

Therapies for Type 2 Diabetes and Coronary Arterial Disease (BARI-2D)

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Studies on prevention of CAD

- A continuing debate regarding the most effective strategy for treating stable ischemic heart disease (SIHD).
 1. Patients with SIHD
 2. Patients with type 2 diabetes as being at high cardiac risk
 - Detection of Ischemia in Asymptomatic Diabetics (DIAD) study**
- Two recent multicenter, randomized trials, regarding the benefits of early revascularization in SIHD
 1. **Patients with SIHD:** Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (**COURAGE**) trial
 2. **Patients with T2DM and SIHD:** Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (**BARI-2D**) trial

Baseline clinical characteristics in **COURAGE** and **BARI-2D** trials

	Courage	BARI-2D
Year of initial publication	2008	2009
Period of recruitment	1999–2004	2001–2005
Entry criteria	CAD by catheter plus positive stress or angina	CAD by catheter plus T2DM plus positive stress or angina
Type of revascularization and randomization	PCI + OMT vs OMT	PCI + OMT vs OMT CABG + OMT vs OMT
Primary end point	Death/nonfatal MI	Death
Secondary end point	Death/MI/stroke/hospitalization for unstable angina	Death/MI/stroke
Follow-up, y	4.6	5
Patients, <i>n</i>	2287	2368
OMT patients, <i>n</i>	1149	1192
Revascularization patients, <i>n</i>	1138	1176 (798 for PCI, 378 for CABG)
Mean age, y	61	62
Previous MI	38%	32%
T2DM	34%	100%
Angina CCS classification	78% with 0–II 21% with III	60% with 0–II 9% with III–IV
Mean LVEF	61%	57% (82% were normal)
Crossover (medically treated and revascularized during follow-up)	33%	42%

Early revascularization with **PCI in combination with OMT** is **not superior** to **OMT alone** in reducing mortality and other major cardiovascular events

Results of BARI 2D study

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A Randomized Trial of Therapies for Type 2 Diabetes
and Coronary Artery Disease

The BARI 2D Study Group*

Background

- Patients with **type 2 diabetes** have an increased risk of suffering a **cardiovascular event** over **non-diabetic** patients.
- The success of **coronary revascularization** in reducing **myocardial infarction** and **death** in **diabetic** patients with chronic stable angina has **not been established**.
- Similarly, it is **unclear** if **insulin sensitization therapy** offers benefits over **insulin provision therapy** in reducing **cardiovascular events**.

Hypothesis

- Evaluate two **cardiac treatment strategies** and two **glycemic treatment strategies** in patients who were receiving **uniform glycemic control** and **intensive therapy for cardiac risk factors**.

1. The first hypothesis :

prompt revascularization (either surgical or catheter-based) would reduce **long-term rates of death** and **cardiovascular events**, as compared with **medical therapy** alone.

2. The second hypothesis :

insulin sensitization (with a target level for A1c < 7.0%) would reduce **long-term rates of death** and **cardiovascular events**, as compared with **insulin provision**.

➤ **Eligibility criteria** : both T2D with Coronary Artery Dis.

- **Type 2 Diabetes**: insulin or oral OHA
- **Coronary Artery Disease**
 - Documented on angiography
 - 1) **≥ 50% stenosis** of a major epicardial coronary artery a.w + **stress test**
 - 2) **≥ 70% stenosis** of a major epicardial coronary artery and **classic angina**).

Exclusion criteria

Required immediate revascularization

≥ 50% left main coronary disease

Cr ≥ 2.0 mg/dL

A1c ≥ 13.0%

Heart failure: class III, IV

Undergone PCI or CABG within the previous 12 Mon

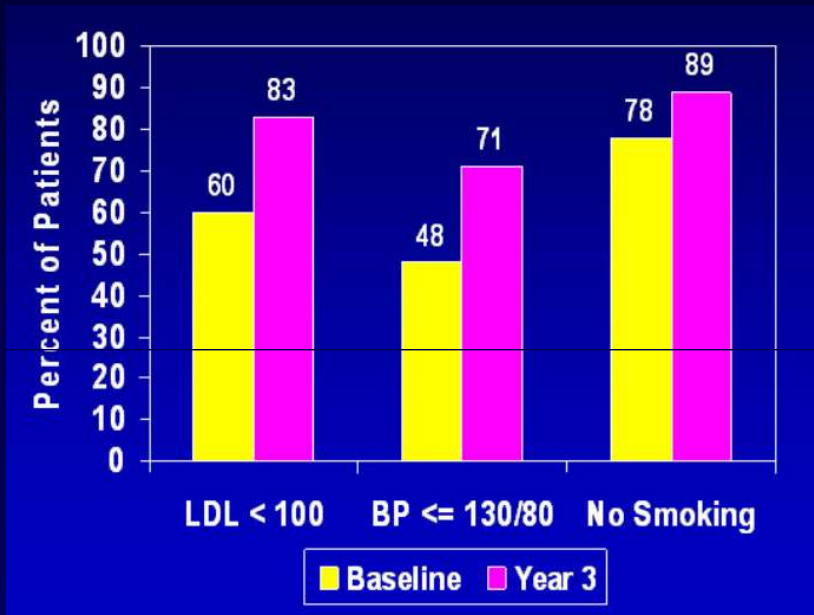
- Randomly assigned to two treatment strategies in a **2- by -2 factorial design** to achieve a target **A1c < 7.0%**.
 - 1) In the **first strategy**, either **prompt coronary revascularization** or **medical therapy**.
 - 2) In the **second strategy**, either **insulin- sensitization** therapy or **insulin- provision** therapy.

		Revasc	Medical	
Glucose Control Strategy	Insulin Providing	592	593	1185
	Insulin Sensitizing	584	599	1183
		1176	1192	2368

Endpoints

- Average **follow-up** time **5.3 years**
- The **primary end point** : **death** from any cause.
- The **secondary end point** : a composite of **death, myocardial infarction, or stroke** (major cardiovascular events).

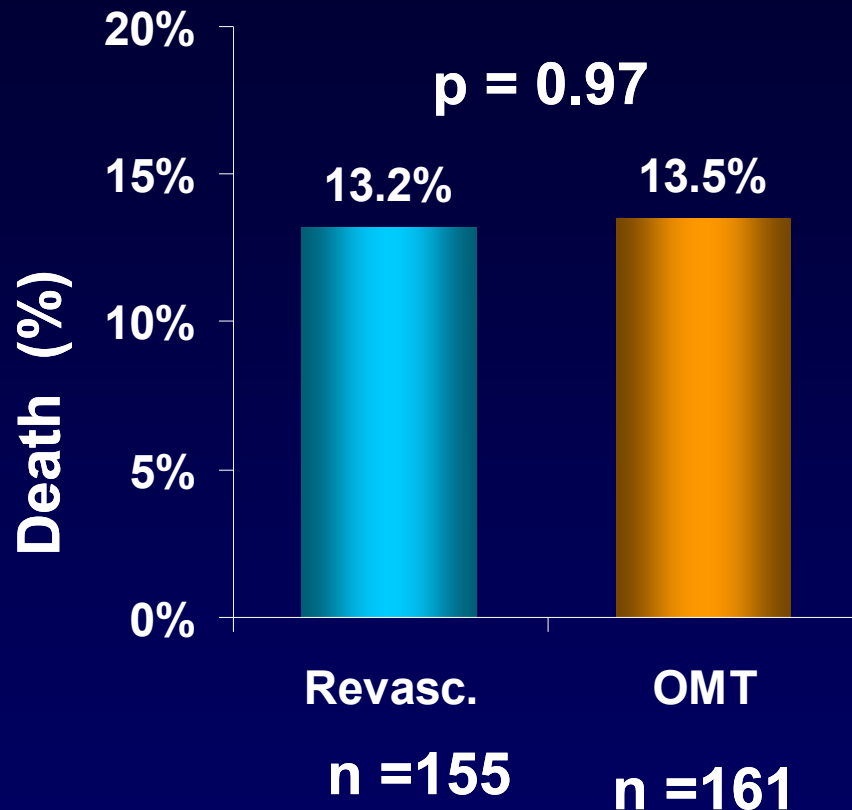
Risk Factor Control



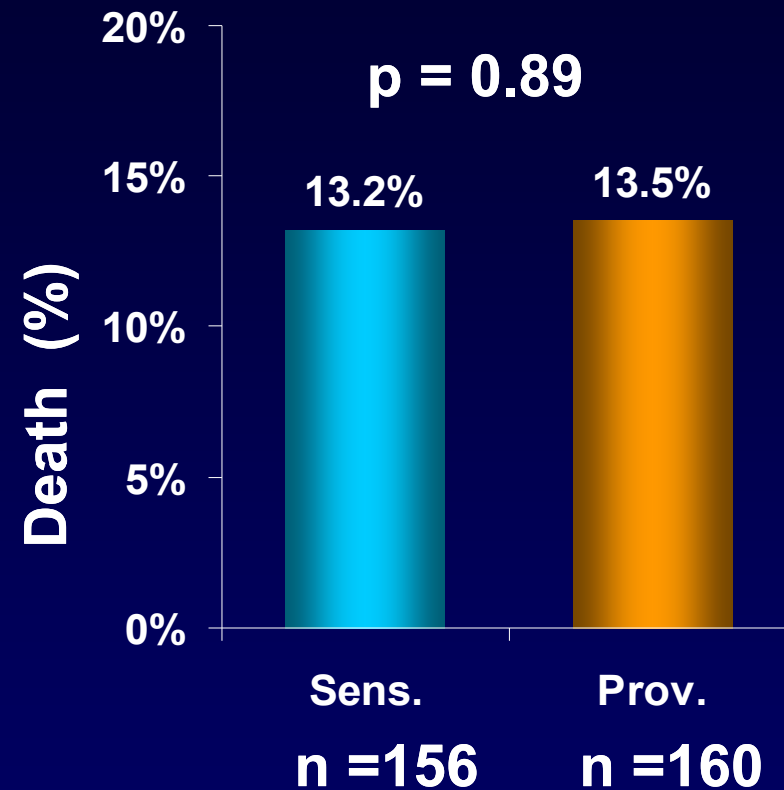
	Baseline	Three Year	
		Revasc	Medical
Beta Blocker	73	84	88
ACE / ARB	77	91	92
Statin	75	95	95
Aspirin	88	94	94

Uniform glycemic control and **intensive therapy** for **cardiac risk factors**

Primary Endpoint

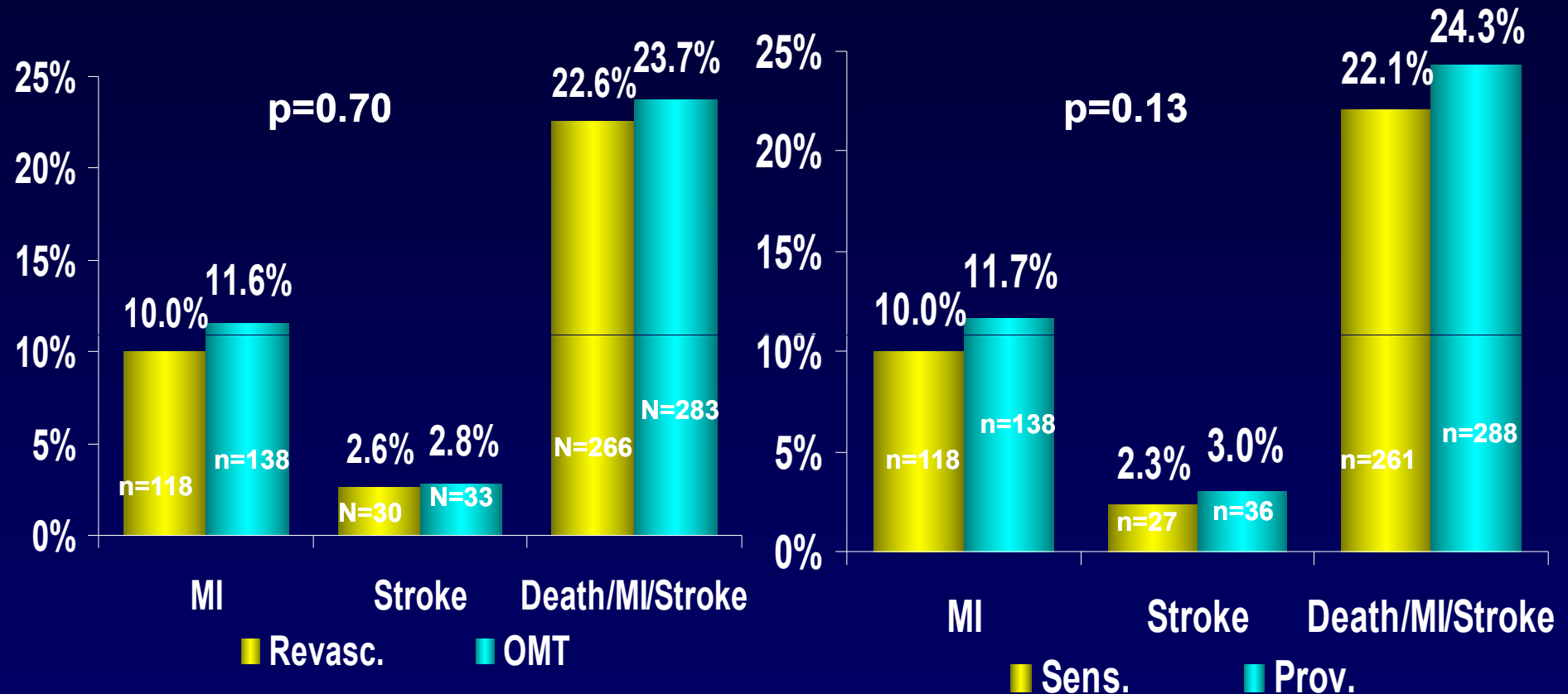


- The **5-year death rate** for the group receiving **revascularization plus optimal medical therapy** was 13.2% vs. 13.5% in the group receiving **optimal medical therapy** alone.



- The **5-year death rate** for the group receiving **insulin sensitization** therapy was 13.2% vs. 13.5% in the group receiving **insulin provision** therapy..

Secondary Endpoint



- The rates of MI, stroke and the combined **secondary endpoint** of death, MI, and stroke were similar between the group receiving **revascularization plus optimal medical therapy** vs. the group receiving **optimal medical therapy** alone.
- The rates of MI, stroke and the combined **secondary endpoint** of death, MI, and stroke were similar between the group receiving **insulin sensitization therapy** vs. the group receiving **insulin provision therapy**.

Summary of BARI-2D study

For all subjects, similar mortality & major cardiovascular events

- Prompt revascularization *versus* OMT (delayed/no revascularization).
- Insulin sensitization *versus* insulin provision

Re-assessment of BARI 2D results
- Focusing confusion points

Summary of BARI-2D study

1. For **all subjects**, similar mortality & major cardiovascular events

- Prompt revascularization versus delayed/no revascularization.
- Insulin sensitization versus insulin provision

2. Among **low risk patients** selected for **PCI**
Similar major cardiovascular events

- Prompt revascularization versus delayed/no revascularization.
- Insulin sensitization versus insulin provision

3. Among **high risk patients** selected for **CABG**
↓ major cardiovascular events

1) Prompt revascularization > delayed/no revascularization

2) **Insulin sensitization** appeared to enhanced the **benefit of revascularization** particularly among the those selected for **CABG**

BARI- 2D reassessment

- A little confusion 1.
 - What **BARI 2D** is **NOT** :
 - A test of **PCI** versus **CABG**
 - A test of individual **diabetes drugs** or a test of different **A1c targets**.
ACCORD, ADVANCE, and VADT trials
 - What **BARI 2D** is :
 - A comparison of **STRATEGIES** for myocardial ischemia.
prompt revascularization vs. medical therapy
 - A comparison of **STRATEGIES** for glycemic control.
insulin sensitization vs. insulin provision

BARI- 2D reassessment

- A little confusion 2.

Multicenter, randomized trials 2- by -2 factorial design

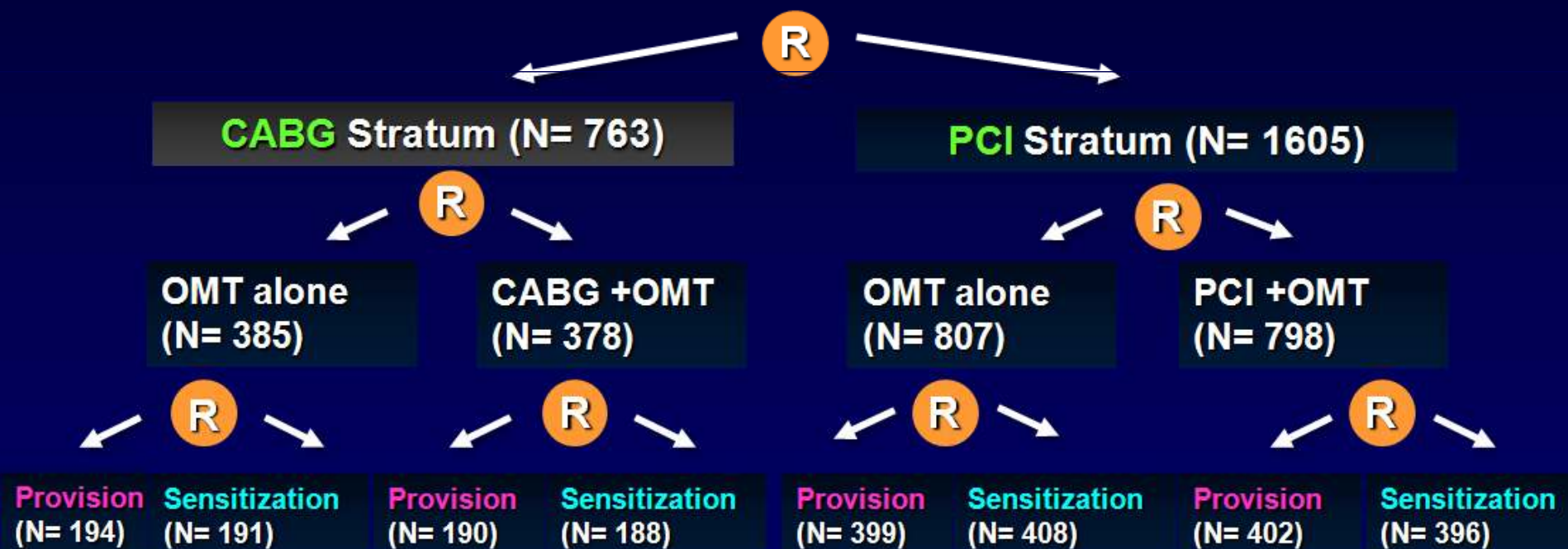
Design of the ACCORD trial

GLYCEMIA TRIAL	BLOOD PRESSURE TRIAL		LIPID TRIAL*		TOTAL
	SYSTOLIC BLOOD PRESSURE < 120 MM HG	SYSTOLIC BLOOD PRESSURE < 140 MM HG	GROUP A	GROUP B	
Intensive therapy (hemoglobin A _{1c} < 6%)	1,178	1,193	1,383	1,374	5,128
Standard therapy (hemoglobin A _{1c} 7.0%–7.9%, inclusively)	1,184	1,178	1,370	1,391	5,123
Total	2,362	2,371	2,753	2,765	
Total		4,733		5,518	10,251

*Treatment group assignment blinded until end of trial. Treatment group A = statin plus fenofibrate placebo; treatment group B = statin plus fenofibrate

Glucose Control Strategy	Revasc	Medical	
	Insulin Providing	592	593
Insulin Sensitizing	584	599	1183
	1176	1192	2368

2368 patients with mild to moderate CAD and Type 2 diabetes prior to randomization. Prospective. Randomized. Mean follow-up 5.3 years



➤ **Revascularization Decision**

- This analysis included 1,773 patients **without previous procedures.** (**no histories** of coronary **revascularization** and >80% of baseline information available)
- Cardiologist a **priori selected revascularization** method based on clinical and angiographic factors

Percutaneous C oronary Intervention (PCI)
or
Coronary Artery Bypass Graft Surgery (CABG)

Baseline Characteristics

Characteristic	Revasc (CABG + OMT or PCI + OMT) (n=1176)	OMT (n=1192)
Age (yrs±SD)	62.3 ± 8.8	62.4 ± 9.0
Male (%)	70.4	70.3
HbA1c (% mean±SD)	7.6 ± 1.6	7.7 ± 1.6
Duration of diabetes (years mean±SD)	10.2 ± 8.5	10.7 ± 8.8
History of MI (%)	31.7	32.4
History of CHF (%)	7.1	6.2
Cerebrovascular event (%)	9.5	10.0
Peripheral artery disease (%)	23.7	23.7
Prior revascularization (%)	22.9	24.2

Baseline Characteristics

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

Table 1

Angiographic characteristics by intended revascularization assignment (excludes patients with previous procedures)

Angiographic Characteristic	Stratum			p Value
	All Patients (n = 1,773)	CABG (n = 655)	PCI (n = 1,118)	
No. of lesions ($\geq 20\%$ DS)	4.6 \pm 2.3	5.7 \pm 2.2	4.1 \pm 2.0	<0.0001
No. of significant lesions ($\geq 50\%$ DS)	2.6 \pm 1.7	3.6 \pm 1.7	2.1 \pm 1.5	<0.0001
No. of lesions $\geq 70\%$ DS	1.1 \pm 1.2	1.7 \pm 1.3	0.8 \pm 1.0	<0.0001
Proximal LAD coronary artery disease ($\geq 50\%$ DS)	12%	19%	8%	<0.0001
No. of total occlusions				<0.0001
0	62%	40%	74.5%	
1	30%	44%	21.7%	
≥ 2	8%	16%	3.8%	
No. of territories* with $\geq 50\%$ DS				<0.0001
0	3%	0.5%	4%	
1	29%	8.7%	41%	
2	36%	37.4%	36%	
3	32%	53.4%	19%	
MJI (%)	46 \pm 24	61 \pm 21	38 \pm 22	<0.0001
Categorical MJI (%)				<0.0001
≤ 25	23%	6%	33%	
26-50	35%	26%	41%	
51-75	28%	42%	20%	
76-100	14%	26%	6%	

Left ventricular ejection fraction (%)	(n = 1,695)	(n = 635)	(n = 1,060)	
Mean	58 ± 11	57 ± 11	58 ± 11	0.54
<50	16%	18%	16%	0.29
<40	5%	6%	4%	0.23
Lesion-level analysis	(n = 8,286)	(n = 3,752)	(n = 4,534)	
DS				<0.0001
<50%	44.5%	38%	50%	
50%–69%	32%	33%	31%	
70%–89%	9%	10%	8%	
90%–100%	14.5%	19%	11%	
Total occlusion (99% or 100% DS)	10%	14%	7%	<0.0001
Distal flow (TIMI grade)				<0.0001
0	7%	10%	5%	
1	4%	4%	3%	
2	4%	5%	3%	
3	85%	81%	89%	
ACC/AHA classification [†]				<0.0001
Type A	30%	27.6%	31.5%	
Type B	46%	43.8%	48.7%	
Type C	24%	28.6%	19.8%	
Ostial [†]	4%	5%	3%	0.009
Side branch [†]	5%	5%	6%	0.08
Nondiscrete	18%	19%	17%	0.04
Moderate/severe tortuosity [†]	24%	25%	24%	0.31
Irregular/ulcerated contour [†]	15%	16%	14%	0.08

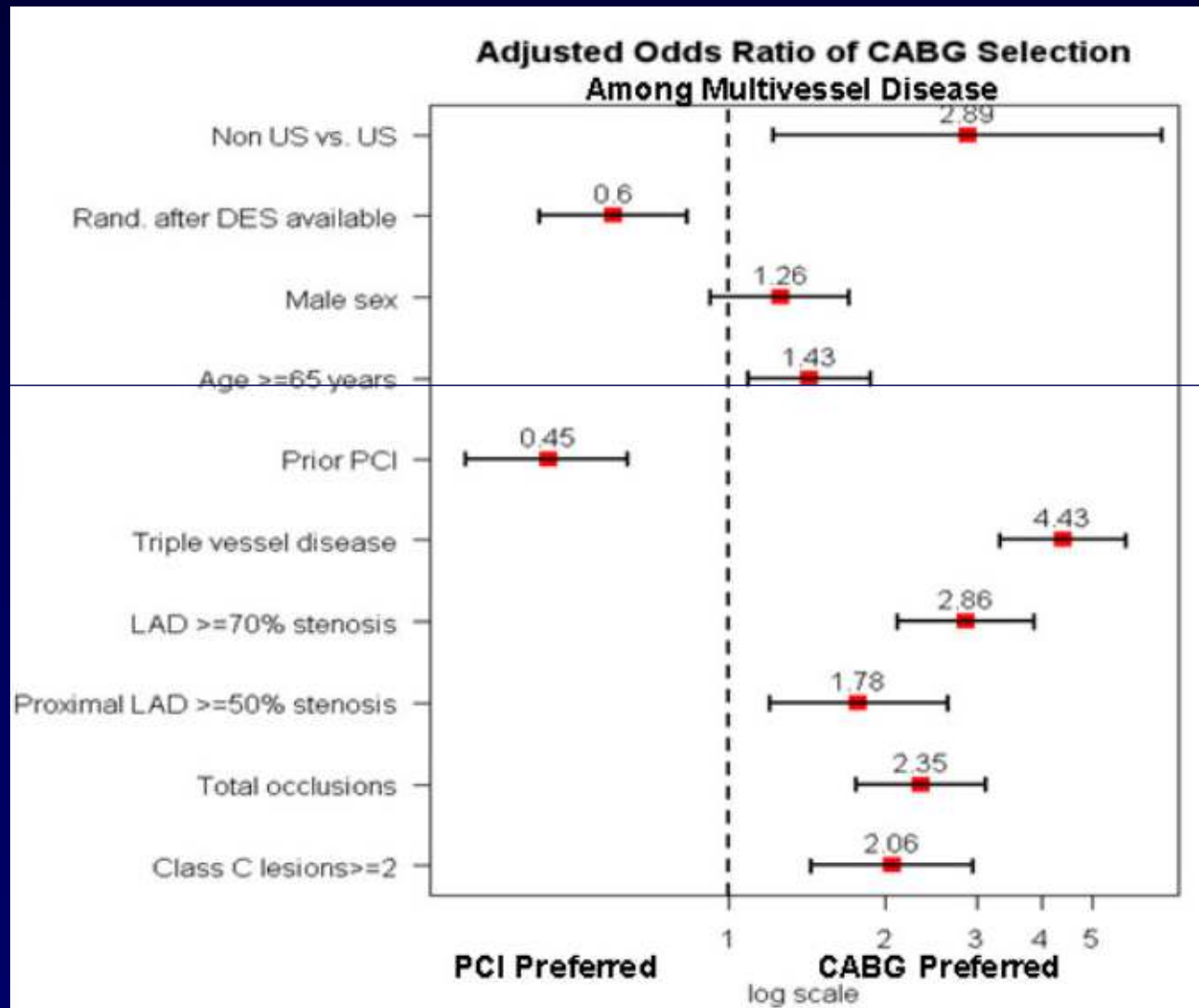
Continuous variables are presented as mean ± SD, and categorical variables are presented as percentages.

* Each of the 3 epicardial coronary arteries supplies 1 territory; a dominant circumflex artery supplies 2 territories.

[†] Assessed only for lesions 50% to 98% DS.

ACC = American College of Cardiology; AHA = American Heart Association; DS = diameter stenosis; LAD = left anterior descending.

Adjusted Odds Ratio of CABG selection among Multivessels



BARI 2D BASELINE CORONARY ANGIOGRAPHIC FINDING

- BARI 2D patients, who by design have **mild or no symptoms**, demonstrate considerable **variation in the extent of CAD and amount of jeopardized myocardium**.

- Evaluate 2 coequal outcome measures in this analysis :
 - (1) the number of lesions **20% diameter stenosis**: reflecting **atherosclerotic burden**
 - (2) the total MJJ (**Myocardial Jeopardy Index**): reflection of the extent of **potential myocardial ischemia**

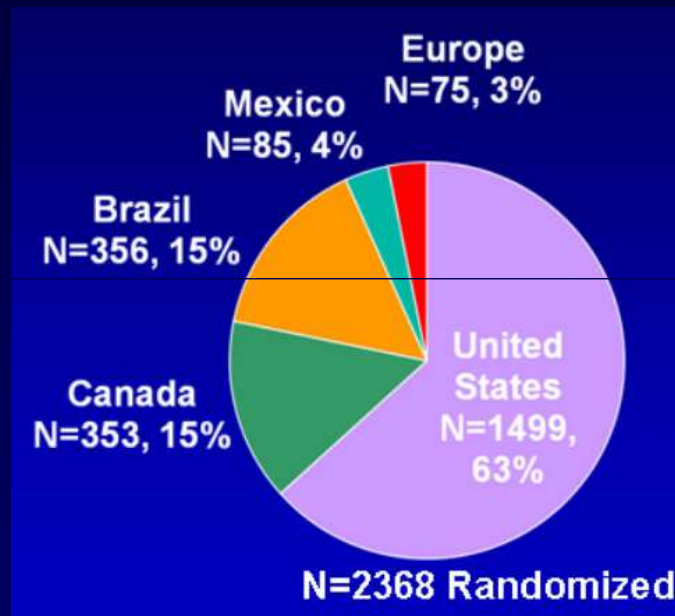
- In conclusion,

- **Coronary arteriographic findings** are consistent with the intent of the design of BARI 2D.

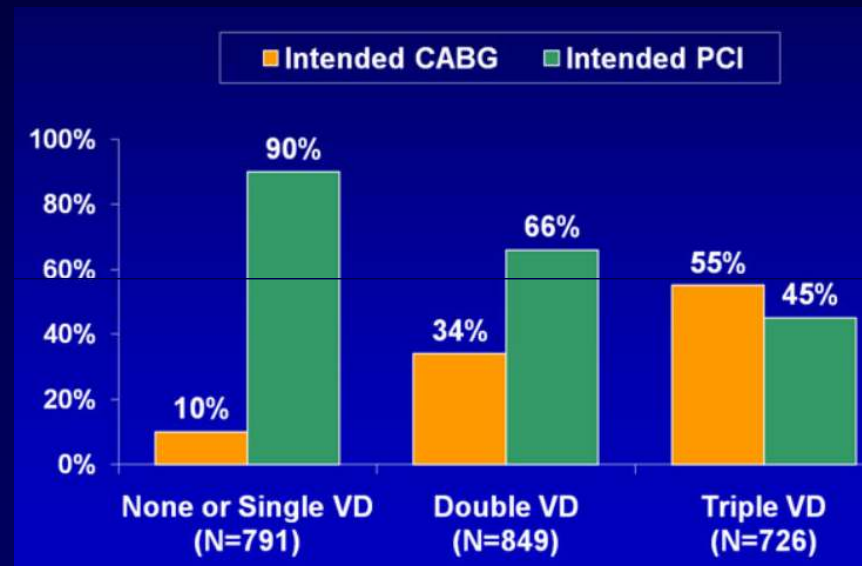
➤ BARI 2 Baseline

- From January 1, 2001, to March 31, 2005
- patients were enrolled at 49 clinical sites

Randomization by region



Intended mode of revascularization by number of vessels

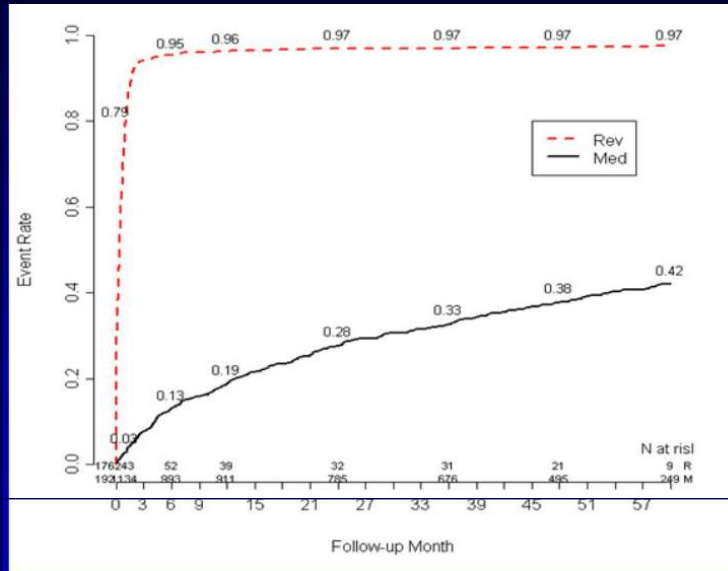


- In general, patients enrolled in the **United States** had a **less severe angiographic profile** compared with patients in Canada, Brazil and Mexico, and the Czech Republic and Austria.
- To a large extent, the **region-specific differences** in angiographic profiles.

BARI- 2D reassessment

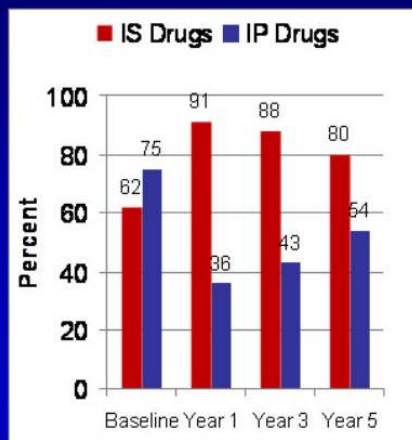
- A little confusion 3.
 - A comparison of **STRATEGIES** for myocardial ischemia.
prompt revascularization vs. medical therapy
 - A comparison of **STRATEGIES** for glycemic control.
insulin sensitization vs. insulin provision

Increased crossovers in drugs and devices

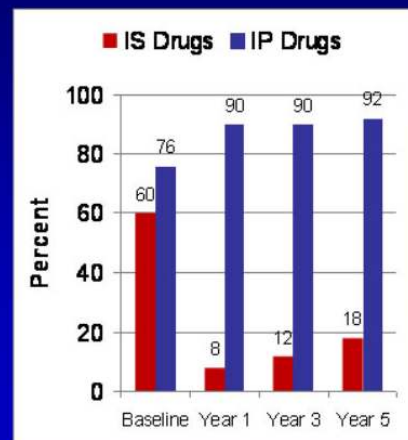


42% of patients in the medical treatment group had undergone revascularization by 5 years

Insulin Sensitization Group



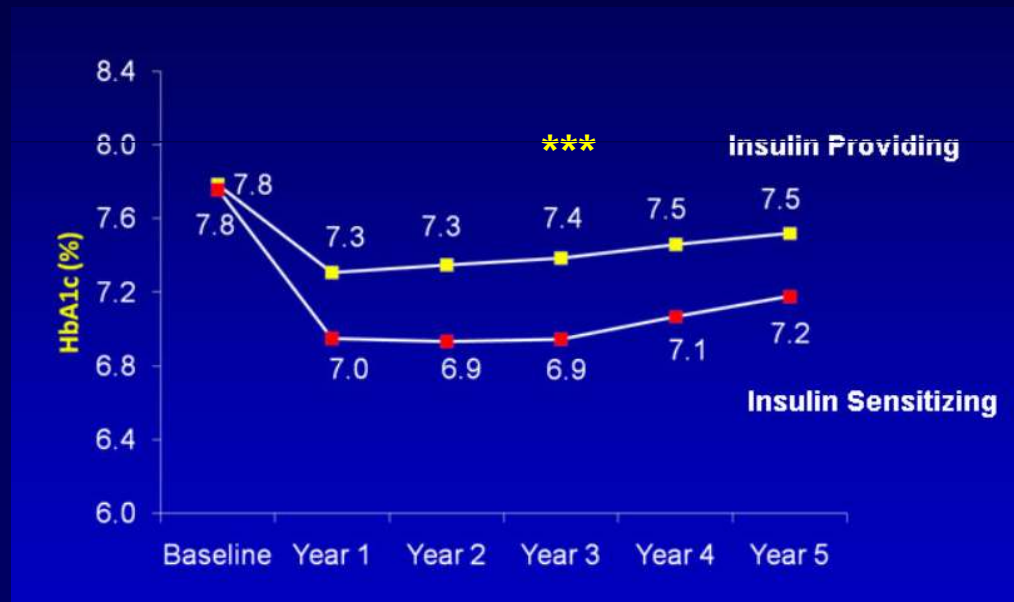
Insulin Provision Group



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

Though hypothesis was to evaluate two **cardiac treatment strategies** and two **glycemic treatment strategies** in patients who were receiving **uniform glycemic control** and **intensive therapy for cardiac risk factors**.

A1c mean over time



Summary of BARI-2D study

1. For **all subjects**, similar mortality & major cardiovascular events

- Prompt revascularization versus delayed/no revascularization.
- Insulin sensitization versus insulin provision

2. Among **low risk patients** selected for **PCI**
Similar major cardiovascular events

- Prompt revascularization versus delayed/no revascularization.
- Insulin sensitization versus insulin provision

3. Among **high risk patients** selected for **CABG**

↓ **major cardiovascular events**

- Prompt revascularization > delayed/no revascularization

1) Insulin sensitization appeared to enhanced the **benefit of revascularization** particularly among the those selected for **CABG**

2) Insulin sensitization was associated with **lower BMI, higher HDL,** and **lower rates of severe hypoglycemia**

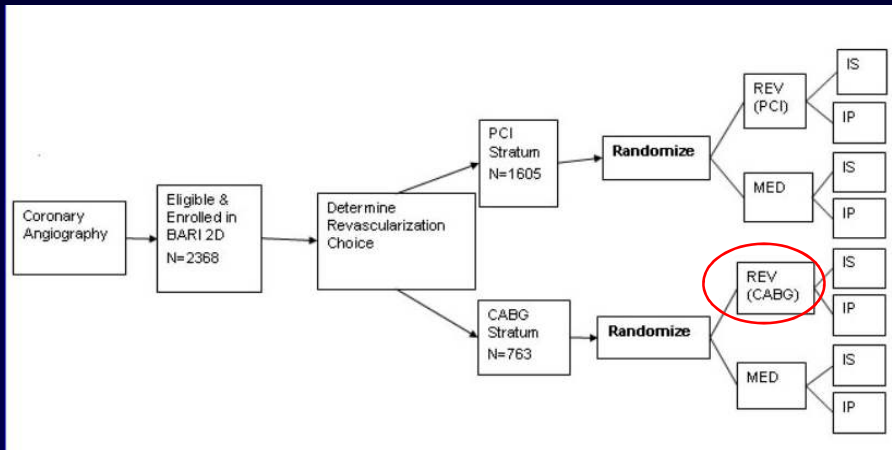
Use of Medications, Risk Factors, and Adverse Events

Variable	All Patients at Baseline	3-Year Follow-up					
		Revascularization	Medical Therapy	P Value	Insulin Sensitization	Insulin Provision	P Value
No. of patients	2368	953	991		977	967	
Risk factor							
Glycated hemoglobin — %	7.7±1.6	7.2±1.3	7.3±1.3	0.22	<u>7.0±1.2</u>	<u>7.5±1.4</u>	<0.001
Insulin — μ U/ml				0.72			<0.001
Median	9.9	7.8	7.9		<u>6.3</u>	<u>10.0</u>	
Interquartile range	5.7–17.0	4.6–15.0	4.6–14.0		3.9–11.0	5.5–19.0	
Cholesterol — mg/dl							
Total	169±41	151±35	150±34	0.60	151±34	151±35	0.77
Low-density lipoprotein	96±33	81±28	79±25	0.25	79±27	80±27	0.41
High-density lipoprotein	38±10	41±11	41±12	0.59	<u>42±12</u>	<u>40±11</u>	<0.001
Triglycerides — mg/dl				0.32			0.27
Median	148	126	131		126	131	
Interquartile range	104–219	89–179	94–179		88–181	95–176	
Blood pressure — mm Hg							
Systolic	131.7±20.0	125.6±15.3	125.2±16.7	0.58	125.3±15.9	125.5±16.1	0.74
Diastolic	74.5±11.2	70.4±10.7	70.3±10.5	0.86	70.1±10.8	70.6±10.3	0.31
Estimated glomerular filtration rate				0.32			0.34
Median	76.3	70.3	70.0		70.3	70.0	
Interquartile range	63.1–91.5	55.0–85.9	53.4–83.5		53.7–85.8	54.3–83.5	

Use of Medications, Risk Factors, and Adverse Events

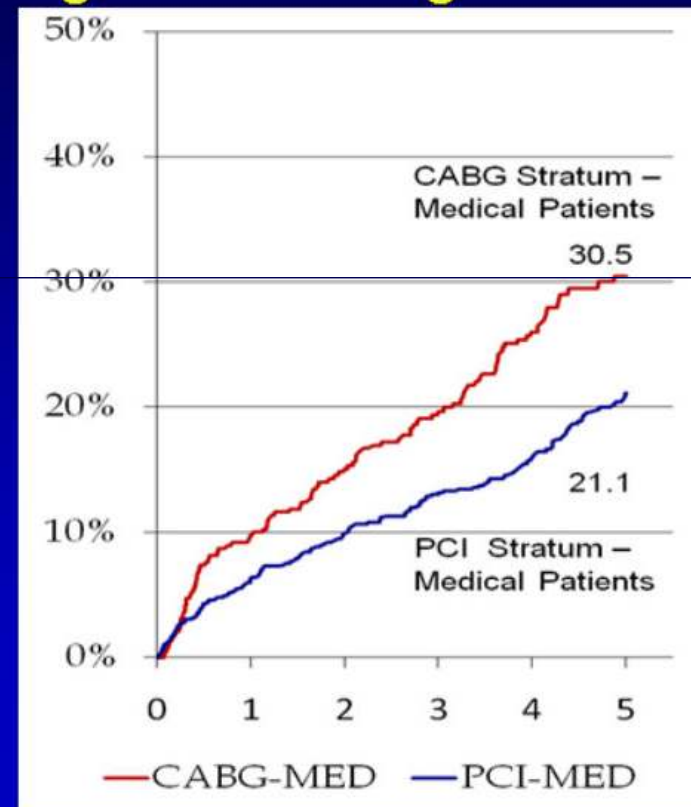
Variable	All Patients at Baseline	3-Year Follow-up					
		Revascularization	Medical Therapy	P Value	Insulin Sensitization	Insulin Provision	P Value
No. of patients	2368	953	991		977	967	
Microalbuminuria or macroalbuminuria (albumin:creatinine ratio, >30) — %	32.6	33.6	34.2	0.80	34.4	33.3	0.62
Body-mass index‡	31.7±6.0	32.0±6.3	32.2±6.2	0.50	<u>31.7±6.3</u>	<u>32.5±6.2</u>	0.003
Smoking in previous yr — %	21.8	10.4	11.2	0.56	<u>12.1</u>	<u>9.5</u>	0.07
Patients meeting target values — %							
Glycated hemoglobin <7.0%	39.6	48.5	47.2	0.60	<u>55.5</u>	<u>40.0</u>	<0.001
Low-density lipoprotein cholesterol <100 mg/dl	59.5	83.3	83.4	0.98	84.2	82.5	0.36
Blood pressure ≤130/80 mm Hg	47.6	71.7	70.7	0.61	72.4	70.0	0.24
Glycated hemoglobin, low-density lipoprotein cholesterol, and blood pressure at target levels	13.4	28.5	28.3	0.93	<u>34.8</u>	<u>22.0</u>	<0.001

CABG oriented Reassessment



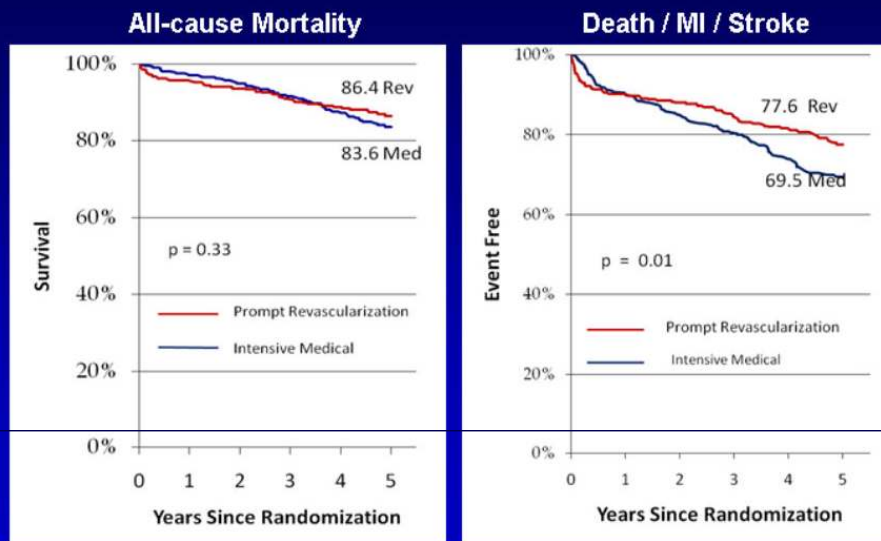
	PCI Intended N=1605	CABG Intended N=763
Age	62.0	63.2
Male	68%	76%
Prior revascularization	29%	13%
Proximal LAD	10%	19%
LVEF < 50	18%	18%
3 Vessel Disease	20%	52%
Total Occlusions	0.48	0.84
Myocardial Jeopardy Index	37.2	59.7

Death / MI/ Stroke Among Medical Assigned Patients

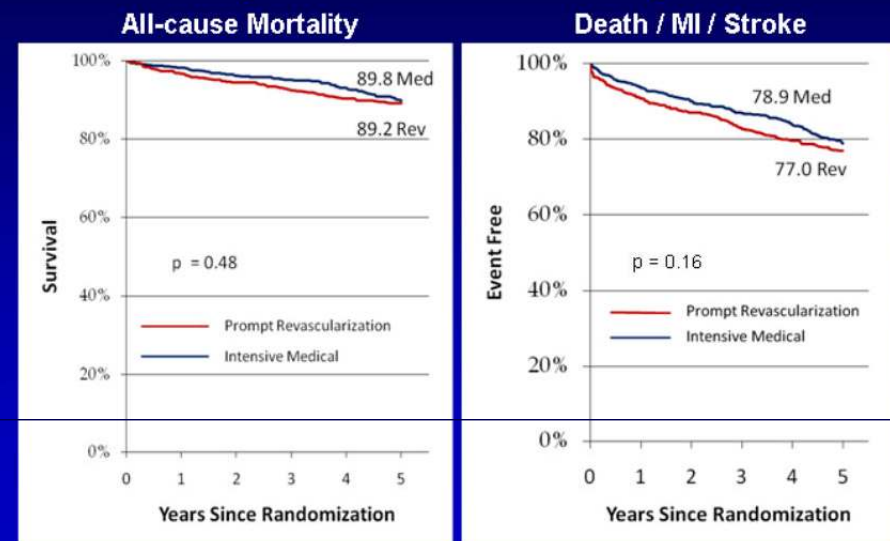


Reanalysis according to CABG and PCI

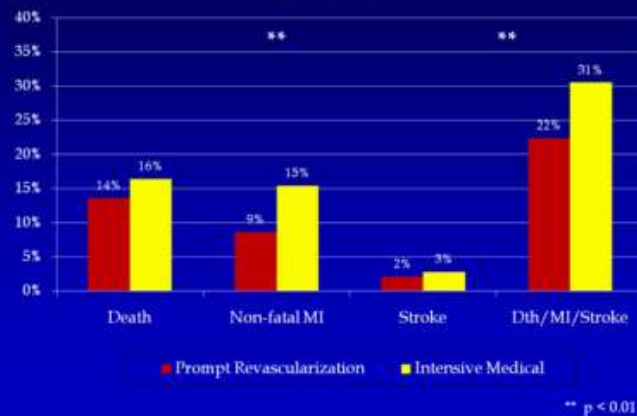
CABG Intended Revascularization Stratum (Higher Risk Patients)



PCI Intended Revascularization Stratum (Lower Risk Patients)



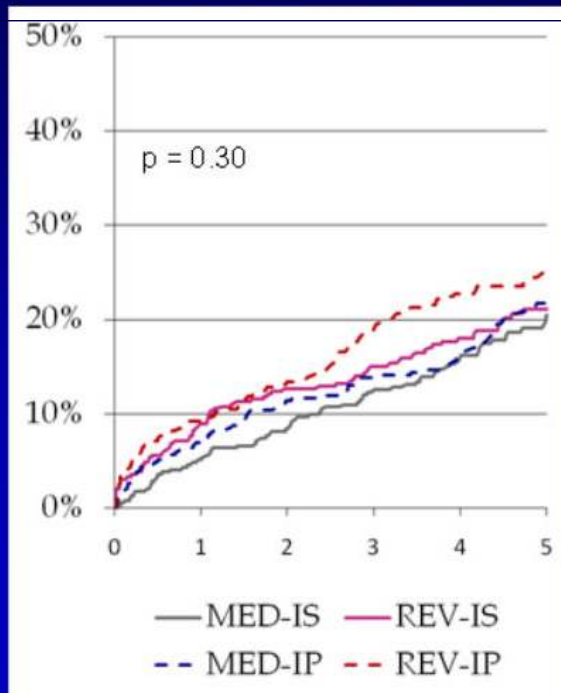
Five-Year Clinical Event Rates CABG Intended Revascularization Stratum N=763



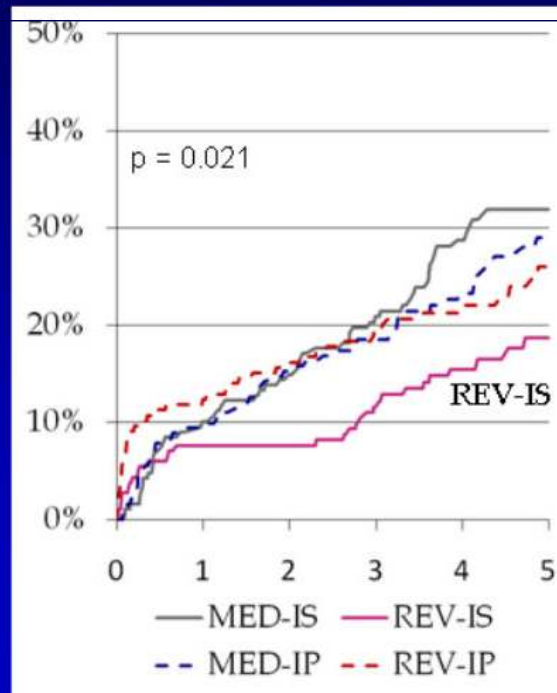
All-Cause Mortality			Death / MI / Stroke		
	Prompt Revasc	Intensive Medical		Prompt Revasc	Intensive Medical
Insulin Sensitization	11.2%	12.3%	Insulin Sensitization	20.3%	24.1%
Insulin Provision	12.2%	12.0%	Insulin Provision	25.2%	24.1%
<i>Interaction p=0.78</i>			<i>Interaction p=0.23</i>		

**4 treatment combination
5-year clinical events rate**

PCI Intended Stratum



CABG Intended Stratum



**Major cardiovascular
events rate**

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			
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

Event rates were lower than expected

- Heterogeneity of diabetic patients
- 0.3% per year in the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) 17 to 12% per year in the German Diabetes and Dialysis trial.
- Clinicians decided on a preferred revascularization approach (PCI or CABG) before randomization
- Higher use of drug-eluting stents and greater use of minimally invasive surgical techniques as the trial progressed.

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2. Among **low risk patients** selected for **PCI** **Similar major cardiovascular events**

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3. Among **high risk patients** selected for **CABG** **↓ major cardiovascular events**

- Prompt revascularization > delayed/no revascularization

1) Insulin sensitization appeared to enhanced the **benefit of revascularization** particularly among the those selected for **CABG**

2) Insulin sensitization was associated with **lower BMI, higher HDL,** and **lower rates of severe hypoglycemia**

감사합니다