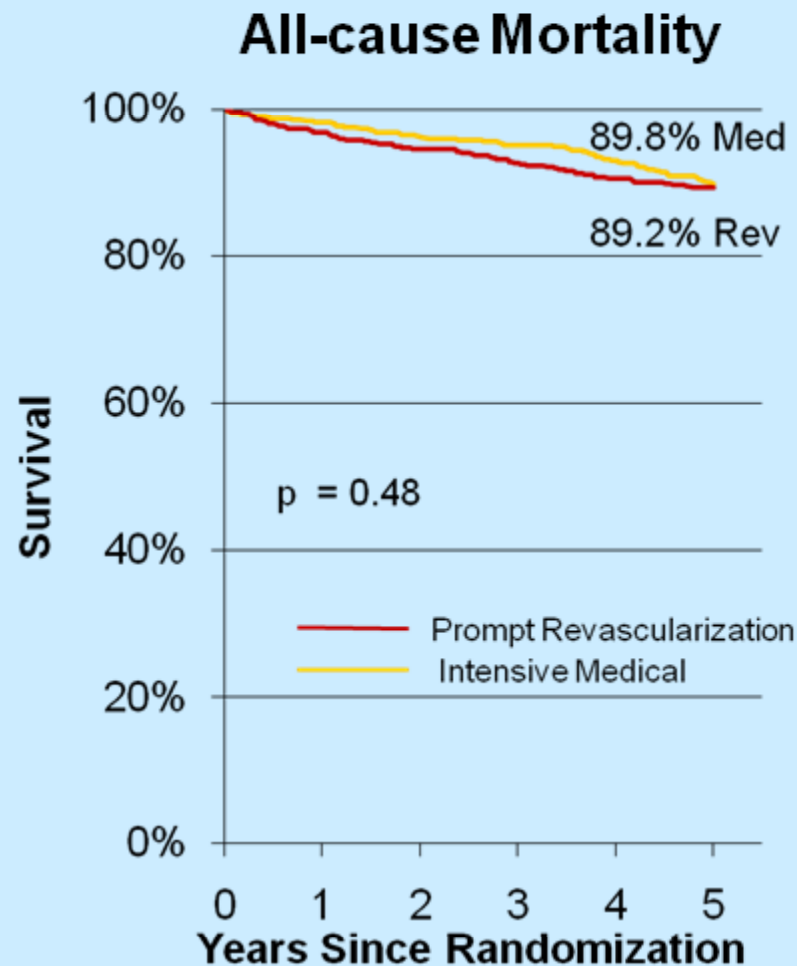


# Freedom from Death / MI / Stroke *Among Medical Assigned Patients*

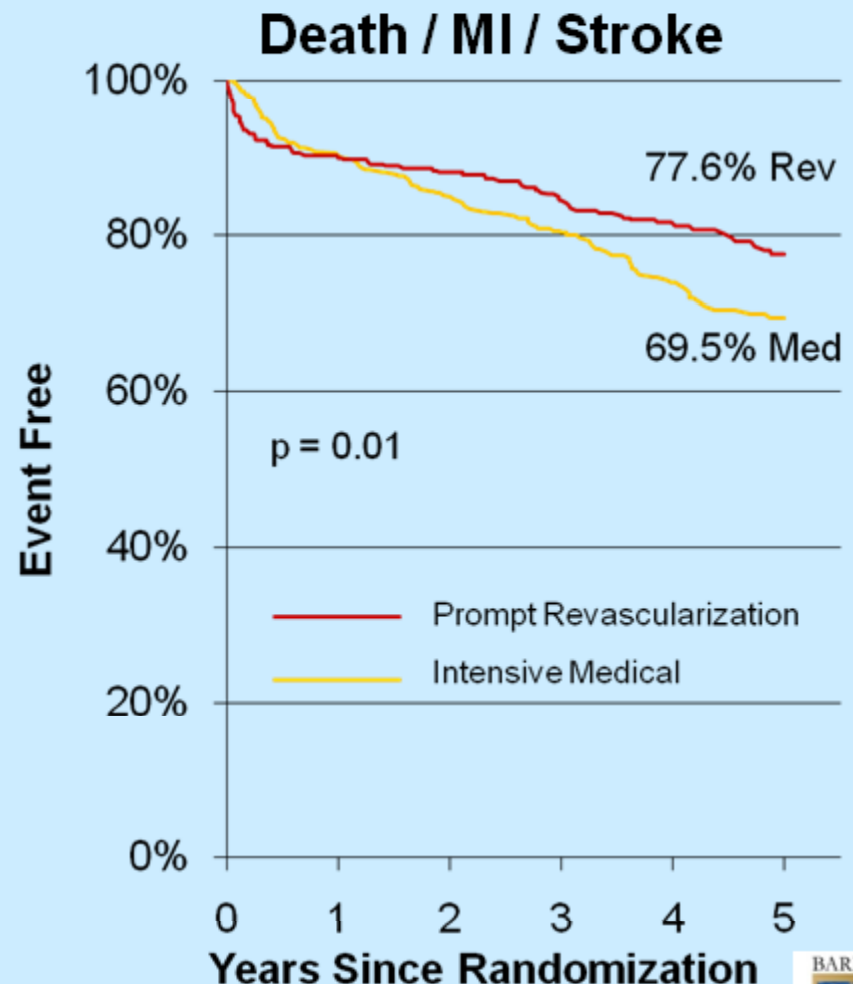
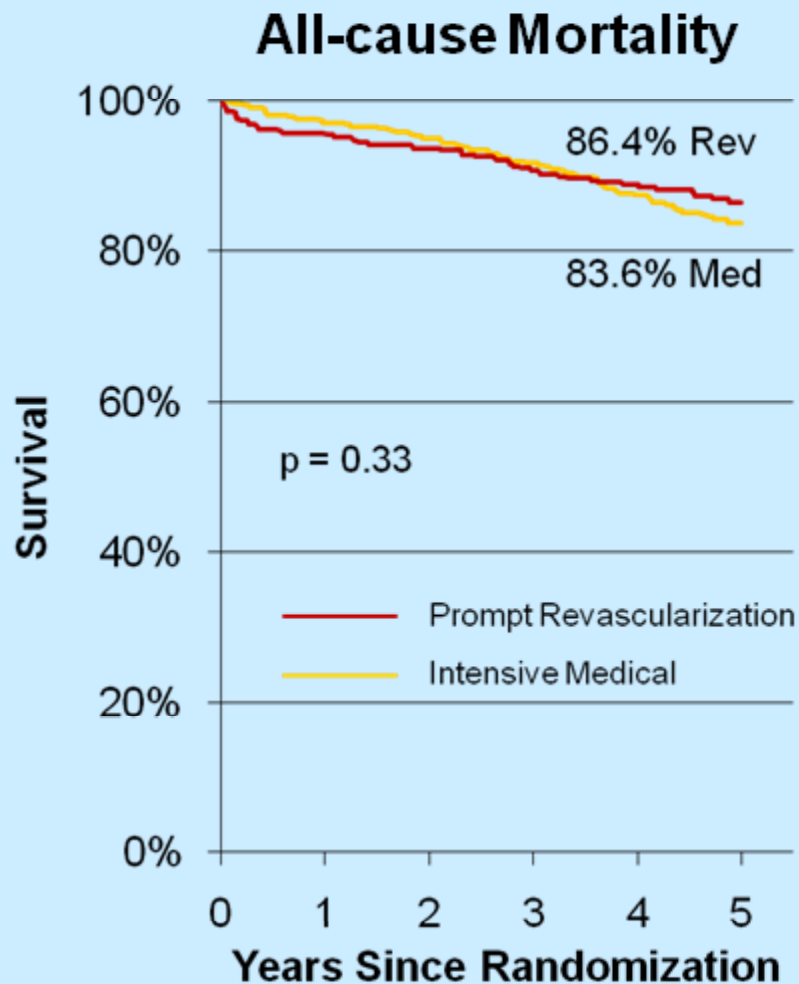




# PCI Intended Revascularization Stratum (Lower Risk Patients)



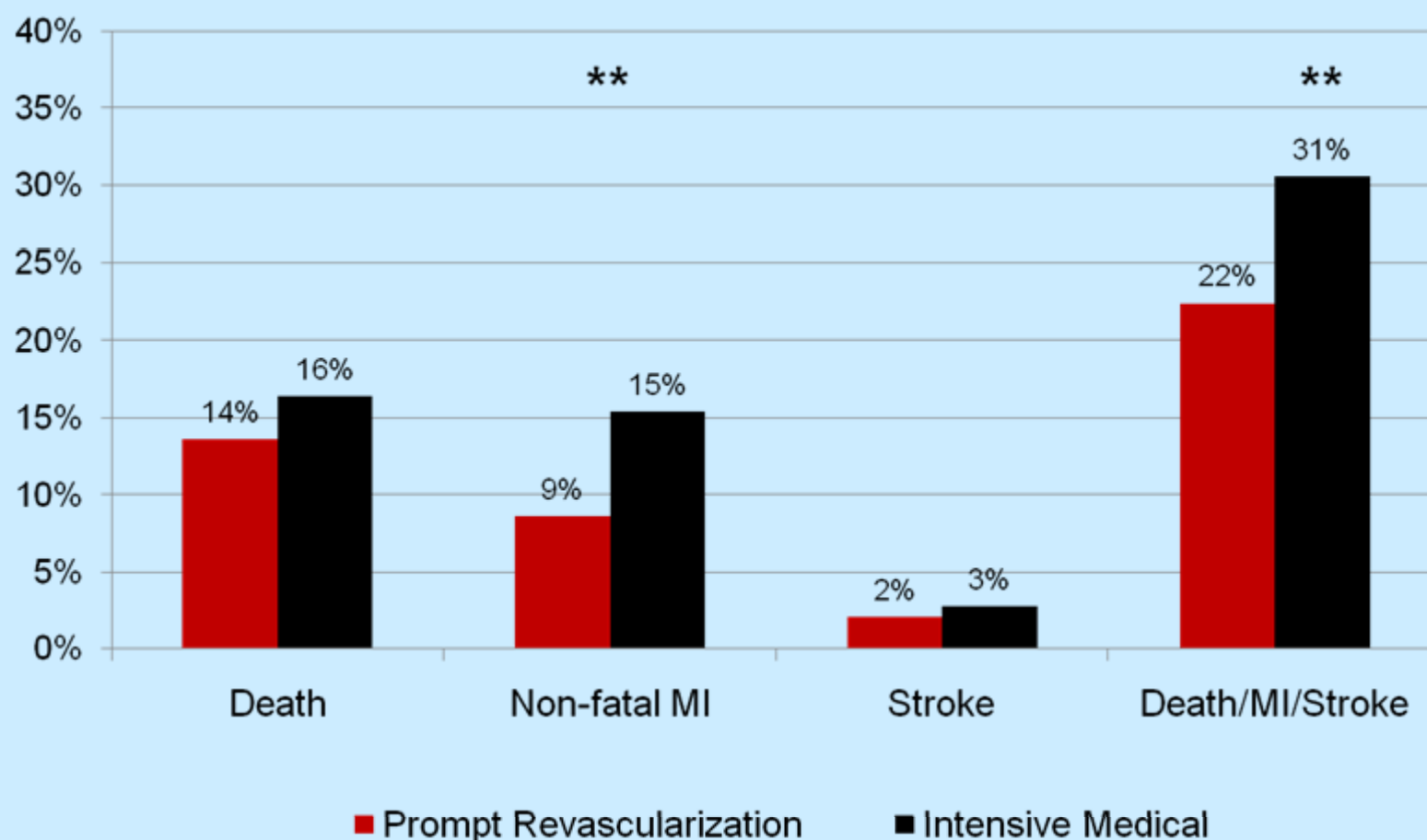
# CABG Intended Revascularization Stratum (Higher Risk Patients)



# Five-Year Clinical Event Rates

## CABG Intended Revascularization Stratum

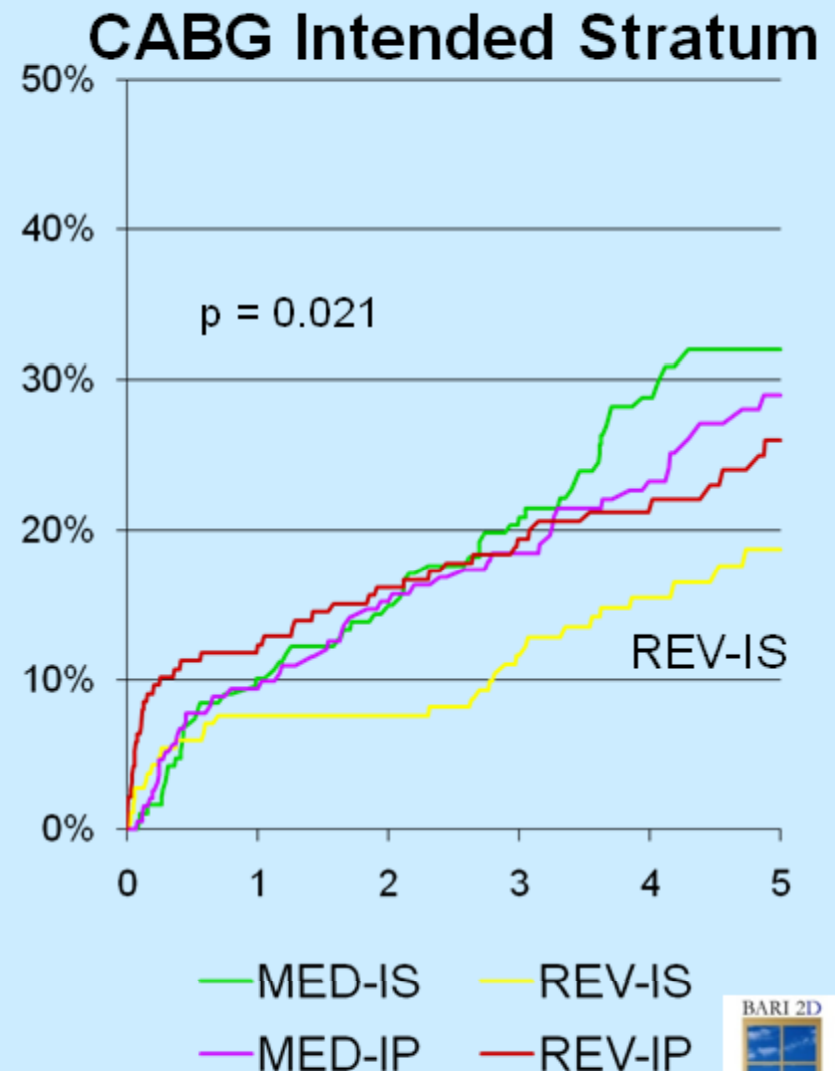
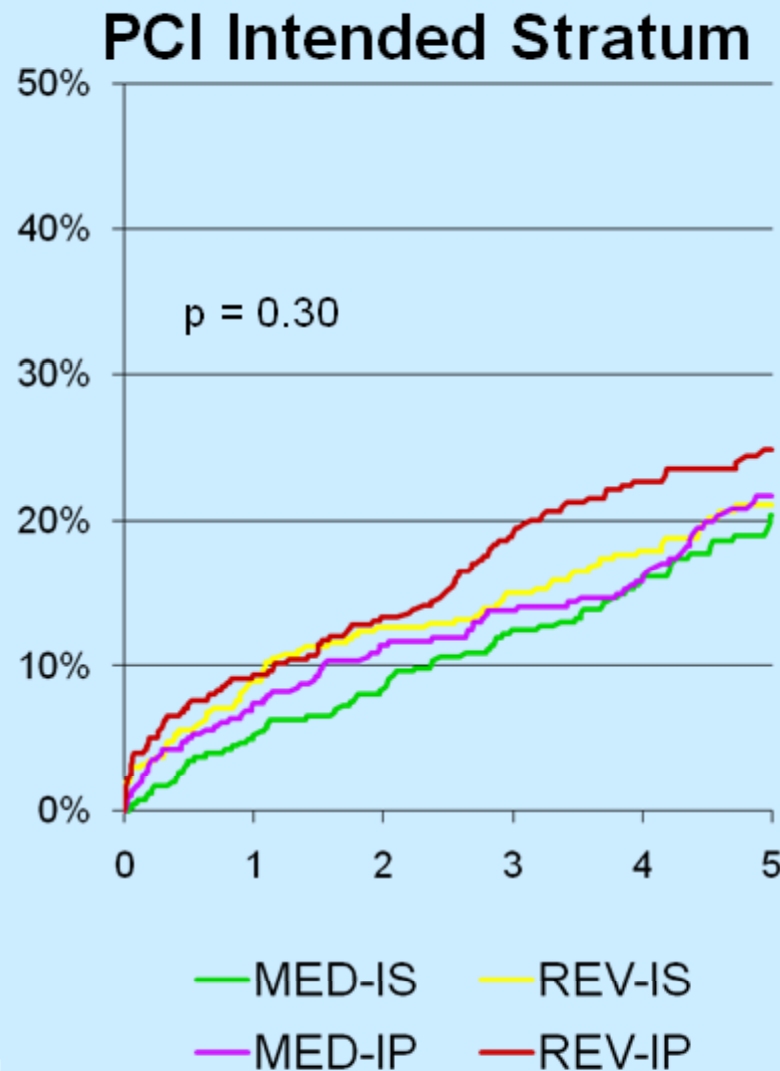
### N=763



\*\*  $p < 0.01$



# Major Cardiovascular Events



# Adverse Event Rates

## by Glycemic Randomized Treatment Assignment

Adverse Event	IS N=1154	IP N=1156	P-value
Hypoglycemia			
Any	53.3%	73.8%	0.001
Severe	5.9%	9.2%	0.003
Peripheral Edema	56.6%	51.9%	0.02
Congestive Heart Failure (CHF)			
All Patients	22.6%	20.0%	0.13
History of CHF *	67.2%	63.5%	0.65
No history of CHF *	19.4%	16.6%	0.09
Bone Fractures	7.6%	6.9%	0.54

\* N=141 patients had a history of CHF and N=2035 had no history of CHF

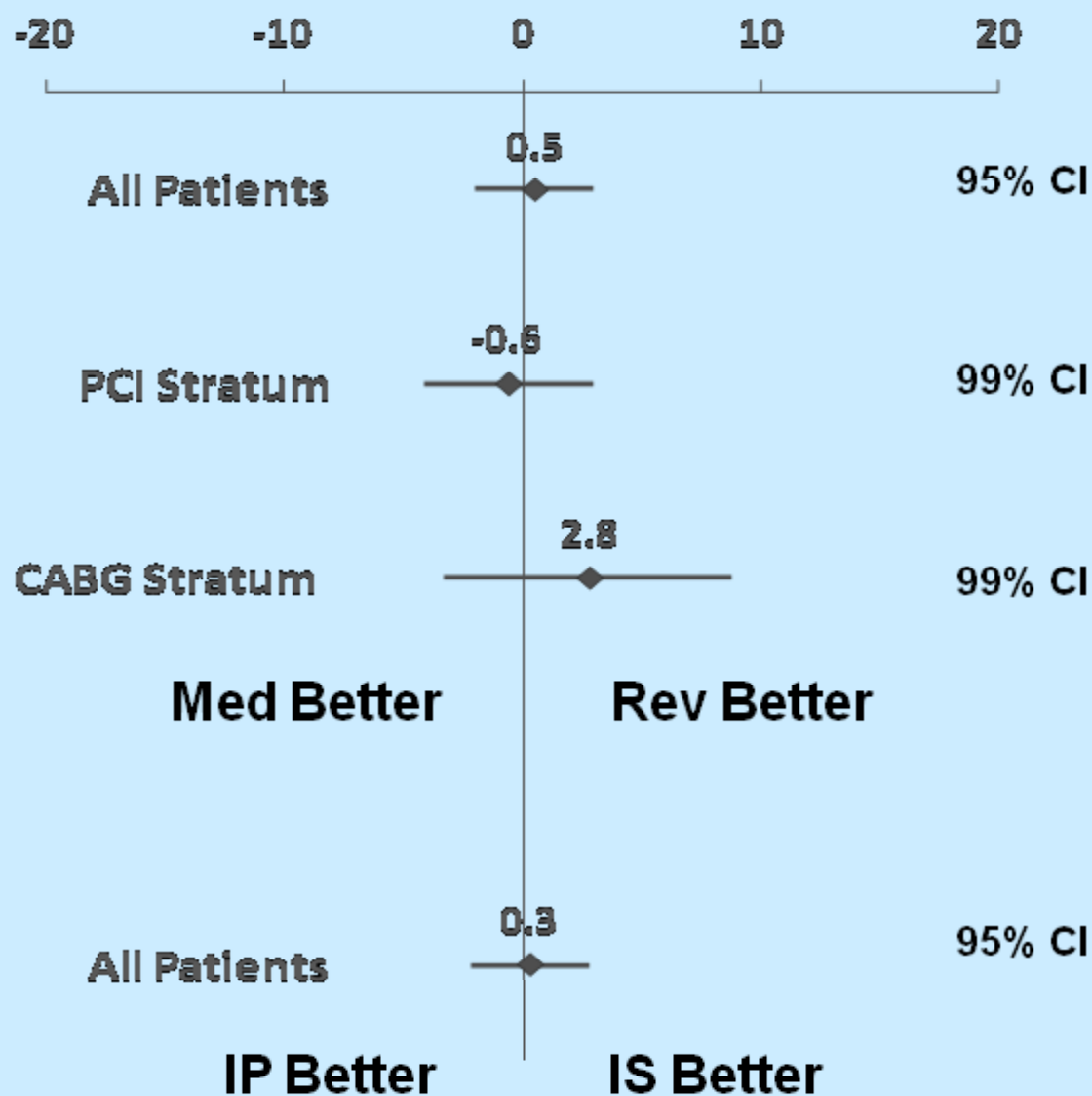


# BARI 2D

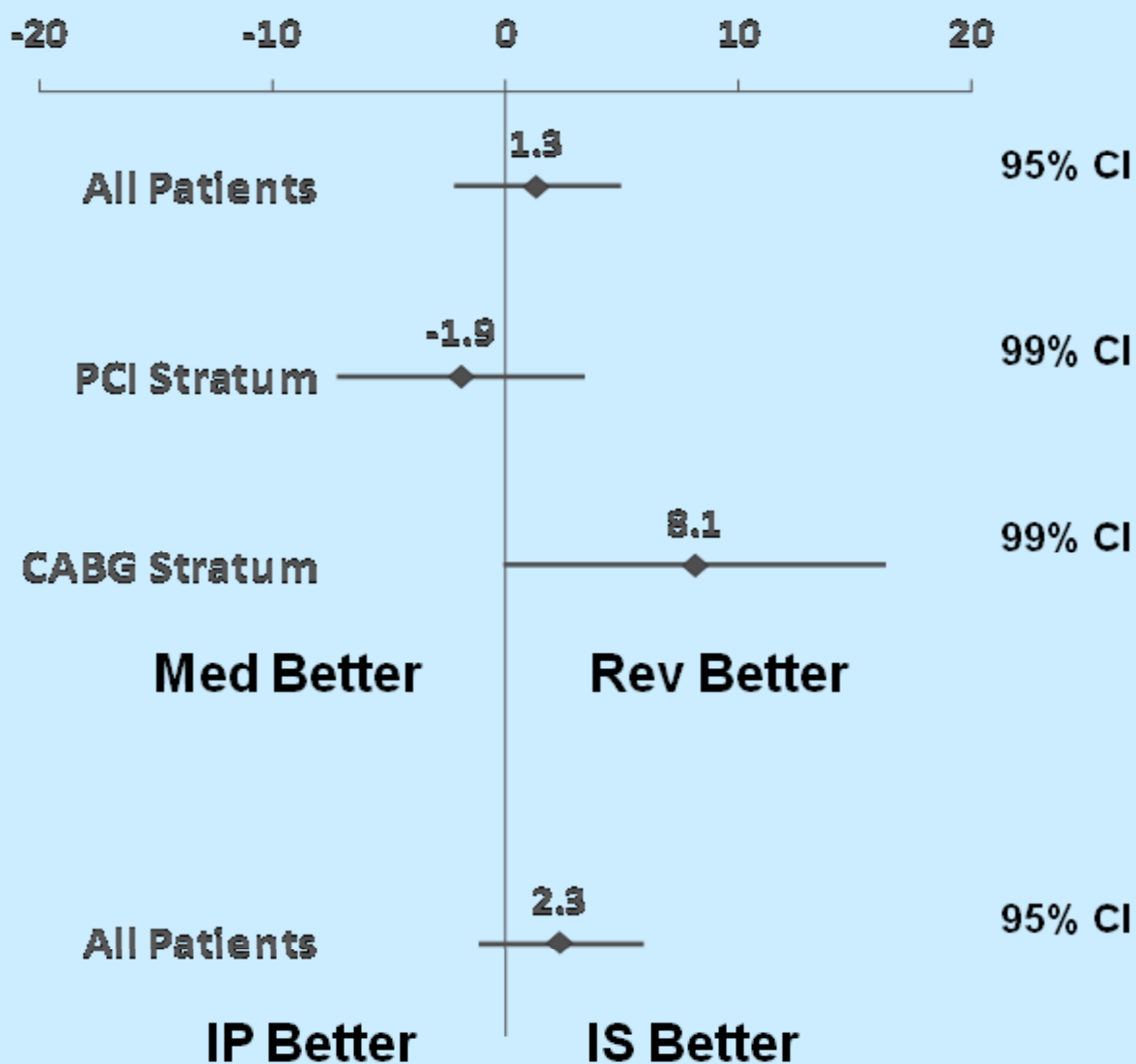
## RECAP AND IMPLICATIONS



# Five-Year All-Cause Death Rates Difference between BARI 2D Randomized Treatment Groups



# Five-Year Major Cardiovascular Event Rates Difference by BARI 2D Randomized Treatment Groups





# **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?

	Baseline	Year 3			USA* 2008
		IS	IP	Overall	
Metformin	54	75	10	42	64
TZDs	19	62	4	33	23
Sulfonylureas	53	18	52	35	40
Insulin	28	28	62	44	28

\*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

	IS	IP
Baseline Weight (Kg)	89.6±19.5	89.6±19.8
3 yr Weight (Kg)	89.9±21.1	91.7±20.7
Gain (Kg)	0.3±8.6	2.1±7.4
Baseline Waist Circumference (cm)	108.0±14.4	107.6±13.7
3 year Waist Circumference (cm)	107.7±15.4	109.1±14.2
Change (cm)	-0.1±9.1	+1.9± 8.4
1+ Severe Hypoglycemia Episode during trial (%)	5.9	9.2





# **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:

Angiographic  
Biochemistry/Genetics  
ECG  
Economics  
Fibrinolysis  
Nuclear

Stanford University  
University of Minnesota  
St. Louis University  
Stanford University  
University of Vermont  
Univ. of Alabama, Birmingham



# BARI 2D Sites

**University of Sao Paulo Heart Institute	St Louis University
**Toronto General Hospital/University Health Network	University of Texas @ Houston
**Texas Health Science @ San Antonio/South Texas	Kaiser-Permanente Medical Center
*Mayo Clinic-Rochester	Henry Ford Heart & Vascular Institute
*Mexican Institute of Social Security	Boston Medical Center
*University Hospitals of Cleveland/CASE Medical School	Fletcher Allen Health Care
*Memphis VA Medical Center/University of Tennessee	Jim Moran Heart & Vascular Institute
*Montreal Heart Institute/Hotel-Dieu-CHUM	Baylor College of Medicine
*Albert Einstein College of Medicine/Montefiore	Duke University
*Fuqua Heart Center/Piedmont Hospital	University of Maryland Hospital
*University of Alabama @ Birmingham	University of Chicago Medical Center
*Northwestern University Medical Center	University of Pittsburgh Medical Center
*Na Homolce Hospital	Washington University/Barnes Jewish Hospital
*Ottawa Heart Institute/Ottawa Hospital-Riverside Campus	Mount Sinai Medical Center
*New York Medical College/Westchester Medical Center	Mid America Heart Institute
*Emory University	University of Michigan
*Washington Hospital Center /Georgetown University	Johns Hopkins Bayview Medical Center
*Quebec Heart Institute/Laval Hospital	Brown University/Rhode Island Hospital
*University of British Columbia/Vancouver Hospital	Houston VA Medical Center
NYU School of Medicine	New York Hospital Queens
Lahey Clinic Medical Center	Wilhelminen Hospital
University of Virginia	St Joseph Mercy Hospital/Michigan Heart PC
University of Minnesota	Ohio State University Medical Center
St Luke's/Roosevelt Hospital Center	Mayo Clinic-Scottsdale
University of Florida	

\*\* ≥ 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)

