ΔΙΑΔΕΡΜΙΚΗ ΣΤΕΦΑΝΙΑΙΑ ΠΑΡΕΜΒΑΣΗ ΣΕ ΕΙΔΙΚΕΣ ΥΠΟΟΜΑΔΕΣ ΑΣΘΕΝΩΝ

Σακχαρώδης Διαβήτης

Λάμπρος Κ. Μόσιαλος
Επεμβατικός Καρδιολόγος
ΓΝ «ΠΑΠΑΓΕΩΡΓΙΟΥ»

Diabetes and Cardiovascular Disease
The basic facts

- Diabetes is increasing rapidly [1]
- Diabetes currently affects 246 million people worldwide and is expected to affect 380 million by 2025[1]

[1] www.idf.org

Diabetes and Cardiovascular Risk

In patients with diabetes:

- ~65% of deaths are due to heart disease and stroke
- Mortality due to heart disease is 2 to 4 times higher than in patients without diabetes
- Stroke is 2 to 4 times more common than in patients without diabetes

American Diabetes Association. National Diabetes Fact Sheet. Available at: http://www.diabetes.org/diabetes-statistics/national-diabetes-fact-sheet.jsp. Accessed January 2007.

Diabetics have significantly higher event rates because of

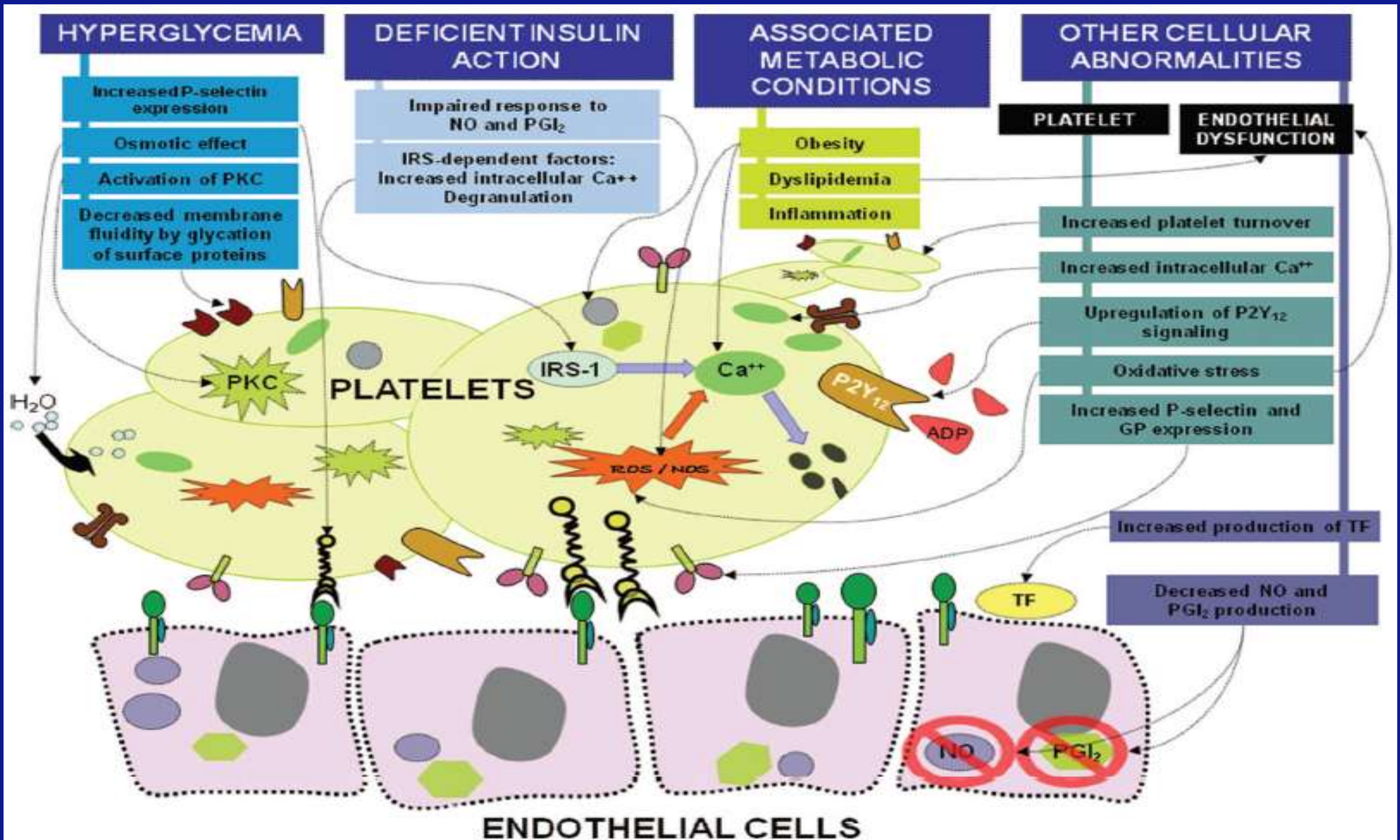
- Endothelial dysfunction
- Diabetic dyslipidemia
- Impaired platelet function
- Altered coagulation / fibrinolysis
- Increased smooth muscle cell proliferation
- Toxic hyperglycemia

Diabetes and outcomes

How does diabetes impact on individual patient outcomes during revascularisation?

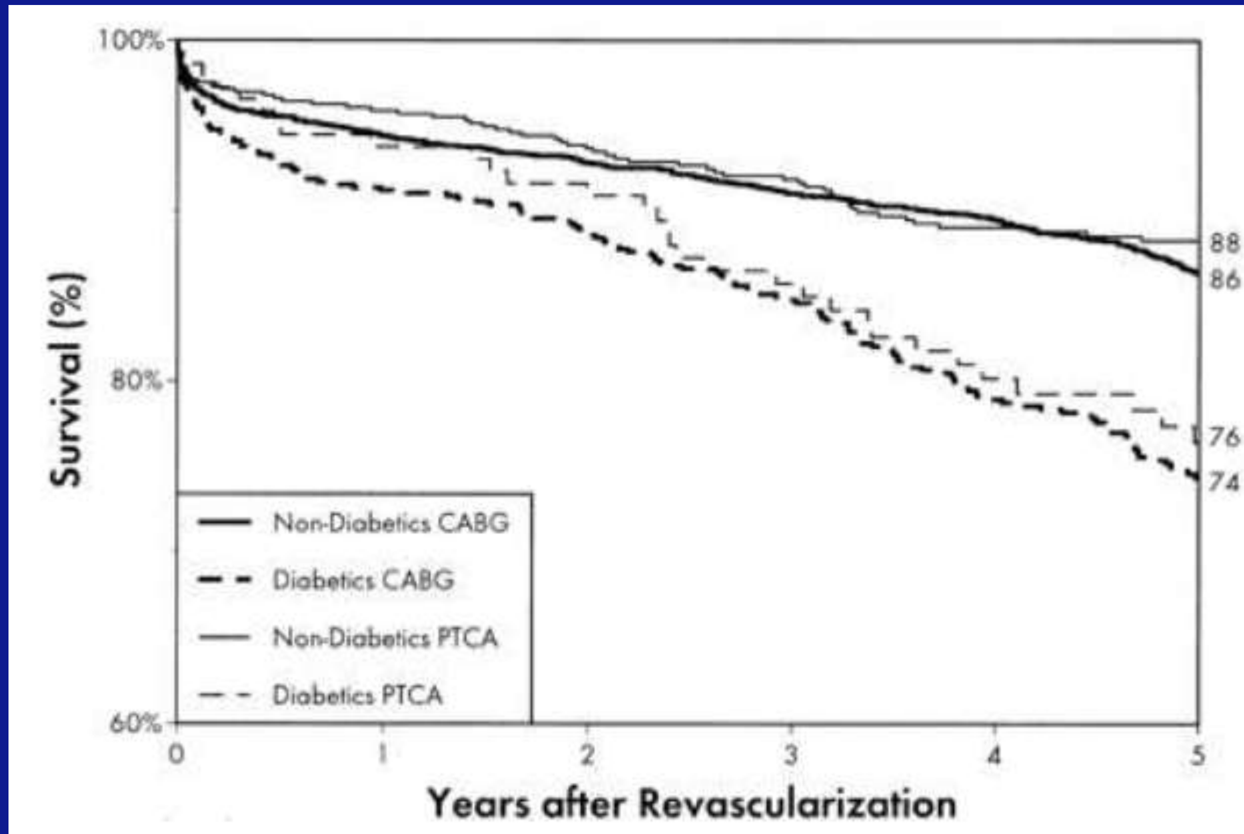
- More extensive atherosclerosis and diffuse multivessel disease
- Smaller vessels
- Longer lesions
- More highly stenotic lesions and greater plaque burden
- Higher incidence of left main disease

Mechanisms involved in platelet dysfunction in DM patients



Coronary Revascularization in DM

Patients with multivessel disease treated by PCI or CABG
DM n=770 /Non DM n=2450



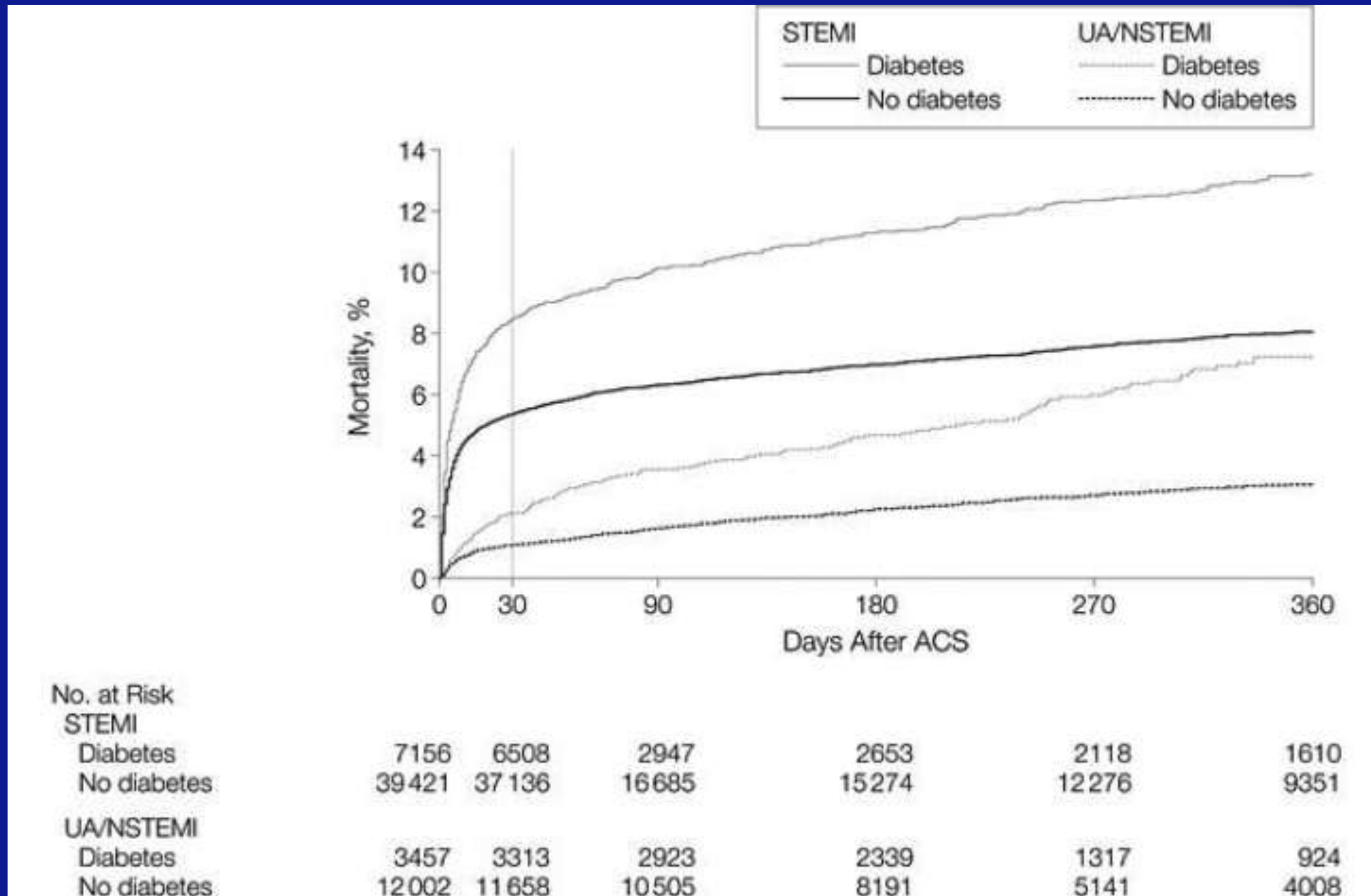
No DM

DM

Barsness et al. Circulation 1997;96:2551-65

Revascularization in ACS –DM Patients

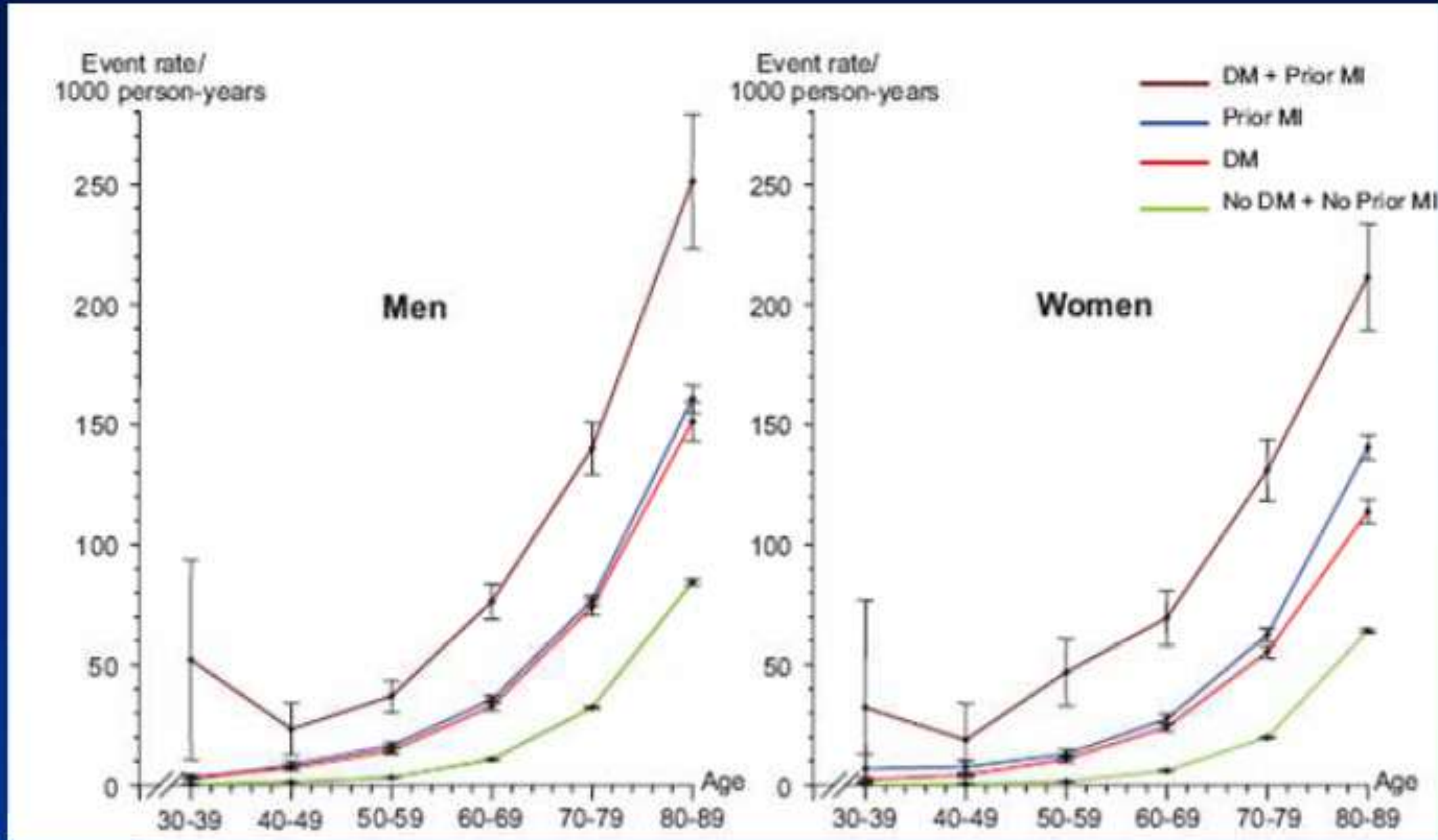
11 TIMI trials from 1997-2006



Donahoe SM et al. JAMA 2007;298:765-75

Risk of Cardiovascular Outcomes in Diabetics

Mortality



Event rates for cardiovascular mortality in men and women stratified by age and sex in relation to DM and a prior MI

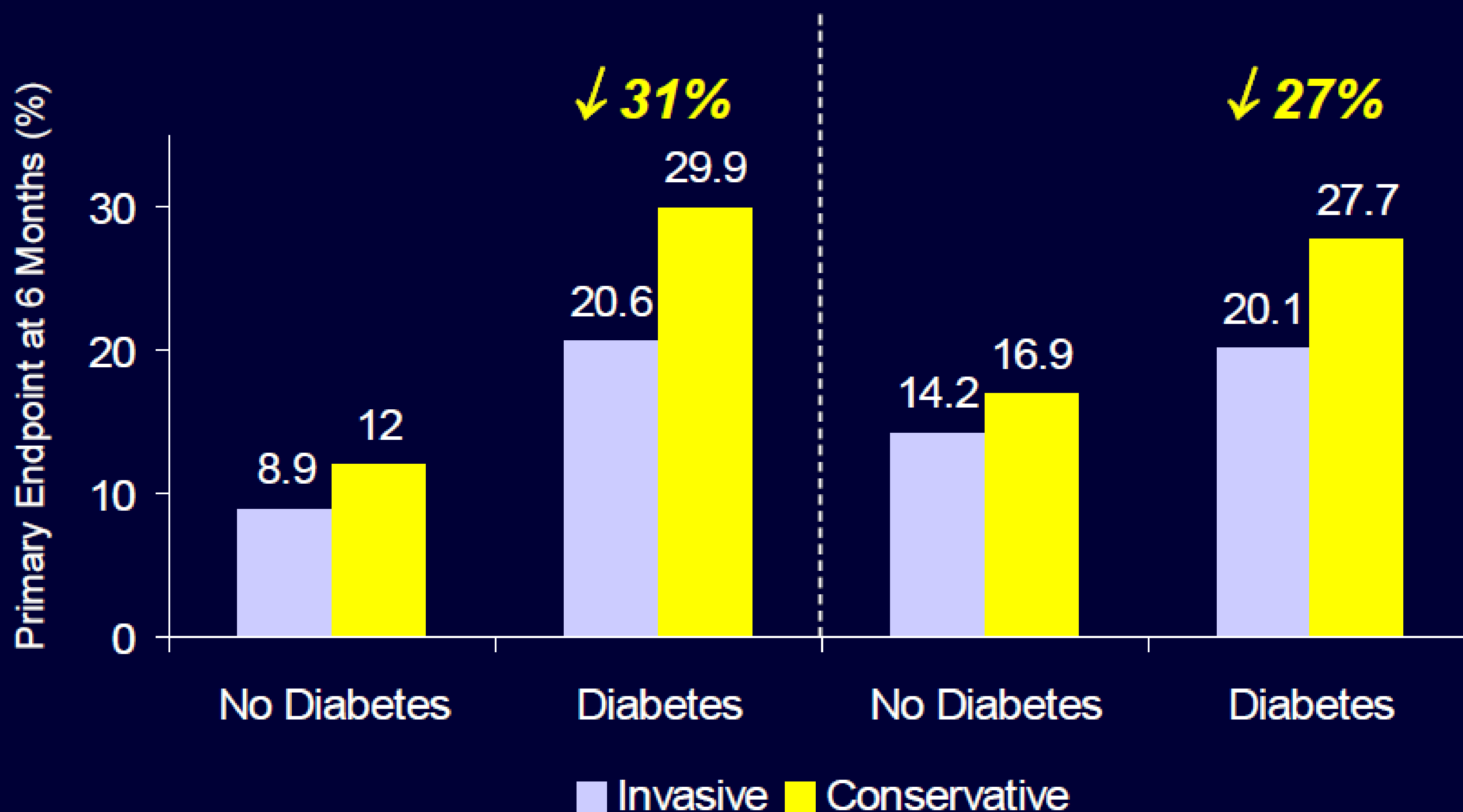
Shramm TK et al

Circulation. 2008 Apr 15;117(15):1945-54

ACS: Invasive vs. Conservative Strategy

Impact of Diabetes Mellitus

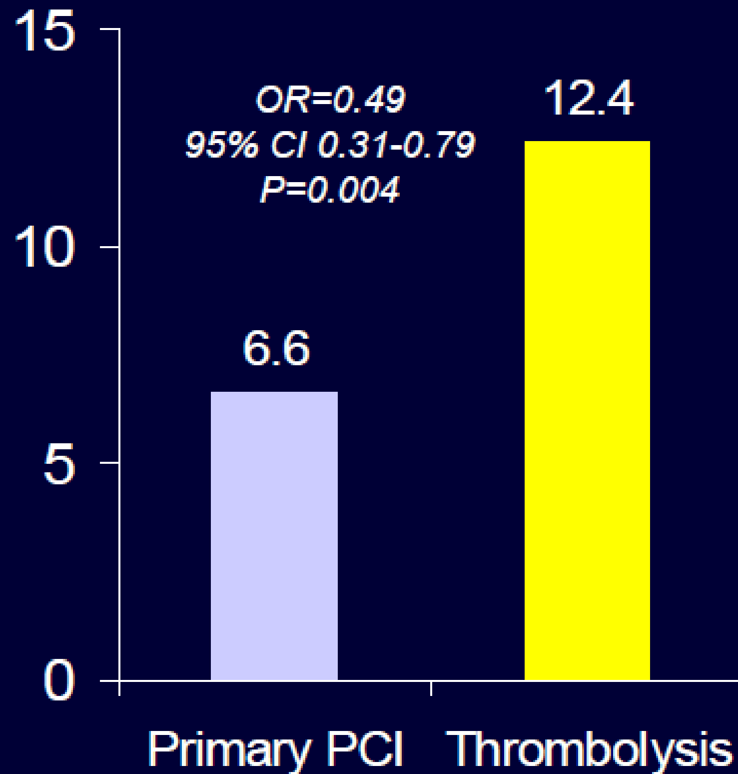
Norhammar A et al. *JACC* 2004;43:585-91
Roffi et al. *Eur Heart J* 2004;25:190-8

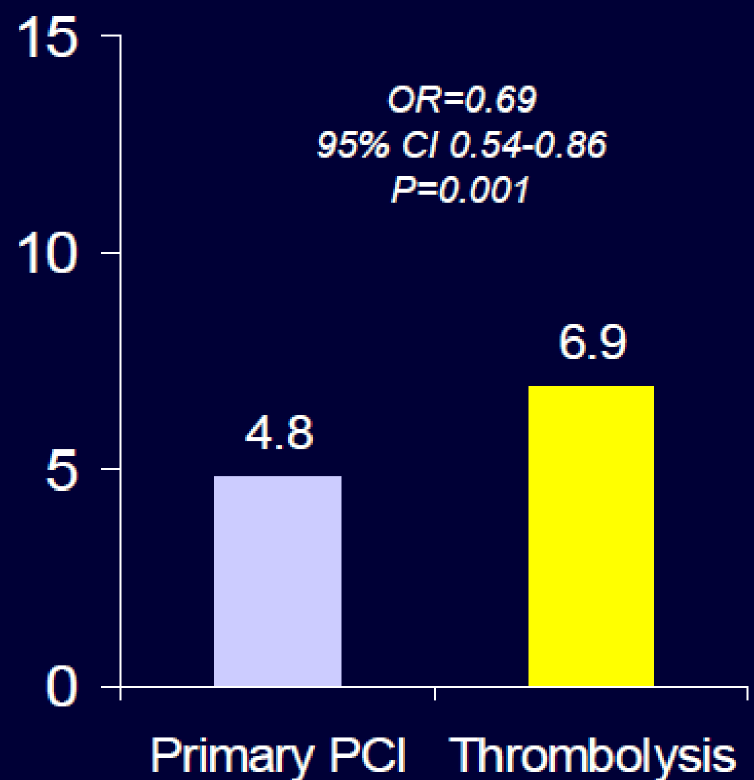


Acute ST-Elevation Myocardial Infarction

Primary PCI versus Thrombolysis in Diabetics

Timmer JR et al. *Arch Intern Med 2007*;167:1353-59





19 RCTs comparing PPCI and Thrombolysis in 6,315 patients

Revascularization in Diabetic Patients With Stable Coronary Disease: Stent or Surgery or Medical Management

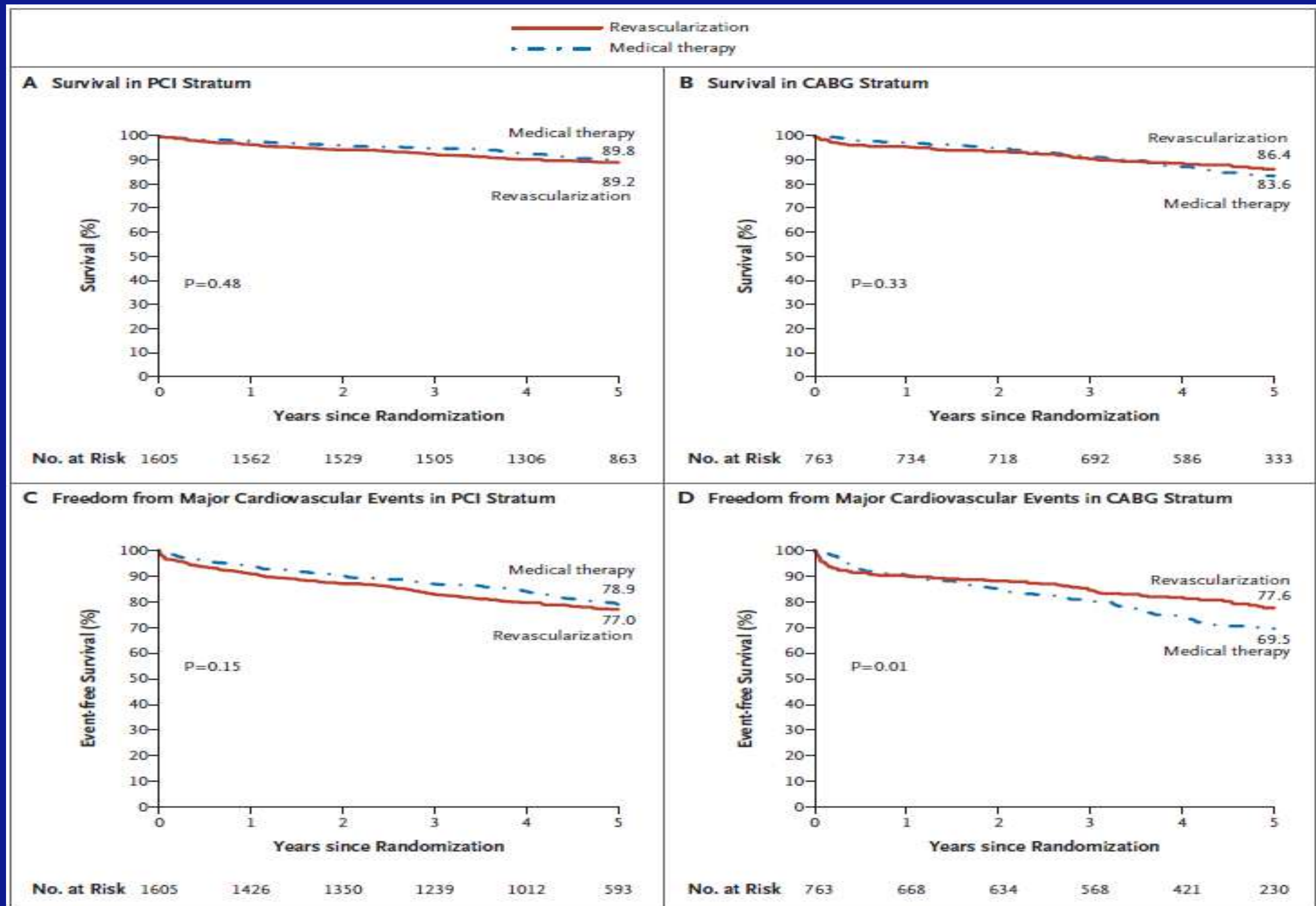
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 11, 2009 VOL. 360 NO. 24

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

The BARI 2D Study Group*

BARI 2D Mortality and MACE



Results of BARI 2 D cannot be extrapolated

- to unstable or in other respect higher risk diabetic patients

- to diabetic patients with unknown coronary anatomy

Impact of Drug-Eluting Stents

35 Randomized trials comparing DES with BMS (3852 DM patients)

BMJ

RESEARCH

Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis

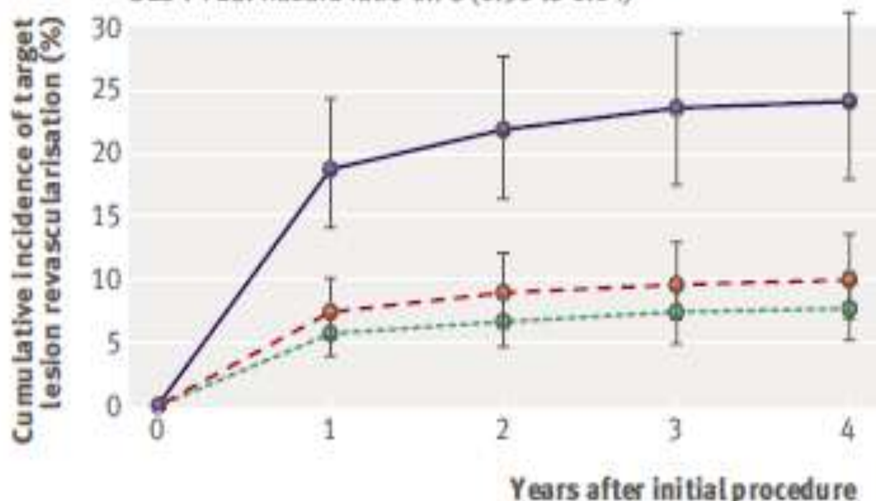
Christoph Stettler, senior research fellow,[1,2,3] Sabin Allemann, research fellow,[1,2] Simon Wandel, research fellow,[1] Adnan Kastrati, professor of cardiology,[4] Marie Claude Morice, professor of cardiology,[5] Albert Schömig, professor of medicine,[4] Matthias E Pfisterer, professor of cardiology,[6] Gregg W Stone, professor of medicine,[7] Martin B Leon, professor of medicine ,[7] José Suárez de Lezo, professor of cardiology,[8] Jean-Jacques Goy, professor of interventional cardiology,[9] Seung-Jung Park, professor of cardiology,[10] Manel Sabaté, associate professor of cardiology,[11] Maarten J Suttorp, head of department ,[12] Henning Kelbaek, associate professor of cardiology ,[13] Christian Spaulding, professor of cardiology ,[14] Maurizio Menichelli, interventional cardiologist,[15] Paul Vermeersch, interventional cardiologist,[16] Maurits T Dirksen, training fellow in cardiology,[17] Pavel Cervinka, cardiologist,[18] Marco De Carlo, vice director,[19] Andrejs Erglis, associate professor of cardiology,[20] Tania Chechi, interventional cardiologist,[21] Paolo Ortolani, interventional cardiologist,[22] Martin J Schalij, professor of cardiology,[23] Peter Diem, head of division ,[2] Bernhard Meier, professor of cardiology,[24] Stephan Windecker, head of invasive cardiology ,[24,25] Peter Jüni, head of division [1,25]

head of division [1,25]

DES-BMS in people with and without DM

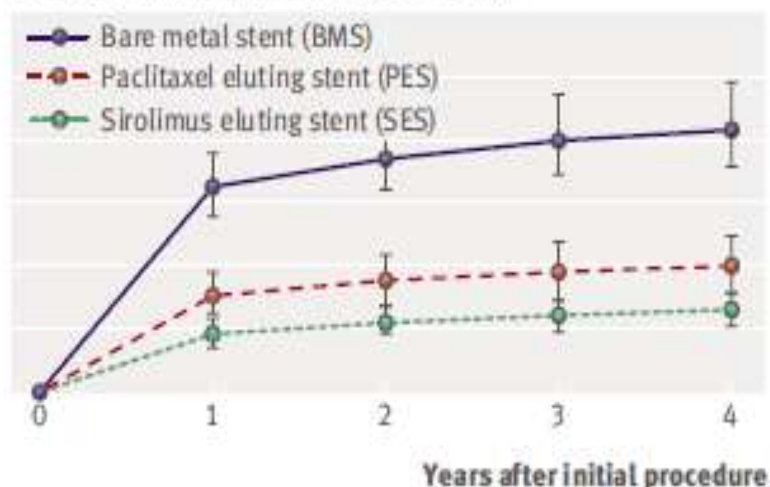
People with diabetes mellitus

SES *v* BMS: hazard ratio 0.29 (0.19 to 0.45)
PES *v* BMS: hazard ratio 0.38 (0.26 to 0.56)
SES *v* PES: hazard ratio 0.78 (0.50 to 1.14)



People without diabetes mellitus

SES *v* BMS: hazard ratio 0.29 (0.19 to 0.42)
PES *v* BMS: hazard ratio 0.46 (0.32 to 0.60)
SES *v* PES: hazard ratio 0.64 (0.49 to 0.84)

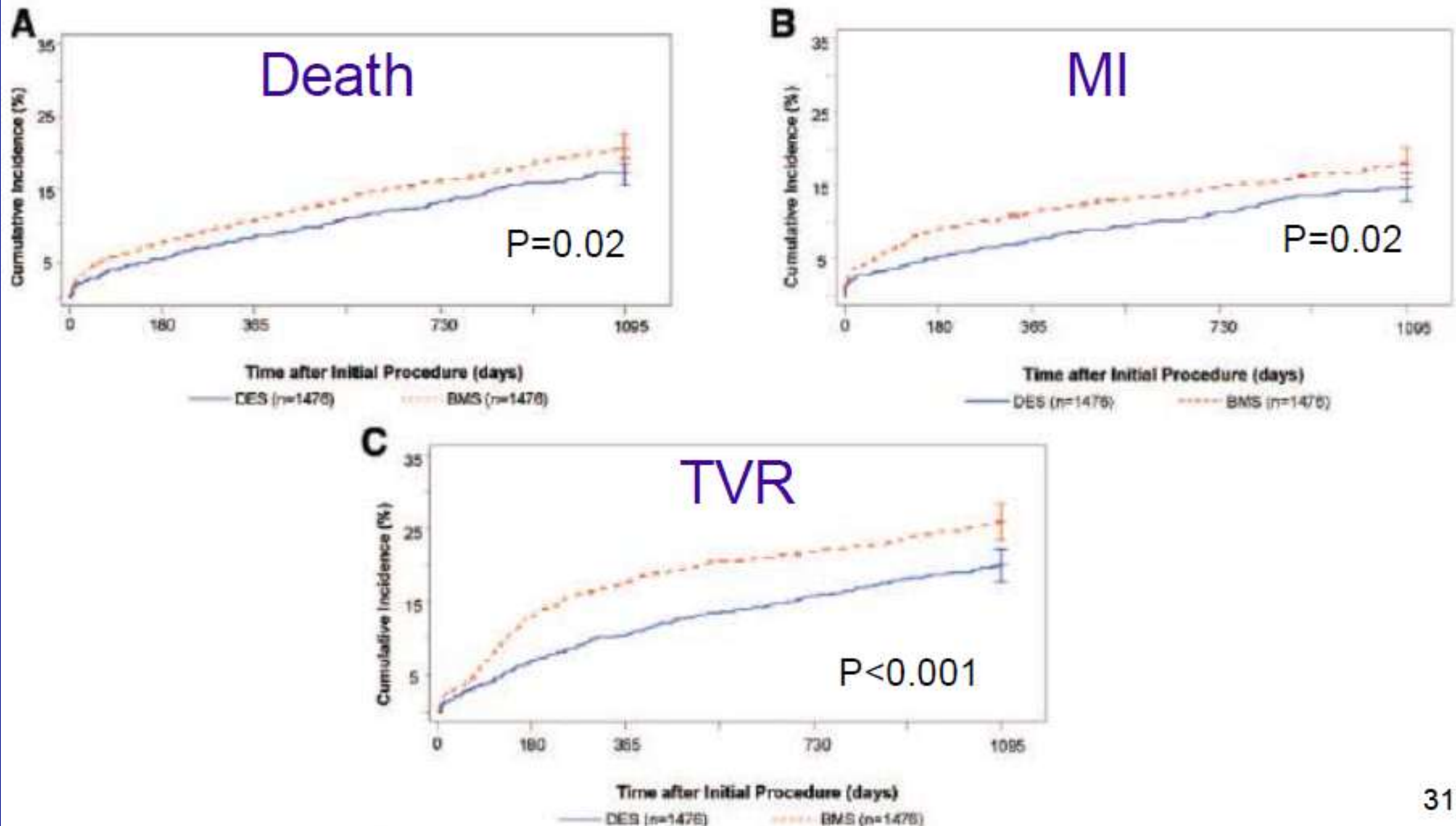


No of events/No of patients

BMS	935	193/935	10/496	4/282	2/185	2851	423/2851	35/1619	6/916	3/711
PES	1171	99/1171	21/946	3/487	3/146	3582	278/3582	66/2844	13/1509	3/691
SES	1122	80/1122	14/780	1/446	2/66	2857	161/2857	34/1963	6/906	1/164

No Difference in Mortality or MI

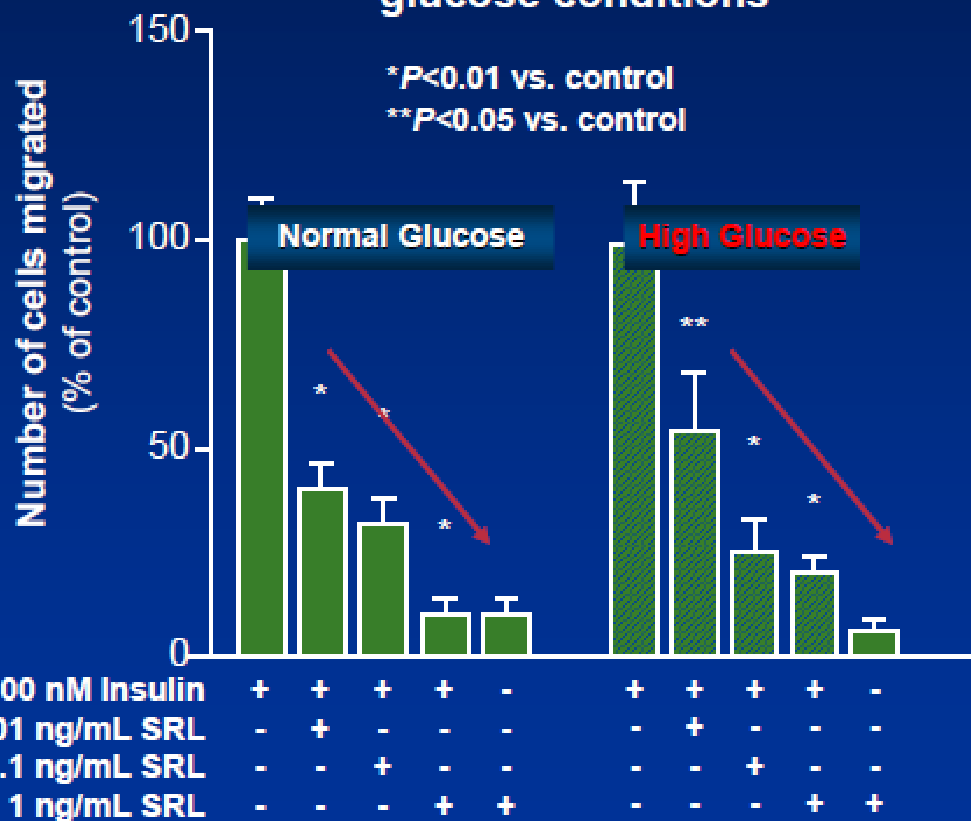
DES or BMS Stenting in Diabetics: The Massachusetts Data Analysis Center Registry

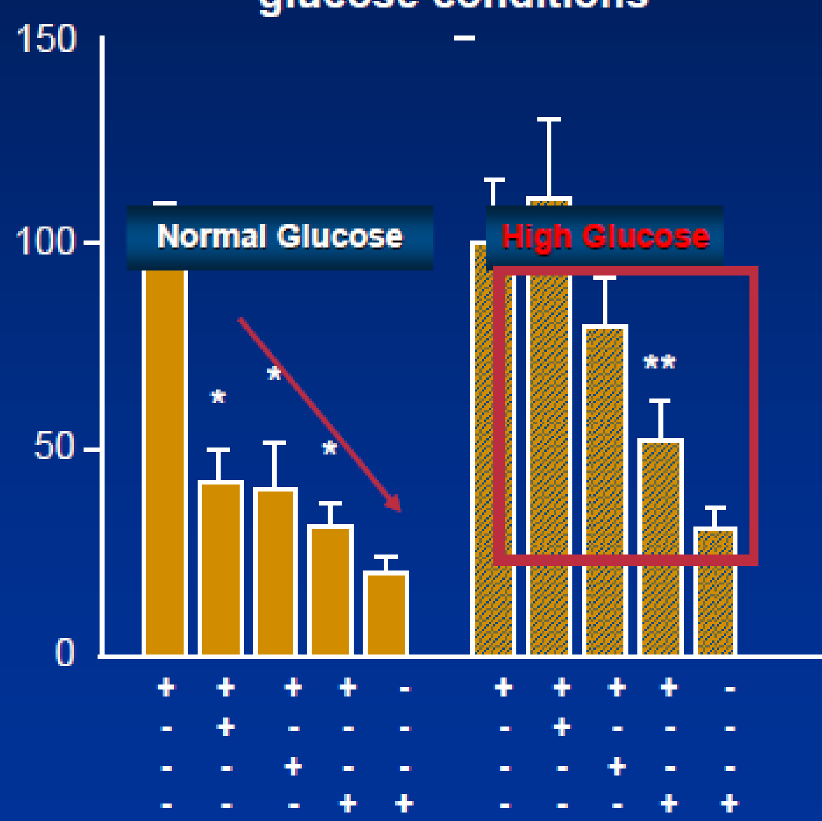


Garg P Circulation 2008;118:2277-2285

Differences among drug-eluting stents

Paclitaxel, but not sirolimus, effectively inhibits migration of Smooth Muscle Cells in Diabetic Model





C. Patterson: Arteriosclerosis, Thrombosis & Vascular Biology, April 2006

EES – PES in DM Patients

Differential Clinical Responses to Everolimus-Eluting and Paclitaxel-Eluting Coronary Stents in Patients With and Without Diabetes Mellitus

Gregg. W. Stone, MD; Elvin Kedhi, MD; Dean J. Kereiakes, MD; Helen Parise, ScD; Martin Fahy, MSc; Patrick W. Serruys, MD, PhD; Pieter C. Smits, MD, PhD

Background—Some (but not all) prior trials have reported differential outcomes after percutaneous coronary intervention with paclitaxel-eluting stents versus stents eluting rapamycin analogs according to the presence of diabetes mellitus. These studies lacked sufficient power to examine individual safety and efficacy end points.

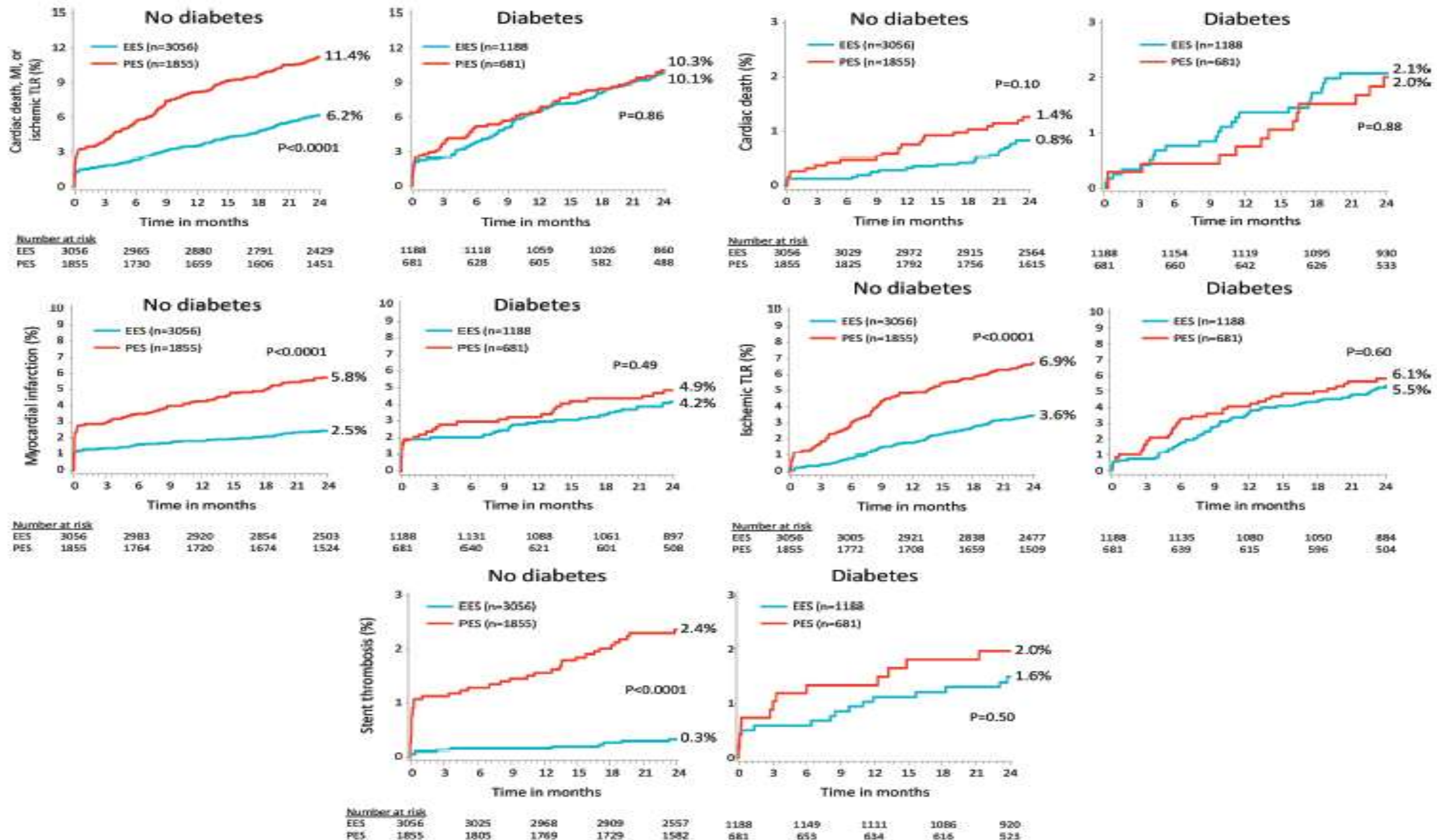
Methods and Results—To determine whether an interaction exists between the presence of diabetes mellitus and treatment with everolimus-eluting stents compared with paclitaxel-eluting stents, we pooled the databases from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SPIRIT) II, SPIRIT III, SPIRIT IV, and A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice (COMPARE) trials in which percutaneous coronary intervention was performed in 6780 patients, 1869 (27.6%) of whom had diabetes mellitus. Patients without diabetes mellitus treated with everolimus-eluting stents compared with paclitaxel-eluting stents had significantly reduced 2-year rates of mortality (1.9% versus 3.1%; $P=0.01$), myocardial infarction (2.5% versus 5.8%; $P<0.0001$), stent thrombosis (0.3% versus 2.4%; $P<0.0001$), and ischemia-driven target lesion revascularization (3.6% versus 6.9%; $P<0.0001$). In contrast, among patients with diabetes mellitus, there were no significant differences between the 2 stent types in any measured safety or efficacy parameter. Significant interactions were present between diabetic status and stent type for the 2-year end points of myocardial infarction ($P=0.01$), stent thrombosis ($P=0.0006$), and target lesion revascularization ($P=0.02$).

Conclusions—We have identified a substantial interaction between diabetes mellitus and stent type on clinical outcomes after percutaneous coronary intervention. In patients without diabetes mellitus, everolimus-eluting stents compared with paclitaxel-eluting stents resulted in substantial 2-year reductions in death, myocardial infarction, stent thrombosis, and target lesion revascularization, whereas no significant differences in safety or efficacy outcomes were present in diabetic patients.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00180310 (SPIRIT II), NCT00180479 (SPIRIT III), NCT00307047 (SPIRIT IV), and NCT01016041 (COMPARE).

(***Circulation*. 2011;124:893-900.**)

Time-to-event curves for major adverse cardiac events



Percutaneous vs. Surgical Approach in Multivessel Disease

SYNTAX-CARDIa DM Subgroup

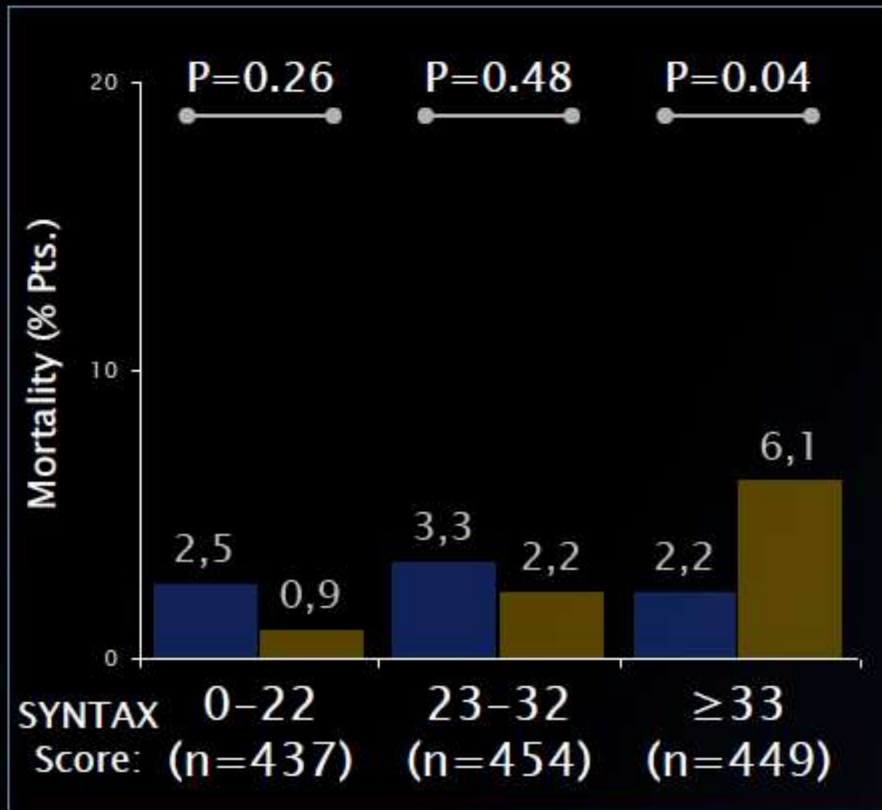
Table 1 One-year events in the diabetic subgroup of SYNTAX trial and in the CARDIa trial

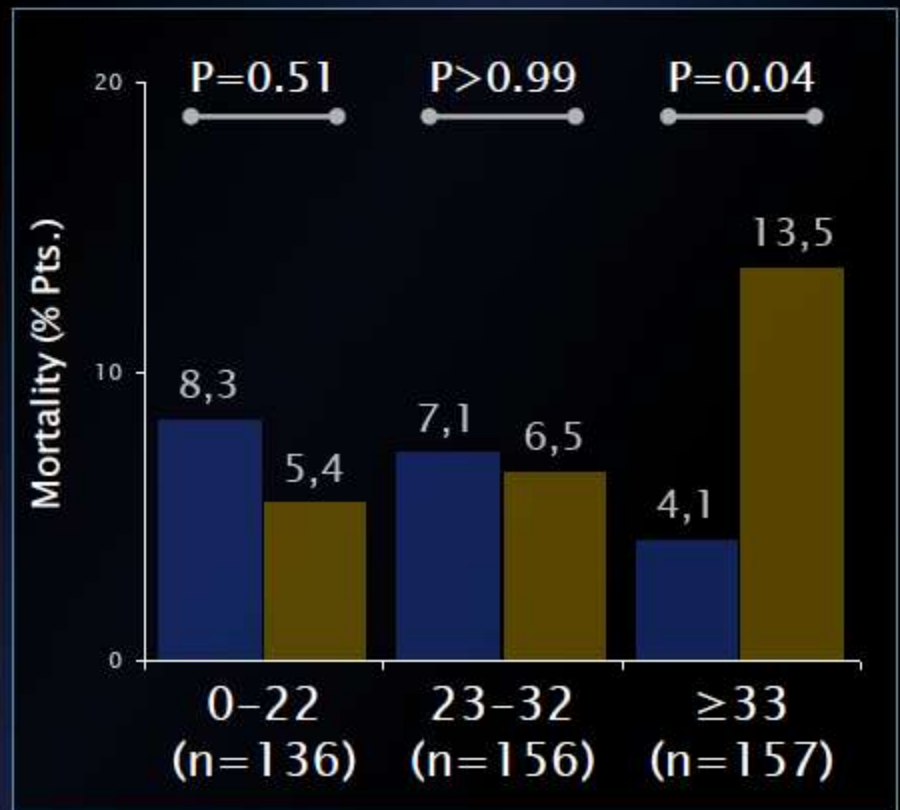
	SYNTAX (n = 452)			CARDIa (n = 510)		
	CABG (n = 221) (%)	PCI (n = 231) (%)	P-value	CABG (n = 248) (%)	PCI (n = 254) (%)	P-value
Death	6.4	8.4	0.43	3.2	3.2	0.97
MI	4.4	4.8	0.83	5.7	9.8	0.088
Stroke	2.5	0.9	0.26	2.8	0.4	0.066
Repeat revascularization	6.4	20.3	<0.001	2.0	11.8	<0.001
Death/MI/stroke	10.3	10.1	0.96	10.5	13.0	0.393
Death/MI/stroke repeat revascularization	14.2	26.0	0.003	11.3	19.3	0.016

Data extracted from refs[30,31].
MI, myocardial infarction.

1 Year Mortality by SYNTAX Score
3VD/LM Diabetic and Non-Diabetic Patients

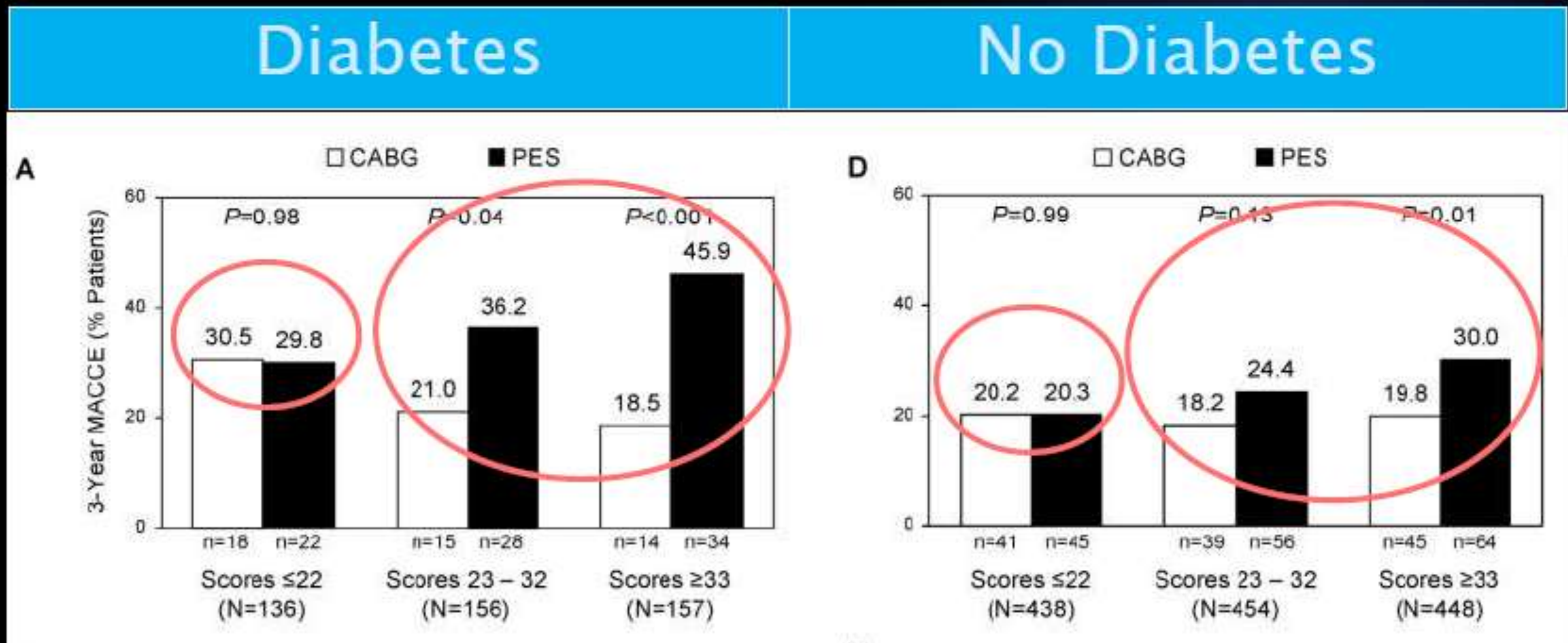
CABG TAXUS





SYNTAX

3 Year Outcomes according to SYNTAX score and Diabetic Status



Syntax 4-Year Follow-up

Table 3. Three-Vessel Disease: 4-Year Follow-up

	CABG	PCI	*P* value
Intermediate Syntax Score	**(n=208)**	**(n=207)**	
Death	12.4%	18.6%	0.048
MI	3.1%	10.5%	0.004
Repeat Revascularization	8.3%	21.0%	0.0005
High Syntax Score	**(n=166)**	**(n=155)**	
Death	6.5%	14.5%	0.02
MI	1.9%	7.9%	0.01
Repeat revascularization	11.2%	26.7%	0.0005

Conclusion

Patients with 3-vessel and/or left main disease

Both diabetic status and lesion complexity impact the relative safety between CABG and PES and should be considered when evaluating treatment options in patients with left main and/or 3-vessel disease

Diabetes (columns) × **Lesion Complexity** (rows)

Lesion Complexity	Non Diabetic	Oral Meds	Insulin
High	CABG	CABG	CABG
Medium	CABG Or PCI	CABG Or PCI	CABG
Low	PCI or CABG	PCI or CABG	CABG

Retroactive weighting of the SYNTAX score against 1- and 5-year SYNTAX outcomes will provide treatment algorithms to help determine the best revascularization option for each patient

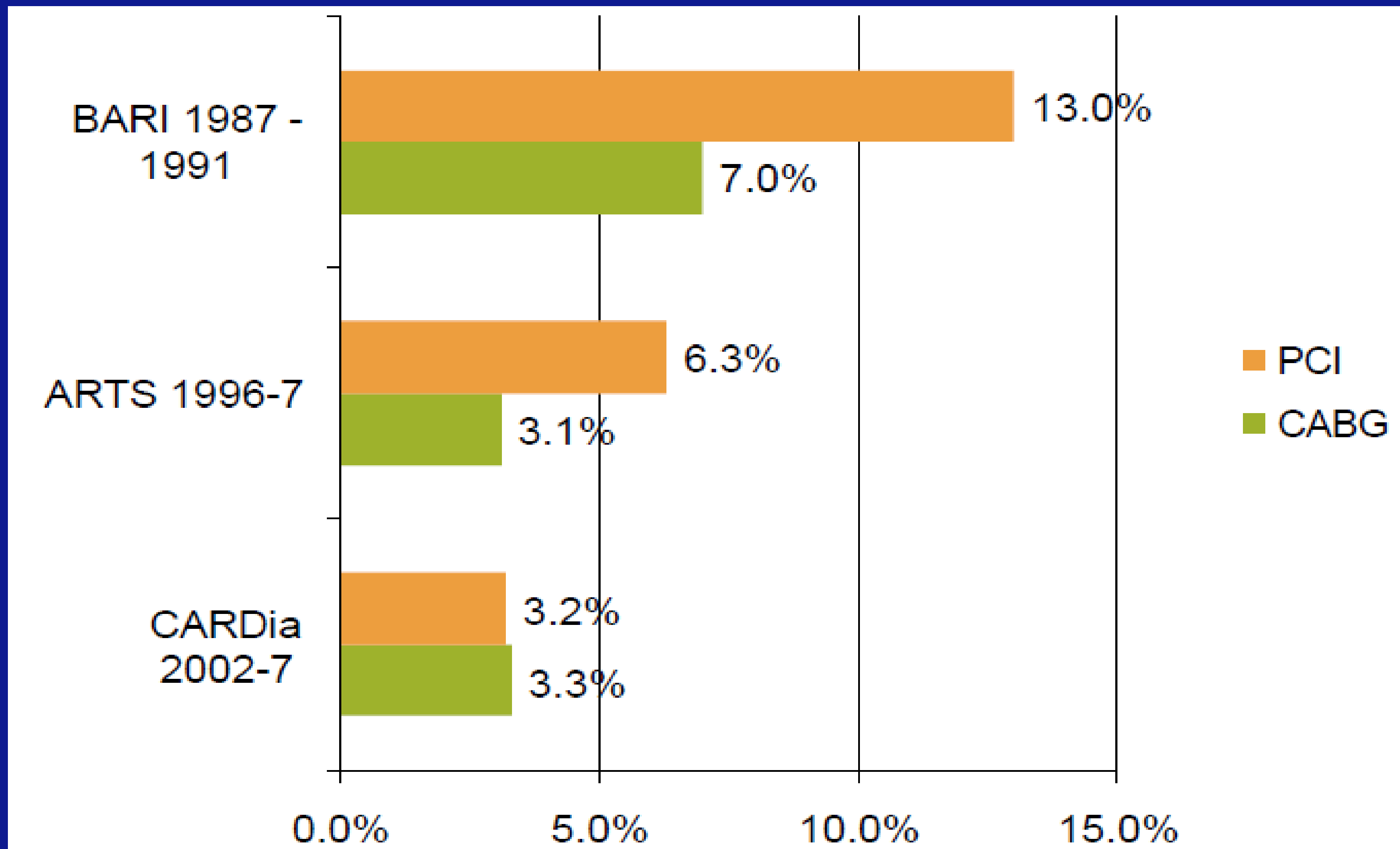
PCI and CABG both improved but PCI is improving faster

More stroke in CABG

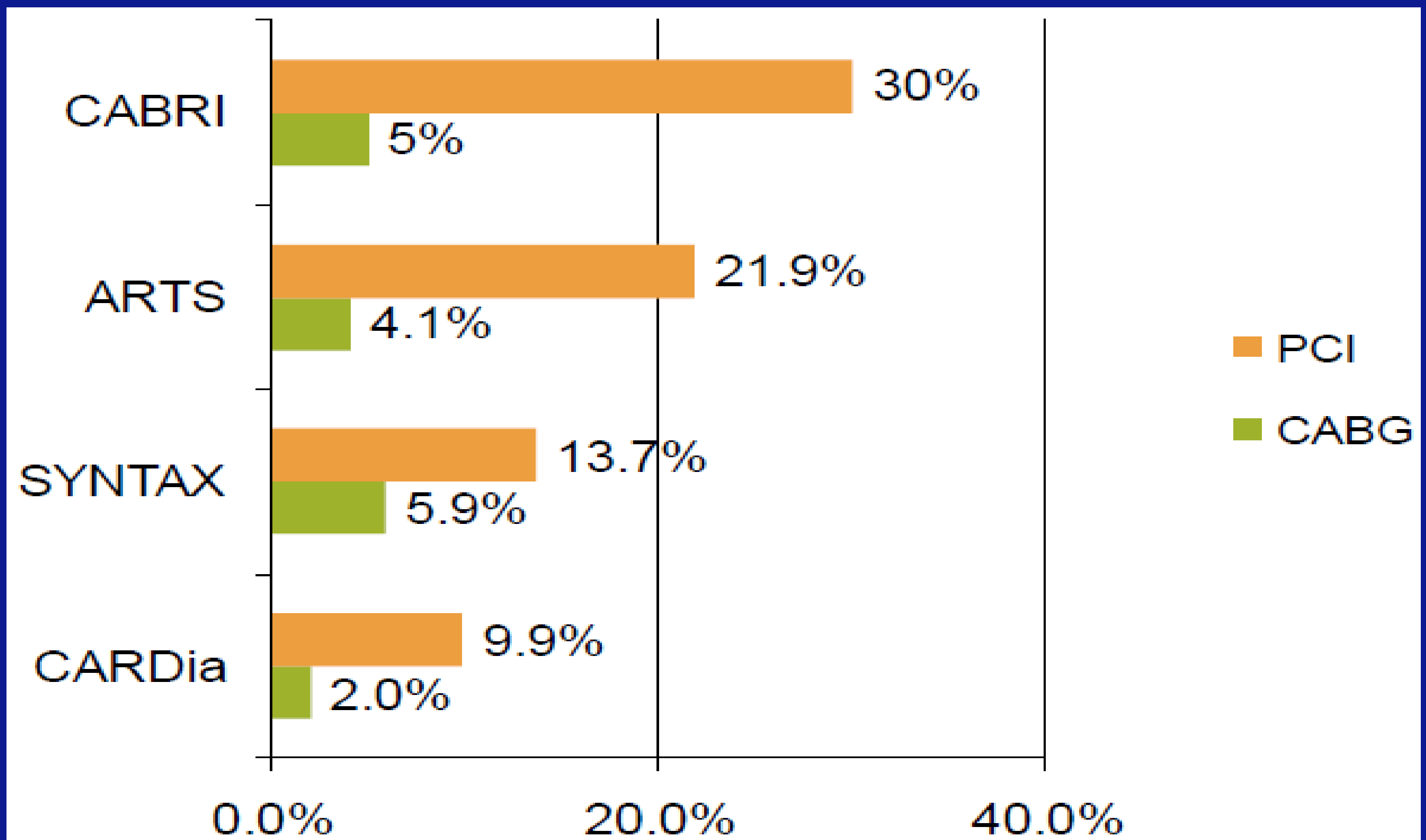
	CABG	PCI
ARTS (ARTS 2)	5.2%	1.8% (0.0%)
CARDia (DES subset)	2.4%	0.4% (0.0%)
SYNTAX	2.2%	0.6%

PCI is improving faster in MV Diabetes

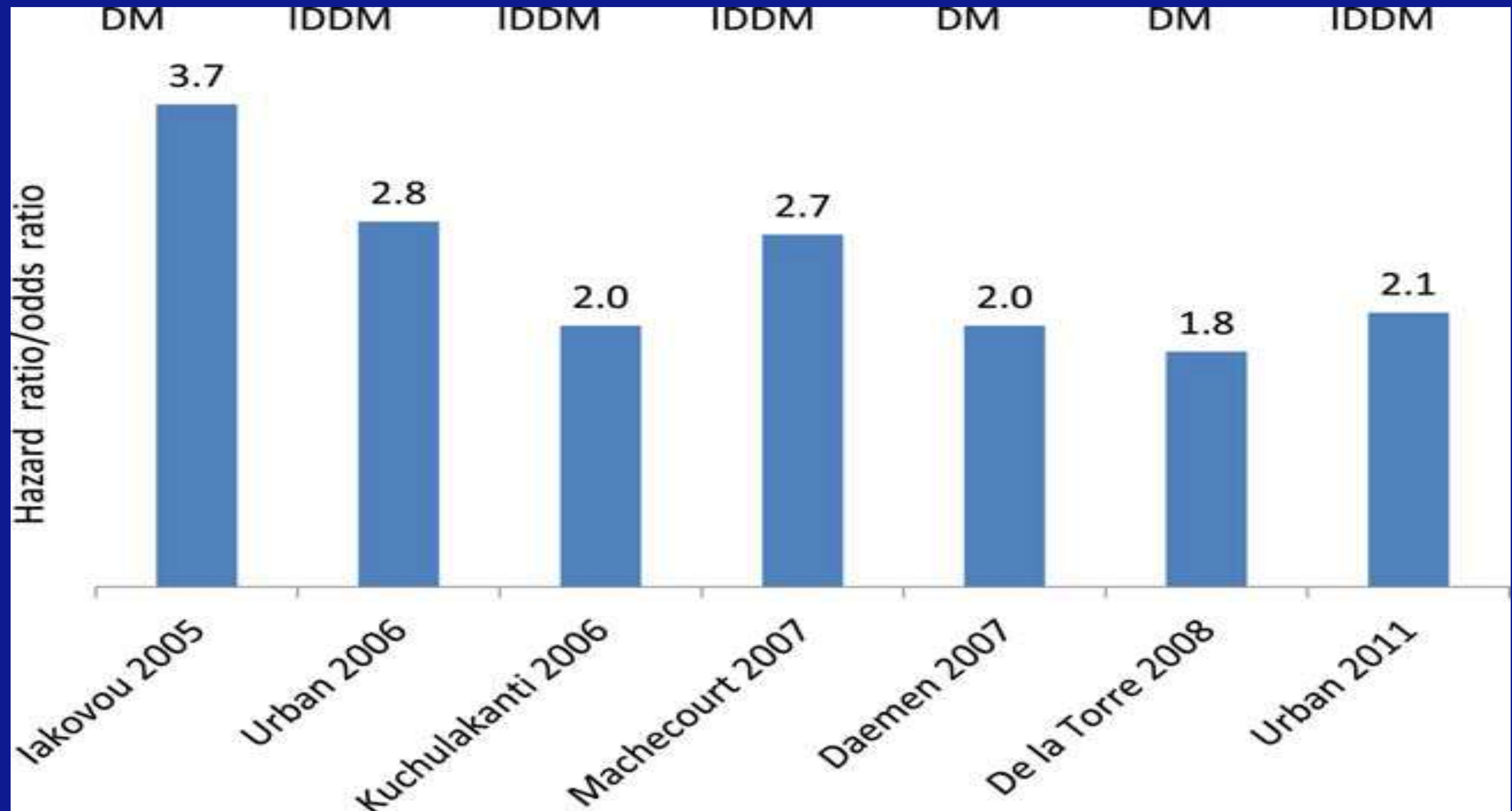
1-year Mortality in DM patients



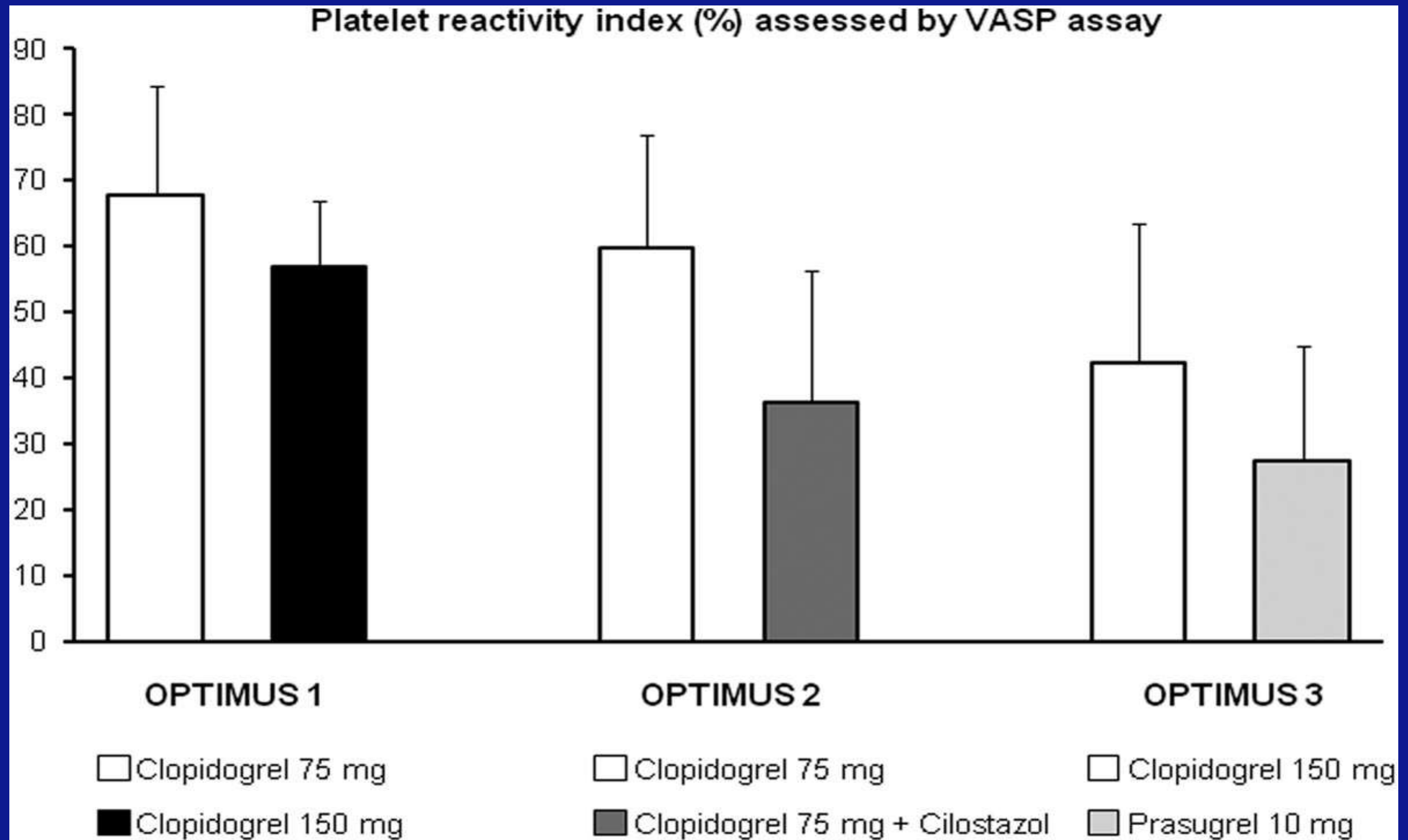
Repeat Revascularization



DM as Predictor of Stent Thrombosis at One-Year in the Era of DES



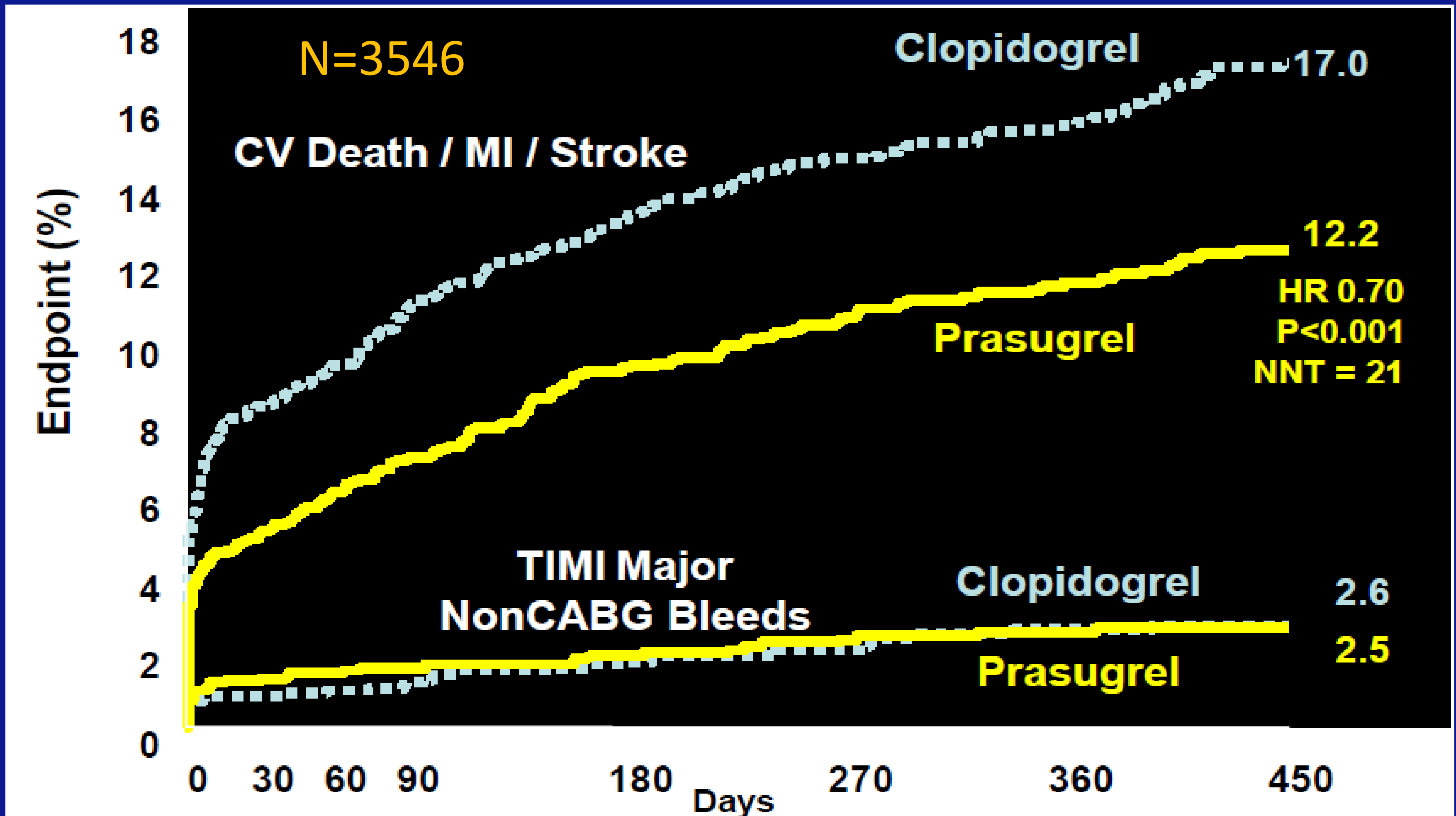
Antiplatelet effects of different treatment strategies



DECLAIRE-DIABETES 2-Year Follow-up

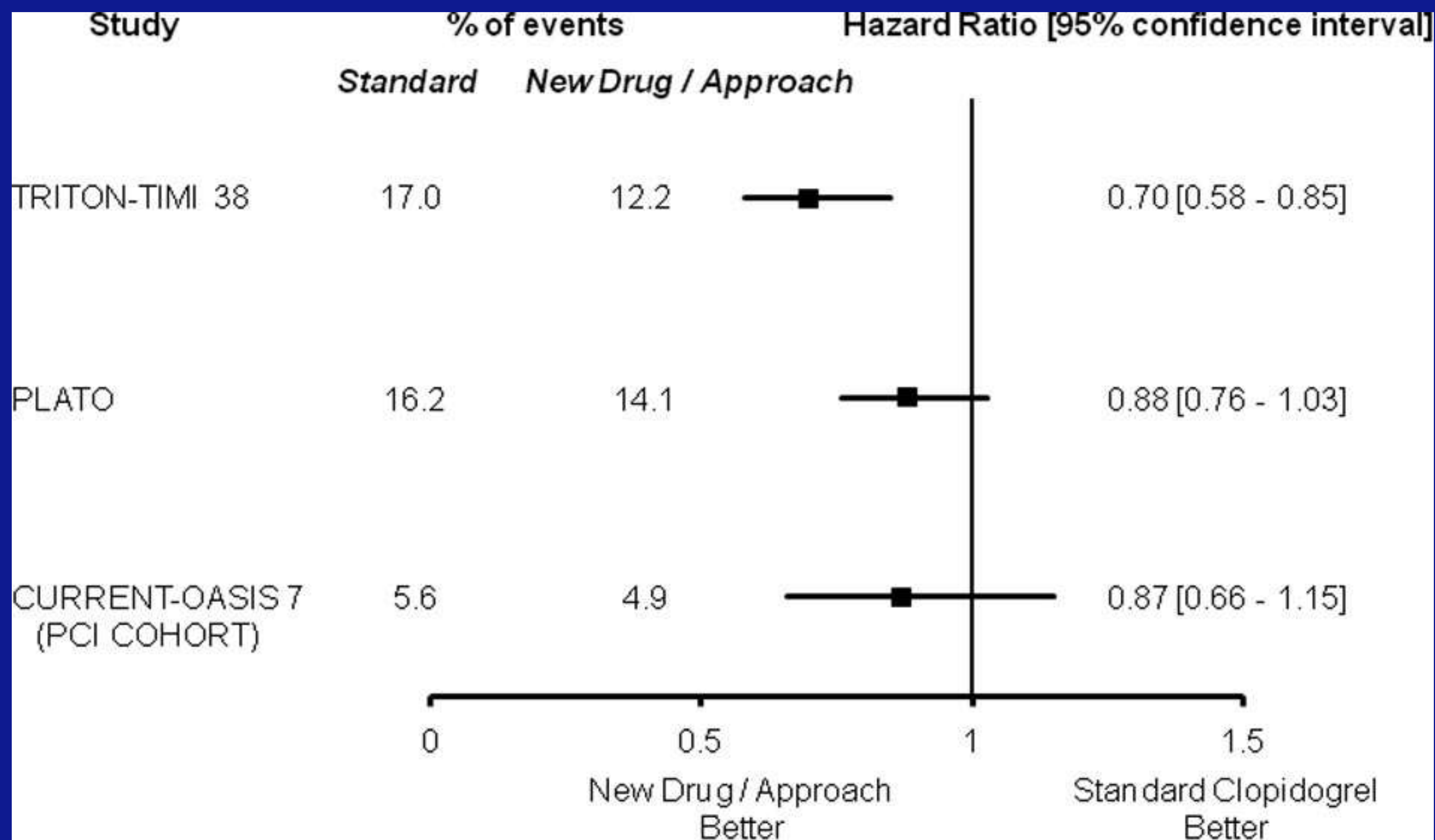
Lee SW et al TCT 2008

TRITON TIMI-38 Diabetic Subgroup

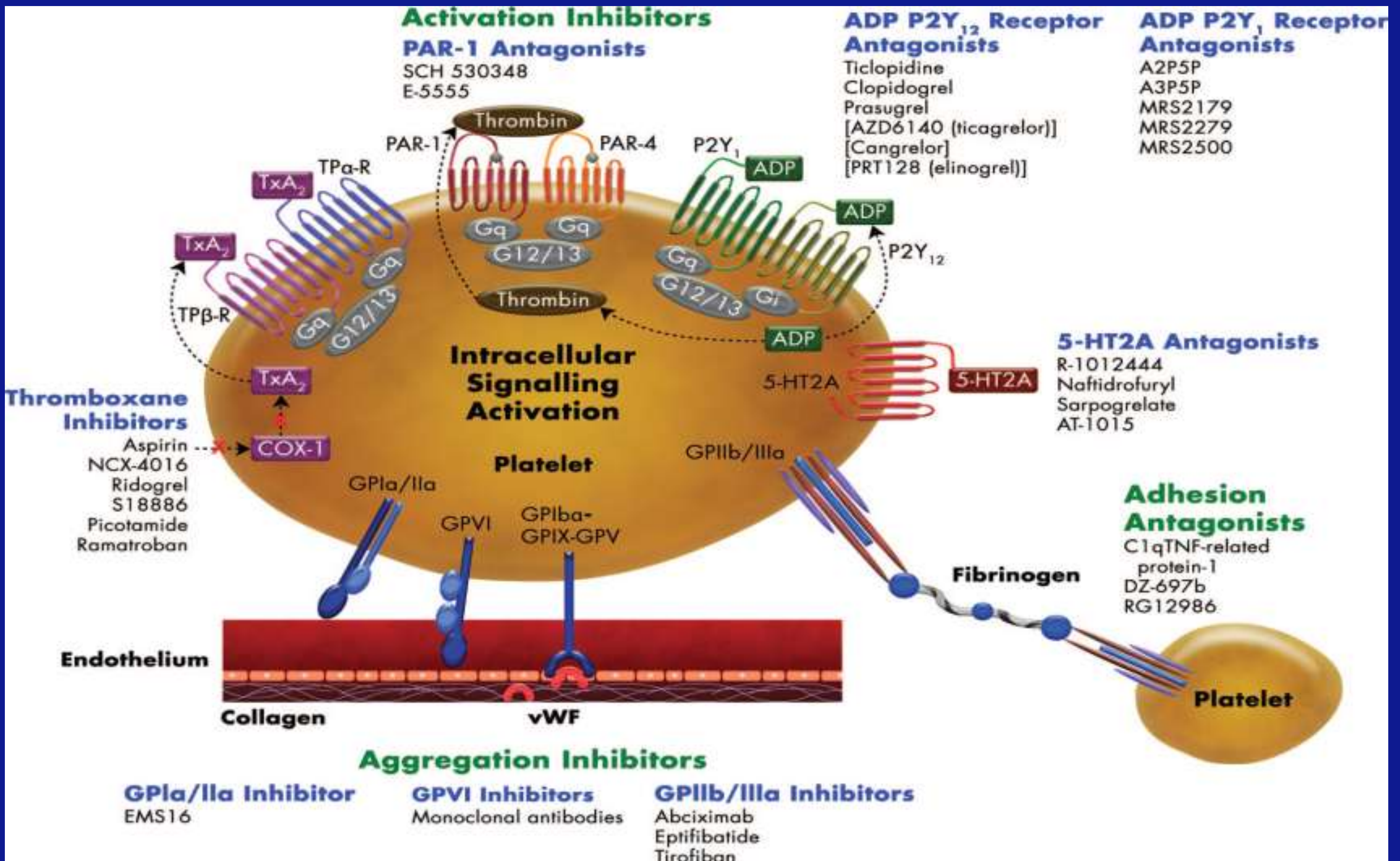


Wiviott SD et al. Circulation 2008;118:1626-36

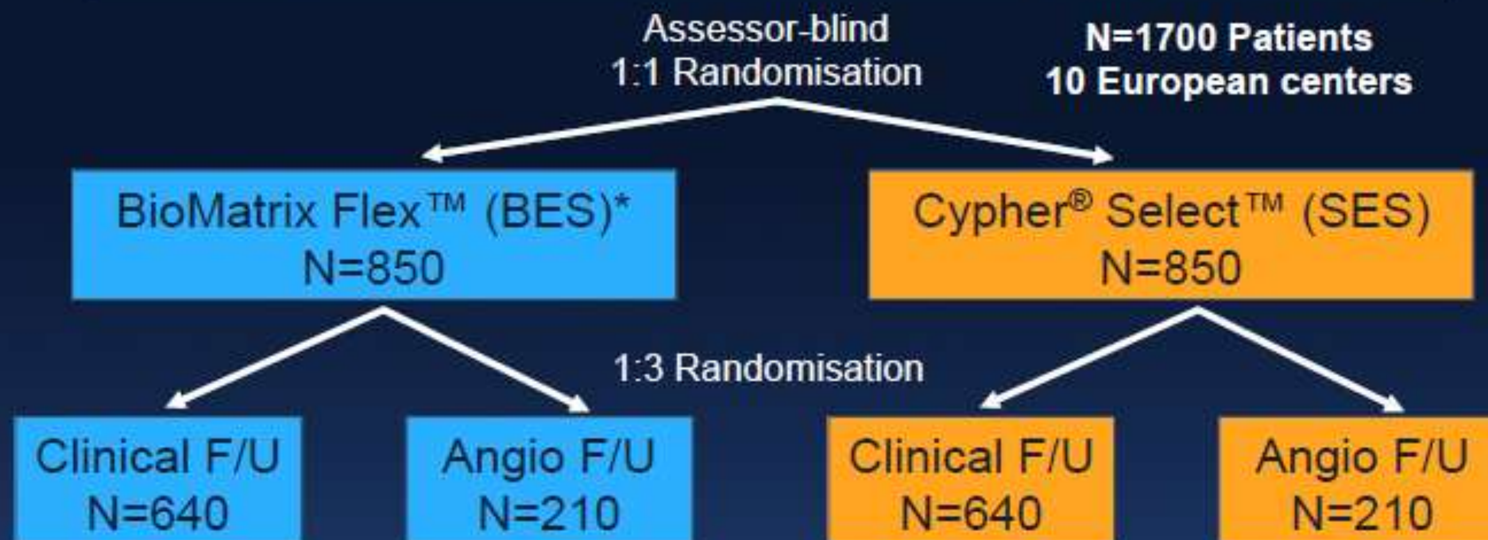
Novel DAPT in DM patients



Currently available and novel antiplatelet agents under development



LEADERS 'all-comers' Trial Design



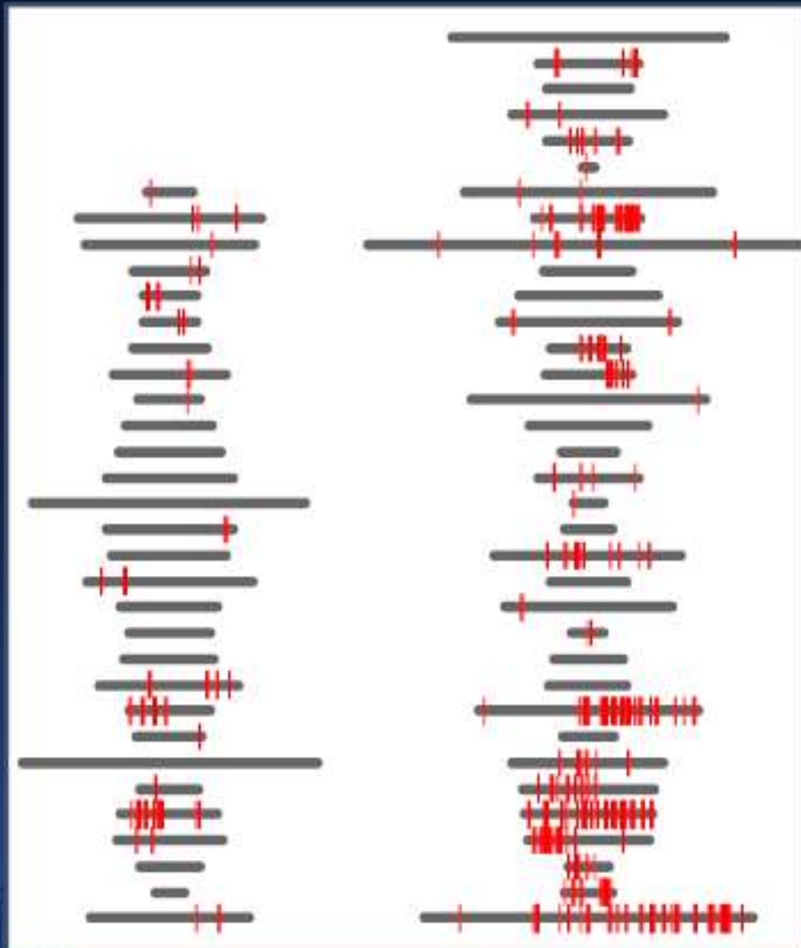
1° endpoint:	**MACE: Cardiac death, MI, clinically-indicated TVR (9 mo)**
2° endpoints:	Death, CV death, MI, TLR, TVR
	Stent thrombosis according to ARC
Angiographic study:	**In-stent % diameter stenosis (9 mo)**
	Late loss, binary restenosis
DAPT recommended for 12 months	

Patient Demographics

	BES 857 Patients	SES 850 Patients
Age in years	65 ± 11	65 ± 11
Male gender	75%	75%
Arterial hypertension	74%	73%
Diabetes mellitus	26%	23%
- insulin-dependent	10%	9%
Hypercholesterolemia	65%	68%
Family history	40%	44%
Smoking	24%	25%
Previous MI	32%	33%
Previous PCI	36%	37%
- with drug-eluting stent	12%	14%
Previous CABG	11%	13%

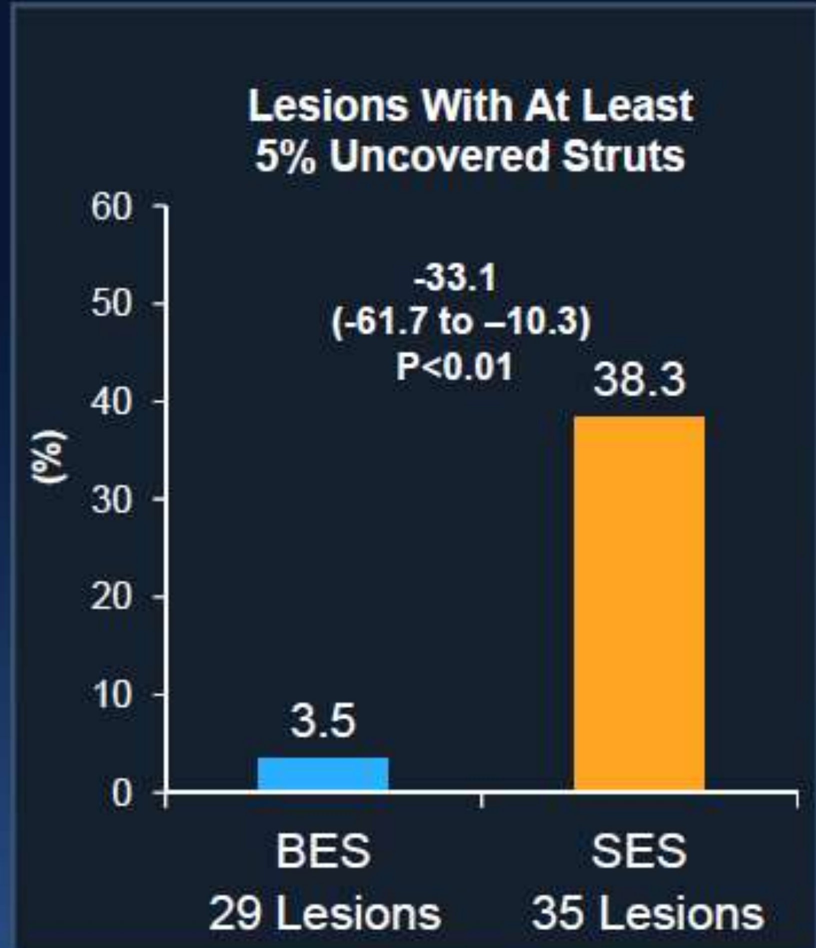
LEADERS - OCT Substudy @ 9 Months

Barlis P et al. Eur Heart J 2010

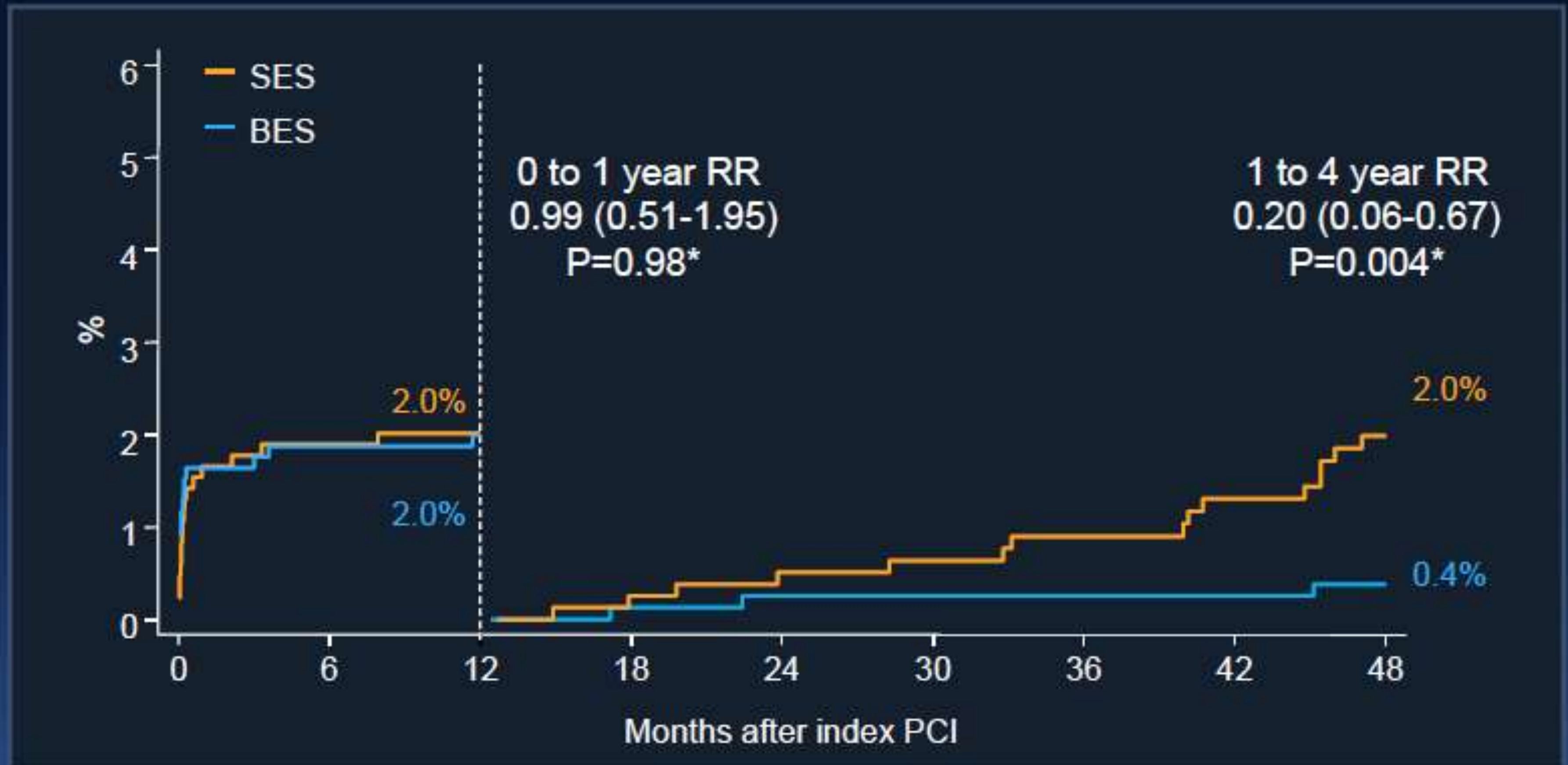


BES
29 Lesions

SES
35 Lesions



Definite ST
Landmark Analysis @ 1 Year



No. at risk

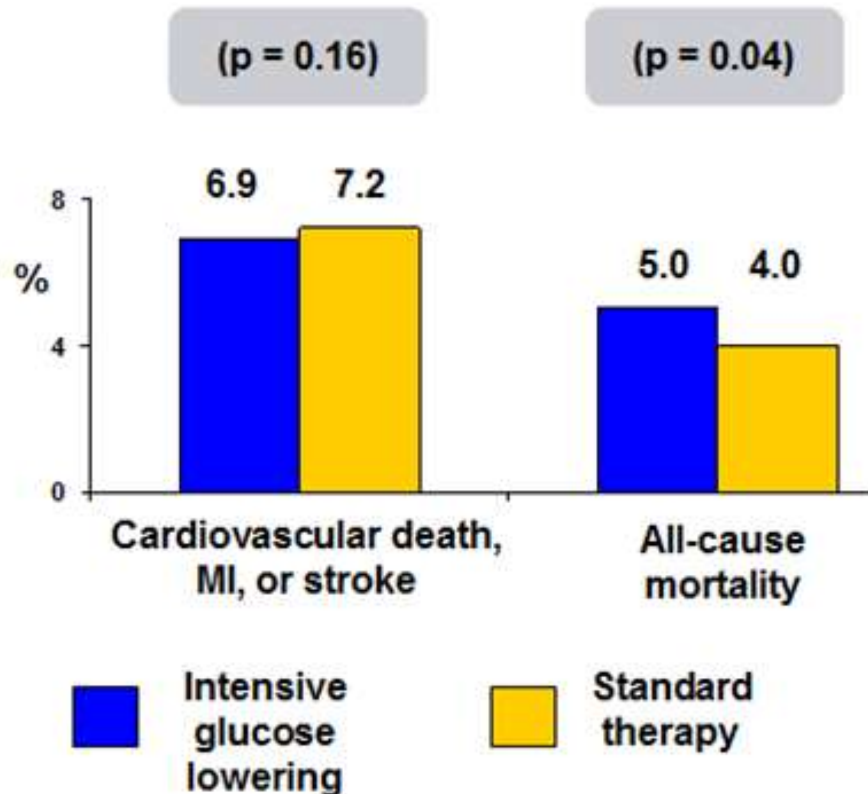
	0	6	12	18	24	30	36	42	48
SES	850	817	801	787	776	759	750	730	714
BES	857	821	804	792	787	780	774	757	746

P for interaction=0.017
* P values for superiority

TCT 2011

ACCORD

Trial design: Type 2 diabetic patients were randomized to intensive therapy (glycated hemoglobin <6%, n = 5,128) versus standard therapy (glycated hemoglobin 7%-7.9%, n = 5,123). Patients were followed for 3.5 years.



Results

- CV death, MI, or stroke: 6.9% vs. 7.2% (p = 0.16), respectively
- All-cause mortality: 5.0% vs. 4.0% (p = 0.04), respectively
- CV mortality: 2.6% vs. 1.8% (p = 0.02), respectively

Conclusions

- Intensive glucose lowering (mean glycated hemoglobin 6.4%) increased all-cause and CV mortality among type 2 diabetics **(Vs 7.5%)**
- National Heart, Lung, and Blood Institute stopped the trial 17 months early
- Other studies testing intensive glycemic control are ongoing

ACCORD Study Group. N Engl J Med 2008;358:2545-59

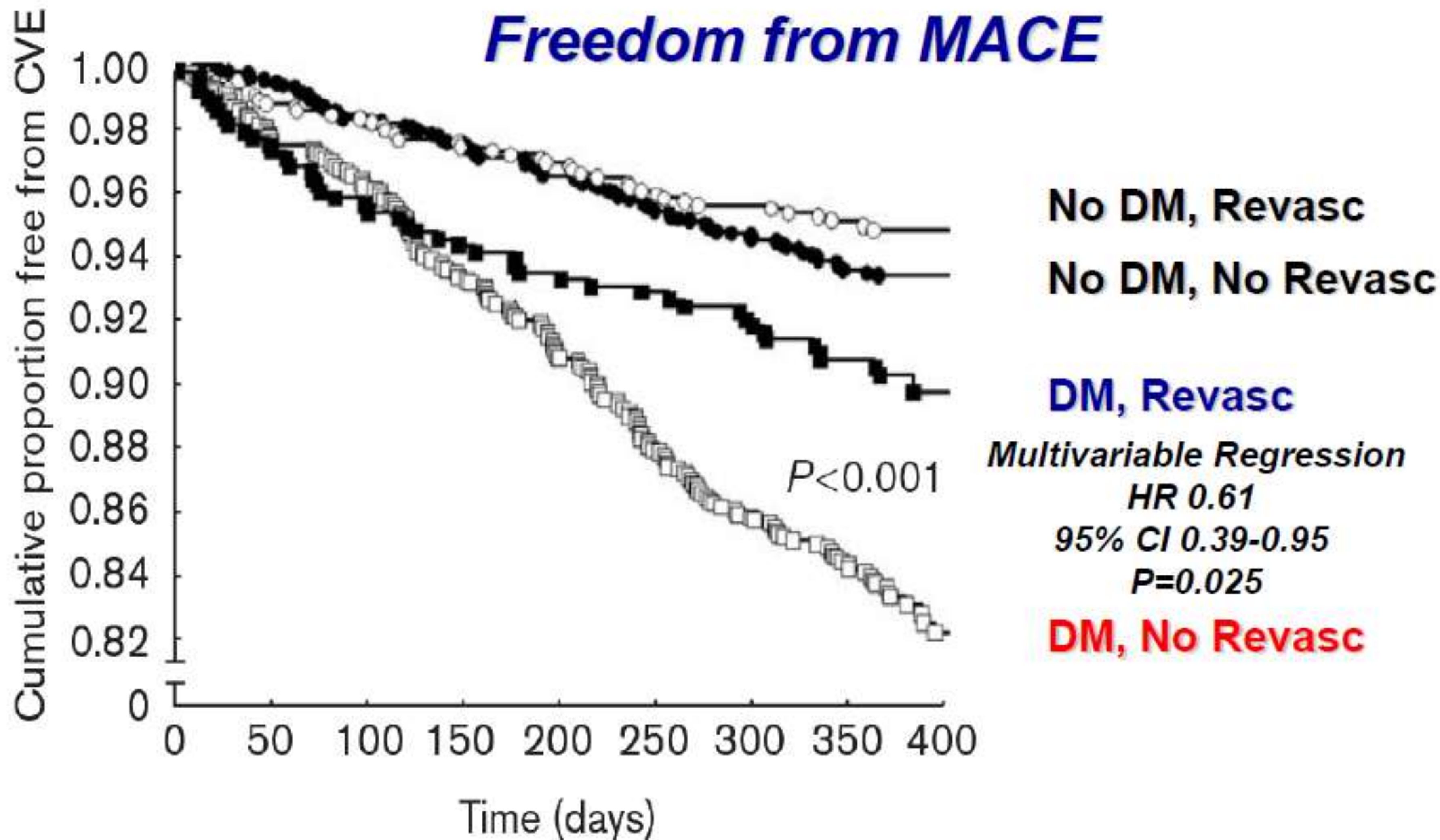
www.cardiosource.com

Conclusions

- Threshold for surgery should be lower in diabetic than in non-diabetic patients
- Increased risk of stroke with CABG
- No DES has established itself as the stent of choice in diabetes but recent data are promising
- Newer generation stents may have a role in reducing the higher rate of stent thrombosis in diabetes
- Consider newer antiplatelet agents for patients diabetes undergoing PCI
- Standard but not intensive glycemic control seems currently the most appropriate management of DM patients

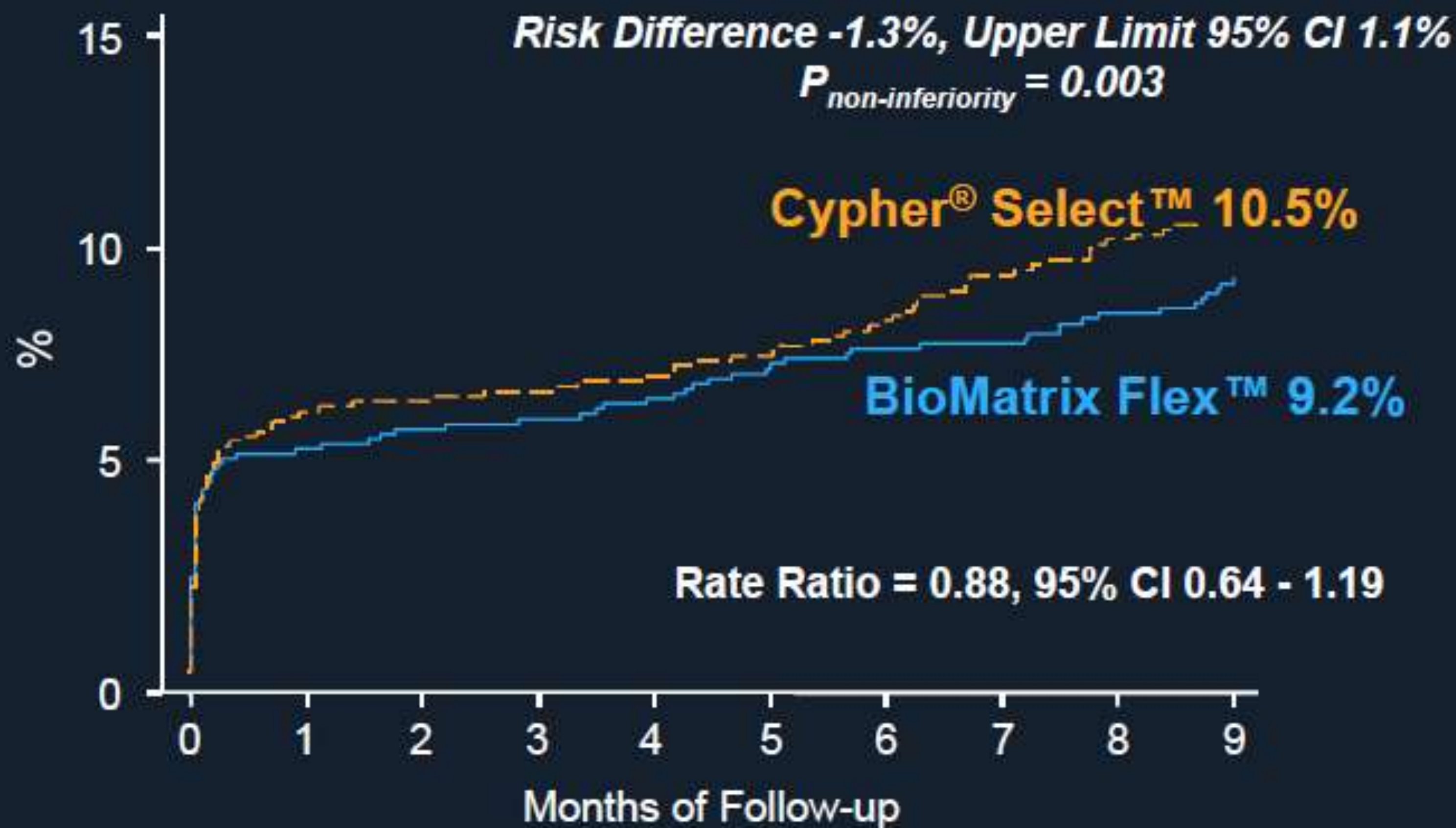
Diabetes and Revascularization
Results from the Euro-Heart Survey

Anselmino et al. *Eur J Cardiovasc Prev Rehabil* 2008;15:216-23



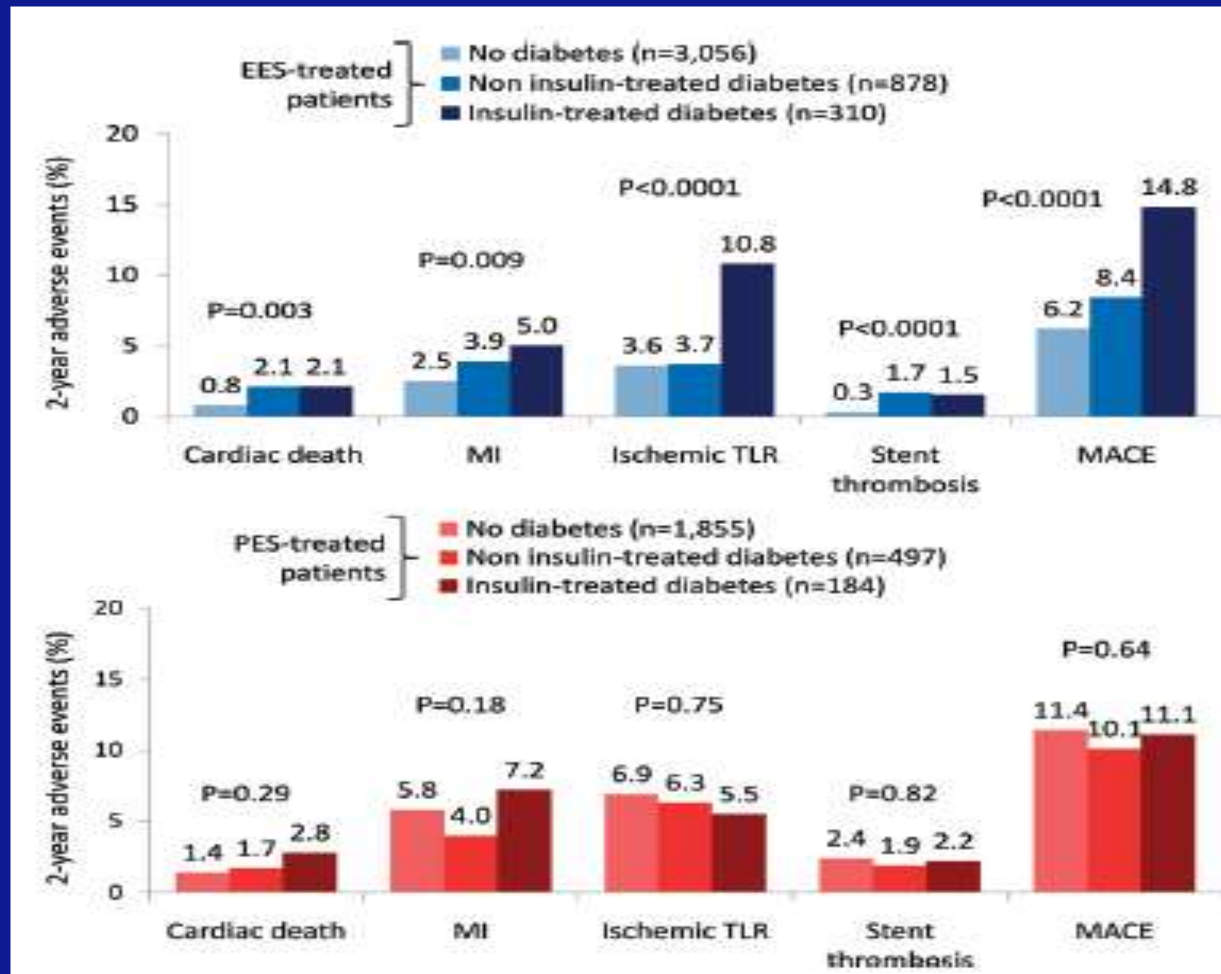
3,488 patients included at 110 centers in 25 European countries

LEADERS Primary Endpoint
MACE (Cardiac Death, MI and ci-TVR) @ 9 Months



Windecker S. et al., The Lancet 2008; 372 No. 9644: 1163-1173

EES – PES in DM Patients



Impact of Diabetes on TLF

XIENCE V TAXUS

TLF (%)

	No diabetes		Diabetes	
	XIENCE V	TAXUS	XIENCE V	TAXUS
TLF (%)	3.1	6.7	6.4	6.9
n/N	52/1652	55/815	49/761	26/379
RR [95%CI] =	0.47 [0.32, 0.68]		0.94 [0.59, 1.49]	
p	p<0.0001		p=0.80	

TLF = cardiac death, target vessel MI, or ischemia-driven TLR

Spirit IV

$P_{interaction} = 0.02$

5-Year Follow-up of Revascularization in Diabetic Patients with Multivessel CAD

Nonrandomized, retrospective analysis of 367 patients from ARTS I and II.

5-Year Outcomes	BMS (n = 112)	SES (n = 159)	CABG (n = 96)
MACCE	53.8%	40.5%	23.4%
Mortality	13.6%	9.0%	8.6%
Repeat Revascularization	43.7%	33.2%	10.7%

MACCE = all-cause mortality, MI, cerebrovascular accident, revascularization

Conclusion: At 5 years, diabetic patients with multivessel disease obtain better overall results whether they are treated with CABG or SES than if they receive BMS, but CABG decreases repeat revascularization vs. stenting.

Onuma Y, et al. *J Am Coll Cardiol Intv.* 2011;4:317-323.