Revascularization in Diabetes: New Insights from the BARI 2D

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Presenter Disclosure Information

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

"Revascularization in Diabetes:
New Insights from the BARI 2D "

The following relationships exist related to this presentation:

No relationships to disclose

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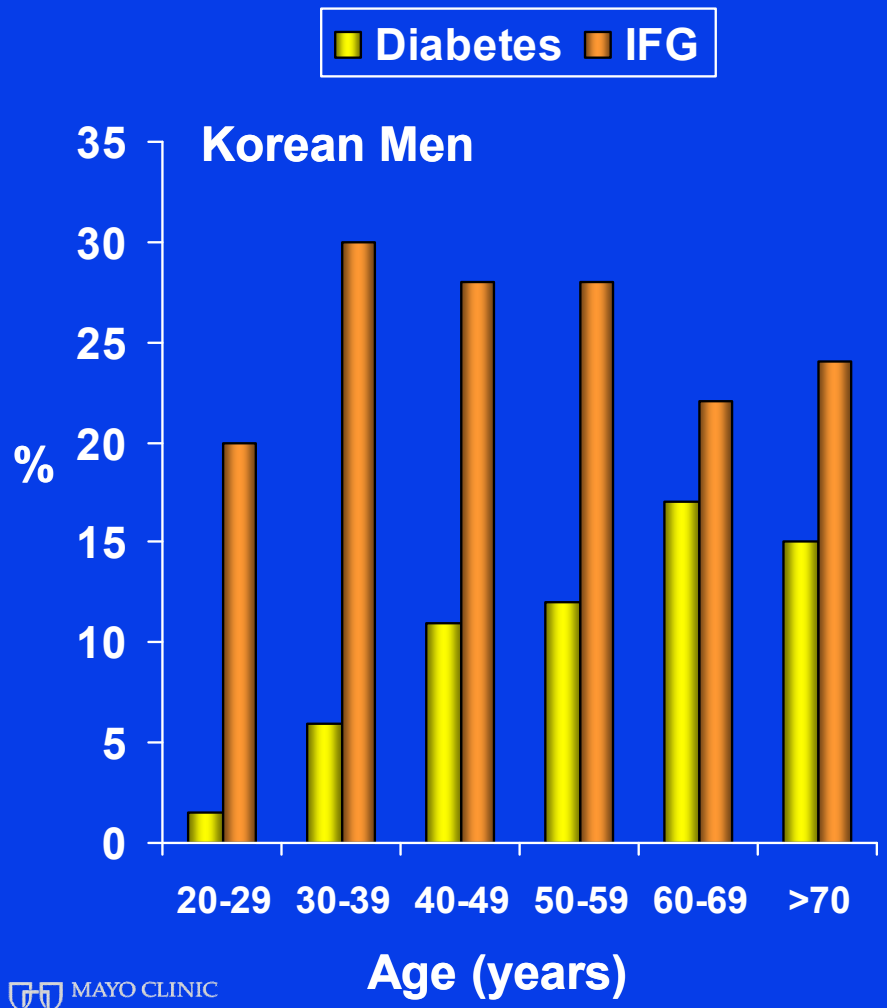
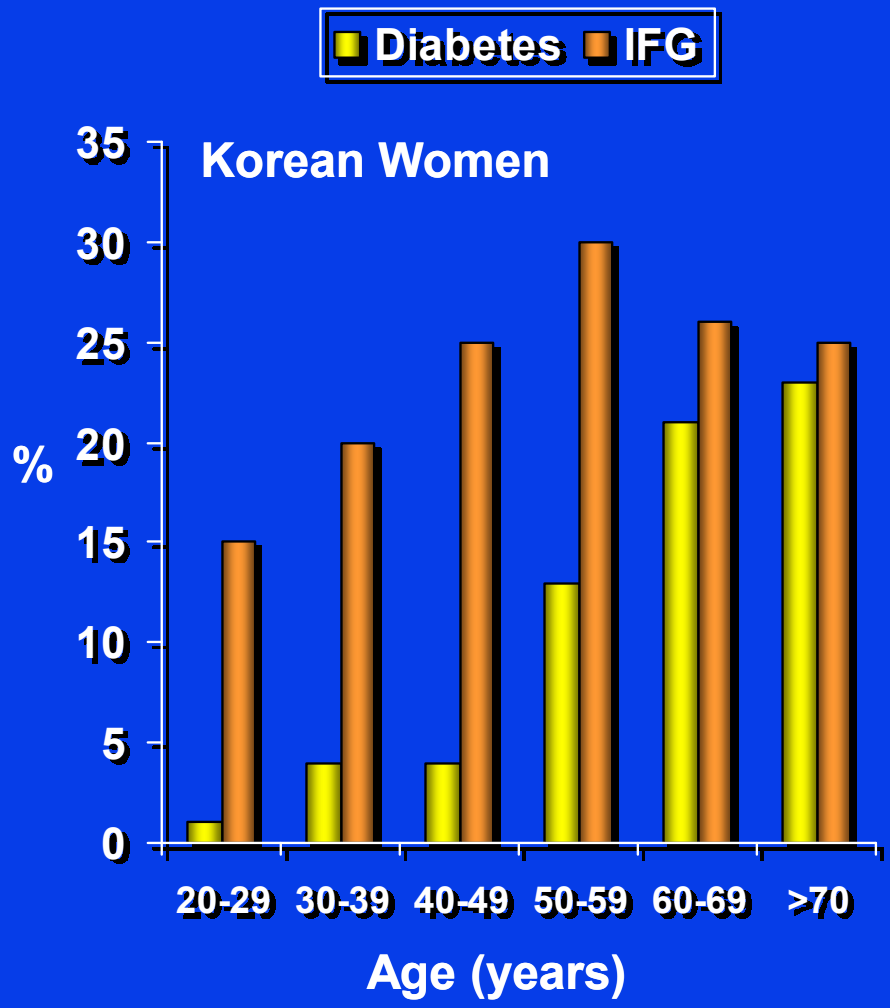
Korea and Diabetes

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

Kim SM et al, Diabetes Care 29:226-231, 2006

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





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Kim SM et al, Diabetes Care 29:226-231, 2006

Angioplasty not best option for diabetics

By Doug Levy
USA TODAY

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

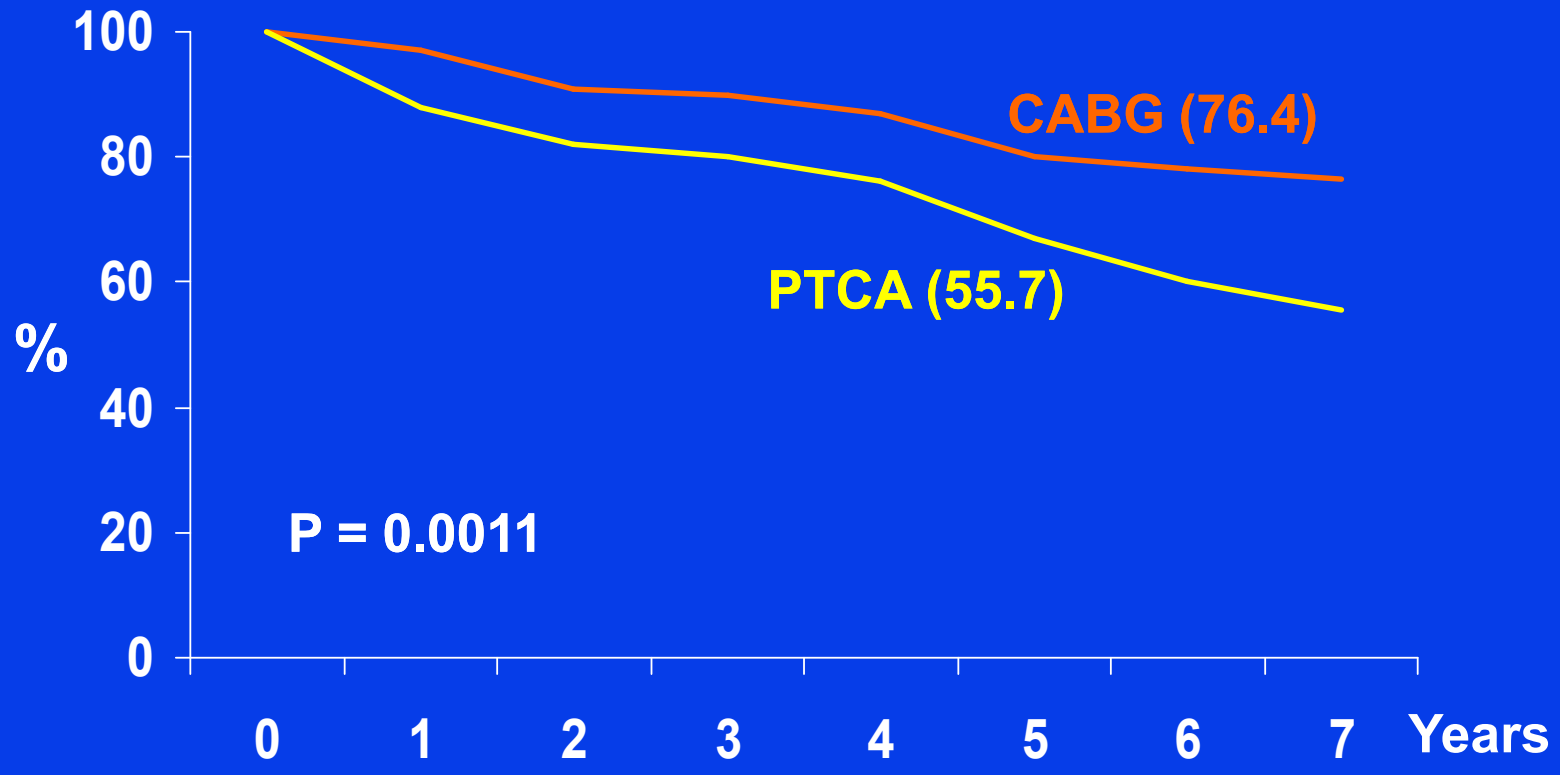
A study of 1,829 people with blockages in two or more heart

Dr. George Sopko, an NHLBI cardiologist. However, the recommendation only applies to patients with both severe diabetes and two or more blocked coronary arteries.

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

BARI - 7 Year Survival

Survival-Patients with Treated Diabetes



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

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Detre, JACC 2000

BARI 2D Clinical Trial

Compare treatment strategies for patients with

- **Type 2 diabetes mellitus**
- **Documented CAD suitable for elective revascularization (1 or more significant lesions)**
- **Documented ischemia**
- **No prior CABG or PCI within the last 12 months**

Revascularization Decision
BARI 2D

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

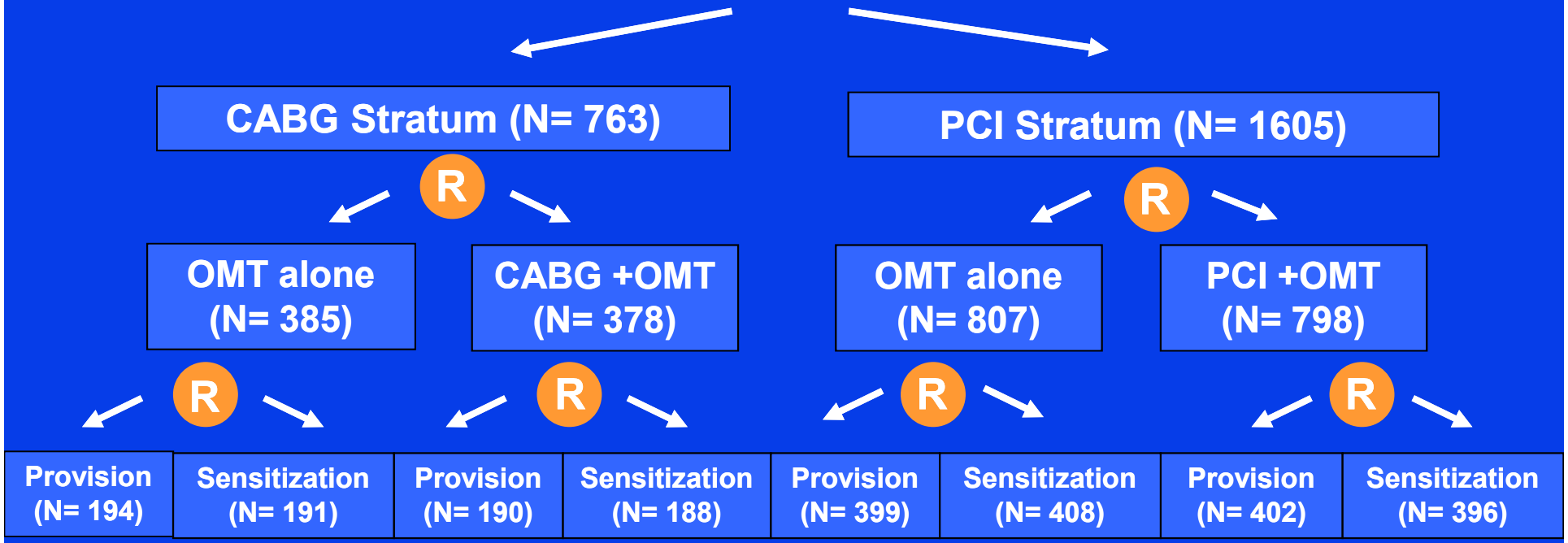
Percutaneous coronary intervention

or

Coronary artery bypass graft surgery

BARI 2D Trial: Study Design

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



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

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BARI 2D Study Group, NEJM 2009

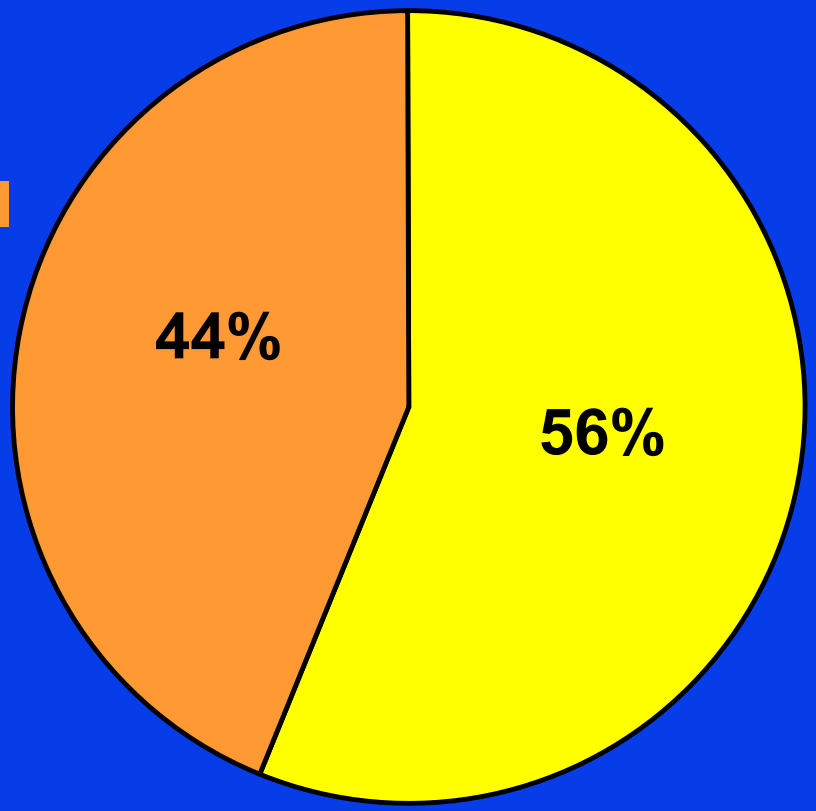
Angiographic Characteristics
2,368 Randomized Patients

CAD diseased vessels	
0/1	33%
2	36%
3	31%
Myocardial jeopardy (mean ± SD)	44±24
Proximal LAD (>50% stenosis)	13%
Total occlusion	41%
Abnormal LV function (<50%)	17%

BARI 2D

1593 patients with MVD

CABG: 11% suitable for PCI



PCI: 49% suitable for CABG

Kim LJ et al, JACC Intv 2:384-92, 2009

BARI 2D

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

Kim LJ et al, JACC Intv 2:384-92, 2009

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

of coronary artery bypass graft (CABG) surgery versus percutaneous coronary intervention (PCI) in diabetic patients with multivessel coronary artery disease (CAD) in the BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) trial.

Background Factors guiding selection of mode of revascularization for patients with diabetes mellitus and multivessel CAD are not clearly defined.

Methods In the BARI 2D trial, the selected revascularization strategy, CABG or PCI, was based on physician discretion, declared independent of randomization to either immediate or deferred revascularization if clinically warranted. We analyzed factors favoring selection of CABG versus PCI in 1,593 diabetic patients with multivessel CAD enrolled between 2001 and 2005.

Results Selection of CABG over PCI was declared in 44% of patients and was driven by angiographic factors including triple vessel disease (odds ratio [OR]: 4.43), left anterior descending stenosis ≥70% (OR: 2.86), proximal left anterior descending stenosis ≥50% (OR: 1.78), total occlusion (OR: 2.35), and multiple class C lesions (OR: 2.06) (all $p < 0.005$). Nonangiographic predictors of CABG included age ≥65 years (OR: 1.43, $p = 0.011$) and non-U.S. region (OR: 2.89, $p = 0.017$). Absence of prior PCI (OR: 0.45, $p < 0.001$) and the availability of drug-eluting stents conferred a lower probability of choosing CABG (OR: 0.60, $p = 0.003$).

Conclusions The majority of diabetic patients with multivessel disease were selected for PCI rather than CABG. Preference for CABG over PCI was largely based on angiographic features related to the extent, location, and nature of CAD, as well as geographic, demographic, and clinical factors. (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes [BARI 2D]; NCT00006305) (J Am Coll Cardiol Intv 2009;2: 384–92) © 2009 by the American College of Cardiology Foundation

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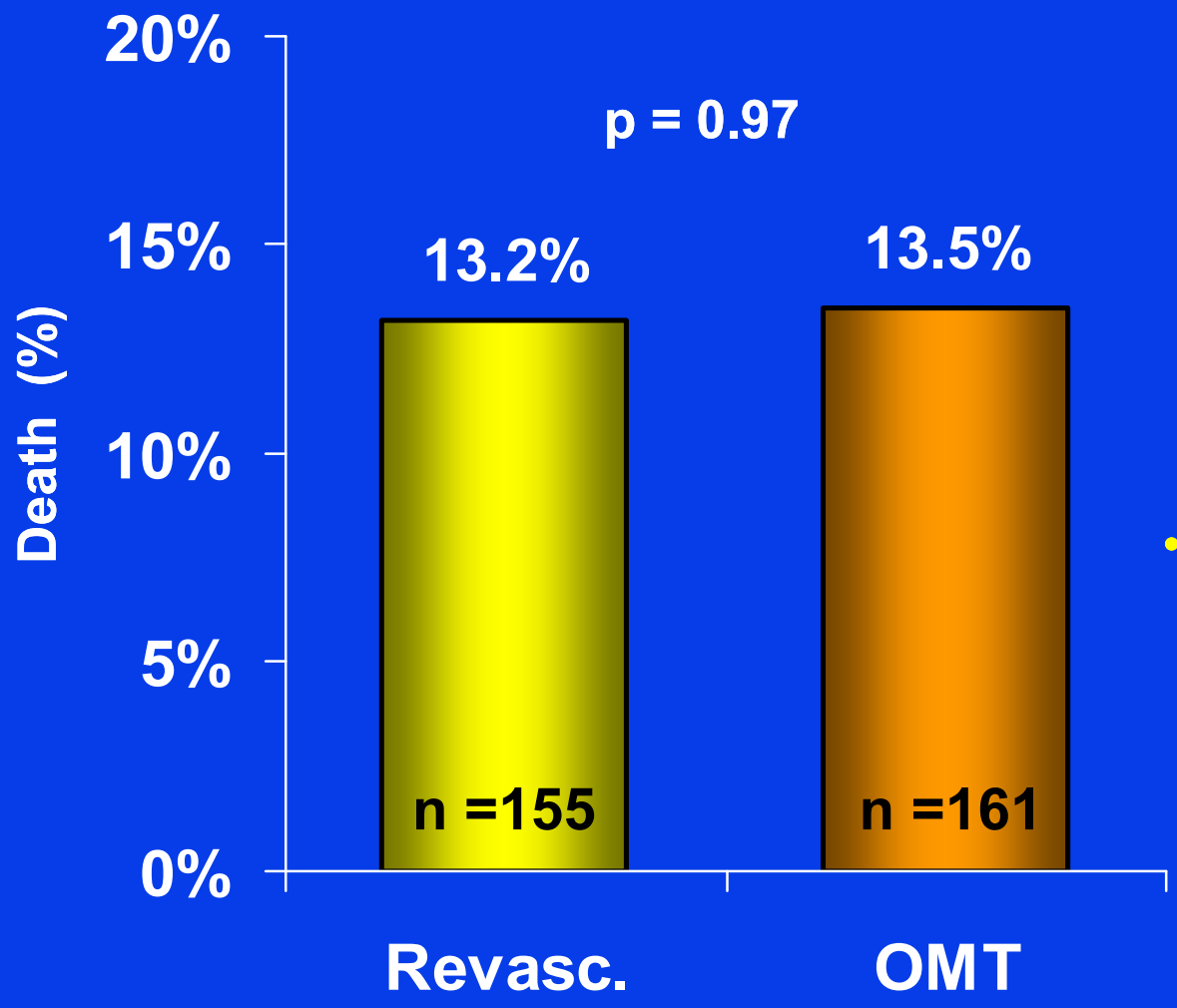
BARI 2D Trial: Primary Endpoint



- The 5-year death rate for the group receiving revascularization plus optimal medical therapy was 13.2% vs. 13.5% in the group receiving optimal medical therapy alone
- The difference between the two treatment groups did not reach statistical significance

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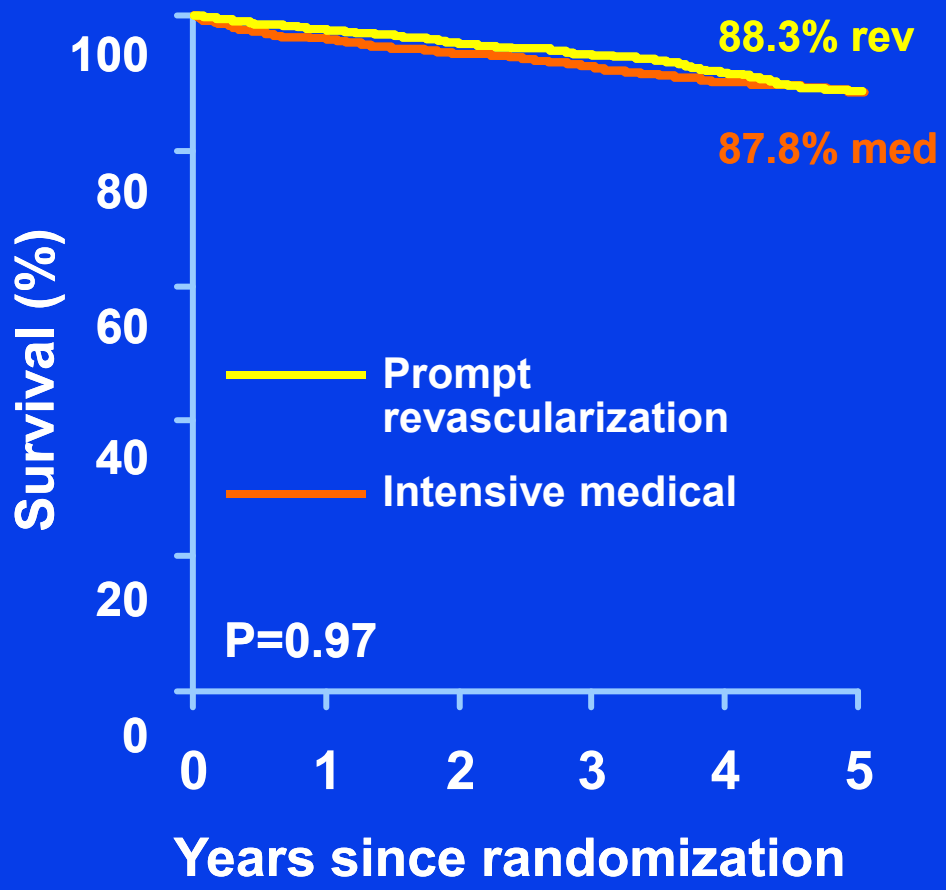
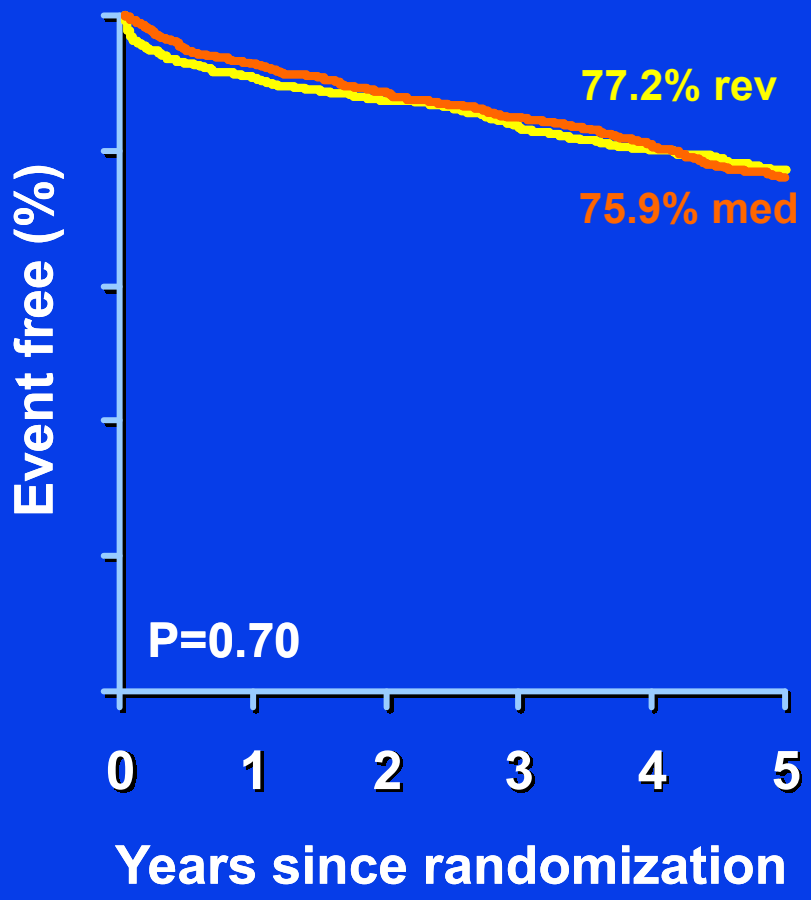
BARI 2D Study Group, NEJM 2009

Prompt Revascularization vs Medical Therapy

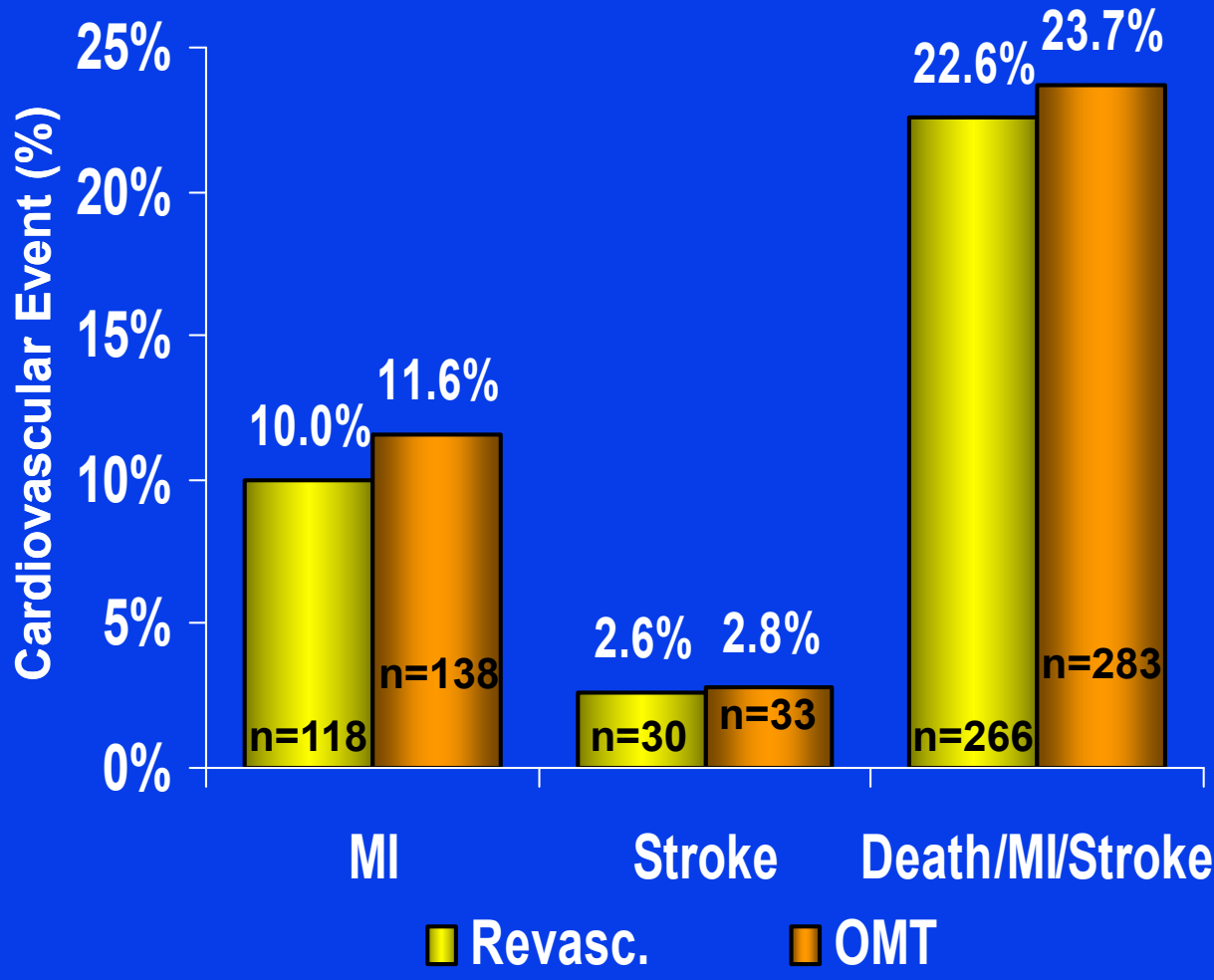
All-Cause Mortality



Death/MI/Stroke



BARI 2D Trial: 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 difference between the two treatment groups for the combined secondary endpoint of death, MI, and stroke did not reach statistical significance (p=0.70)

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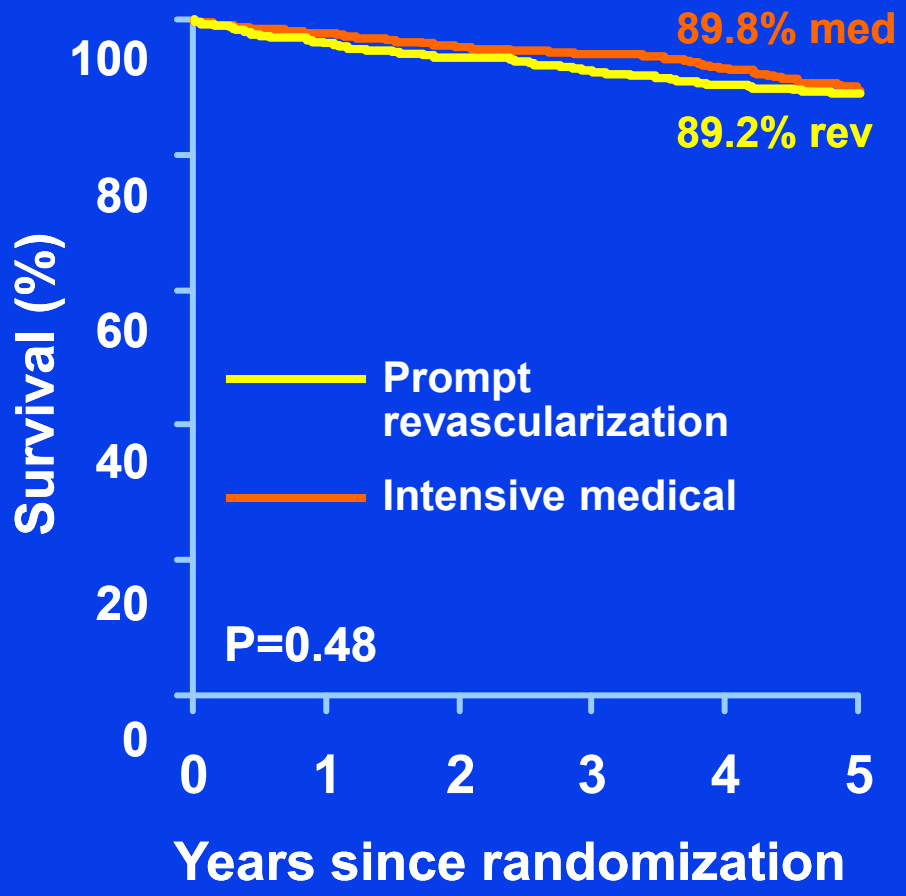
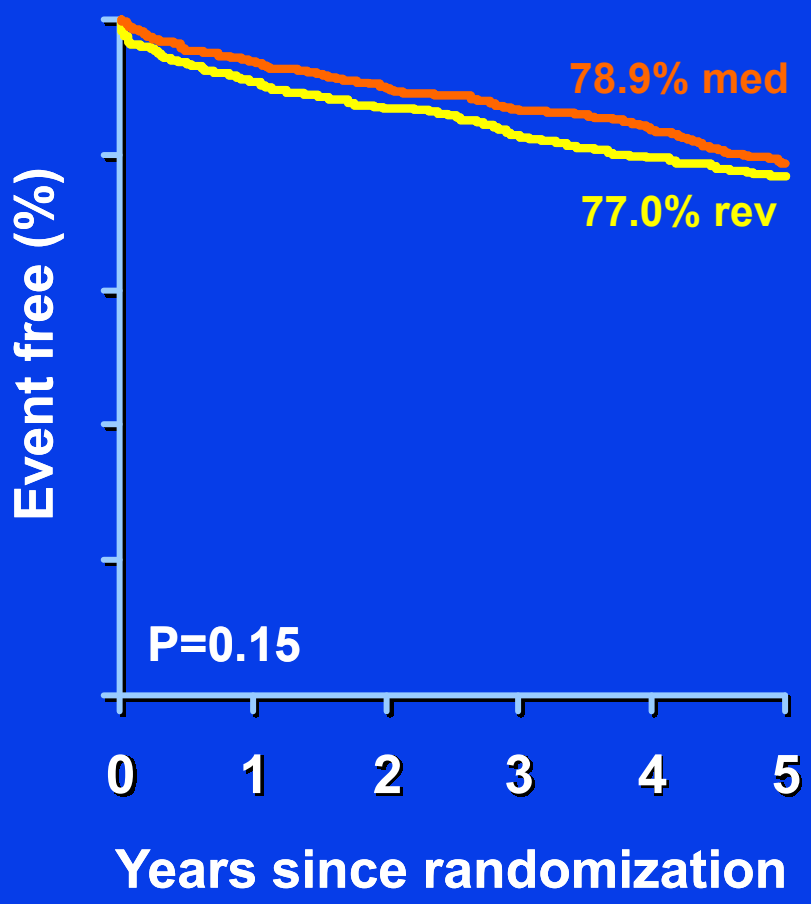
BARI 2D Study Group, NEJM 2009

PCI Intended Revascularization Stratum
Lower Risk Patients

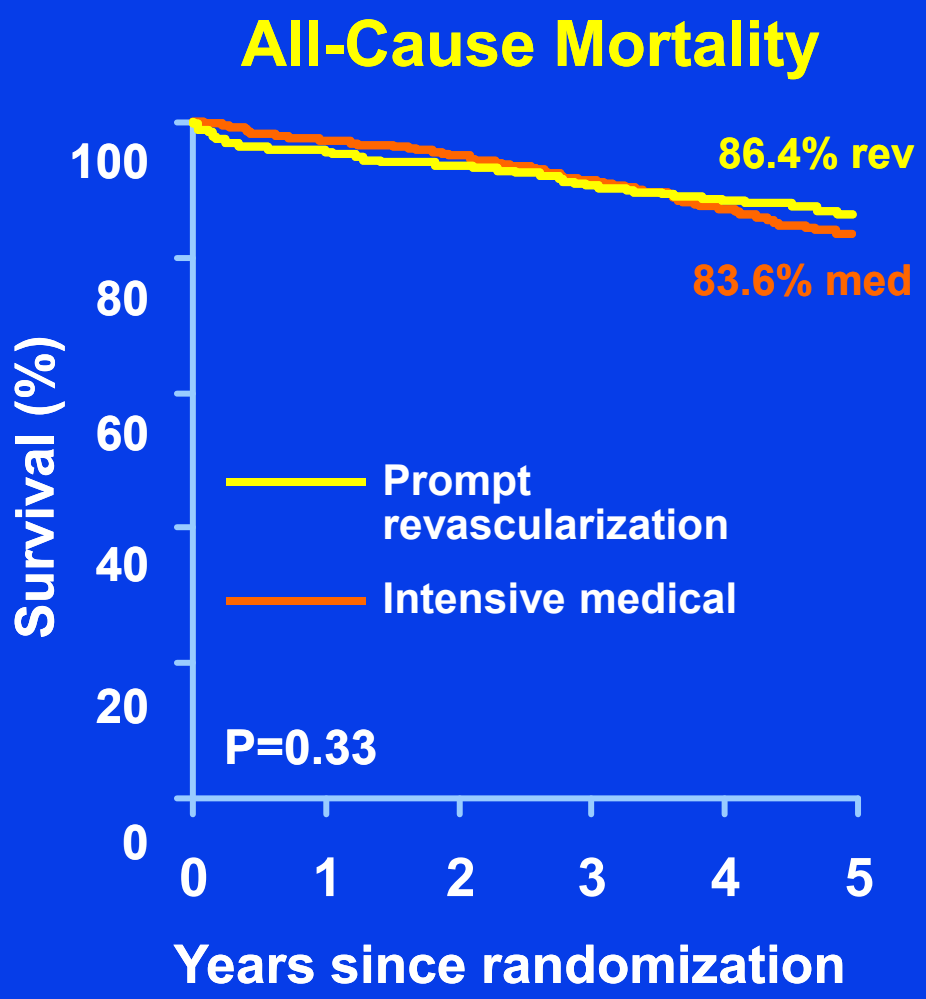
All-Cause Mortality

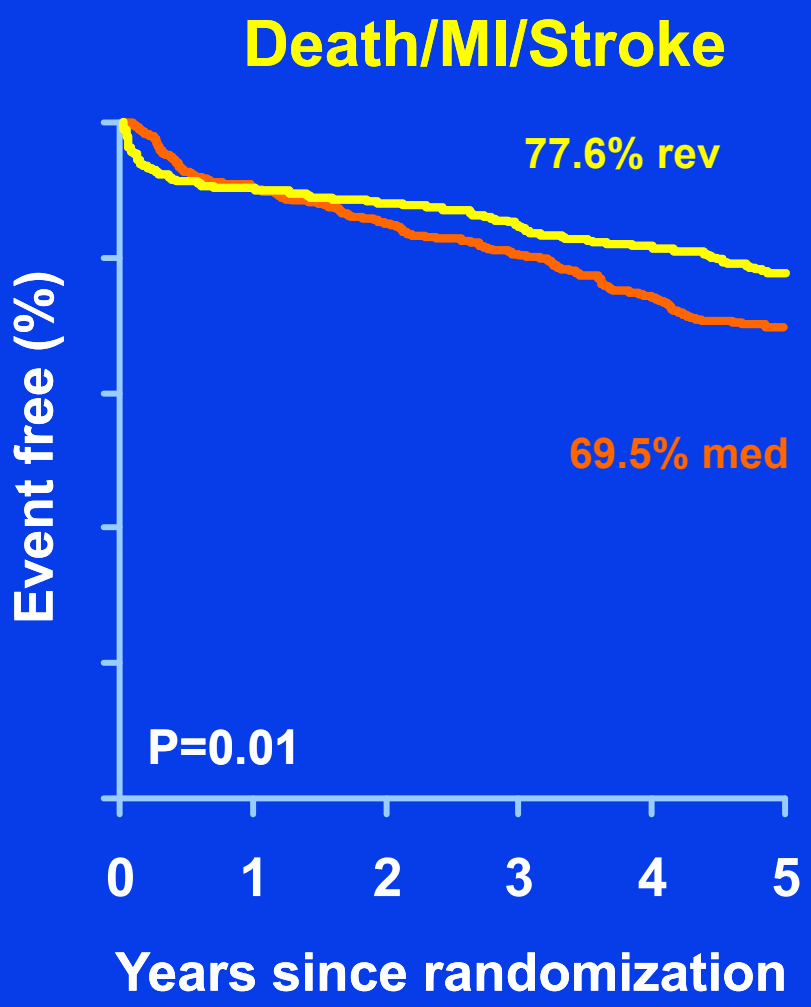


Death/MI/Stroke

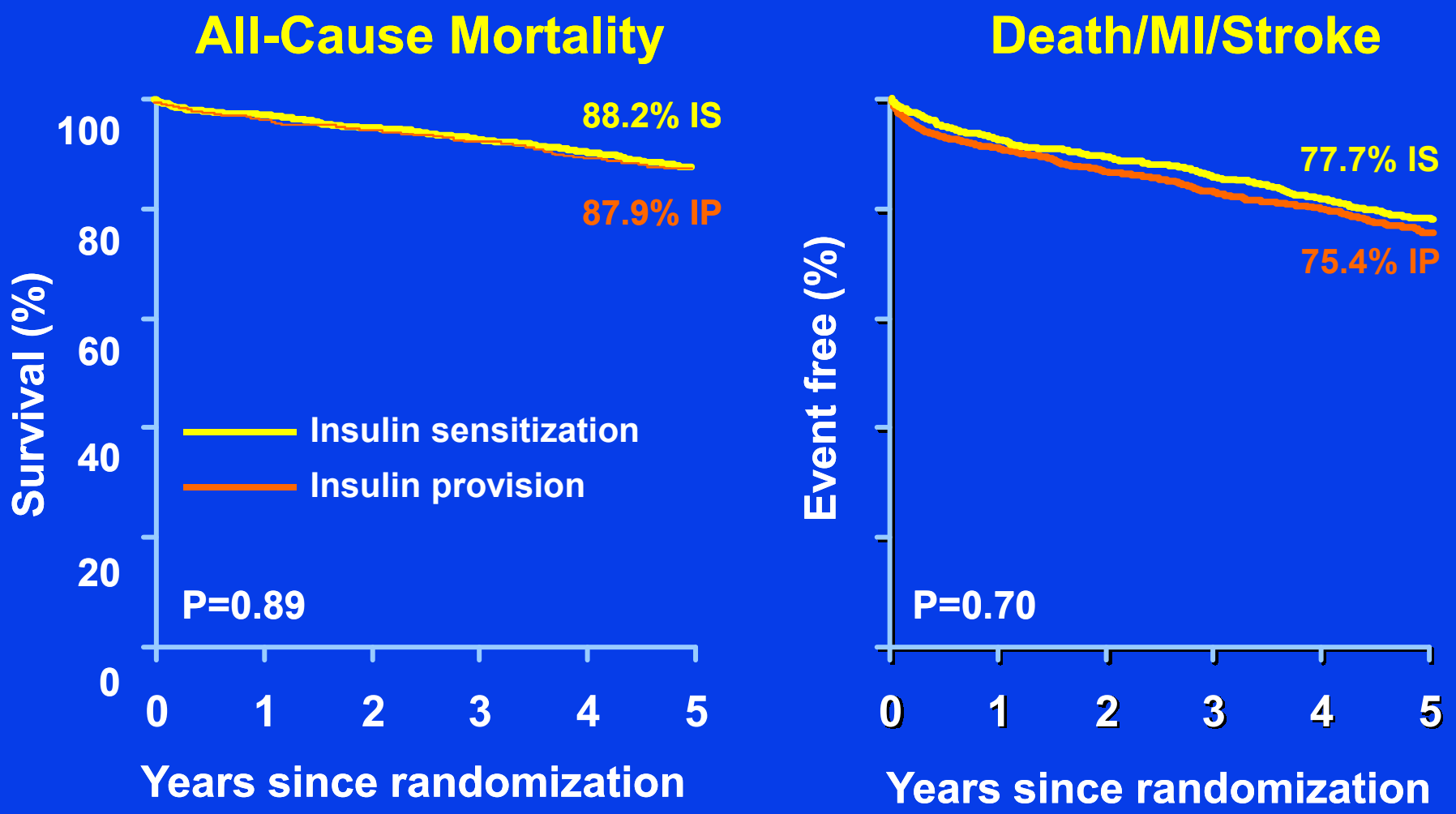


CABG Intended Revascularization Stratum
Higher Risk Patients





Insulin Sensitization vs Insulin Provision



BARI 2D Primary Conclusion

Overall similar mortality and CV events

- Prompt revascularization vs delayed or no revascularization
- Insulin sensitization vs insulin provision

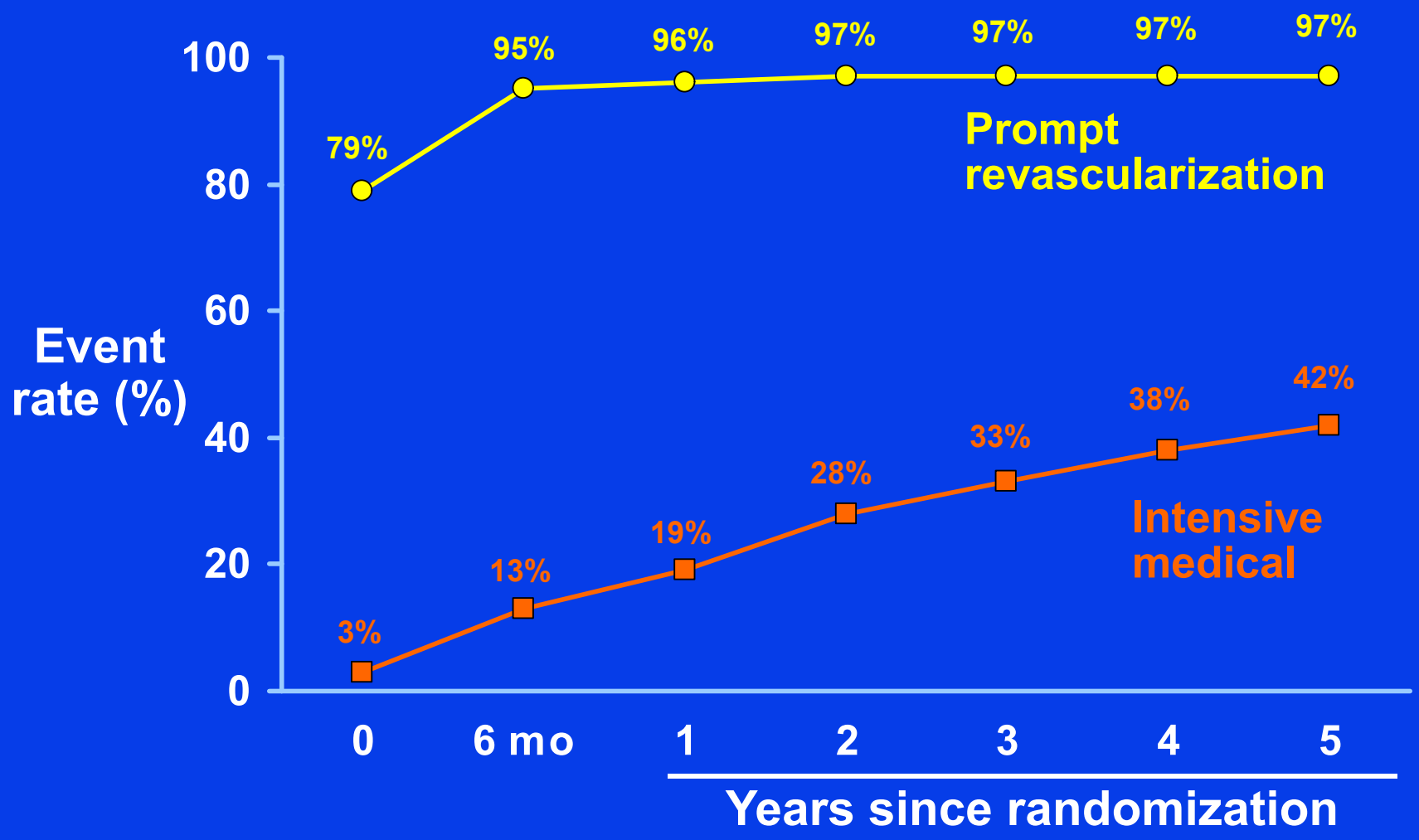
Among high-risk patients selected for CABG

- Prompt revascularization reduces major CV events compared with delayed or no revascularization (P=0.01)

Among lower-risk patients selected for PCI

- Prompt revascularization and delayed or no revascularization had similar rates for major CV events

Cumulative Rate of First Revascularization



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Conclusions

- Optimal medical therapy is required for diabetic patients with CAD
- Despite optimal medical therapy, 42% of diabetic patients will still undergo revascularization during 5 years FU
- Revascularization strategies chosen depend in large part on severity and extent of disease
- Clinical decision making still works

Another problem caused by deforestation

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There are no facts, only interpretations.

-Friedrich Nietzsche

There are no facts, only interpretations.

-Friedrich Nietzsche

Life is better served without a helping of diabetes.


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Revascularization Decision
BARI 2D

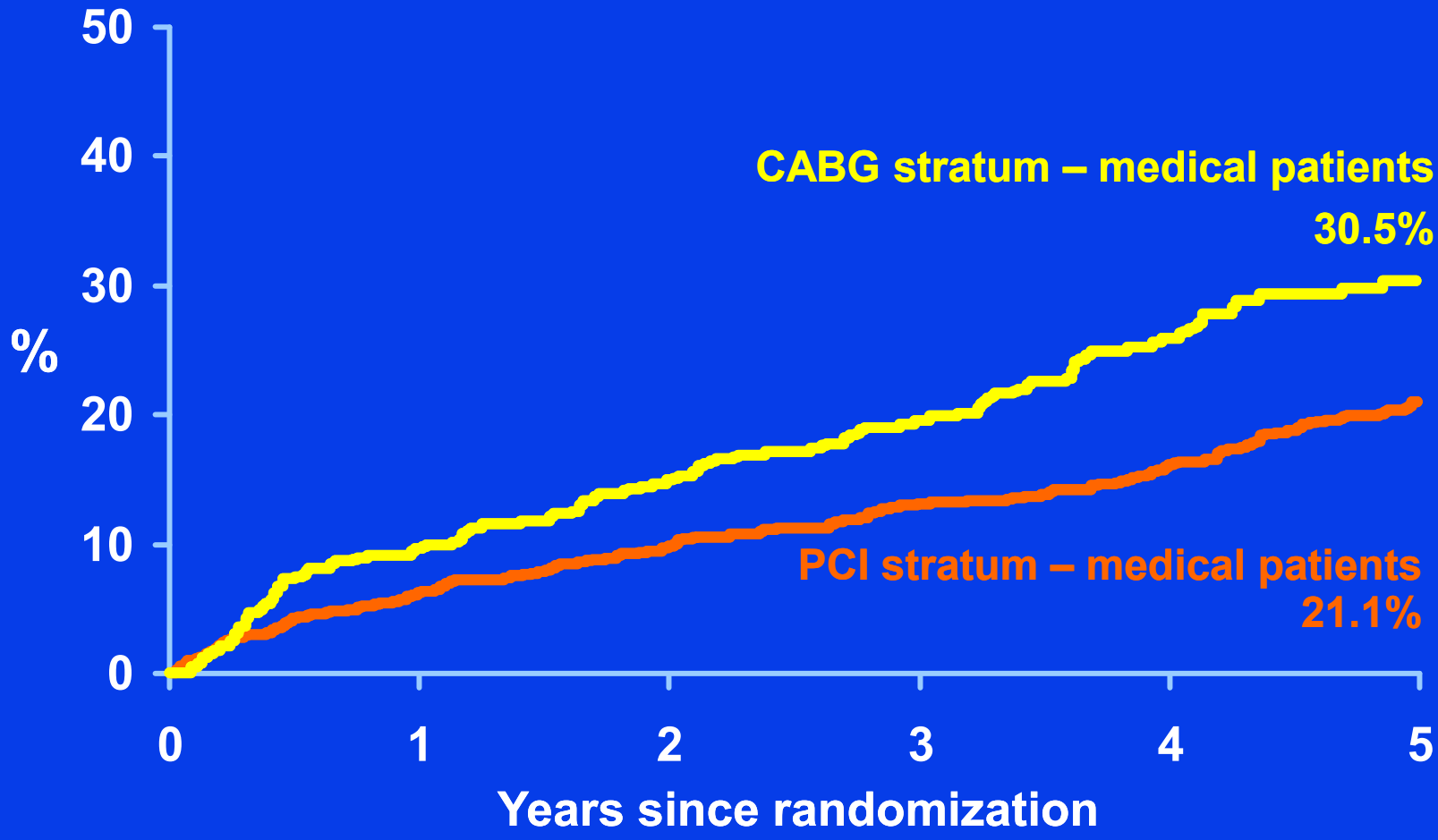
Cardiologist a priori selected revascularization method based on clinical and angiographic factors

Percutaneous coronary intervention

or

Coronary artery bypass graft surgery

Death/MI/Stroke Among Medical Assigned Patients



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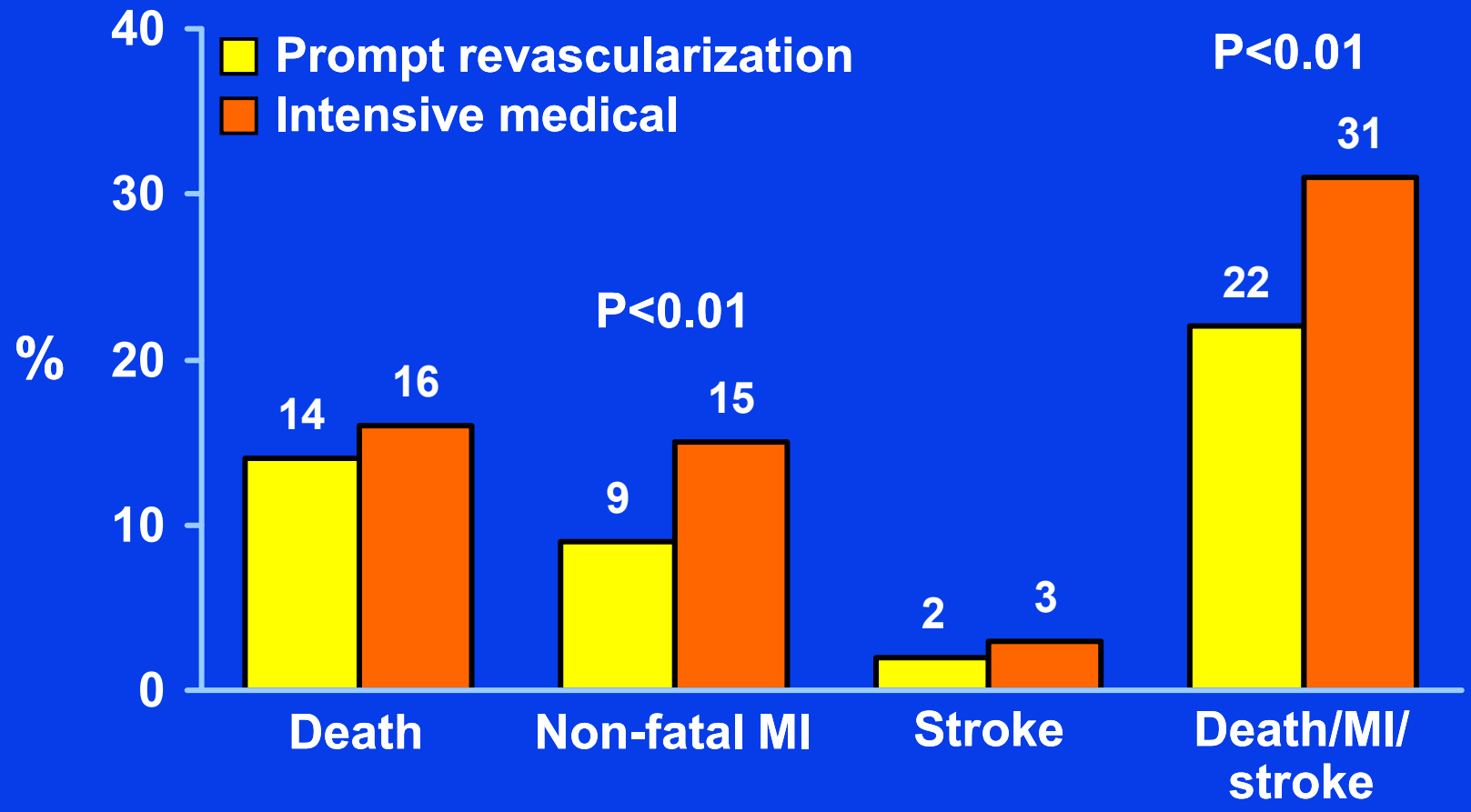
5-Year Clinical Event Rates
CABG Intended Revascularization Stratum
n=763



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BARI 2D Primary Conclusions

Similar mortality and major cardiovascular events, overall for

- **Prompt revascularization vs delayed or no revascularization**
- **Insulin sensitization vs 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**

4 Treatment Combinations
5-Year Clinical Event Rates – All Patients (n=2,368)

	All-cause mortality		Death/MI/stroke	
	Prompt revasc	Intensive medical	Prompt revasc	Intensive medical
Insulin sensitization (%)	11.2	12.3	20.3	24.1
Insulin provision (%)	12.2	12.0	25.2	24.1
Interaction P	0.78		0.23	

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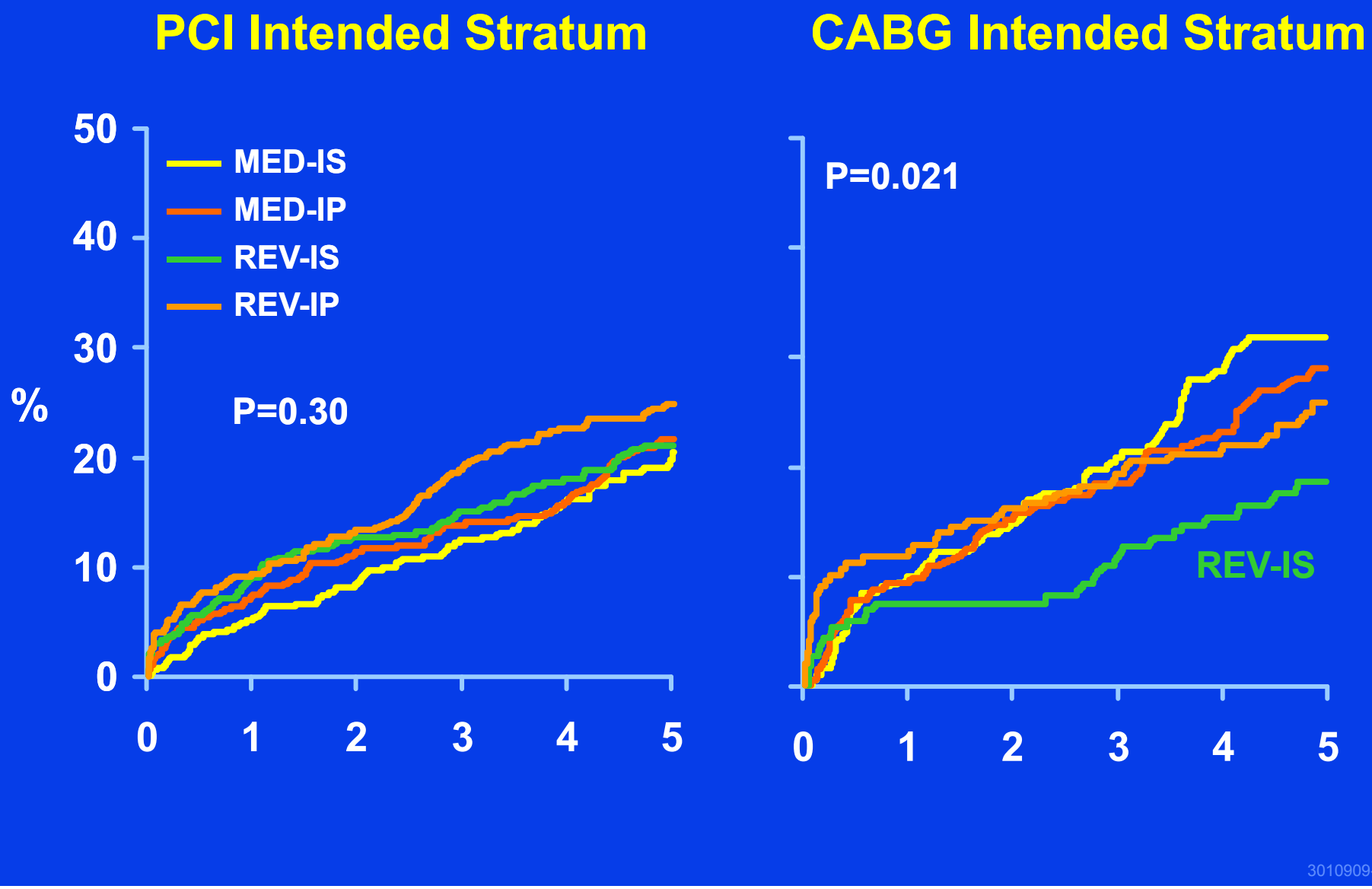
Major Cardiovascular Events



Adverse Event Rates
Glycemic Randomized Treatment Assignment

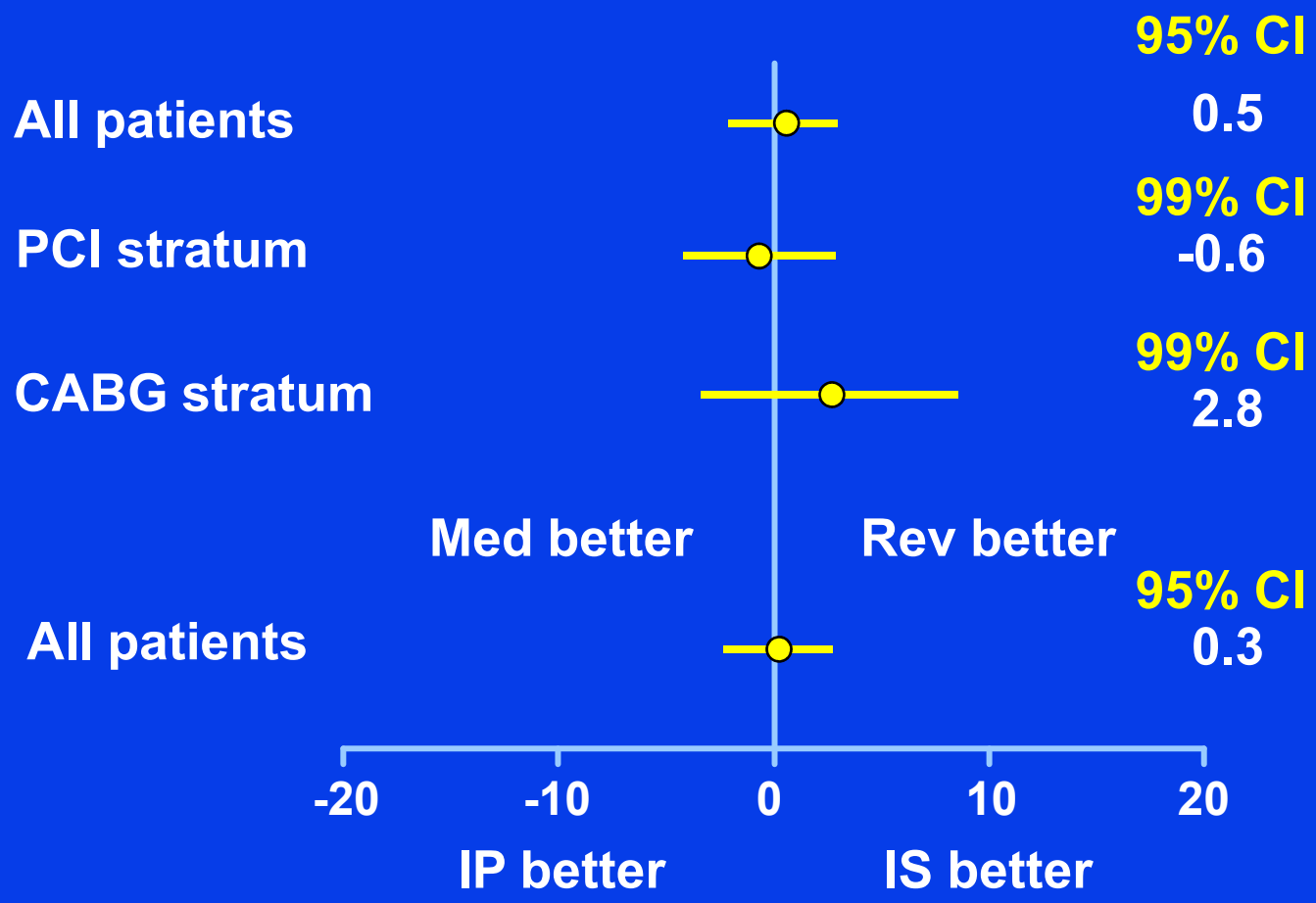
Adverse event	IS n=1,154 (%)	IP n=1,156 (%)	P
Hypoglycemia			
Any	53.3	73.8	0.001
Severe	5.9	9.2	0.003
Peripheral edema	56.6	51.9	0.02
Congestive heart failure			
All patients	22.6	20.0	0.13
Hx of CHF*	67.2	63.5	0.65
No Hx of CHF*	19.4	16.6	0.09
Bone fractures	7.6	6.9	0.54

*141 pt had a Hx of CHF and 2,035 had no Hx of CHF

Additional BARI 2D Observation

- Insulin sensitization appeared to enhance the benefit of revascularization particularly among the those selected for CABG
- Insulin sensitization was associated with lower BMI, higher HDL and lower rates of severe hypoglycemia

5-Year All-Cause Death Rates
Difference Between BARI 2D Randomized Treatment Groups



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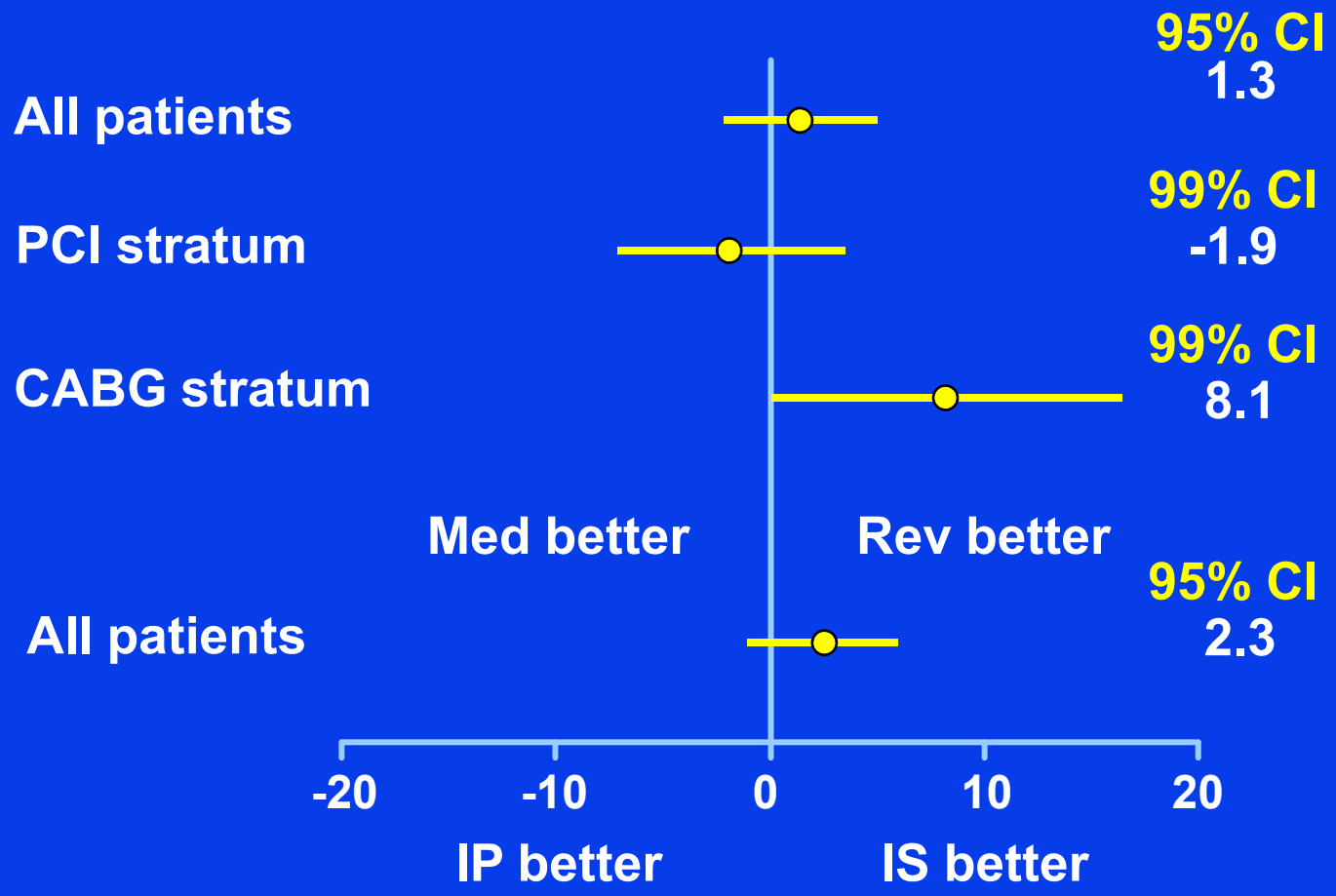
5-Year Major Cardiovascular Event Rates
Difference by BARI 2D Randomized Treatment Groups



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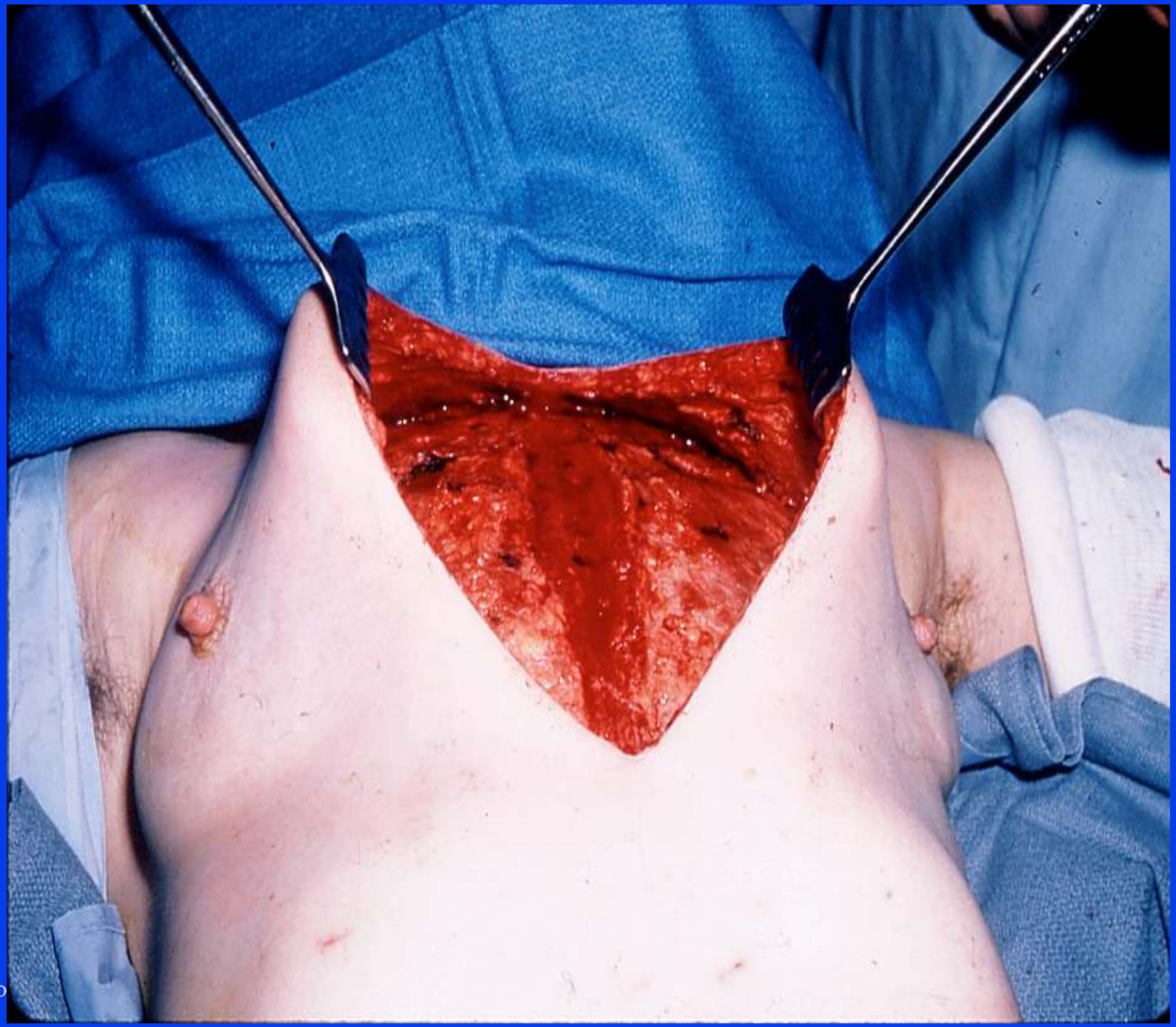


NIDDK Fact Sheet

- 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 2-4 times higher than rates among adults without diabetes

BARI 2D Trial: Background

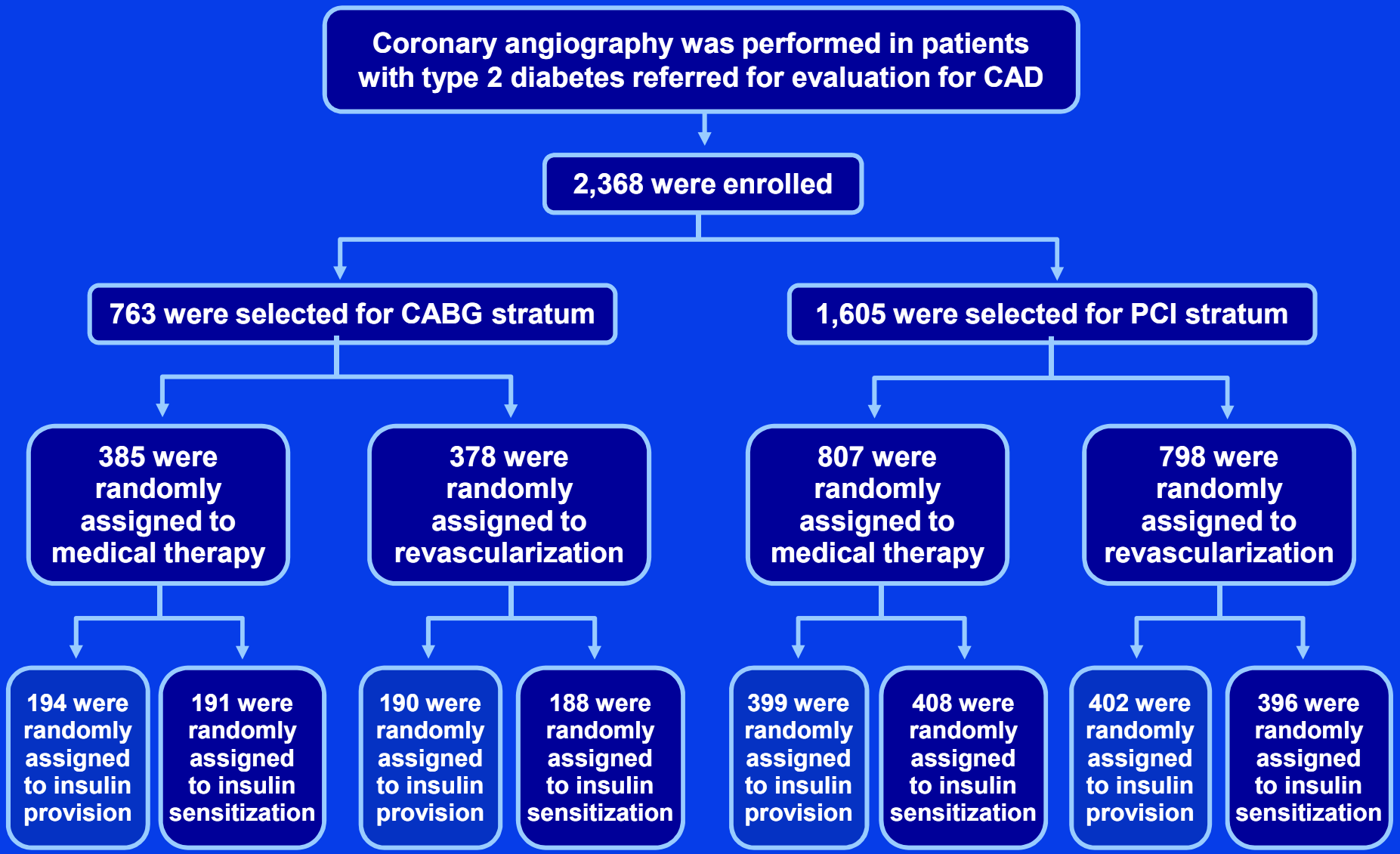
- Patients with Type 2 diabetes have an increased risk of suffering a cardiovascular event over non-diabetic patients.
- The success of coronary revascularization in reducing myocardial infarction and death in diabetic patients with chronic stable angina has not been established.
- Similarly, it is unclear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

BARI 2D Study Group, NEJM 2009

BARI 2D Primary and Principal Secondary Endpoints

- All-cause mortality
- Major cardiovascular events: composite of death/MI/stroke
- Average follow-up 5.3 years

Enrollment Flow Diagram



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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)

Demographic and Clinical History
2,368 Randomized Patients

Age (mean yr)	62.4
Female (%)	30
Ethnic/racial minority (%)	34
Myocardial infarction Hx (%)	32
Congestive heart failure Hx (%)	7
Hx of stroke or TIA (%)	10
Peripheral artery disease (%)	24

Cardiac Clinical Characteristics
2,368 Randomized Patients

	%
Angina status	
No angina or anginal equivalents	18.0
Anginal equivalents	21.4
Stable angina CCS 1-2	42.5
Stable angina CCS 3-4	8.6
Unstable angina	9.5
Prior PCI	20.0
Prior stent	13.0
Prior CABG	6.0

Diabetes Clinical History
2,368 Randomized Patients

Duration of diabetes (mean yr)	10.4
<6 months	8%
6 months-5 years	25%
5-10 years	24%
10-20 years	29%
≥20 years	14%
HbA_{1c} % (mean)	7.7
Receiving insulin	28%
Micro or macroalbuminuria (ACR >30)	33%
Neuropathy (MNSI clinical score >2)	50%

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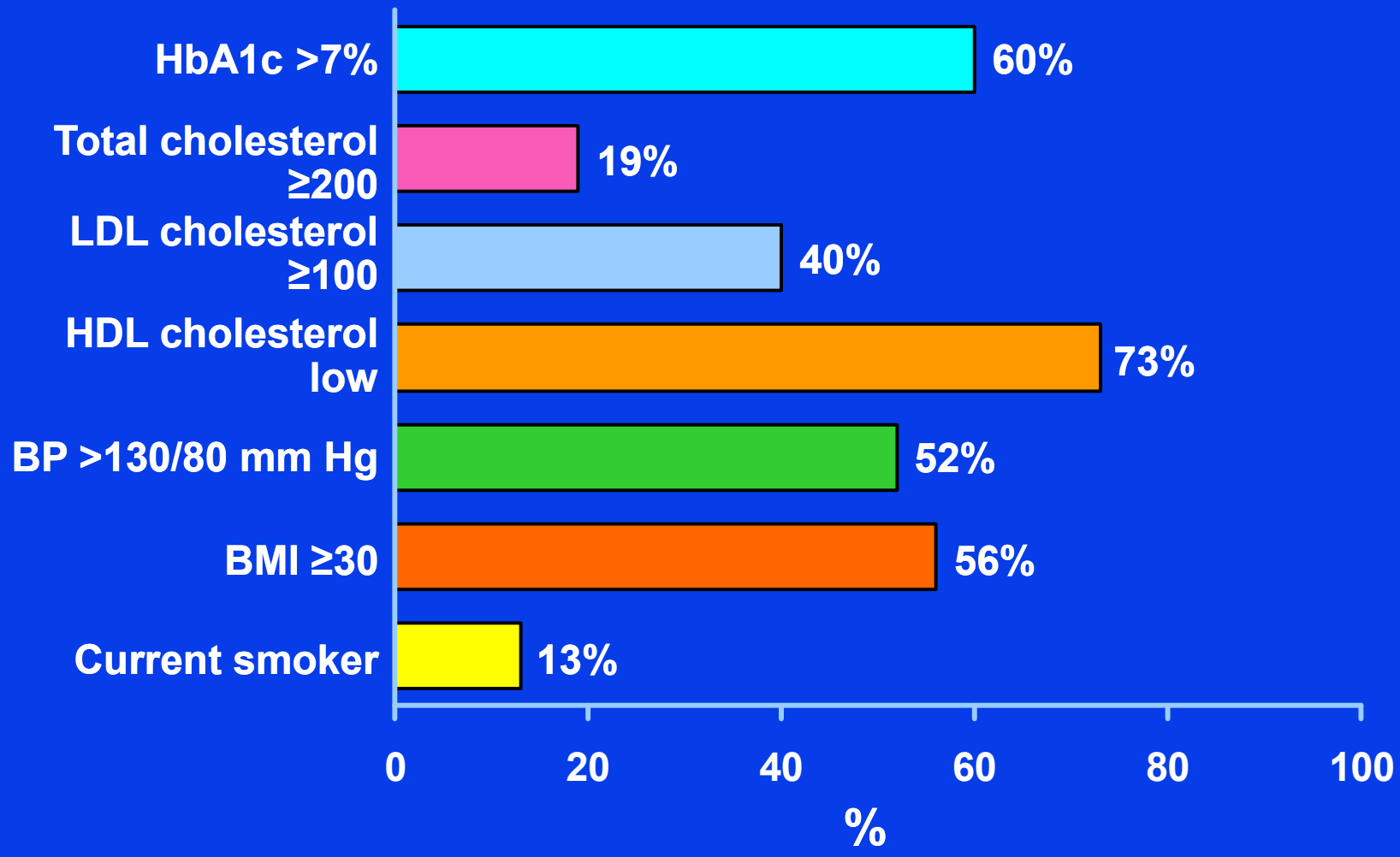
Risk Factor Status Among BARI 2D Patients at Baseline



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BARI 2D Trial: 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 (yrs 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

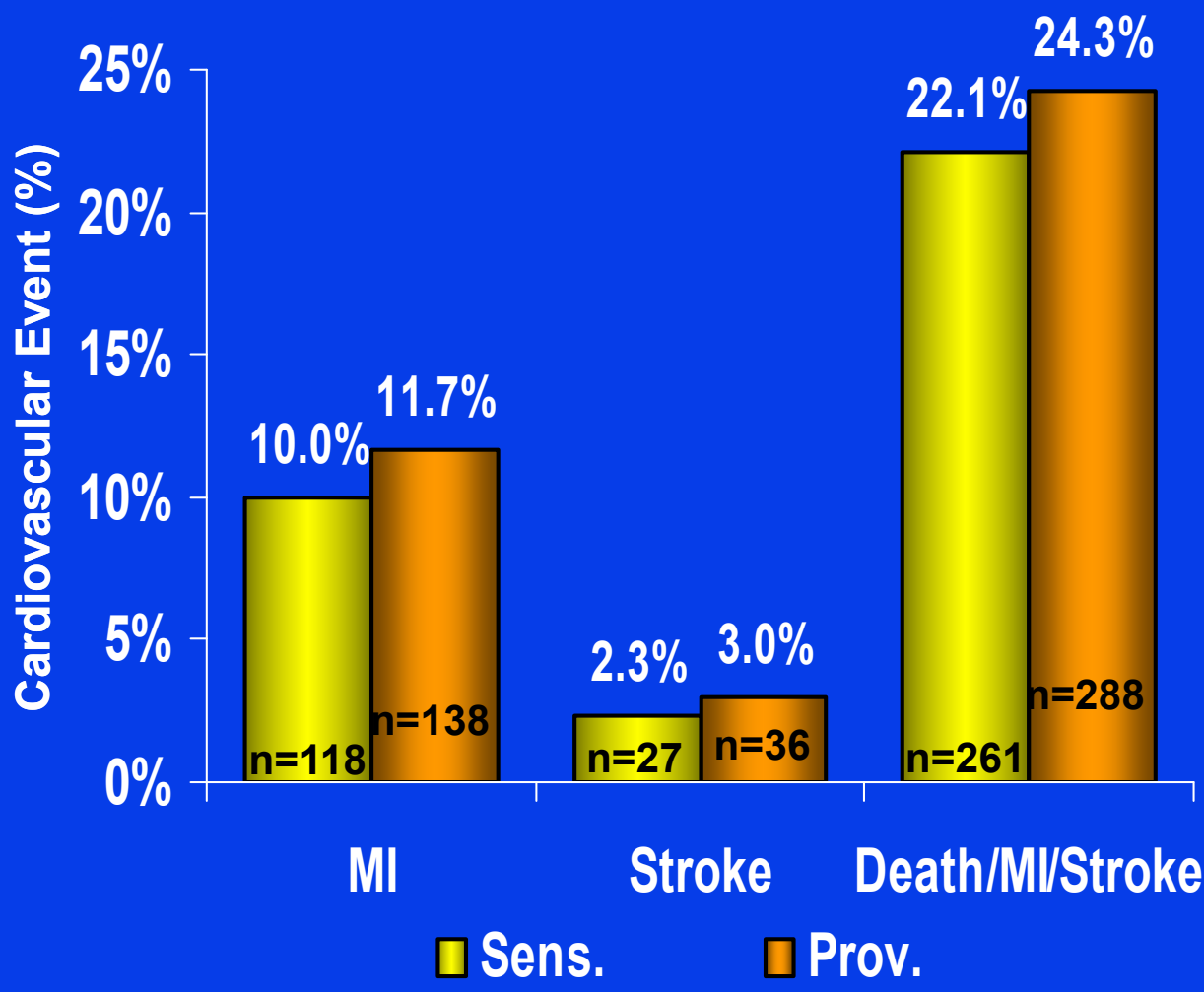
BARI 2D Study Group, NEJM 2009

BARI 2D Trial: 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 (yrs 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

BARI 2D Study Group, NEJM 2009

BARI 2D Trial: Secondary Endpoint



- The rates of MI, stroke and the combined secondary endpoint of death, MI, and stroke were similar between the group insulin sensitization therapy vs. the group receiving insulin provision therapy.
- The difference between the two treatment groups for the combined secondary endpoint of death, MI, and stroke did not reach statistical significance (p=0.13)

BARI 2D Study Group, NEJM 2009

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BARI 2D Trial: Limitations

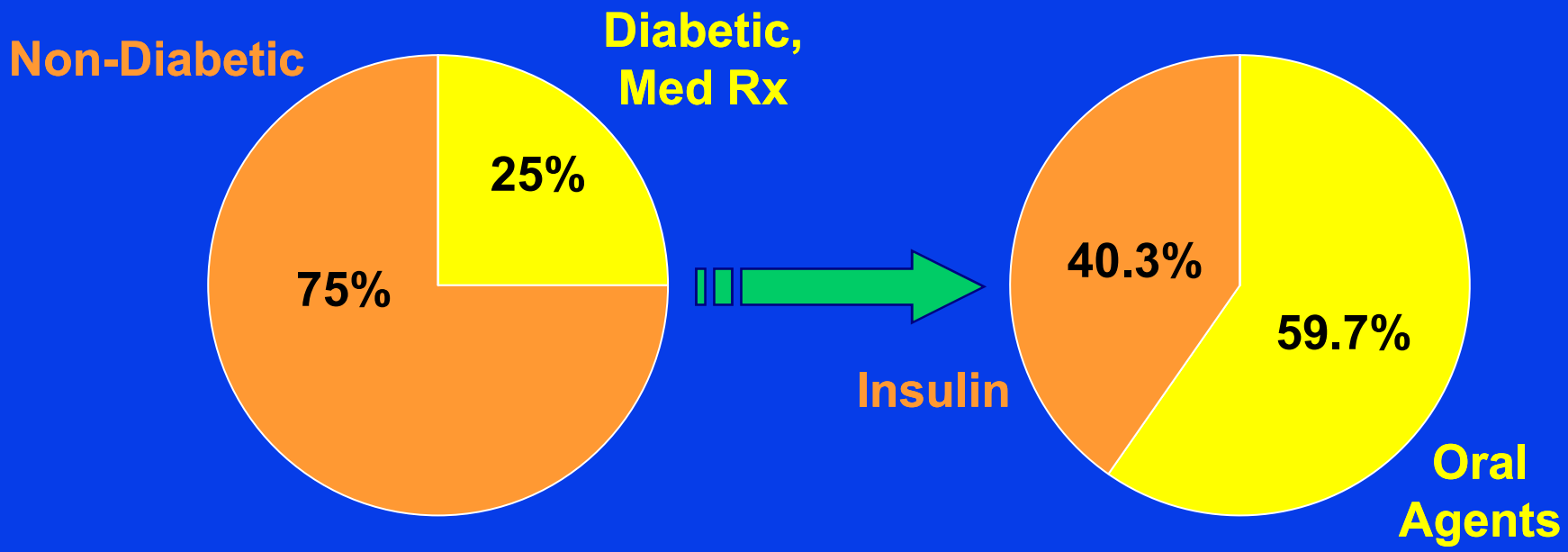
- Patients who are at high risk for MI and, therefore, stand to benefit the most from revascularization were excluded from the trial.

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

BARI 2D Study Group, NEJM 2009

SYNTAX Trial
With and Without

N=1800



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Banning AP et al, JACC 55:2010

SYNTAX Trial
With and Without

	Non-Diabetic n=1348	Diabetic n-452	P
Male	79.9	71.0	<0.001
BMI	27.5	29.5	<0.001
Current tobacco	21.7	15.8	<0.006
CHF	3.7	7.4	0.001
PVD	8.2	14.6	<0.001

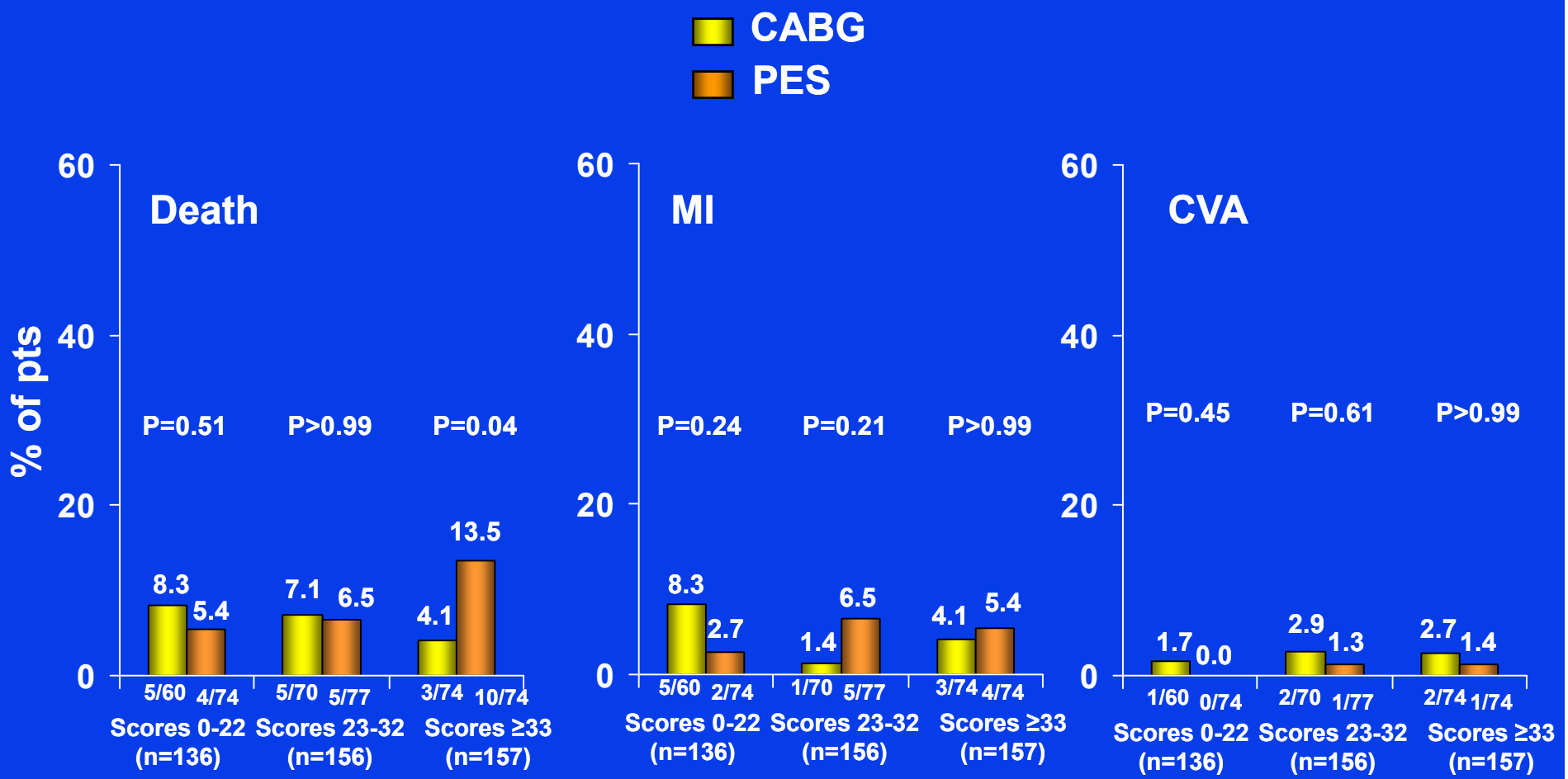
Banning AP et al, JACC 55:2010

SYNTAX Trial
With and Without

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

Banning AP et al, JACC 55:2010

SYNTAX Trial
Diabetic Patient Outcomes - 1 Year F/U



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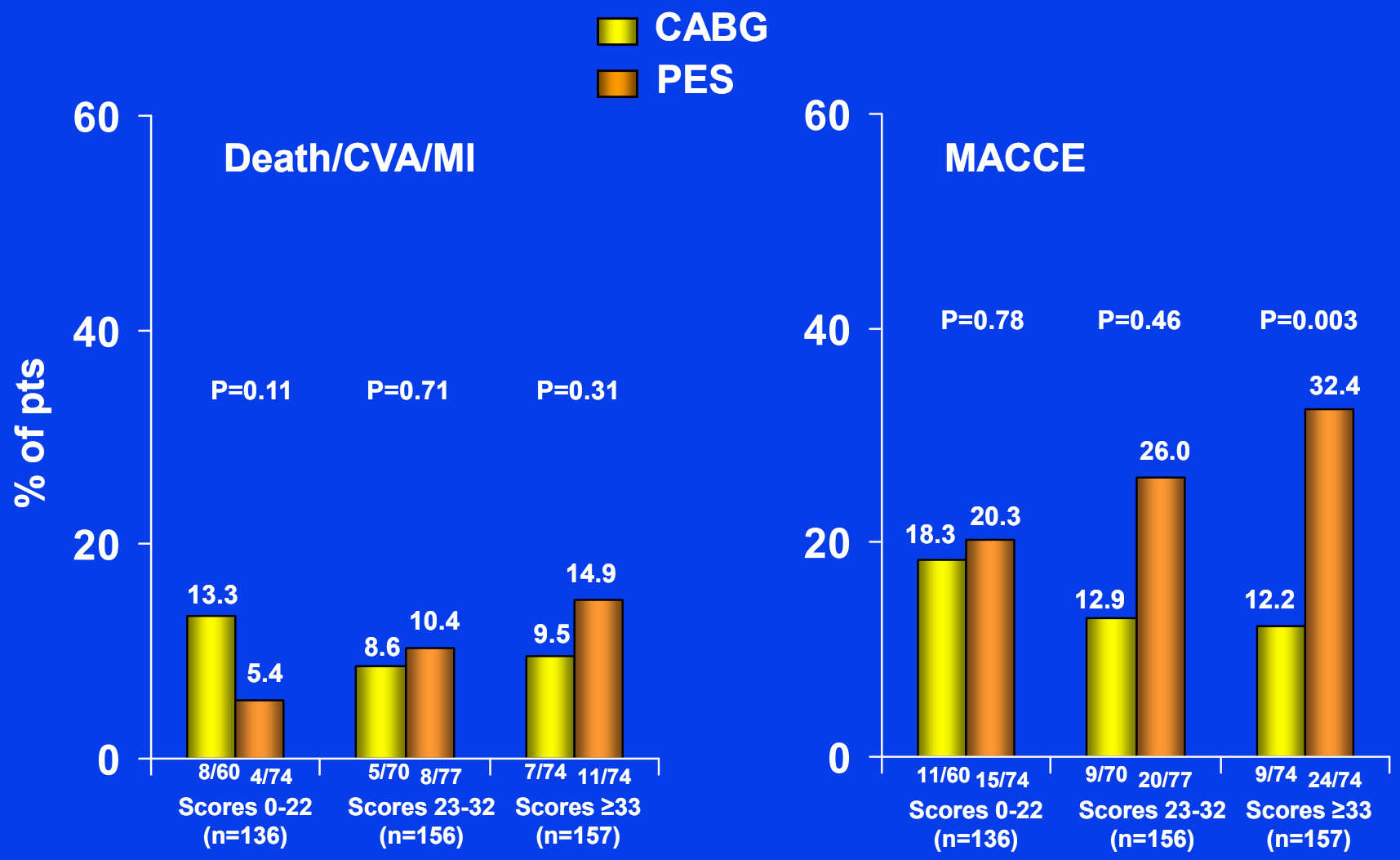
SYNTAX Trial
Diabetic Patient Outcomes - 1 Year F/U



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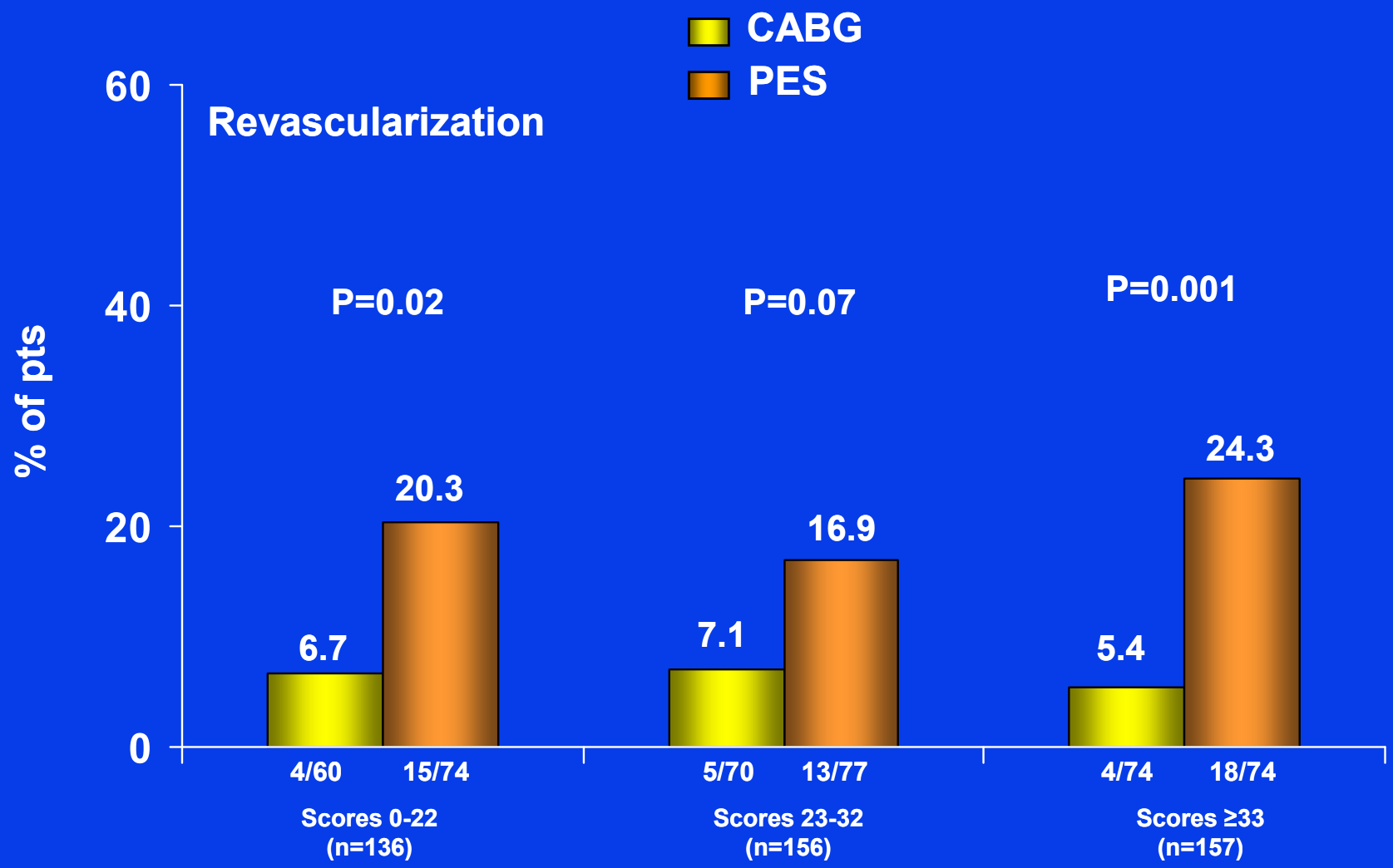
SYNTAX Trial
Diabetic Patient Outcomes - 1 Year F/U



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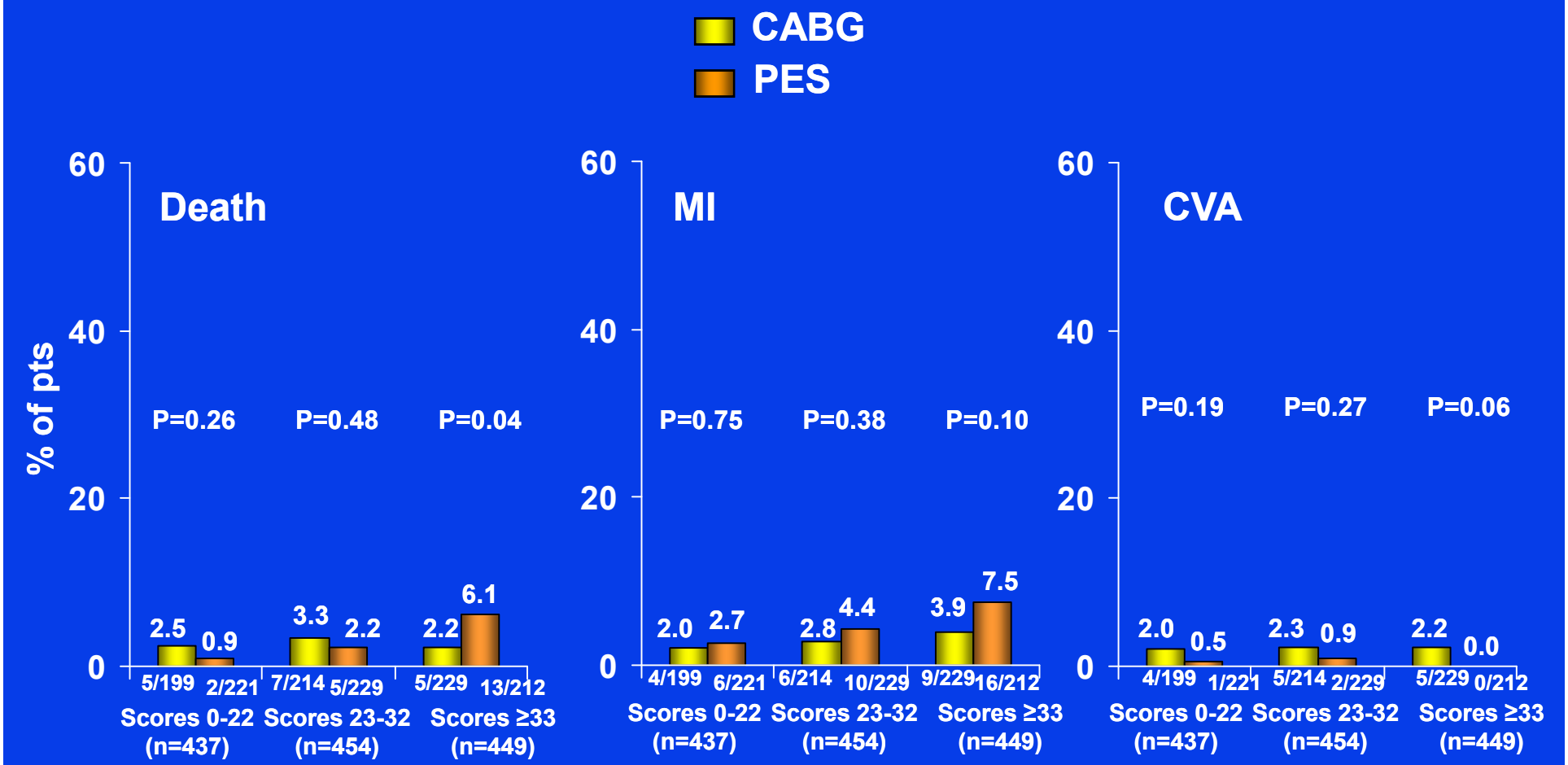
SYNTAX Trial
With & Without Medically Treated Diabetes
1 Year F/U

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

Banning AP et al, JACC 55:2010

SYNTAX Trial
Non-Diabetic Patient Outcomes - 1 Year F/U



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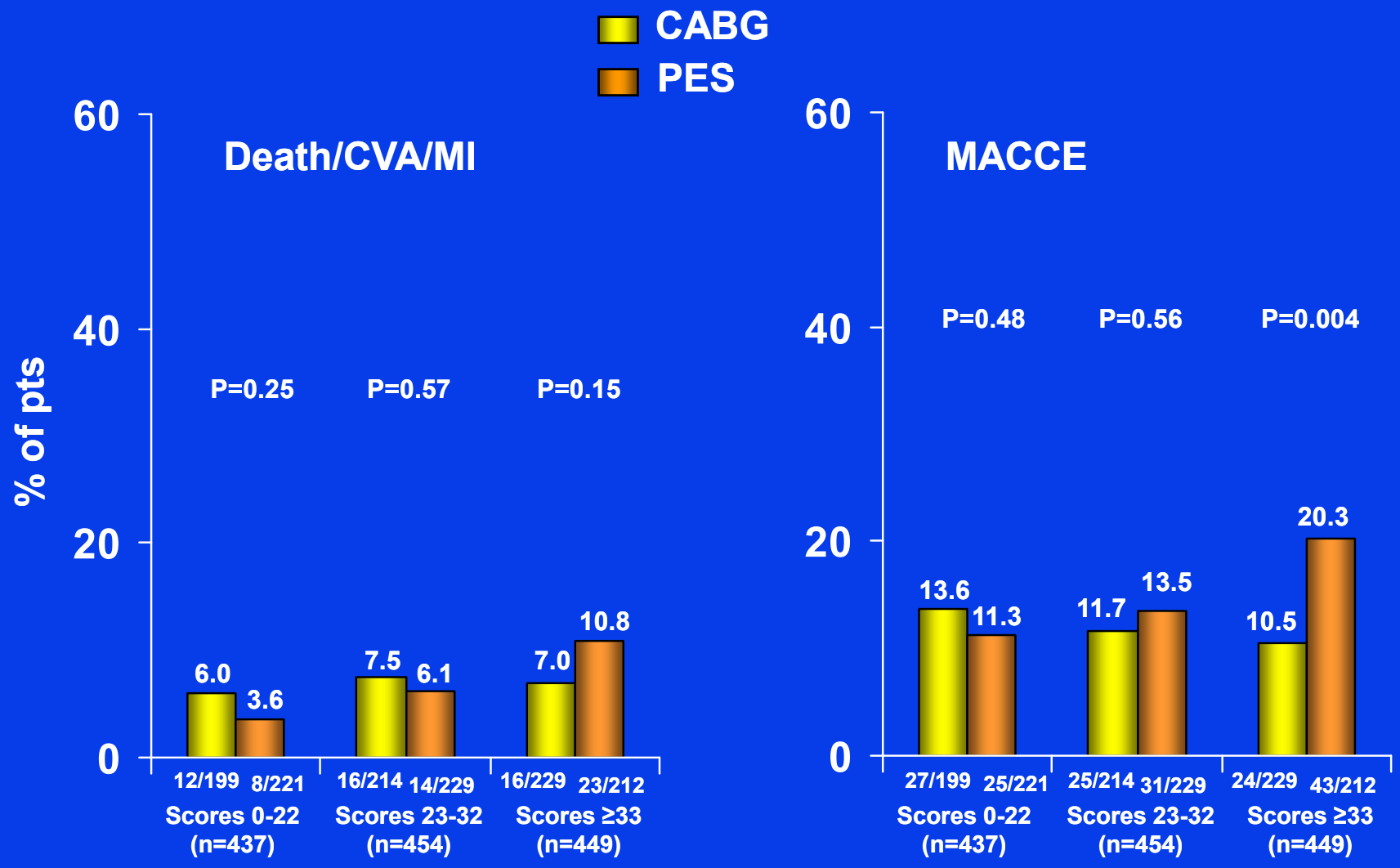
Banning AP et al, JACC 55:2010

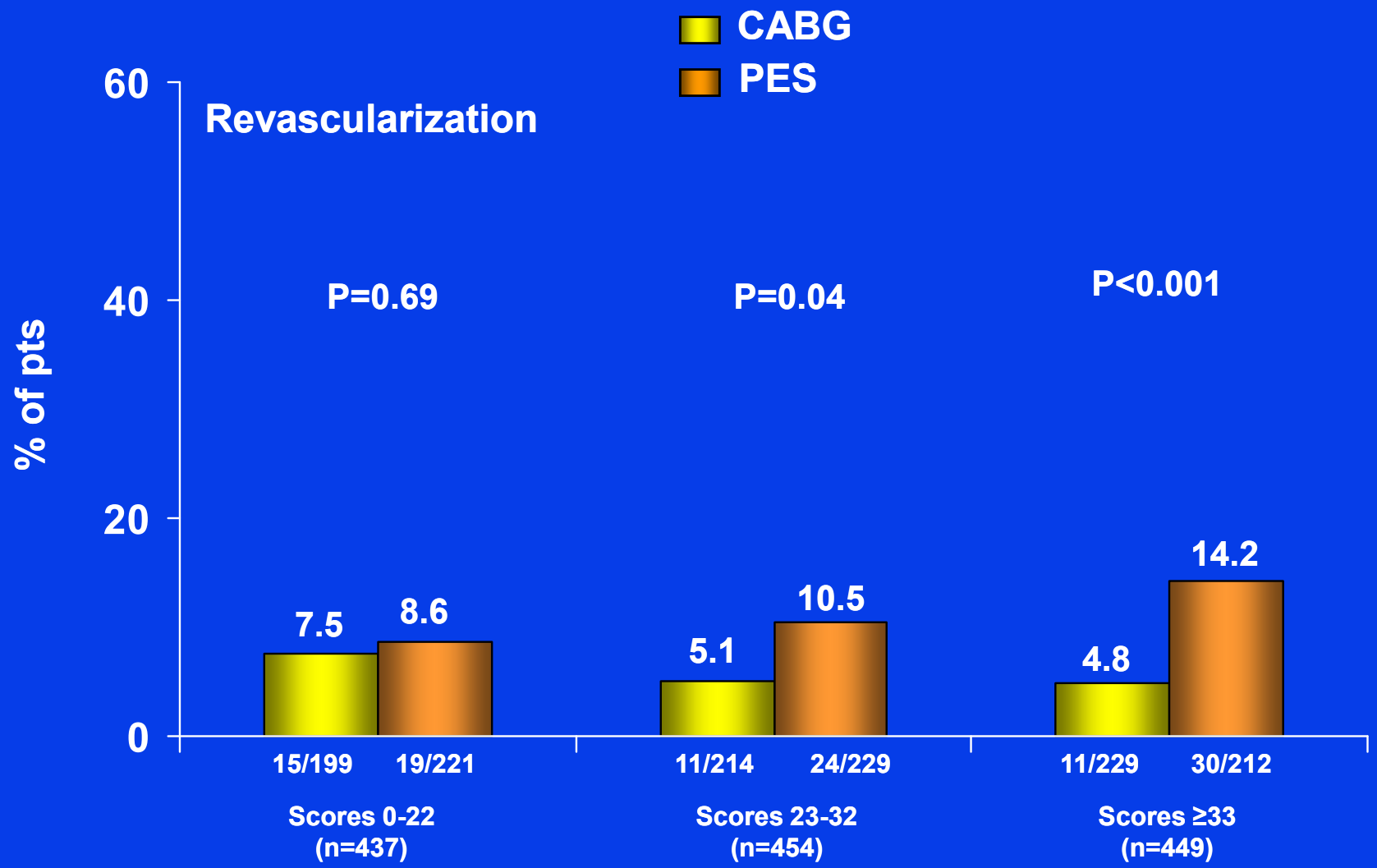
SYNTAX Trial
Non-Diabetic Patient Outcomes - 1 Year F/U



MAYO CLINIC

Banning AP et al, JACC 55:2010

SYNTAX Trial
Non-Diabetic Patient Outcomes - 1 Year F/U



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Banning AP et al, JACC 55:2010

SYNTAX Trial
With & Without Medically Treated Diabetes
1 Year F/U

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

Banning AP et al, JACC 55:2010

SYNTAX Trial
With & Without Medically Treated Diabetes
1 Year F/U

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

Banning AP et al, JACC 55:2010

SYNTAX Trial
With & Without Medically Treated Diabetes
1 Year F/U

	Medically Treated Diabetes (n=452)			
	CABG n=221	PES n=231	RR (95% CI)	P
Graft occlusion/ST	2.2 (4/186)	2.9 (6/209)	1.33 (0.38-4.66)	0.76
Acute (≤ 1 d)	0.0 (0/206)	0.0 (0/230)	--	--
Subacute (2-30 d)	0.0 (0/206)	1.8 (4/228)	--	0.13
Late (31-365 d)	2.0 (4/201)	0.9 (2/220)	0.46 (0.08-2.47)	0.43
Efficacy Outcomes				
Repeat Revasc	6.4 (13/204)	20.3 (46/227)	3.18 (1.77-5.71)	<0.001
PCI	4.4 (9/204)	16.7 (38/227)	3.79 (1.88-7.65)	<0.001
CABG	2.0 (4/204)	4.0 (9/227)	2.02 (0.63-6.47)	0.22

MAYO CLINIC

Banning AP et al, JACC 55:2010

Randomized Clinical Trials of Revasc & DM

	Diabetic Patients		All Diabetic Patients
	BARI n=353	SYNTAX n=452	BARI 2D n=2368
Randomization	PCTA vs CABG	DES vs CABG	All revasc vs Med Rx
F/U reported	10 yrs	1 yr	5 yrs
PCI method	PTCA	Taxus DES	35% DES
Patients	Multivessel CAD	LMCA, MV CAD	Elective, LM excluded
Primary endpoint	Death 5 yrs	Death, MI, stroke or revasc 1 yr	Death 5 yrs
Death	PTCA: 34.5% CABG: 19.4% p=0.002	DES: 8.4% CABG: 6.4% p=0.43	All revasc: 11.7% Med Rx: 12.2% p=0.97

Dauerman HL, JACC 55:2010

Randomized Clinical Trials of Revasc & DM

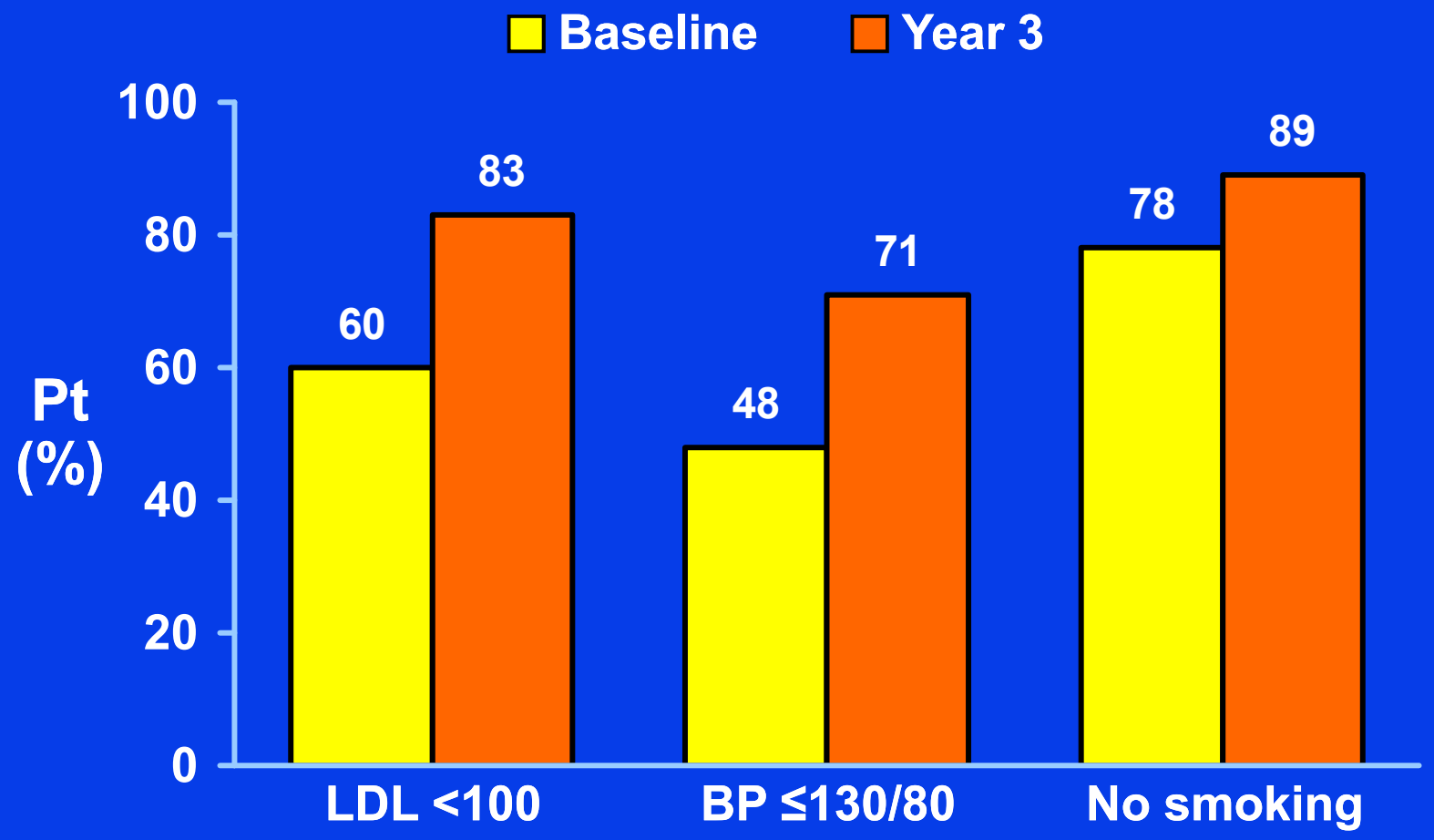
	Diabetic Patients		All Diabetic Patients
	BARI n=353	SYNTAX n=452	BARI 2D n=2368
Death MI Stroke	Not reported	At 1 yr: DES: 10.1% CABG: 10.3% p=0.96	At 5 yrs: All revasc: 22.8% Med Rx: 24.1% p=0.70
Death MI Stroke Revasc	Not reported	DES: 26.0% CABG: 14.2% p=0.003	Not reported
Repeat Revasc	PTCA: 69.9% CABG: 11.1% (at 7 yrs)	DES: 20.3% CABG: 6.4% p<0.001	42% of Med Rx pts crossover to revasc group

Dauerman HL, JACC 55:2010

SYNTAX Trial
What Can We Say

- There is still room for good clinical judgment in decision making

Risk Factor Control



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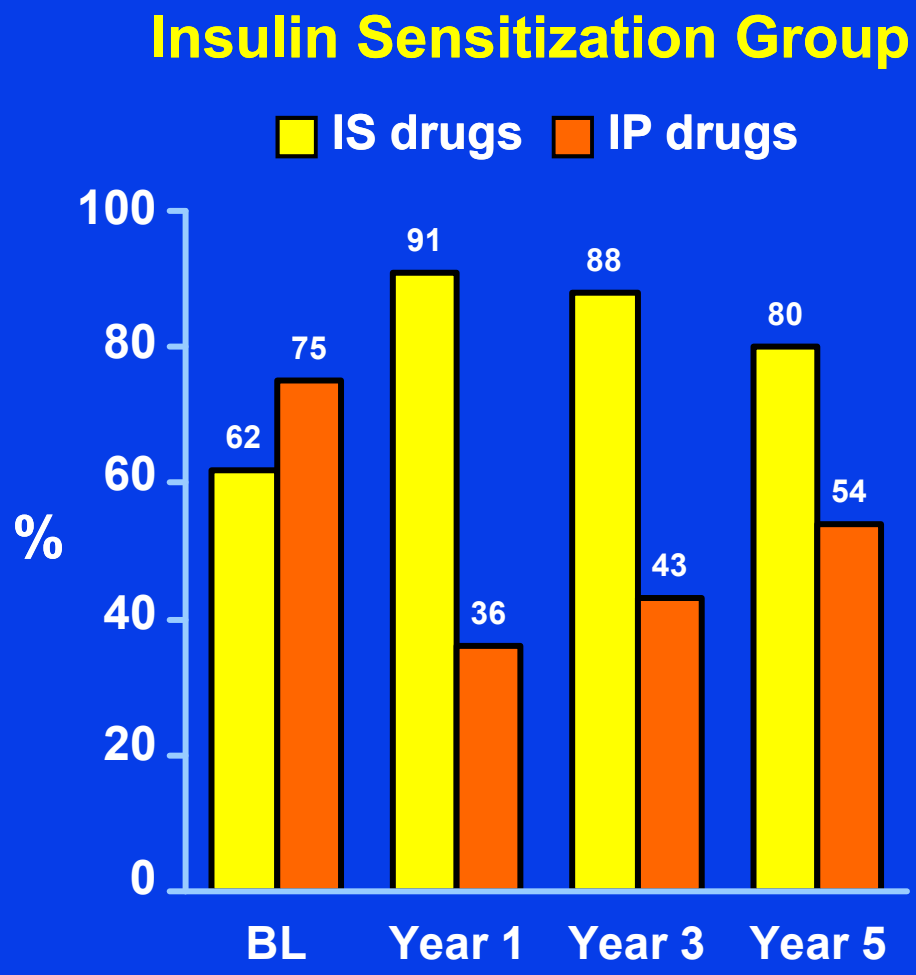
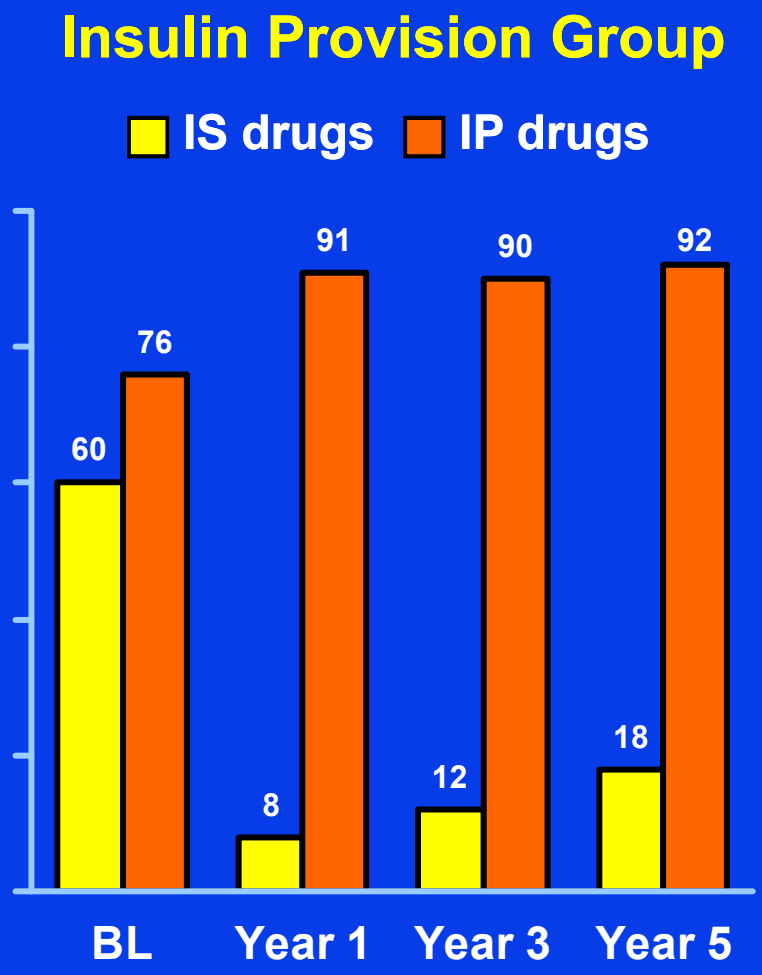
Risk Factor Measures

Mean	Base-line	3 year			
		Rev	Med	IS	IP
LDL (mg/dL)	96	81	79	79	80
HDL (mg/dL)	38	41	41	42	40
SBP (mm Hg)	132	126	125	125	126
DBP (mm Hg)	75	70	70	70	71
BMI (kg/m^2)	31.7	32.0	32.2	31.7	32.5

Drug Use
Randomized Treatment Assignment





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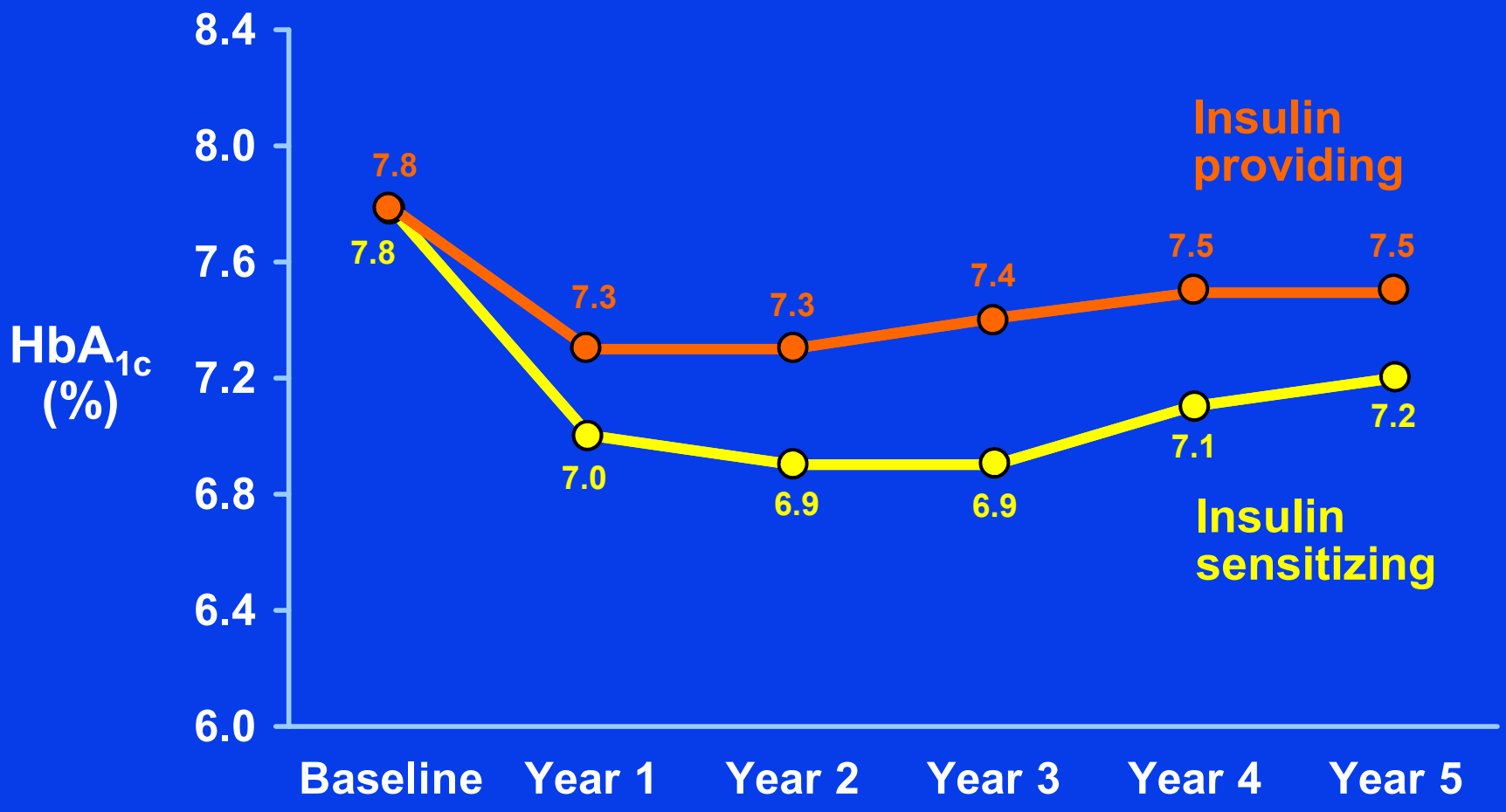
Diabetes Medication Use

Medication	Baseline (%)	3 year IS (%)	3 year 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



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3010909-73

Cardiovascular Medication Use

Medication	Baseline (%)	3 year Revasc (%)	3 year Medical (%)
Beta blocker	73	84	88
ACE/ARB	77	91	92
Statin	75	95	95
Aspirin	88	94	94

Summary

- Excellent risk factor control
- Randomized treatment strategies effectively implemented for
  - Prompt revascularization vs delayed/no revascularization
  - Insulin sensitization vs insulin provision

Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D)

5-Year Results

American Diabetes Association Conference
June 7, 2009

Robert Frye, MD
Mayo Clinic – Rochester

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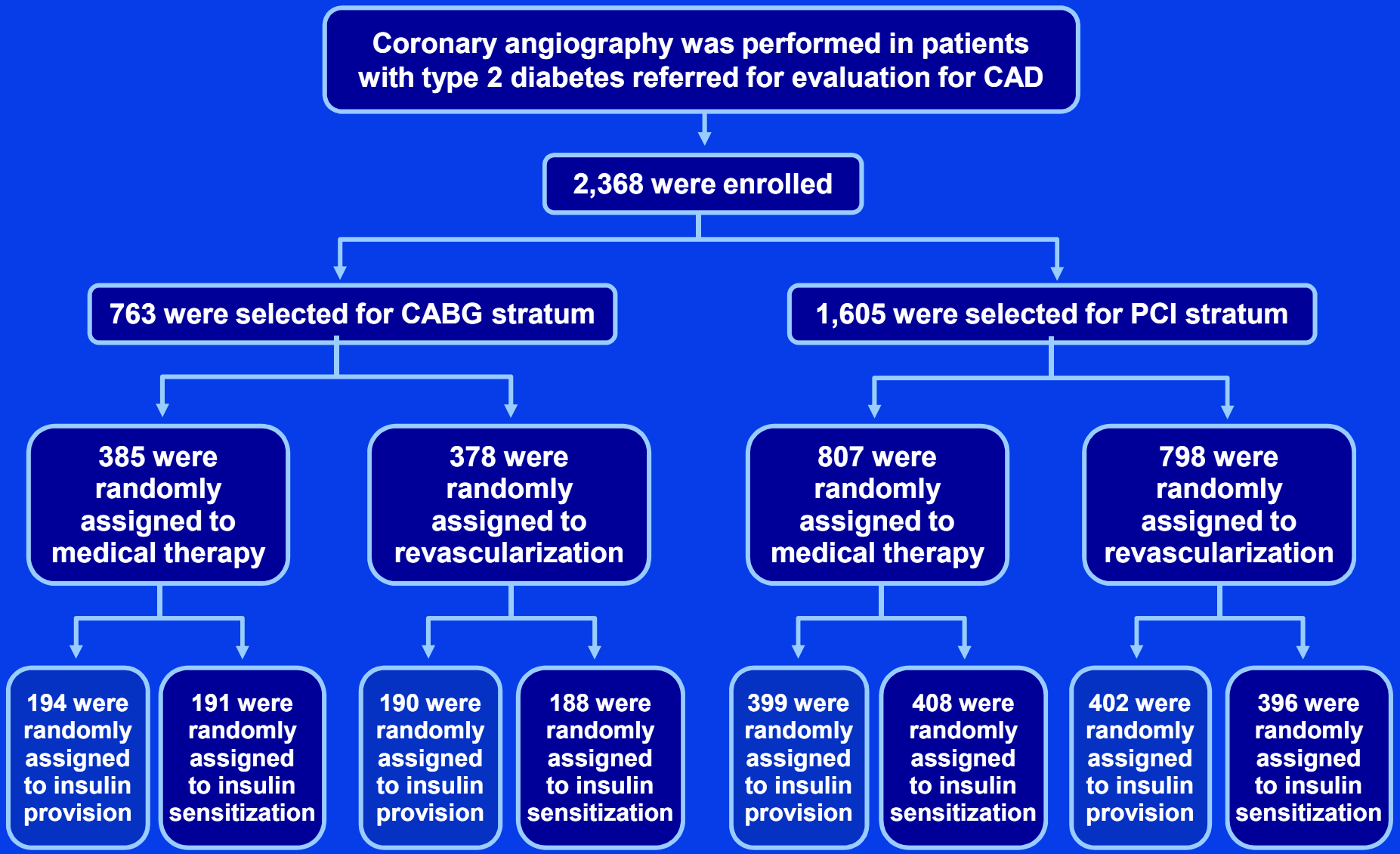
BARI 2D Primary and Principal Secondary Endpoints

- All-cause mortality

  Major cardiovascular events

- Composite of death/MI/stroke
- Average follow-up 5.3 years

Enrollment Flow Diagram



Baseline Characteristics by Randomization Stratum

	PCI intended n=1,605	CABG intended n=763
Age (mean years)	62.0	63.2
Male (%)	68.0	76.0
Prior revasc (%)	29.0	13.0
Proximal LAD (%)	10.0	19.0
LVEF <50 (%)	18.0	18.0
3 vessel disease (%)	20.0	52.0
Total occlusion (mean number)	0.48	0.84
Myocardial jeopardy (mean %)	37.2	59.7

BARI 2D in the Context of Current Clinical Practice and Recent Trials

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

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

ACCF/SCAI/STS/AATS/AHA/ASNC: Circulation 119:1330, 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**

Does Glycemic Control Explain the Apparent Benefit of Combined CABG and IS Therapy

	Mean 3-year HbA1c	
	IS	IP
PCI stratum		
Prompt	6.9±1.1	7.5±1.4
Delayed	7.2±1.3	7.5±1.3
CABG stratum		
Prompt	6.9±1.1	7.4±1.3
Delayed	7.1±1.4	7.5±1.4

Does any other "on Rx" factor appear to be different in the CABG/IS subgroup? No

BARI 2D
Diabetes Implications

- Overall both insulin sensitizing and insulin providing approaches appear appropriate in BARI 2D eligible patients
- Further analyses will determine whether these strategies differ in other secondary outcomes

BARI 2D: Diabetes Management
Implications

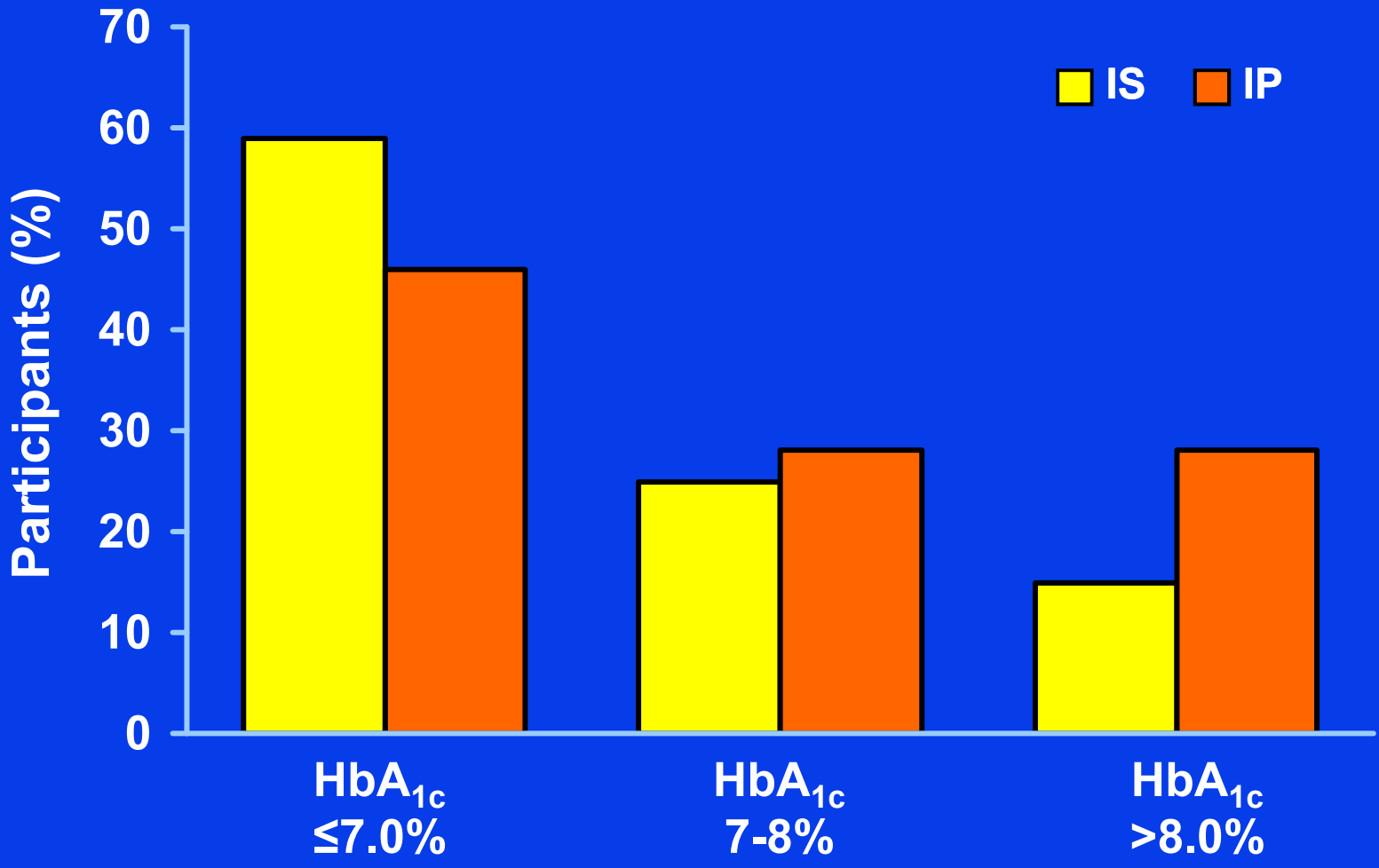
However there is suggestive evidence that IS therapy may have a number of potential advantages over IP

- **The benefit of prompt CABG in terms of mortality/ CVD events appeared stronger in those receiving IS therapy**
- **IS therapy showed a borderline (P=0.06) benefit over IP in those receiving prompt revascularization**
- **HbA_{1c} target value was more frequently achieved in the IS group**
- **Severe hypoglycemia was less frequent in the IS group**
- **Weight and waist circumference change were less adverse in the IS group**

Can Any Difference Between IS and IP CVD/Death Results be Explained by the Difference in HbA_{1c} Between Them?

Study	Δ HbA_{1c}	Δ CVD outcome
BARI 2D	0.5%	NS
ADVANCE	0.6%	NS
ACCORD	1.1%	NS
VADT	1.6%	NS

Achievement of HbA1c Goals in BARI 2D



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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-yr 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


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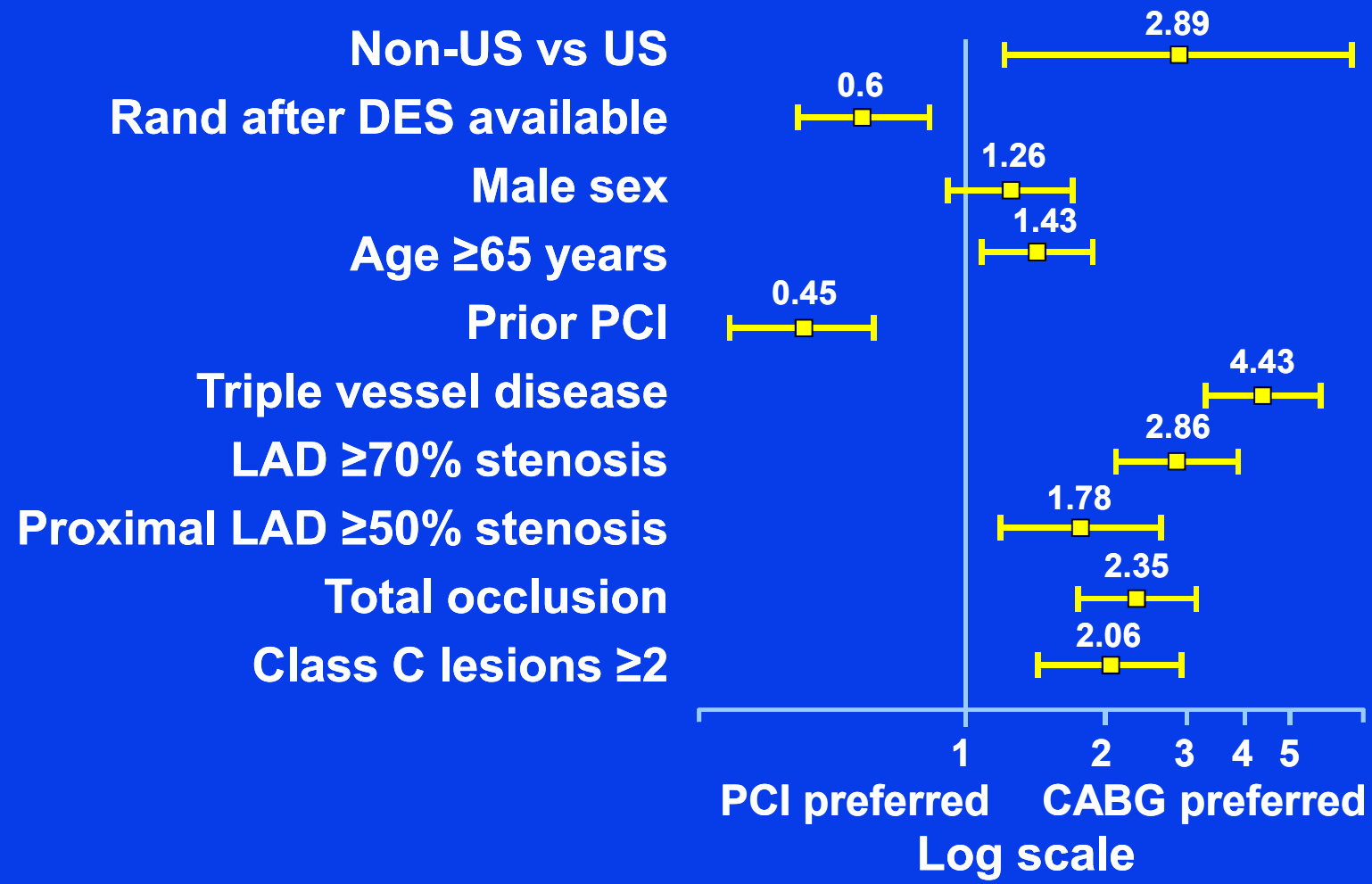
Adjusted Odds Ratio of CABG Selection Among Multivessel Disease



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BARI 2D Goals

Setting

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

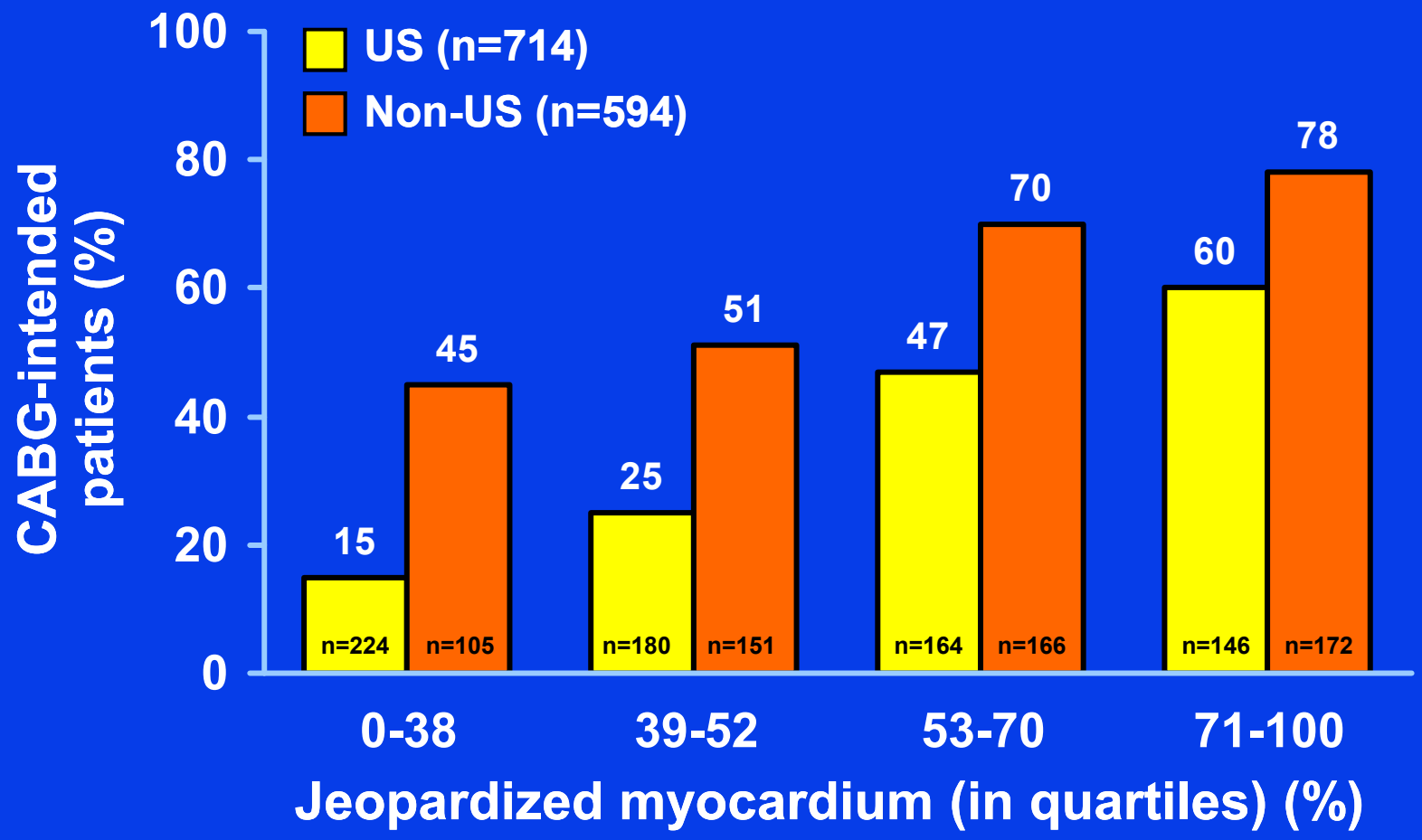
Compare

- Prompt revascularization **vs** delayed or no revascularization
- Insulin sensitizing strategy **vs** an insulin providing strategy for glycemic management with target HbA_{1c} <7.0%

SYNTAX and Diabetes

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

BARI 2D



Kim LJ et al: J Am Coll Cardiol Intv 2:384, 2009

MAYO CLINIC

3038666-91

Title/drp–author: WT/BK – Holmes, David
Sub/drp–Job#: YW105/BK – 3038666

Subject: BARI 2D Kim

Background: BU3
Banner/brdr: 0-40-159/BU41
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Plot/brdr: open/BU41
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PPT shooting instructions
PPT File to Server
(3 images)

Artist: mls Start Date: 4-12-10

COLOR REFERENCE ONLY

Match: Mayo2bu-2002 (CP1111378)

MAYO CLINIC

CARDia Trial

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

Kapur A et al, J Am Coll Cardiol 55:432-40, 2010

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doi:10.1016/j.jacc.2009.10.014

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

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 randomized to PCI plus stenting (and routine abciximab) or CABG. The primary comparison used a noninferiority method with the upper boundary of the 95% confidence interval (CI) not to exceed 1.3 to declare PCI noninferior. Bare-metal stents were used initially, but a switch to Cypher (sirolimus drug-eluting) stents (Cordis, Johnson & Johnson, Bridgewater, New Jersey) was made when these became available.

Results At 1 year of follow-up, the composite rate of death, MI, and stroke was 10.5% in the CABG group and 13.0% in the PCI group (hazard ratio [HR]: 1.25, 95% CI: 0.75 to 2.09; p = 0.39), all-cause mortality rates were 3.2% and 3.2%, and the rates of death, MI, stroke, or repeat revascularization were 11.3% and 19.3% (HR: 1.77, 95% CI: 1.11 to 2.82; p = 0.02), respectively. When the patients who underwent CABG were compared with the subset of patients who received drug-eluting stents (69% of patients), the primary outcome rates were 12.4% and 11.6% (HR: 0.93, 95% CI: 0.51 to 1.71; p = 0.82), respectively.

Conclusions The CARDia (Coronary Artery Revascularization in Diabetes) trial is the first randomized trial of coronary revascularization in diabetic patients, but the 1-year results did not show that PCI is noninferior to CABG. However, the CARDia trial did show that multivessel PCI is feasible in patients with diabetes, but longer-term follow-up and data from other trials will be needed to provide a more precise comparison of the efficacy of these 2 revascularization strategies. (The Coronary Artery Revascularisation in Diabetes trial; ISRCTN19872154) (J Am Coll Cardiol 2010;55:432–40) © 2010 by the American College of Cardiology Foundation

Baseline Clinical Characteristics of CARDia Trial Patients

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

Kapur A et al: J Am Coll Cardiol 55:432, 2010

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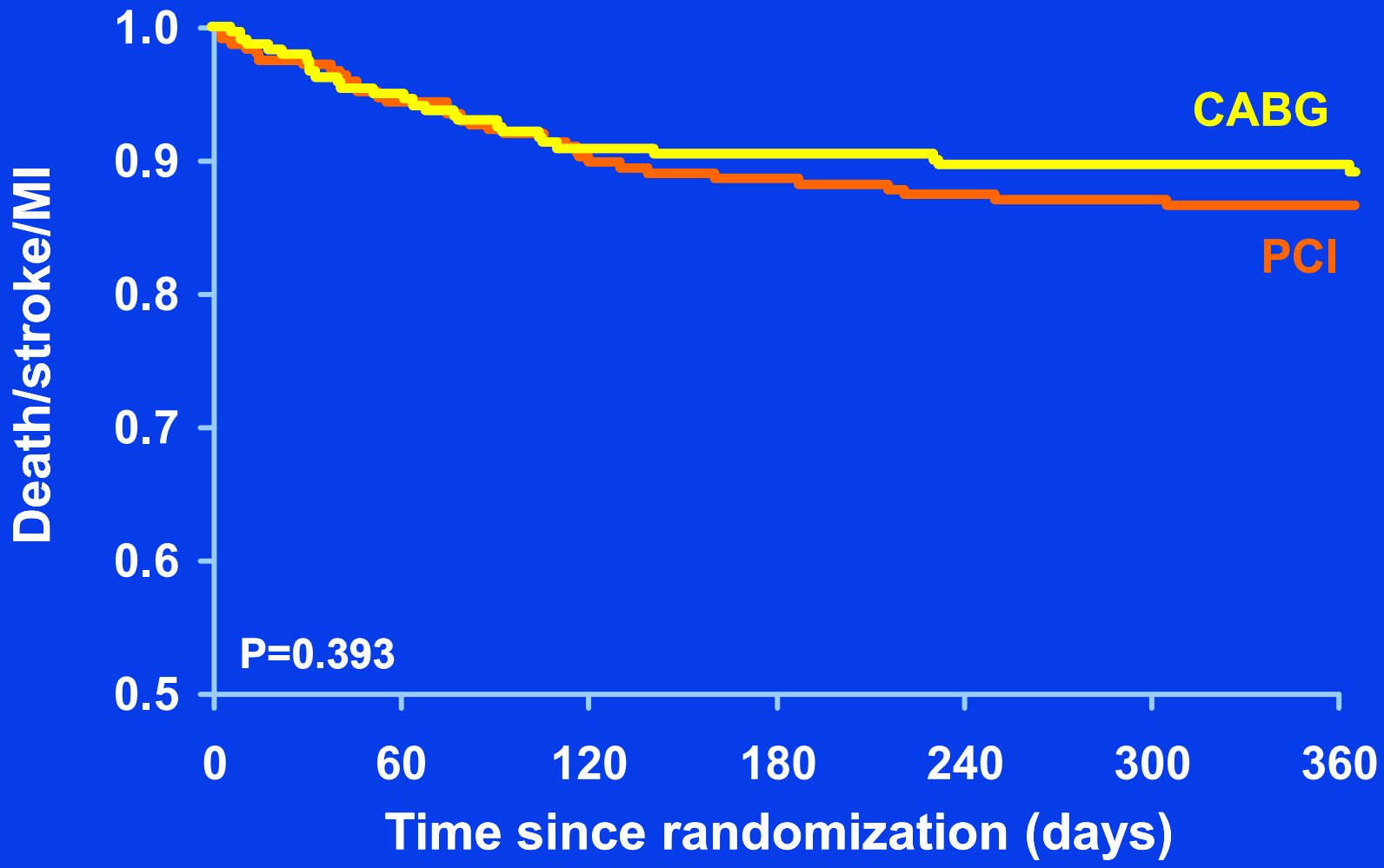
Baseline Clinical Characteristics of CARDia Trial Patients

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

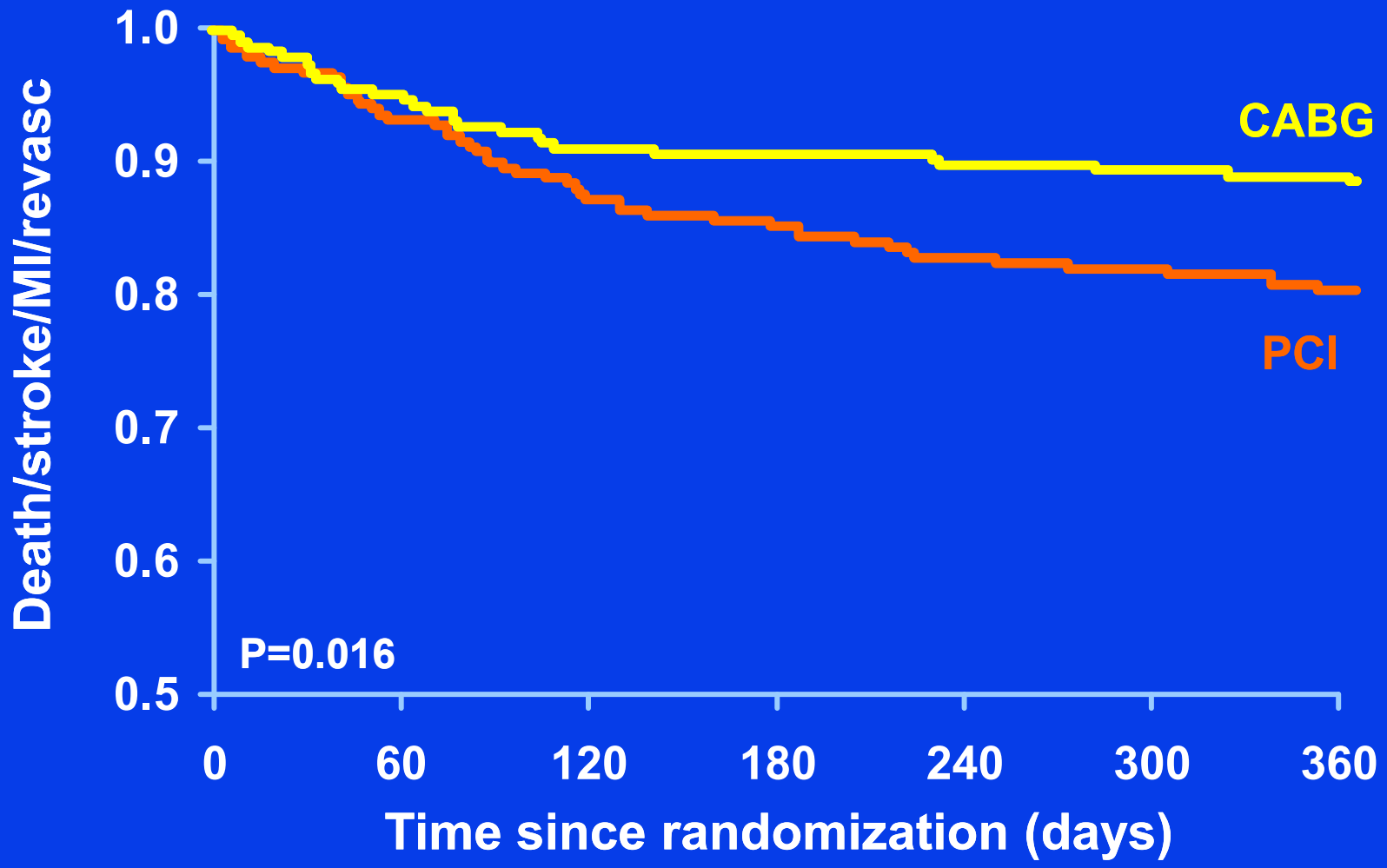
Kapur A et al: J Am Coll Cardiol 55:432, 2010

Primary End Point Event-Free Survival
CABG vs PCI



Kapur A et al: J Am Coll Cardiol 55:432, 2010

MACCE Event-Free Survival
CABG vs PCI



Kapur A et al: J Am Coll Cardiol 55:432, 2010

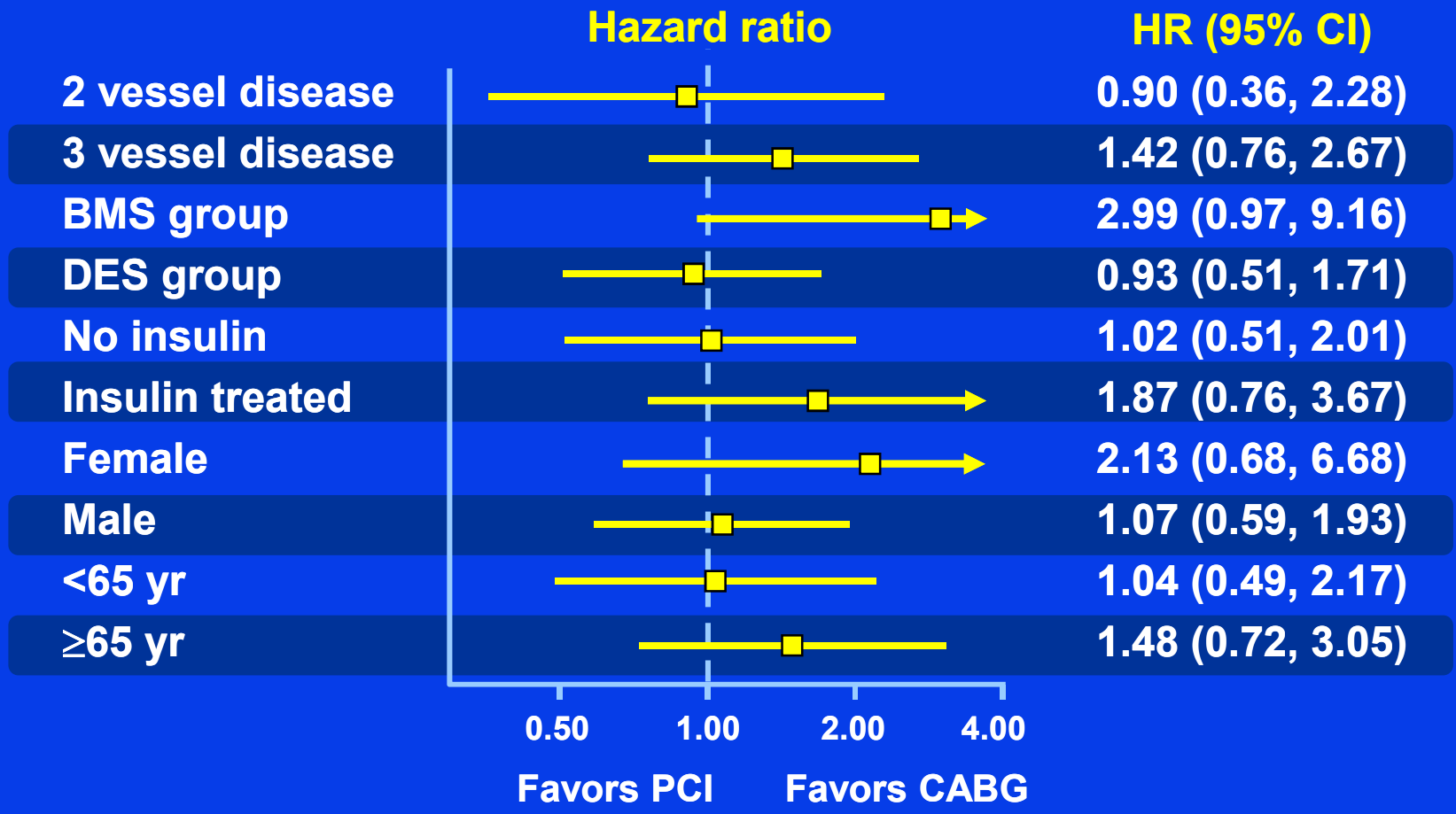
Major End Points at 1 Year

Adjudicated events post-randomization	CABG (n=248)		PCI (n=254)		
	No.	%	No.	%	P
Death	8	3.2	8	3.2	0.97
Nonfatal MI	14	5.7	25	9.8	0.088
Periprocedural MI	11	4.4	12	4.7	0.819
Late MI*	3	1.2	14	5.5	0.016
Nonfatal stroke	7	2.8	1	0.4	0.066
Composite outcome of d, nonfatal MI, and nonfatal stroke at 1 yr: primary outcome	26	10.5	33	13.0	0.393
Further revasc at 1 yr	5	2.0	30	11.8	<0.001
Composite outcome of d, nonfatal MI, nonfatal stroke, and repeat revasc at 1 yr: secondary outcome	28	11.3	49	19.3	0.016
TIMI major bleed	15	6.1	3	1.2	0.009

*Late MI defined as occurring >7 days after index revasc proc

Kapur A et al: J Am Coll Cardiol 55:432, 2010

Forest Plot of Death, Myocardial Infarction and Stroke in Key Subgroups



Kapur A et al: J Am Coll Cardiol 55:432, 2010

Title/drp–author: WT/BK – Holmes, David
Sub/drp–Job#: YW105/BK – 3038674

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PPT File to Server
(7 images)

Artist: mls Start Date: 4-12-10

COLOR REFERENCE ONLY

Match: Mayo2bu-2002 (CP1111378)

MAYO CLINIC

3038674-101


HELVETIORUM
FIDEI AC VIRTUTI

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

African proverb


Oh, crap! Was that TODAY?
REGAN

Diabetes Mellitus

- I know what we do but the answers to the questions we ask keep changing

? ? ? ? ? ? ? ? ? ? ? ? ?

- Screening for ischemia
- Specific treatment regimen: IS vs IP
- Specific IS drug
- Revascularization versus medical therapy
- Specific revascularization strategy
- Adjunctive therapy after PCI

Systematic Review
PCI vs CABG

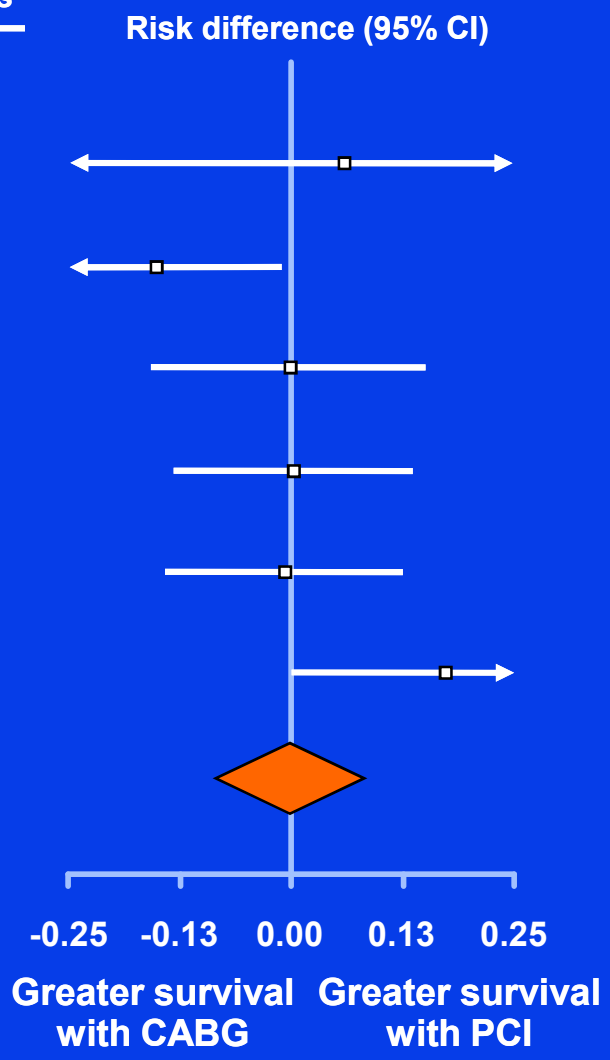
- 23 randomized clinical trials
- 5,019 patients assigned PCI
- 4,944 patients assigned CABG
- Outcomes of interest

  Survival, myocardial infarction, stroke, angina, additional revascularization

Bravata: Ann Intern Med 147:703, 2007

5-Year Survival in Diabetics

Study, year	Surviving patients/all patients	
	PCI	CABG
AWESOME, 2002	8/11	8/12
BARI, 1997; 1996	45/69	75/93
EAST, 2000	26/29	27/30
ERACI II, 2005	35/39	35/39
MASS II, 2006	47/56	50/59
RITA, 1998	27/29	25/33
Overall	188/233	220/266



Ann Int Med 147:708, 2007

MAYO CLINIC

CP1298619-5

Systematic Review
PCI vs CABG

Diabetics

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

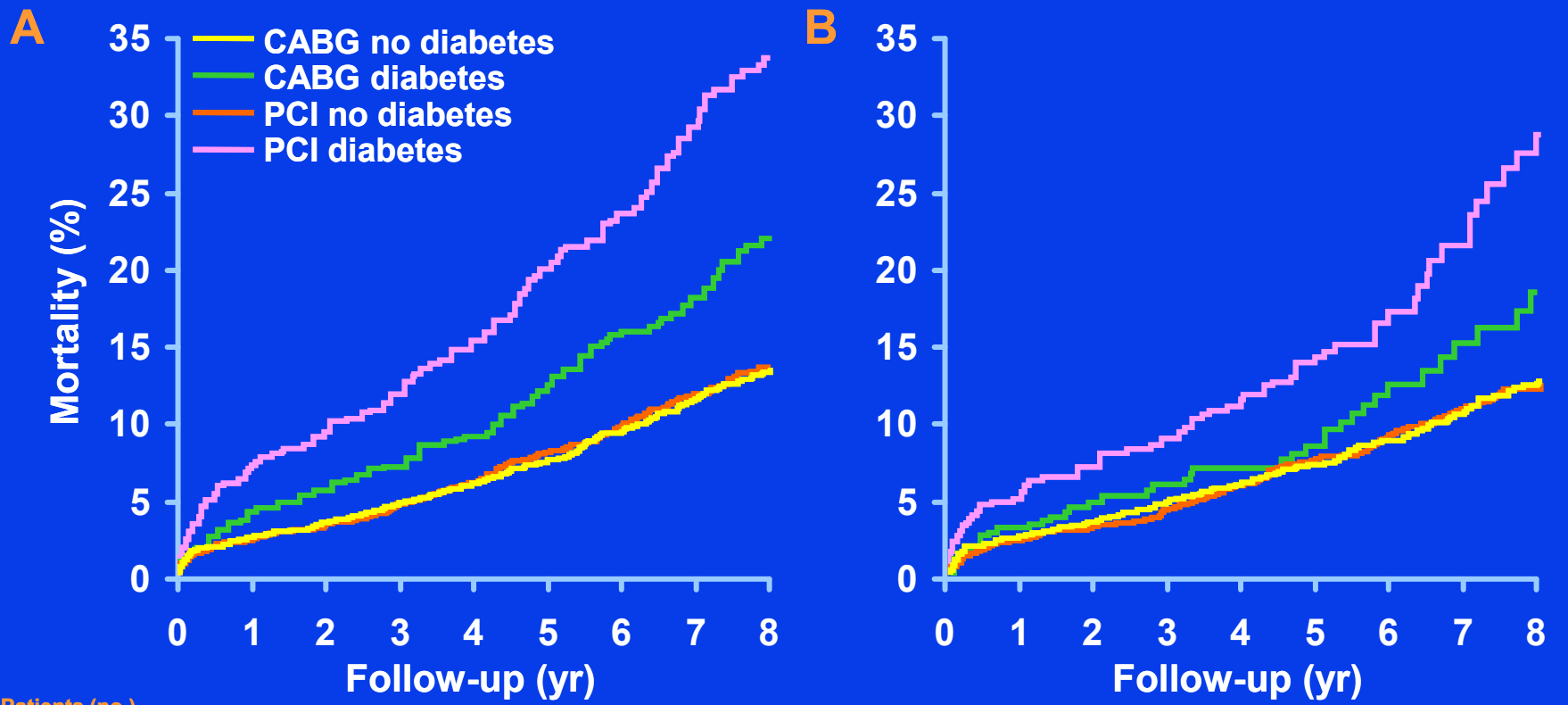
Bravata: Ann Intern Med 147:703, 2007

CABG vs PCI
Multivessal CAD

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

Hlatky MA et al: Lancet 373:1190-97, 2009

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



Patients (no.)									
CABG no diabetes	3,263	3,169	3,089	2,877	2,677	2,267	1,592	1,380	1,274
CABG diabetes	615	587	575	532	498	421	257	225	200
PCI no diabetes	3,298	3,217	3,148	2,918	2,725	2,281	1,608	1,393	1,288
PCI diabetes	618	574	555	508	475	373	218	179	160

2,529	2,457	2,382	2,179	1,992	1,598	940	747	655
435	420	410	371	344	278	120	91	73
2,556	2,493	2,432	2,215	2,031	1,606	946	750	655
445	421	408	369	344	258	110	81	66

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Hlatky MA et al: Lancet 373:1190-97, 2009

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Page last updated at 23:00 GMT, Wednesday, 8 July 2009 00:00 UK

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Tests raise life extension hopes

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

Rapamycin was discovered on Easter Island

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

The findings, published in the journal Nature, raise the prospect of being able to slow down the ageing process in older people.

CABG vs DES in Patients with Multivessel Disease and Diabetes

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

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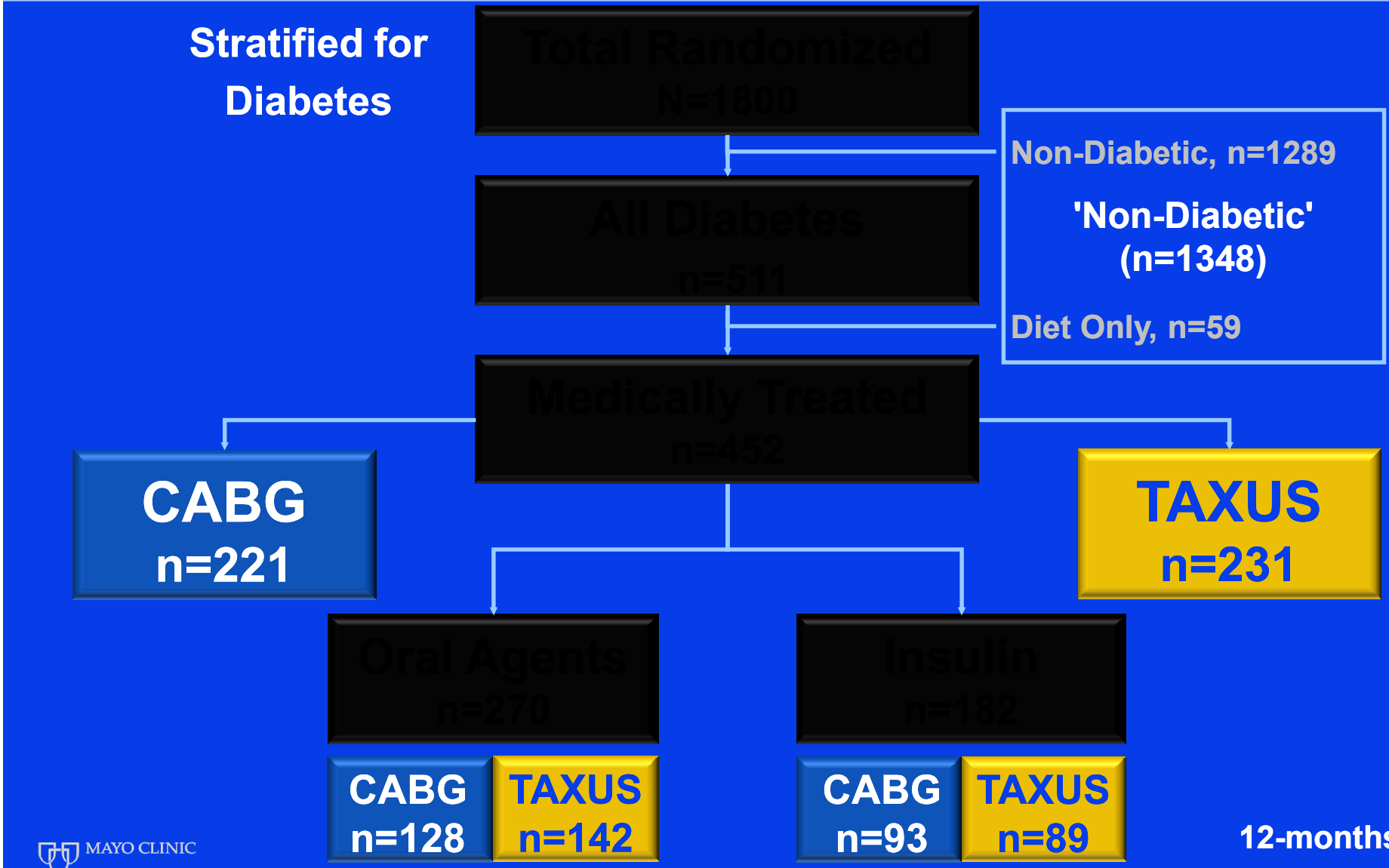
*Diabetic patients from ARTS I & II (Macaya, EuroIntervention. 2006;2:69-76)
†As of 22 September 2008; Enrollment ongoing.

Patients with Diabetes in SYNTAX
Randomized Cohort, Intent-to-Treat



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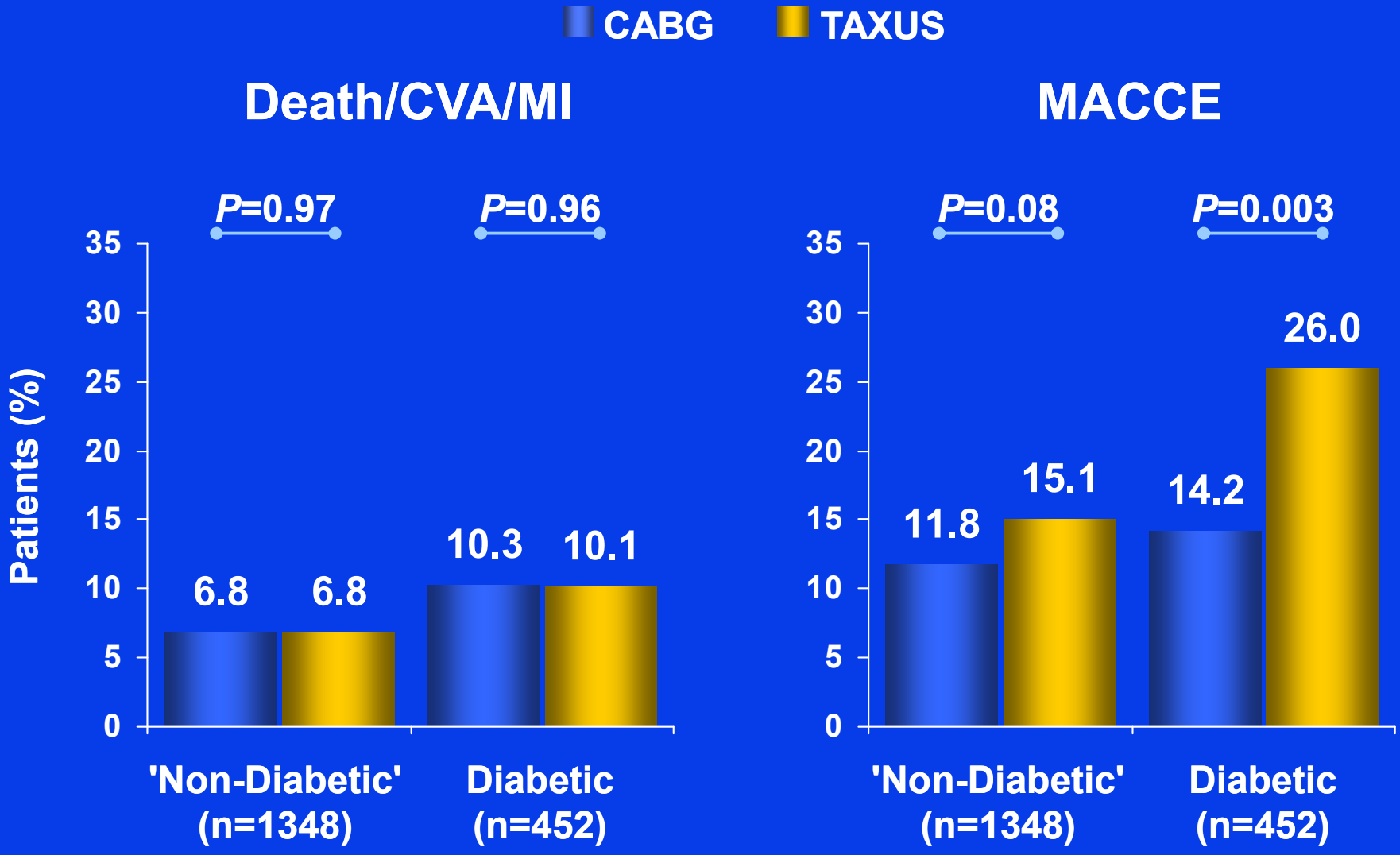
Outcome According to Diabetic Status at 12 Months



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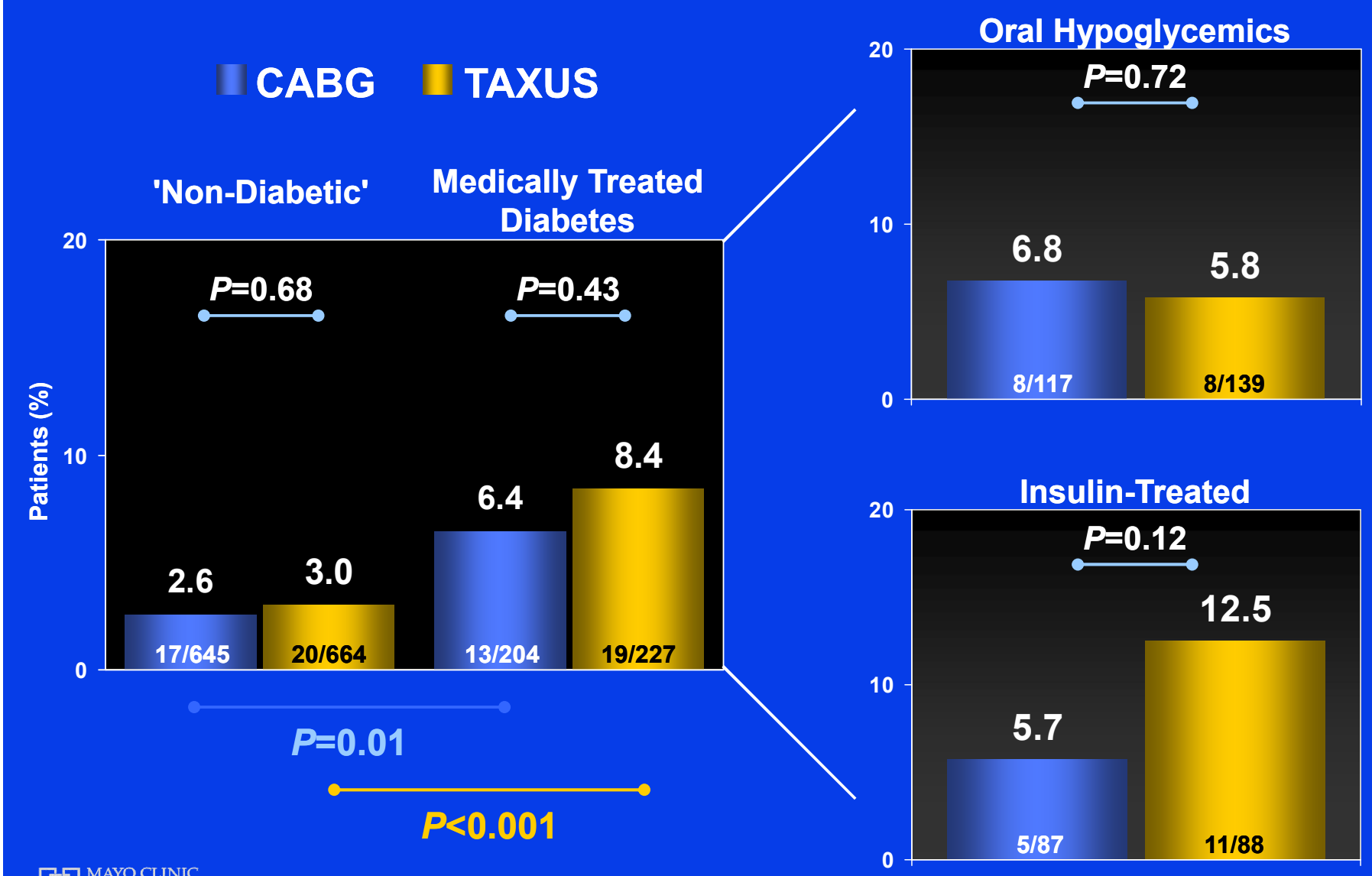
Serruys, ESC 2008

Death (All-Cause) at 12 Months



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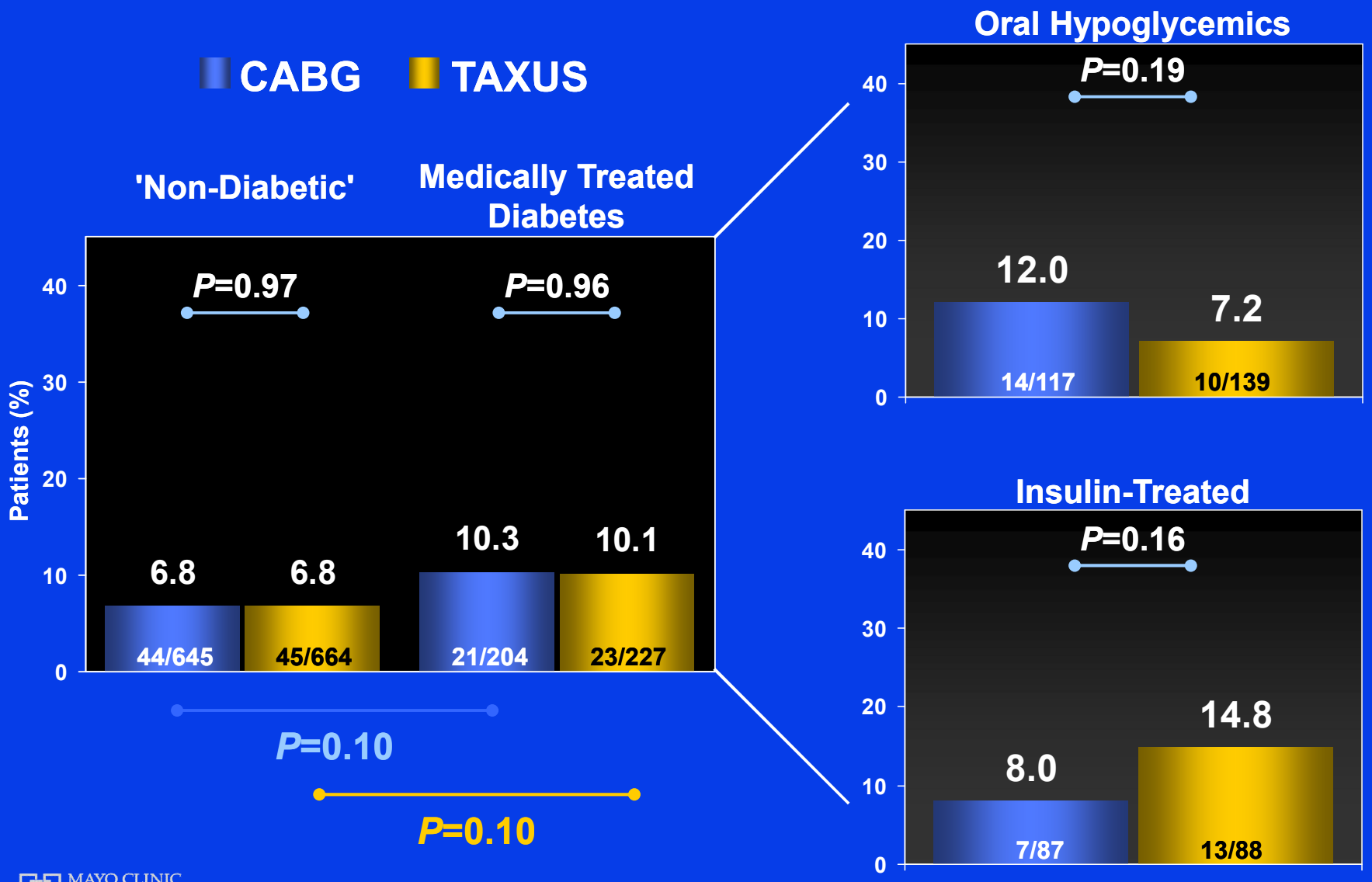
Death/CVA/MI at 12 Months



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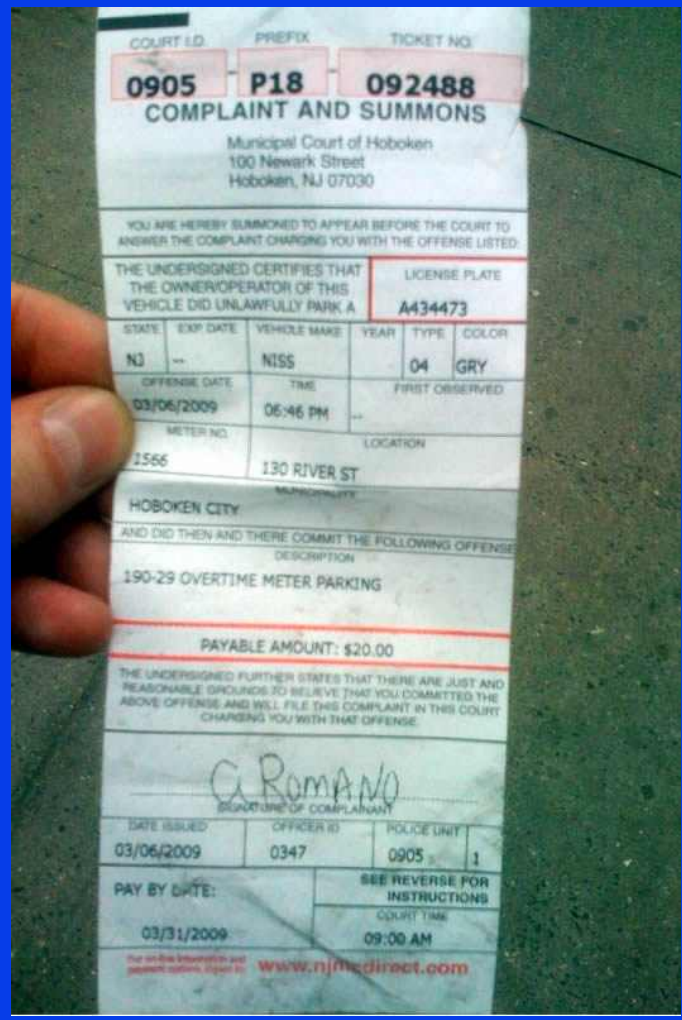
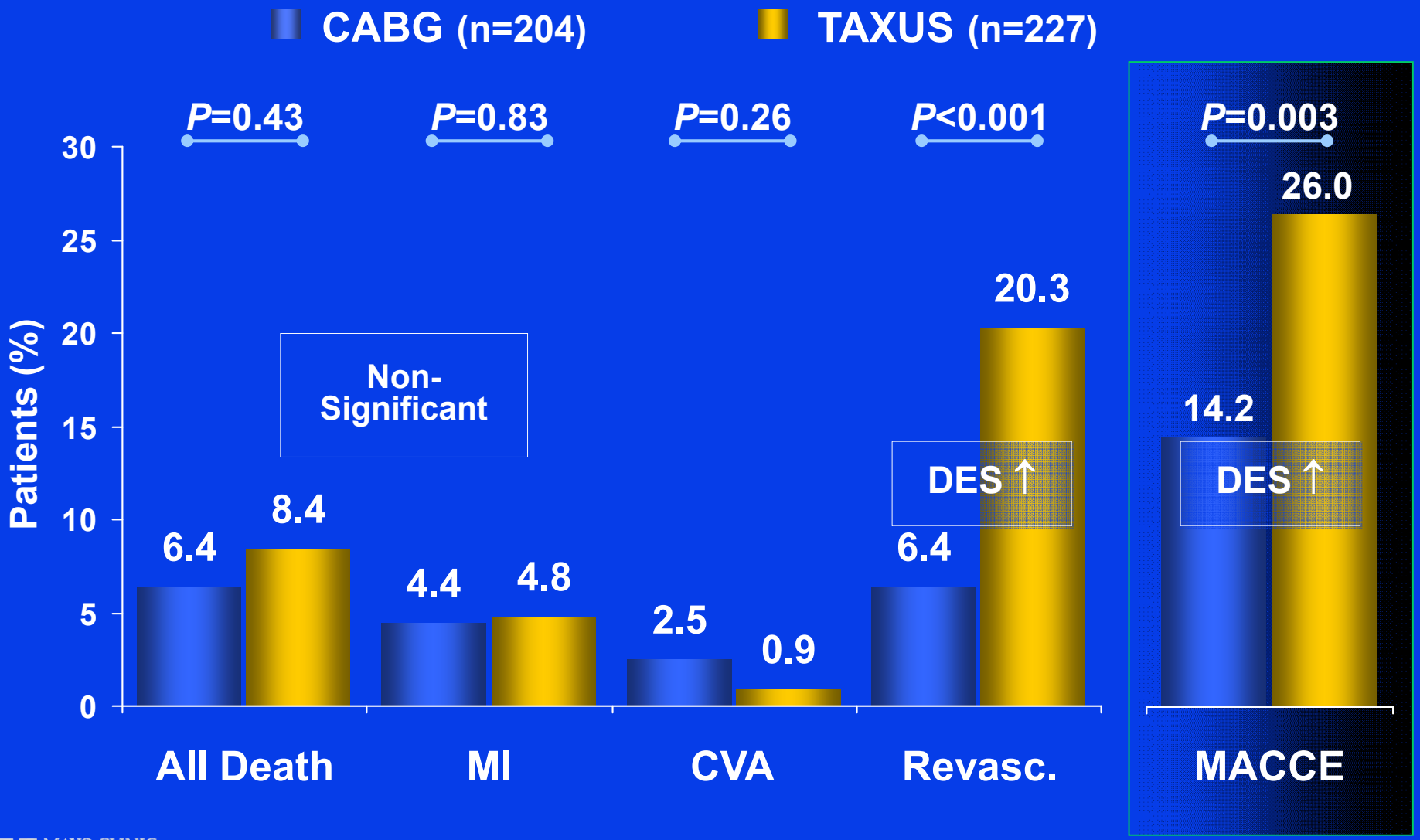
Murder

Parking Ticket



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



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*Medically treated diabetes

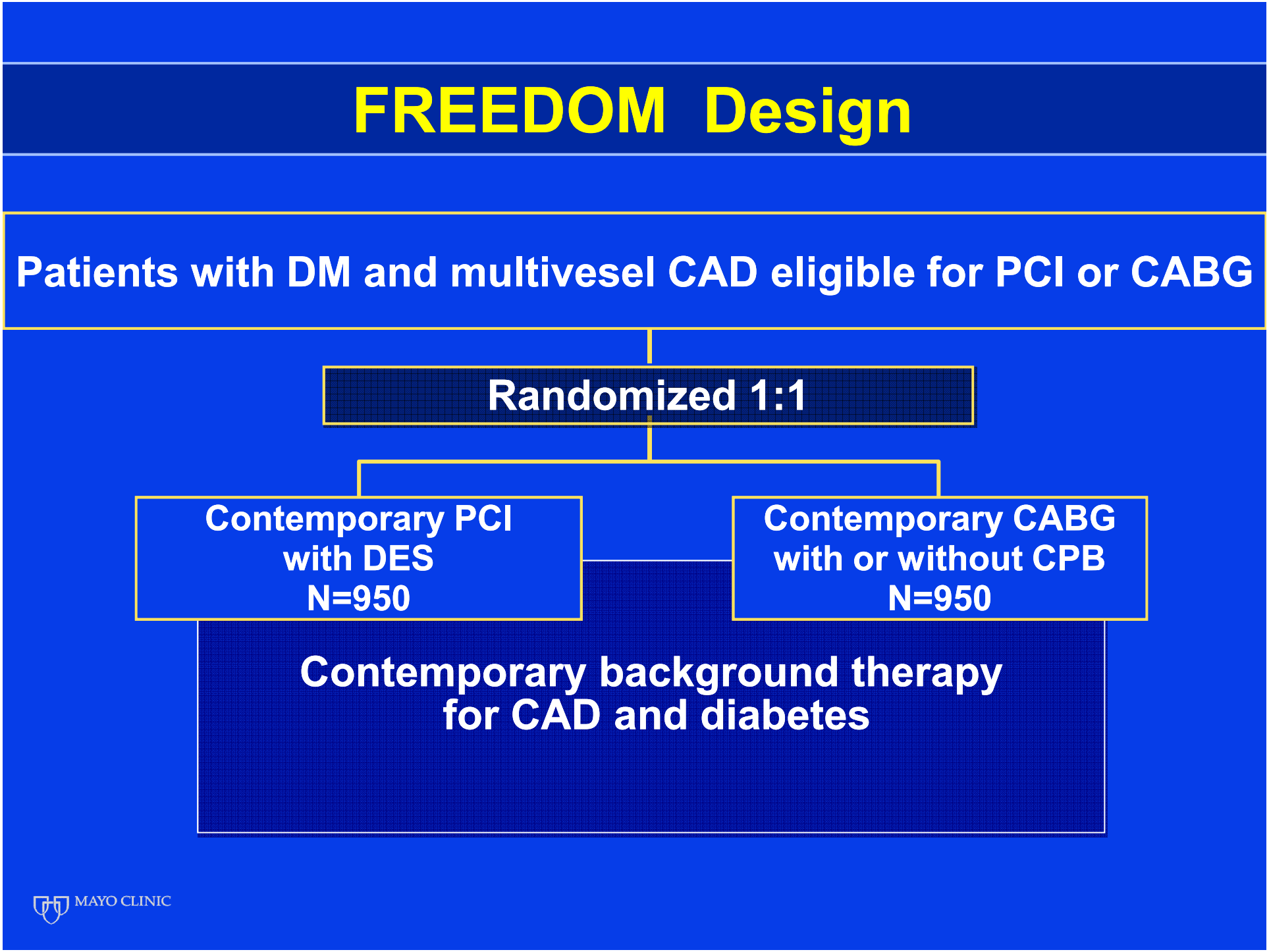
Summary: 12-Month Outcomes

- Patients without Diabetes
  - No significant difference in MACCE in CABG versus TAXUS
  - Increased revascularization in TAXUS
  - Increased stroke with CABG
- Patients with Diabetes
  - Significantly increased MACCE with TAXUS, driven by increased revascularization
  - Significantly increased mortality compared to non-diabetics in both CABG and TAXUS groups
- Revascularization rates in TAXUS are increased in diabetic patients compared to non-diabetics
- In CABG group, revascularization rates are comparable regardless of diabetic status

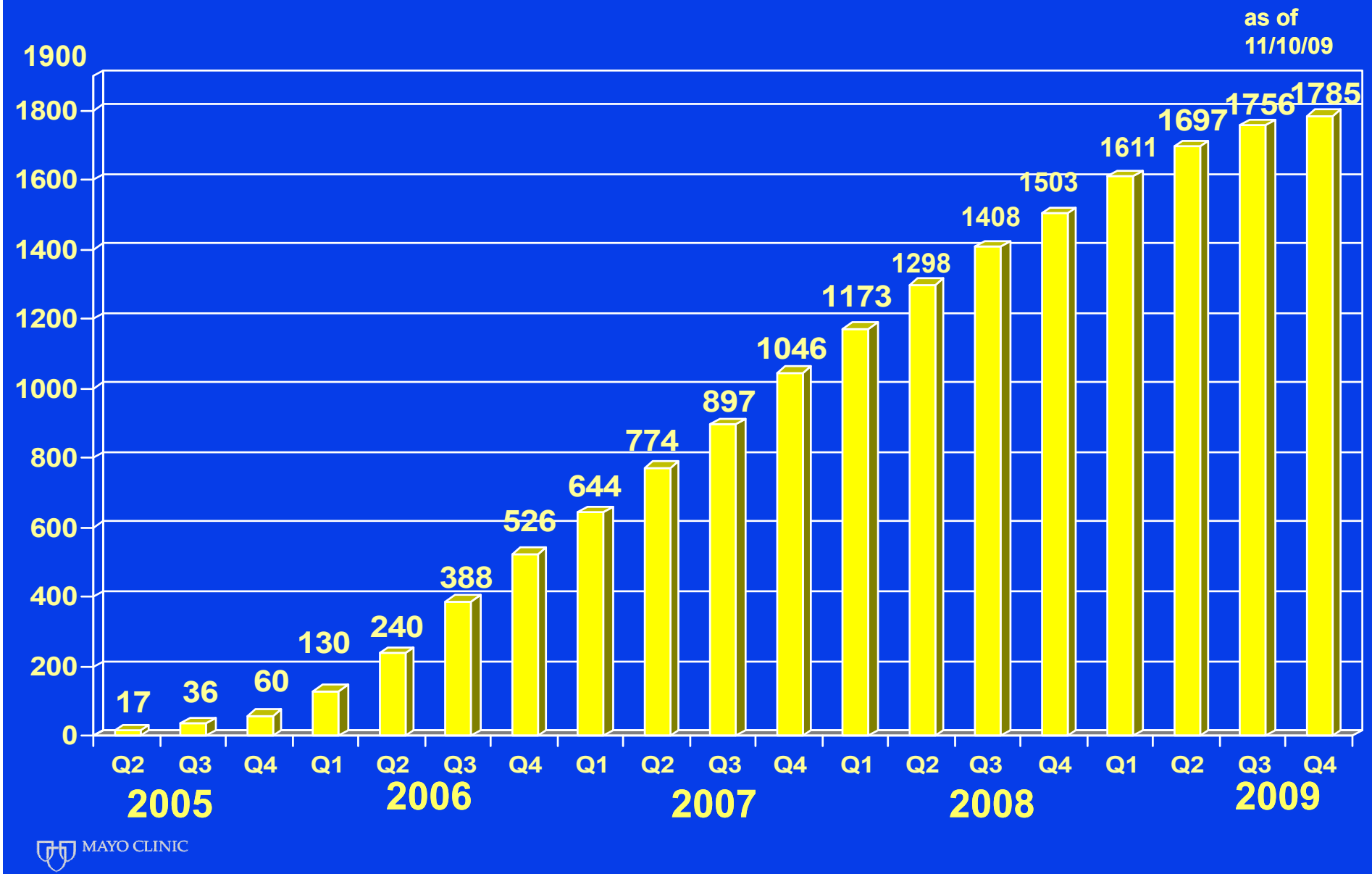
FREEDOM Trial

Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease

FREEDOM Design



FREEDOM Recruitment



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History of Present Illness

	A (N=739)	B (N=734)
Stable Coronary Heart Disease	67.1%	70.5%
Acute Coronary Syndrome (ACS)	32.9%	29.5%
ST elevation MI (>72 hrs prior to admission)	19.2%	17.8%
Non-ST elevation ACS	80.8%	82.2%
NYHA CHF Classification (Class III/IV excluded)		
Class I	74.0%	71.4%

PCI Procedure Summary

	PCI/DES
Staging: % unstaged procedure % staged procedure % staged procedures involving >1 hospitalization	66.2% 33.8% 71.2%
Mean total # of lesions attempted across all stages	4.2 ± 1.5
Mean total # drug-eluting stents placed per patient (across all stages)	4.3 ± 1.8
Reopro used during index procedure (stage 1 for staged procedures)	49.7%
Heparin administered	83.9%
Bivalirudin administered	14.9%

Lesion Characteristics in PCI/DES Arm

	Lesions
Reference vessel diameter (mm):	
<2.5	16.4%
2.5-3.0	49.4%
3.0-3.5	25.4%
3.5-4.0	7.8%
>4.0	0.9%
Chronic total occlusion	4.8%
Bifurcation lesion	11.6%
Balloon angioplasty alone	3.6%
Direct stenting	28.5%

FREEDOM Trial

- Effect of PCI (DES) versus CABG on composite of all cause death, non fatal infarction and stroke with a minimum follow up of 2 years
- Evaluate the need for the secondary endpoint of repeat revascularization between PCI and CABG (N.B. difference from SYNTAX)
- Study the differences in Quality of Life and Cost Effectiveness between the two strategies
- Facilitate comparisons between performance of two DES in this patient group
- It will not tell us whether BARI 2D was right about revascularization versus optimal medical therapy

“In your case, Dave, there’s a choice—elective surgery, outpatient medical therapy, or whatever’s in the box that our lovely Carol is holding.”

PCI vs CABG
MV Disease in Diabetics
Conclusions

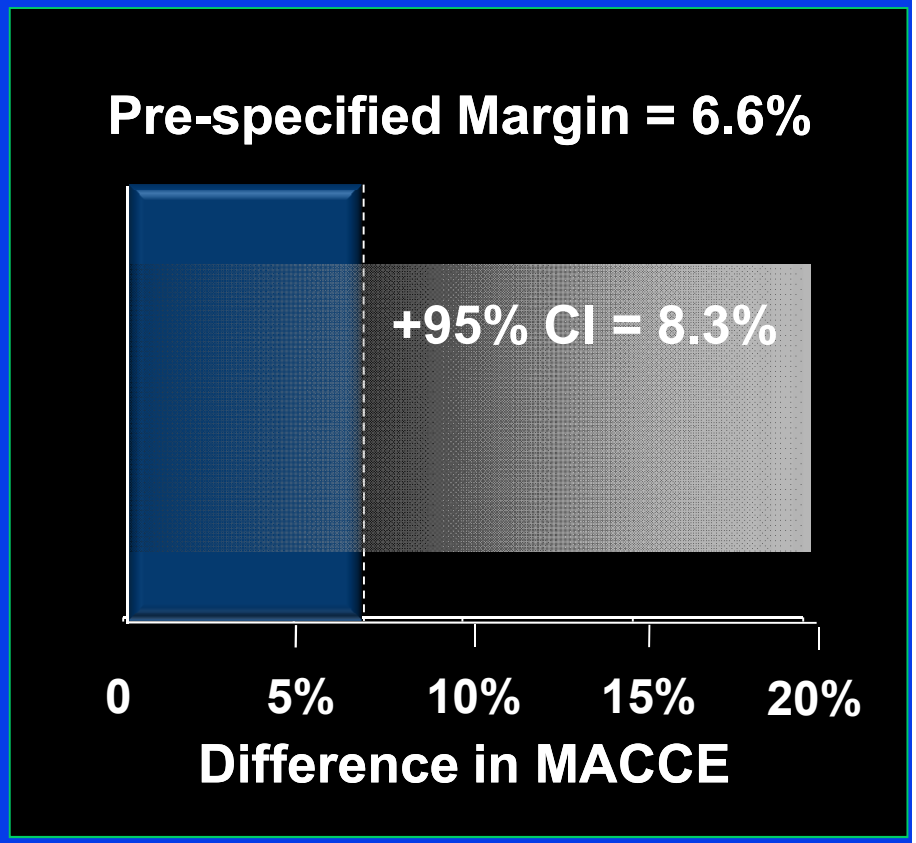
Clinical judgment still works

Primary Endpoint: 12-month MACCE Difference
Non-inferiority analysis

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

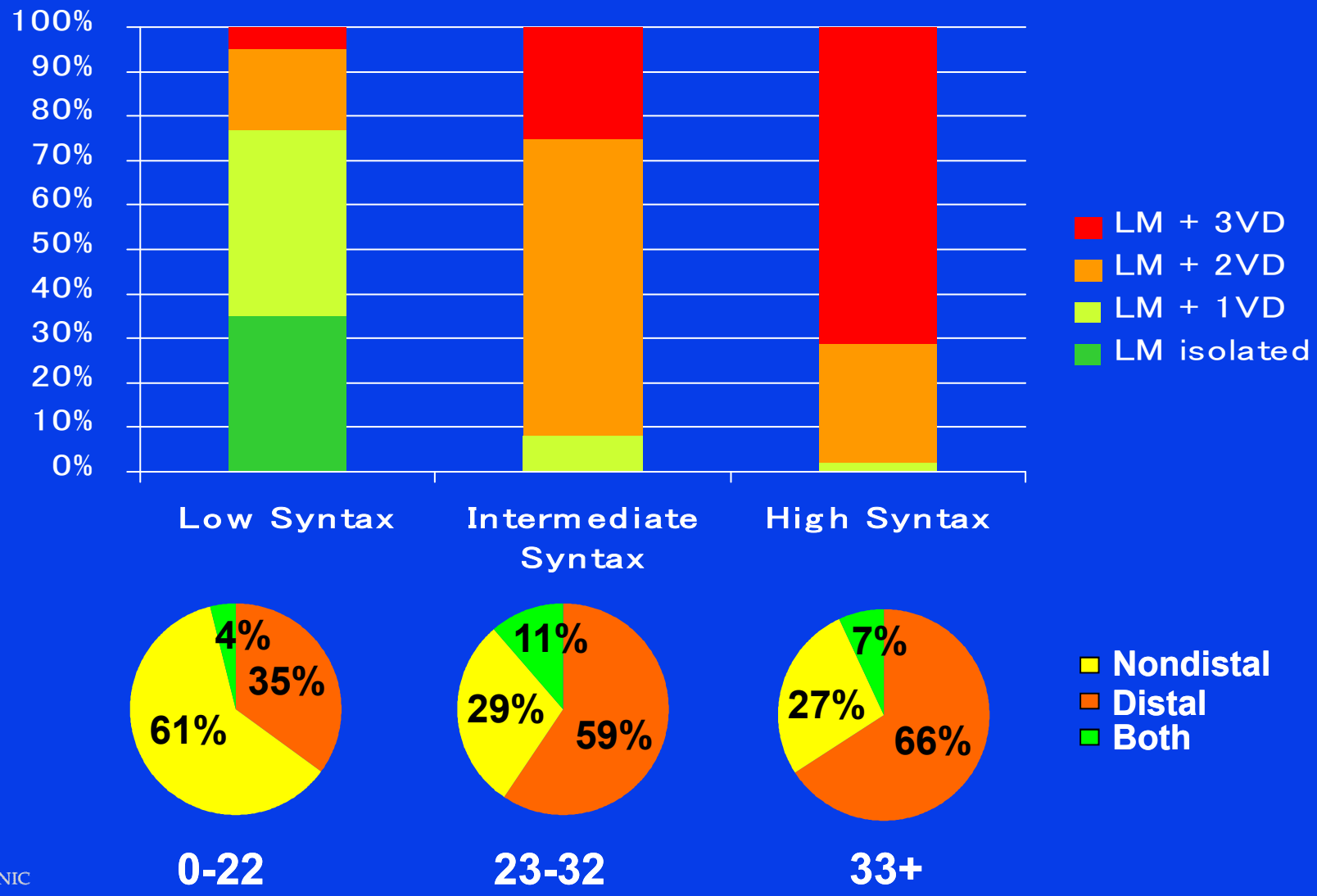
ARTS I (2VD 66%, 3VD 33%):
MACCE difference 14%

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



The criteria for non-inferiority comparison was not met for the primary endpoint, further comparisons for the LM and 3VD subgroups are observational only and hypothesis generating

Vessel Distribution in LM Population According to Syntax Score Terciles



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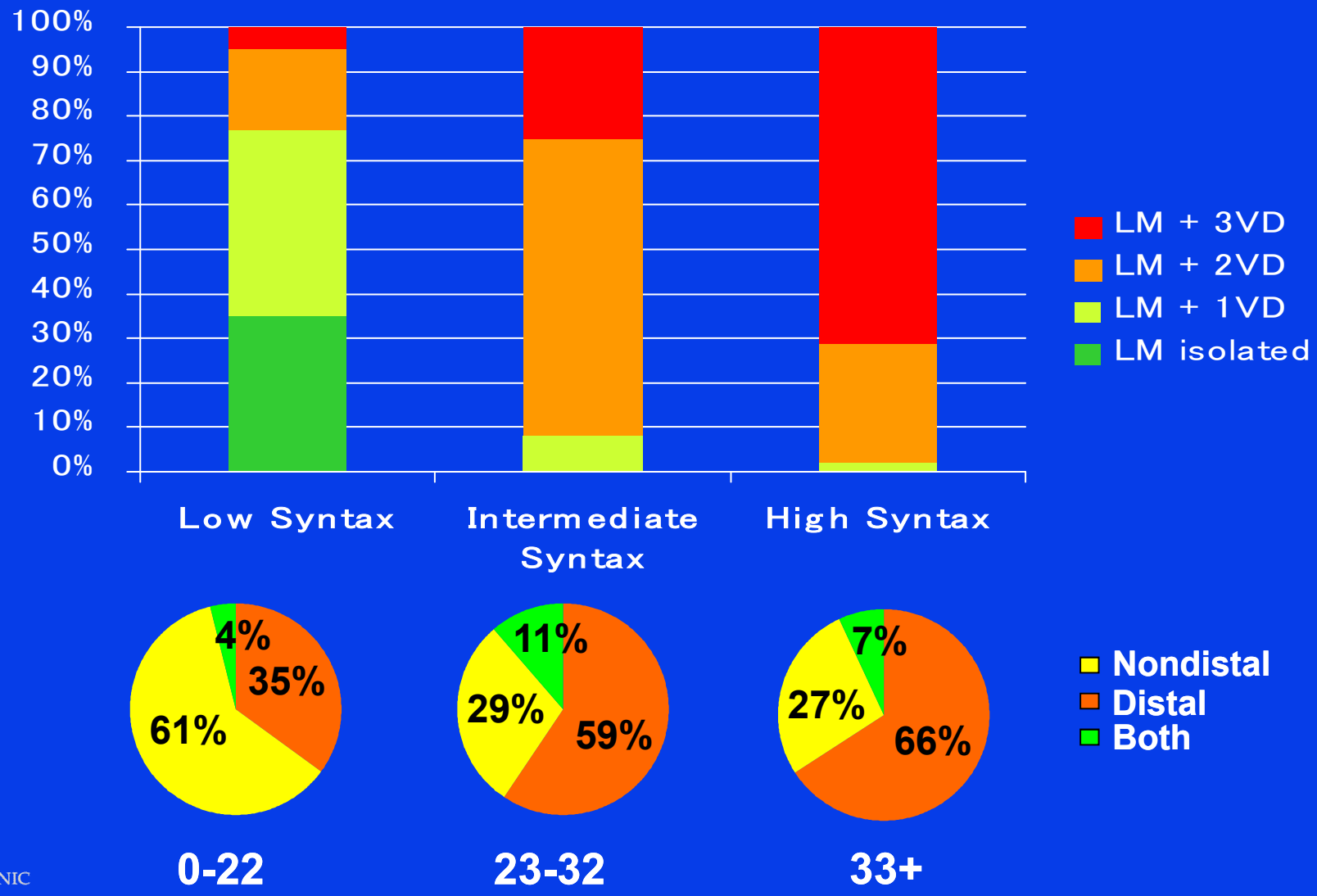
Vessel Distribution in LM Population According to Syntax Score Terciles



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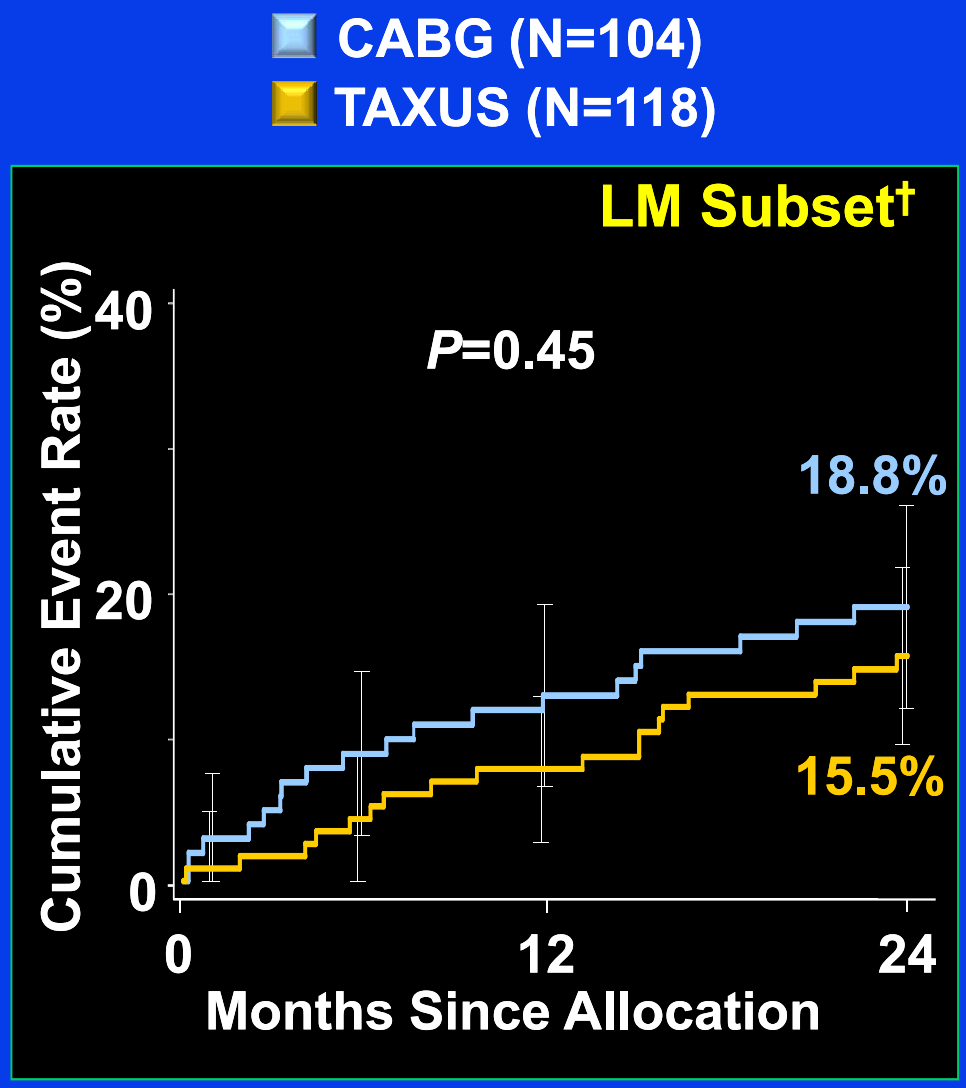
MACCE to 2 Years by SYNTAX Score Tercile Low Scores (0-22)

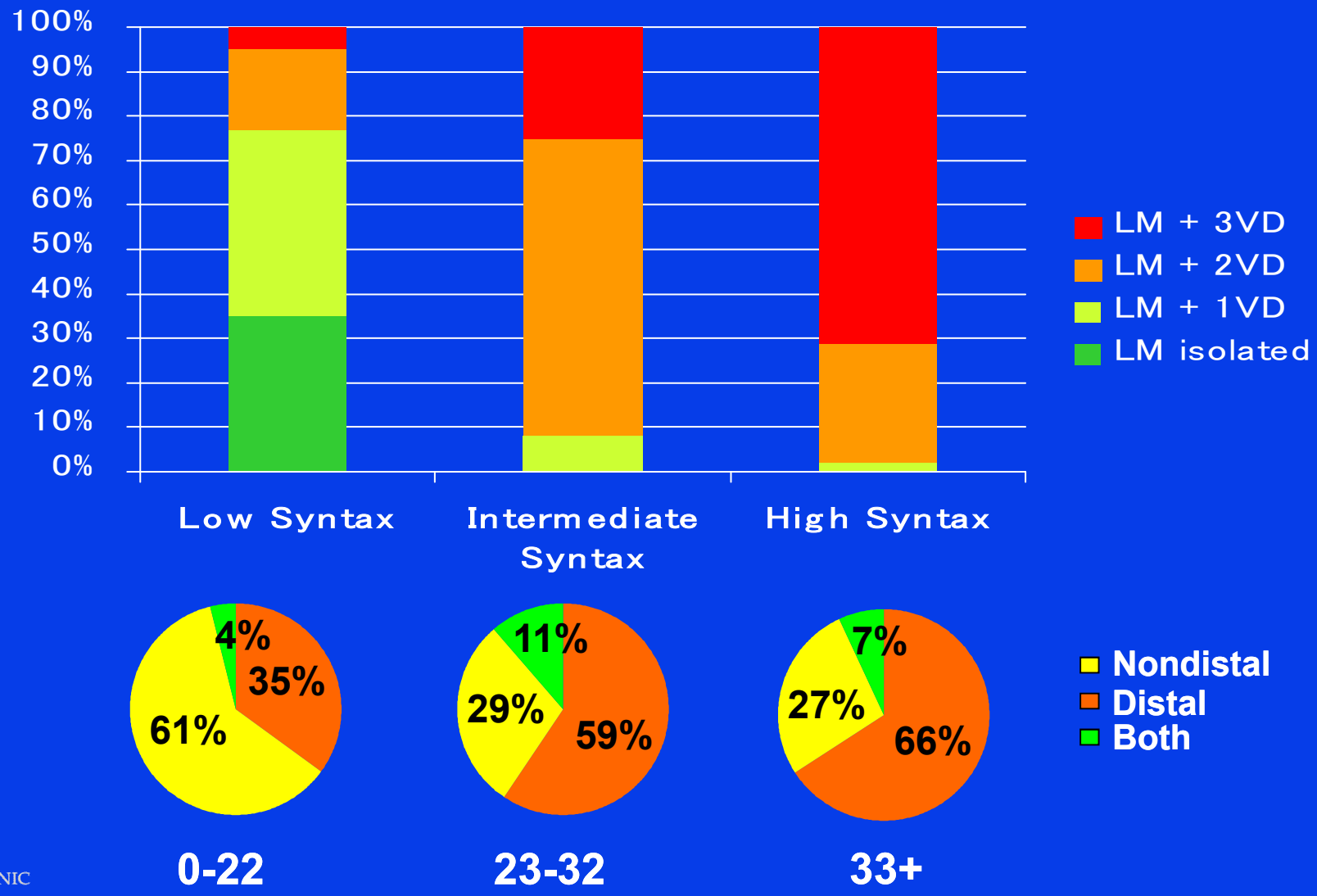
	CABG	PCI
Death	4.9% >	0.9%
CVA	4.1% >	0.9%
MI	2.0% <	3.6%
Death, CVA or MI	9.9% >	4.5%
Revasc.	10.1% >	14.7%

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



†Patients with isolated LM or LM +1, +2 or +3 vessel disease
Site-reported Data; ITT population

Vessel Distribution in LM Population According to Syntax Score Terciles



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DIAD Study
Screening in Type 2 Diabetes

- 1,123 patients with type 2 diabetes but no symptoms of CAD
- Random assignment to screening with MPI or not
- Main outcome of cardiac death or non fatal MI

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

DIAD Study

	No Screening N=562	Screening N=561
Age (yrs)	60.8	60.7
Duration DM (yrs)	8.9	8.2
BMI	31.0	31.1
HAIC	7.0	7.2
PVD	9.0	9.0

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

DIAD Study

	No Screening N=562	Screening N=561
Oral agents	64	63
Insulin	9	11
Insulin and oral	13	13
Diet	14	14

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

ORIGINAL CONTRIBUTION

Cardiac Outcomes After Screening for Asymptomatic Coronary Artery Disease in Patients With Type 2 Diabetes

The DIAD Study: A Randomized Controlled Trial

Conclusion In this contemporary study population of patients with diabetes, the cardiac event rates were low and were not significantly reduced by MPI screening for myocardial ischemia over 4.8 years.

diac deaths (3.0%) among the not-screened group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.44-1.88; $P = .73$). Of those in the screened group, 409 participants with normal results and 50 with small MPI defects had lower event rates than the 33 with moderate or large MPI defects; 0.4% per year vs 2.4% per year (HR, 6.3; 95% CI, 1.9-20.1; $P = .001$). Nevertheless, the positive predictive value of having moderate or large MPI defects was only 12%. The overall rate of coronary revascularization was low in both groups: 31 (5.5%) in the screened group and 44 (7.8%) in the unscreened group (HR, 0.71; 95% CI, 0.45-1.1; $P = .14$). During the course of study there was a significant and equivalent increase in primary medical prevention in both groups.

Conclusion In this contemporary study population of patients with diabetes, the cardiac event rates were low and were not significantly reduced by MPI screening for myocardial ischemia over 4.8 years.

Trial Registration clinicaltrials.gov Identifier: NCT00769275

JAMA. 2009;301(15):1547-1555 www.jama.com

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ALMOST 200 MILLION PEOPLE worldwide have type 2 diabetes.[1] Coronary artery disease (CAD) is a major health concern and the leading cause of death in individuals with type 2 diabetes.[2] CAD is often asymptomatic in these patients until the onset of myocardial infarction or sudden cardiac death.[3] Type 2 diabetes is also widely recognized as a CAD risk equivalent.[4]

The current standard of care for type 2 diabetes emphasizes the reduction of cardiovascular risk factors.[2,5] However, there has also been substantial interest in the early detection of asymptomatic CAD by screening of patients with type 2 diabetes.[6] Recent studies have shown that CAD can be detected noninvasively in a significant number of these individuals.[7-9] Inducible ischemia[7,10,11] and coronary artery calcium[9,11] each have

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Follow-up Events

	Patients					
	No screening n=562		Screening n=561			
	No.	%	No.	%	HR (95% CI)	P
Primary events	17	3.0	15	2.7	0.88 (0.44-1.8)	0.73
Myocardial infarction	10	1.7	7	1.3	0.82 (0.34-2.0)	0.66
Cardiac death	7	1.2	8	1.4	1.1 (0.41-3.1)	0.80
Secondary events	14	2.5	21	3.7	1.5 (0.77-3.0)	0.23
Unstable angina	3	0.5	4	0.7	1.3 (0.30-6.0)	0.70
Heart failure	7	1.2	7	1.2	1.0 (0.35-2.9)	0.99
Stroke	5	0.9	10	1.8	2.0 (0.69-5.9)	0.20
Revascularizations	44	7.8	31	5.5	0.71 (0.45-1.1)	0.14
PTCA	27	4.8	15	2.7	0.90 (0.48-1.7)	0.74
CABG surgery	20	3.6	16	2.9	0.81 (0.42-1.6)	0.76
Death						
All cause	15	2.7	18	3.2	1.2 (0.69-2.4)	0.60
Noncardiac	8	1.4	10	1.8	1.3 (0.49-3.2)	0.63

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

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

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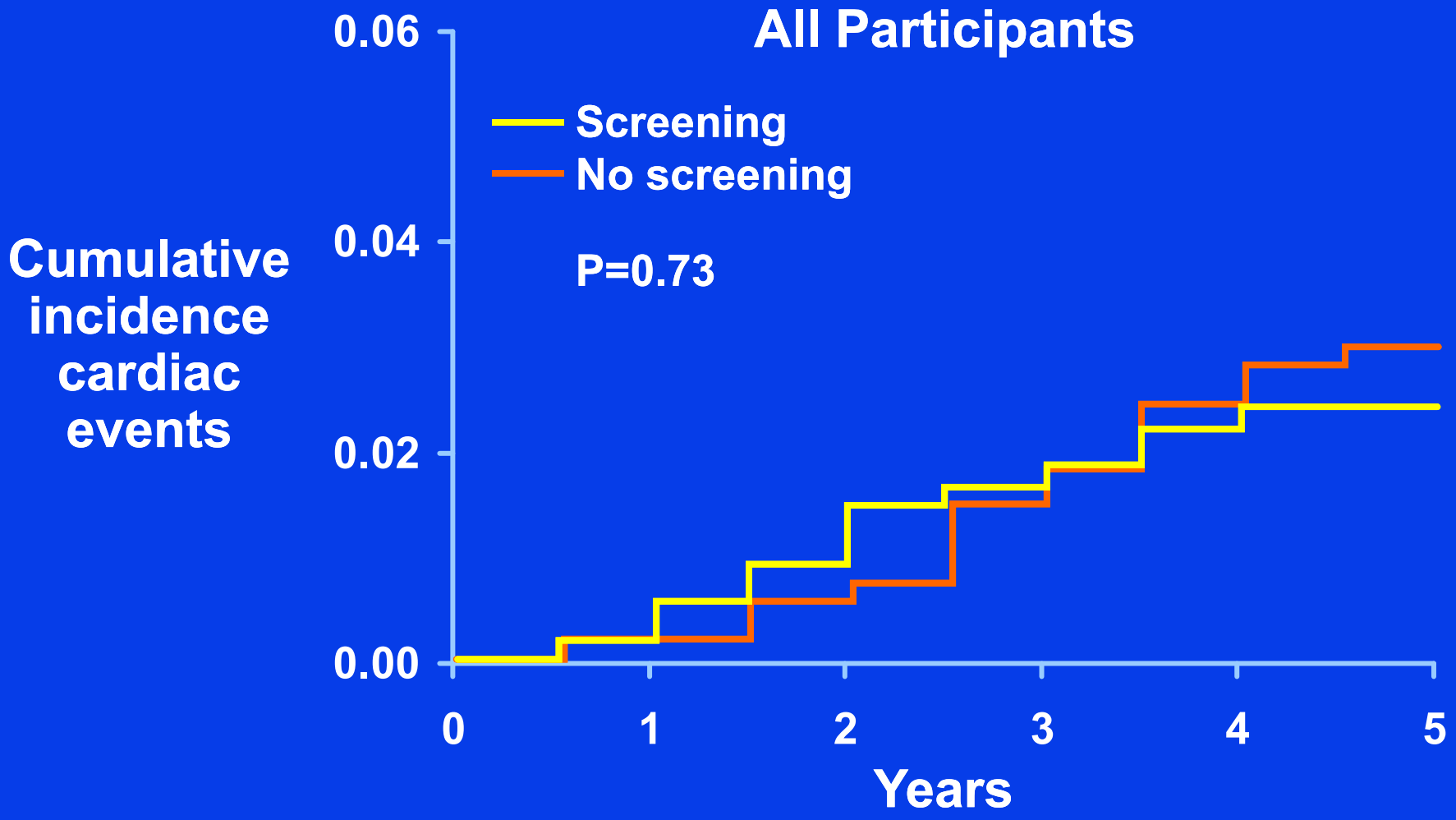
Cardiac Events



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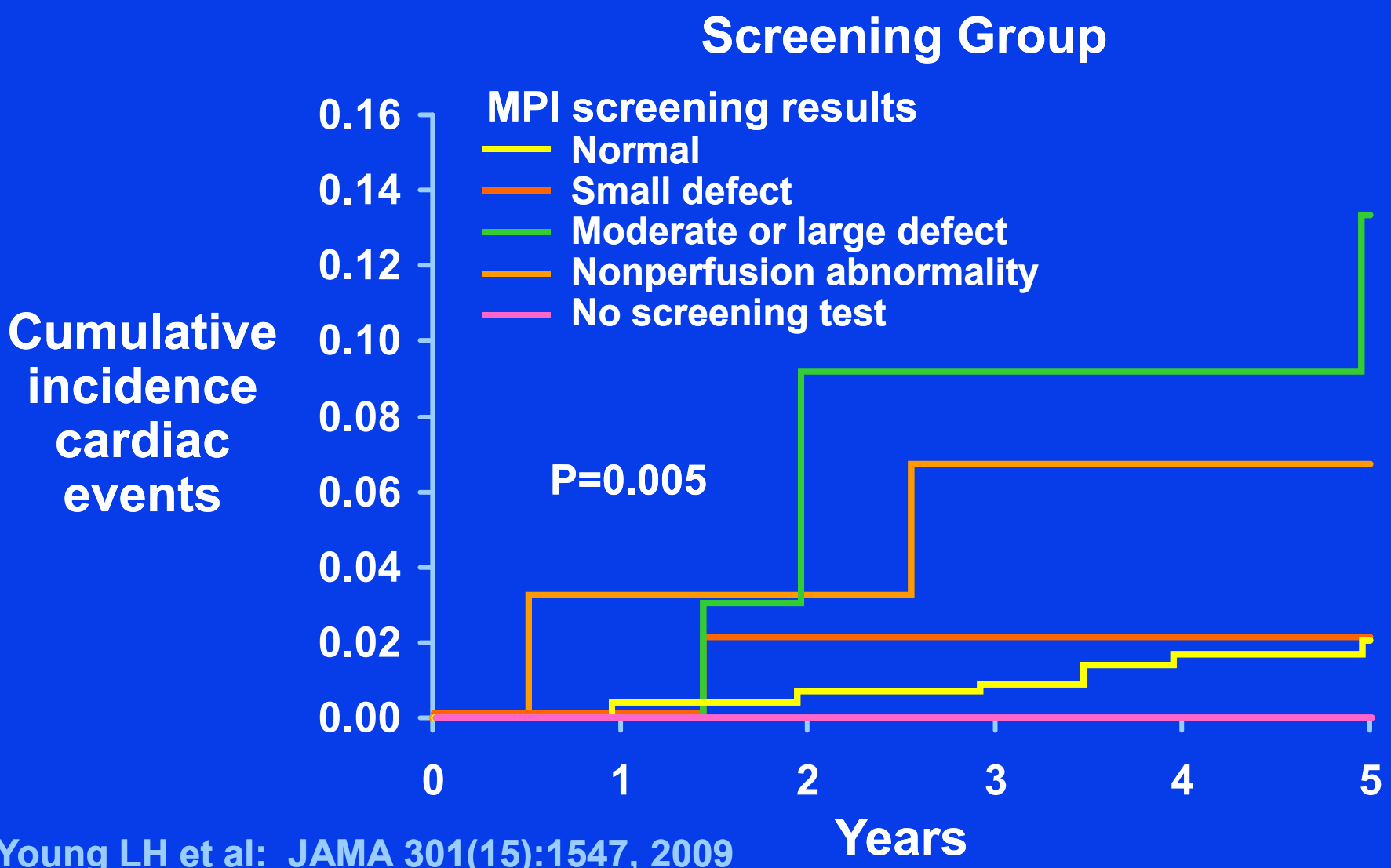
Cardiac Events by Screening Group



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Events According to Findings of Screening Myocardial Perfusion Imaging (n=522)

	Patients with normal imaging (n=409)	Small perfusion defect (n=50)	Moderate or large perfusion defect (n=33)	Nonperfusion abnormality (n=30)	
	Patient (%)	Patient (%)	Patient (%)	Patient (%)	P
Patients	78	10	6	6	
Primary events	2.0	2.0	12.1	6.7	0.005
Myocardial infarction	1.7		0	6.7	0.14
Cardiac death	0.5	2.0	12.1	3.3	<0.001
Secondary events	3.2	2.0	9.1	13.3	0.01
Unstable angina	0.2		3.0	6.7	<0.001
Heart failure	1.2		0	6.7	0.08
Stroke	1.7	2.0	6.1		0.31
Revascularizations	3.9	4.0	21.2	20.0	<0.001
PTCA	2.2	2.0	9.1	6.7	0.43
CABG surgery	1.7	2.0	12.1	13.3	0.001
Death					
All Cause	2.2	4.0	15.2	3.3	0.002
Noncardiac	1.7	2.0	3.0		0.90

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

Follow-Up

	Patients				
	No screening n=562		Screening n=561		P
	No.	%	No.	%	
Additional cardiac testing					
Nonprotocol stress test	170	30	118	21	<0.001
Abnormal nonprotocol stress test	45	26	28	24	0.60
Coronary angiogram <120 d	3	0.5	25	4.4	<0.001
Revascularization <120 d	2	0.36	9	1.6	0.03
Total coronary angiograms	66	12	80	14	0.20
No. of vessels >70% stenosis					
0	22	33	40	50	0.05
1	21	32	11	14	
2	13	20	19	23	
3	10	15	10	12	

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

Medication Use

	Patients								
	Baseline		5 yr		Baseline		5 yr		P
	No.	%	No.	%	No.	%	No.	%	
Pharmacological treatment									
Insulin treatment	126	22	141	29	134	24	171	35	0.54
Oral anti-hyperglycemic agents	482	86	444	91	480	86	447	92	0.81
Lipid-lowering drugs	272	48	377	78	255	45	365	76	0.32
Statins	228	41	327	67	209	37	324	67	0.25
Antihypertensive drugs	320	57	362	75	315	56	355	74	0.79
ACE or angiotensin receptor blockers	229	41	218	45	206	37	210	43	0.17
Aspirin	261	46	356	73	241	43	364	74	0.24

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

Title/drp–author: WT/BK – Holmes, David
Sub/drp–Job#: YW105/BK – 3022700

Subject: DIAD Study, Young

Background: BU3
Plot/brdr: open/BU41
Banner/brdr: 0-40-159/BU41
x, y only

Side title: YW105
• /colhdgs: YW105
Text: WT/BK
Highlight: YO114
Subdue: BU31
Footnotes: BU41

PPT shooting instructions
PPT File to Server
(7 images)

Artist: KK
Start Date: 11-10-09

COLOR REFERENCE ONLY

Match: Mayo2bu-2002 (CP1111378)

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Bob's
Gallery
Hours

Problems with Bypass Surgery

- Morbidity of the procedure
- Saphenous vein grafts
- Acceleration of underlying native coronary disease
- Informed consent

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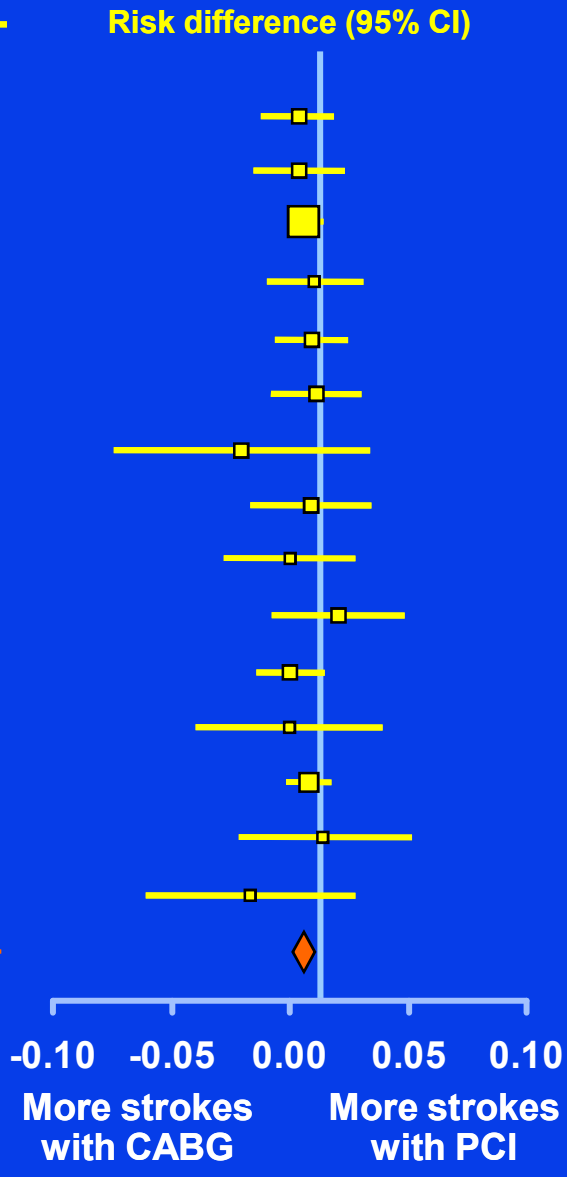
Procedural Stroke Risk

Study, year Procedural stroke	Surviving patients/all patients PCI	 CABG
ARTS, 2001	590/600	592/605
AWESOME, 2001	220/222	229/232
BARI, 1996	913/915	907/914
EAST, 1994	197/198	191/194
ERACI II,2001	225/225	223/225
GABI, 1994	182/182	175/177
Drenth et al, 2002	50/51	51/51
Diegeler et al, 2002	110/110	109/110
MASS, 1995	72/72	70/70
MASS II, 2004	203/205	197/203
Octostent, 2003	138/138	142/142
Cisowski et al, 2002	50/50	50/50
RITA, 1992	509/510	496/501
Hong et al, 2005	119/119	69/70
SIMA, 2000	62/63	60/60
Overall	3,640/3,660	3,561/3,604



Ann Int Med 147:708, 2007

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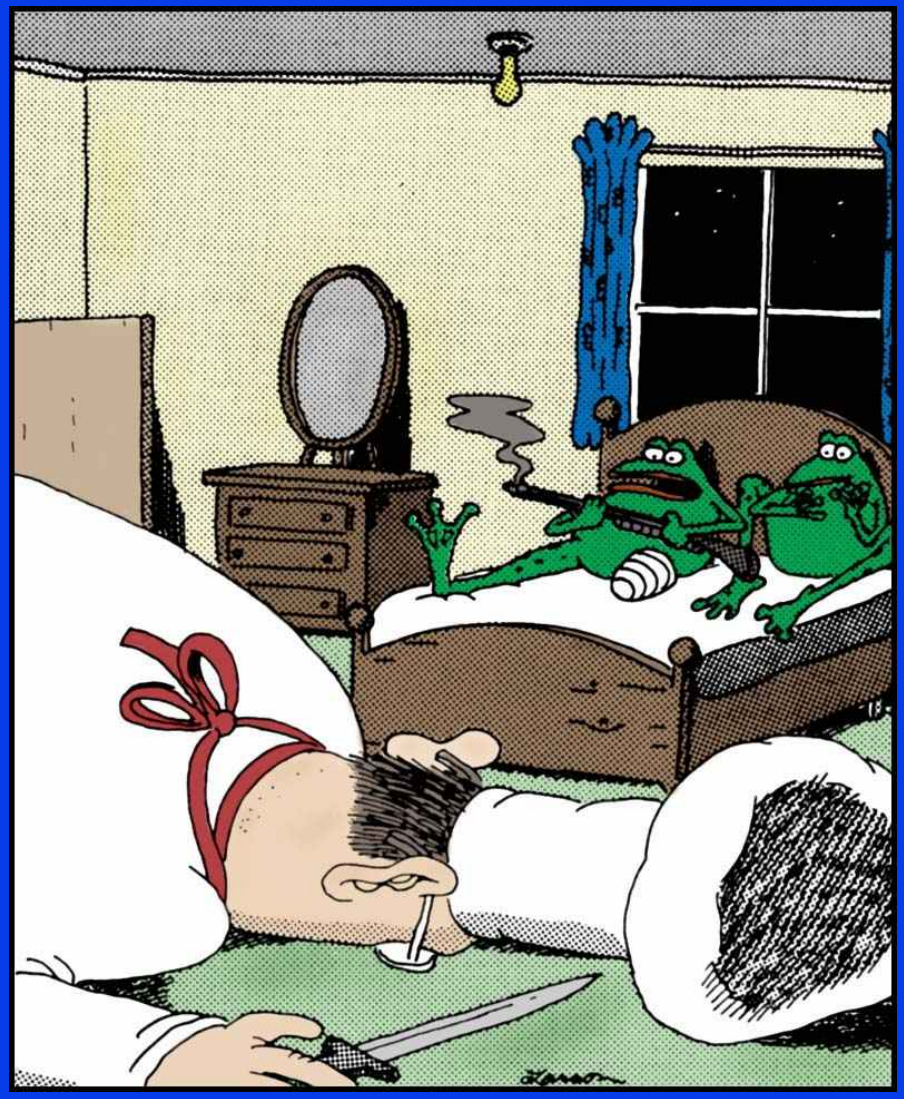


“Ha! That finishes it!...I always knew he’d be back one day to get the other one!”

Problems with Bypass Surgery

- Morbidity of the procedure
- Saphenous vein grafts
- Acceleration of underlying native coronary disease
- Informed consent

What Surgeons Do Not Tell You

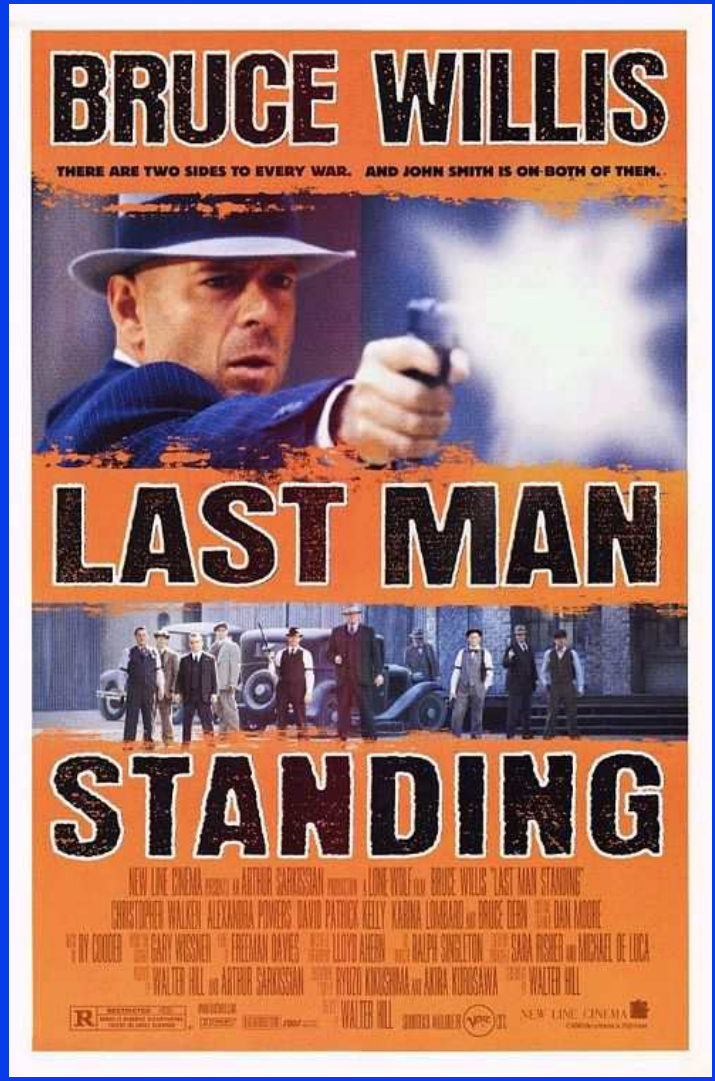
- I am going to put you to sleep
- I am going to put a small hose into your breathing tube and breathe for you. I will also put a smaller tube somewhat lower for drainage
- I am going to divide your breast bone with a saw and then singe the ends to stop bleeding and then spread open your chest
- I am going to pick up and and then stop your heart

What the Surgeon Does Not Tell You

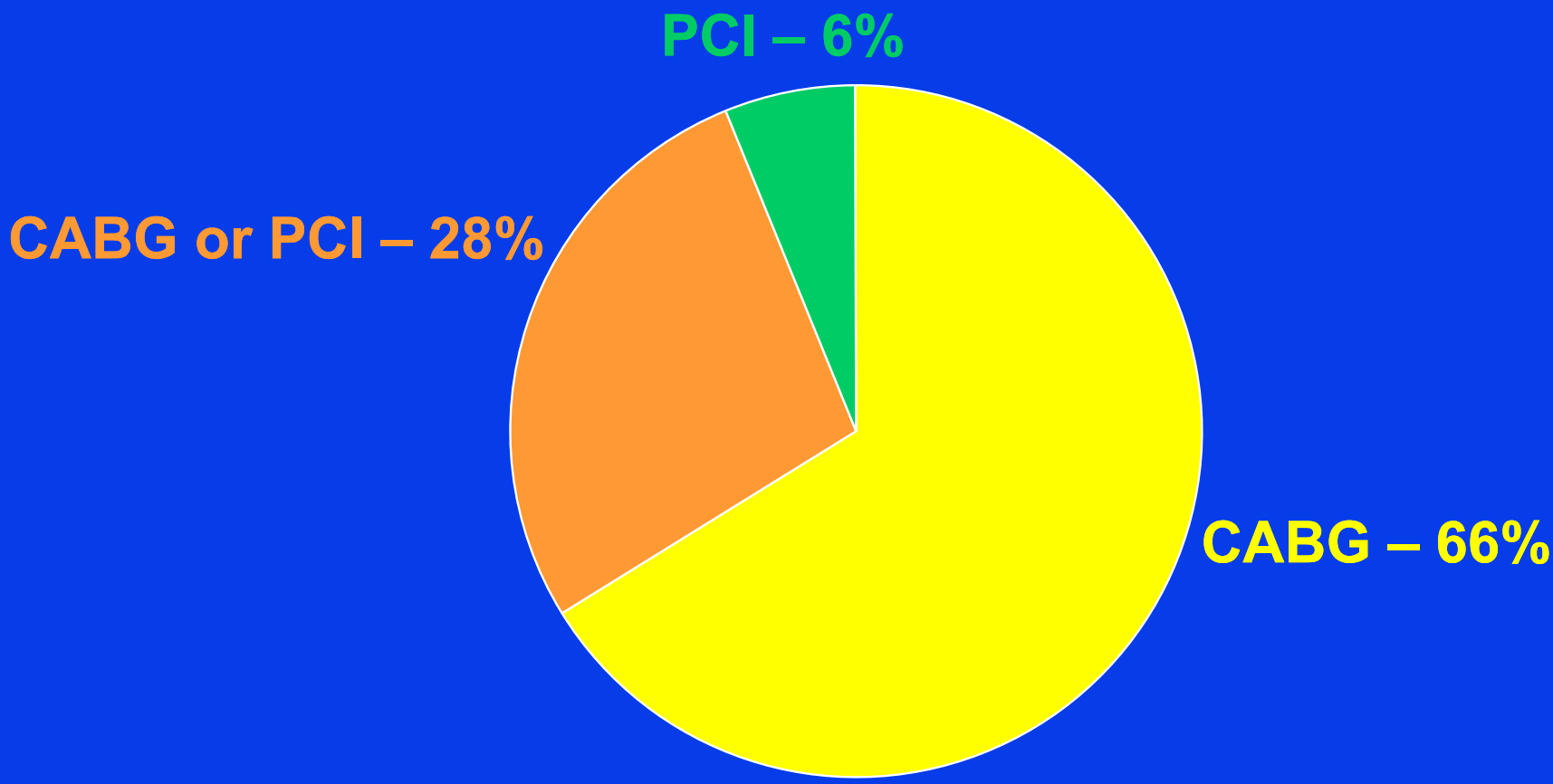
- I am going to make a long cut in your leg and remove veins
- I am going to do some hookups in your chest
- I am going to then take baling wire to put you back together again
- I am going to wake you up and tell you that everything is GREAT!

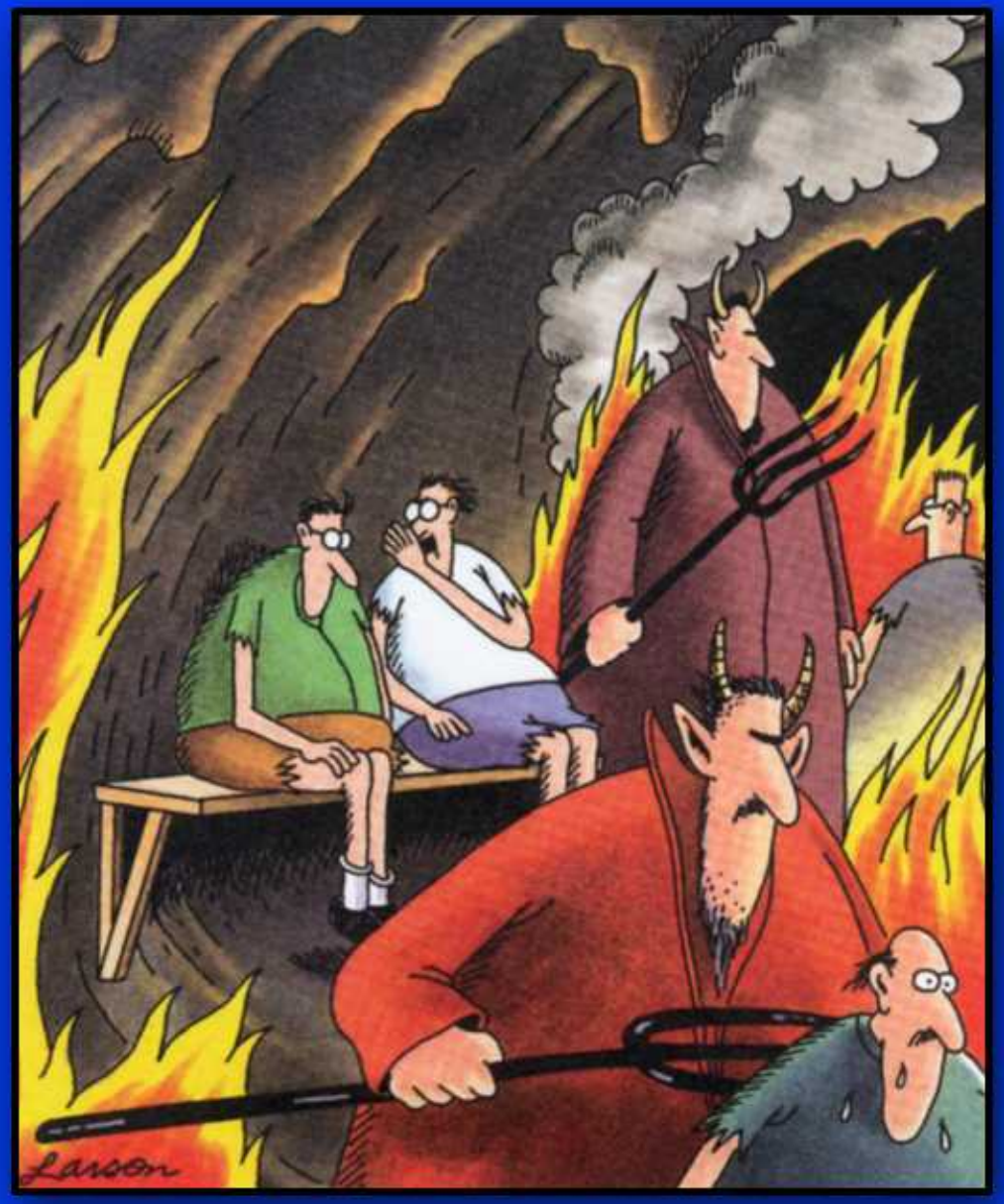
“Great”
appears to be a relative term

Who is left?


BRUCE WILLIS
THERE ARE TWO SIDES TO EVERY WAR. AND JOHN SMITH IS ON BOTH OF THEM.
LAST MAN
STANDING

3 Vessel & Left Main Disease
Post SYNTAX



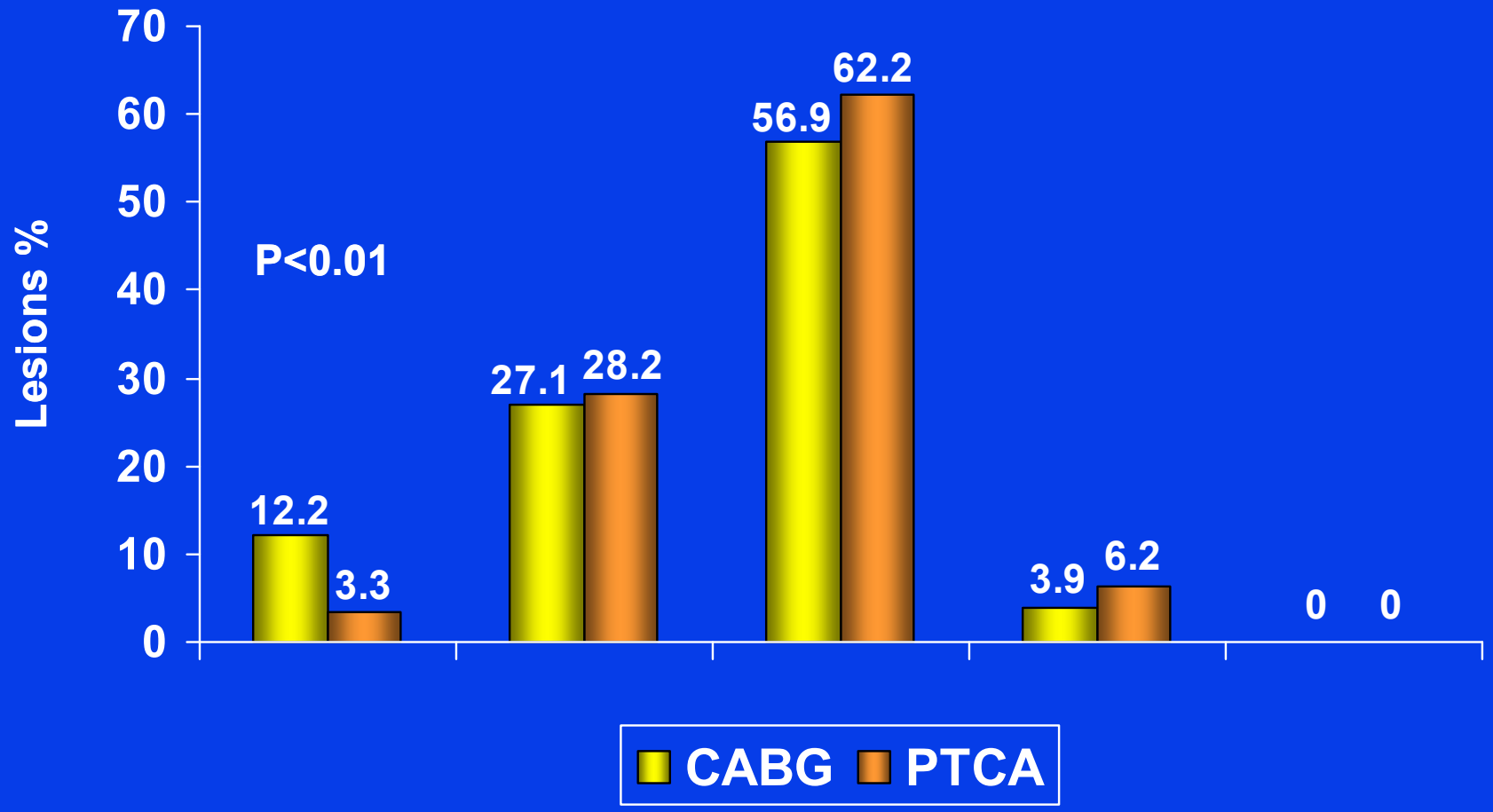


“I hate this place.”

"It was back in '52 that the hits stopped coming."

“More quarters! For God’s sake, more quarters!”

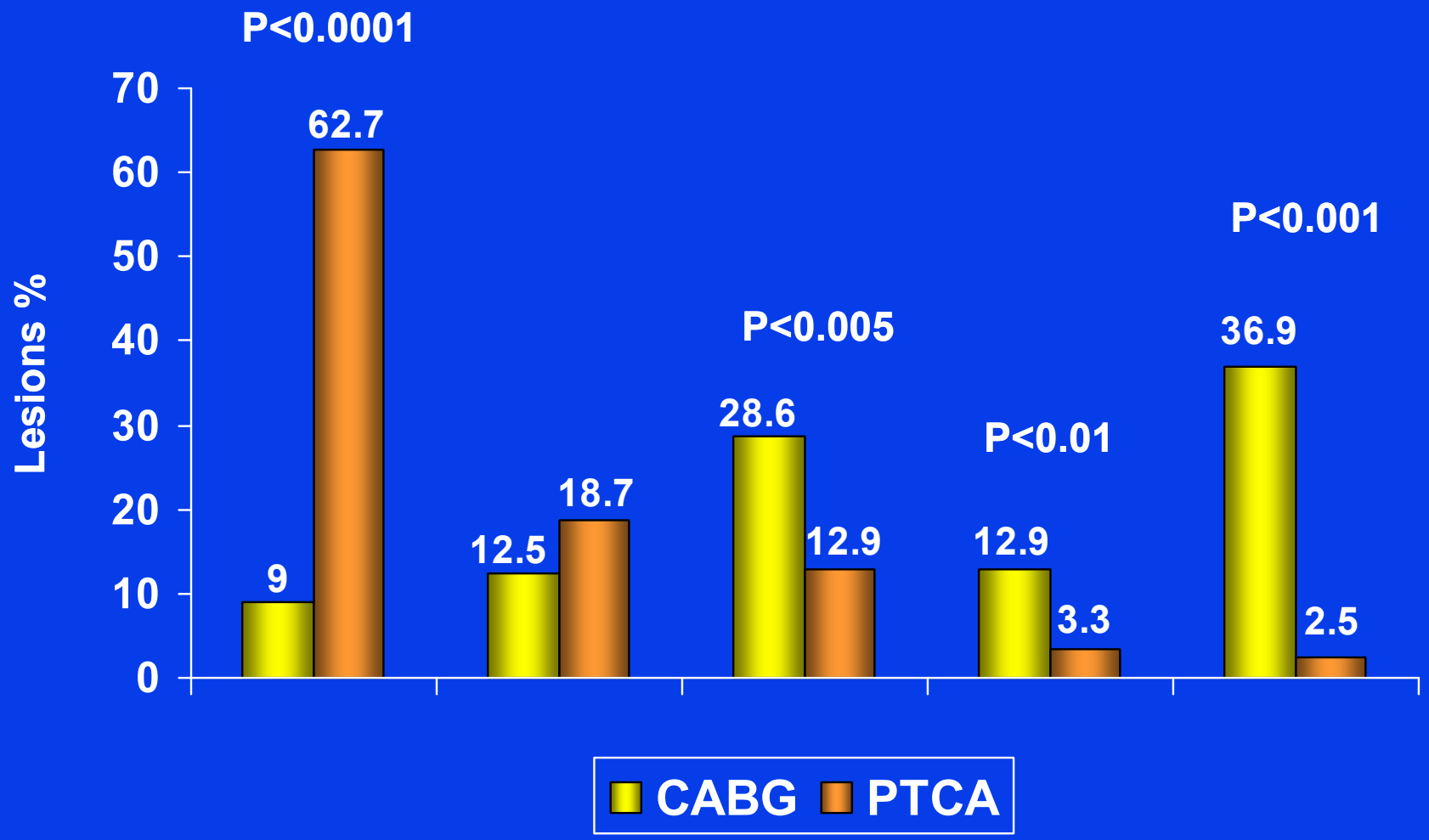
Lesion Severity in Native Vessels before Treatment



MAYO CLINIC

Rupprecht HJ et al, Eur Heart J 17:1192-1198, 1996

Lesion Severity in Native Vessels 6 Months after Treatment



MAYO CLINIC

Rupprecht HJ et al, Eur Heart J 17:1192-1198, 1996

The son of Enoch and the father of Lamech (father of Noah), whom he fathered at the age of 187. “And all the days of Methuselah were nine hundred sixty and nine years: and he died in the year of the Great Flood”.

The BARI 2D Study Group
Event Rates at 5 Years

Variable	Death from Any Cause		
	Revasc	Medical Therapy	P
All patients (n=1828)			
Insulin sensitization (%)	11.1	12.3	0.81
Insulin provision (%)	12.2	12.0	0.85
P value	0.75	0.90	0.78
PCI stratum (n=1065)			
Insulin sensitization (%)	10.2	10.1	0.67
Insulin provision (%)	11.4	10.3	0.56
P value	0.79	0.94	0.92
CABG stratum (n=763)			
Insulin sensitization (%)	13.4	17.1	0.34
Insulin provision (%)	13.9	15.6	0.67
P value	0.83	0.71	0.72

NEJM 360:2503, 2009

The BARI 2D Study Group
Event Rates at 5 Years

Variable	Major Cardiovascular Events		
	Revasc	Medical Therapy	P
All patients (n=1828)			
Insulin sensitization (%)	20.3	24.1	0.29
Insulin provision (%)	25.2	24.1	0.63
P value	0.059	0.85	0.23
PCI stratum (n=1065)			
Insulin sensitization (%)	21.1	20.4	0.36
Insulin provision (%)	24.9	21.7	0.28
P value	0.30	0.51	0.84
CABG stratum (n=763)			
Insulin sensitization (%)	18.7	32.0	0.002
Insulin provision (%)	26.0	29.0	0.58
P value	0.066	0.51	0.07

NEJM 360:2503, 2009

Title/drp–author: WT/BK – Holmes, David
Sub/drp–Job#: YW105/BK – 3009346

Subject: BARI 2D NEJM 2009

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

Plot/brdr: open/BU41
x, y only

PPT shooting instructions
PPT File to Server
(2 images)

Artist: mls Start Date: 6-26-09

COLOR REFERENCE ONLY

Match: Mayo2bu-2002 (CP1111378)

MAYO CLINIC

The Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial

BARI 2D Trial

Presented at the American Diabetes Association (ADA) Annual Scientific Sessions 2009 in New Orleans

Prior CABG and STEMI
APEX-AMI Trial

- 5745 STEMI patients with planned primary PCI
- 128 (2.2%) had prior CABG
- Evaluate 90 day clinical outcomes

Welsh (under review)

Prior CABG and STEMI
APEX-AMI Trial

Characteristics	No Prior CABG (n=5617)	Prior CABG (n=128)	P
Age, yrs, median (IQR)	61 (52, 71)	69 (58.3, 76)	<0.001
Female, n (%)	1306 (23.3)	18 (14.1)	0.014
Hypertension, n (%)	2749 (49.0)	90 (70.3)	<0.001
Prior MI, n (%)	612 (10.9)	82 (64.1)	<0.001
Prior PCI, n (%)	881 (9.2)	32 (36.7)	<0.001
Prior CHF, n (%)	187 (3.3)	21 (16.4)	<0.001
DM, n (%)	187 (15.7)	32 (25.0)	0.007

Welsh (under review)

Prior CABG and STEMI
APEX-AMI Trial

90-Day Clinical Outcomes, n (%)	No Prior CABG (n=5617)	Prior CABG (n=128)	P
Death	256 (4.6)	15 (11.9)	0.001
CHF	267 (4.8)	8 (6.3)	0.4
Shock	188 (3.3)	8 (6.3)	0.082
Death/CHF/Shock	565 (10.1)	21 (16.4)	0.019

Welsh (under review)

Prior CABG and STEMI
APEX-AMI Trial

Angio & Revasc Characteristics	No Prior CABG (n=5617)	Prior CABG (n=128)	P
Primary PCI, n (%)	5272 (93.9)	101 (78.9))	<0.001
No urg revasc (no urg csurg or primPCI), n (%)	242 (5.0)	24 (18.8)	<0.001
Post PCI TIMI flow, n (%) in those with primPCI	N=5272	N=101	<0.001
0/1	110 (2.1)	6 (6.2)	<0.001
2	328 (6.3)	11 (11.3)	<0.001
3	4800 (91.6)	80 (82.5)	<0.001

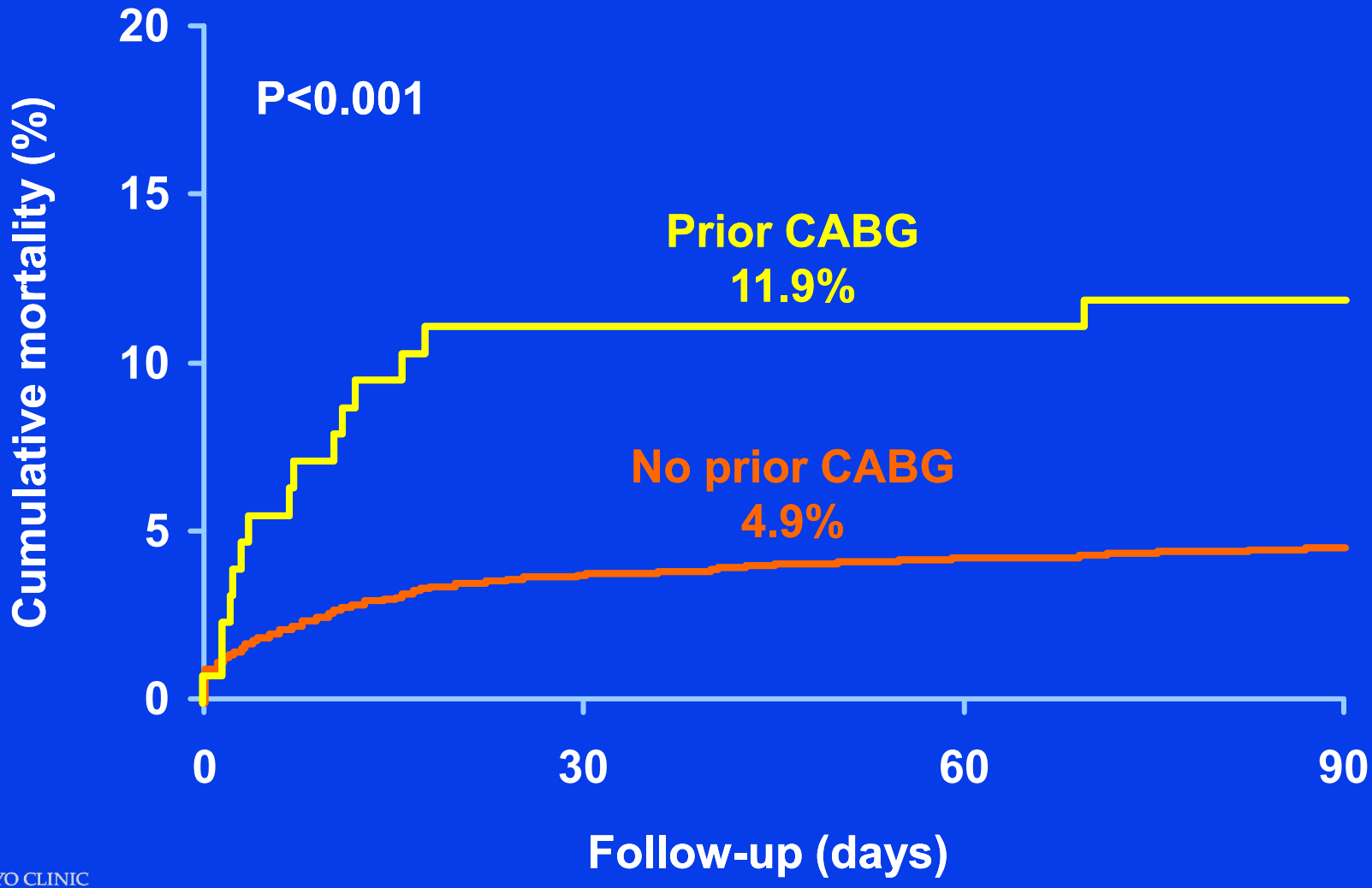
Welsh (under review)

Prior CABG and STEMI
APEX-AMI Trial

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

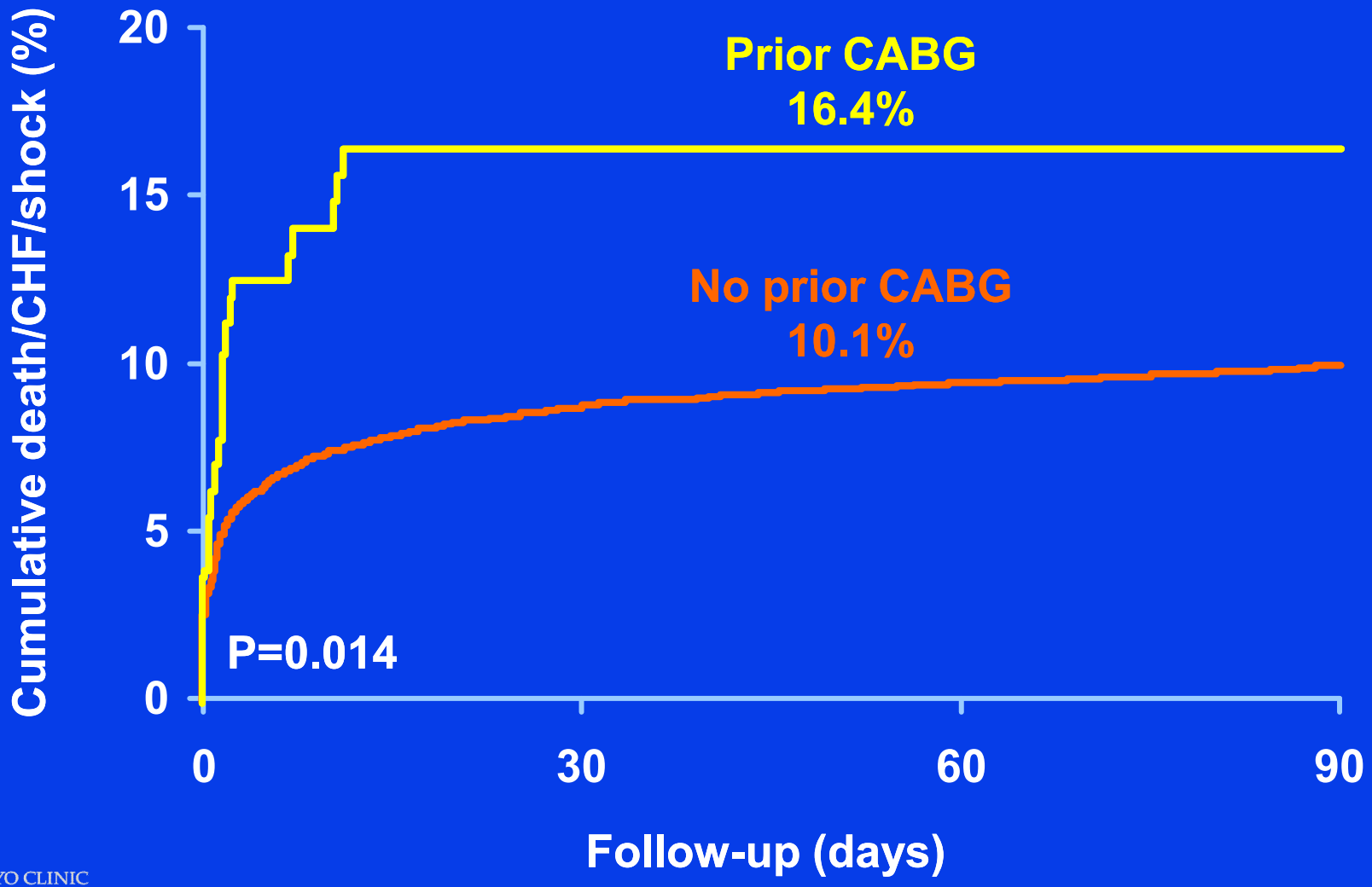
Welsh (under review)

90-Day Mortality According to Prior CABG



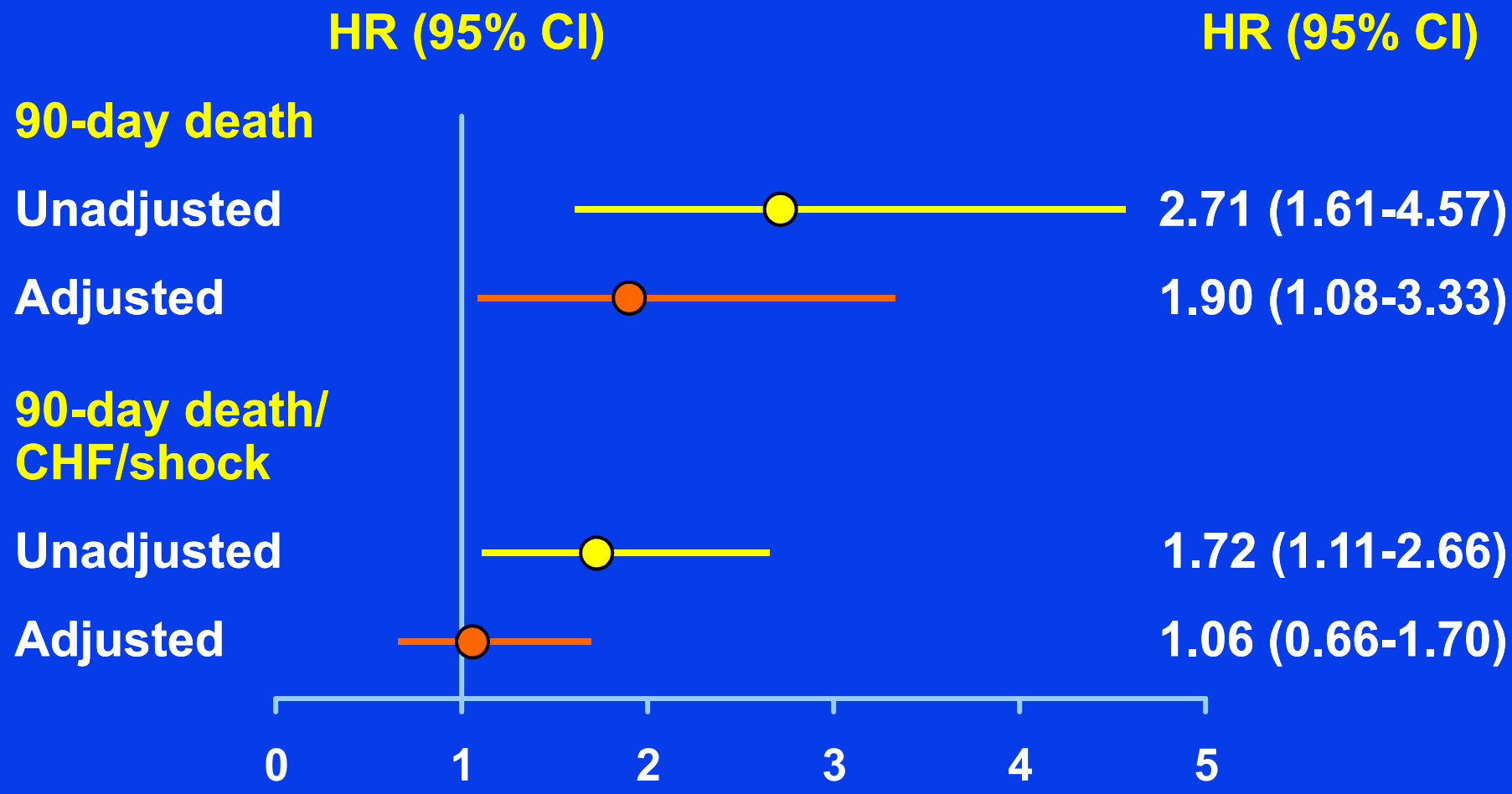
MAYO CLINIC

90-Day Death/CHF/Shock According to Prior CABG



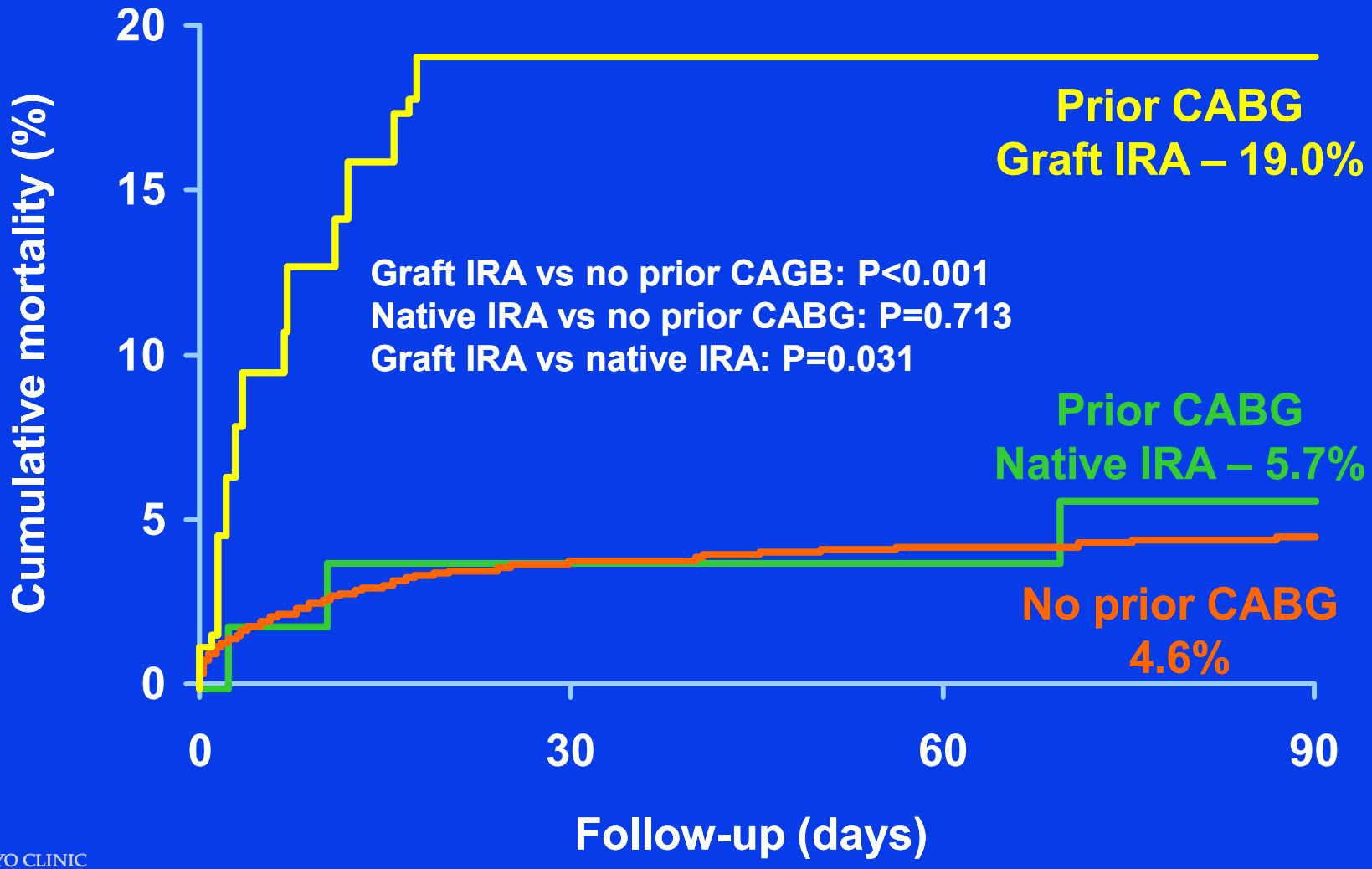
MAYO CLINIC

Associations Between Prior CABG and 90-Day Clinical Outcomes



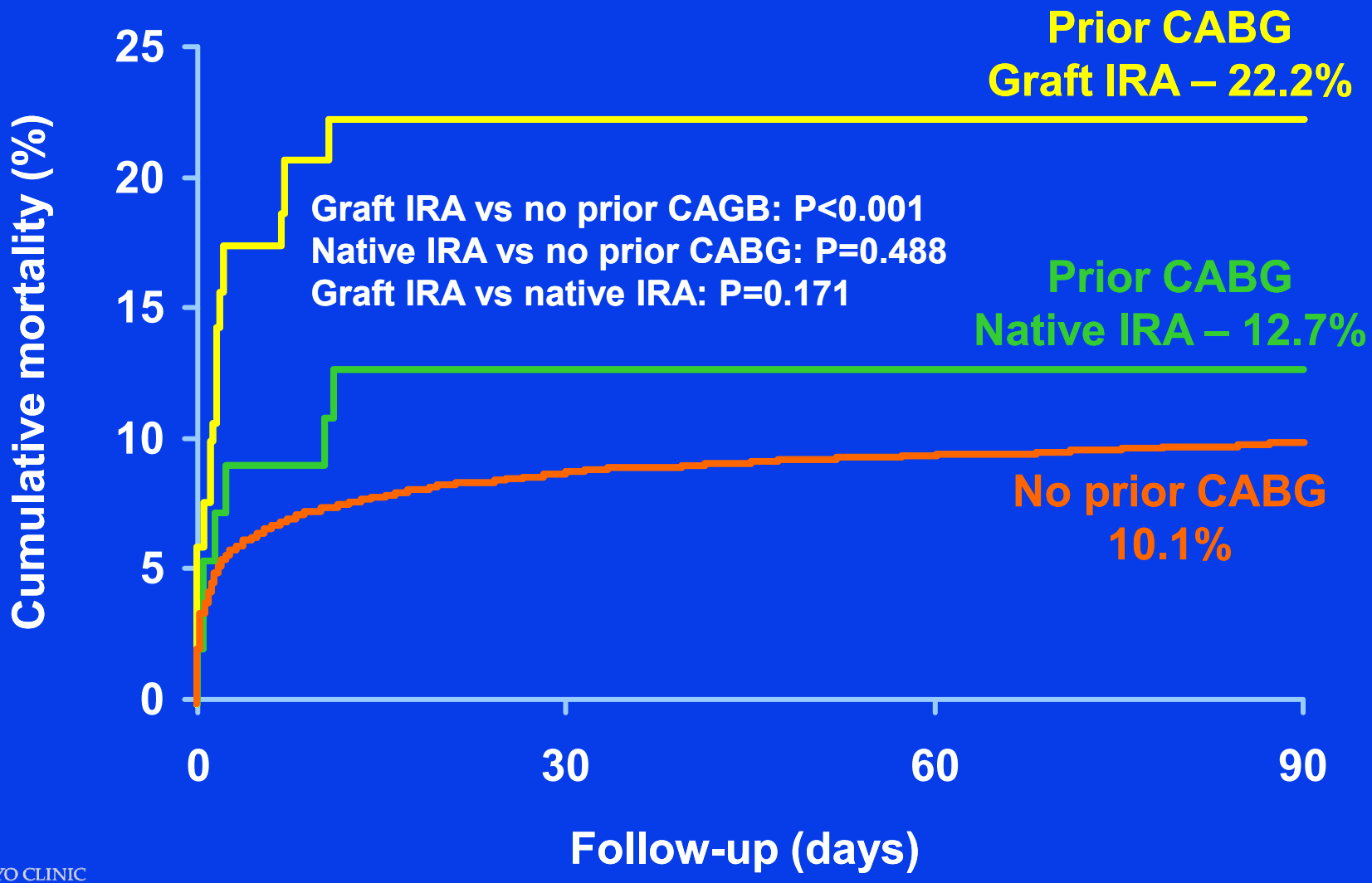
MAYO CLINIC

90-Day Mortality According to Prior CABG – Graft vs Native IRA



MAYO CLINIC

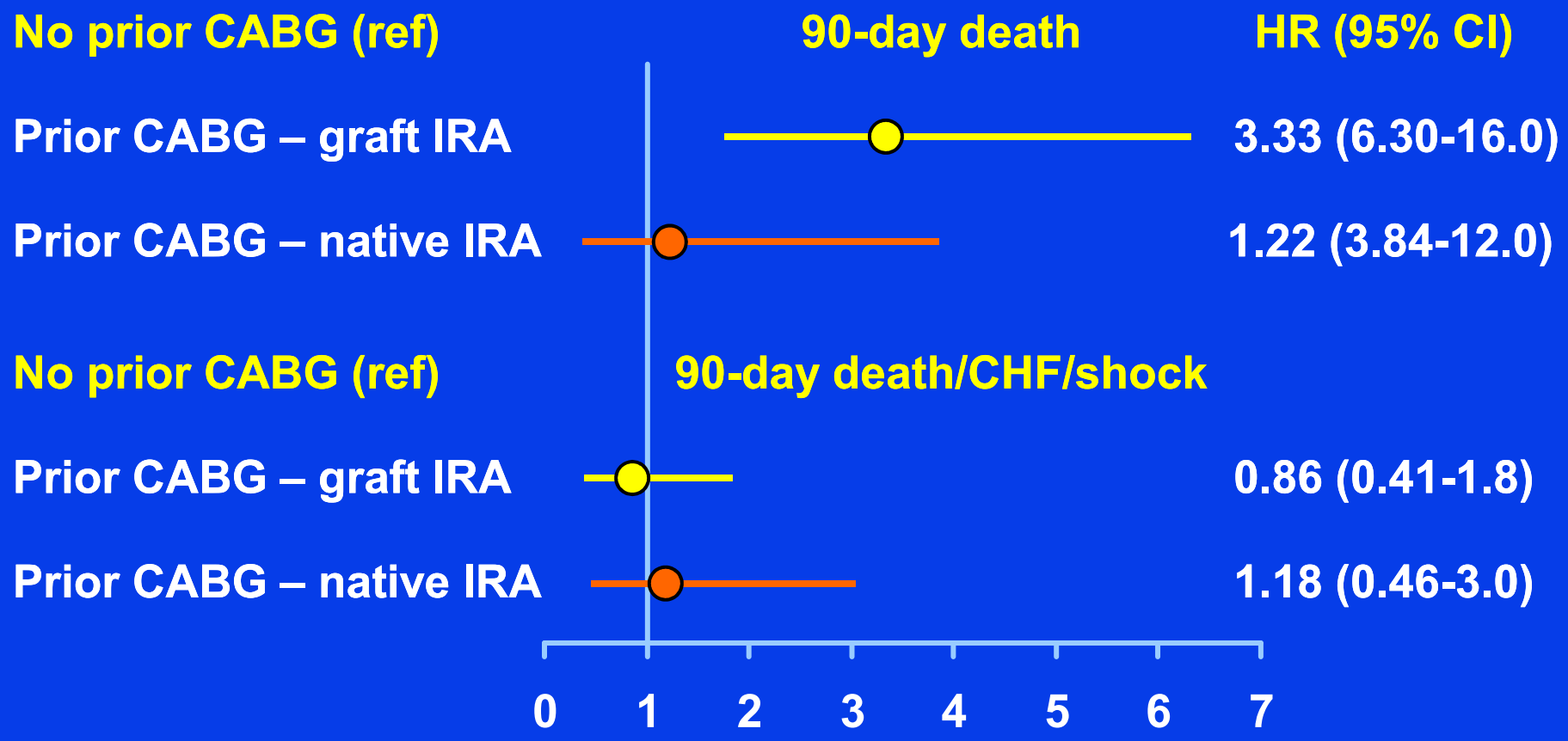
90-Day Death/CHF/Shock According to Prior CABG – Graft vs Native IRA



MAYO CLINIC

3010788-178

Adjusted Associations Between Prior CABG – Graft vs Native IRA and 90-Day Clinical Outcomes



MAYO CLINIC

Title/drp–author: WT/BK – Holmes, David
Sub/drp–Job#: YW105/BK – 3010788

Apex Prior CABG Figures

Background: BU3

Banner/brdr: BU2/BU41

Side title: YW105

• /colhdgs: YW105

Text: WT/BK

Highlight: YO114

Subdue: BU31

Footnotes: BU41

Plot/brdr: open/BU41
x, y only

PPT shooting instructions
PPT File to Server
(6 images)

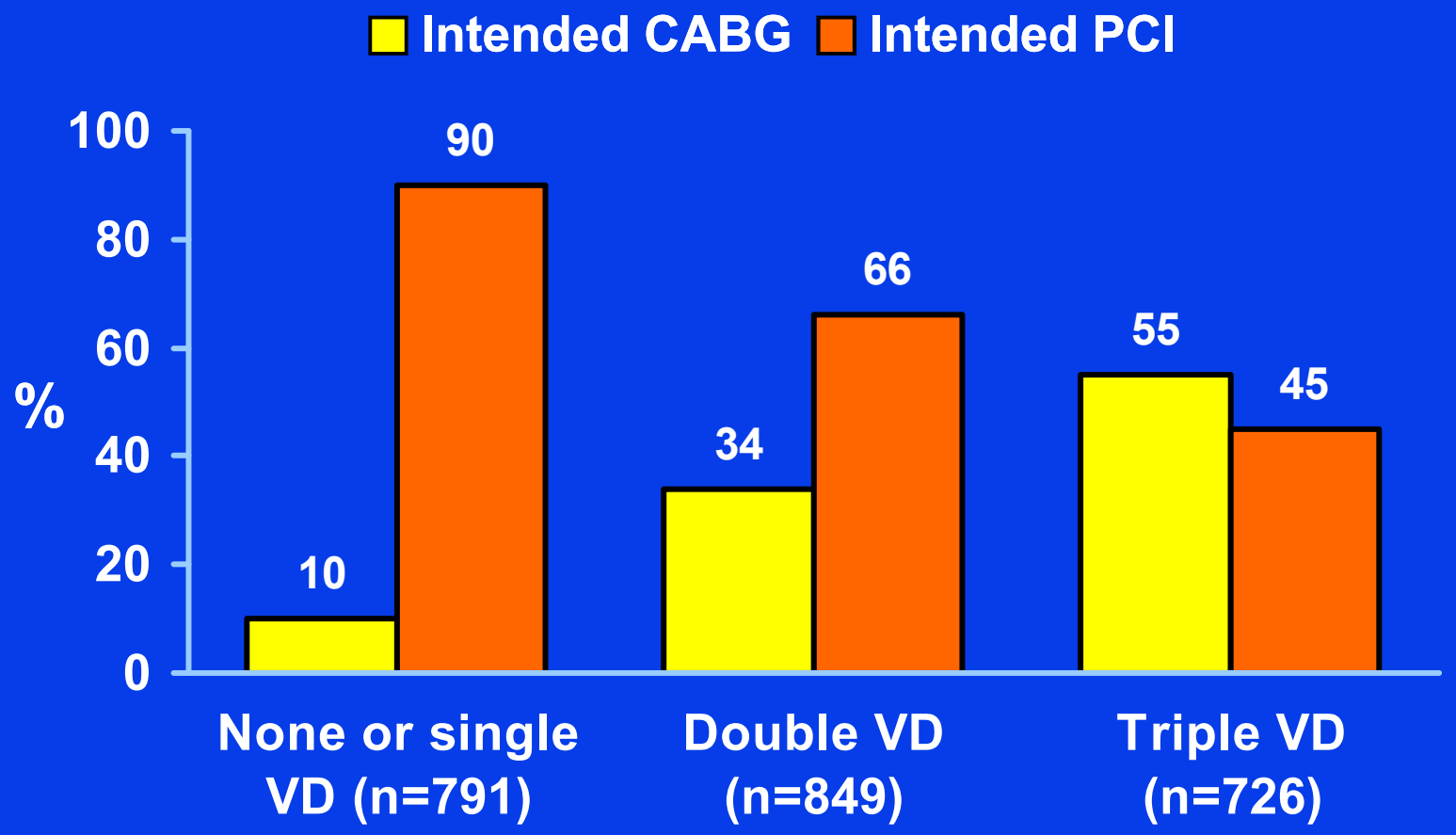
Artist: DV Start Date: 7-9-09

COLOR REFERENCE ONLY

Match: Mayo2bu-2002 (CP1111378)

MAYO CLINIC

Intended Mode of Revascularization by Number of Diseased Vessels



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BARI 2D Randomization
2 x 2 Factorial Design

Glucose control strategy	Ischemic control strategy: Prompt revasc	Ischemic control strategy: Medical	
Insulin provision	592	593	1,185
Insulin sensitization	584	599	1,183
	1,176	1,192	2,368

BARI 2D in the Context of Current Clinical Practice and Recent Trials

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

	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

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BARI 2D in the Context of Current Clinical Practice and Recent Trials
COURAGE Trial

- Our PCI results are consistent with the results from COURAGE, in which the majority of participants did not have diabetes
- COURAGE did not study CABG – further BARI2D analyses will address the effect of PCI on angina

BARI 2D in the Context of Current Clinical Practice and Recent Trials

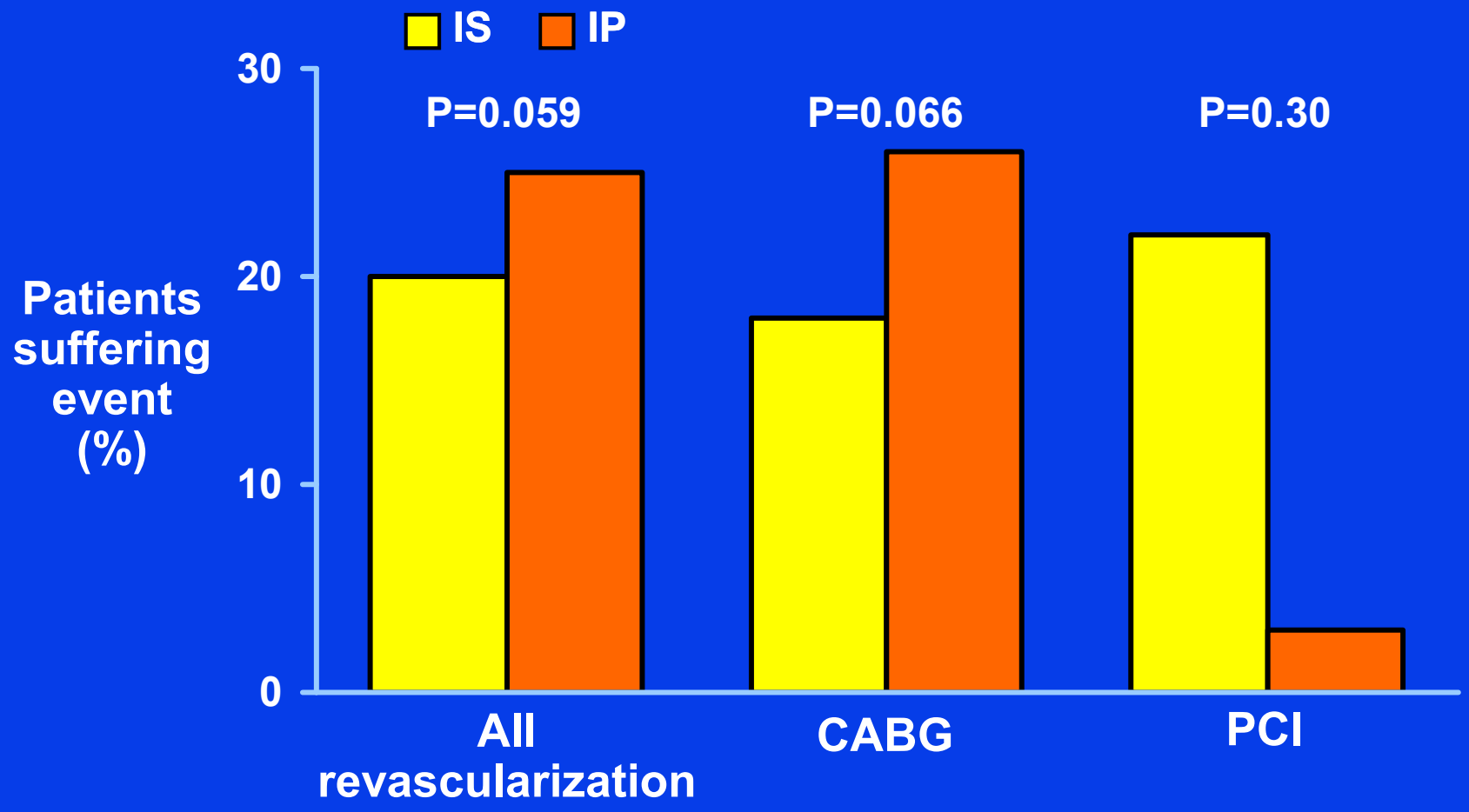
Intensive glycemic control trials (ADVANCE, ACCORD and VADT)

- BARI 2D does not address the question of intensive glycemic control as all subjects were treated with a target A_{1C} of <7.0%

TZD (rosiglitazone) therapy

- BARI 2D assessed therapeutic strategies rather than any specific drug
- No safety concerns were seen for the IS group in which over 60% were using TZD's, predominately rosiglitazone
- These results are thus consistent with RECORD

Effect of Insulin Sensitizing vs Insulin Providing Strategy on Death/Non-Fatal MI or Stroke Among Patients Assigned to Prompt Revascularization



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Do the Results of BARI 2D Suggest Any Changes Should be Made to Current Diabetes Management Practices?

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

Conclusions

- In patients with type 2 diabetes and stable CAD with documented ischemia, mortality does not differ according to either prompt or delayed revascularization strategies or by diabetes management strategies of insulin provision or sensitization
- In appropriately chosen type 2 diabetic patients, CABG is superior to aggressive medical therapy alone in reducing the combined incidence of death, non-fatal MI and non-fatal stroke

Final Lesson from BARI 2D

Therapeutic decisions regarding management of the CAD and glycemia in type 2 diabetes should be made jointly by the patient's cardiologist, diabetologist and/or primary care physician

Title/drp–author: WT/BK – Holmes, David
Sub/drp–Job#: YW105/BK – 3010909

Subject: BARI presentation

Background: BU3

Banner/brdr: BU2/BU41

Side title: YW105

• /colhdgs: YW105

Text: WT/BK

Highlight: YO114

Subdue: BU31

Footnotes: BU41

Plot/brdr: open/BU41
x, y only

PPT shooting instructions
PPT File to Server
(57 images)

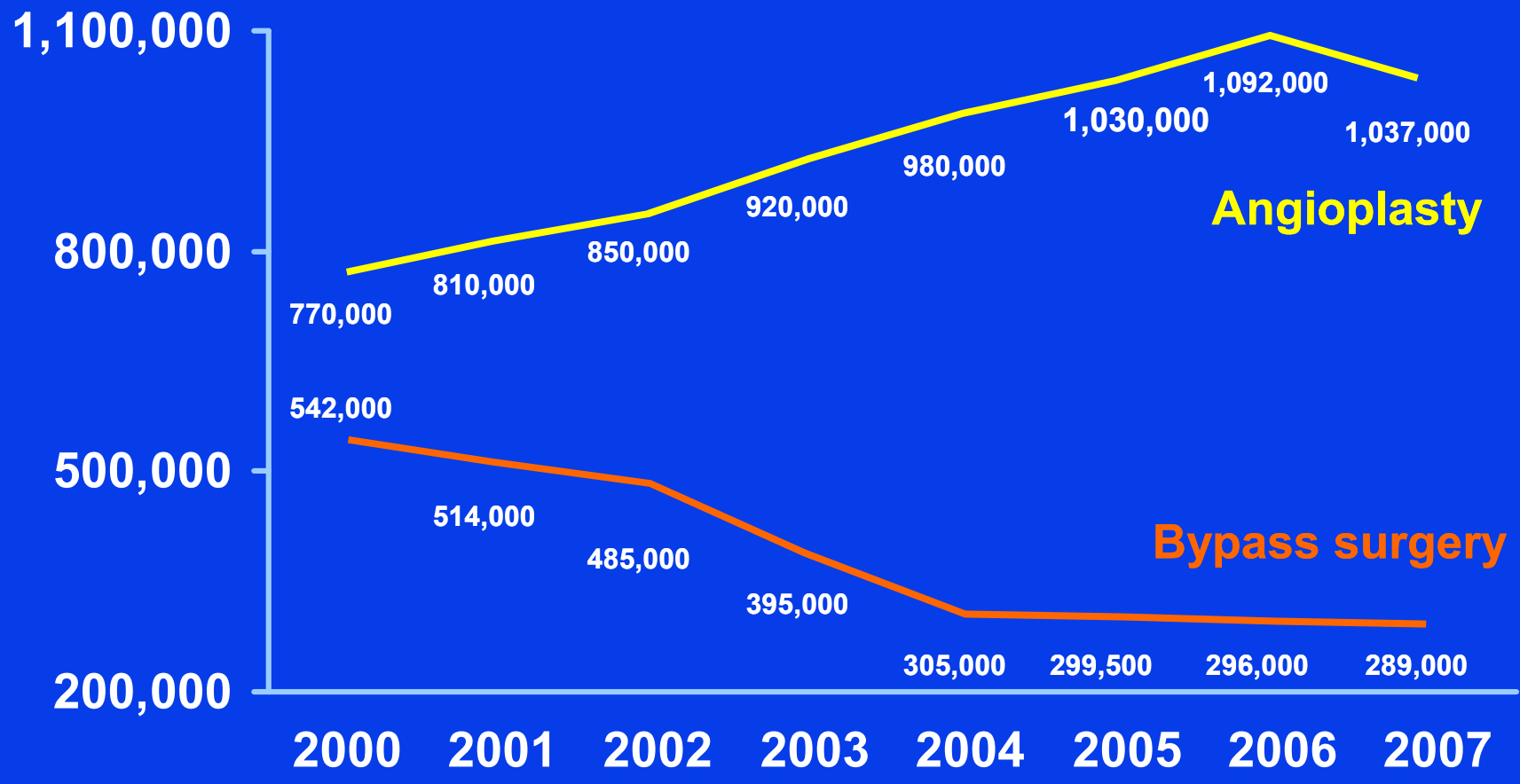
Artist: mls Start Date: 7-10-09

COLOR REFERENCE ONLY

Match: Mayo2bu-2002 (CP1111378)

MAYO CLINIC

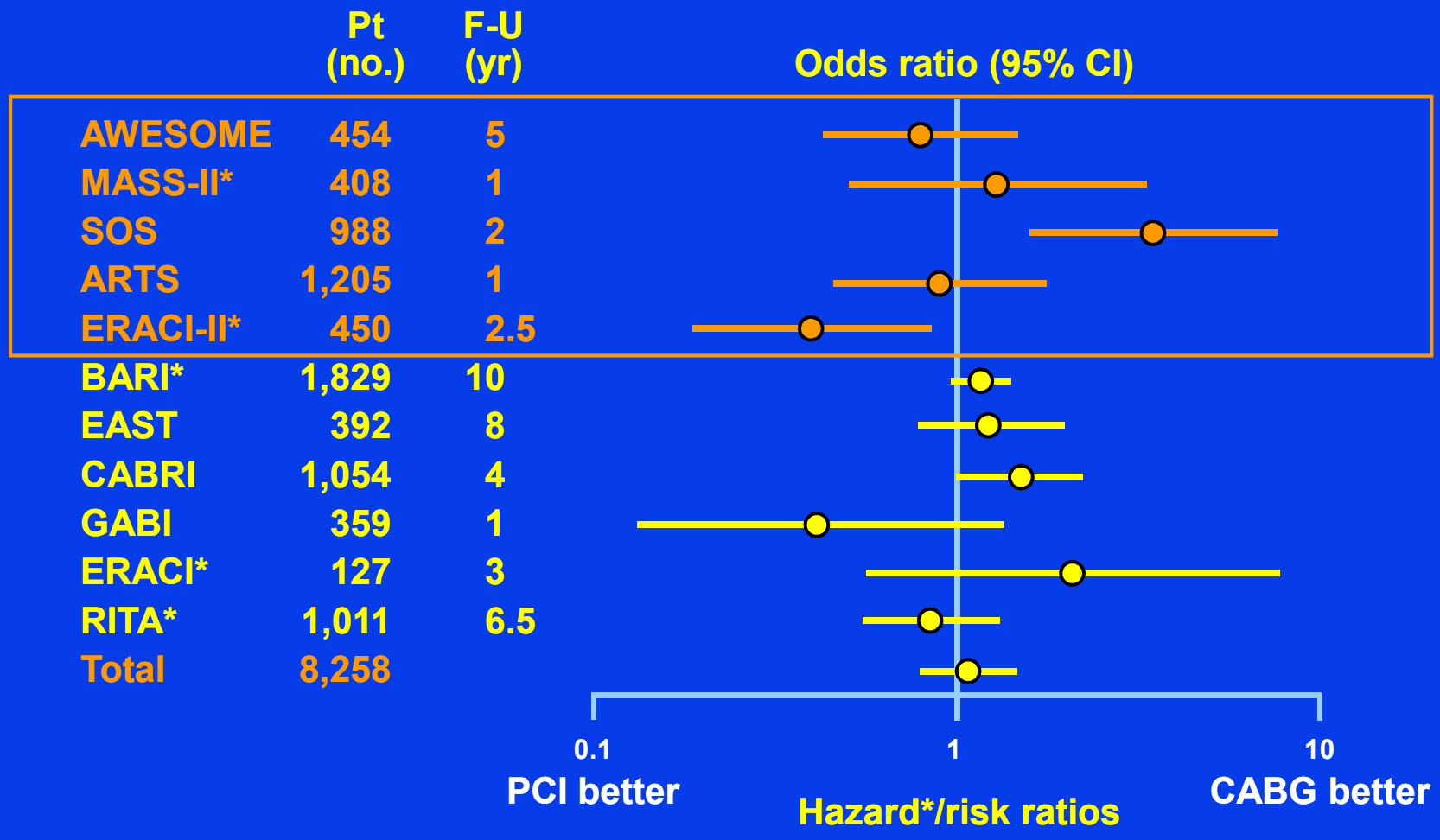
PCI vs CABG: New vs Old Technology



Sources: Cordis Database, Morgan Stanley

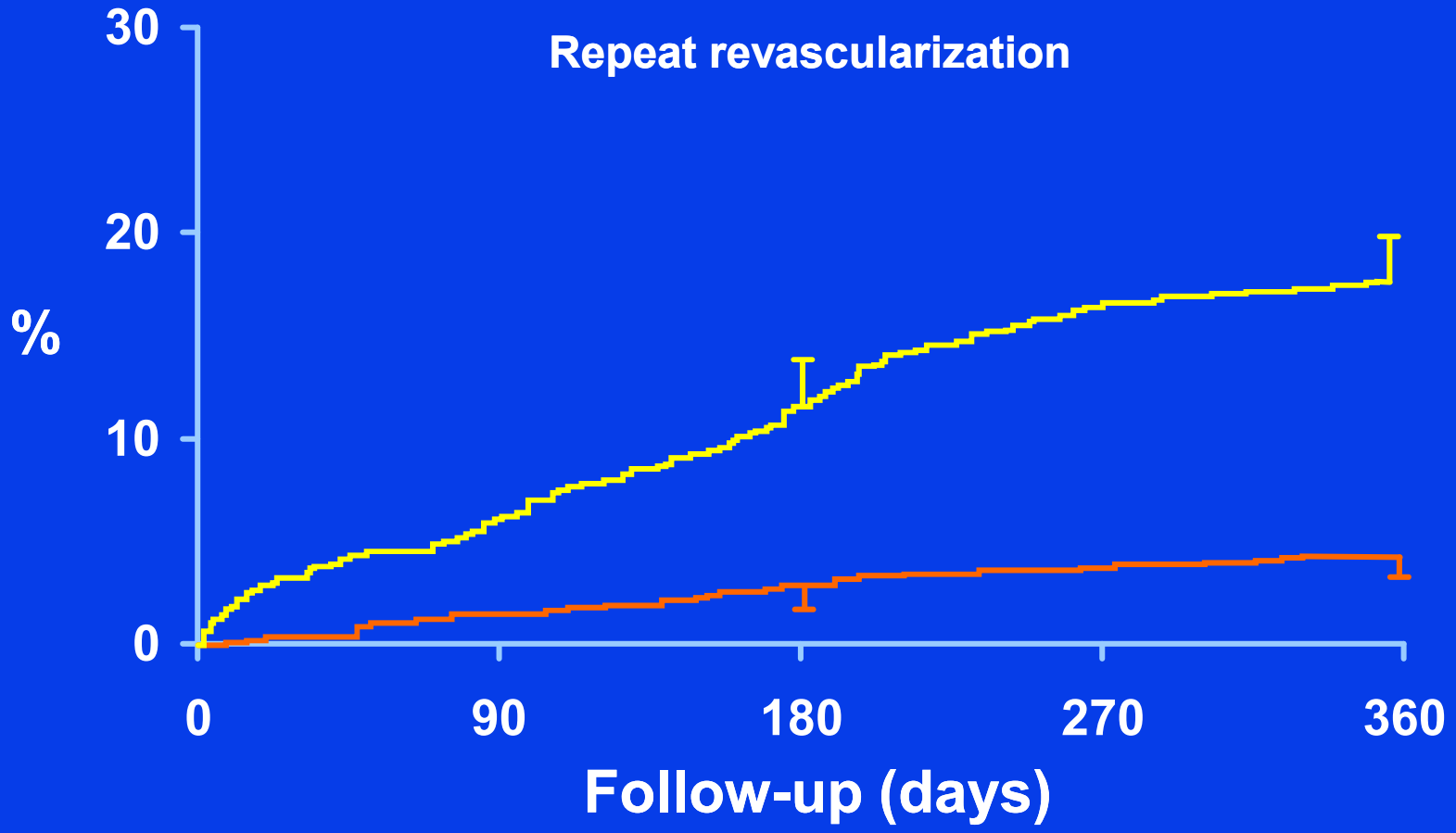
MAYO CLINIC

PCI vs CABG
Mortality



Holmes DR Jr., Berger PB: compelx Intervention. Textbook of Interventional Cardiology, 4th Edition, Topol EJ, editor, 2003:201-22

1-Year Rates of Repeat Revascularization in 4 CABG vs Stent Assisted PCI Trials



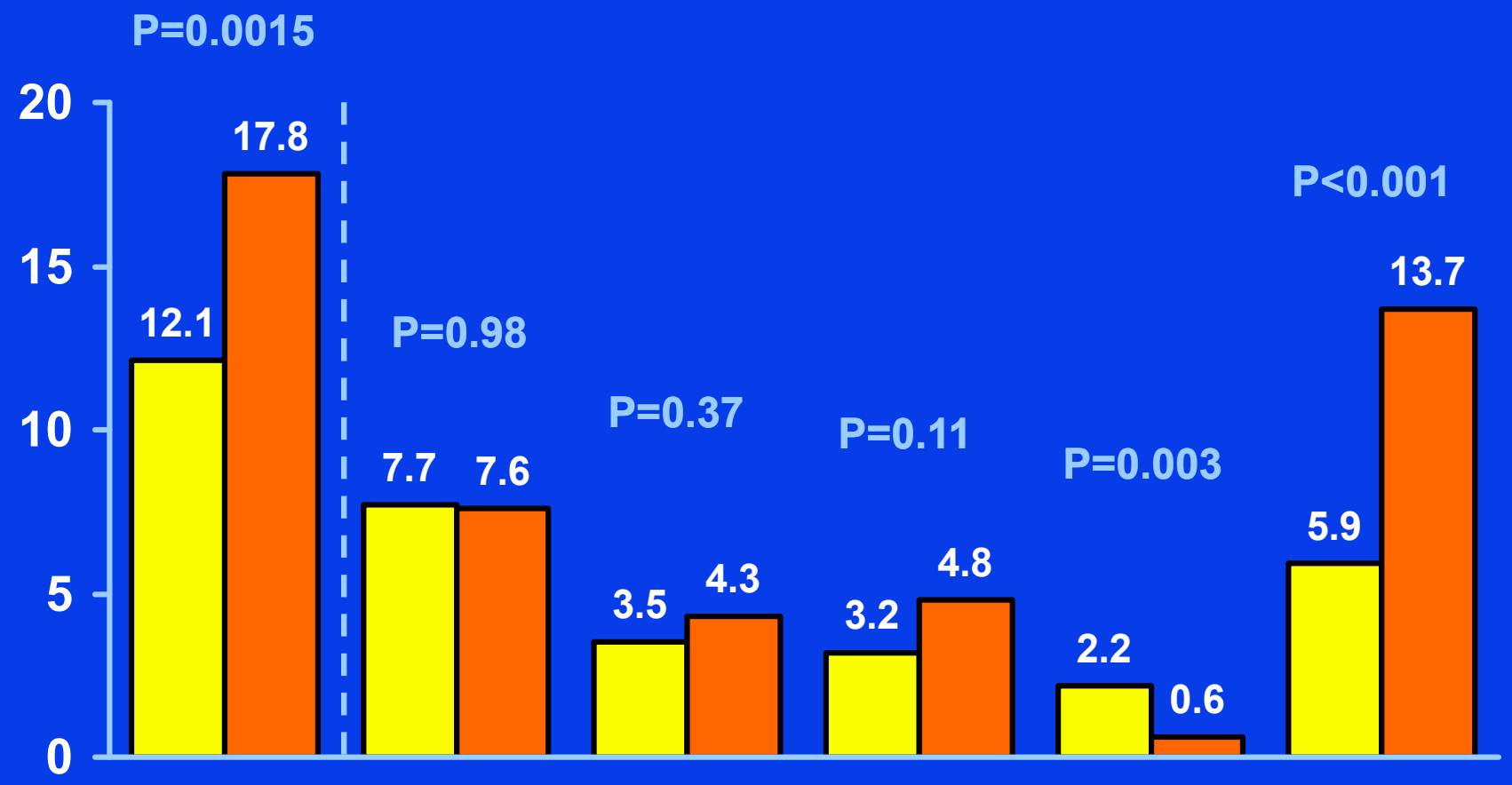
Do repeat revascularization rates = durability?

Mercado et al: J Thoracic Cardiovasc Surg, 2005

PREVENT 4

Type of event	Patients			
	CABG + edifoligide (n=1508)		CABG + placebo (n=1506)	
	No.	%	No.	%
Atrial fibrillation	379	25.1	402	26.7
Perioperative MI in CABG surgery	145	9.6	149	9.9
Renal failure	49	3.2	50	3.3
Bleeding requiring reoperation	40	2.7	36	2.4
Pneumonia	33	2.2	37	2.5
Stroke	28	1.9	18	1.2
Adult respiratory distress syndrome	10	0.7	16	1.1
Mediastinitis	9	0.6	12	0.8
Pulmonary embolism	12	0.8	5	0.3

SYNTAX
1-Year Clinical Outcomes



MAYO CLINIC

Original Article

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

Edward L. Hannan, et al N Engl J Med, Volume 358(4):331-341, Jan 24, 2008

Mortality (after adjustment) 7.3% for DES Vs. 6.0% for CABG

This 1.3% absolute difference (P=0.03) yields a NNT of 77

If we need to do 77 bypasses to save one life, I believe the mortality benefit is clinically meaningless!

This point was completely missed by the lay press

SYNTAX Trial Design

62 EU sites +  23 U.S. sites

Heart team (surgeon & interventionalist)

Amenable for both treatment options

Randomized arms n=1,800

CABG n=897 vs **TAXUS n=903**

DM 28.5% | Non-DM 71.5% | DM 28.2% | Non-DM 71.8%

Amenable for only 1 treatment approach

2 registry arms n=1,275

CABG n=1,077 | **PCI n=198**

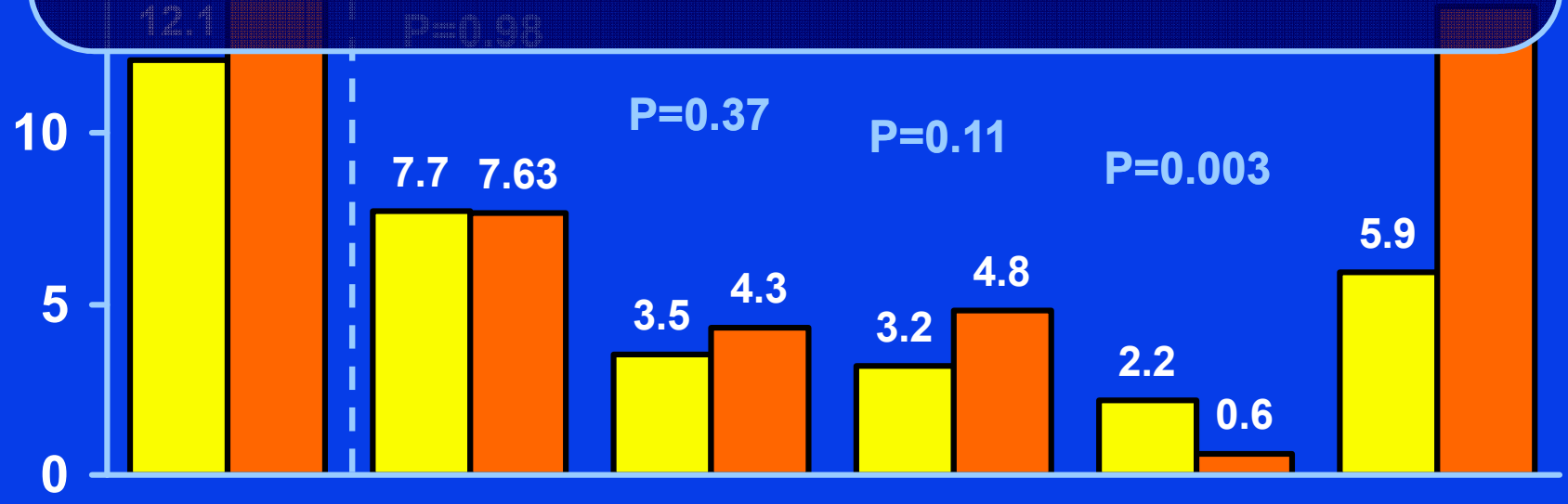
TAXUS® Express® Stent

SYNTAX
1-Year Clinical Outcomes

Number needed to prevent analysis

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

At the cost of almost 4 times as many strokes



Serruys and Mohr: ESC, 2008

*Primary endpoint

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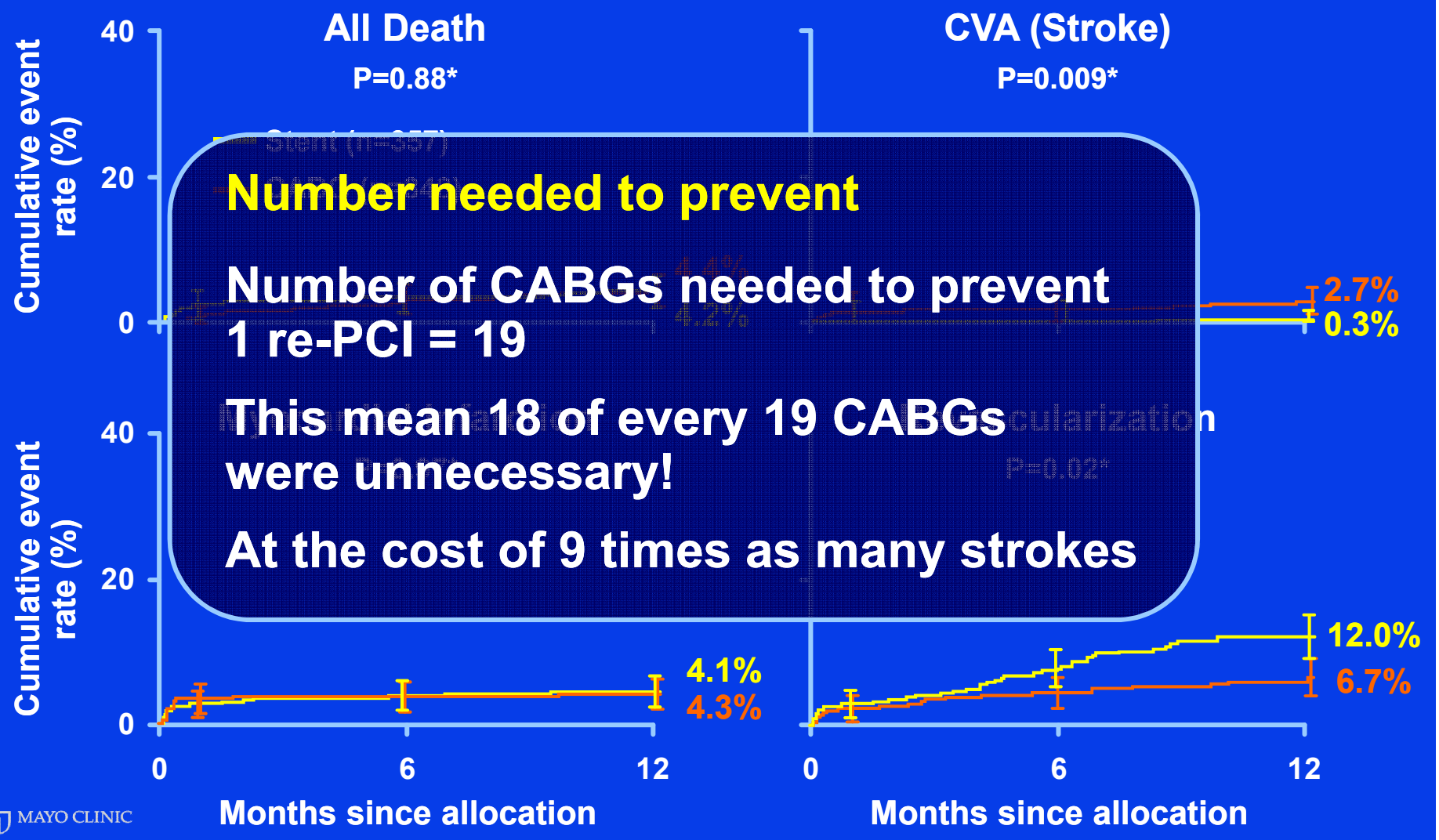
Adverse Events to 12 Months
Left Main Subset



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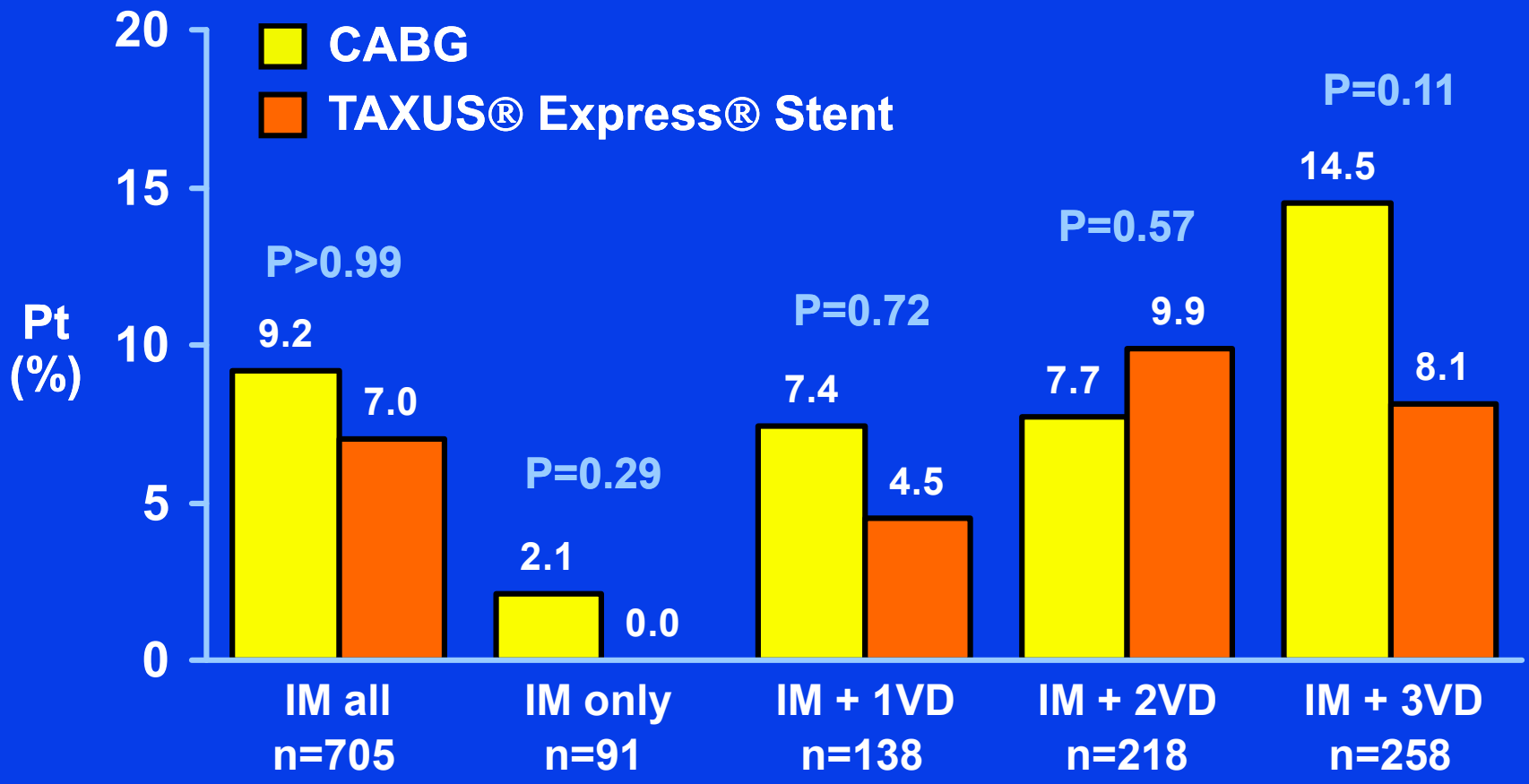
3011192-199

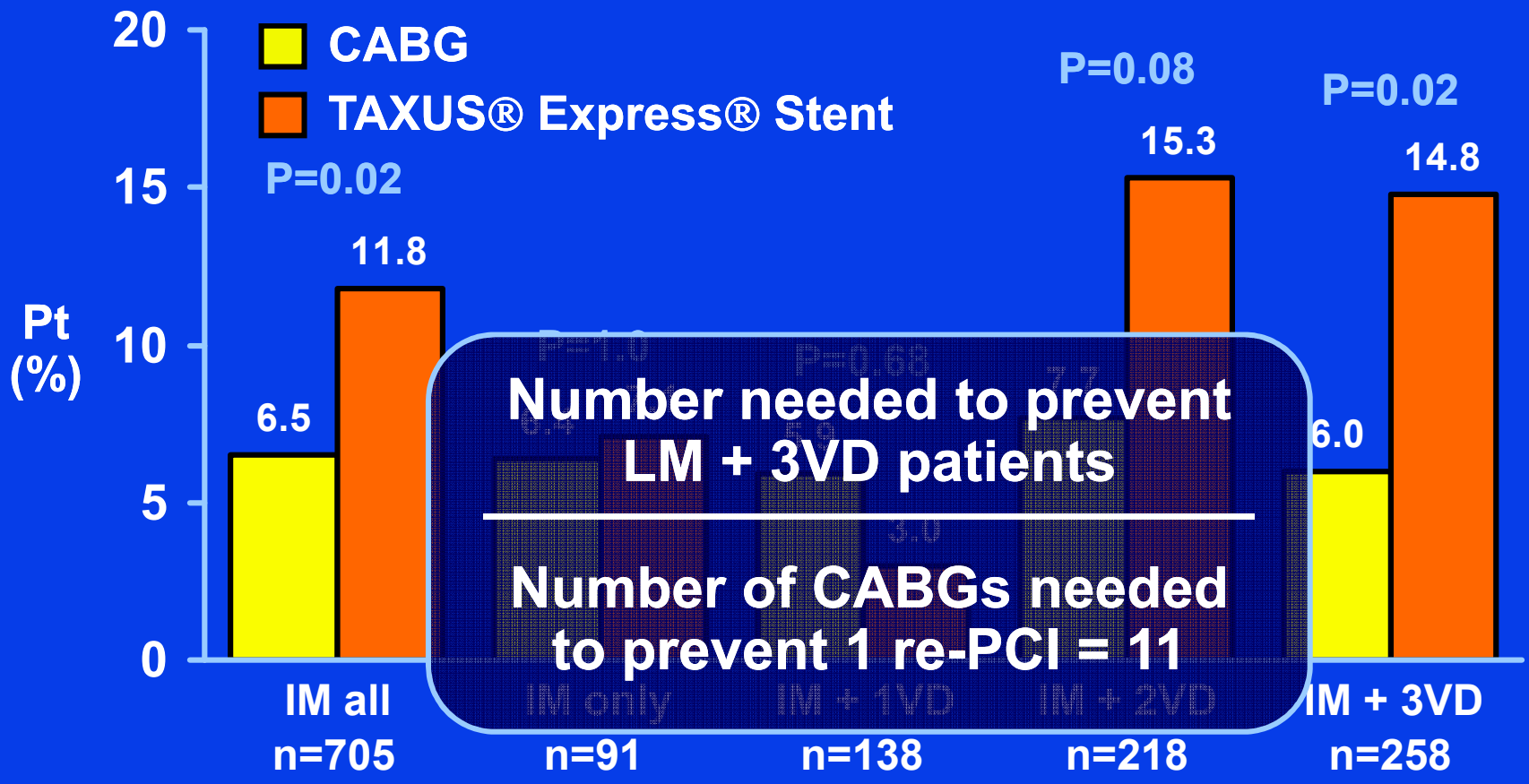
Safety at 12 Months (Death/CVA/MI)
Left Main Subset



ITT population; presented by Dr. Serruys: TCT 2008

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

Revascularizations at 12 Months
Left Main Subset



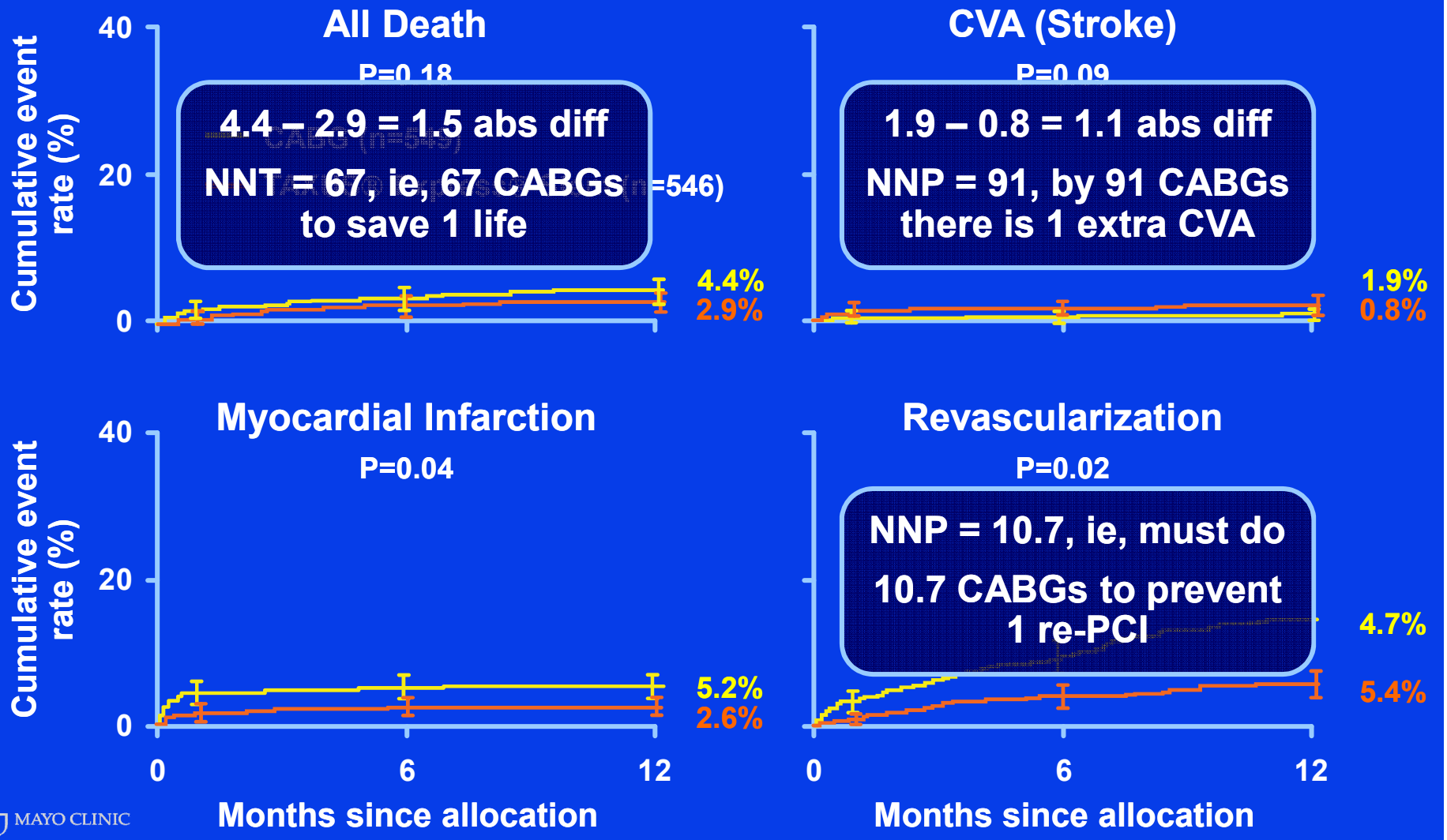
Number needed to prevent LM + 3VD patients

Number of CABGs needed to prevent 1 re-PCI = 11

ITT population; presented by Dr. Serruys: TCT 2008

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

Adverse Events to 12 Months
Left Main Subset

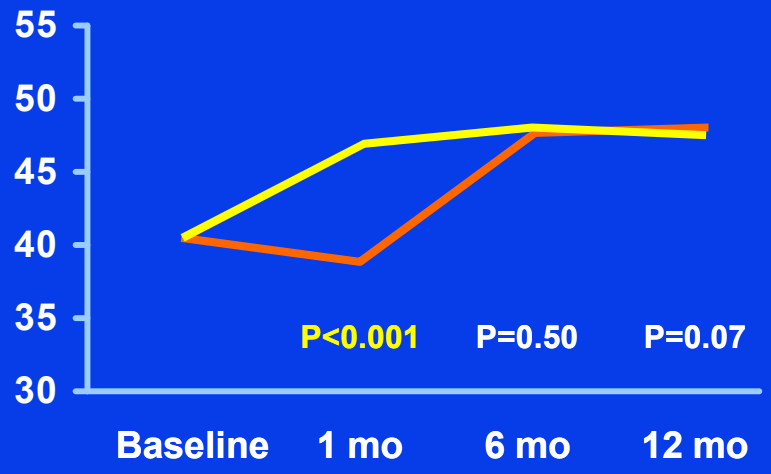


MAYO CLINIC

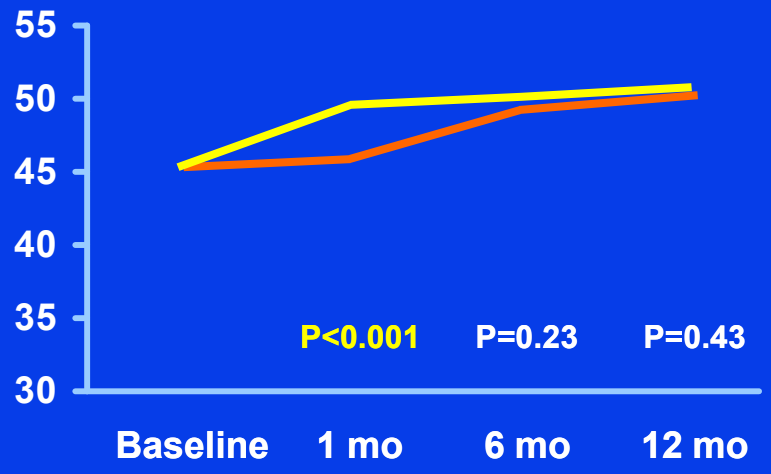
3011192-202

Generic QOL and Utilities

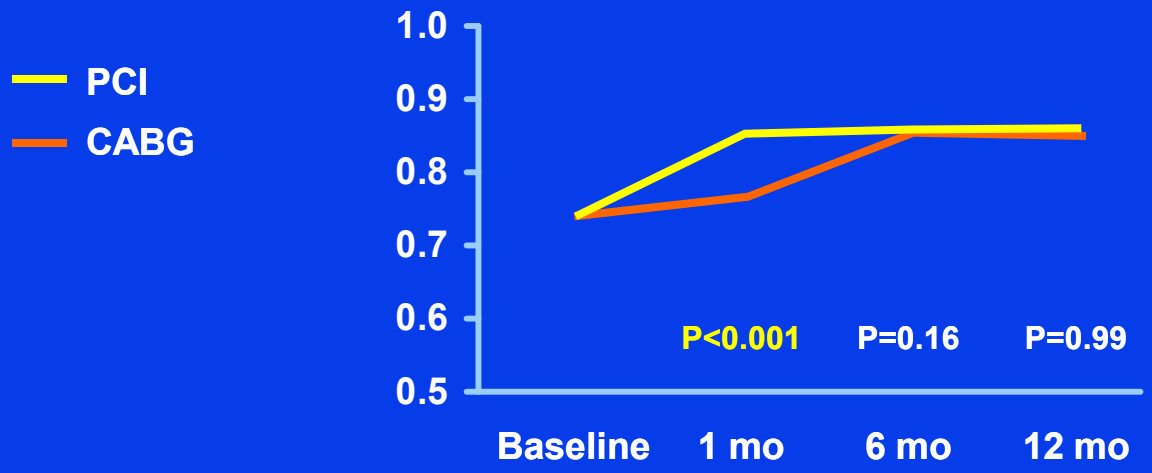
SF-36 Physical Component Summary



SF-36 Mental Component Summary



EQ-SD Utilities (US)



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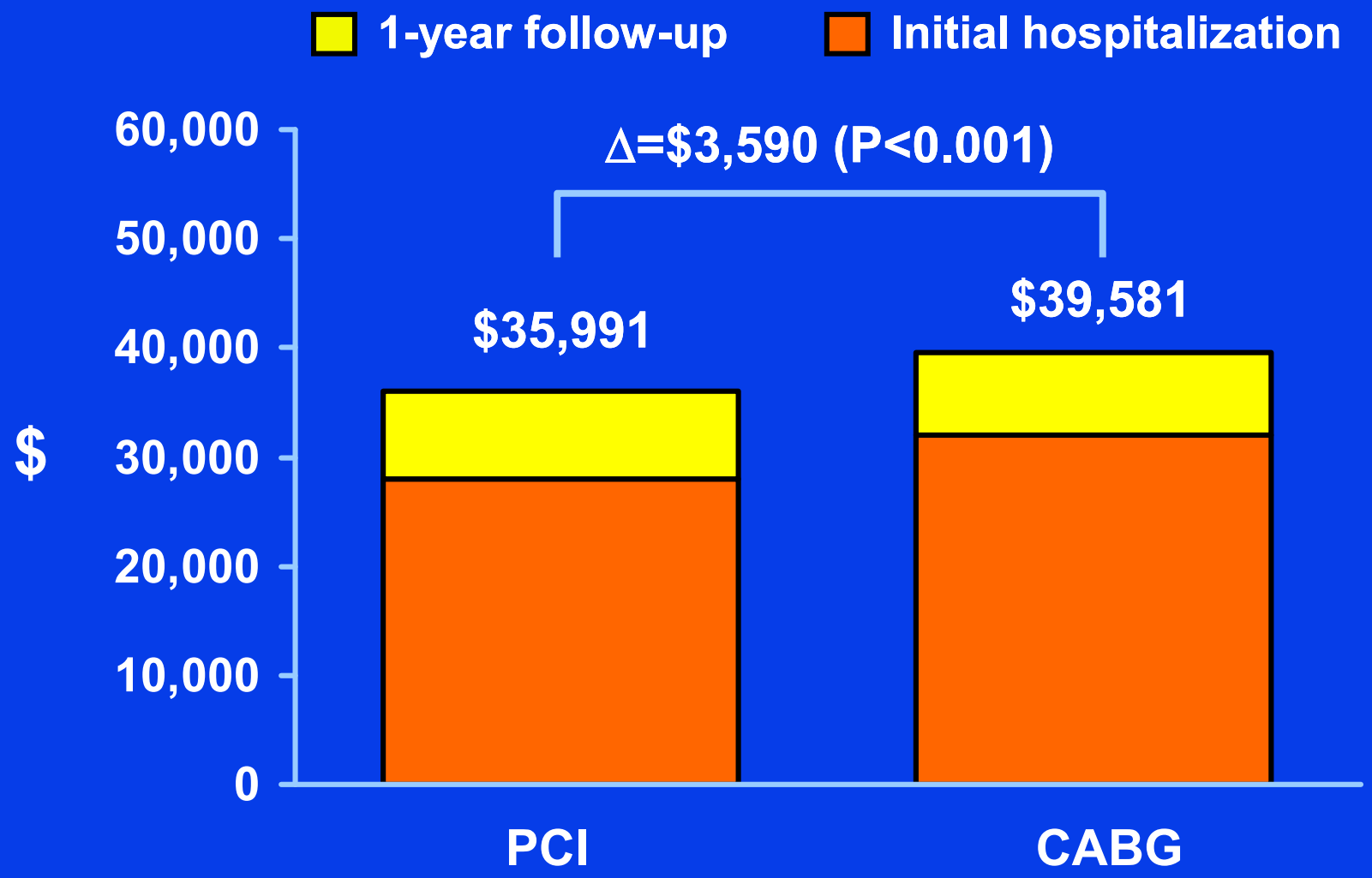
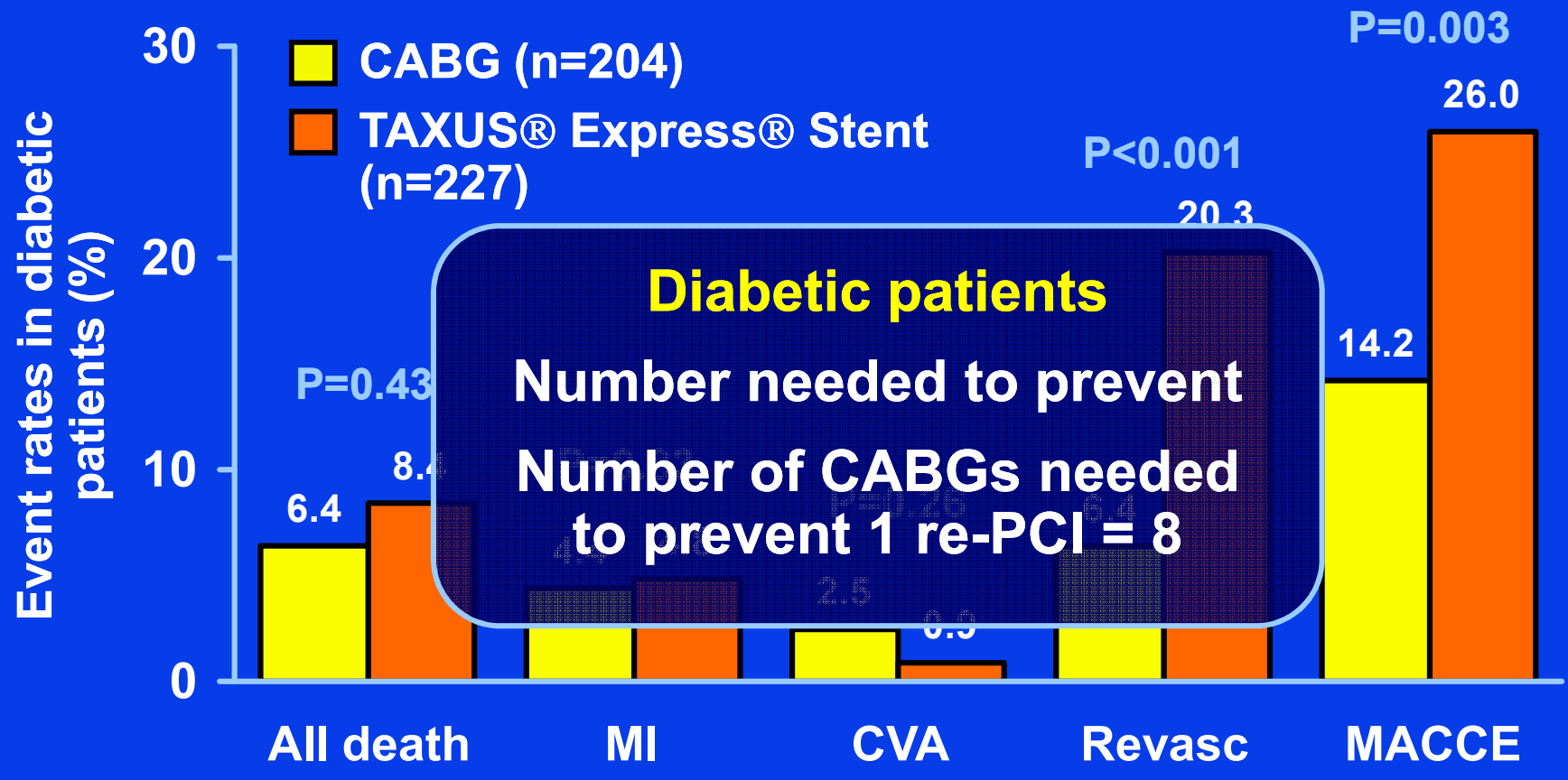
3011192-203

Total 1-Year Costs



MAYO CLINIC

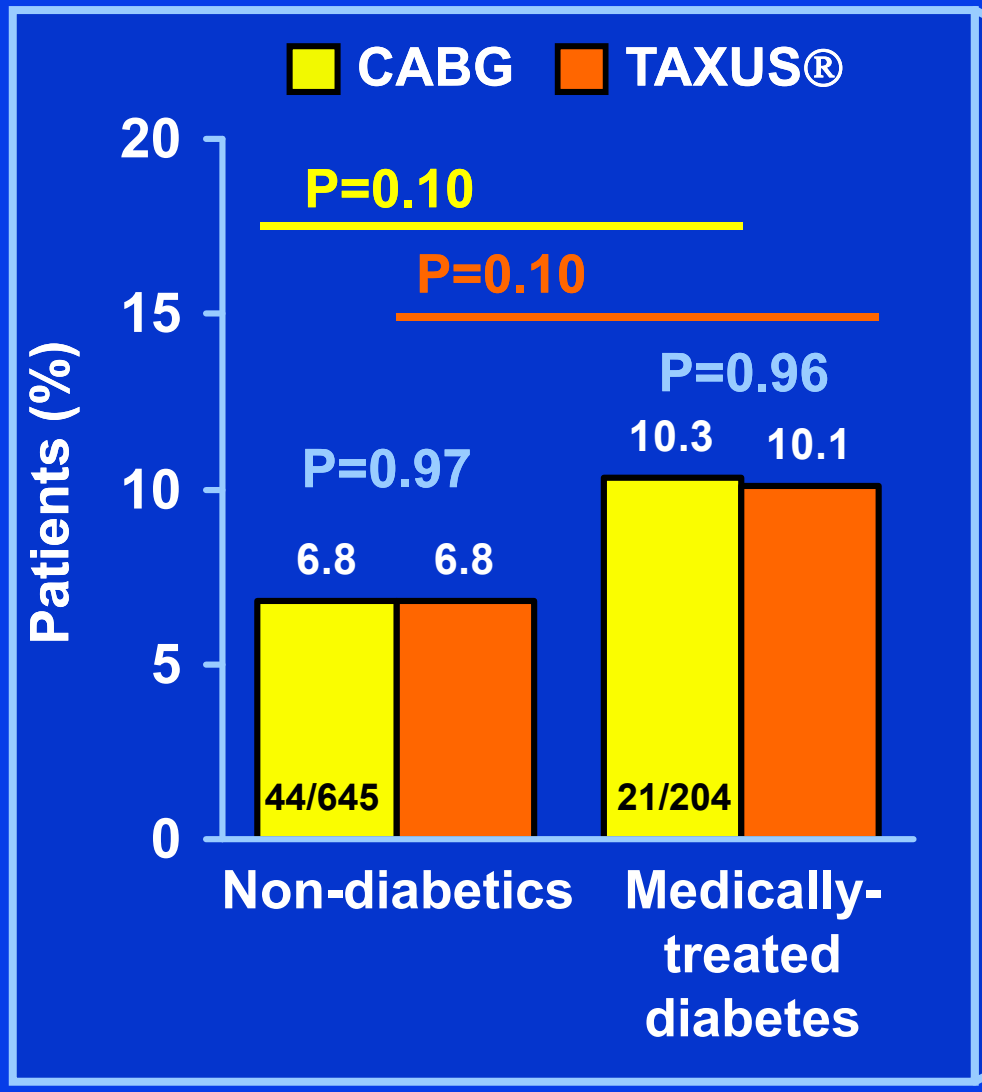
Higher 12-Month MACCE in Diabetics* Driven by Revascularization

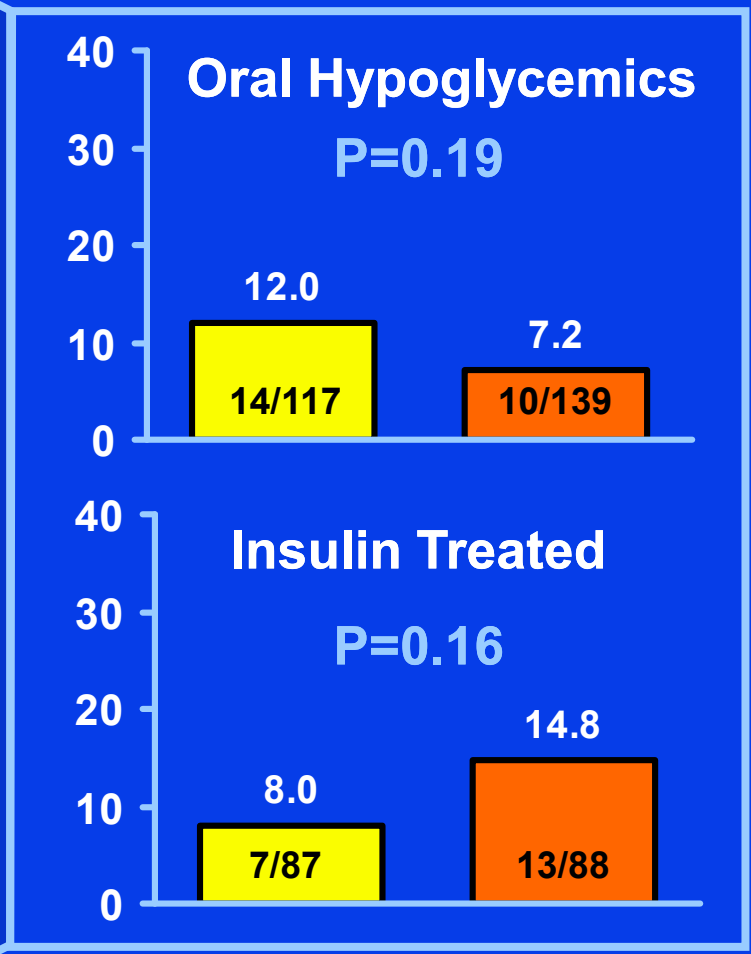


Medically treated diabetics; presented by Dr. Dawkins: TCT 2008

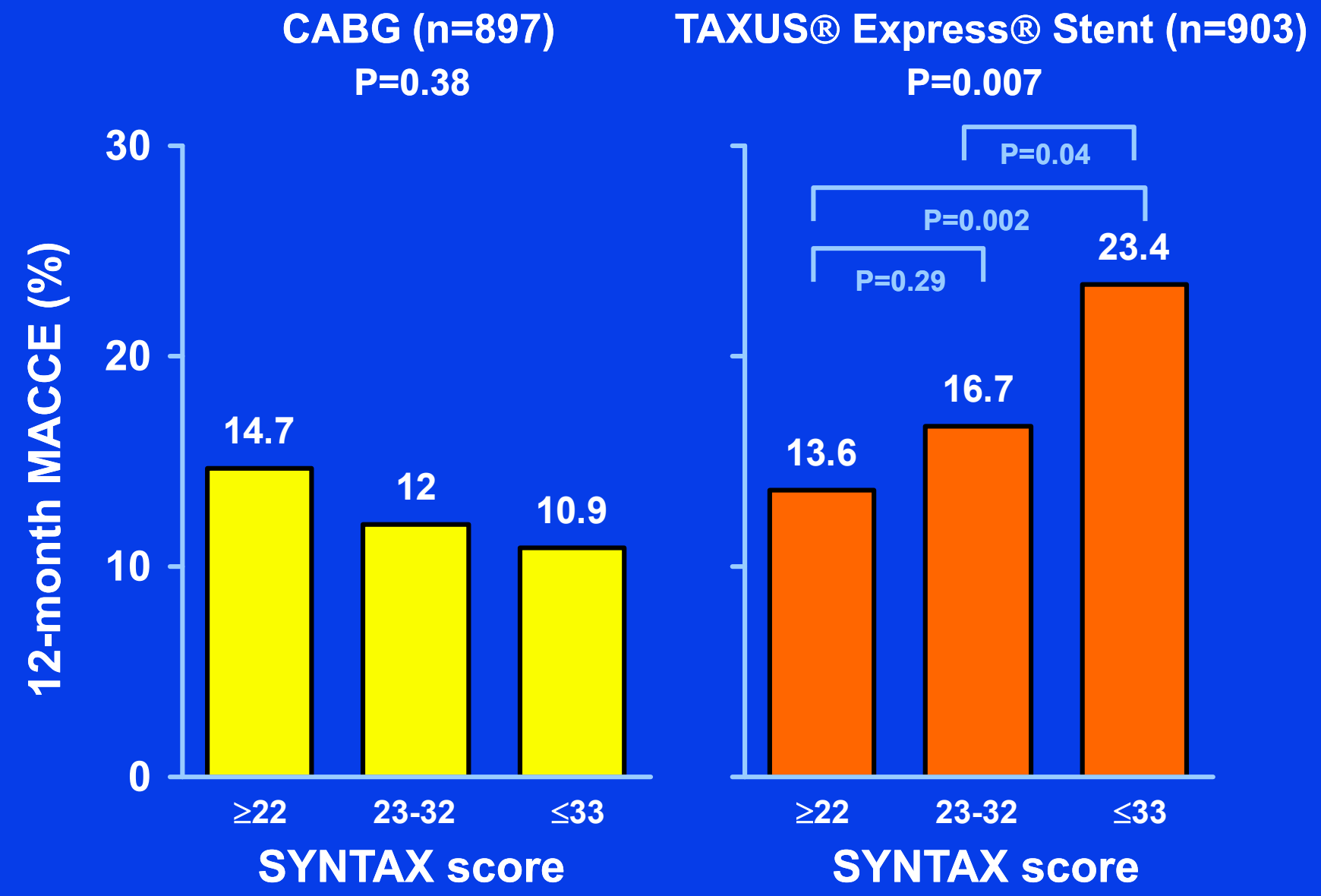
The TAXUS® Express® Stent System has not been specifically indicated for pateints with diabetes

Death/CVA/MI at 12 Months
Diabetic Subgroups



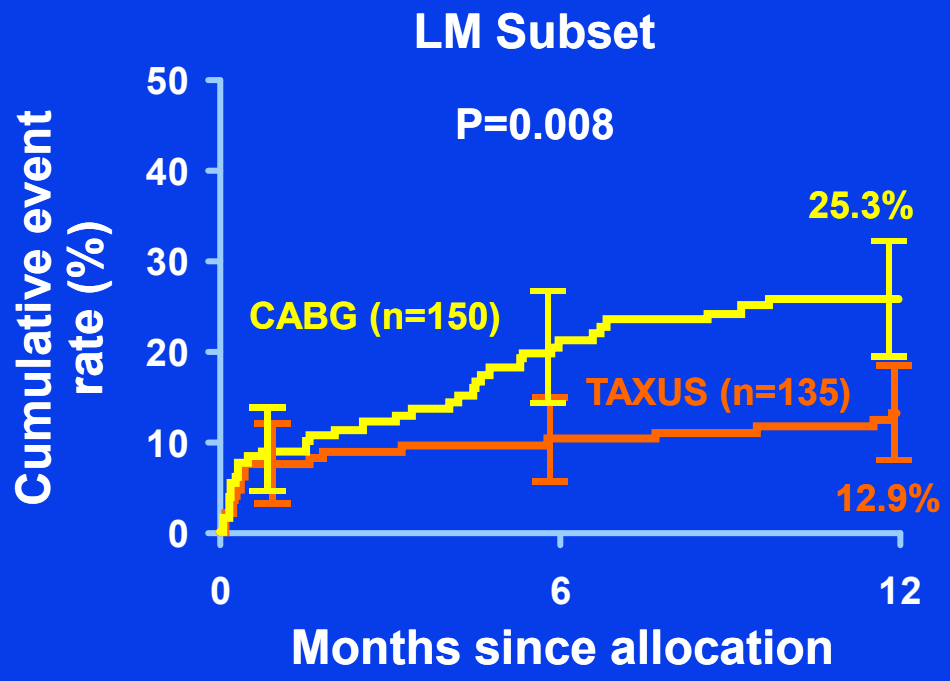


MACCE to 12 Months vs SYNTAX Score™



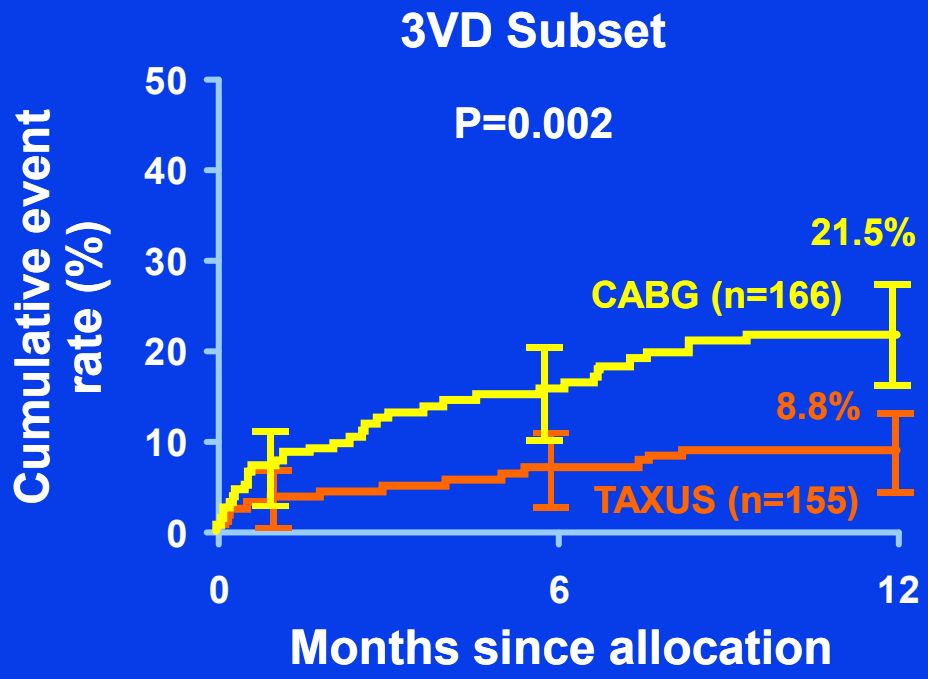
MACCE to 12 Months by SYNTAX Score
Tertile High Score (33+)

	CABG	PCI	P
Death	4.1%	9.7%	0.06
CVA	3.4%	0.8%	0.22
MI	6.0%	7.6%	0.65
Death, CVA or MI	10.8%	14.1%	0.40
Revasc	4.9%	17.8%	0.001



MACCE to 12 Months by SYNTAX Score
Tertile High Score (33+)

	CABG	PCI	P
Death	1.2%	6.5%	0.02
CVA	1.2%	0.0%	0.50
MI	1.9%	6.5%	0.04
Death, CVA or MI	4.3%	9.7%	0.07
Revasc	5.1%	16.6%	0.001



Title/drp–author: WT/BK – Holmes, David
Sub/drp–Job#: YW105/BK – 3011192

Subject: Teirstein Presentation

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

Plot/brdr: open/BU41
x, y only

PPT shooting instructions
PPT File to Server
(28 image)

Artist: KK Start Date: 7-14-09

COLOR REFERENCE ONLY

Match: Mayo2bu-2002 (CP1111378)

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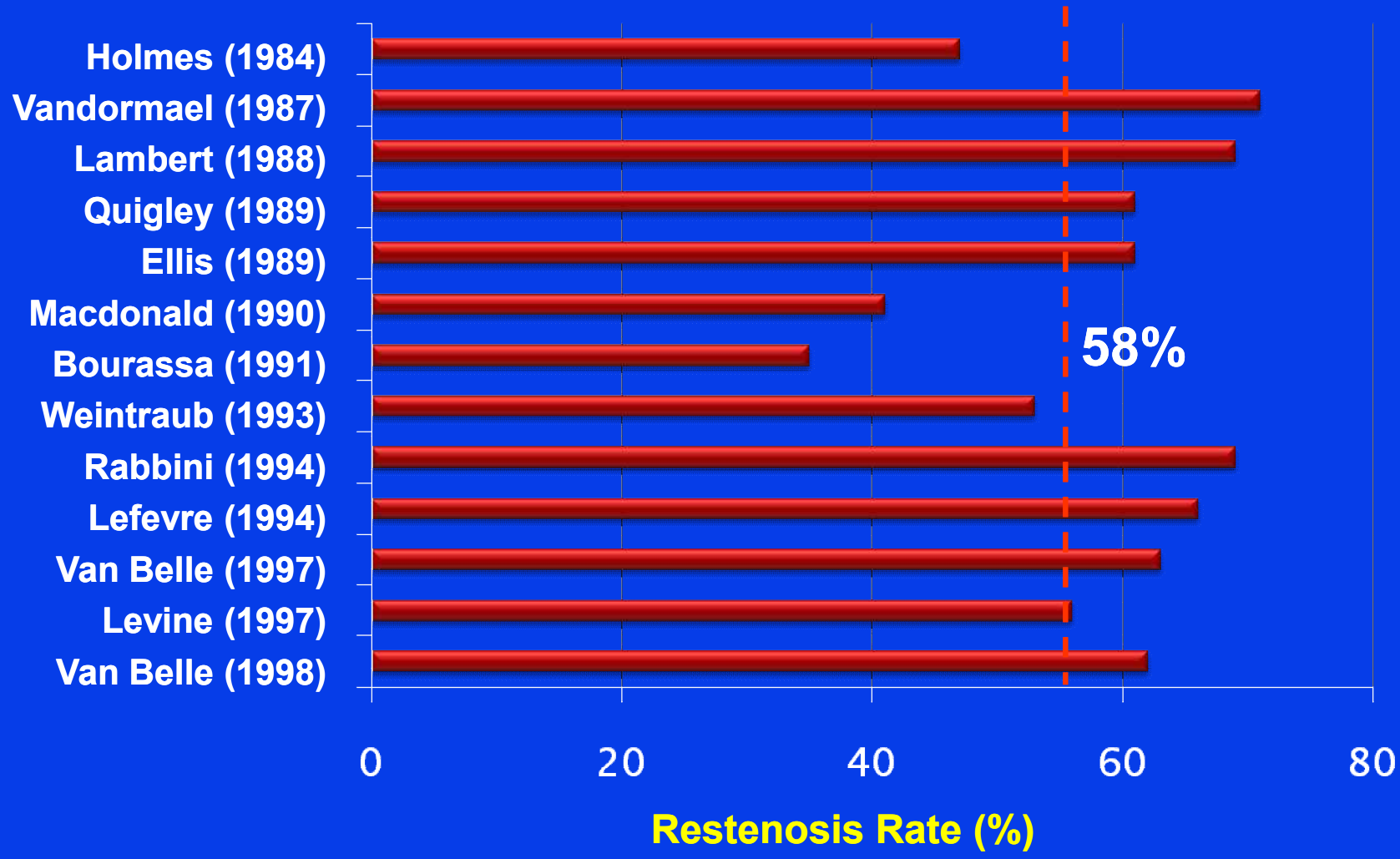
3011192-210

58% Average Restenosis Rate in Diabetes Following POBA



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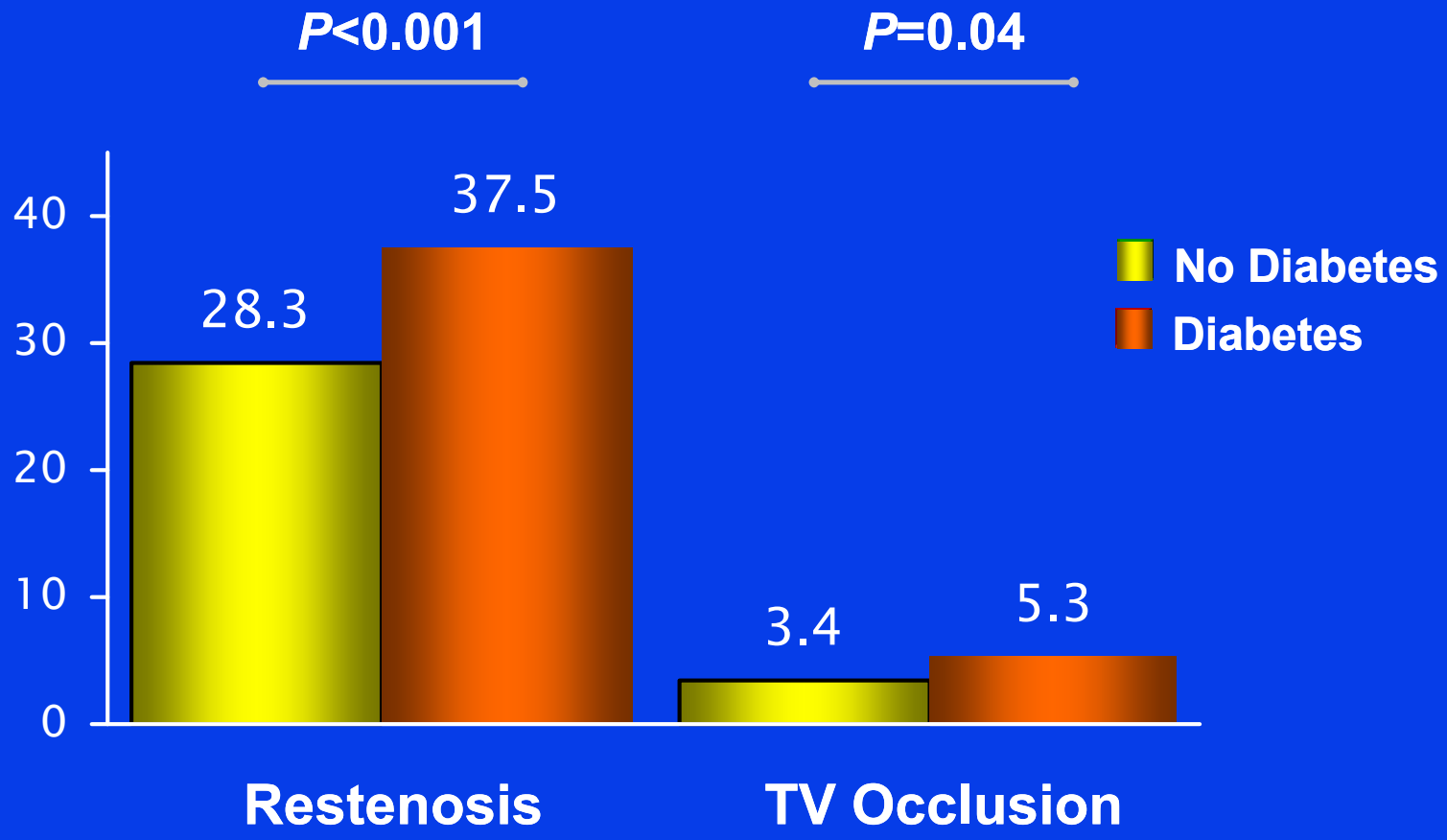
J Am Coll Cardiol 1999;34:476-485

Restenosis Increased in Diabetes Following BMS Implantation

6-Month Rates



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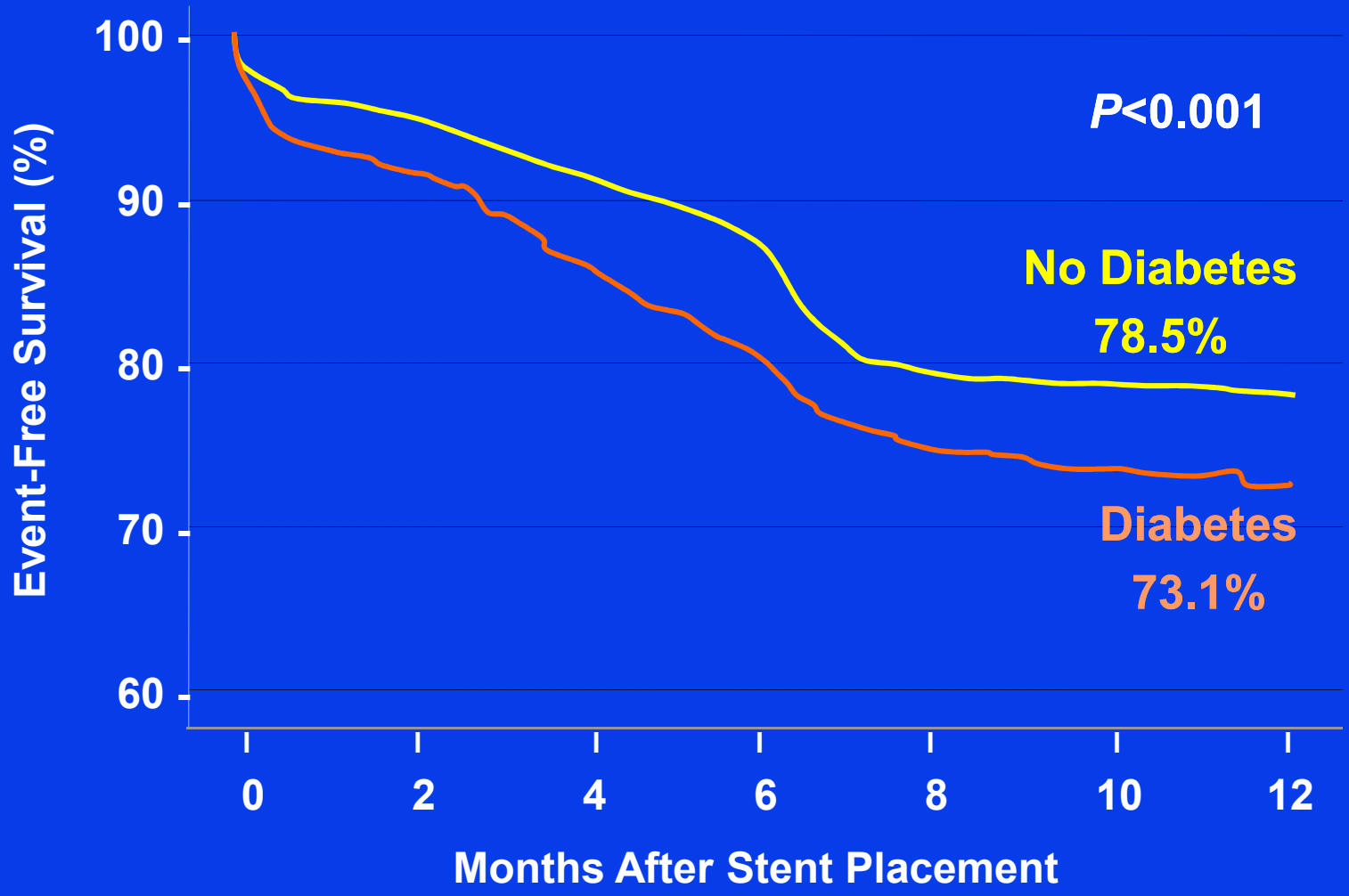
J Am Coll Cardiol 1998;32:1866-1873

Diabetes Also Increases Mortality After Bare Metal Stenting



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J Am Coll Cardiol 1998;32:1866-1873

What About Diabetic Patients with 3-Vessel and/or Left Main Disease?

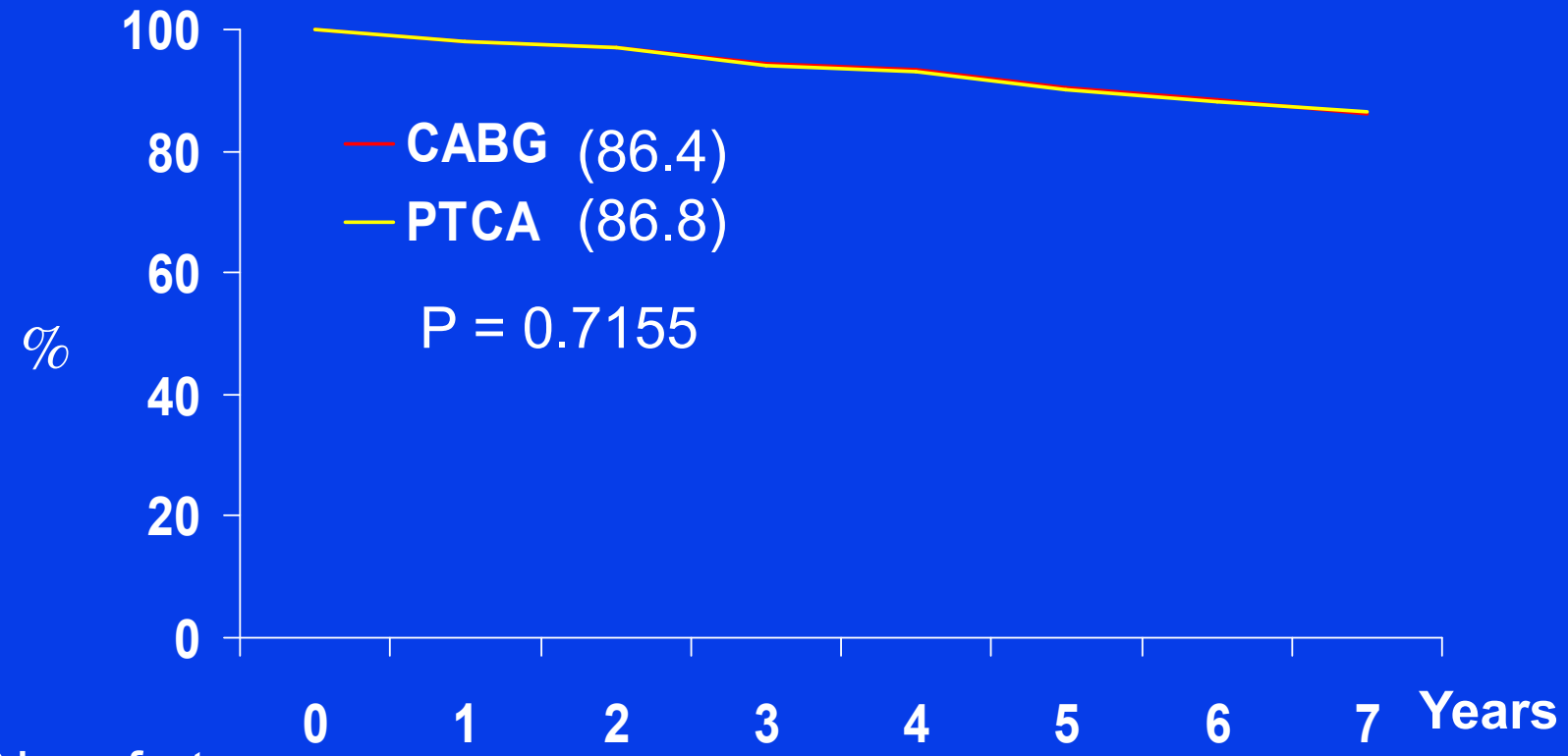
- Current guidelines recommend CABG
- Estimated 34% of patients with Class I indications for CABG receive PCI in the DES era

What is the optimal treatment?

J Am Coll Cardiol 2008;51:172-209
Circulation 2007;116II:795

BARI - 7 Year Survival

Survival-Patients without Treated Diabetes



No. of pts								
CABG	734			699				490
PTCA	742			703				509

Detre, JACC 2000

Amount of Disease
BARI vs SYNTAX

	BARI	SYNTAX
3VD	44%	71%
LMCA	0	29%
# sig. lesions	3.4	4.6
Diffuse disease	?	13.4%
1-yr survival	90%	92%*

*Death/CVA/MI

COURAGE Trial
What are the Lessons?

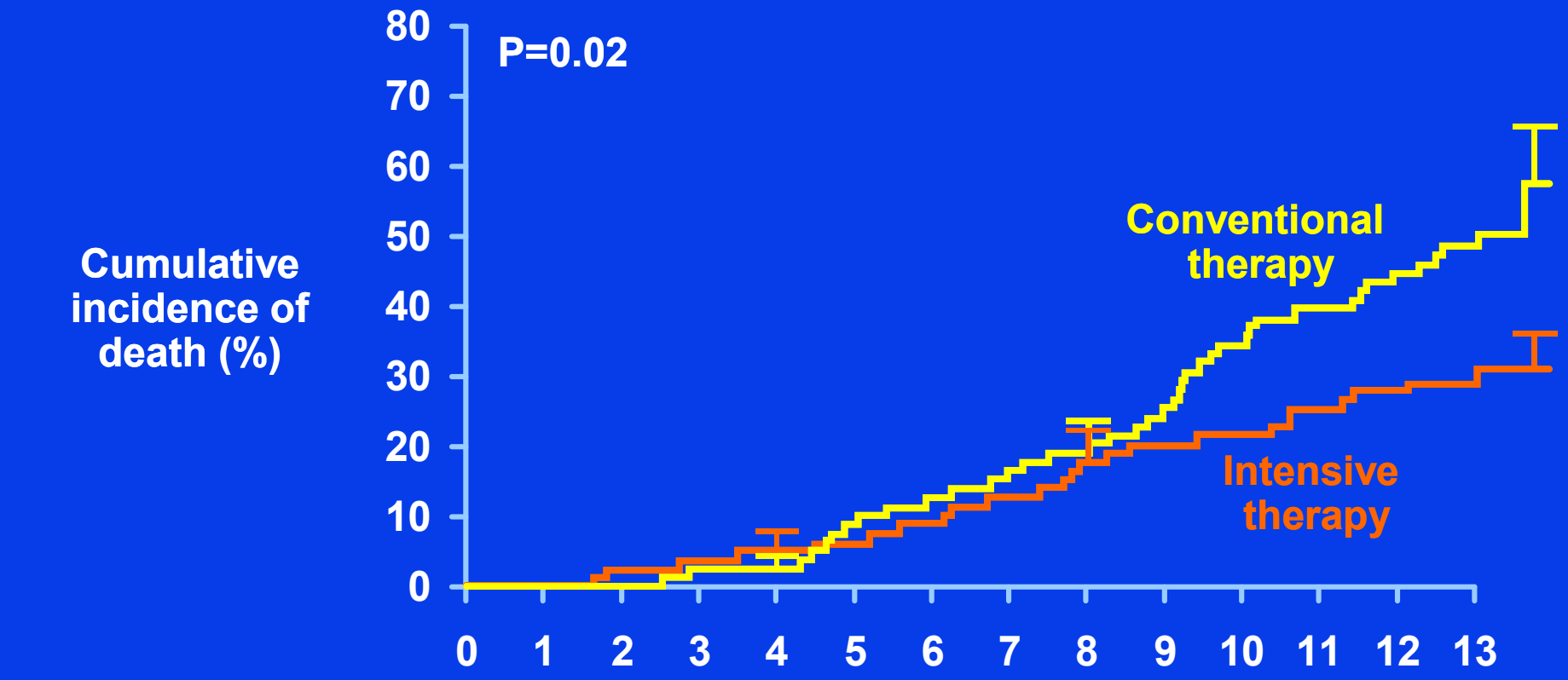
Medical therapy needs to be optimal, closely followed, specific metrics of treatment objectives

Mortality in Type 2 Diabetes Multifactorial Intervention

- STENO-2 study randomly assigned 160 patients with type 2 diabetes and micro-albuminuria to conventional therapy or intensive therapy
- Targets:
  - HAIC <6.5%
  - Cholesterol <175
  - Triglycerides <150
  - BP <130/80
- Approach – tight glucose regulation, RAS blockers, ASA, lipid lowering agents
- Primary endpoint all cause mortality at 13.3 yrs

Gaede P et al: N Engl J Med 358:580, 2008

Risk of Death



Numbers at risk

Intensive therapy	80	78	75	72	65	62	57	39
Conventional therapy	80	80	77	69	63	51	43	30

Gaede P et al: N Engl J Med 358:580, 2008

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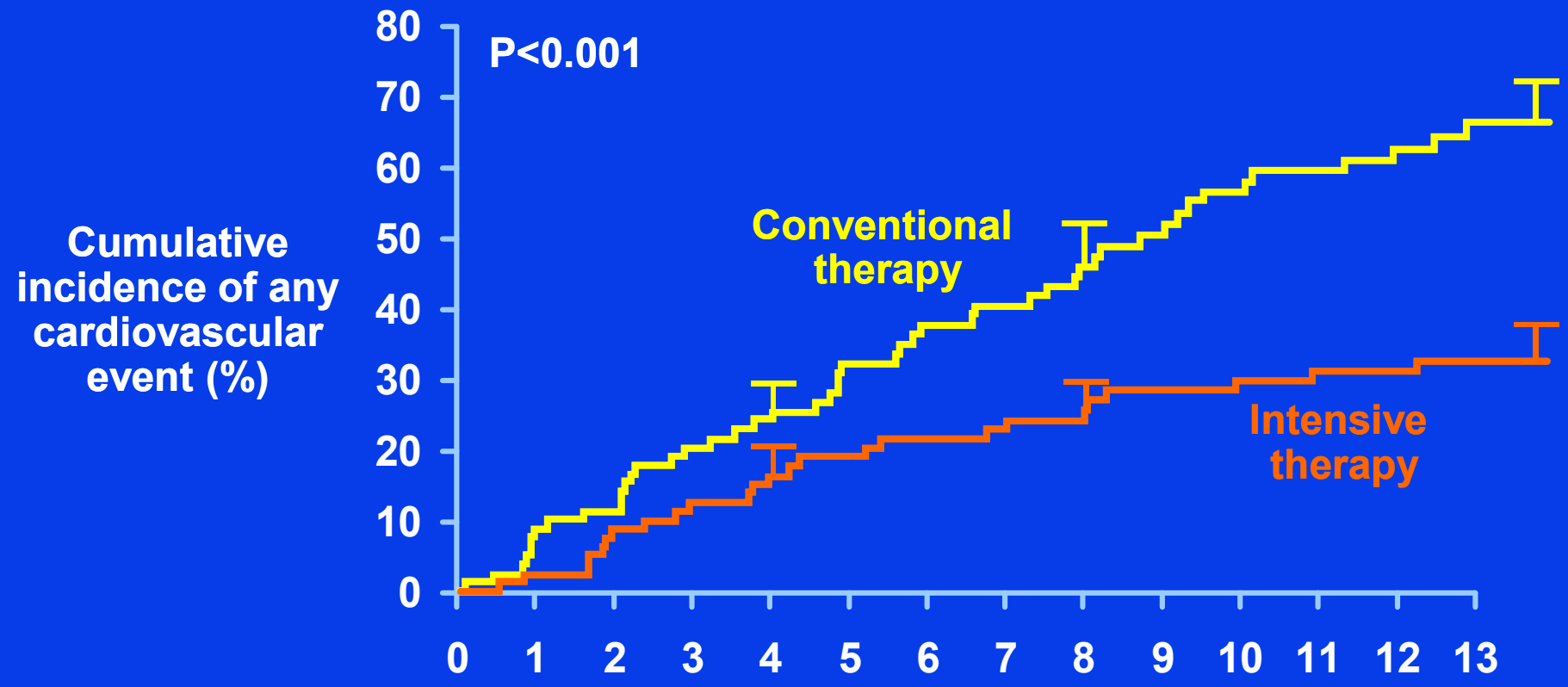
Risk of any cardiovascular event

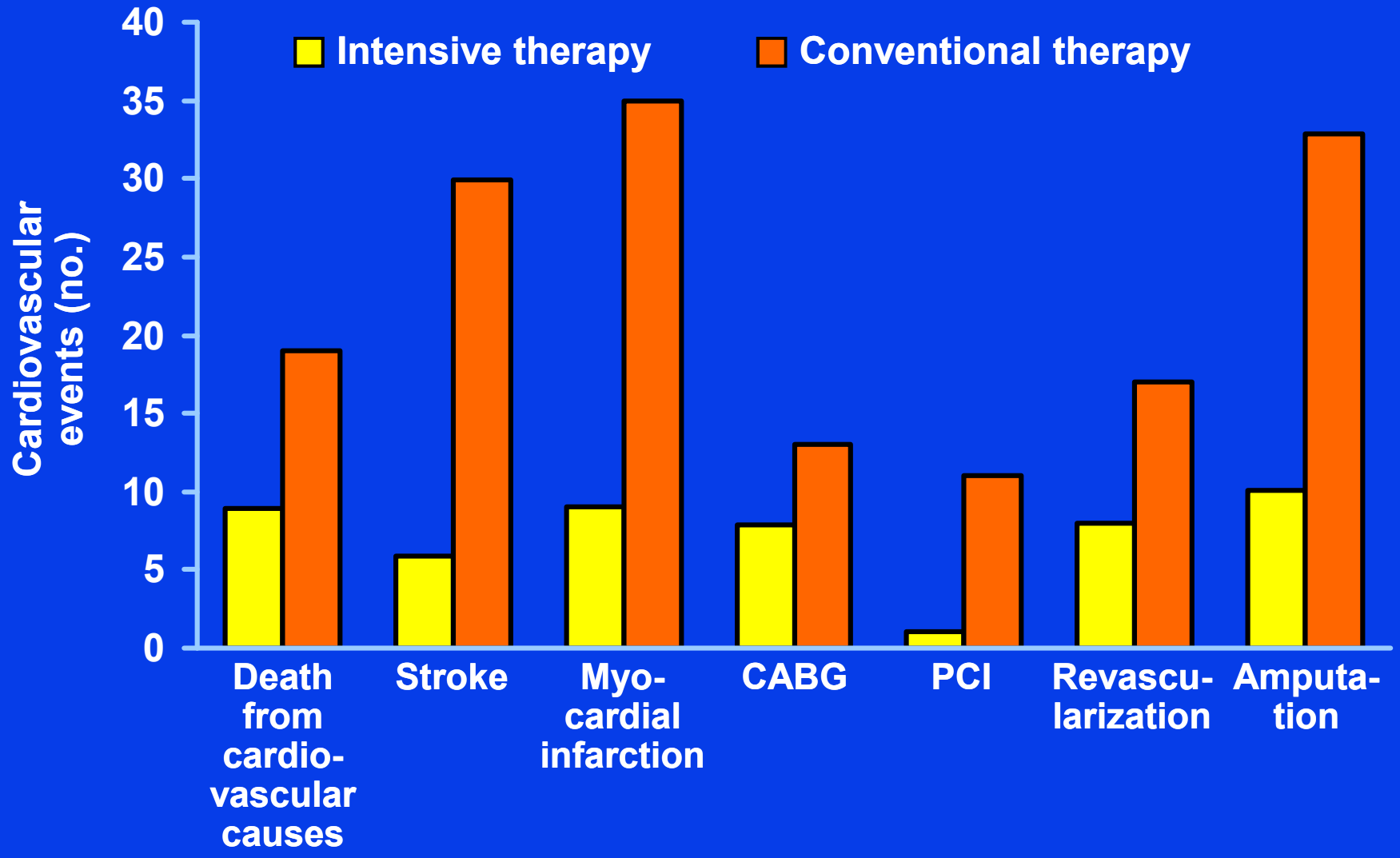


Numbers at risk

Intensive therapy	80	72	65	61	56	50	47	31
Conventional therapy	80	70	60	46	38	29	25	14

Gaede P et al: N Engl J Med 358:580, 2008

Risk of Death



Gaede P et al: N Engl J Med 358:580, 2008

Clinical Implications

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

BARI 2D

- Multicenter RCT 49 sites
- 2,368 patients with type 2 diabetes and stable CAD
- Randomization to revascularization (CABG or PCI) vs standardized medical therapy
- Primary endpoint – cardiovascular events

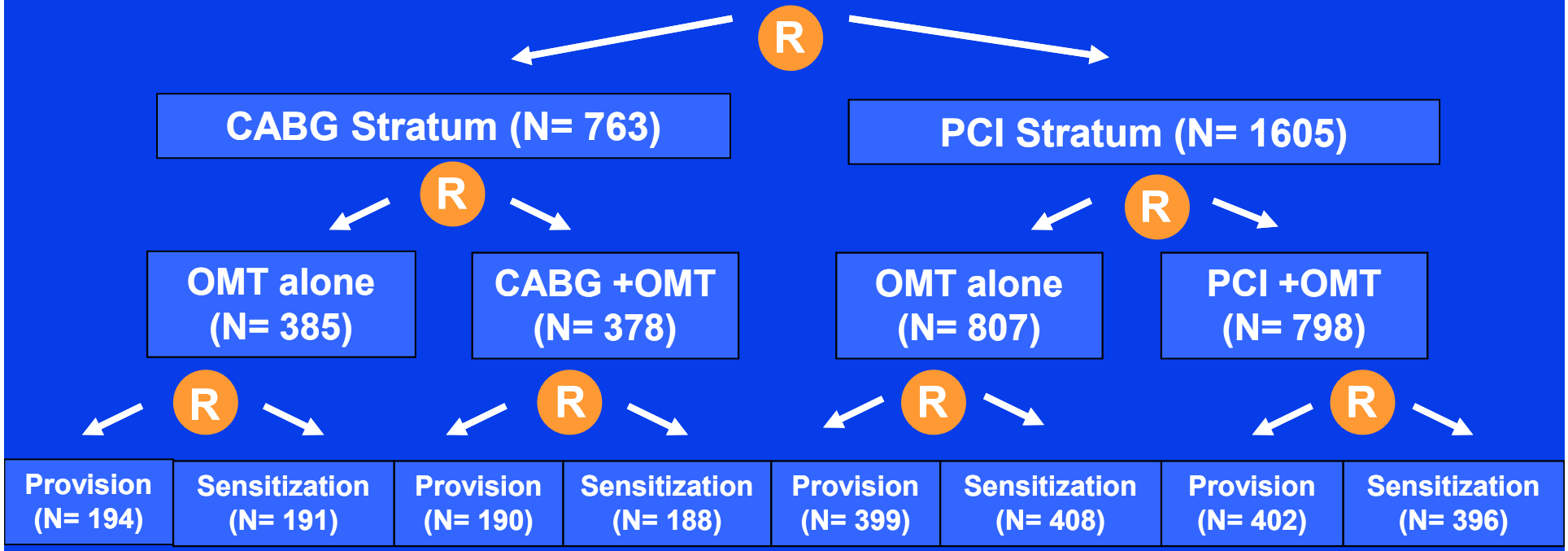
BARI 2D Study Group, Am Heart J 2008;156:528-536

What are the outstanding issues?

- Diabetes
- Acute myocardial infarction
- Chronic total occlusion
- LMCA or MVD
- Dual antiplatelet therapy

BARI 2D Trial: Study Design

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



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

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BARI 2D Study Group, NEJM 2009


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