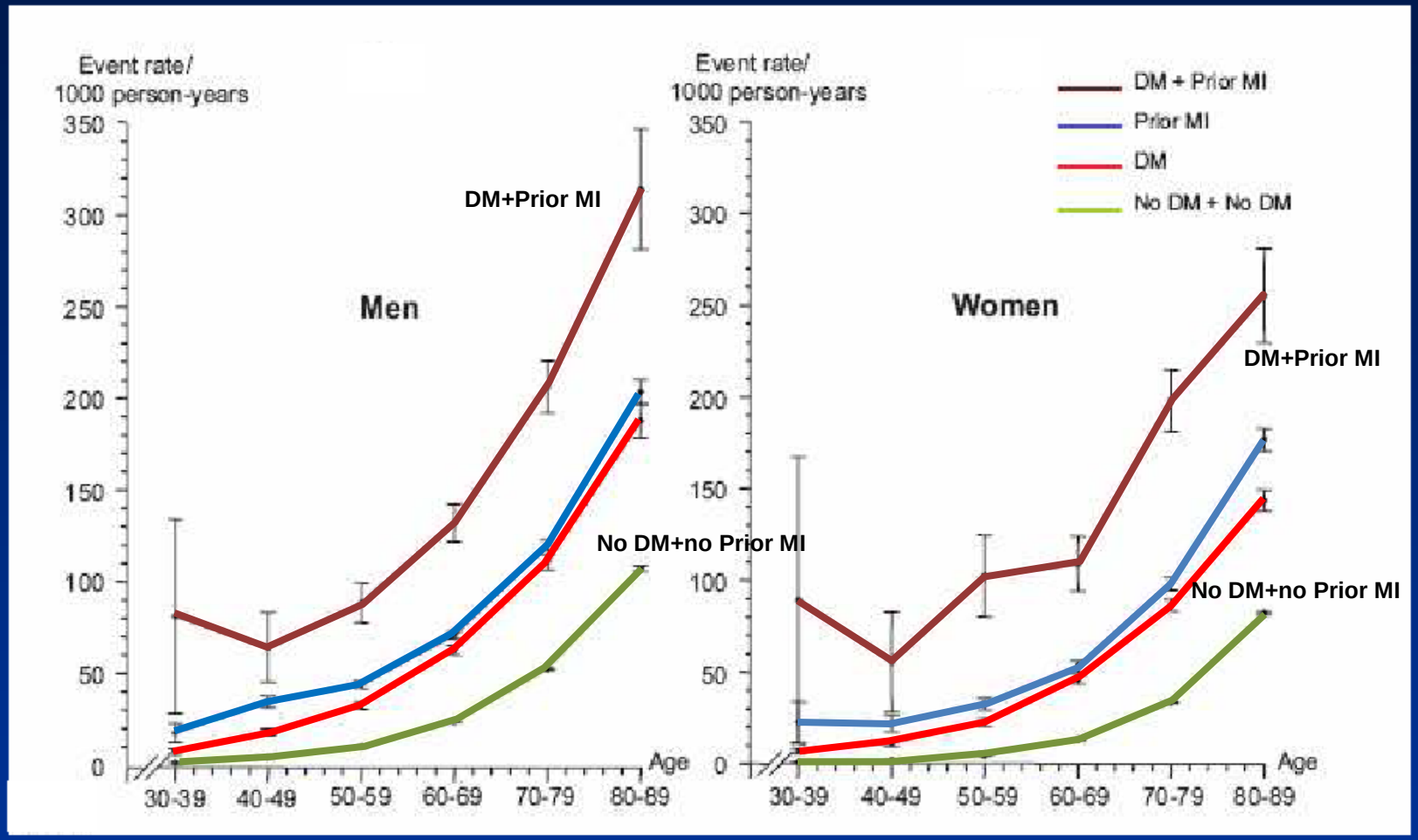
Αγγειοπλαστική σε διαβητικούς ασθενείς

Σταύρος Χατζημιλτιάδης
Αναπληρωτής Καθηγητής Καρδιολογίας
Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Νοσοκομείο ΑΧΕΠΑ

Risk of Cardiovascular Outcomes in Diabetics



Event rates for the composite end point of MI (nonfatal), stroke (nonfatal), and cardiovascular death in men and women stratified by age in relation to DM and a prior MI

Shramm TK et al Circulation. 2008:117:1945-54

Typical Features of Diabetic CHD

Necropsy findings

- Prevalent myocardial infarction (I ,II ↑)
- High-grade atherosclerosis
- Multivessel disease
- Frequent subclinical atherosclerosis

Angiographic findings

- Coronary calcification
- High prevalence of left main disease
- ↓Coronary collaterals
- ↑ACC/AHA Class C lesions

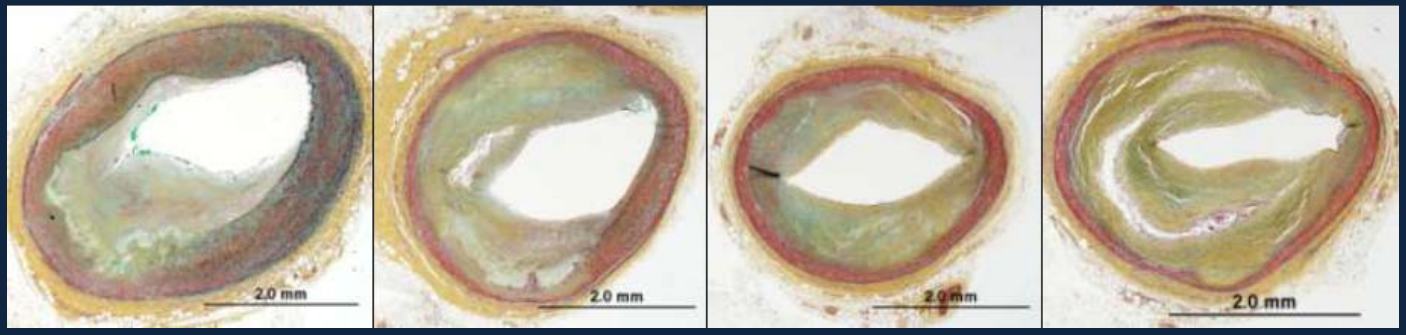
IVUS findings

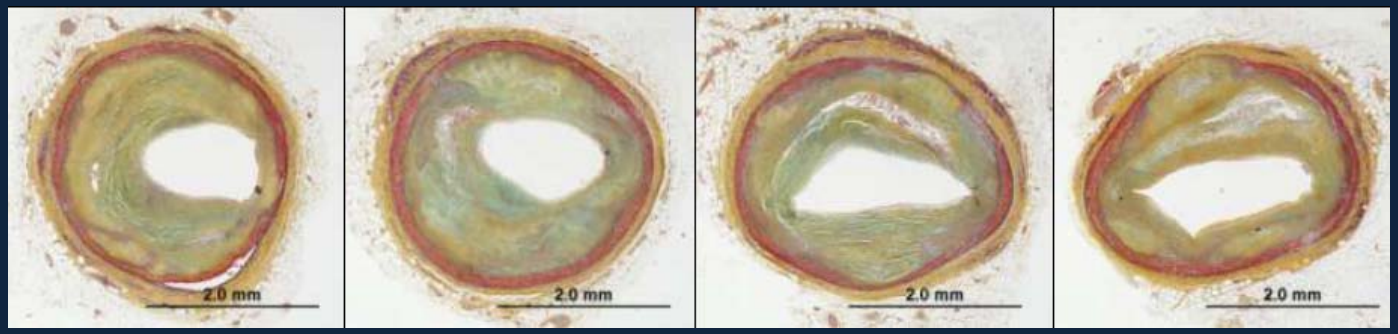
- Constrictive coronary remodeling ±
- Diffuse atherosclerosis

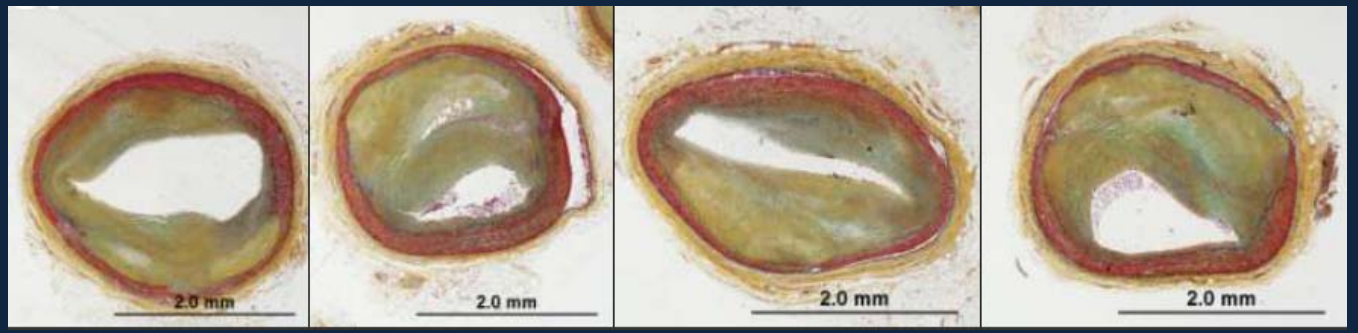
Diffuse long lesion in a diabetic patient (LAD)

PROX

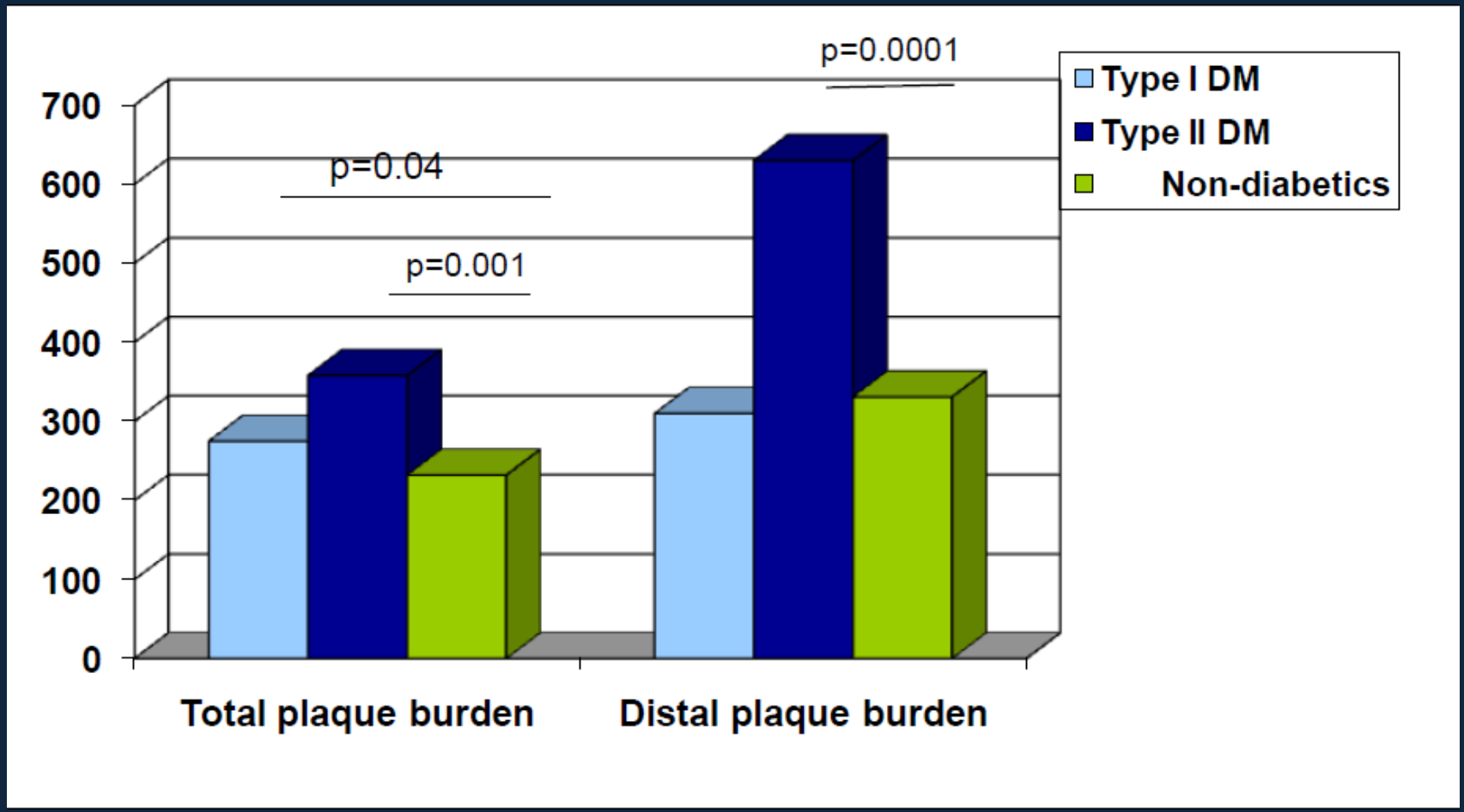
distal







Morphologic Findings of Coronary Atherosclerotic Plaques in Diabetics: A Postmortem Study

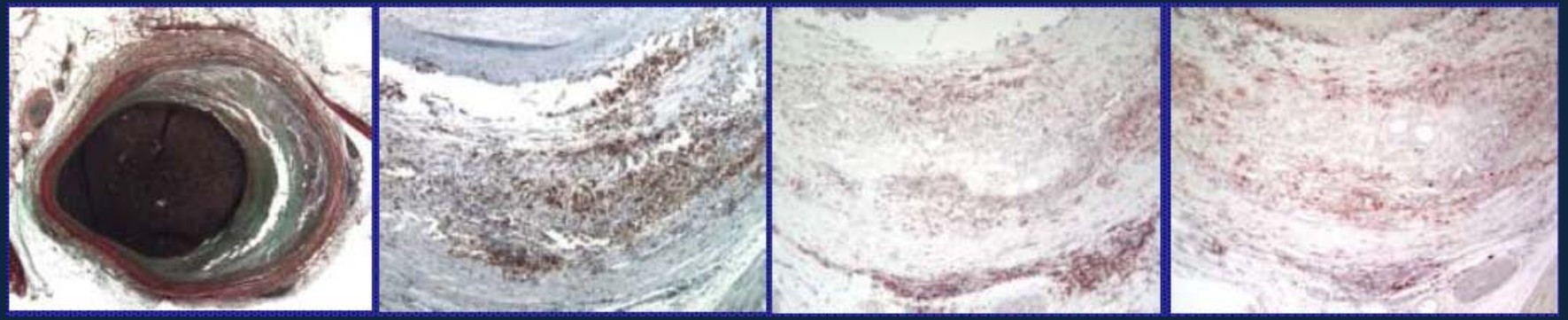


Burke A et al, Arterioscler Thromb Vasc Biol. 2004;24:1266-1271

Morphologic Findings of Coronary Atherosclerotic Plaques in Diabetics: A Postmortem Study

Insulin dependent

Glucose intolerant

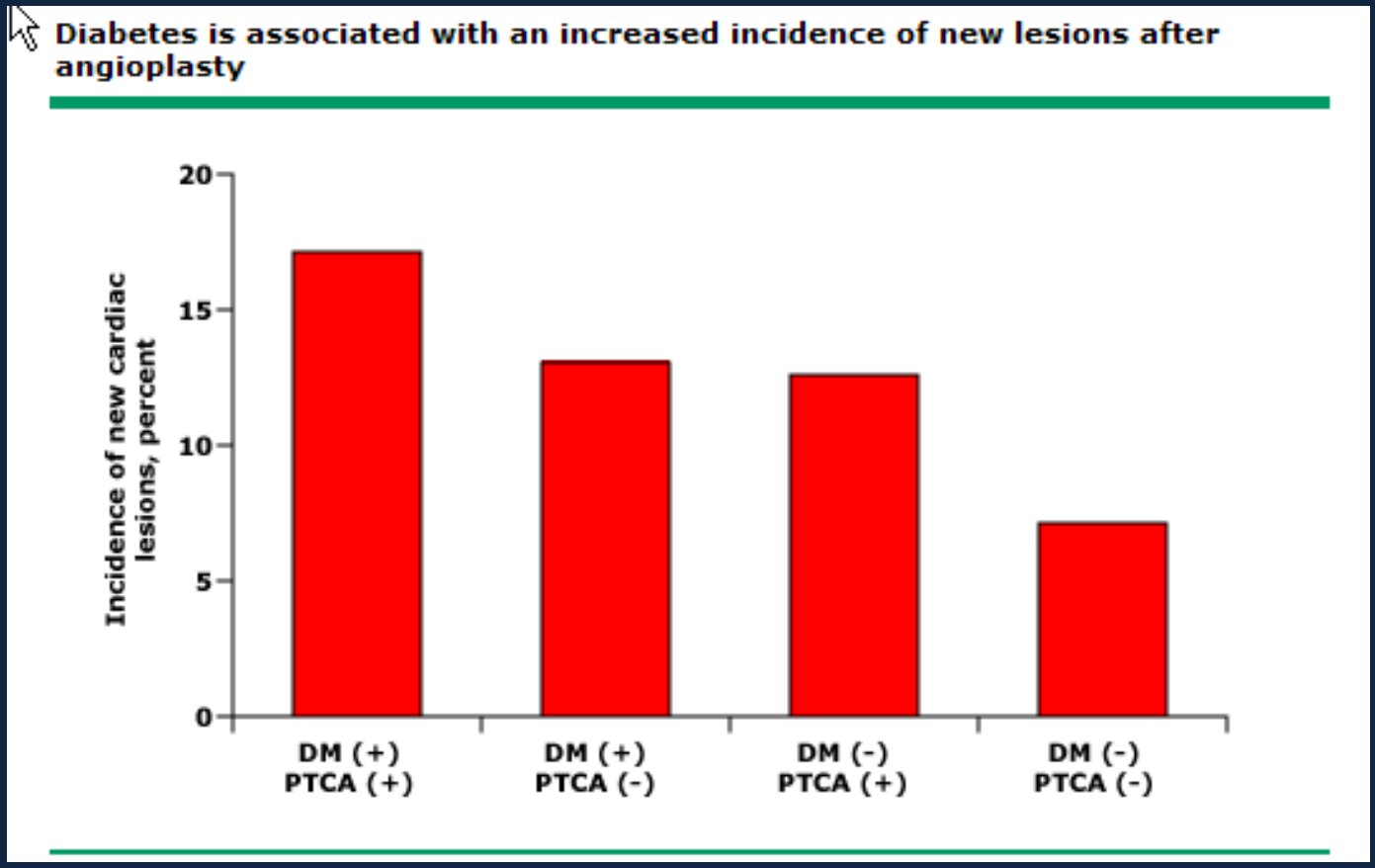


Non-Diabetic

Diabetes influence on platelet function and coagulation

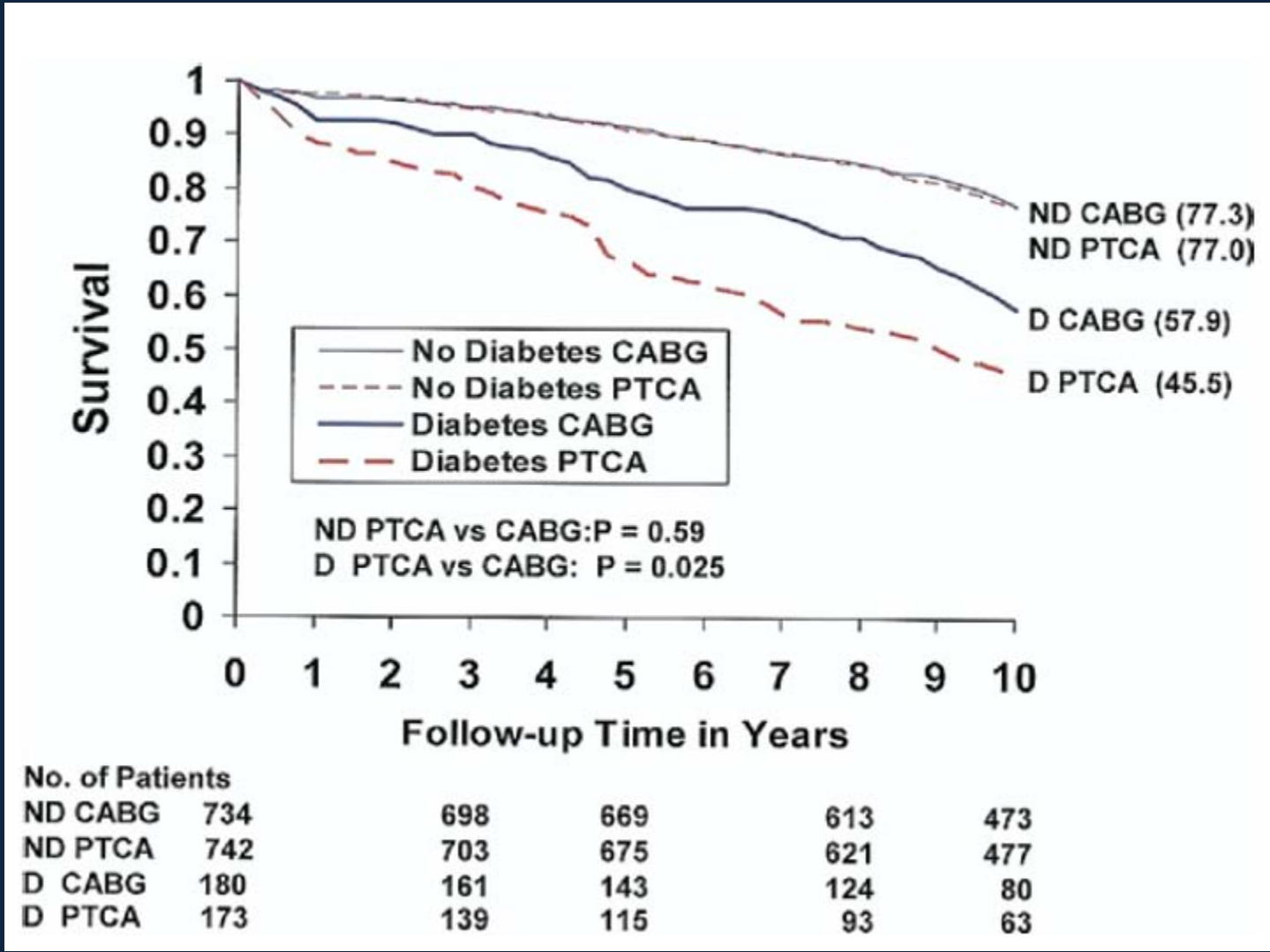
- Increased platelet reactivity
  - Osmotic effect of glucose on platelets.
- Enhanced inhibitory effects of GP IIb-IIIa antagonists
  - Platelet surface proteins exhibit glycation that parallels HbA1c.
  - Glycation of GP IIb-IIIa decreases the rate of binding of fibrinogen but not abciximab.
- Increased propensity to generate thrombin
  - the increased thrombin generation is associated with greater concentrations of insulin.

Long-term angiographic follow-up of coronary balloon angioplasty in patients with diabetes mellitus: a clue to the explanation of the results of the BARI study (Balloon Angioplasty Revascularization Investigation)



Rosenman Y et al, J Am Coll Cardiol, 1997; 30:1420-1425

BARI: 10 years survival in non-diabetics and diabetics (recruitment 1988 -1991)



J Am Coll Cardiol 2007;49:1600–6

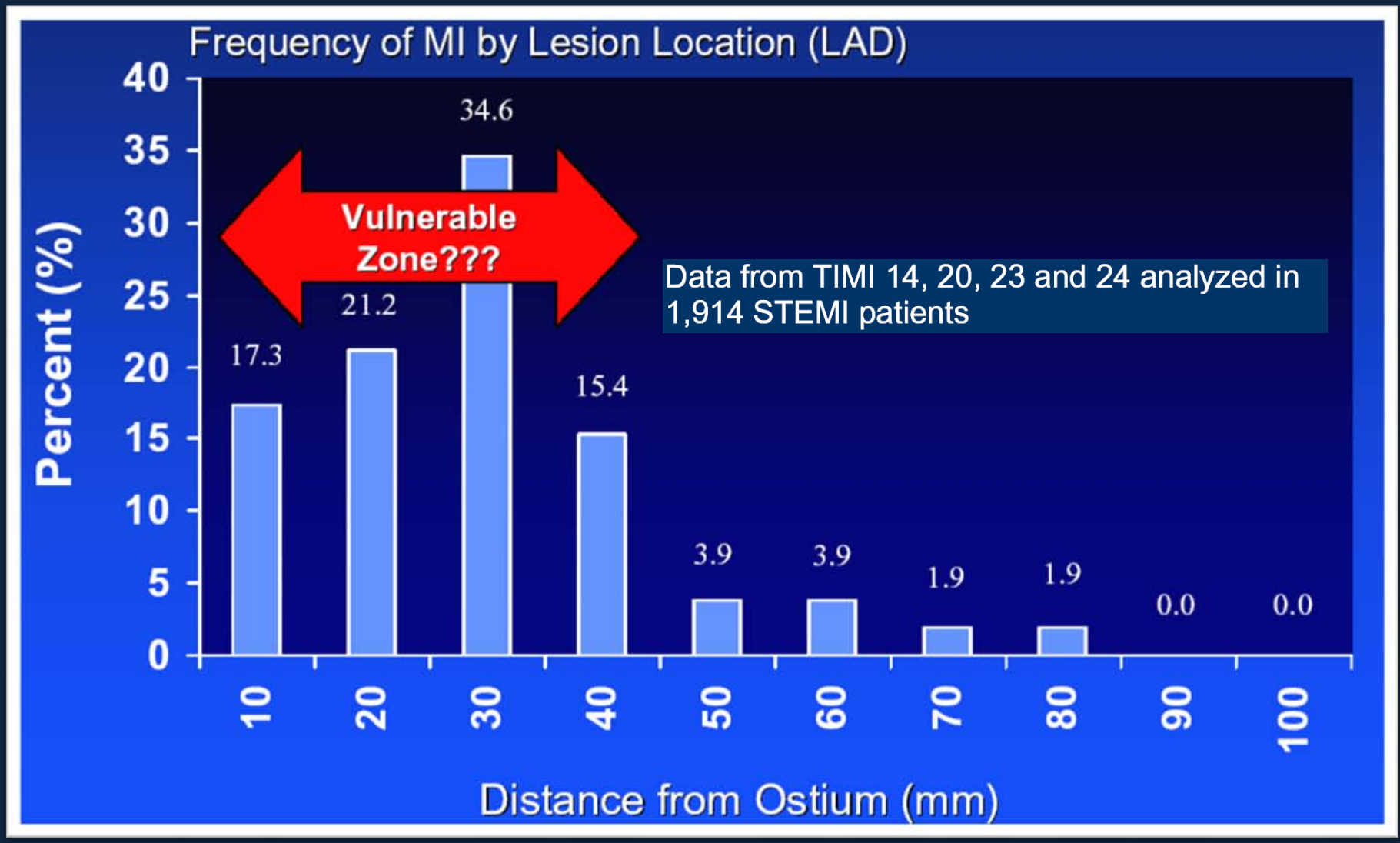
Myocardial infarction mortality in diabetic patients: a clue to the explanation of the results of the BARI study.

BARI RCT+ Registry

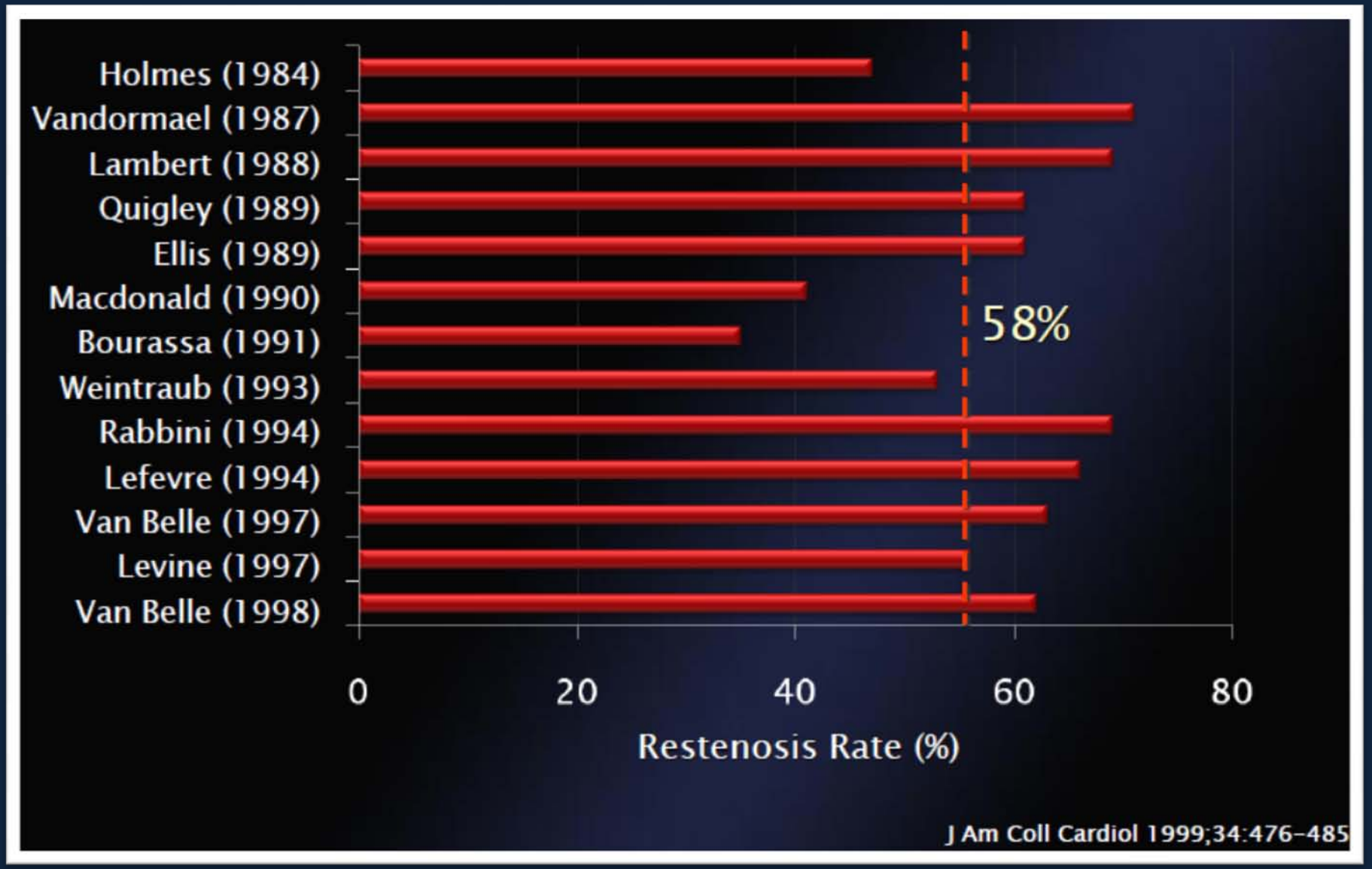
- No difference in *incidence* of MI after PTCA or CABG
- CABG pts have significantly improved long-term survival after Q-MI (HR=0.09, p<0.001)
- Suggests that more complete revasc after CABG may improve pt's tolerance of MI

Detre KM et al. NEJM 2000;342:989-97

Beyond restenosis: lesion location

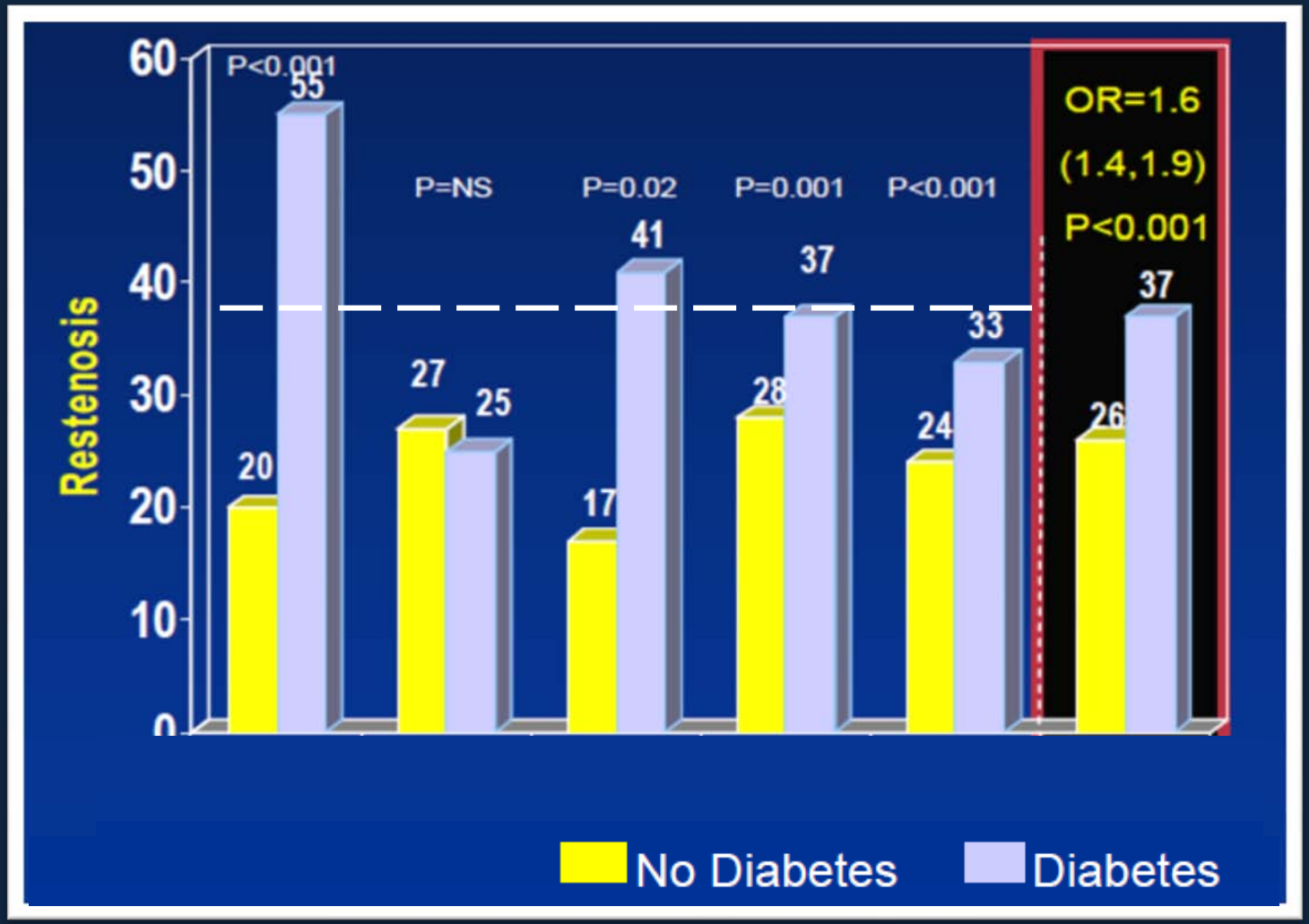


58% Average Restenosis Rate in Diabetes Following POBA



BMS and diabetes

Restenosis Remains Increased



* Data presented by Carrozza ESC 2007 **Elezi S, Kastrati A, Pache J, et al. JACC. 1998;32(7):1866-1873

*** Kornowski R, Mintz GS, Kent KM, et al. *Circulation. March 18, 1997 1997;95(6):1366-1369*

DES and diabetes

Data from small randomized trials including only diabetic pts

Diabetes 1 trial 360 pts, 9 month Fup

	BMS vs	Cypher	
TLR	31.3%	7.3%	p<0.05

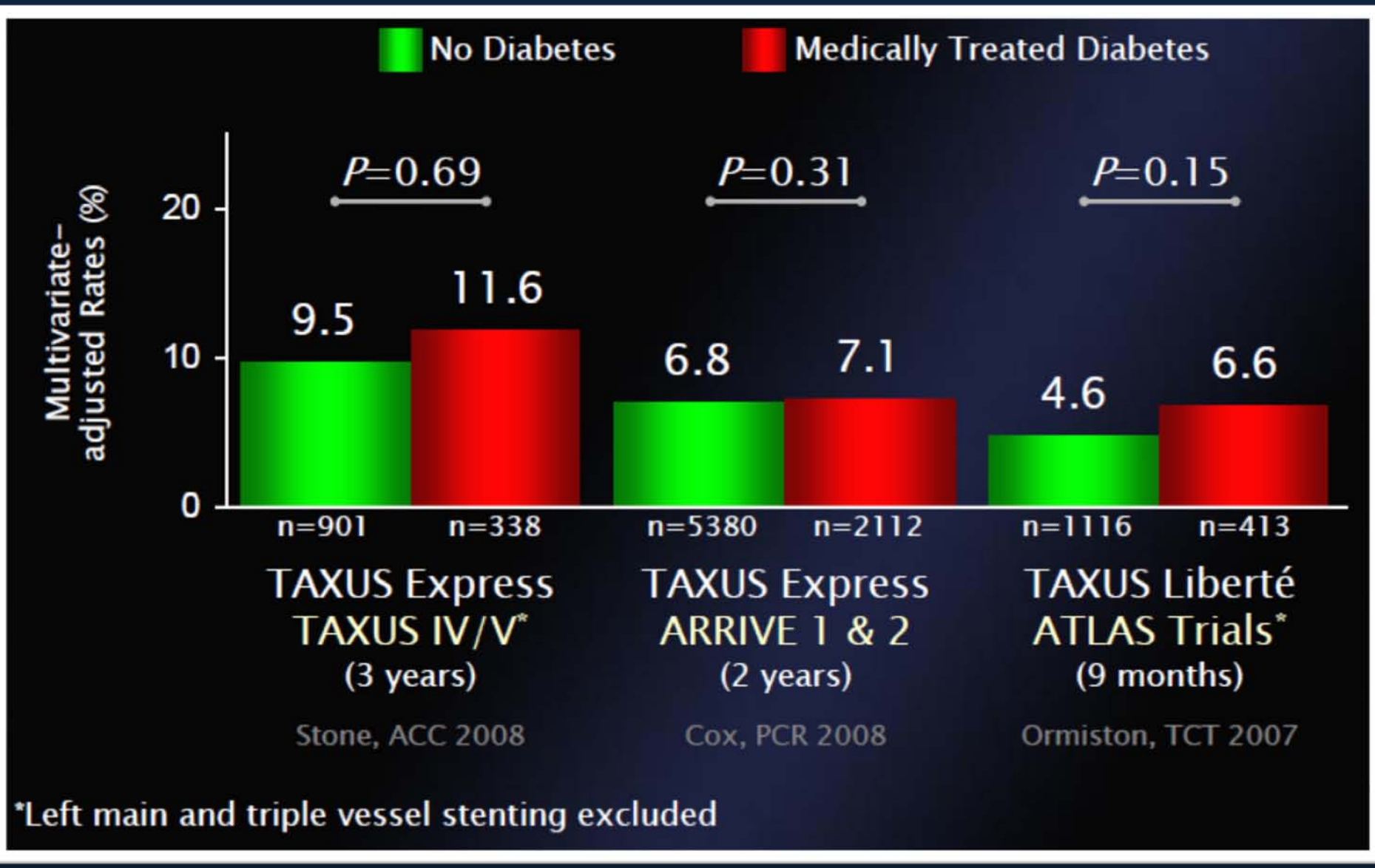
Scorpius 200 pts, 8 month Fup

	BMS vs	Cypher	
TLR	25% vs	5.3%	p<0.05

ISAR diabetes 250 pts, 6 month Fup

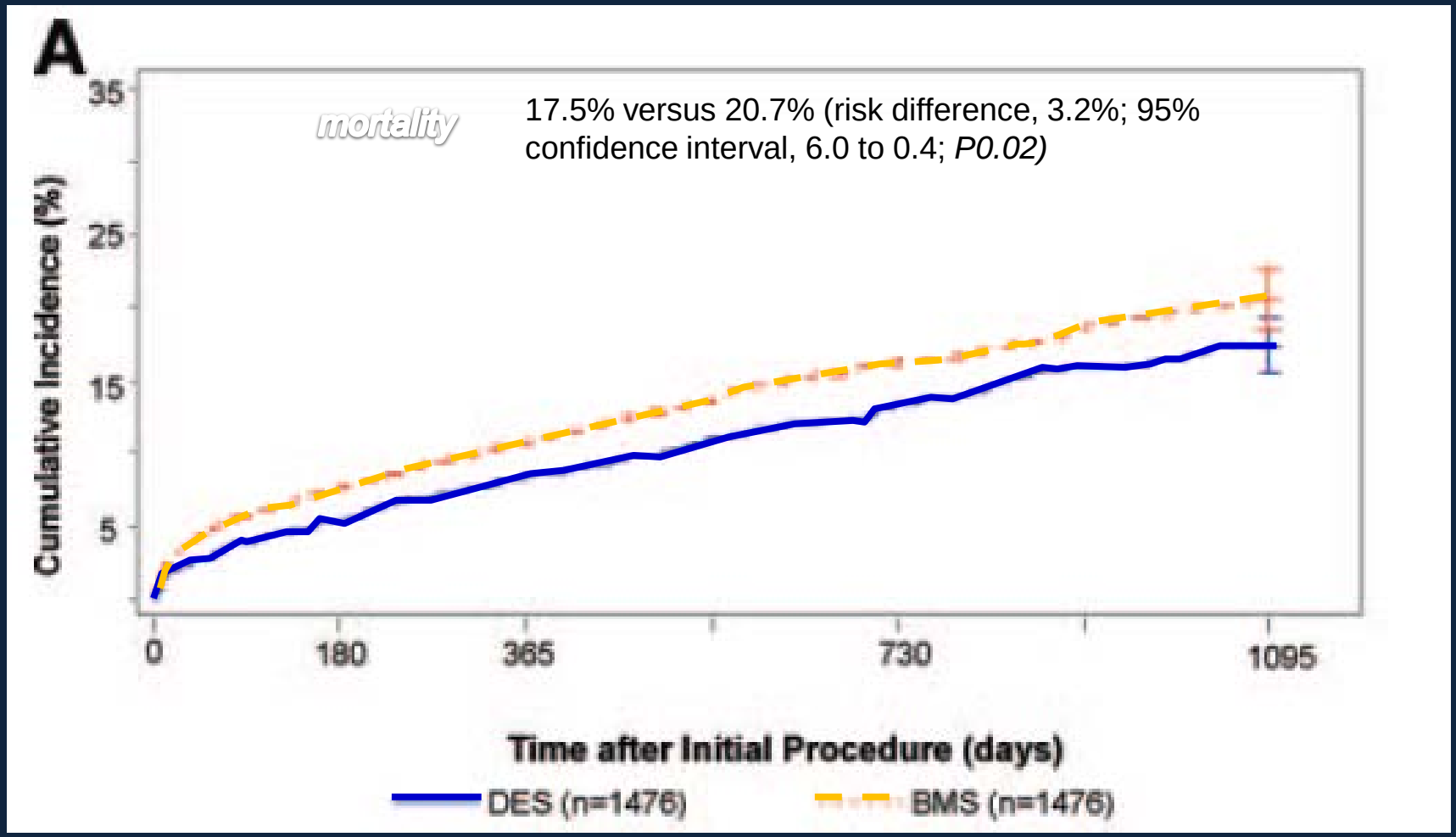
	Taxus vs	Cypher	
TLR	12% vs	6%	p= ns

Comparable TLR in Diabetics and Non-Diabetics in TAXUS Studies



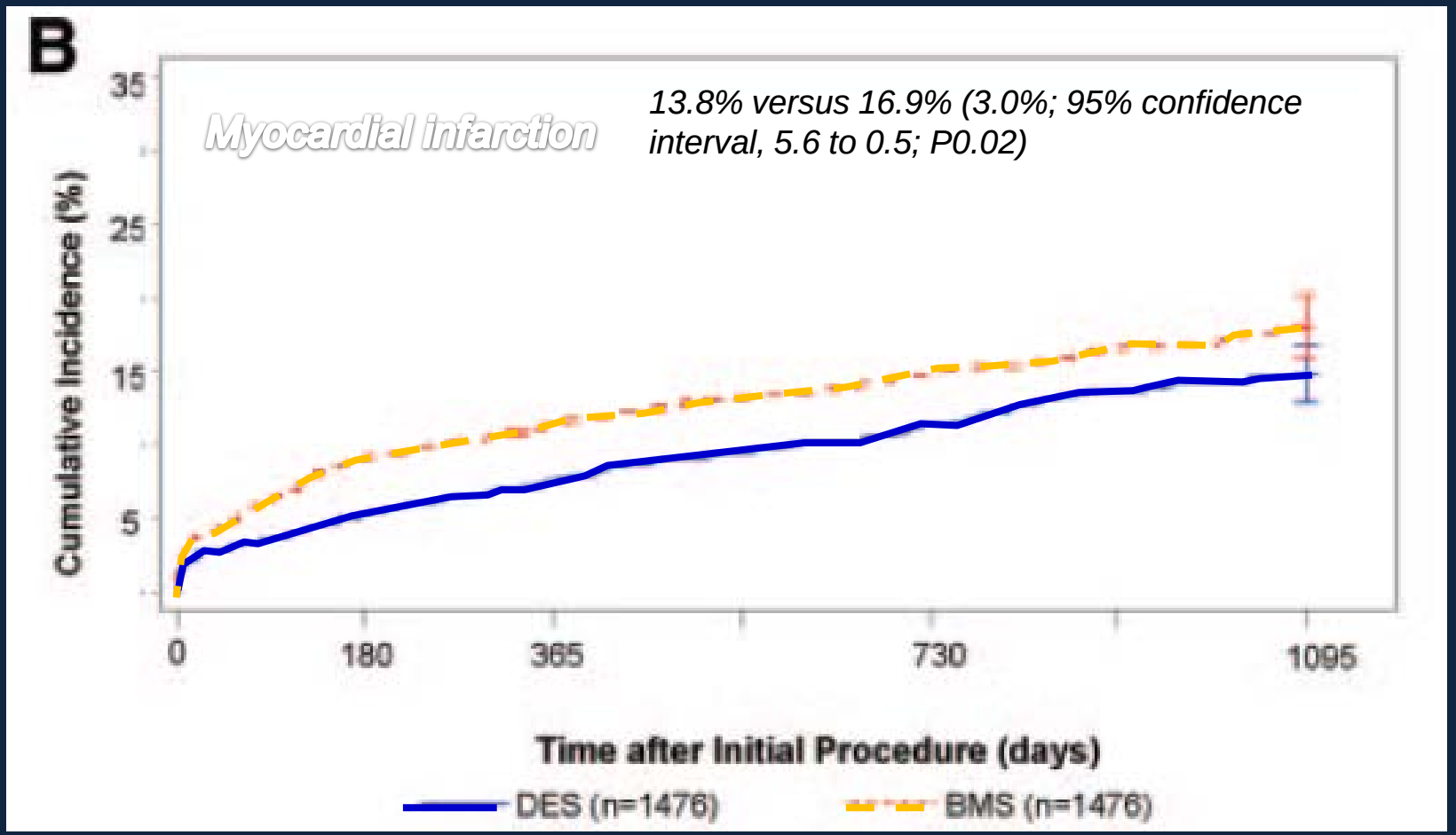
DES or BMS in Patients With Diabetes Mellitus

Mandatory Massachusetts Data Analysis Center Registry (Based on propensity-score analysis of 1:1 matched DES versus BMS patients (1476 DES:1476 BMS))



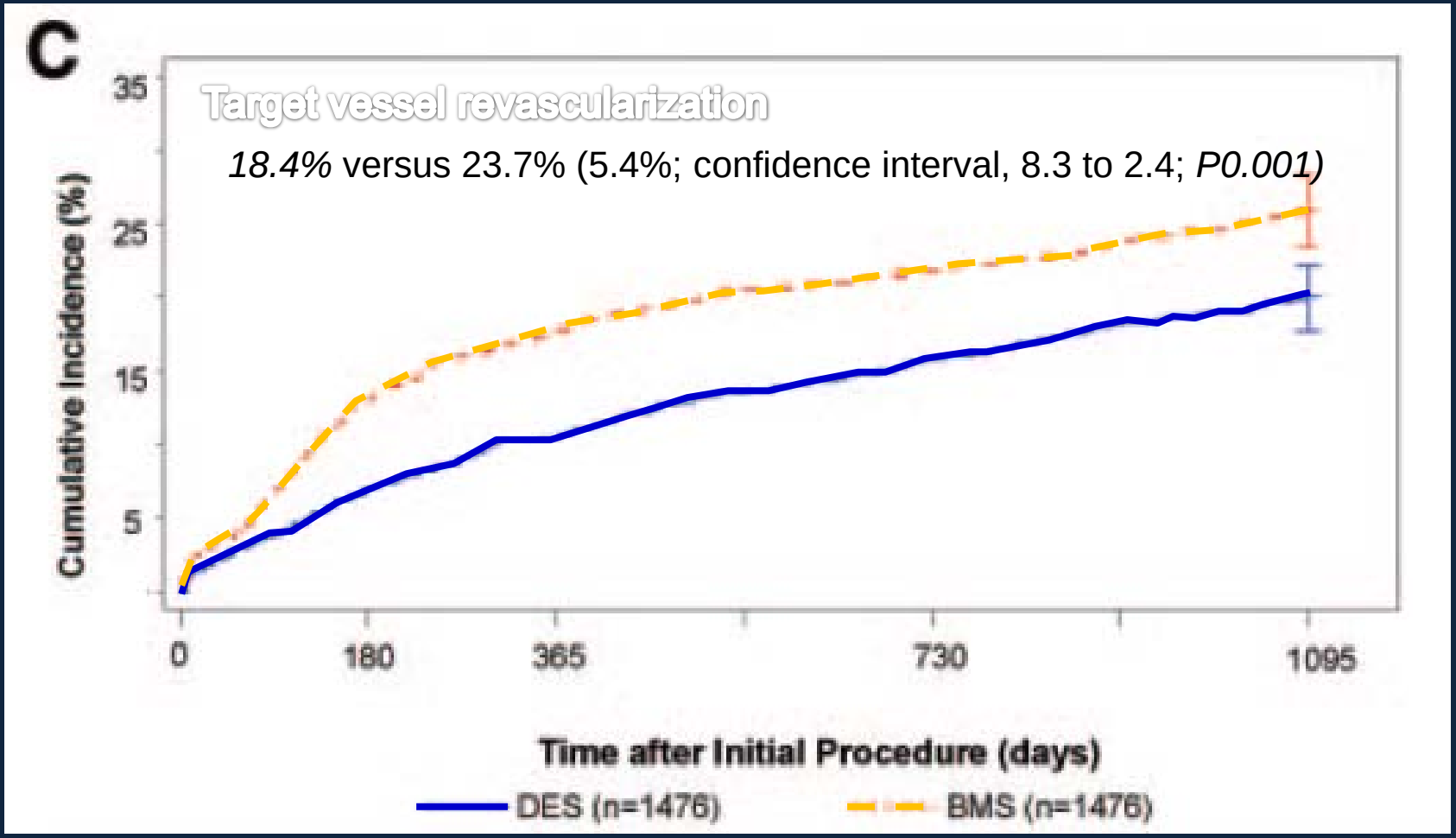
Mauri, Circulation. 2008;118

DES or BMS in Patients With Diabetes Mellitus



Mauri, Circulation. 2008;118

DES or BMS in Patients With Diabetes Mellitus



Mauri, Circulation. 2008;118

Drug-Eluting Stent Thrombosis: Results From the Multicenter Spanish Registry ESTROFA (Estudio ESpañol sobre TROmbosis de stents FArmacoactivos)

The cumulative incidence was 2% at 3 years

Of 23,500 patients treated with DES, definite stent thrombosis (ST) developed in 301: 24 acute, 125 subacute, and 152 late. Of the late, 62 occurred >1 year (very late ST).

Table 4 Multivariate Analysis for Predictors of ST in a Subgroup of 14,120 Patients

Predictor	Hazard Ratio	95% Confidence Interval	p Value
Acute-subacute ST			
ACS	2.6	1.3–4.9	0.0027
STEMI	6.9	4–12	<0.0001
Renal failure	3.1	1.05–9.2	0.038
Diabetes	1.75	1.04–2.95	0.035
Stent length	1.08	1.06–1.1	0.0001
LAD	2.2	1.4–3.7	0.0011
Late ST			
STEMI	5.2	5.5–7.6	<0.0001
LAD	3.03	2.07–4.4	<0.0001
Stent length	1.07	1.05–1.09	<0.0001

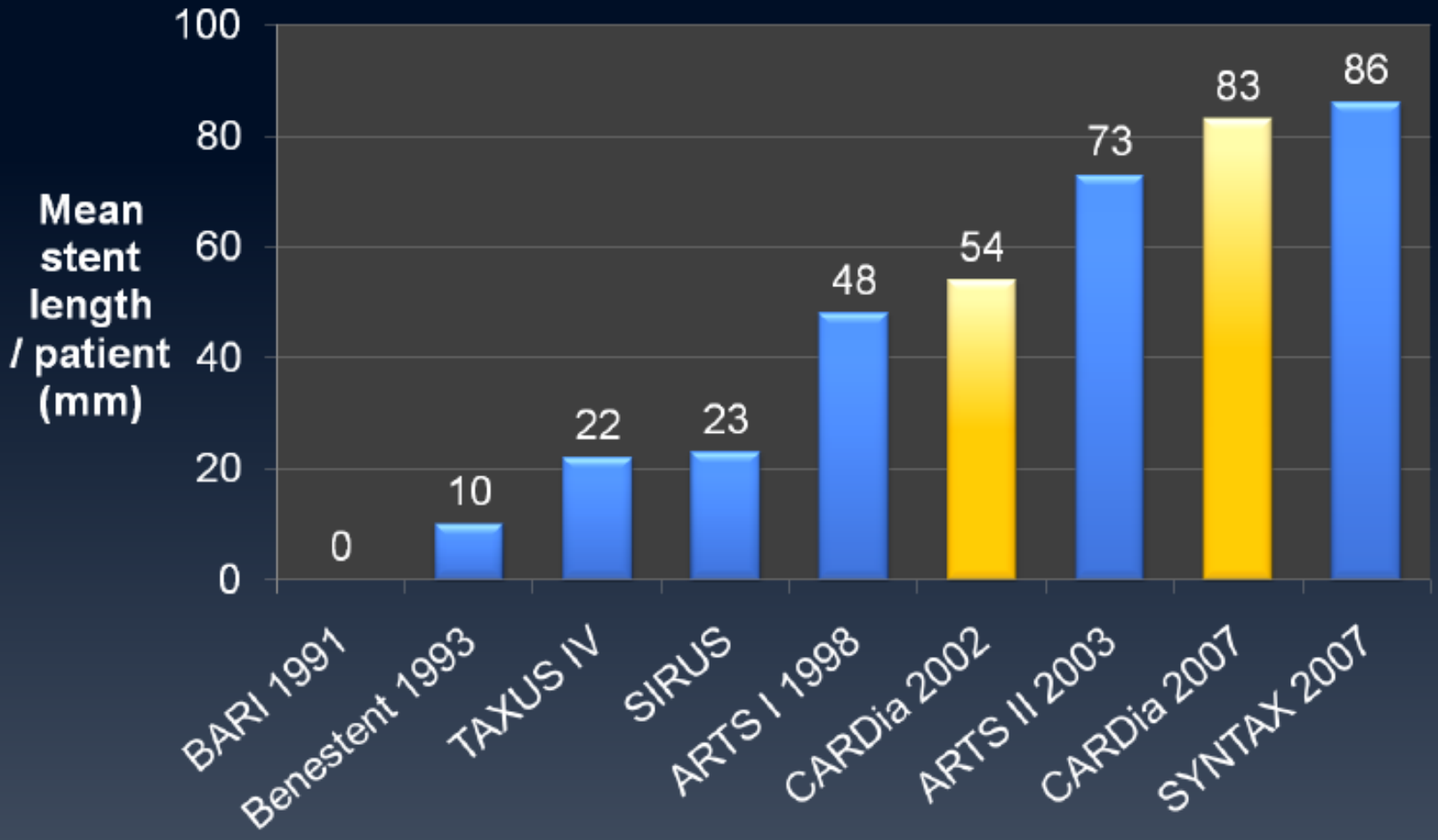
J Am Coll Cardiol 2008;51:986–90

CABG vs DES in Patients with Multivessel Disease and Diabetes

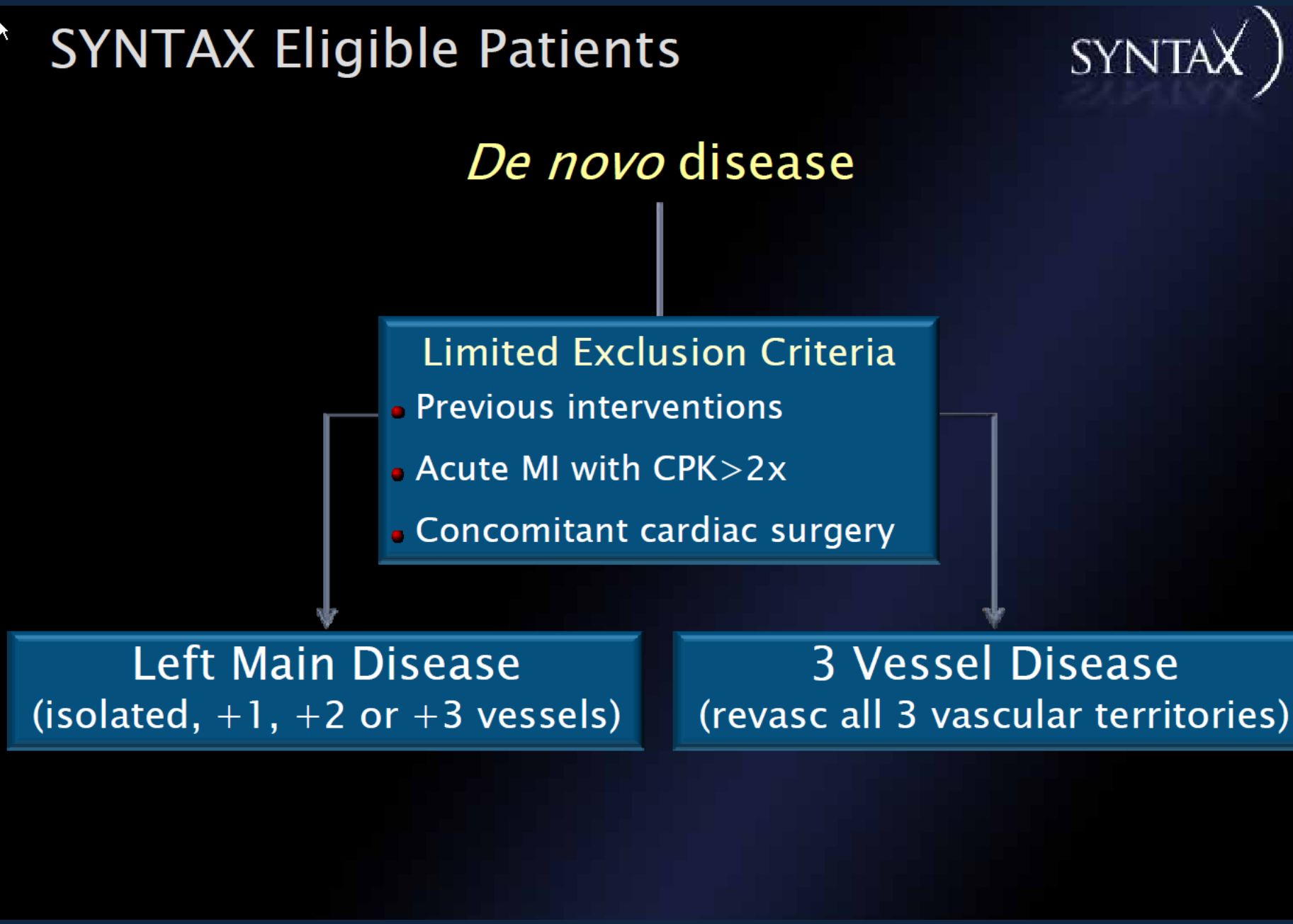
Name	N (DM pts)	Design		DES Type (%)	Death	Revasc	CVA
ARTS I/II*	255	Reg.	MVD	SES 100%	=	DES ↑	DES ↓
Ben-Gal 06	518	Reg.	SVD & MVD	SES 100%	NR	DES ↑	NR
Briguori 07	218	Reg.	SVD & MVD	SES 67, PES 33%	=	DES ↑	=
Lee 07	205	Reg.	MVD	SES 75, PES 11%	=	DES ↑	DES ↓
Mack 08	1450	Reg.	SVD & MVD	DES 73.1%	=	DES ↑	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%	?	?	?

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

Increase in stent usage reflecting increase in patient complexity



SYNTAX Eligible Patients



Procedural Characteristics
PCI Randomized Cohort

SYNTAX

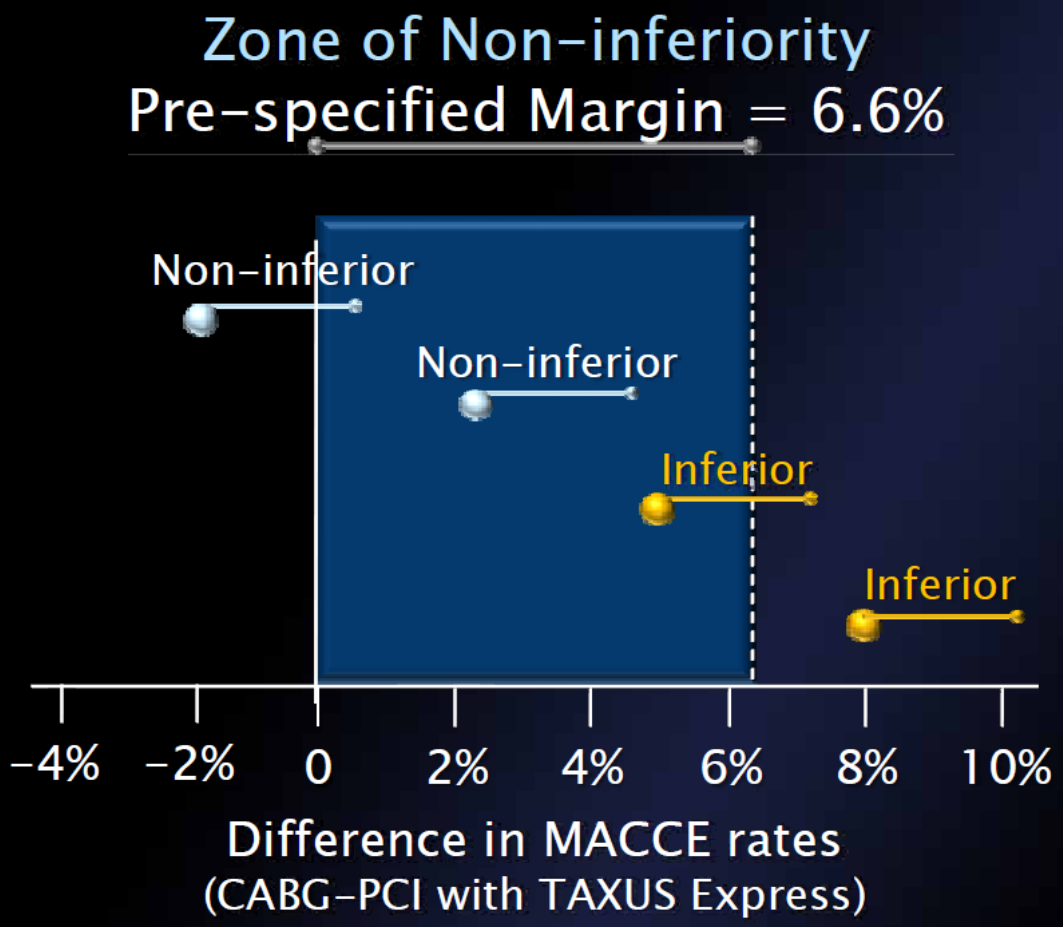
Patient-based	TAXUS N=903
Staged procedure, %	14.1
Lesions treated/pt, mean ± SD	3.6 ± 1.6
No. stents implanted, mean ± SD	4.6 ± 2.3
Total length implanted, mm ± SD	86.1 ± 47.9
Range, mm	8 – 324
Long stenting (>100 mm), %	33.2

Procedural Characteristics
CABG Randomized Cohort

SYNTAX

	CABG N=897
Off-pump surgery, %	15.0
Graft revascularization, %	
At least one arterial graft	97.3
Arterial graft to LAD	95.6
LIMA+venous	78.1
Double LIMA/RIMA	27.6
Complete arterial revascularization	18.9
Radial artery	14.1
Venous graft only	2.6
Grafts per patient, mean • •SD	2.8 ± 0.7
Distal anastomosis/pt, mean • •SD	3.2 ± 0.9

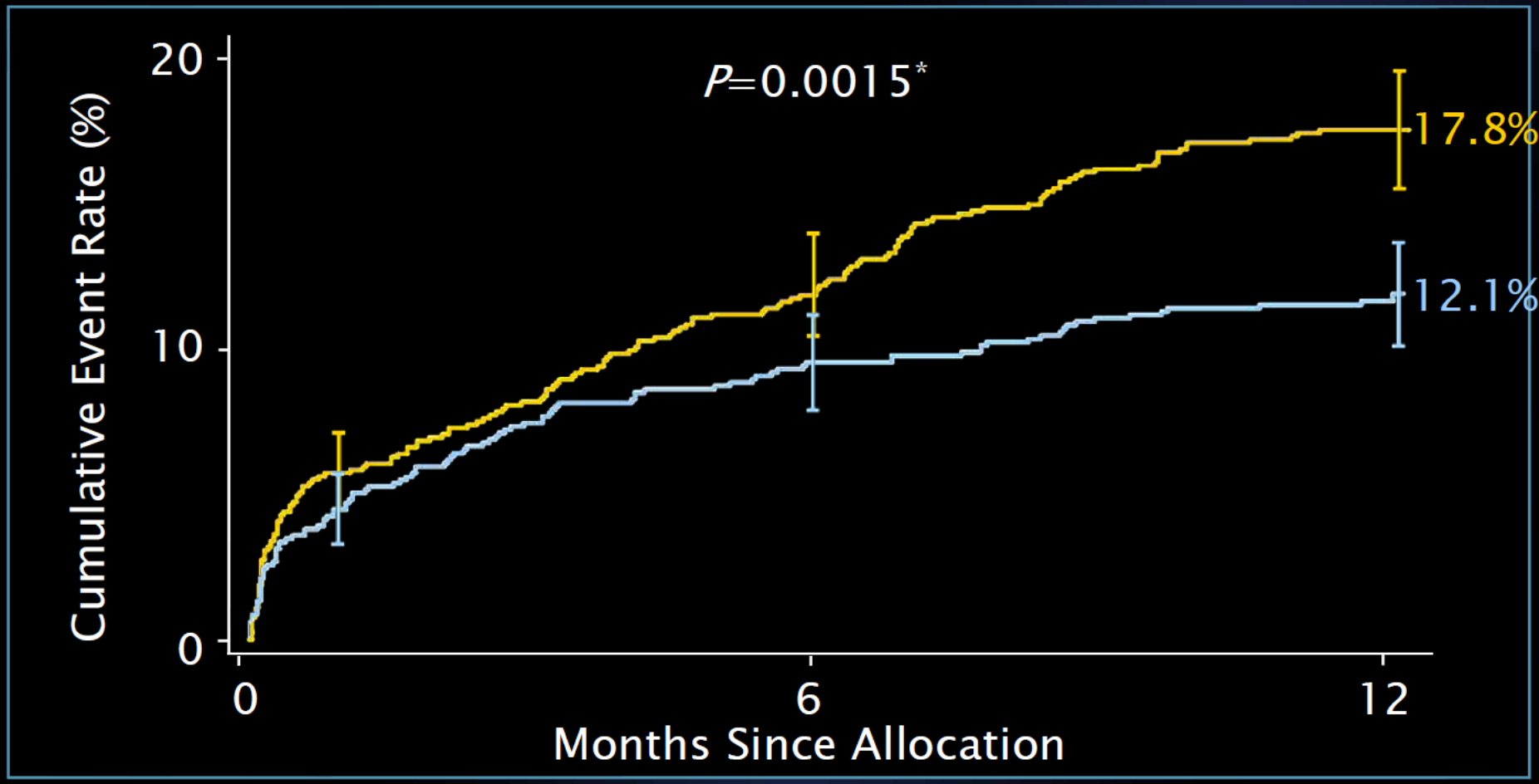
Primary Endpoint (12 Month MACCE)
Non-inferiority to CABG



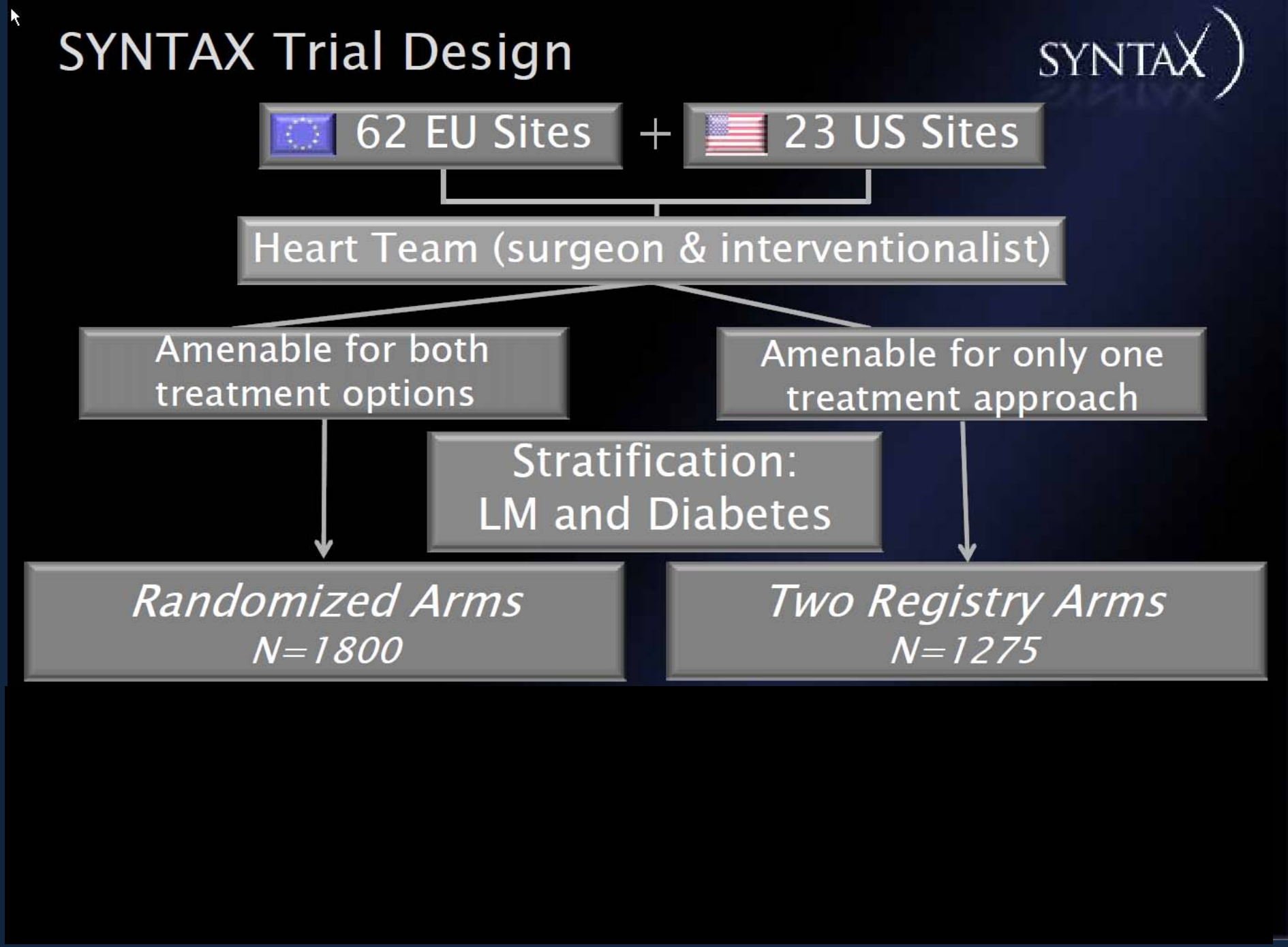
MACCE to 12 Months

SYNTAX

CABG (N=897) TAXUS (N=903)

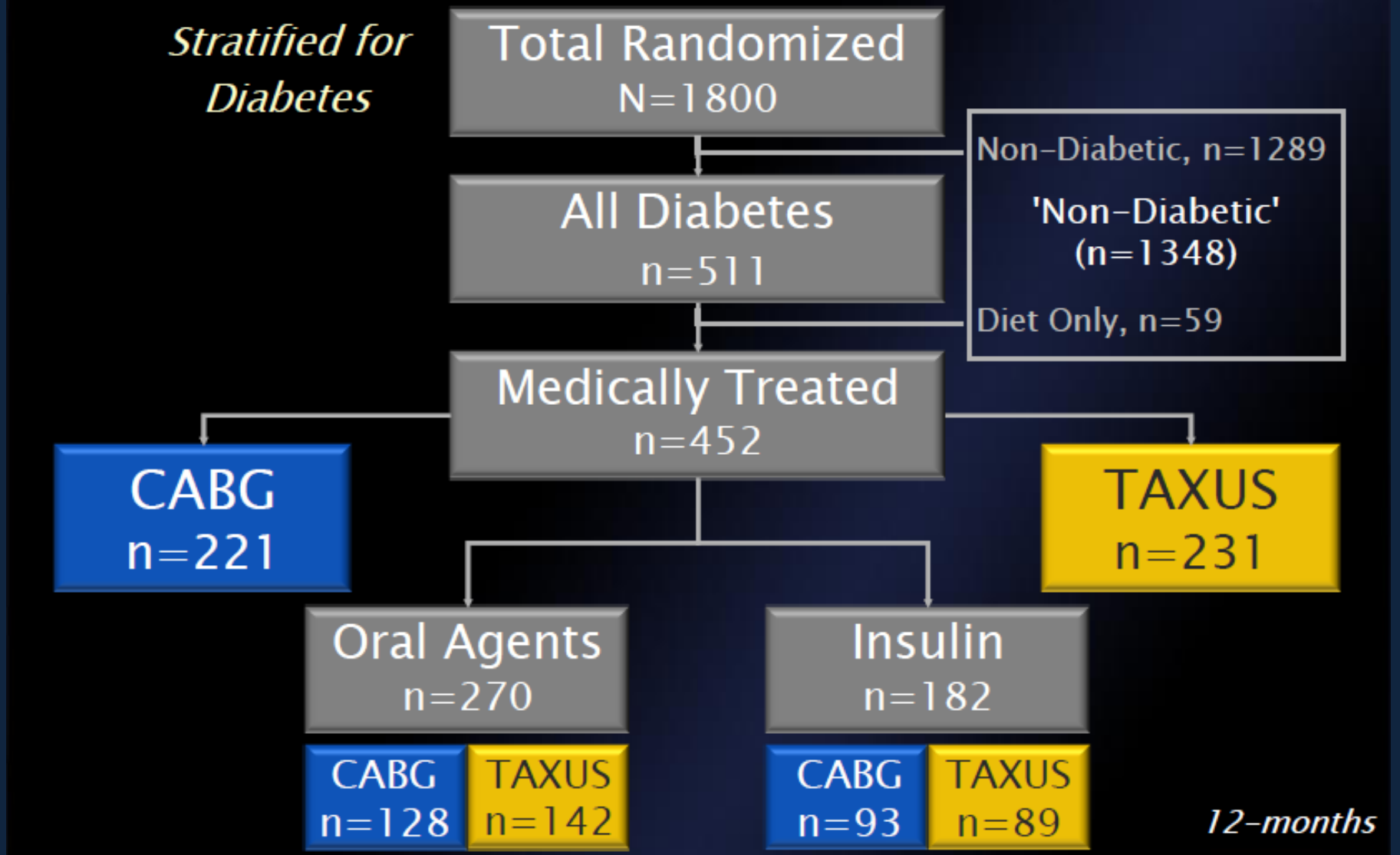


SYNTAX Trial Design



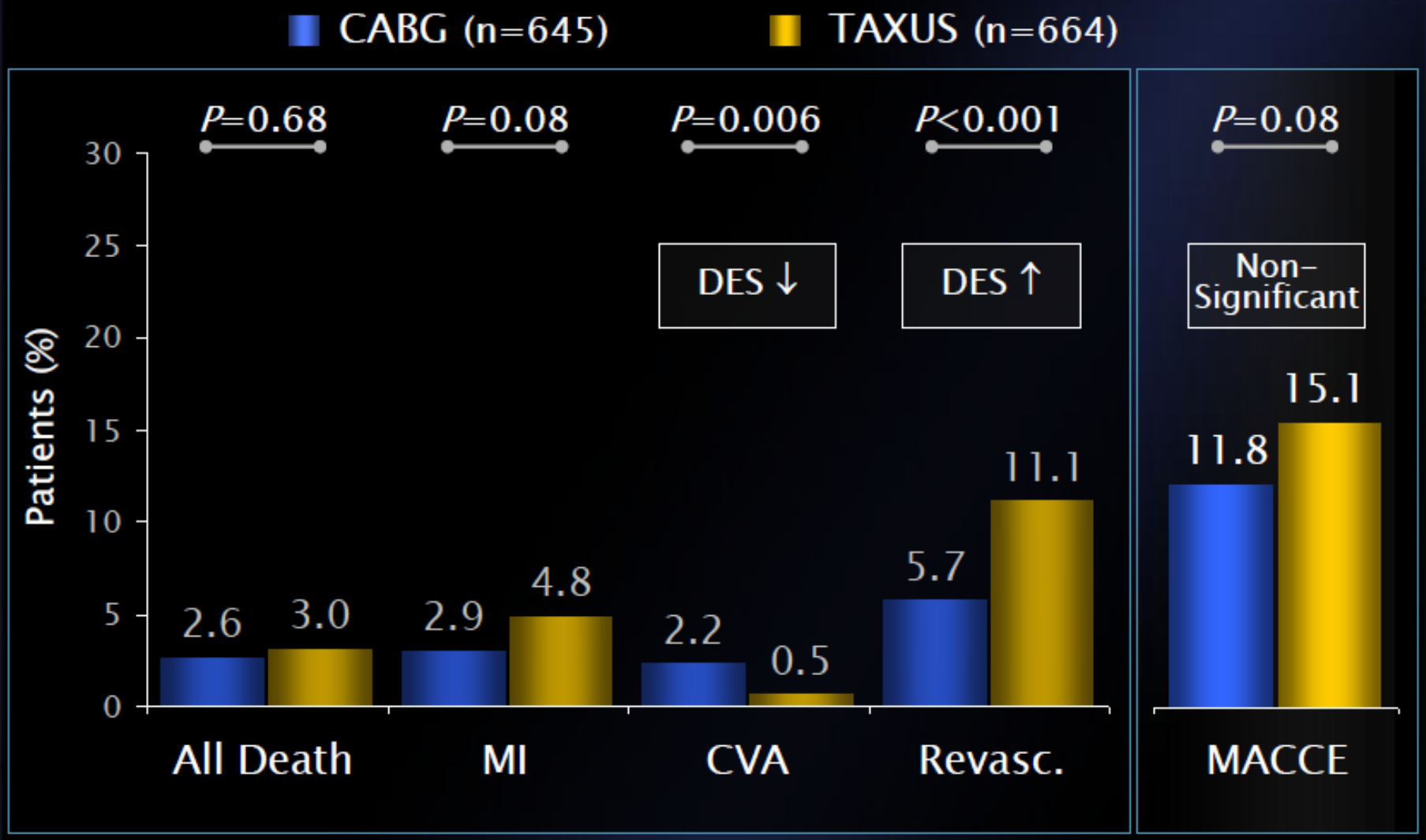
Patients with Diabetes in SYNTAX

Randomized Cohort, Intent-to-Treat



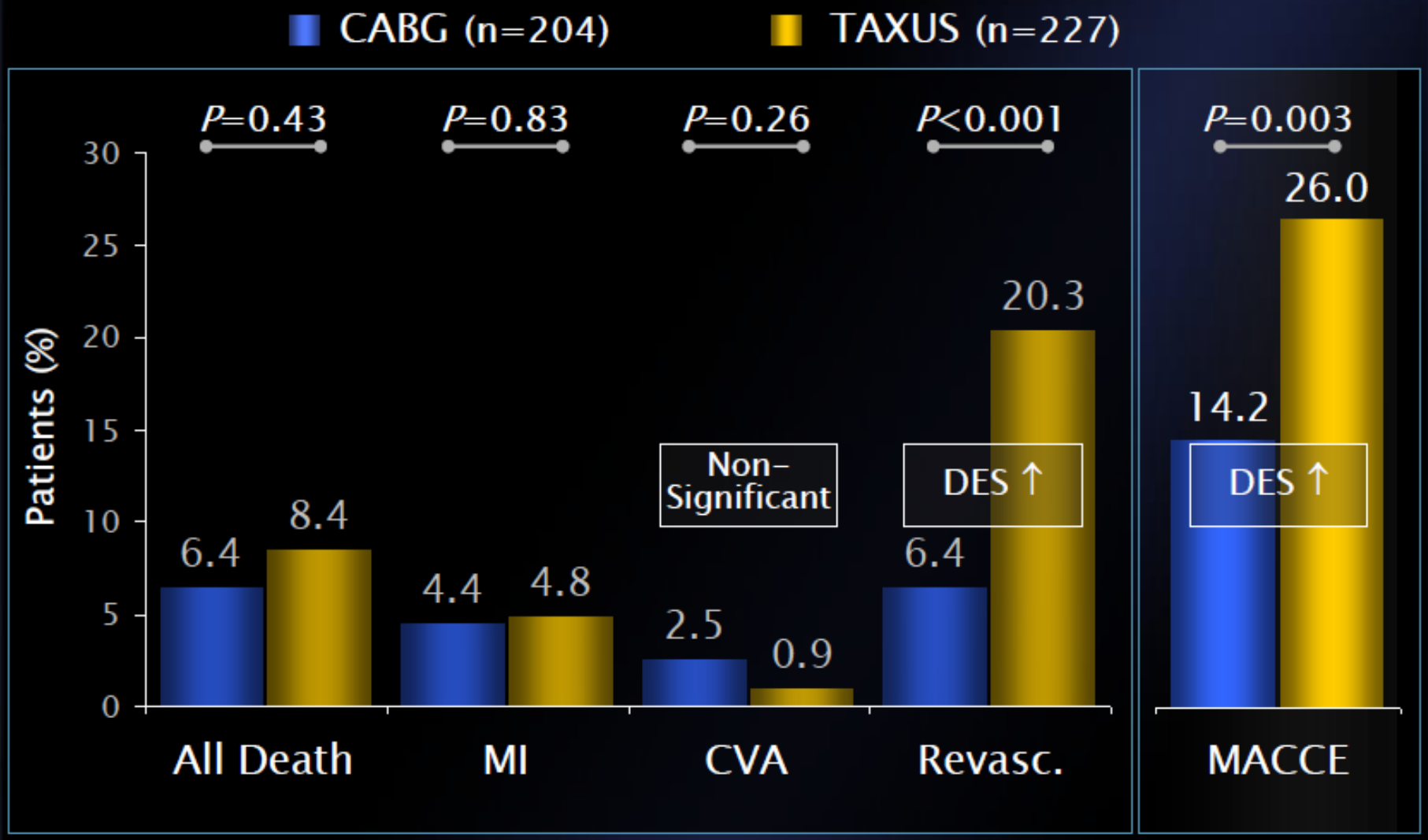
No Significant Increase in MACCE in 'Non-Diabetics' at 12 Months

SYNTAX



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

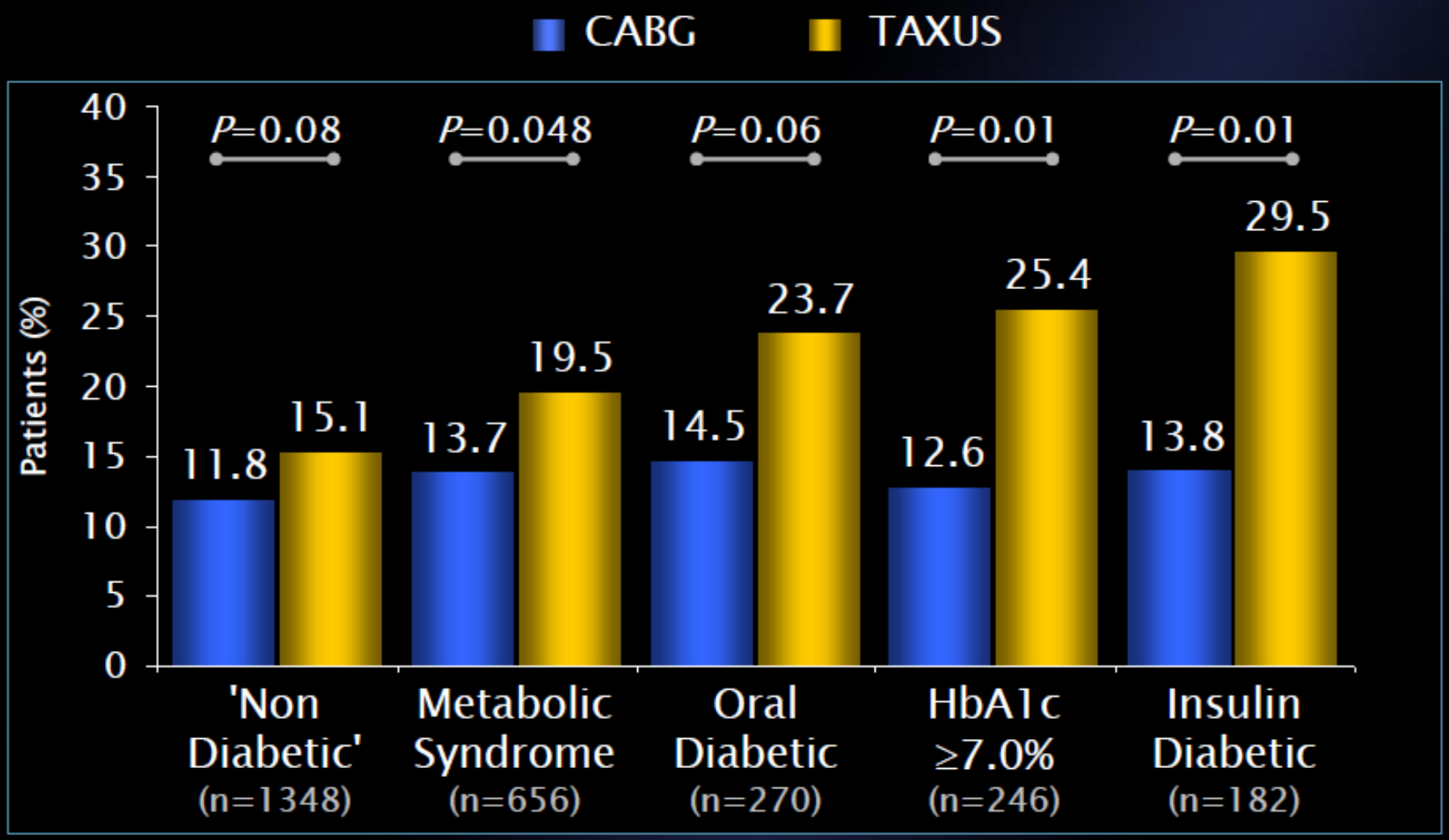
SYNTAX



*Medically treated diabetes

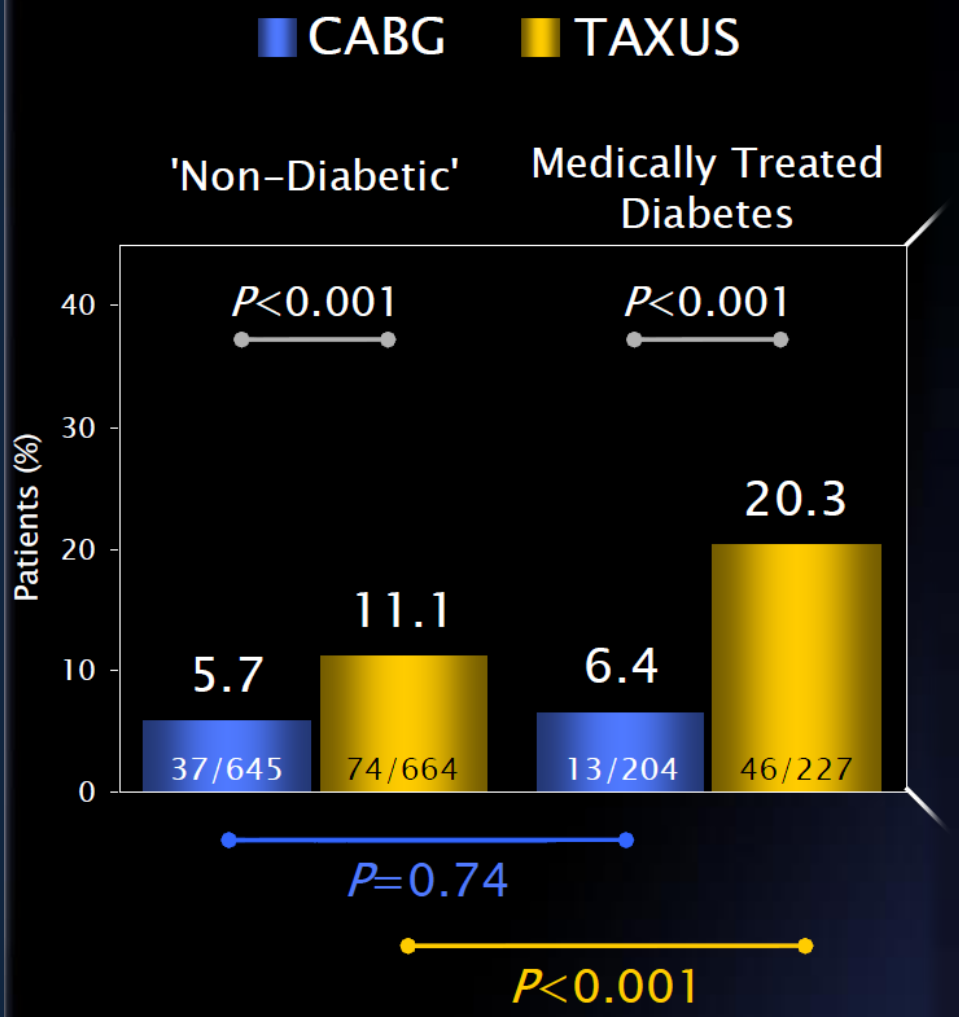
MACCE at 12 Months in Subgroups

SYNTAX



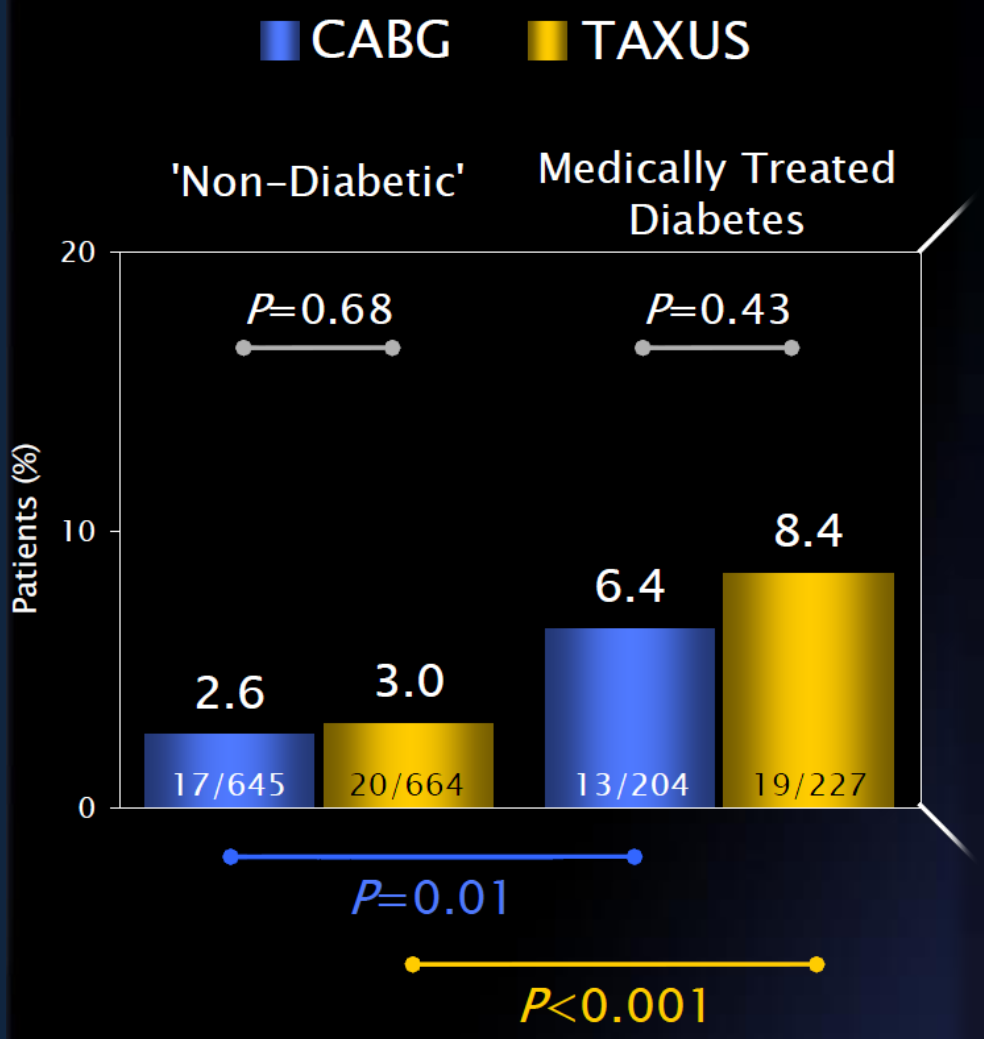
Patients may belong to more than one group

Revascularization at 12 Months
Increased in Diabetes, Driving MACCE

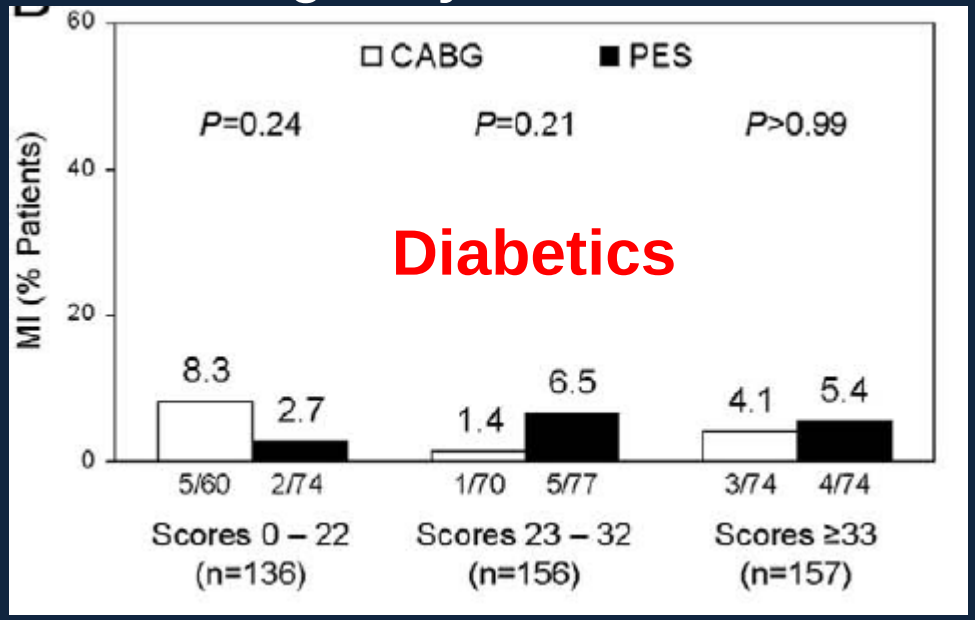


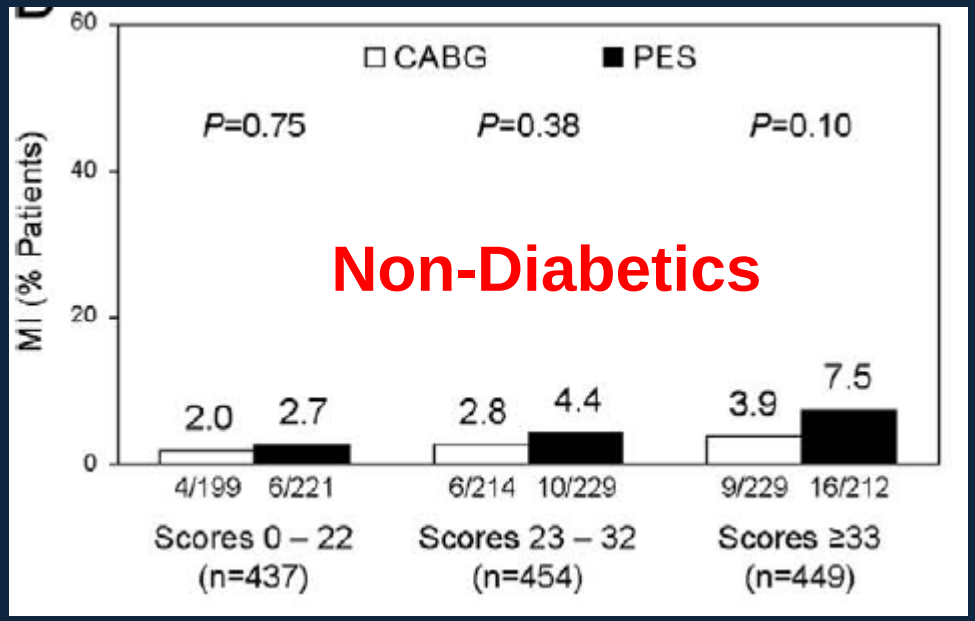
Includes <u>any</u> revascularization (any vessel)

Death (All-Cause) at 12 Months



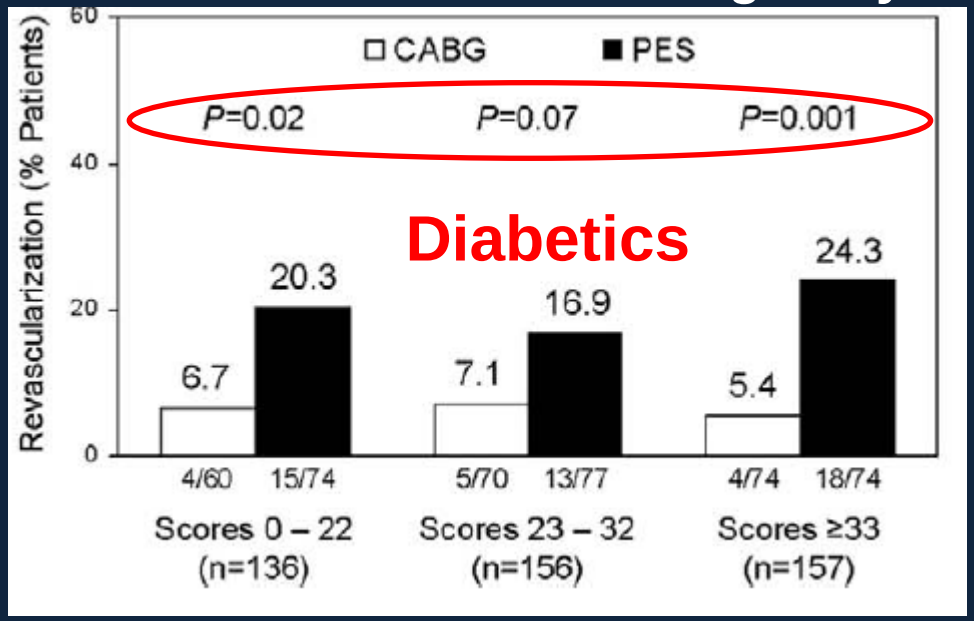
MI at 12 months according to Syntax score

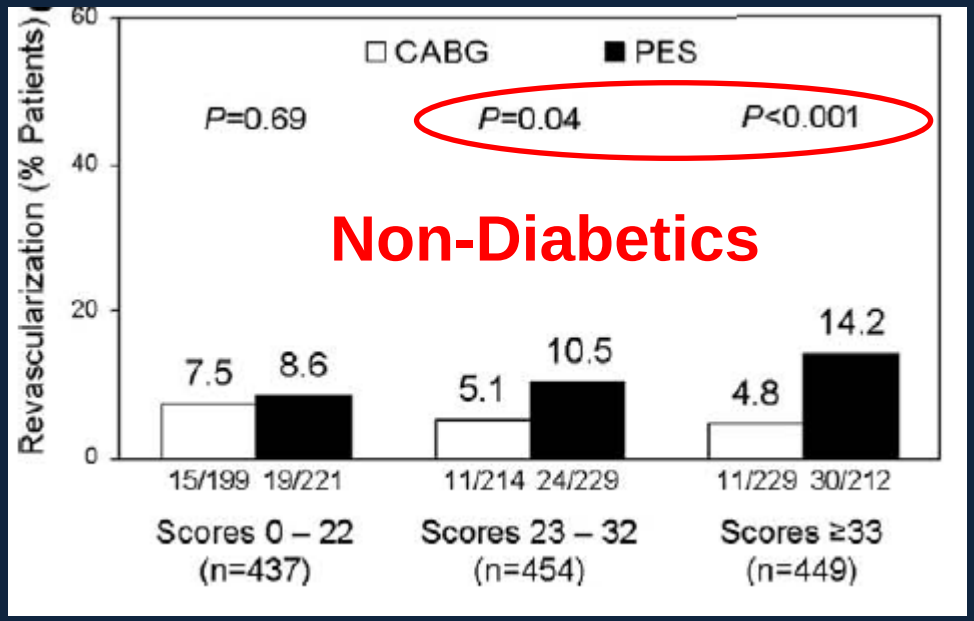




(Banning AP et al, J Am Coll Cardiol 2010;55:1067–75

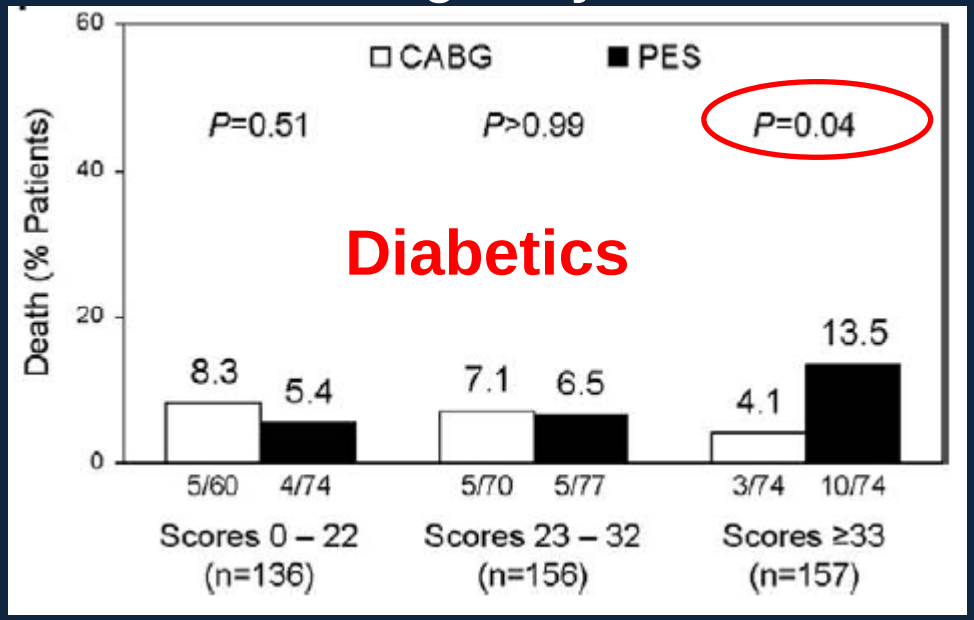
Revascularization at 12 months according to Syntax score

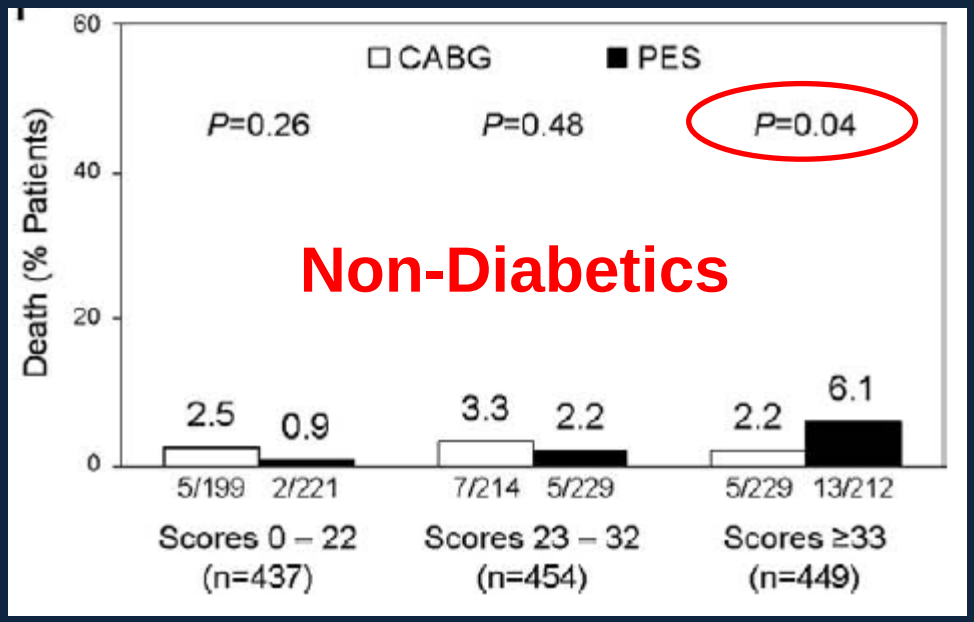




(Banning AP et al, J Am Coll Cardiol 2010;55:1067–75

Death at 12 months according to Syntax score



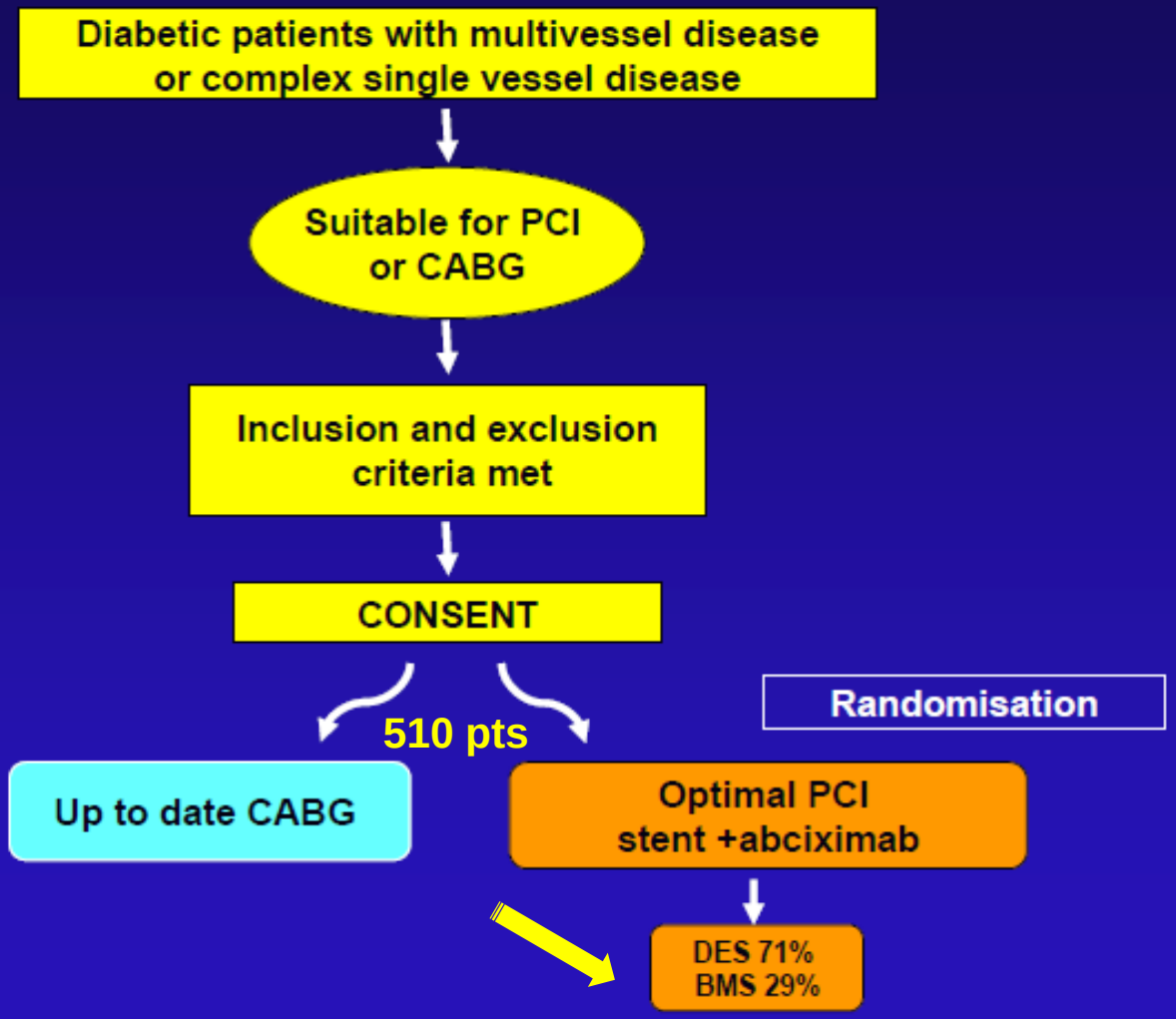


(Banning AP et al, J Am Coll Cardiol 2010;55:1067–75

Summary: 12-Month Outcomes

- Patients without Diabetes
  - No significant difference in MACCE in CABG versus TAXUS
- Patients with Diabetes
  - Significantly increased MACCE with TAXUS, driven by increased revascularization

CARDia Trial Design



J Am Coll Cardiol 2010;55:432–40

Main Exclusion Criteria

- Informed consent could not be obtained
- Age >80 years
- Previous CABG or PCI
- Left main stem disease
- Cardiogenic shock
- Recent ST elevation myocardial infarction
- Contraindications to abciximab, aspirin and clopidogrel

J Am Coll Cardiol 2010;55:432–40

PCI procedural details

Use prior to procedure of:

- aspirin - 100%
- clopidogrel - 94%
- abciximab - 95%

- 3 vessel disease - 65%
- 3 vessels treated in these patients - 88%

J Am Coll Cardiol 2010;55:432–40

CABG procedural details

- 3 vessel disease - 58%
- 3 vessels treated in these patients - 90%

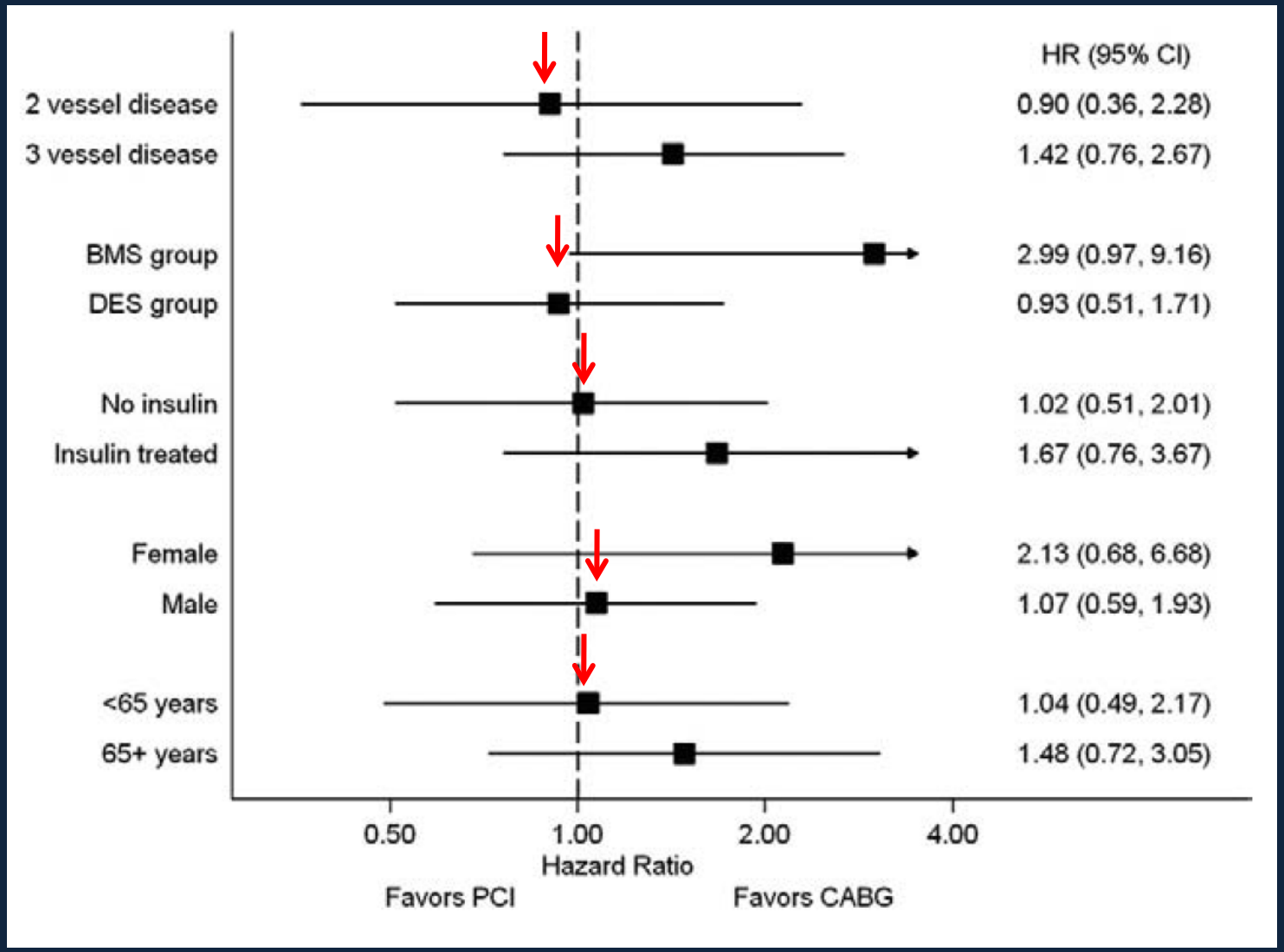
J Am Coll Cardiol 2010;55:432–40

Results – adjudicated events – intention to treat analysis

Adjudicated events post randomisation	CABG (245)	PCI (251)	p value	OR and 95% CI
Death	3.3 % (8)	3.2% (8)	0.83	0.98 (0.36,2.64)
Non fatal MI	5.7% (14)	8.4% (21)	0.25	1.51 (0.75,3.03)
Non fatal stroke	2.5% (6)	0.4% (1)	0.09	0.16 (0.02,1.33)
Death, MI and stroke at one year – primary outcome	10.2% (25)	11.6% (29)	0.63	1.15 (0.65,2.03)

J Am Coll Cardiol 2010;55:432–40

Key Subgroups in the CARDIA trial



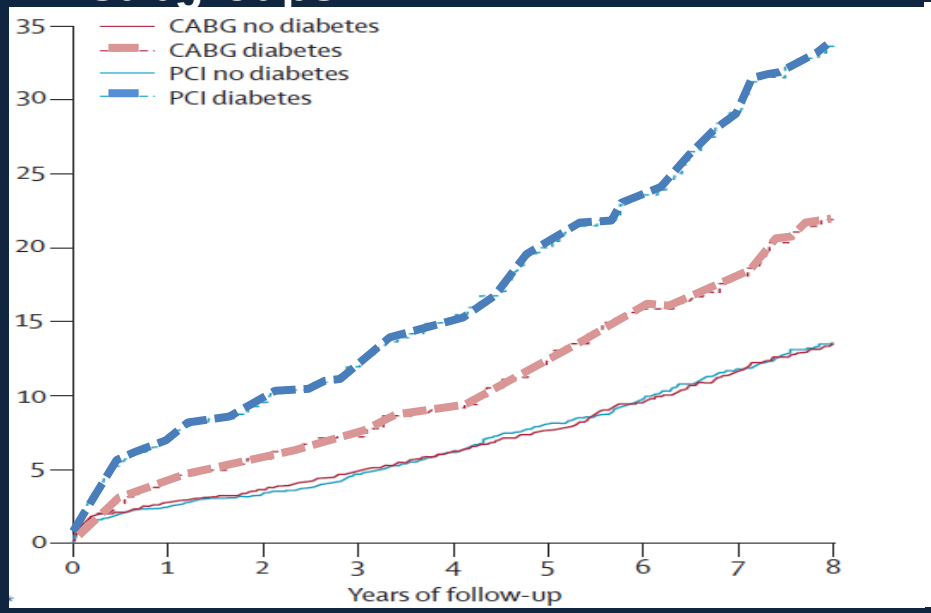
J Am Coll Cardiol 2010;55:432–40

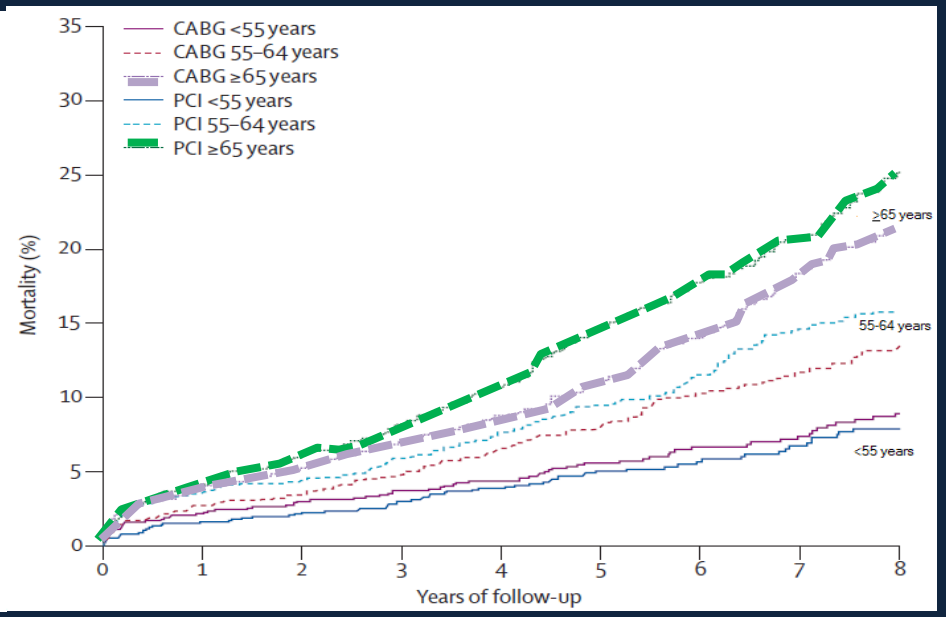
PCI vs CABG TRIALS

CABG compared with PCI for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials.
Hlatky M et al, Lancet 2009; 373: 1190–97

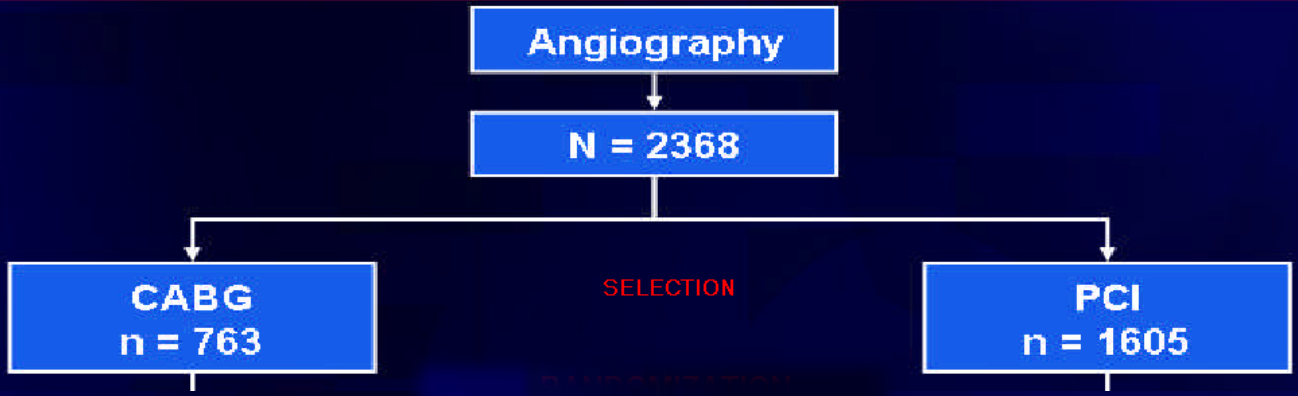
Long-term mortality is similar after CABG and PCI in most patient subgroups with multivessel coronary artery disease, so choice of treatment should depend on patient preferences for other outcomes.

CABG might be a better option for patients with diabetes and patients aged 65 years or older because mortality was found to be lower in these subgroups.





BARI 2D: Enrollment, randomization, and treatments

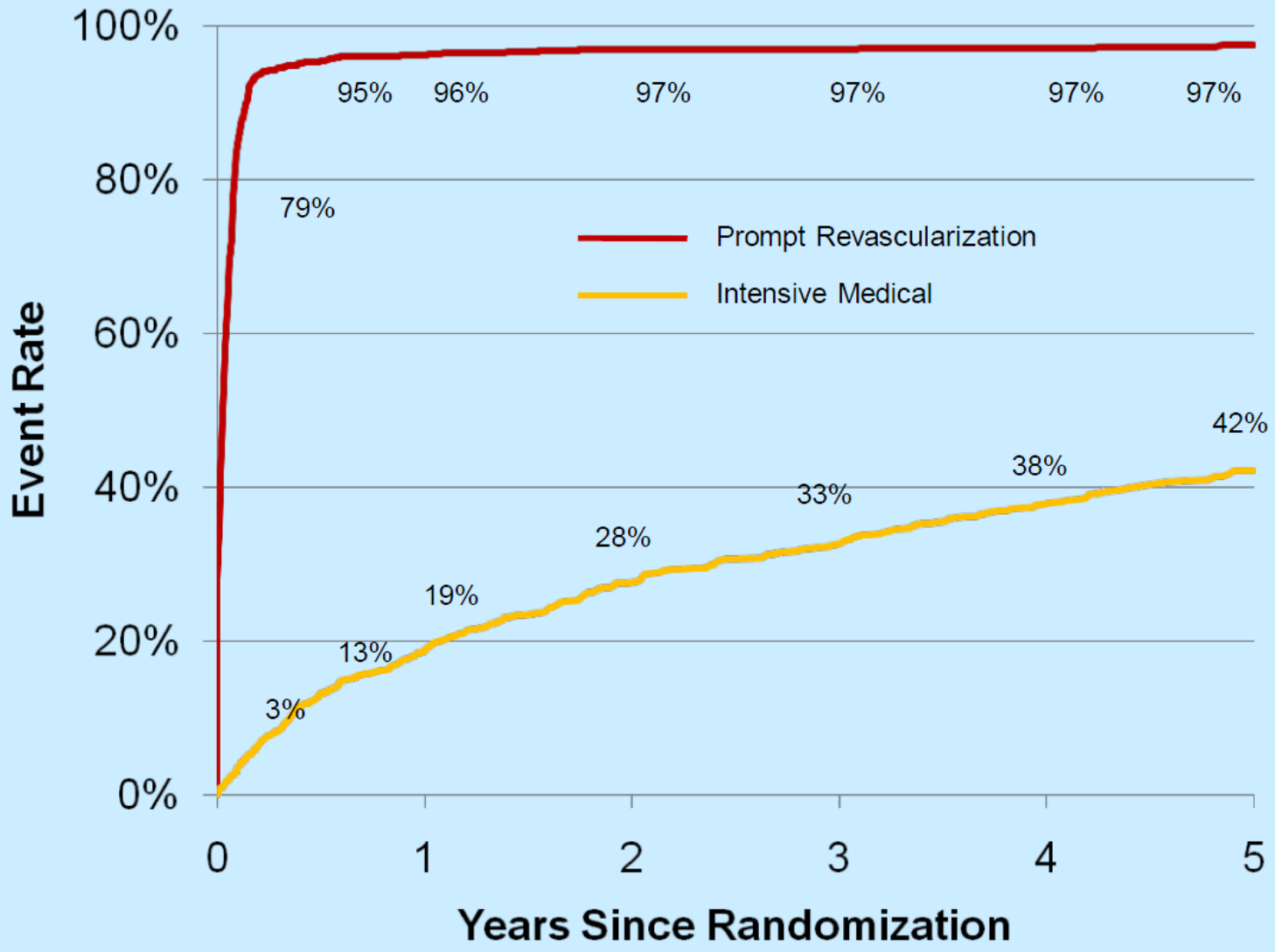


Met = metformin; TZD = thiazolidinedione;
SU = sulfonylurea

BARI 2D Study Group. *N Engl J Med.* 2009;360:2503-12.
Magee MF et al. *Am J Cardiol.* 2006;97(suppl):20G-30G.

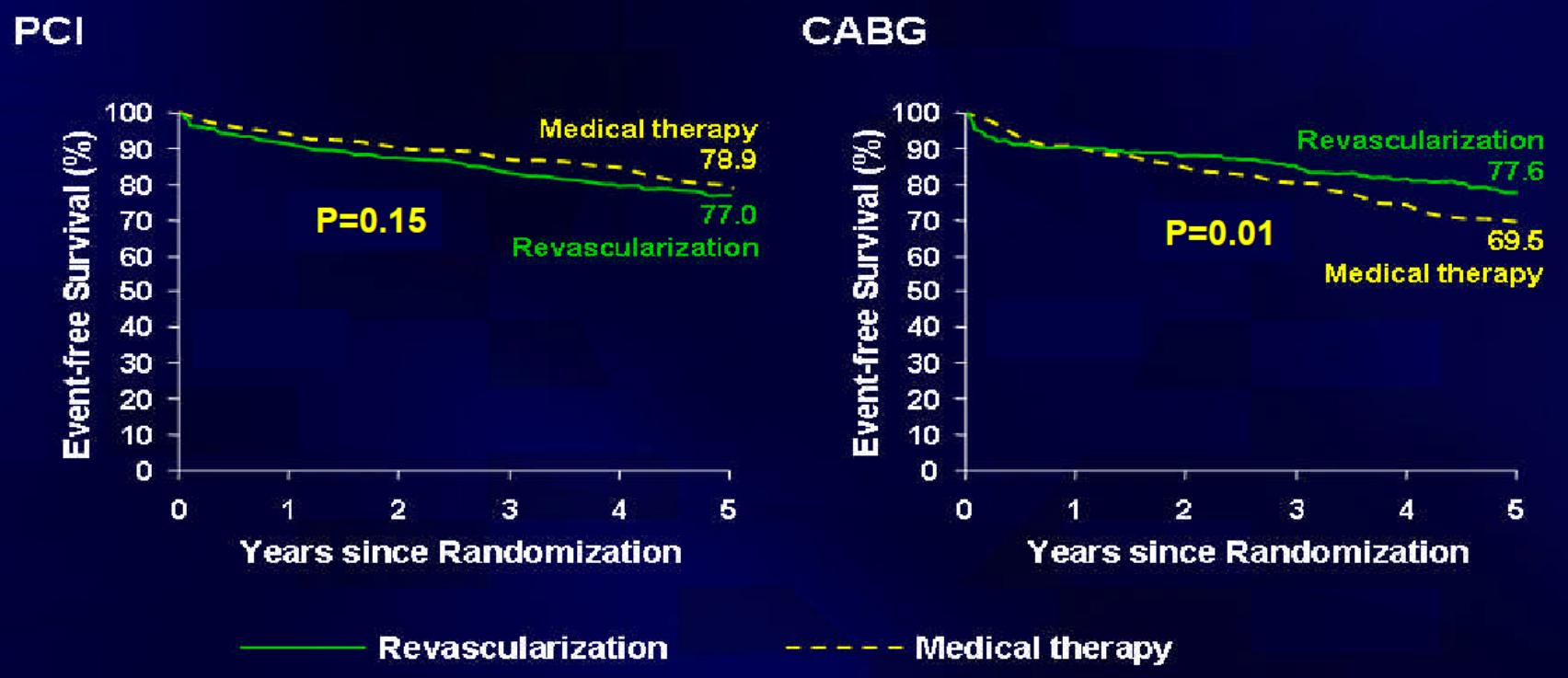
N Engl J Med 2009;360:2503-15.

Cumulative Rate of First Revascularization



The BARI 2 study group, N Engl J Med 2009;360:2503-15.

BARI 2D: Death, MI, stroke for medical therapy vs type of revascularization



BARI 2D Study Group. *N Engl J Med.* 2009;360:2503-12.

3 vessel disease	20%	52%
Significant LAD disease	10%	19%
Ejection Fraction	57 (11)	57 (11)

BARI 2D Primary Conclusions

In patients with Type 2 Diabetes and stable ischemia…

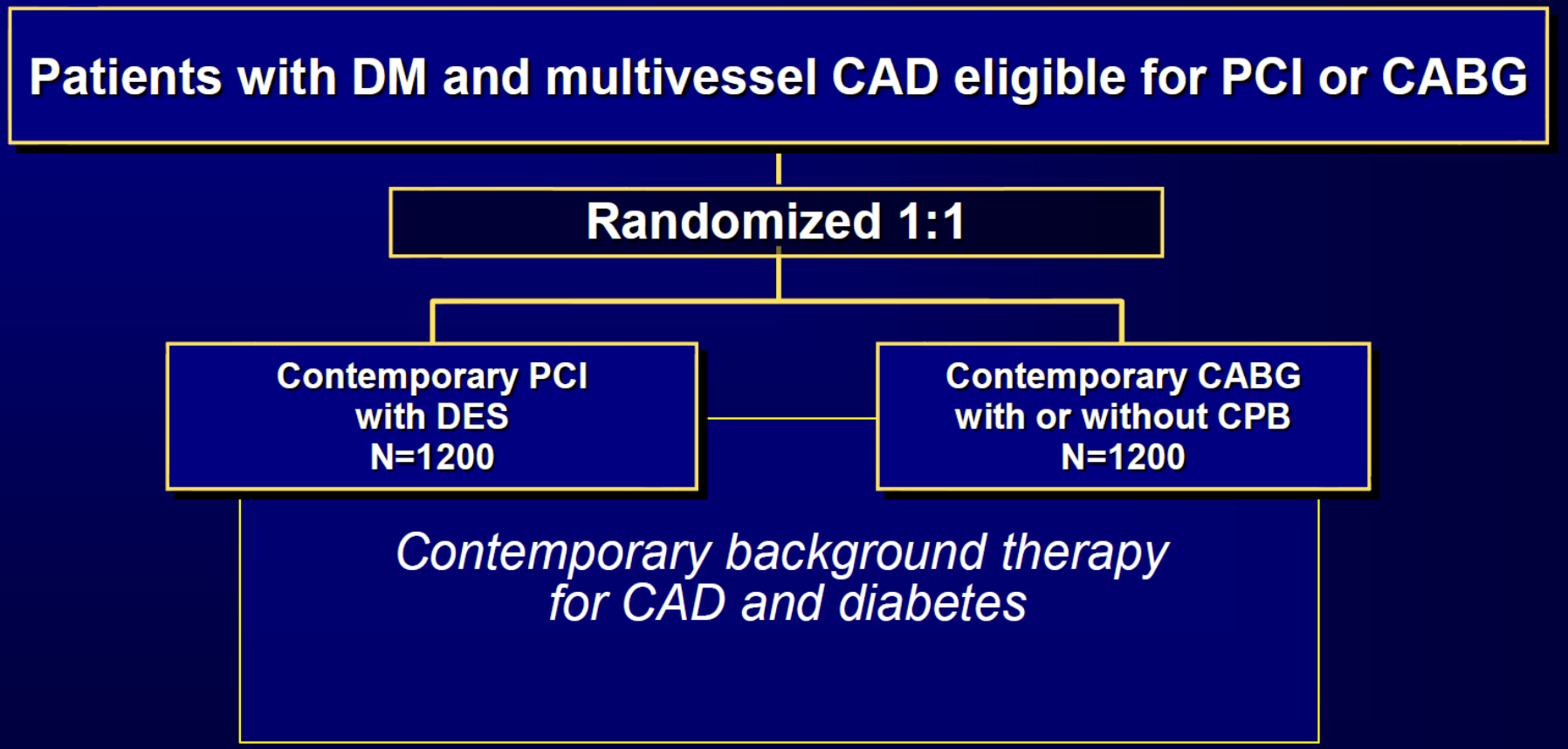
Among high risk patients selected for CABG

- 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.

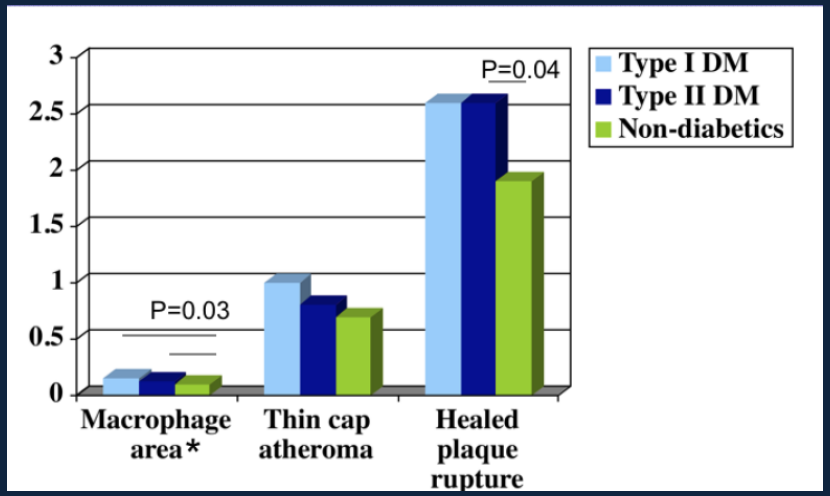
FREEDOM Design

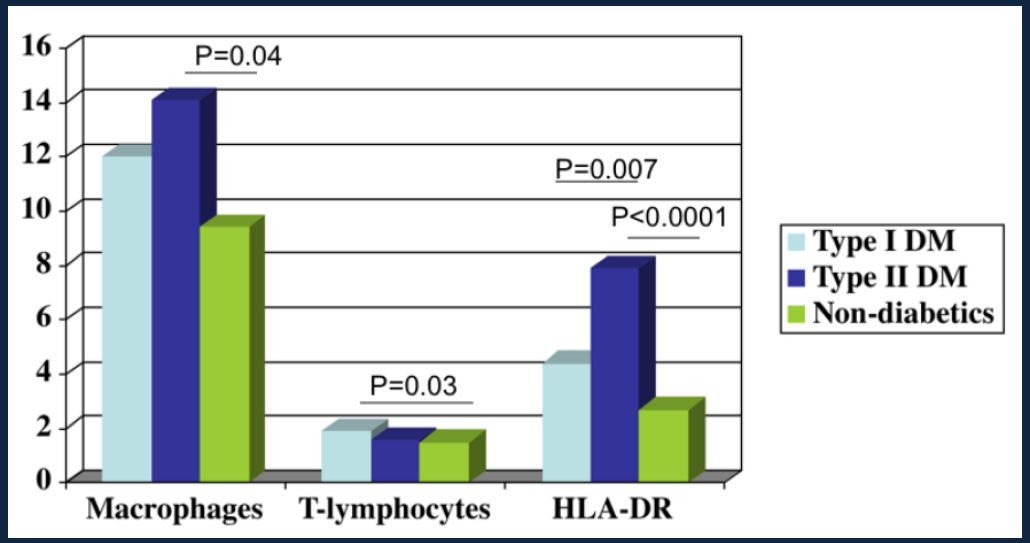


Fuster V, Steering Committee

Final Conclusions

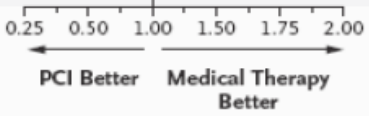
- Complex diabetic patients remain the most challenging group for revascularization, both for surgeons and interventional cardiologists.
- Patients recruited into revascularization trials are increasingly complex
- Non inferiority of PCI compared to surgery not shown in recent trials (SYNTAX, CARDia)
- Despite this the gap in outcome between PCI and surgery is progressively decreasing





Burke A et al, Arterioscler Thromb Vasc Biol. 2004;24:1266-1271

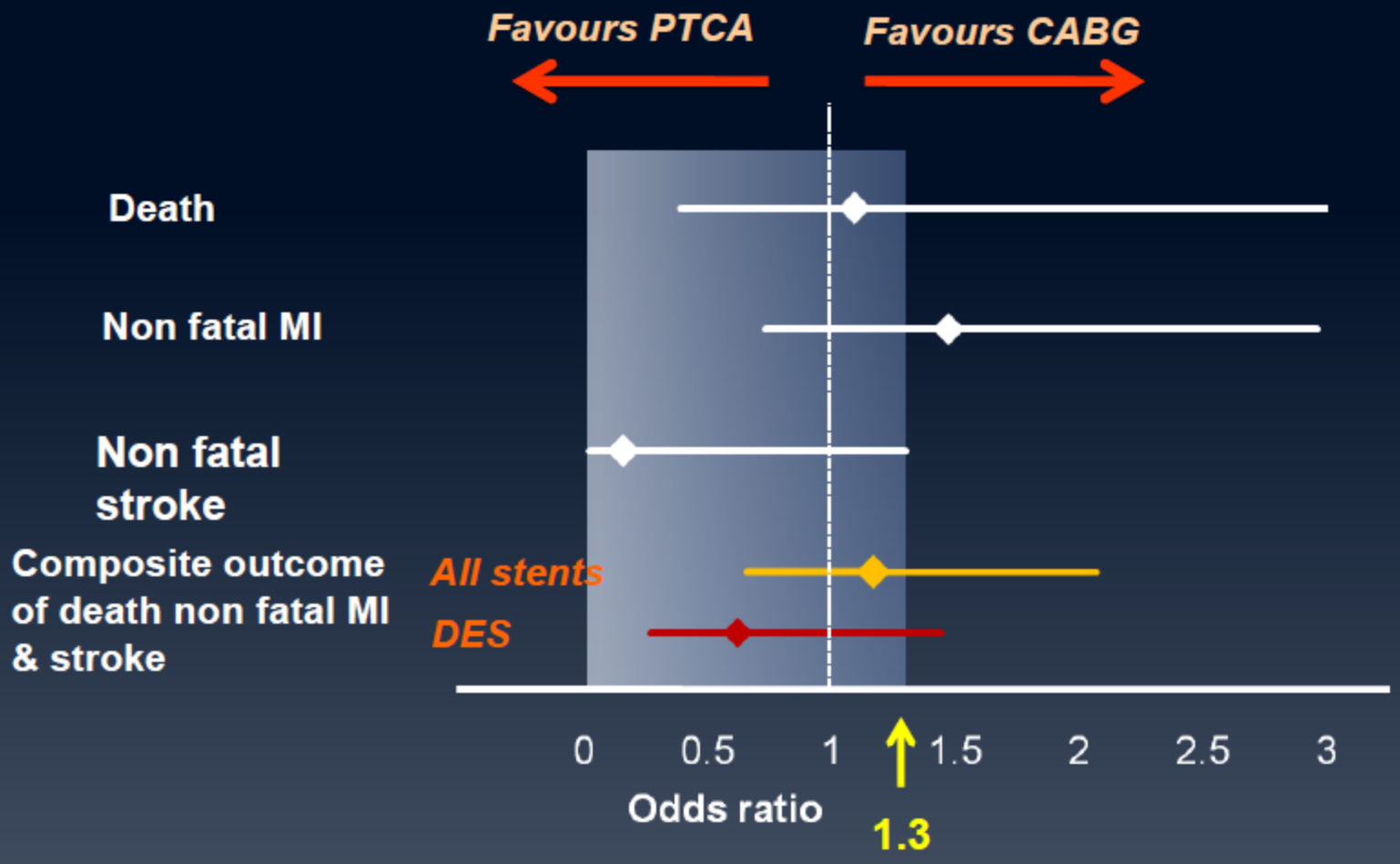
Baseline Characteristics	No. of Patients	Hazard Ratio (95% CI)	Event Rate for the Primary Outcome		P Value
			PCI	Medical Therapy	
Overall	2287	1.05 (0.87–1.27)	0.19	0.19	
Sex					0.03
Male	1947	1.15 (0.93–1.42)	0.19	0.18	
Female	338	0.65 (0.40–1.06)	0.18	0.26	
Myocardial infarction					0.15
Yes	876	0.91 (0.69–1.21)	0.23	0.25	
No	1371	1.22 (0.93–1.60)	0.17	0.14	
Extent of CAD					0.65
Multivessel disease	1581	1.04 (0.84–1.30)	0.21	0.21	
Single-vessel disease	700	1.17 (0.76–1.80)	0.15	0.12	
Smoking					0.71
Current	653	1.00 (0.71–1.41)	0.20	0.21	
Not current	1631	1.08 (0.86–1.36)	0.19	0.18	
Diabetes					0.33
Yes	766	0.99 (0.73–1.32)	0.25	0.24	
No	1468	1.20 (0.92–1.56)	0.17	0.15	
CCS angina class					0.73
0 or I	964	1.01 (0.75–1.38)	0.17	0.20	
II or III	1371	1.09 (0.85–1.40)	0.20	0.18	
Ejection fraction					0.72
≤50%	406	1.14 (0.77–1.70)	0.28	0.26	
>50%	1848	1.05 (0.84–1.32)	0.17	0.16	
Age					0.62
>65 yr	904	1.10 (0.83–1.46)	0.24	0.22	
≤65 yr	1381	1.00 (0.77–1.32)	0.16	0.16	
Previous CABG					0.81
No	2039	1.04 (0.84–1.29)	0.17	0.17	
Yes	248	0.98 (0.52–1.82)	0.34	0.29	
Race					0.43
White	1963	1.08 (0.87–1.34)	0.19	0.18	
Nonwhite	322	0.87 (0.54–1.42)	0.19	0.24	
Health care system					0.17
Canadian	932	1.27 (0.90–1.78)	0.17	0.14	
U.S. non-VA	387	0.71 (0.44–1.14)	0.15	0.21	
U.S. VA	968	1.06 (0.80–1.38)	0.22	0.22	



Follow up 2.5-7 years (mean 4.6 years)

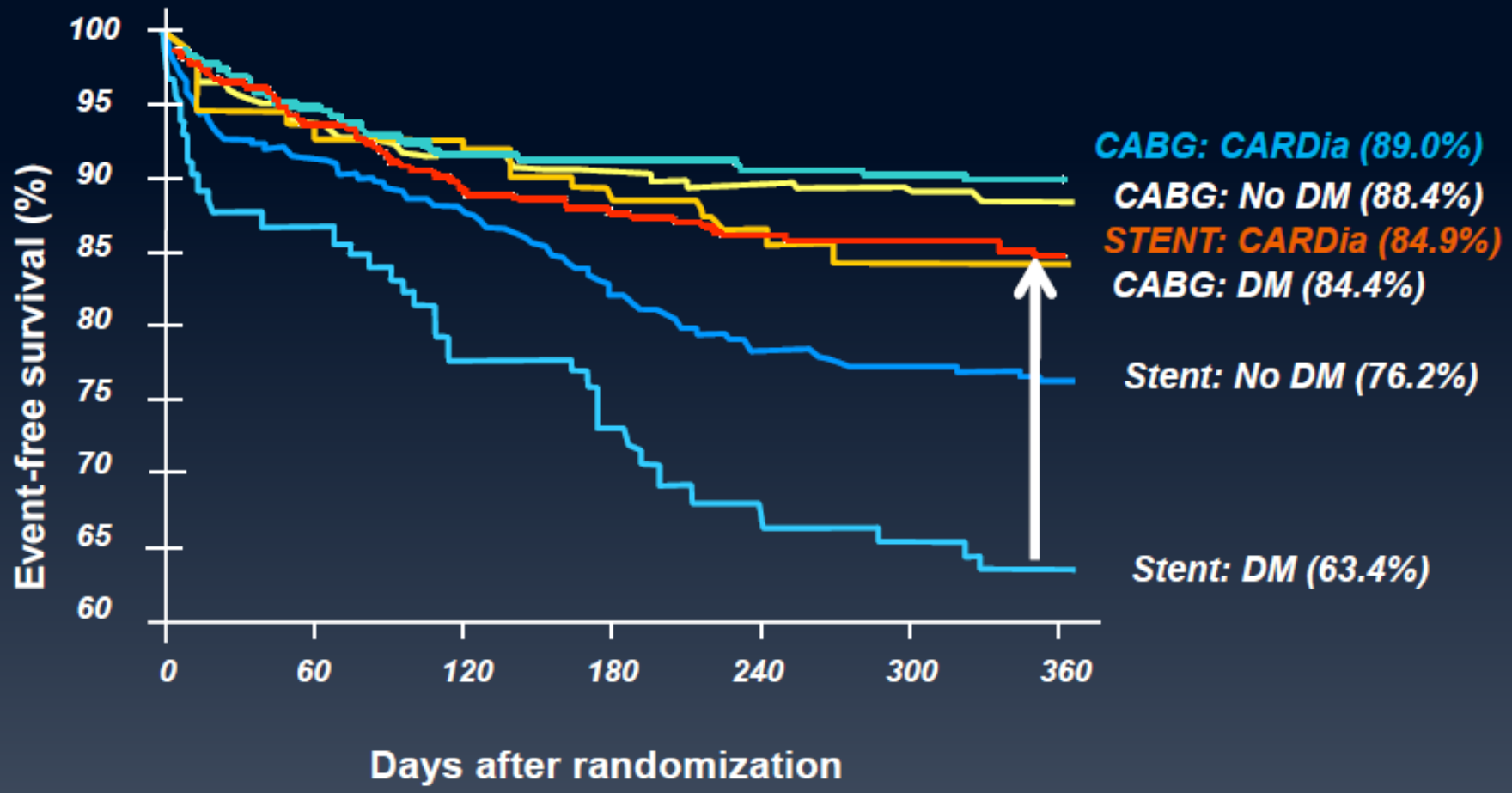
COURAGE Trial, *New Engl J Med 2007:356;1503*

Primary outcome and composites with CI related to non inferiority margin



How far have we come?

Primary outcome at one year: CARDia compared to ARTS I

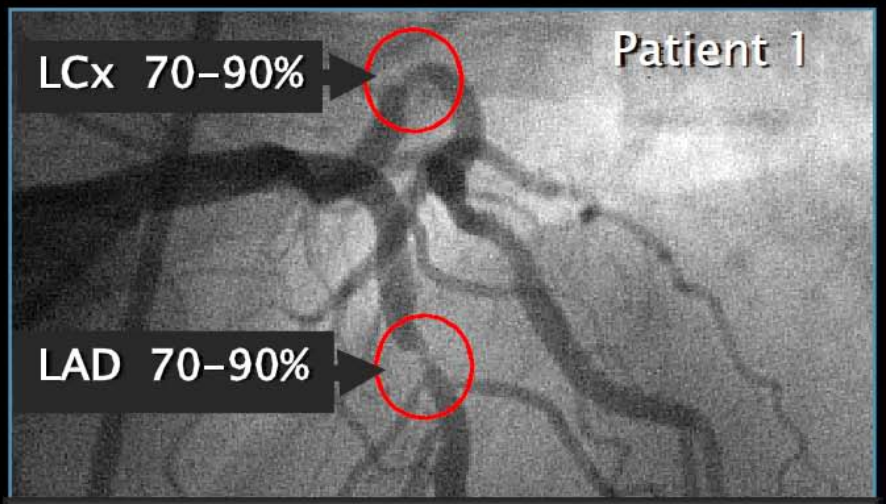


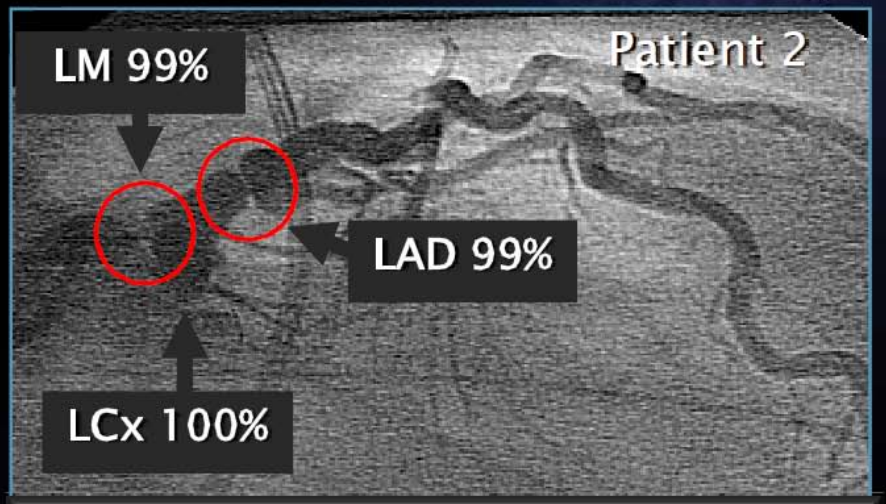
CARDia: Main Conclusions

- No apparent difference between PCI and CABG at one year in:
  - Death
  - Composite of Death, MI and stroke
- More repeat revascularisation in the PCI group
- PCI may now be considered a reasonable strategy in diabetic patients with multivessel disease
- Longer follow up is needed

There is '3-vessel disease' and '3-vessel disease'

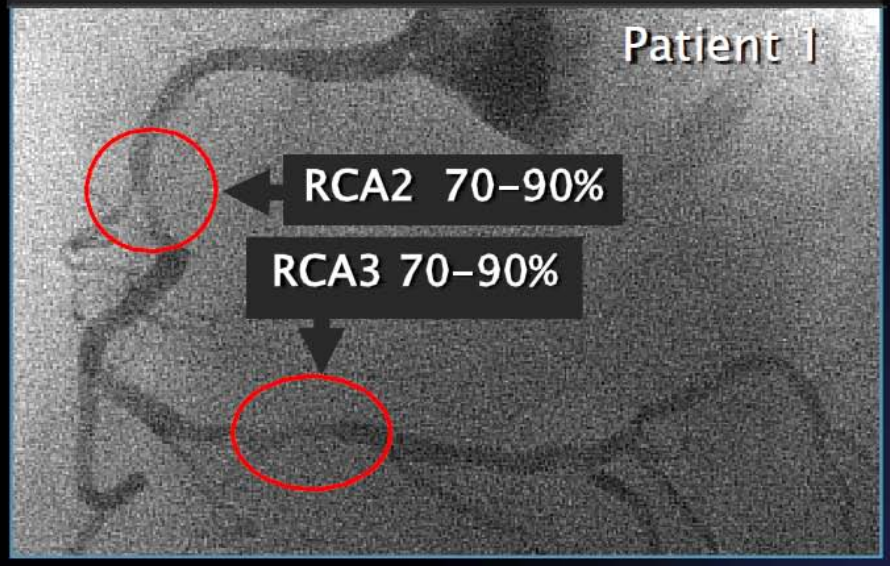
SYNTAX

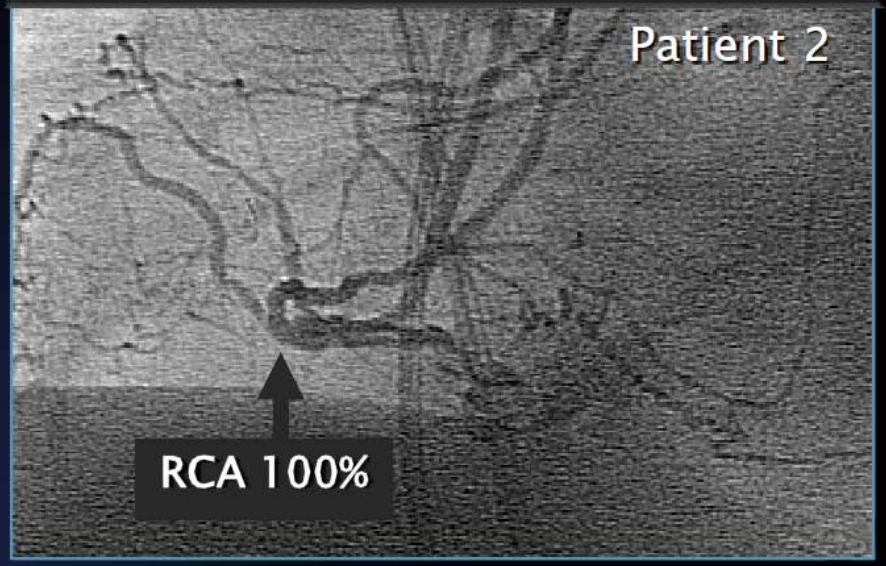




SYNTAX SCORE 21

SYNTAX SCORE 52





Medically Treated Diabetes and Metabolic Syndrome* in SYNTAX

*ATP 2001 Definition
(JAMA 2001;285:2486-2497)

Medically Treated Diabetes (n=452)

- 57% with Metabolic Syndrome
- 48% with HbA1c ≥7.0%

Metabolic Syndrome (n=656)

- 39% with Diabetes
- 24% with HbA1c ≥7.0%

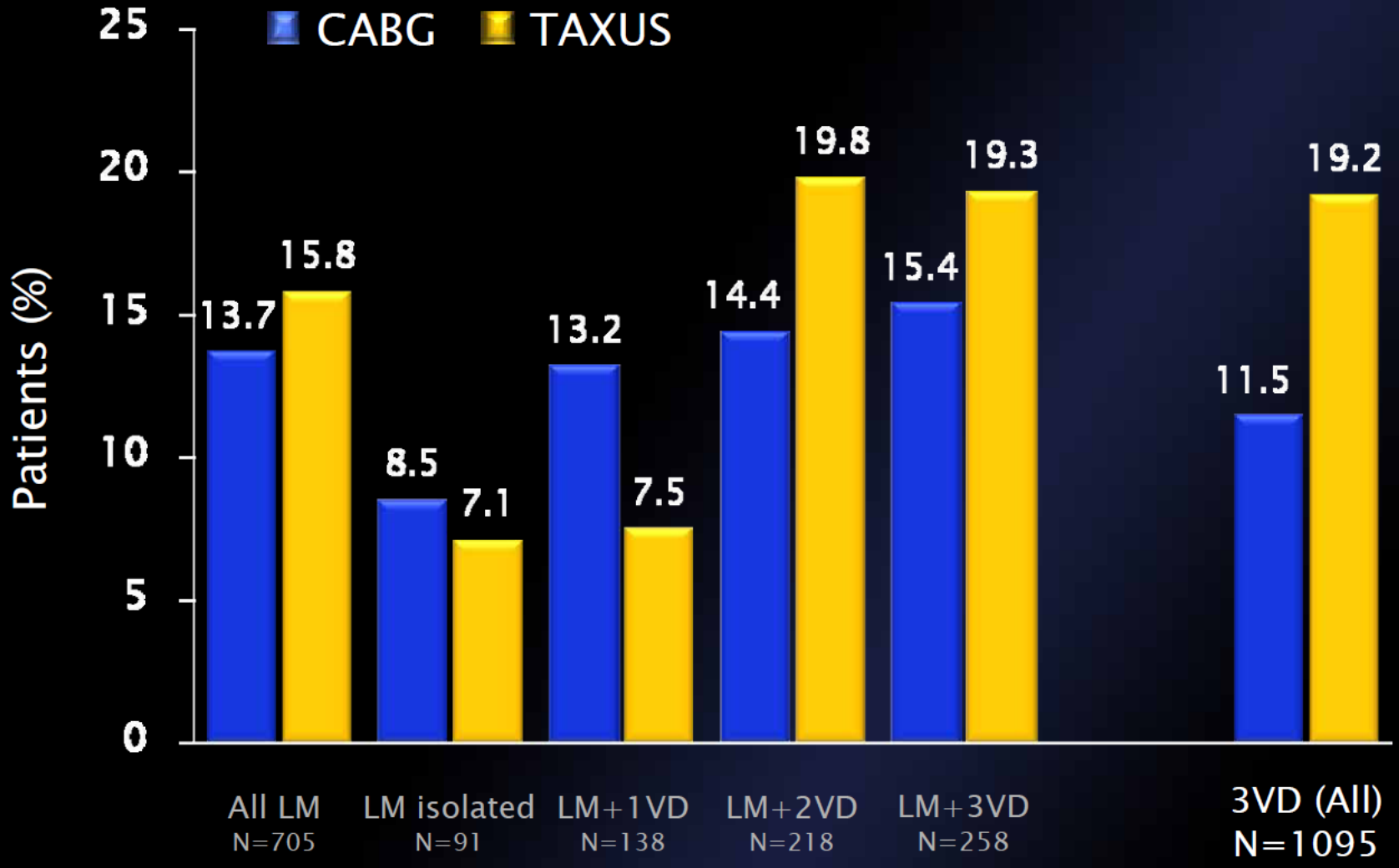
*Includes patients with unknown metabolic syndrome status

ESC 2008

	SYNTAX	CARDIA
Trial design	Non inferiority	Non inferiority
Recruitment	1800	510
% diabetcs	28%	100%
1° end point FU	1 year	1 year
1° end point	MACCE + revasc	MACCE - revasc
Stent	TAXUS	CYPHER 29% BMS

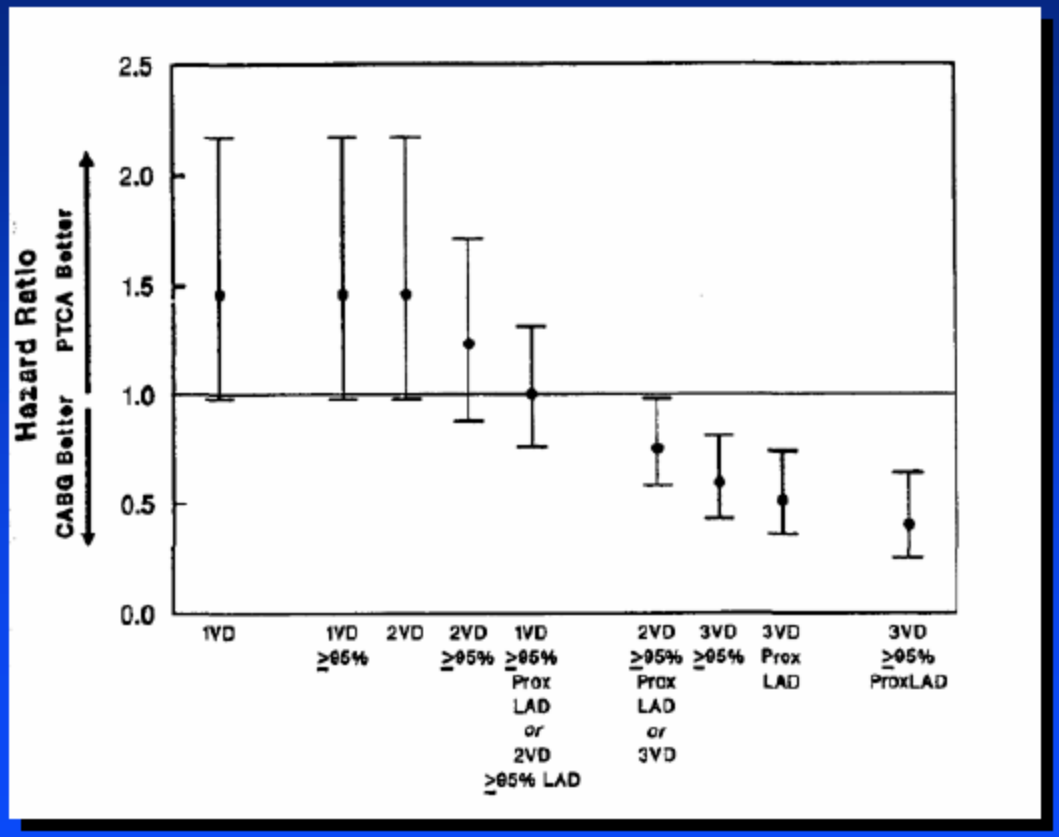
12 Month Subgroup MACCE Rates

SYNTAX



Ongoing Trials Comparing CABG With PCI

	Population	Treatment	N	Follow-Up	Primary Endpoint
BARI 2D[1]	• Type 2 DM with CAD treated with PCI or CABG • Objective ischemia or angina	1. PCI + medical management vs. medical management 2. CABG + medical management vs. medical management	2,368	5 years	5-year mortality
CARDia[2]	• Diabetes with >2-vessel CAD • Consensus by cardiologist and surgeon that patient is suitable for revascularization	Optional PCI (aspirin, clopidogrel, abciximab, and sirolimus-eluting stents vs. optional CABG (≥1 actual graft with LIMA to CAD)	600 (projected)	2-5 years	Death, MI, stroke
FREEDOM[3]	Diabetes with ≥2-vessel CAD suitable for PCI or CABG	PCI with sirolimus-eluting stents vs. CABG	2,400 (projected)	5 years	Death, MI, CVA
COMBAT[4]	LMCA stenosis >50%, angina, documented ischemia, suitable for PCI or CABG, lesions outside LMCA suitable for PCI or CABG	Sirolimus-eluting stent vs. CABG	1,730 (projected)	5 years	All-cause mortality, MI, stroke
SYNTAX[5]	• 3-vessel CAD • SES LMT	Paclitaxel-eluting stent vs. CABG, stratified by diabetes treatment	1,500	5 years	MACE



Duke Databank

- 9200 pts undergoing initial diagnostic cath between 1984-90
- Analyzed by initial medical treatment, adjusted for baseline covariates
- Benefits of CABG vs. PTCA most pronounced in highest risk groups

Mark DB et al. *Circulation* 1994;89:2015-25

Conclusions

I. Most lesions treated in diabetic patients are « off label »

II. Poor clinical outcomes such as death or MI are highly relevant in this population and related to other angiographic and clinical features, not affected by DES

III. Restenosis may be underreported due to silent ischemia

IV. Large randomized trials comparing DES/BMS in complex situations are still missing or ongoing (MVD)

V. Conversely, the small randomized studies included mostly single de novo lesions, with a comparative BMS not always appropriate

Conclusions

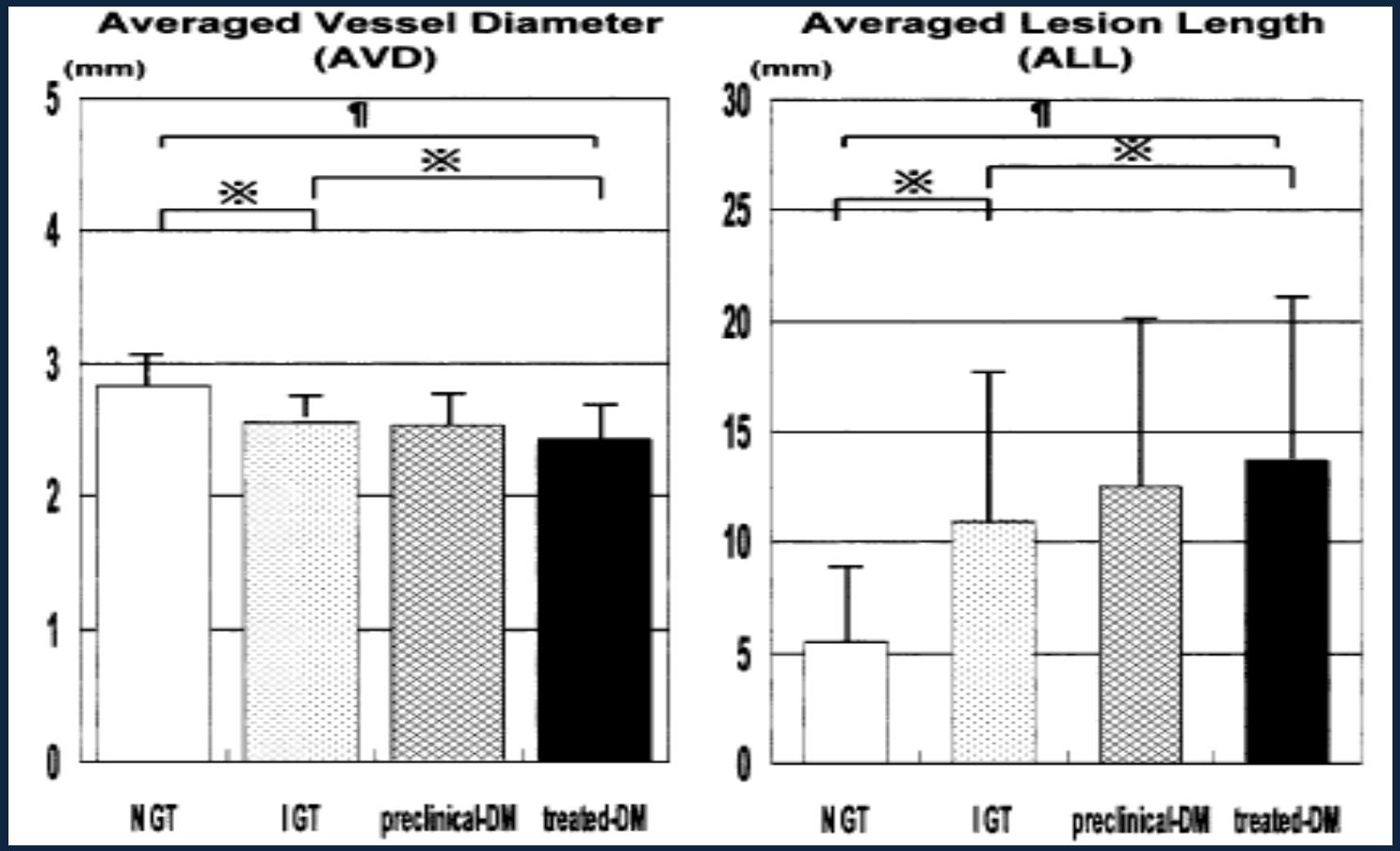
I. Events rates for ischemic endpoints (death, myocardial infarction) are 2 fold higher in diabetic than non-diabetic patients

II. Event rates for TLR are 1.5 fold higher in diabetic then non-diabetic patients

III. DES reduce TLR by 50-70% compared with BMS in diabetic and non-diabetic patients, but NNT is lower in diabetic patients due to a higher baseline risk and SES perform better than PES

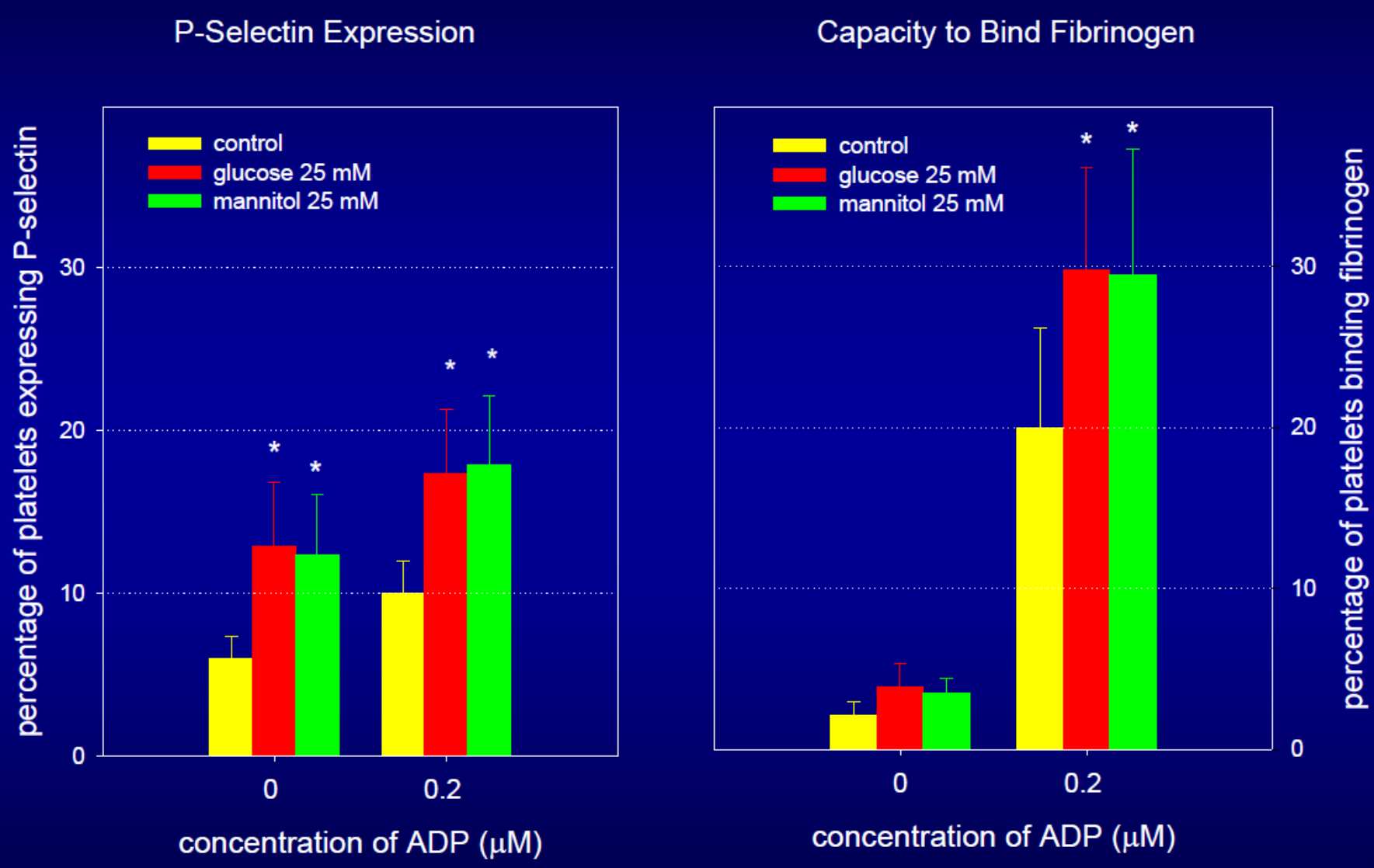
IV. Rates of death, cardiac death, and myocardial infarction are similar for DES (SES or PES) and BMS

Quantitative Coronary Angiographic Studies of Patients With Angina Pectoris and Impaired Glucose Tolerance



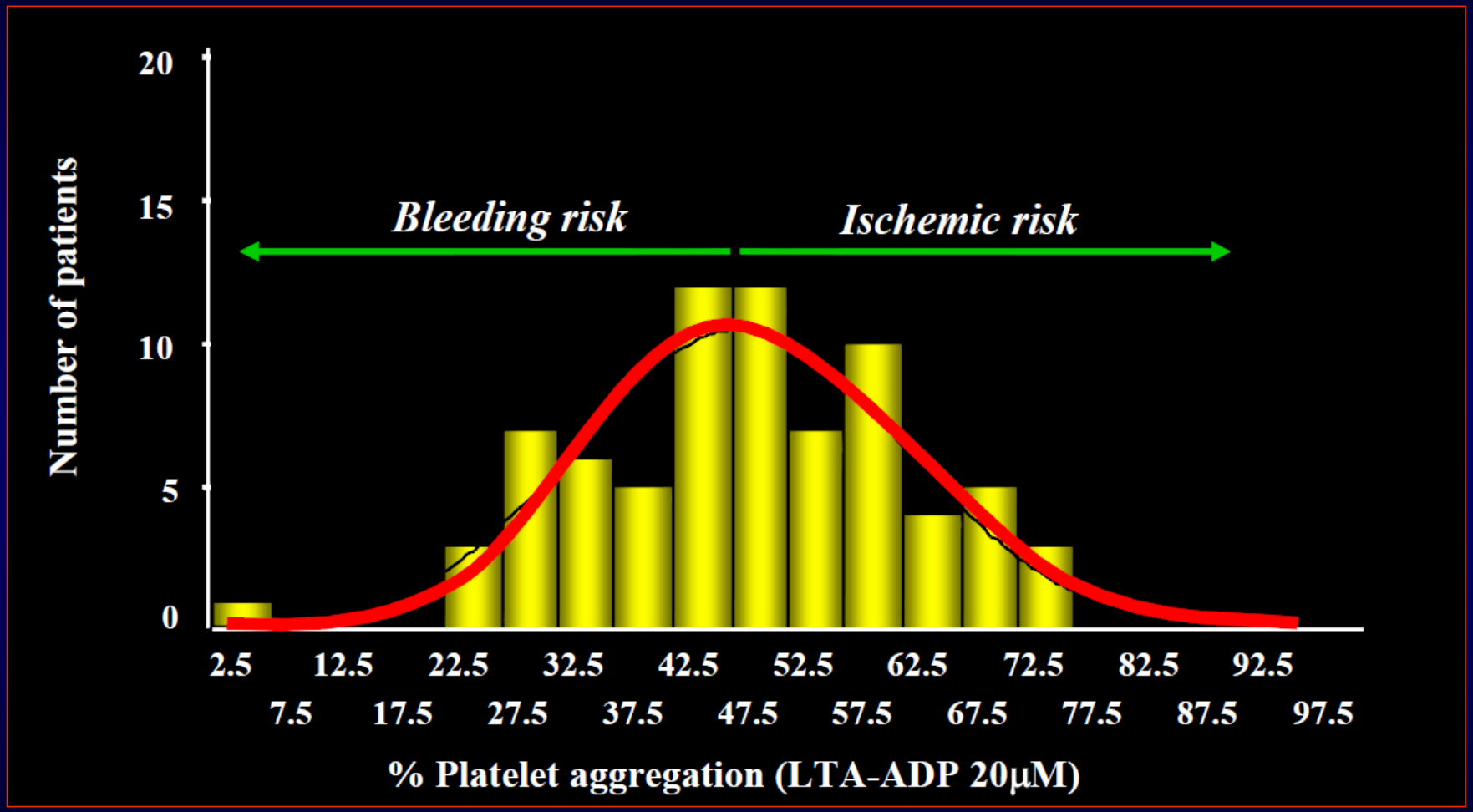
Diabetes Care, 2005 ;28:2217–2222

The Influence of Glucose and Mannitol on Platelet Function



* $p < 0.05$ compared with control

Individual response variability to dual antiplatelet therapy



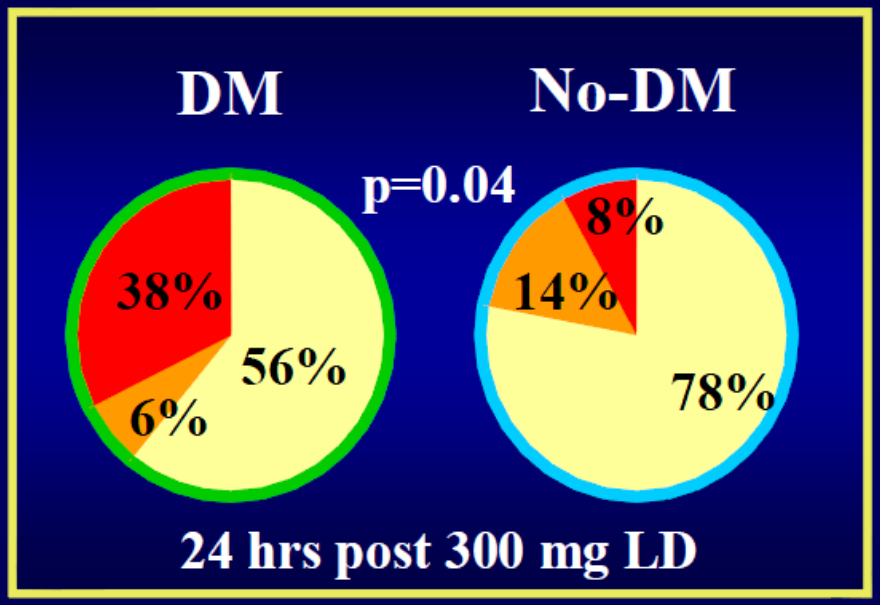
Angiolillo DJ et al. Am J Cardiol 2006; 97: 38-43

* Suggested therapeutic threshold for $P2Y_{12}$ inhibition as in the PREPARE POST-STENTING study showed that patients with post-treatment platelet reactivity above this value were at very high risk of clinical events (*Gurbel PA et al. J Am Coll Cardiol 2005;46:1820-6*).

OPTIMUS

Influence of Diabetes Mellitus on Clopidogrel-induced Antiplatelet Effects

Acute phase of treatment



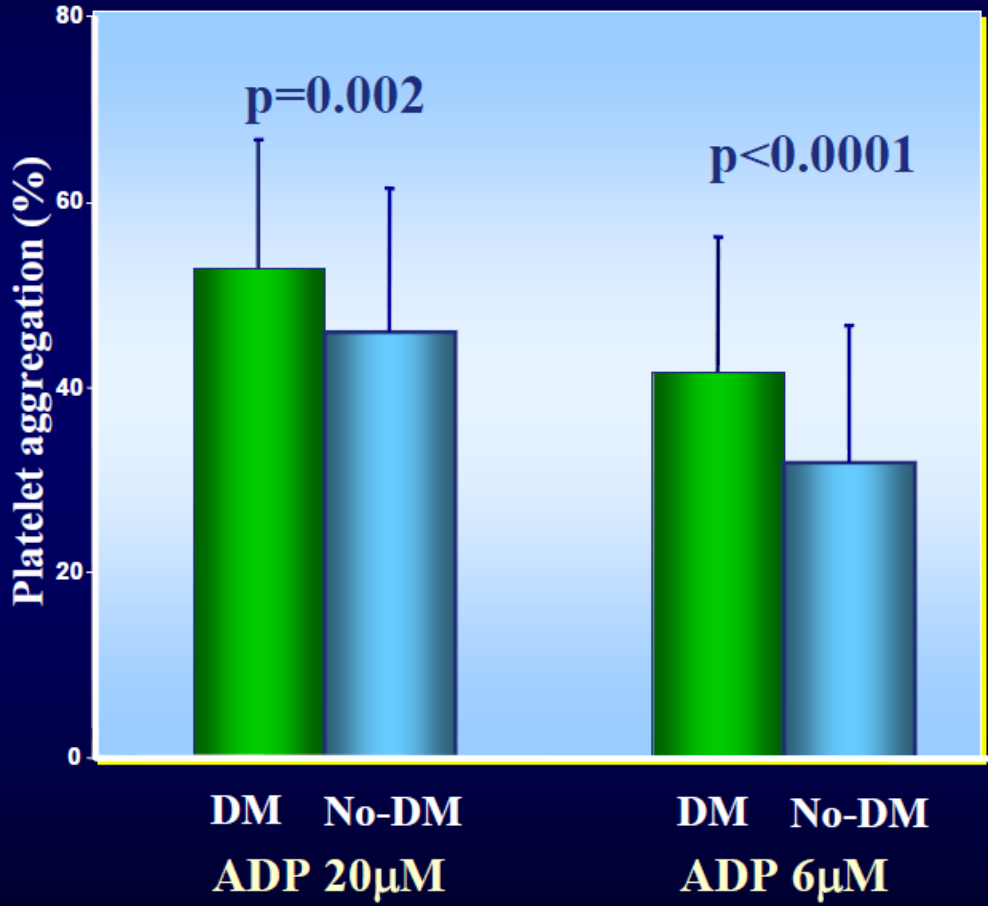
Non responders (Platelet inhibition <10%)

Low responders (Platelet inhibition 10-29%)

Responders (Platelet inhibition >30%)

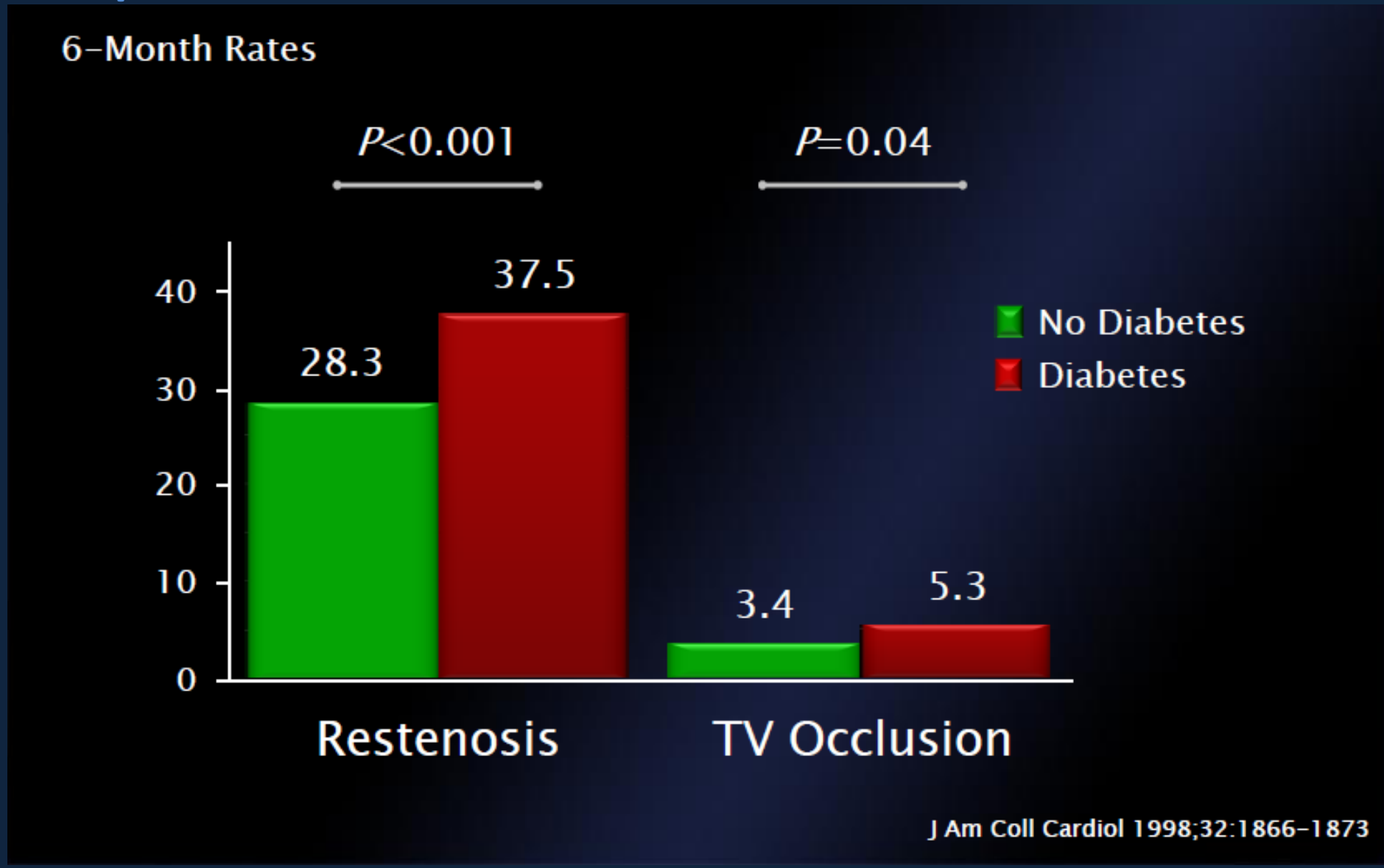
Angiolillo DJ et al. Diabetes 2005; 54:2430-5

Long-term phase of treatment



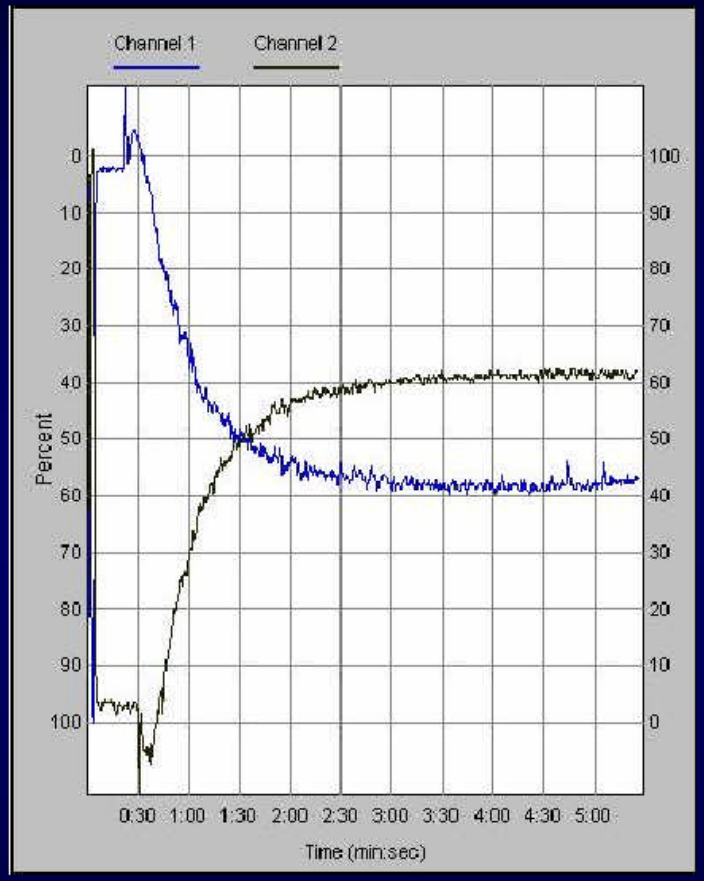
Angiolillo DJ et al. J Am Coll Cardiol 2006; 48: 298-304

Restenosis Increased in Diabetes Following BMS Implantation



J Am Coll Cardiol 1998;32:1866-1873

Definition of Suboptimal Clopidogrel Responders



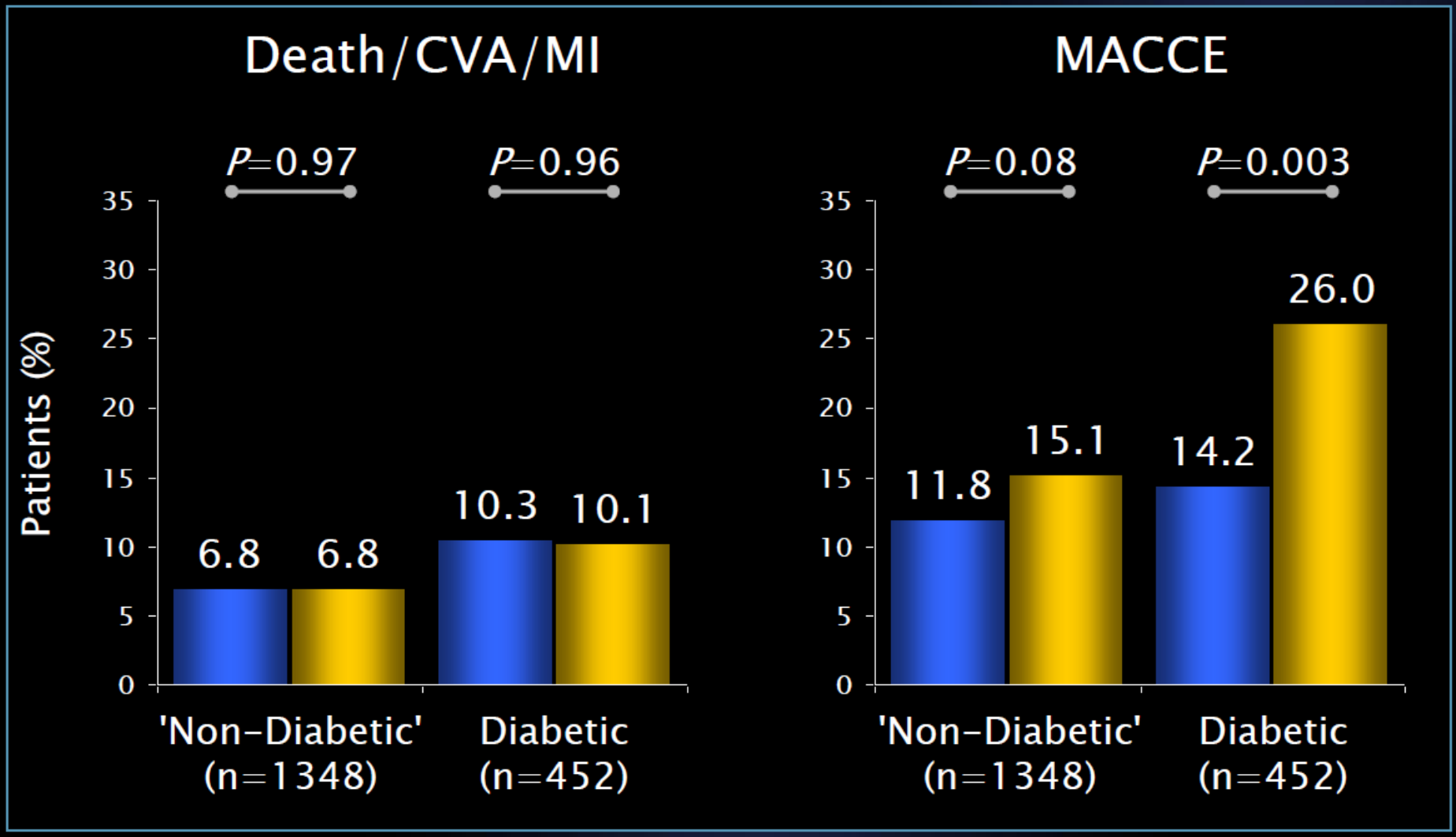
Assay: Light transmittance Aggregometry

Agonist: 20 μmol/L ADP

Value: Agg_{max} >50% *

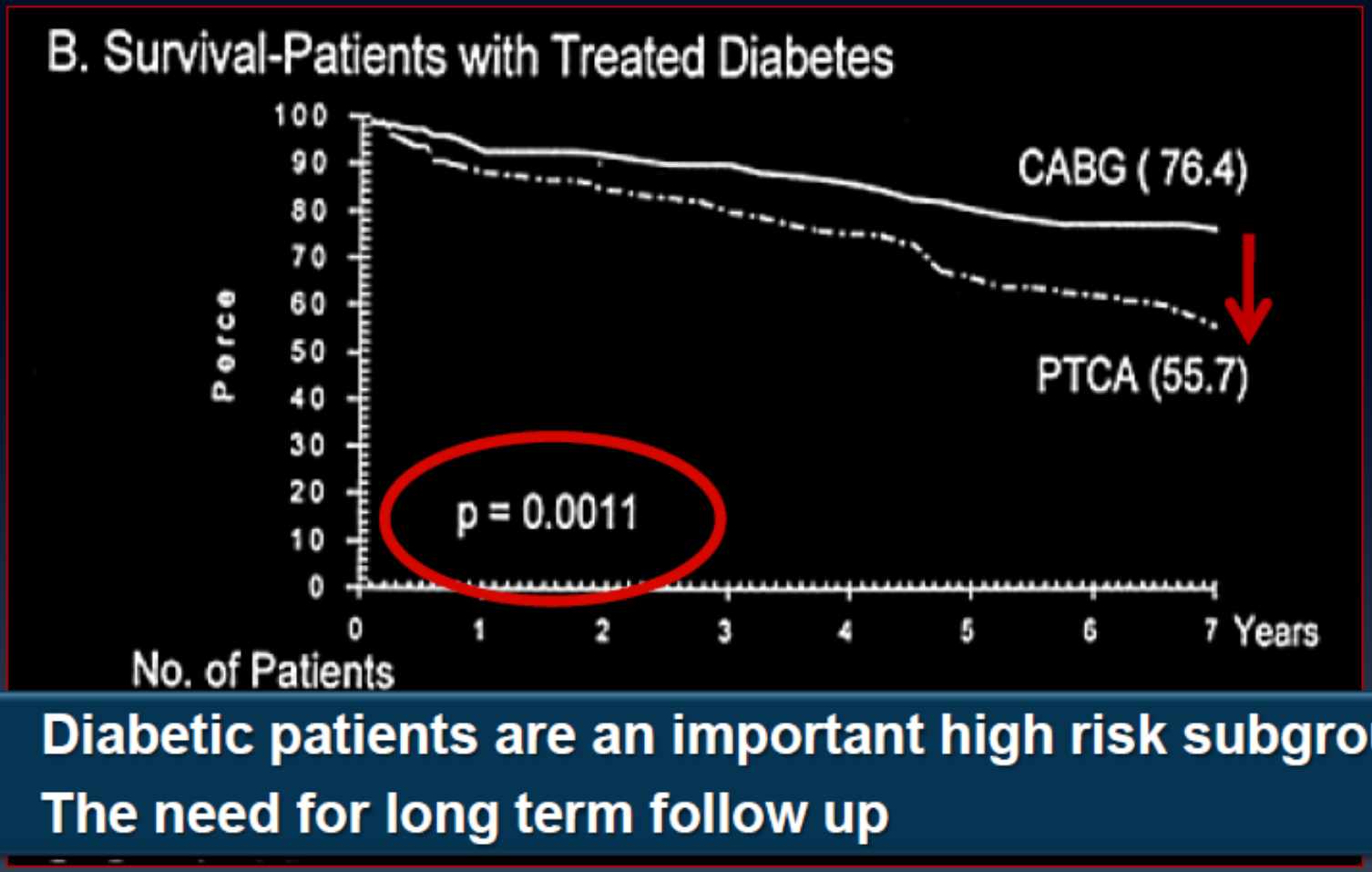
* Suggested therapeutic threshold for $P2Y_{12}$ inhibition as in the PREPARE POST-STENTING study showed that patients with post-treatment platelet reactivity above this value were at very high risk of clinical events (*Gurbel PA et al. J Am Coll Cardiol 2005;46:1820-6*).

Outcome According to Diabetic Status at 12 Months



Serruys, ESC 2008

BARI: Seven year outcome in diabetics

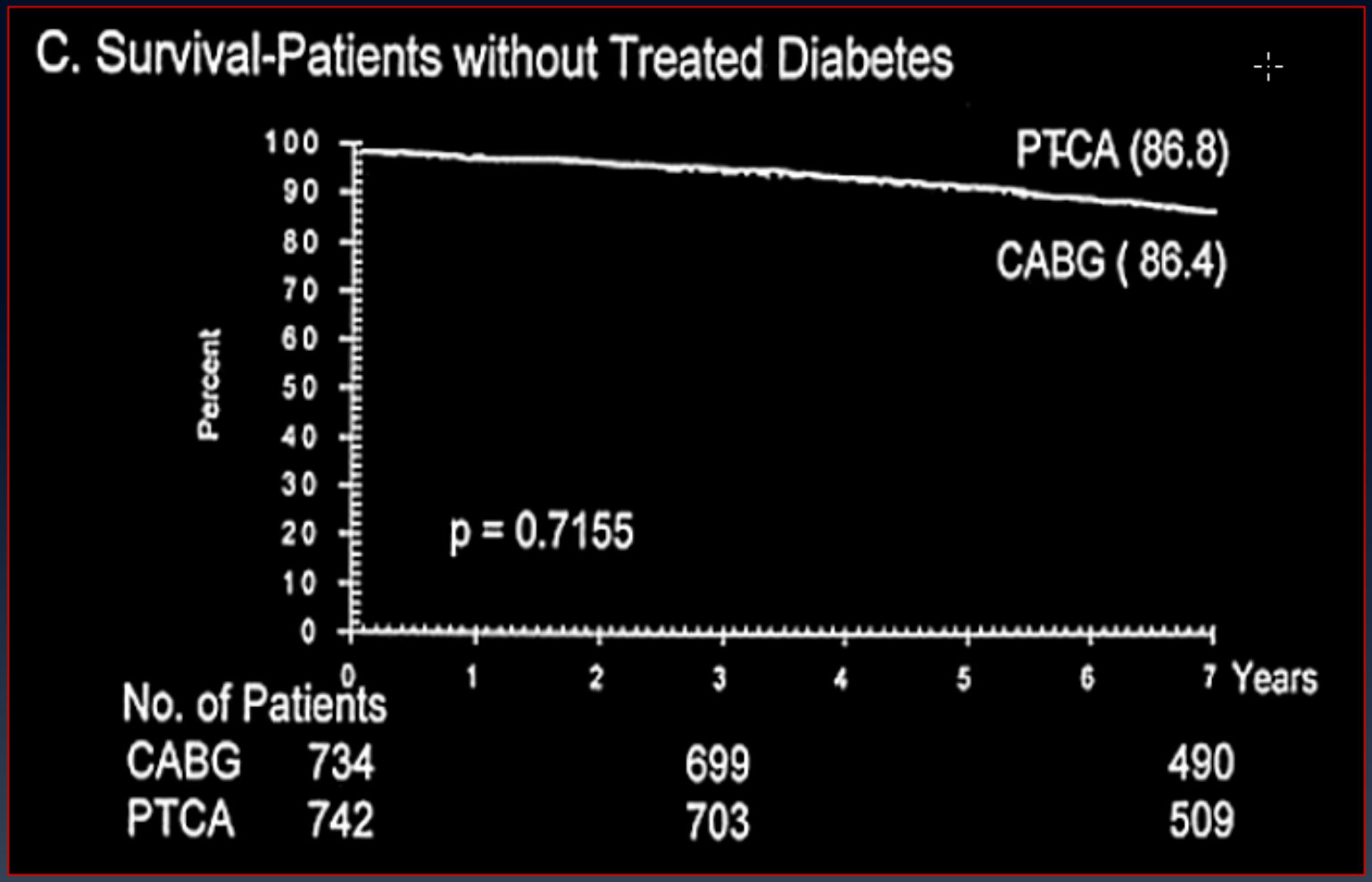


Diabetic patients are an important high risk subgroup

The need for long term follow up

BARI Investigators, J Am Coll Cardiol 2000, 35: 1122-29

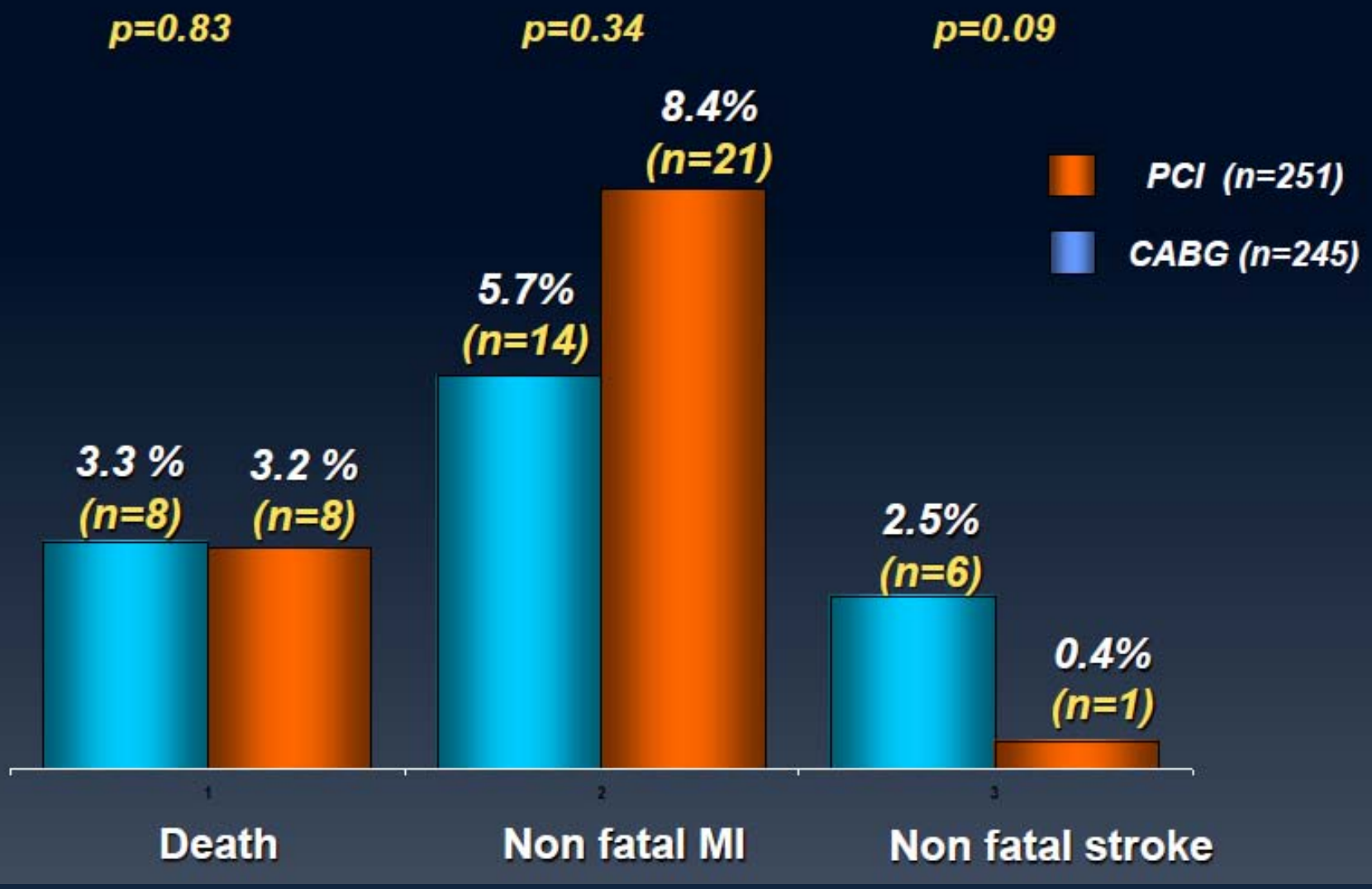
BARI: Seven year outcome in non diabetics



1476 of 1829 patients (81%)

BARI Investigators, J Am Coll Cardiol 2000, 35: 1122-29

Individual 1 year outcomes



ARC Proposed Standard Definition

1) Stent Thromboses will fall into one of three types of evidence:

Definite / Confirmed

Acute Coronary Syndrome (ACS) AND Angiographic/Pathologic Confirmation

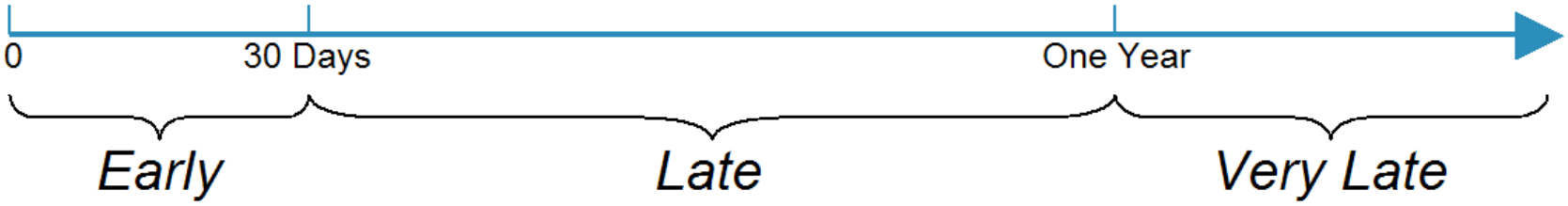
Probable

Unexplained Death (≤ 30 days) OR Target Vessel MI without angiographic confirmation of stent thrombosis or other identified culprit lesion

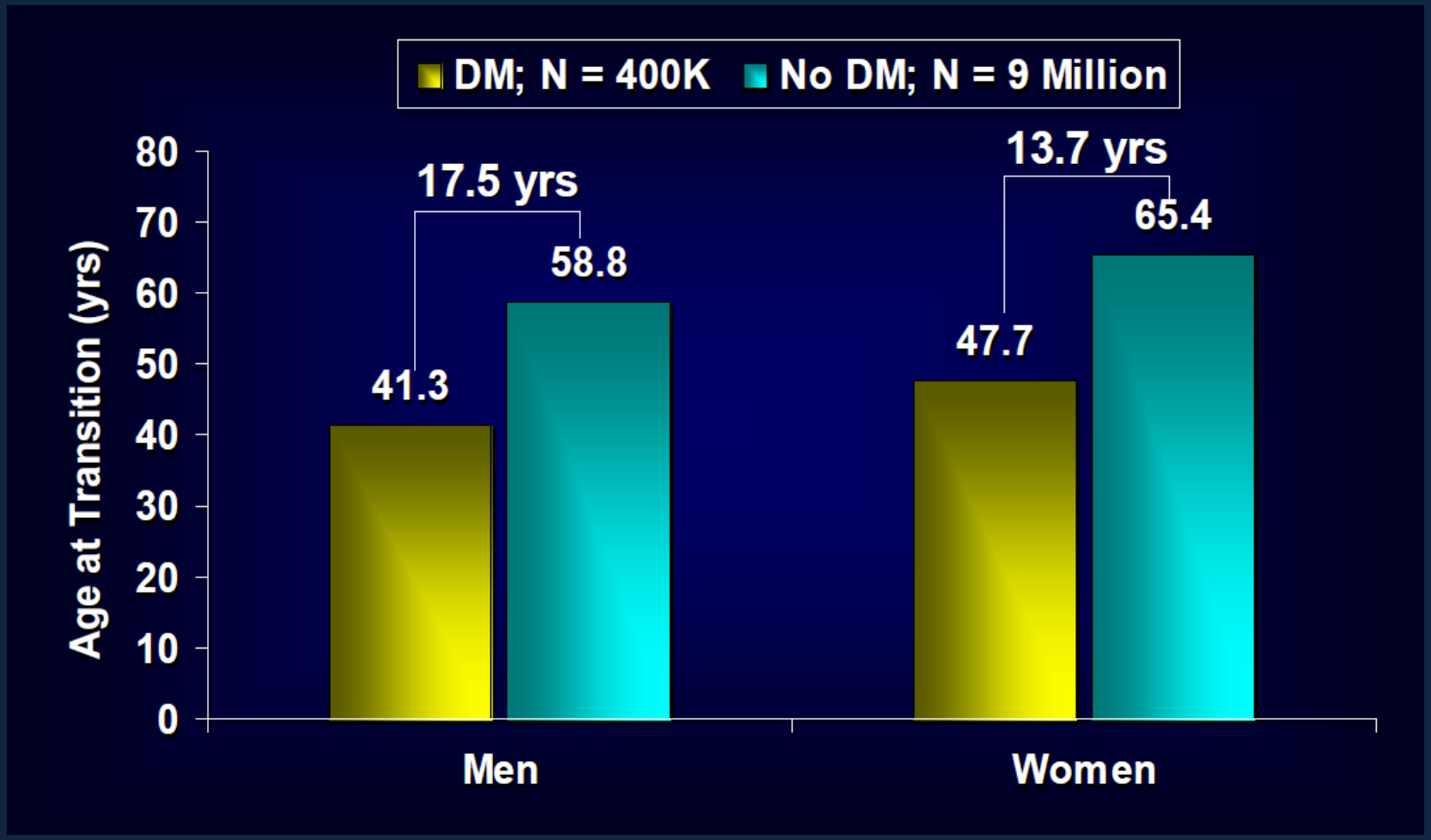
Possible

Unexplained Death (>30 days)

2) Stent Thromboses will also fall into one of three time periods:

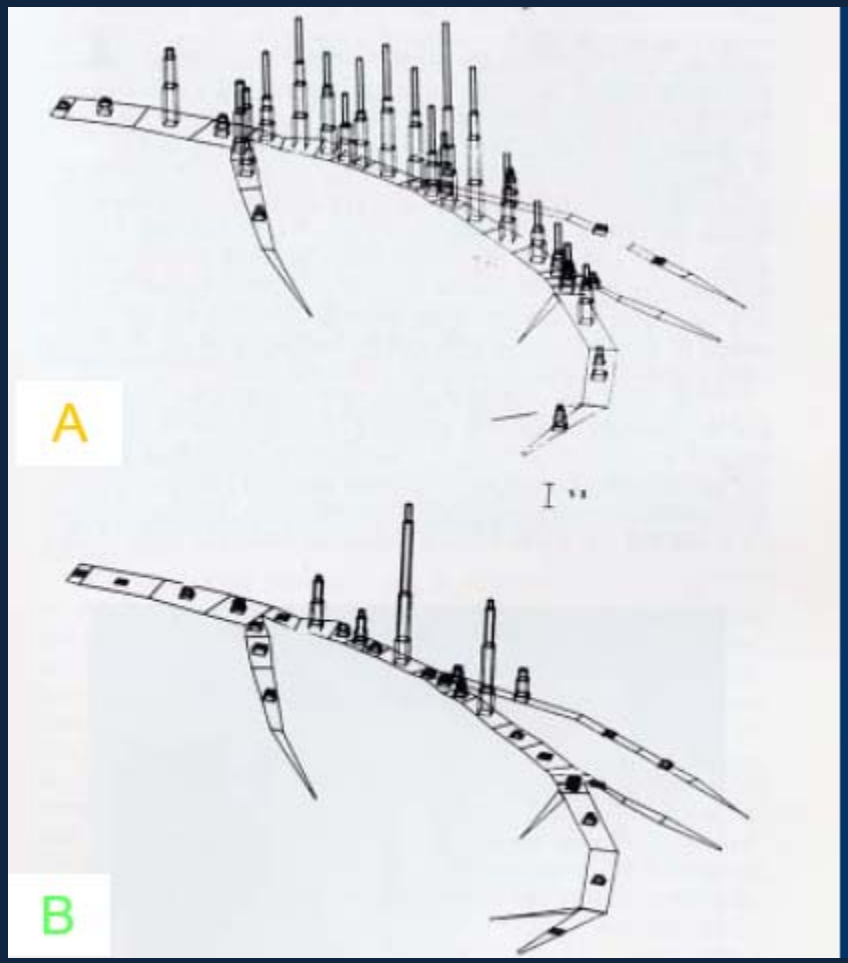


Diabetes confers an equivalent risk to ageing 15 years



G Booth,The Lancet,2006 ; 368: 29-36

Beyond restenosis: lesion location



A. LAD lesions in stable angina

n=302

B. LAD lesions in ACS

n=308

Gotsman et al. AJC 1992;70:715

Influence of Diabetes Mellitus on Clopidogrel-induced Antiplateles Effects (Acute phase)