Impact of Diabetes on Long-term Outcomes of Drug Eluting Stents in Asian Patients

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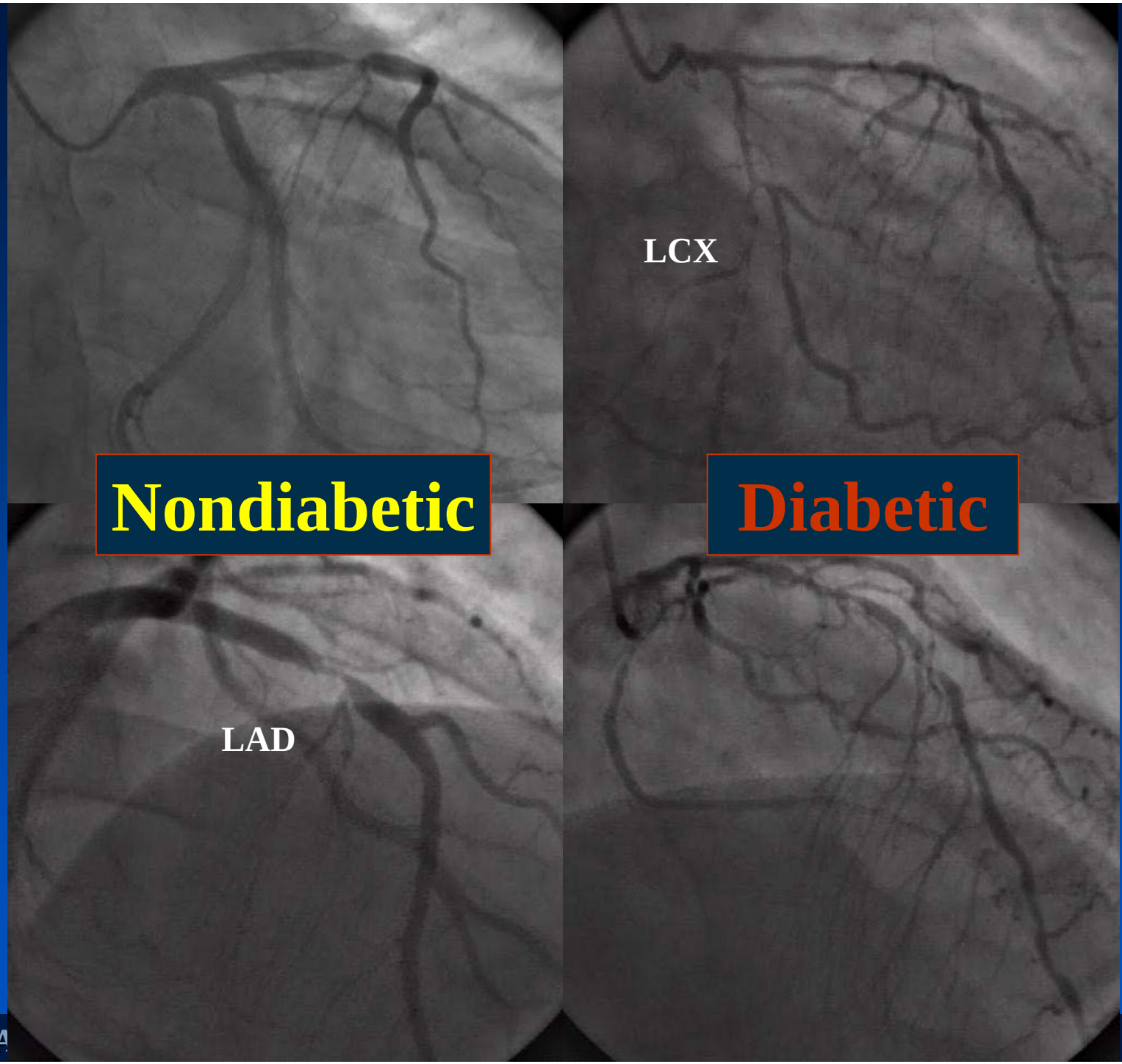
Diabetes
; Different Disease Pattern


LCX
Nondiabetic
Diabetic
LAD

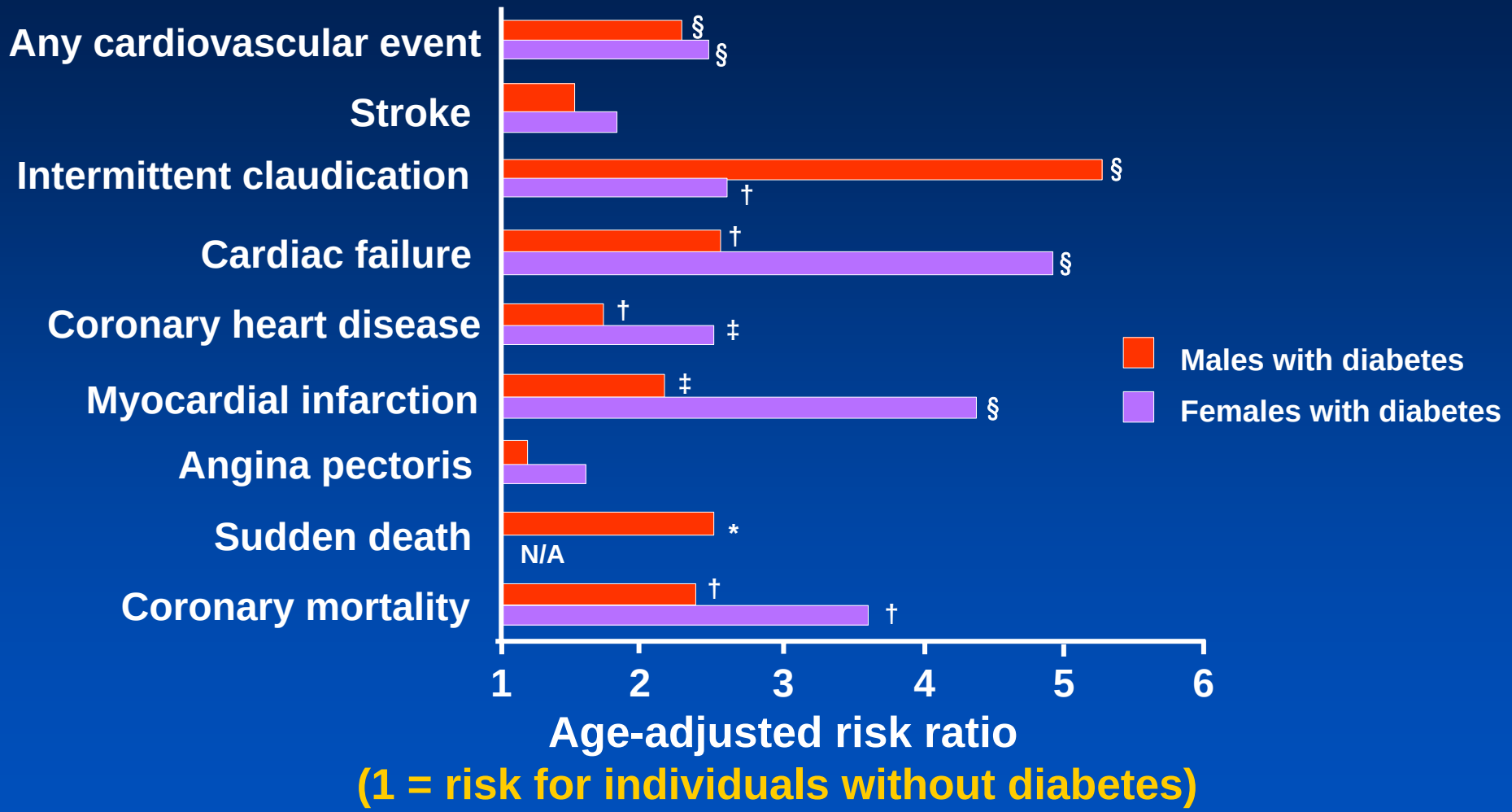
Anatomy of CAD in Diabetics

- Small vessel caliber (impaired remodeling or diffuse atherosclerosis)
- High incidence of multi-vessel disease
- High incidence of left main stem disease
- Complex lesion morphology; total occlusion
- Poor collateral development
- Increased coronary calcification

Diabetic patients tend to have a **more aggressive form of CAD** compared to non-diabetics

Diabetes
; Cardiovascular Morbidity and Mortality

Type 2 DM increases the risk of CVD

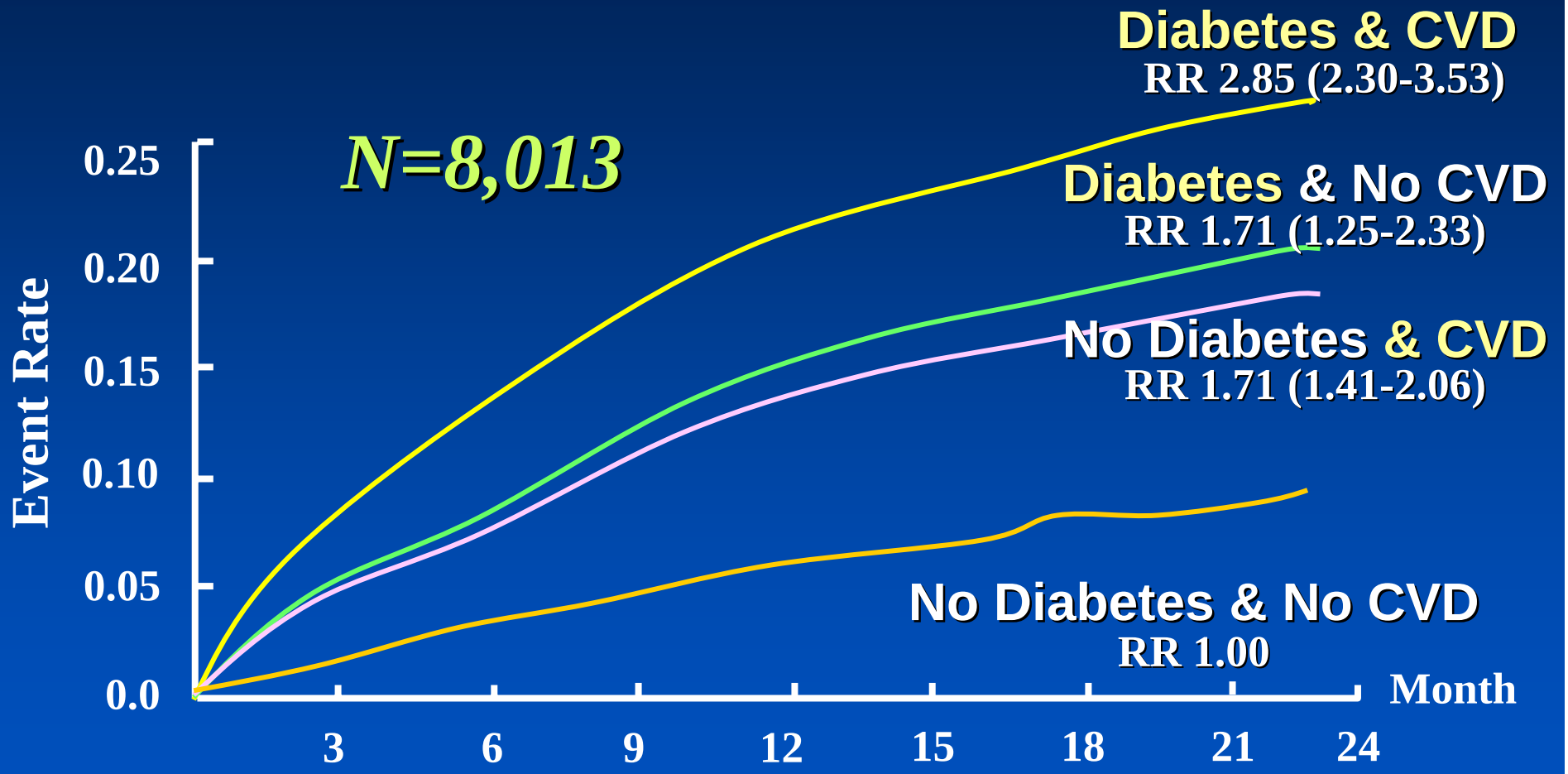


*$P < 0.1$; †$P < 0.05$; ‡$P < 0.01$; §$P < 0.001$

Am Heart J 1990; 120:672–676.

Diabetes & Cardiovascular Mortality

OASIS Registry

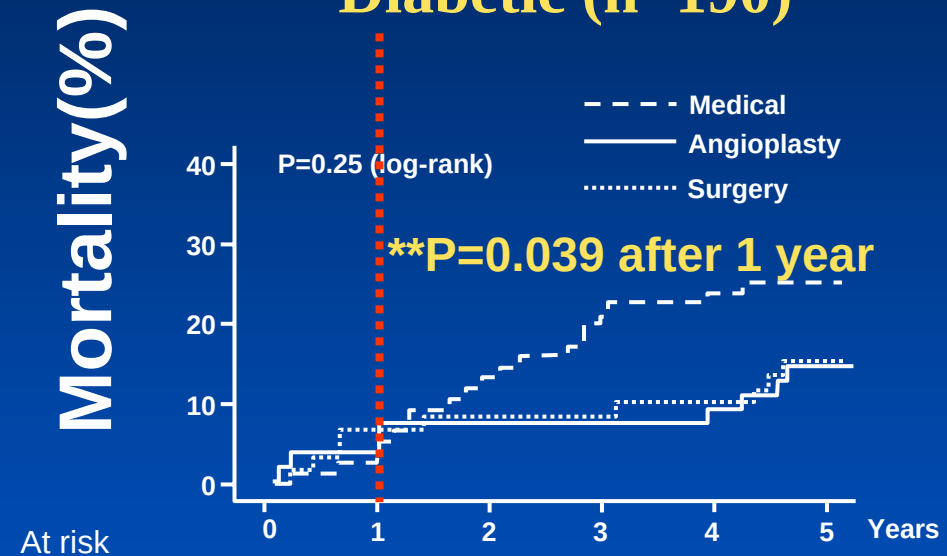


Malmberg K, et al. Circ 2000;102:1014-1019

Diabetes
; Revascularization Treatment (PCI or CABG)

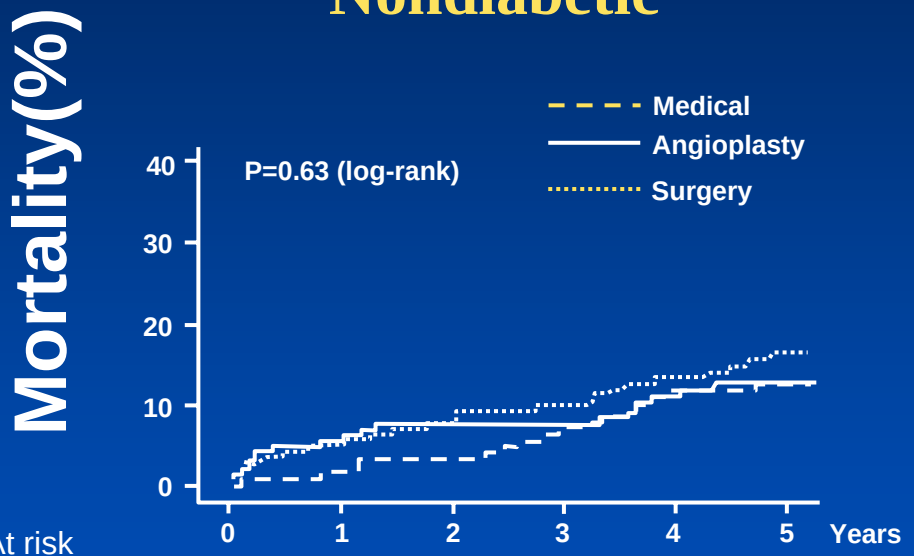
Medical vs. PCI vs. CABG
in stable multi-vessel CAD (n=611pts)
MASS II RCT

Diabetic (n=190)



At risk						
Medical	75	73	65	59	57	56
Angioplasty	56	53	51	51	50	47
Surgery	59	55	54	54	53	50

Nondiabetic



At risk						
Medical	128	126	124	119	113	112
Angioplasty	149	141	128	138	133	130
Surgery	144	137	133	130	125	121

*PCI = BMS era

Soares, PR et al. Circulation 2006; 114:I420

MASS II Study:
Revascularization in Diabetics

- Surgery, PCI, and medical treatment did not influence the risk of death for nondiabetic subjects.
- For diabetic subjects, percutaneous or surgical revascularization was associated with a protective effect compared with medical treatment, significantly decreasing the risk of death after 1 year and up to 5 years.
- Therefore, aggressive invasive revascularization should be considered in diabetic patients to improve long-term outcomes

Diabetes
; PCI Treatment

Suggested Biological Influence of Diabetes on PCI outcomes

Enhanced Platelet Activation and Release of Growth Factors

Accelerated Proliferation and Migration of Smooth Muscle Cells

Impaired Fibrinolysis (elevated t-pa, PAI-1, D-dimer)

Increased Inflammation (CRP, fibrinogen)

Excessive Matrix Deposition

Delayed Wound Healing

Endothelial Dysfunction

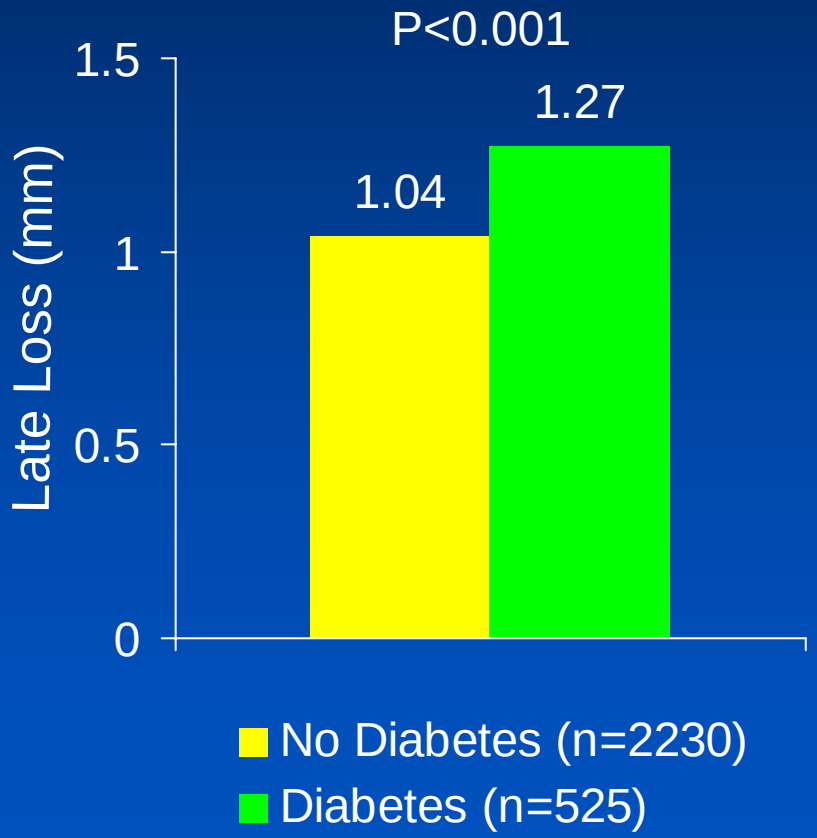
(1) Increased intimal proliferation at the stented site
(2) Rapid progression of non-culprit lesions

Diabetes
; In the era of BMS

Neointimal Hyperplasia in Diabetic Patients

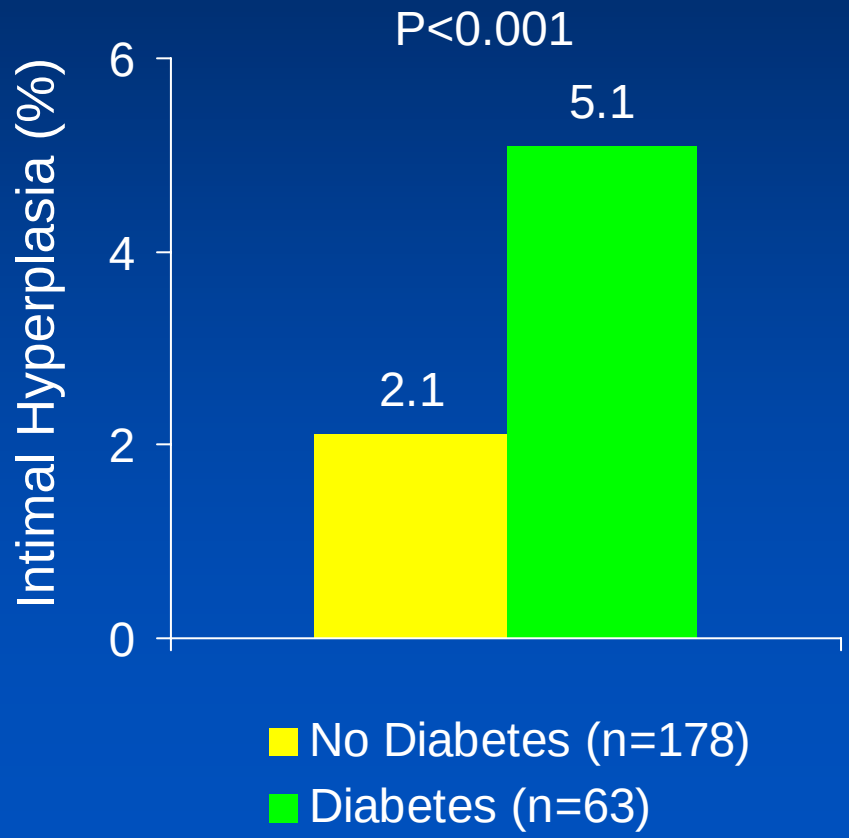
Late Loss

Elezi S et al. *JACC* 1998;32:1866



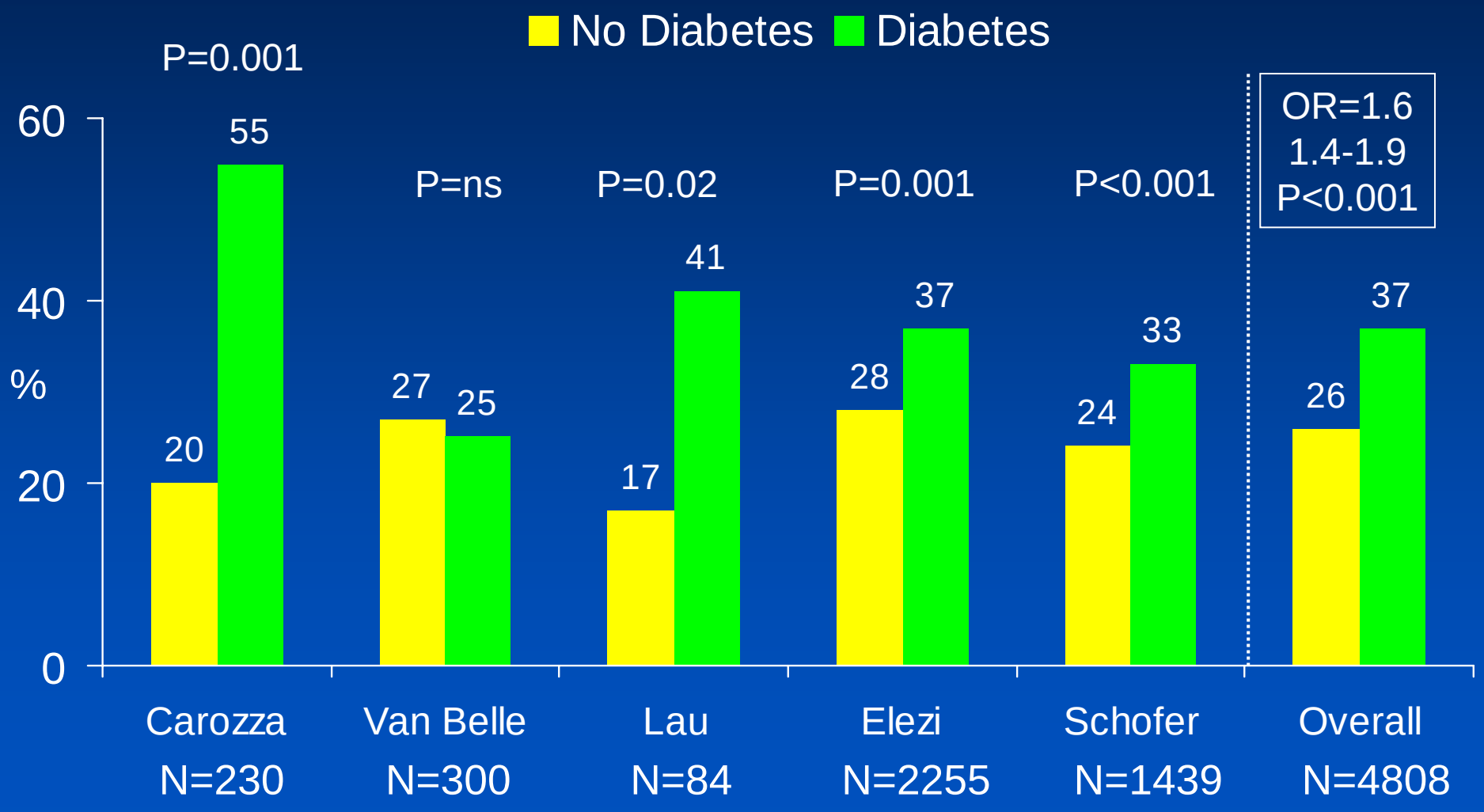
Neointimal Hyperplasia

Kornowski et al. *Circulation* 1997;95:1366



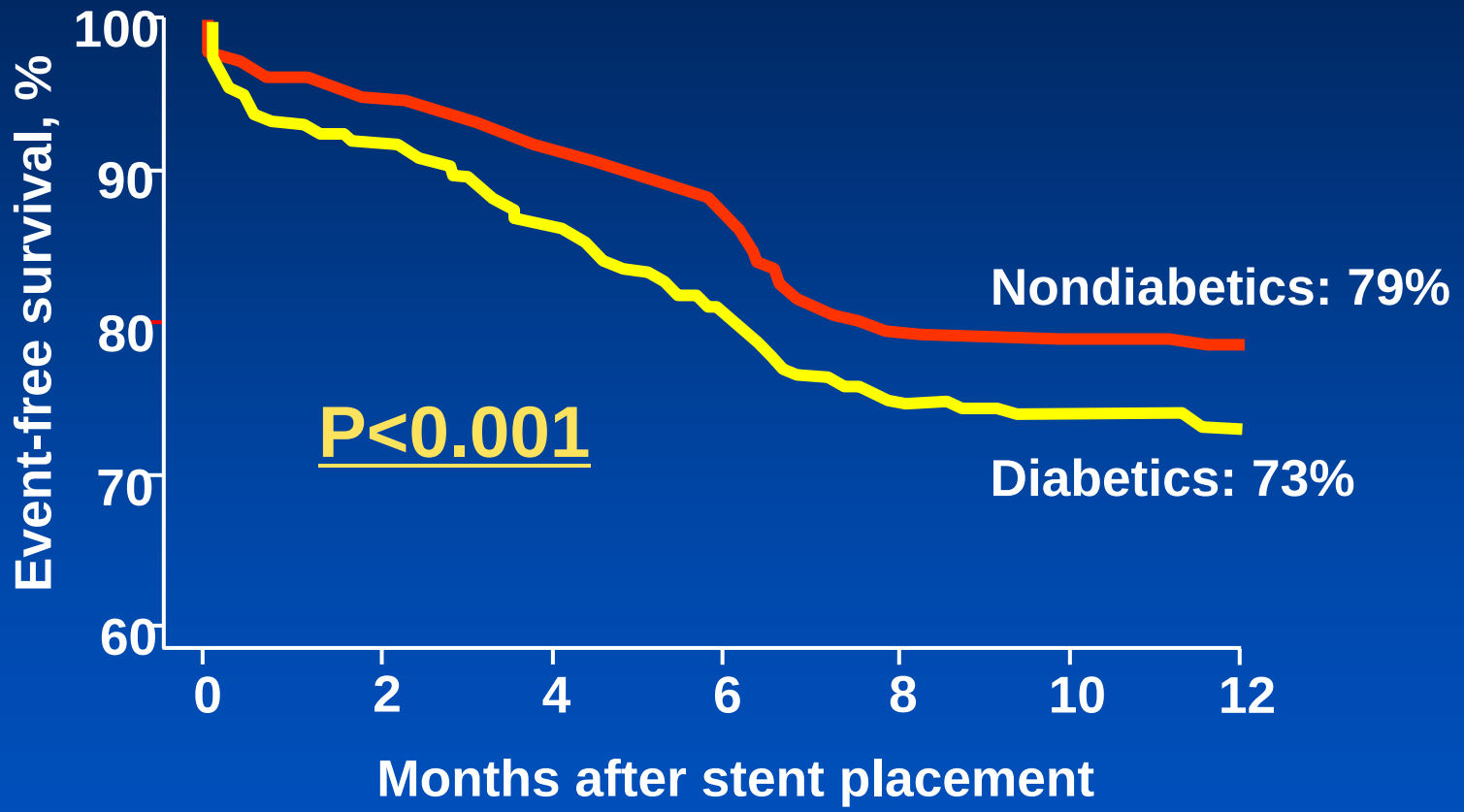
Risk of Restenosis in BMS

Diabetic vs Nondiabetic Patients



MACE: Death, MI, TLR in BMS

Diabetes vs. non-diabetics



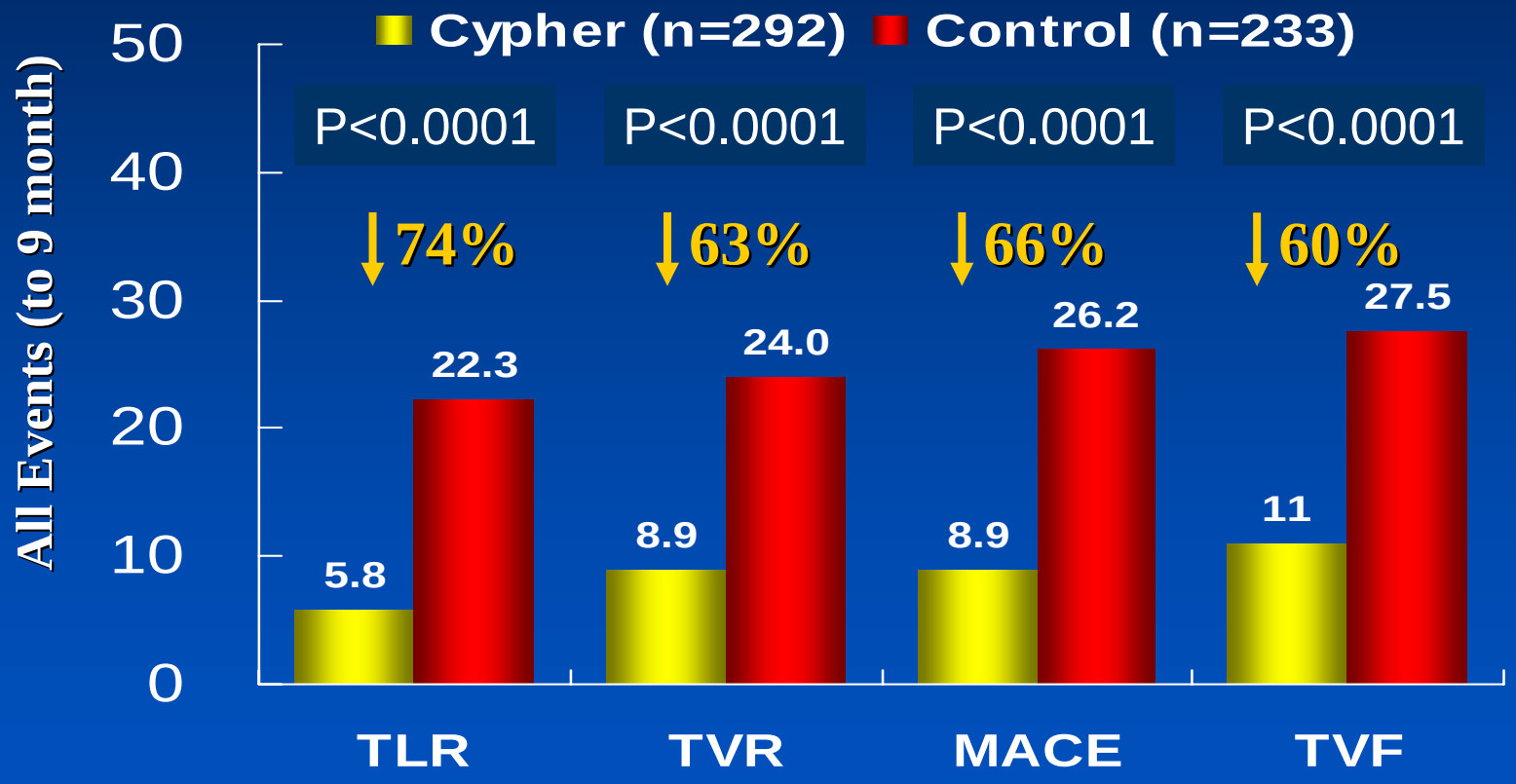
Kastrati A, et al. JACC 1998;32:1866

Diabetes is independent predictor of restenosis and MACE in the era of BMS

Diabetes
; In the era of DES

CYPHER Trials Meta-Analysis in Diabetes

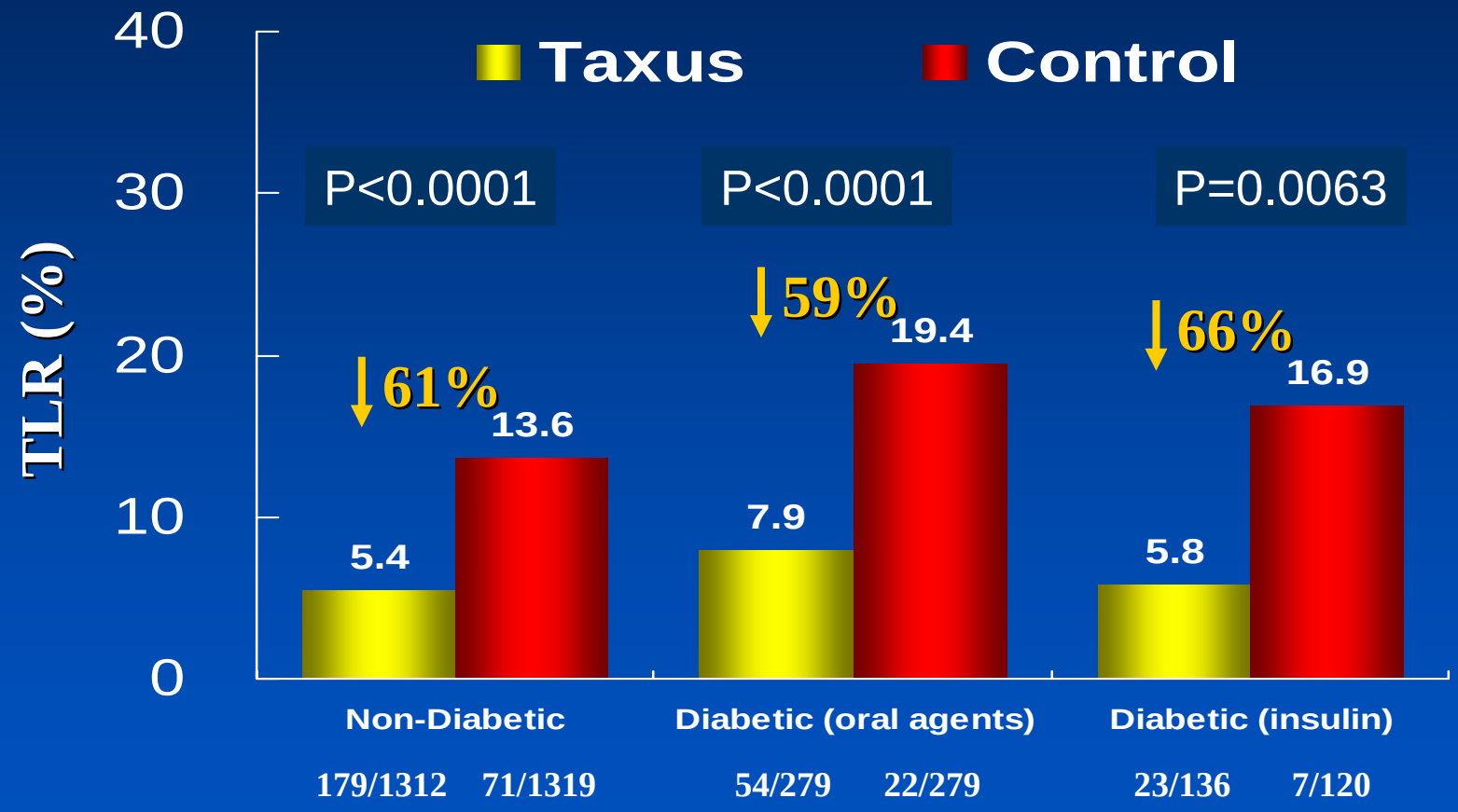
RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, DIRECT, SVELTE



Abizaid et al. Angioplasty Summit 2005

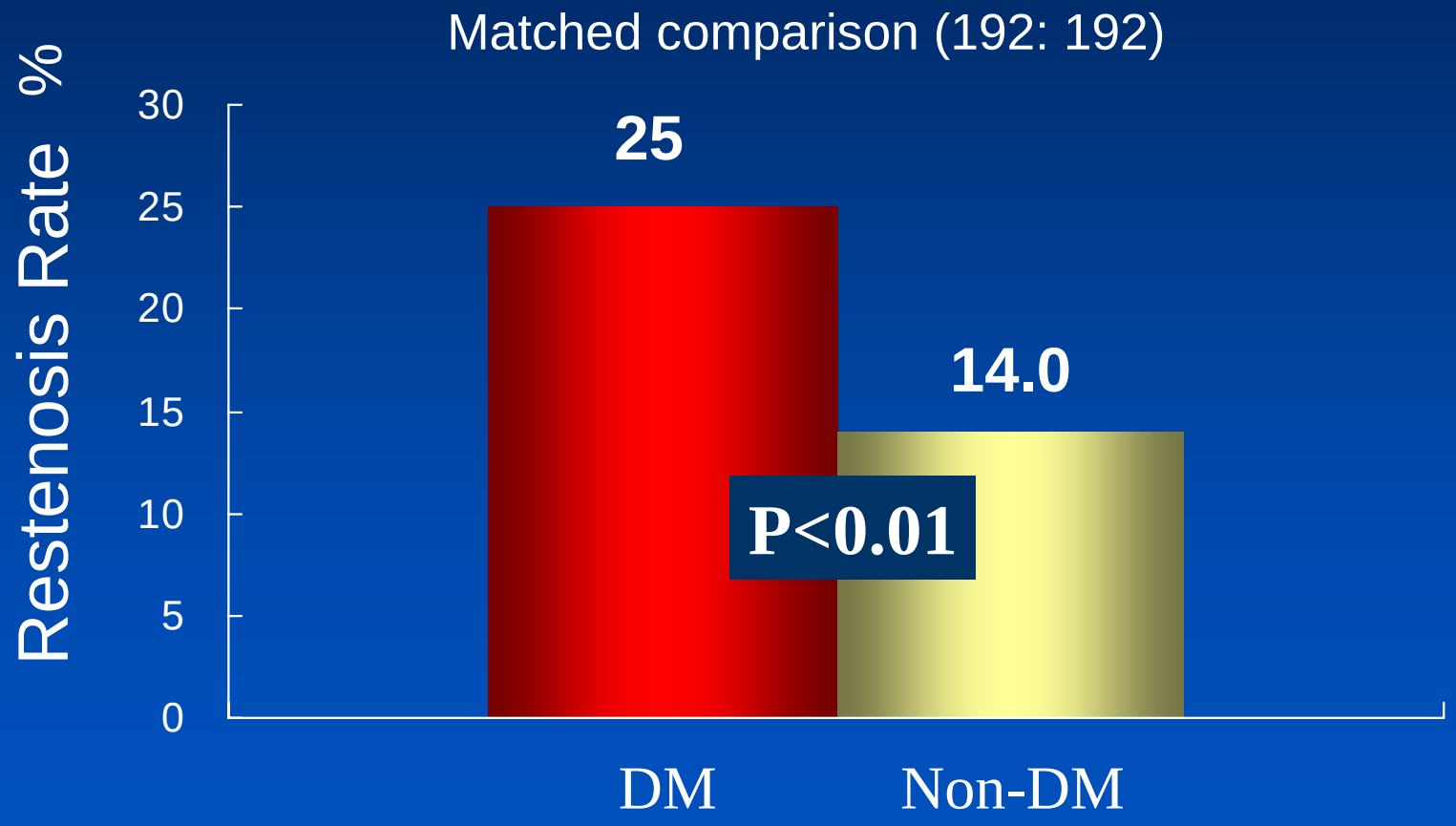
TAXUS Trials Meta-Analysis in Diabetes

TAXUS II, IV, V, VI



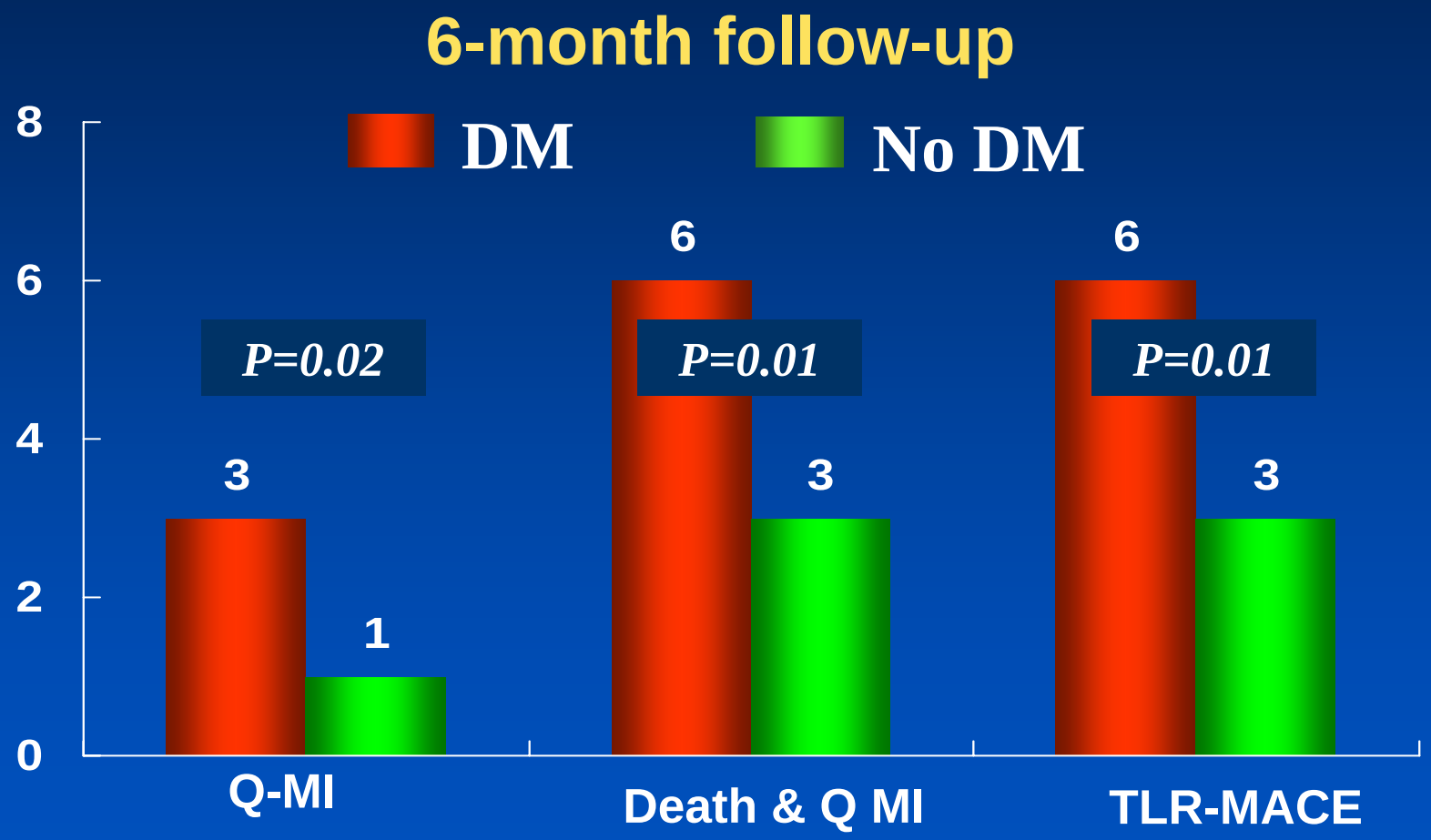
Stone GW et al. Angioplasty Summit 2005

However, Diabetic patients still have higher Restenosis rate compare to non-diabetics even in the era of DES.



Radke PW et al. Am J Cardiol 2006;98:1218

Higher MACE in Diabetics after SES



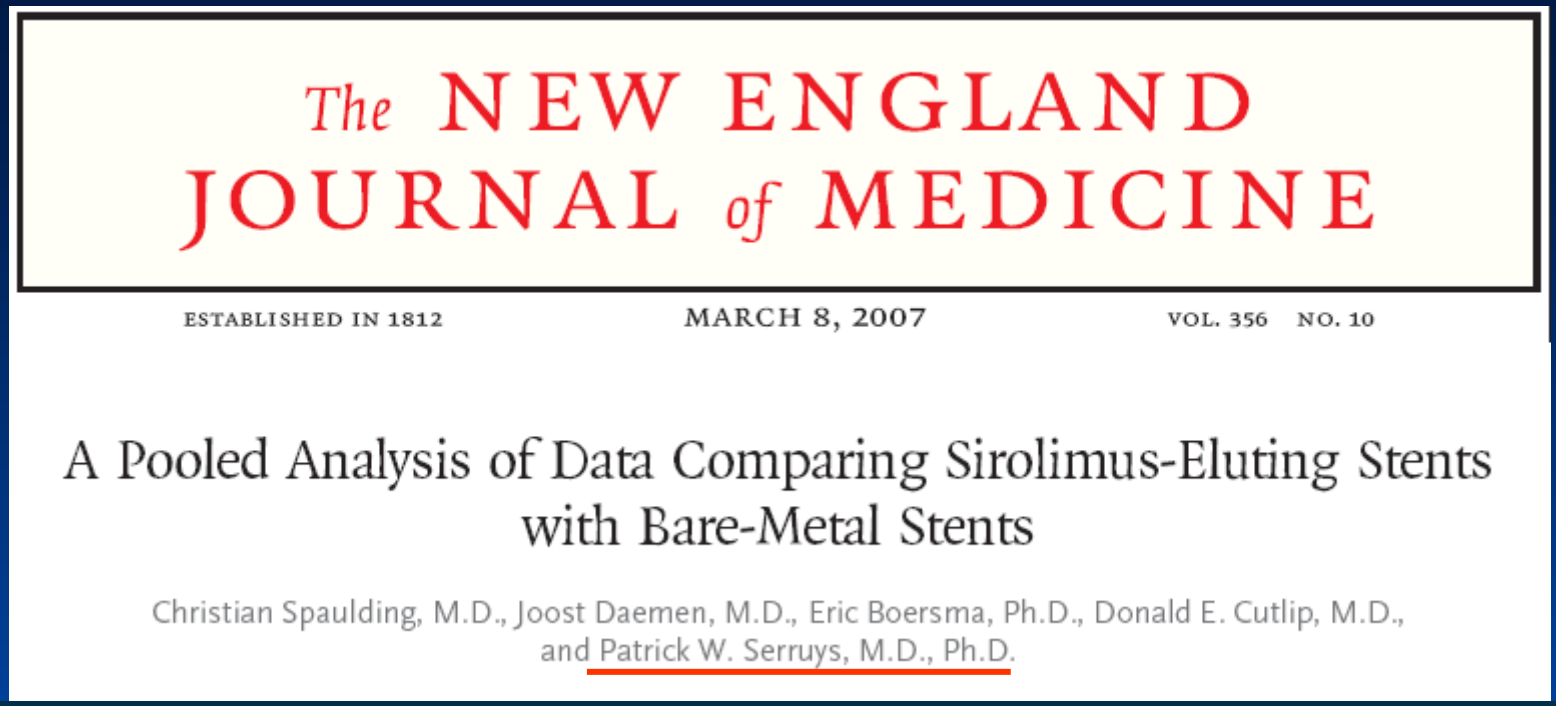
Kuchulakanti et al. Am J Cardiol 2005;96:1100

Risk of Restenosis in DES

Multivariate Predictors of In-Segment Restenosis after SES

	OR	95% CI	p
ISR	4.16	1.63-11.01	<0.01
Ostial lesion	4.84	1.81-12.07	<0.01
Diabetes	2.63	1.14-6.31	0.02
Stent length	1.42	1.21-1.68	<0.01
Ref diameter	0.46	0.24-0.87	0.03
LAD	0.30	0.10-0.69	<0.01

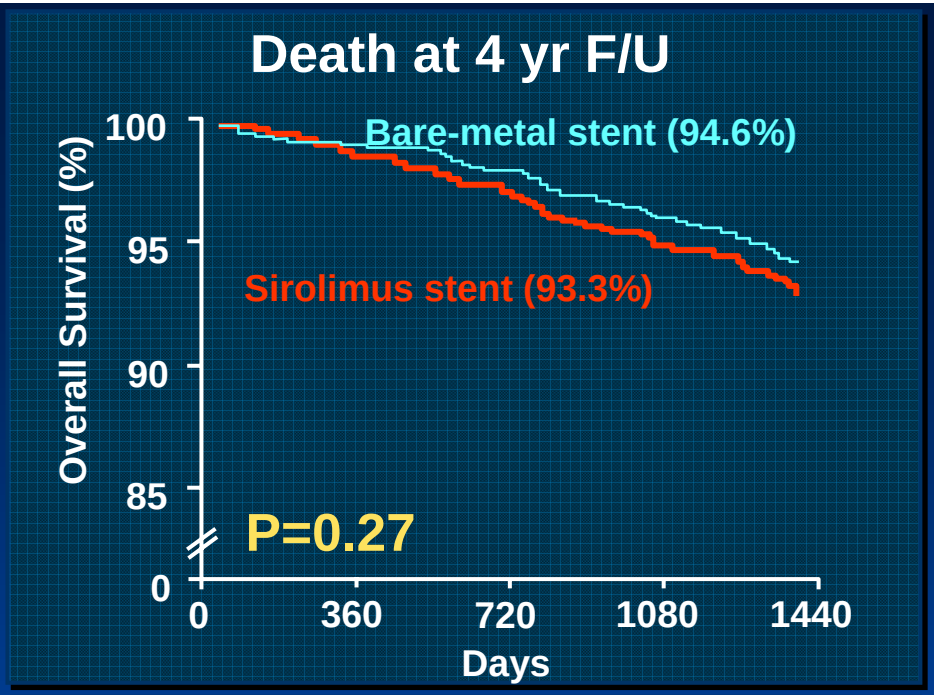
Lemos PA et al. Circulation 2004;109:1366-1370

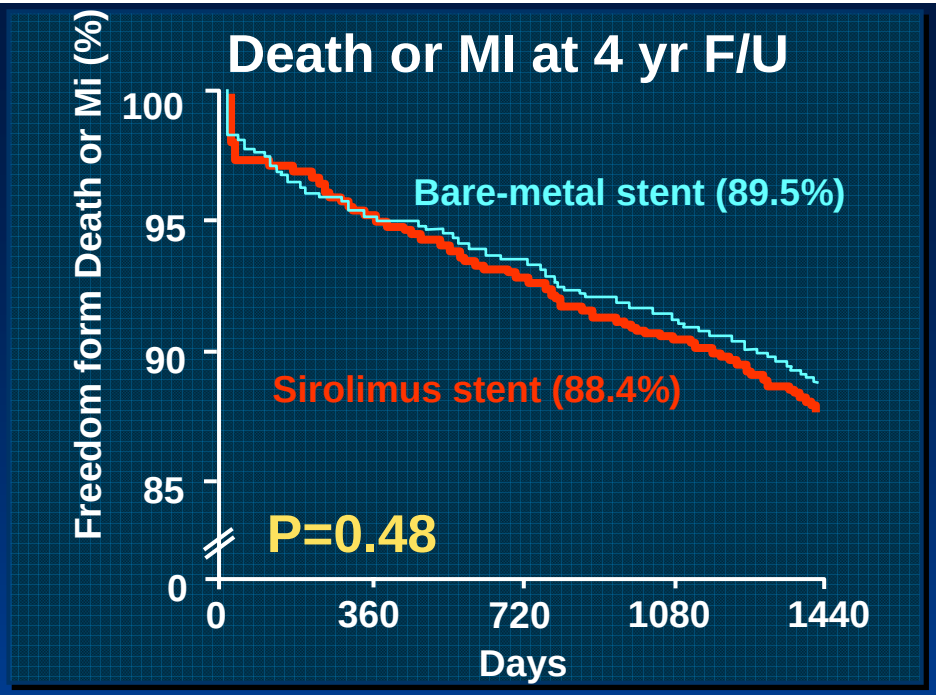


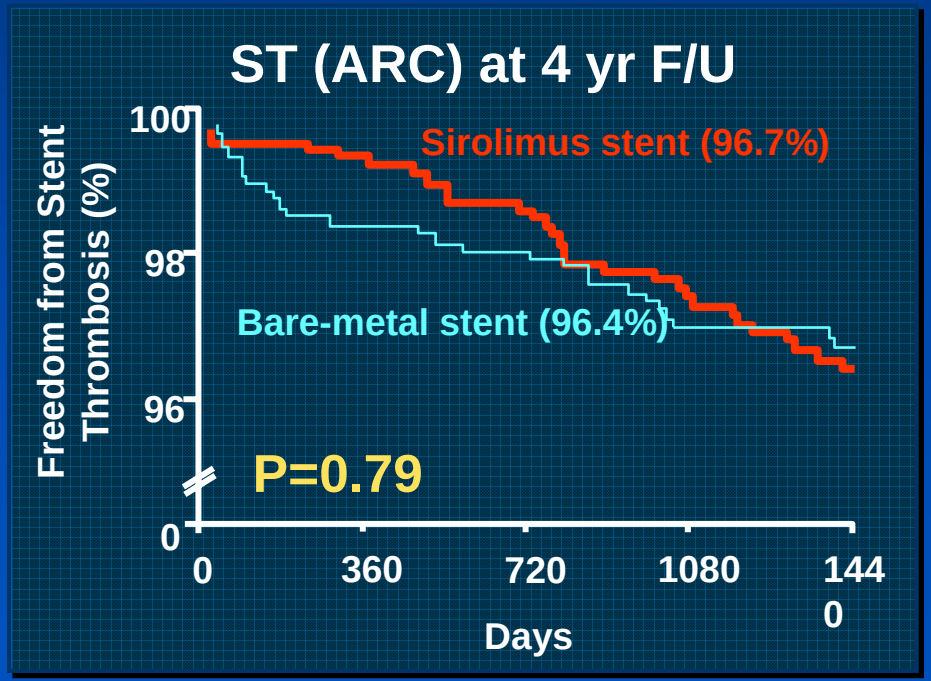
Pooled analysis of 1748 patients in 4 RCTs comparing SES with BMS

(Pivotal SES Trials: RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS)

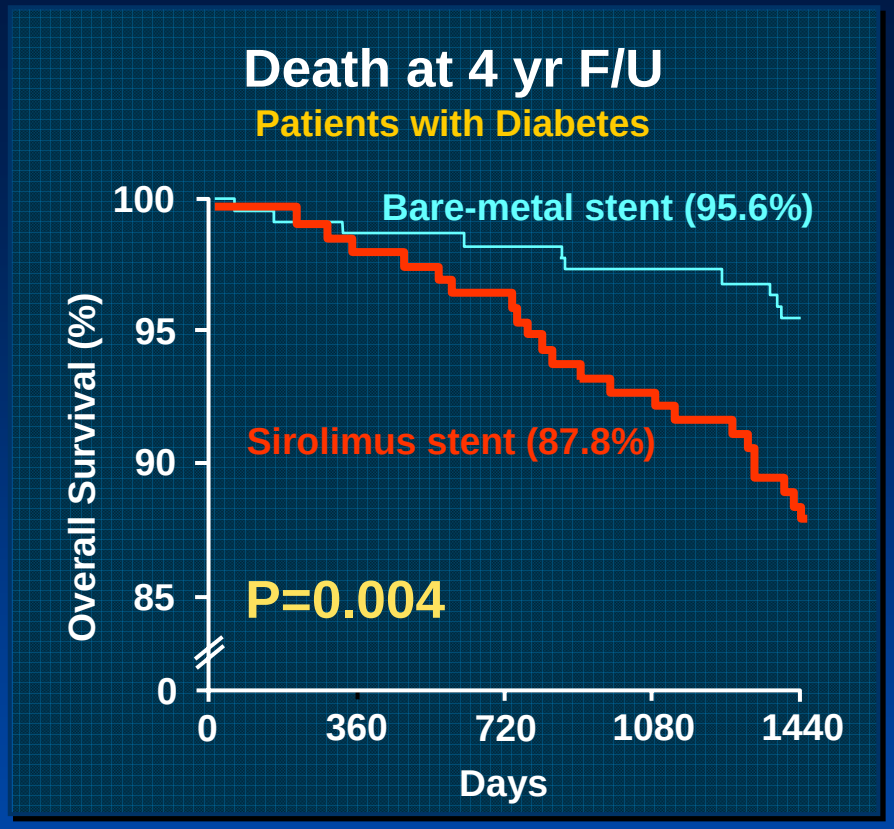
NEJM 2007;356:989-97

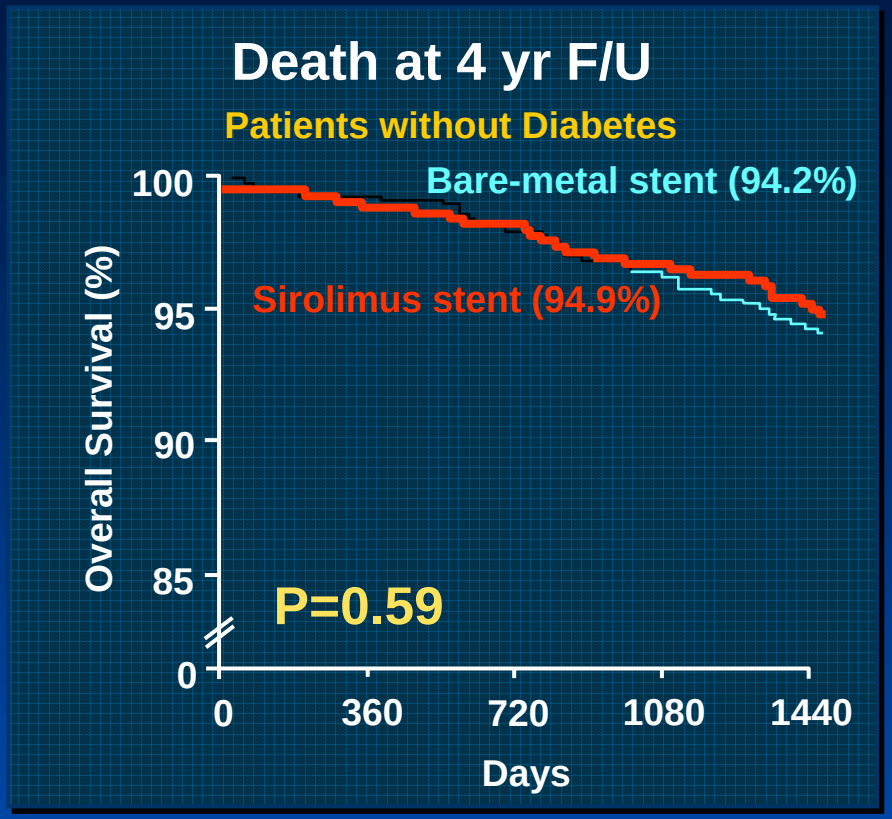






No difference in rates of death, MI, or stent thrombosis at 4 year





Significant difference in rates of deaths from both cardiovascular and noncardiovascular cause in Diabetic Patients at 4 year F/U

Impact of diabetes mellitus on long-term outcomes in the drug-eluting stent era

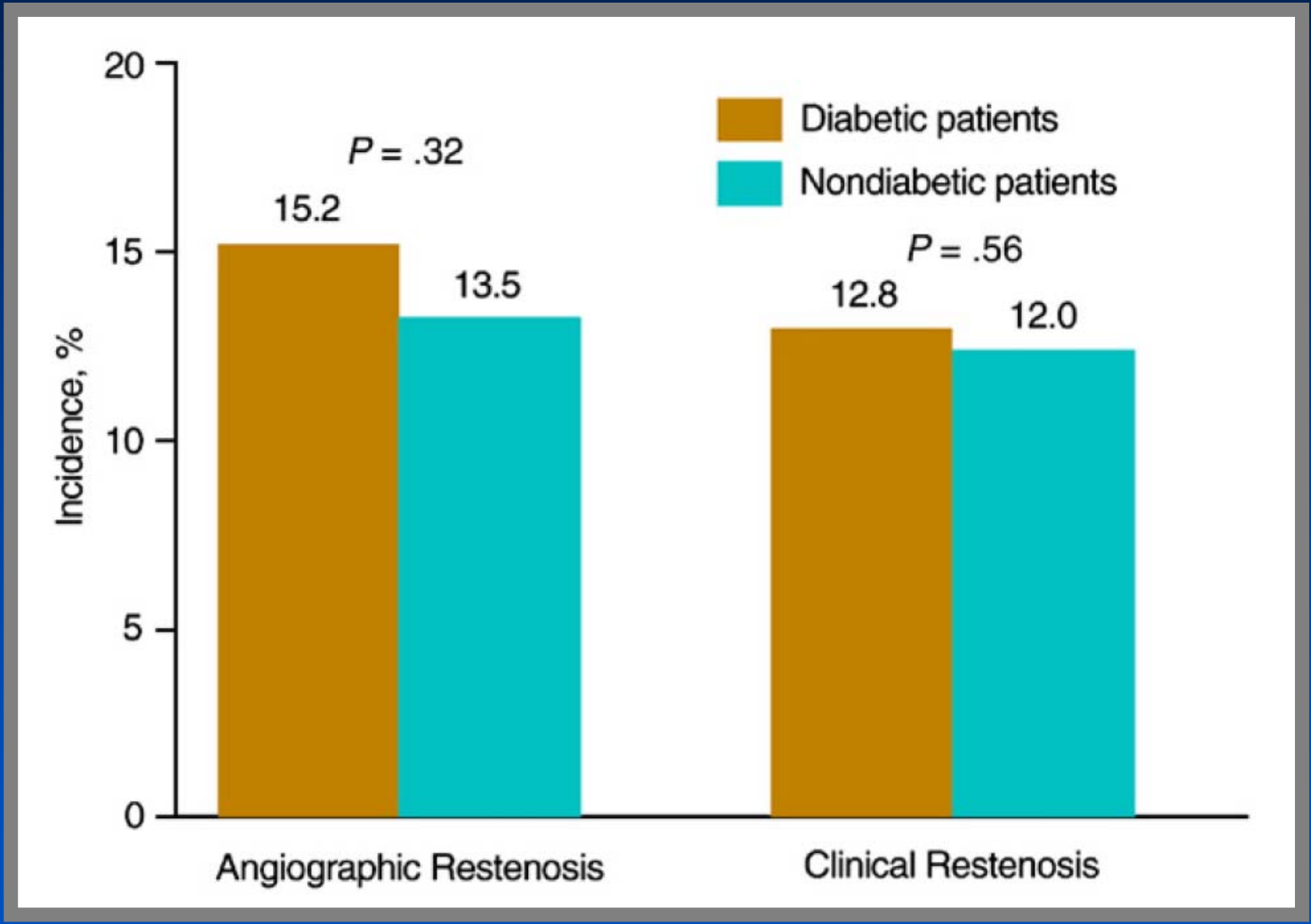
Raisuke Iijima, MD, Gjin Ndrepepa, MD, Julinda Mehilli, MD, Christina Markwardt, MD, Olga Bruskina, MD, Jürgen Pache, MD, Maryam Ibrahim, MD, Albert Schömig, MD, and Adnan Kastrati, MD *Munich, Germany*

Prospective database of 2557 patients in 2 centers

: Diabetes (n=727) vs. Non-diabetes (n=1830)

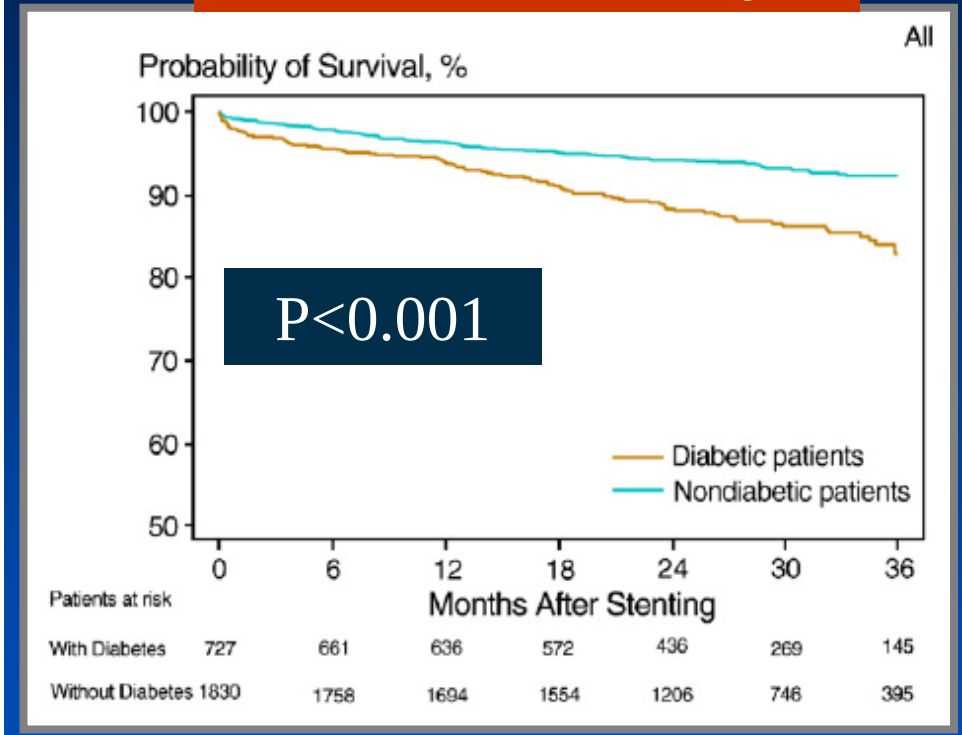
Am Hear J 2007;154:688-93

Angiographic and clinical restenosis (TLR)

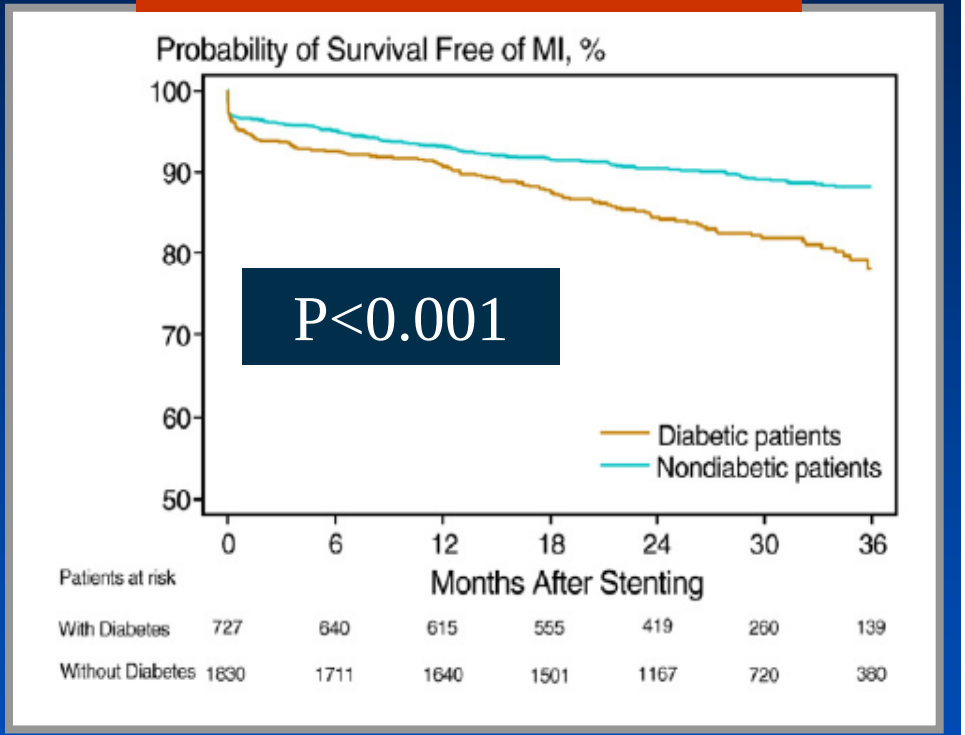


Long-term clinical outcome

All-cause mortality



Death or MI



Diabetes is
independent predictor of 3 year mortality

Incidence, Predictors, and Outcome of Thrombosis After Successful Implantation of Drug-Eluting Stents

JAMA 2005;293:2126-2130

- **Diabetes (HR 3.71, 95% CI, 1.74–7.89).**

Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study

Joost Daemen, Peter Wenaweser, Keiichi Tsuchida, Linda Abrecht, Sophia Vaina, Cyrill Morger, Neville Kukreja, Peter Jüni, Georgios Sianos, Gerrit Hellige, Ron T van Domburg, Otto M Hess, Eric Boersma, Bernhard Meier, Stephan Windecker, Patrick W Serruys

Lancet 2007;369: 667–78

- **Diabetes (HR 2.03, 95% CI, 1.07–3.83).**

Diabetes is
independent predictors of stent thrombosis

General Concerns about Diabetic Influence in Patients Undergoing PCI with DES

- Still higher restenosis rate and MACE in diabetics compare to non-diabetics
- Higher mortality after PCI with DES ?
- Higher incidence of stent thrombosis ?

Prognostic Influence of Diabetes Mellitus on Long-Term Clinical Outcomes and Stent Thrombosis Following Drug-Eluting Stent Implantation in Asian Patients

Overall 3160 patients:

Diabetes (n=865) vs. Non-diabetes (n=2295)

during 3-year follow-up.

Outcomes of study

- Primary end-point
  ; Composite of death, nonfatal MI, or TVR

- Secondary end-points
  ; Death, MI, TLR, TVR, and stent thrombosis (ARC criteria)

Clinical characteristics is different

Variable	Diabetes (n=865)	Non-diabetes (n=2295)	*P*
Age (years)	62.7±9.1	59.7±10.6	<0.001
Female	312 (36.1)	619 (27.0)	<0.001
Hypertension	533 (61.6)	1066 (46.4)	<0.001
Lipid profiles			
Total cholesterol (mg/dl)	178.2±53.3	172.2±48.5	0.003
Triglyceride (mg/dl)	161.2±102.8	147.0±93.5	0.005
HDL cholesterol (mg/dl)	41.9±17.3	43.2±15.1	0.10
Current smoking	201 (23.2)	719 (31.3)	<0.001
Renal failure	50 (5.8)	30 (1.3)	<0.001
Previous myocardial infarction	99 (11.4)	198 (8.6)	0.02
Previous coronary angioplasty	161 (18.6)	383 (16.7)	0.20
Previous coronary artery bypass graft	31 (3.6)	53 (2.3)	0.05

Clinical characteristics is different

Variable	Diabetes (n=865)	Non-diabetes (n=2295)	*P*
Clinical indication			<0.001
Stable angina	450 (52.0)	1074 (46.8)	
Unstable angina	334 (38.6)	865 (37.7)	
Myocardial infarction	81 (9.4)	356 (15.5)	
Multivessel disease	585 (67.6)	1280 (55.8)	<0.001
Left ventricular ejection fraction (%)	57.9±9.3	58.6±8.7	0.04
Medications at discharge			
Warfarin	10 (1.2)	21 (0.9)	0.54
Statin	498 (57.6)	1240 (54.0)	0.07
β-Blocker	631 (72.9)	1629 (71.0)	0.28
Calcium Channel Blocker	417 (48.2)	1129 (49.2)	0.62
ACE inhibitor	536 (62.0)	1271 (55.4)	0.001

Lesion characteristics is different

Variable	Diabetes (n=865)	Non-diabetes (n=2295)	*P*
Treated lesions, No.	**1301**	**3190**	
Left anterior descending artery	637 (49.0)	1579 (49.5)	0.74
Left main artery	83 (6.4)	224 (7.0)	0.44
Lesion Characteristics			
ACC/AHA type B2 or C lesion	1008 (77.5)	2330 (73.0)	0.002
Ostial	84 (6.5)	271 (8.5)	0.02
Bifurcation	236 (18.1)	501 (15.7)	0.05
Total occlusion	70 (5.4)	181 (5.7)	0.70
Restenotic lesion	68 (5.2)	183 (5.7)	0.50

Procedure related characteristics is different

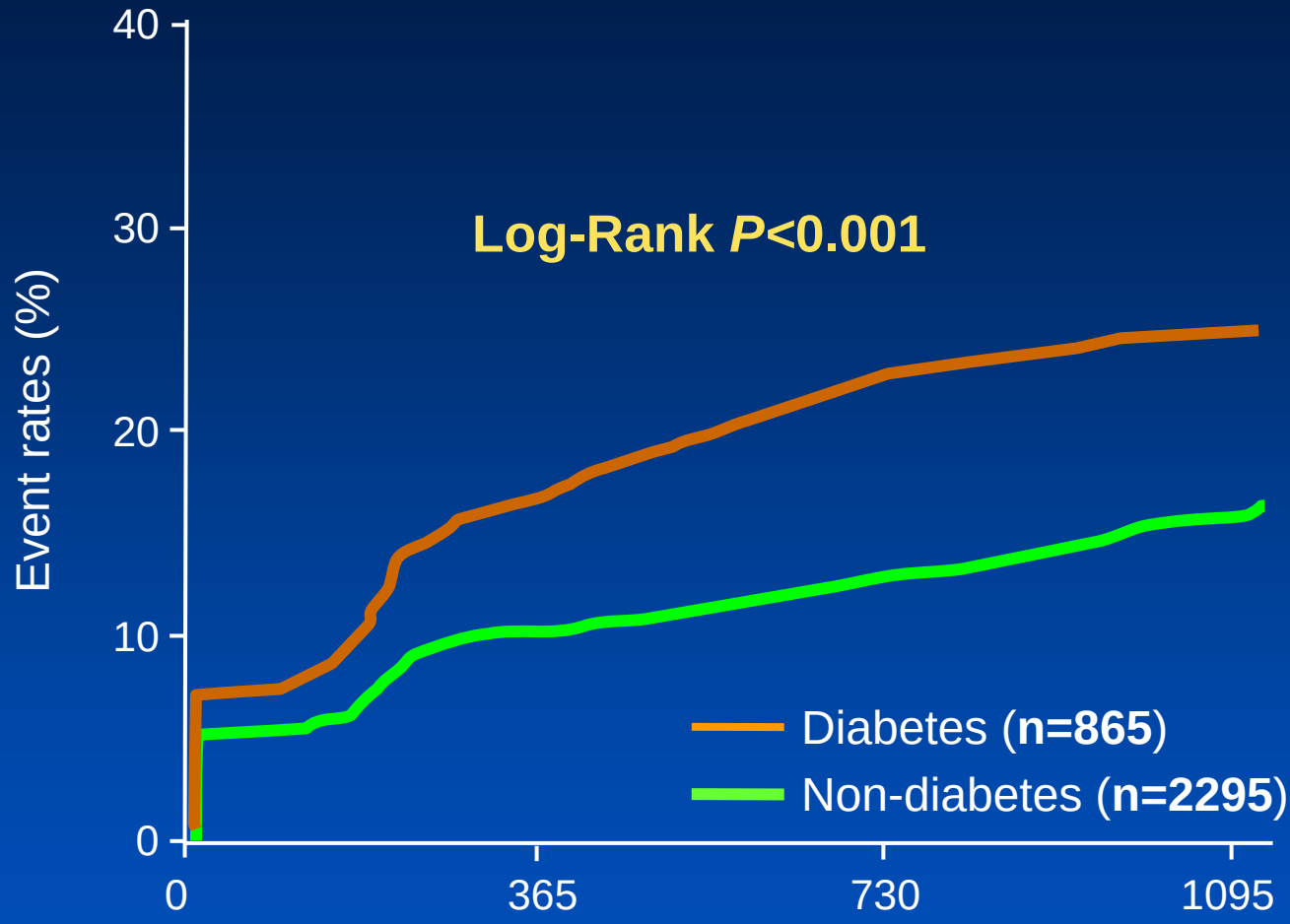
Variable	Diabetes (n=865)	Non-diabetes (n=2295)	*P*
Treated lesions, No.	**1301**	**3190**	
Direct stenting	174 (13.4)	553 (17.3)	0.001
IVUS guidance	798 (61.3)	2099 (65.8)	0.01
DES type			0.06
Sirolimus-eluting stent	976 (75.0)	2478 (77.7)	
Paclitaxel-eluting stent	325 (25.0)	712 (22.3)	
Number of stents per patient	2.1±1.2	1.8±1.1	<0.001
Total stent length per patient (mm)	53.5±33.3	46.0±29.8	<0.001
Average stent diameter per patient (mm)	3.1±0.3	3.2±0.3	<0.001
Use of Glycoprotein IIb/IIIa inhibitors	24 (2.8)	69 (3.0)	0.73

Adjusted HRs of Clinical Outcomes

Diabetic vs. Non-diabetics

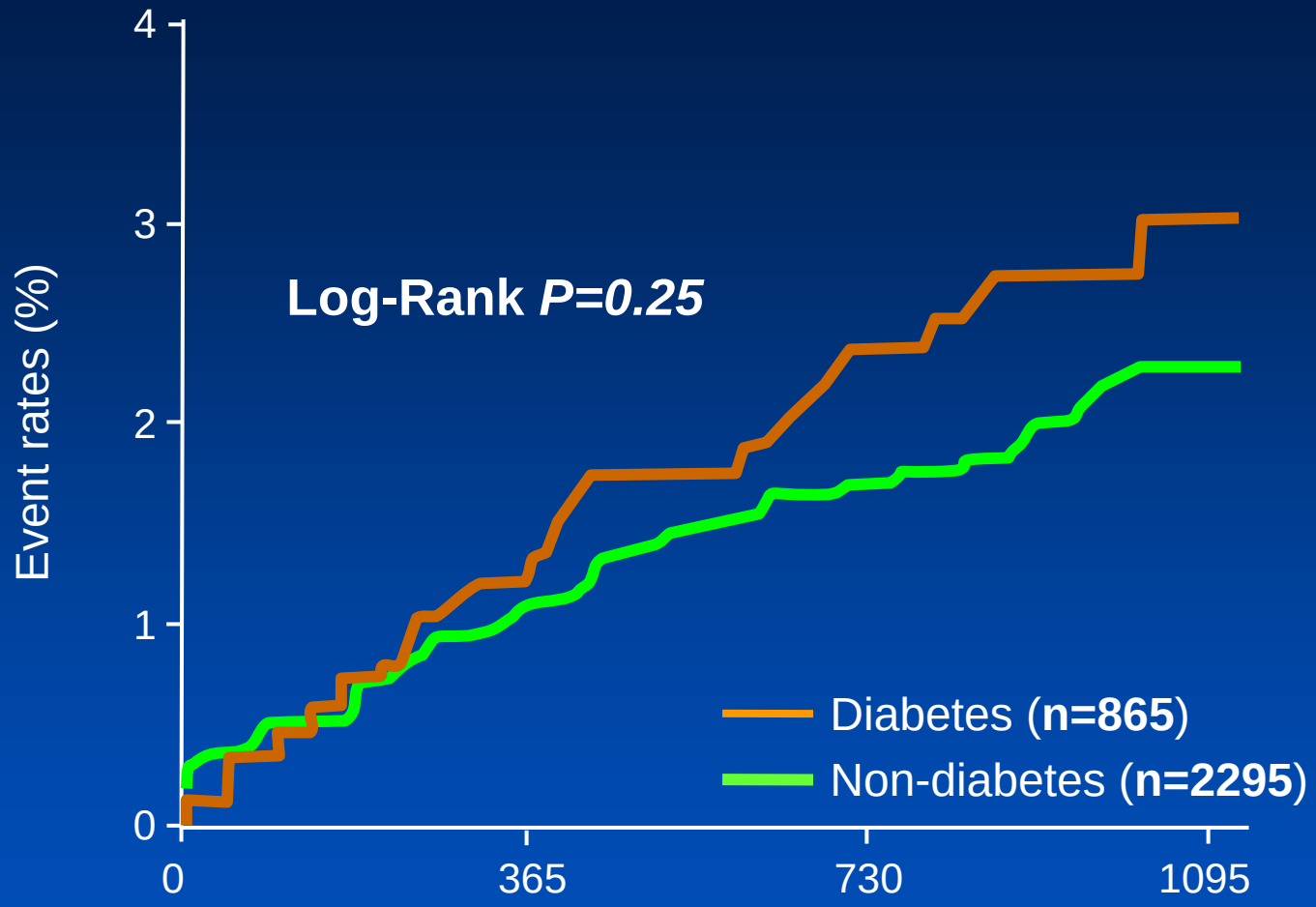
Outcome	HR	95% CI	P
Death	1.35	0.89-2.05	0.16
MI	1.08	0.78-1.50	0.63
TLR	1.06	0.78-1.43	0.71
TVR	1.37	1.04-1.81	0.03
Death/MI	1.18	0.92-1.53	0.20
Death/MI/TVR	1.24	1.02-1.51	0.03
Stent thrombosis			
Definite	0.62	0.20-1.84	0.41
Definite/probable	0.87	0.37-2.06	0.77
Any	1.14	0.69-1.99	0.64

Composite of Death, MI, or TVR



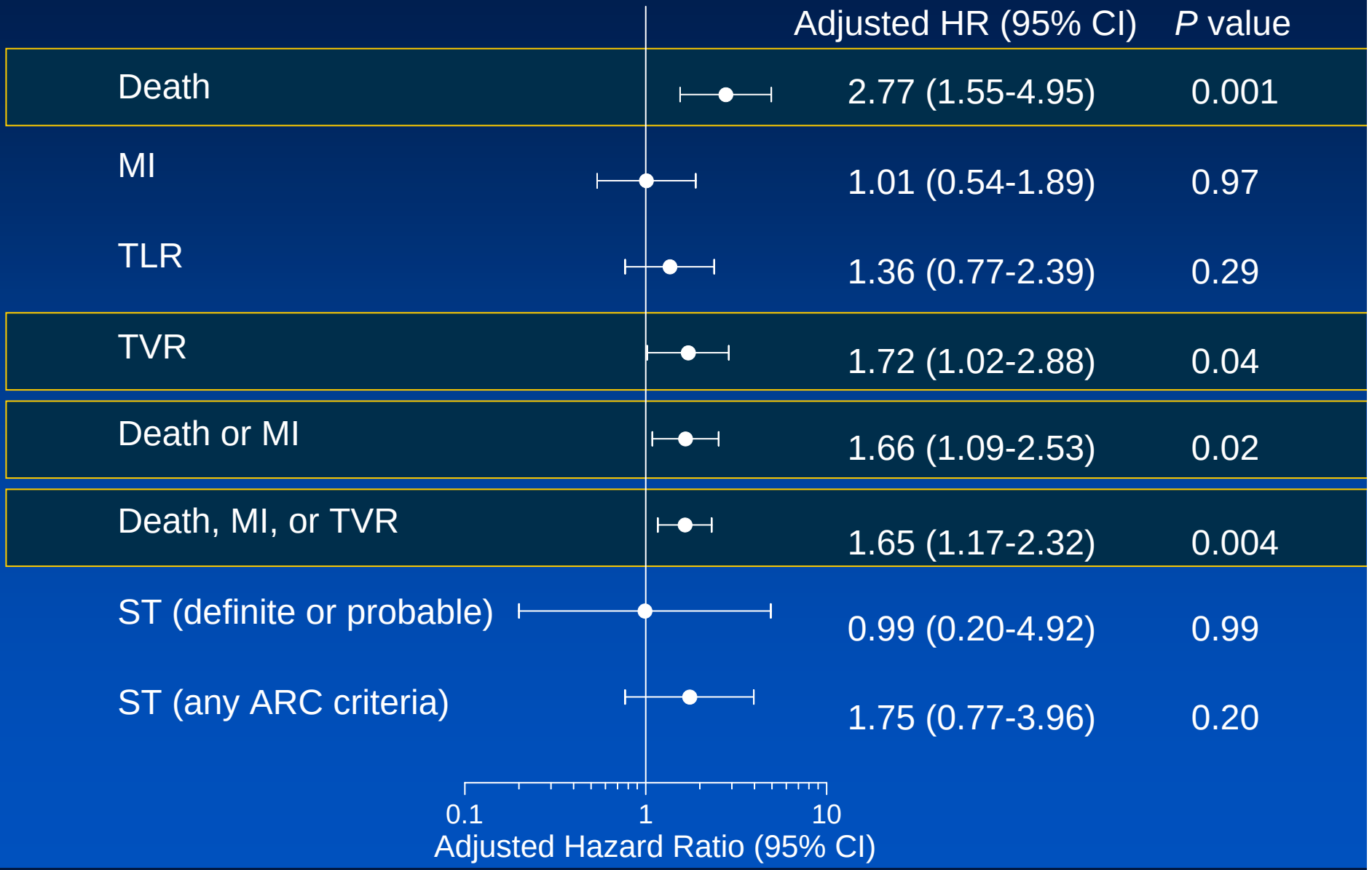
No. at Risk				
Diabetes	865	730	457	195
Non-diabetes	2295	2057	1339	581

Stent Thrombosis

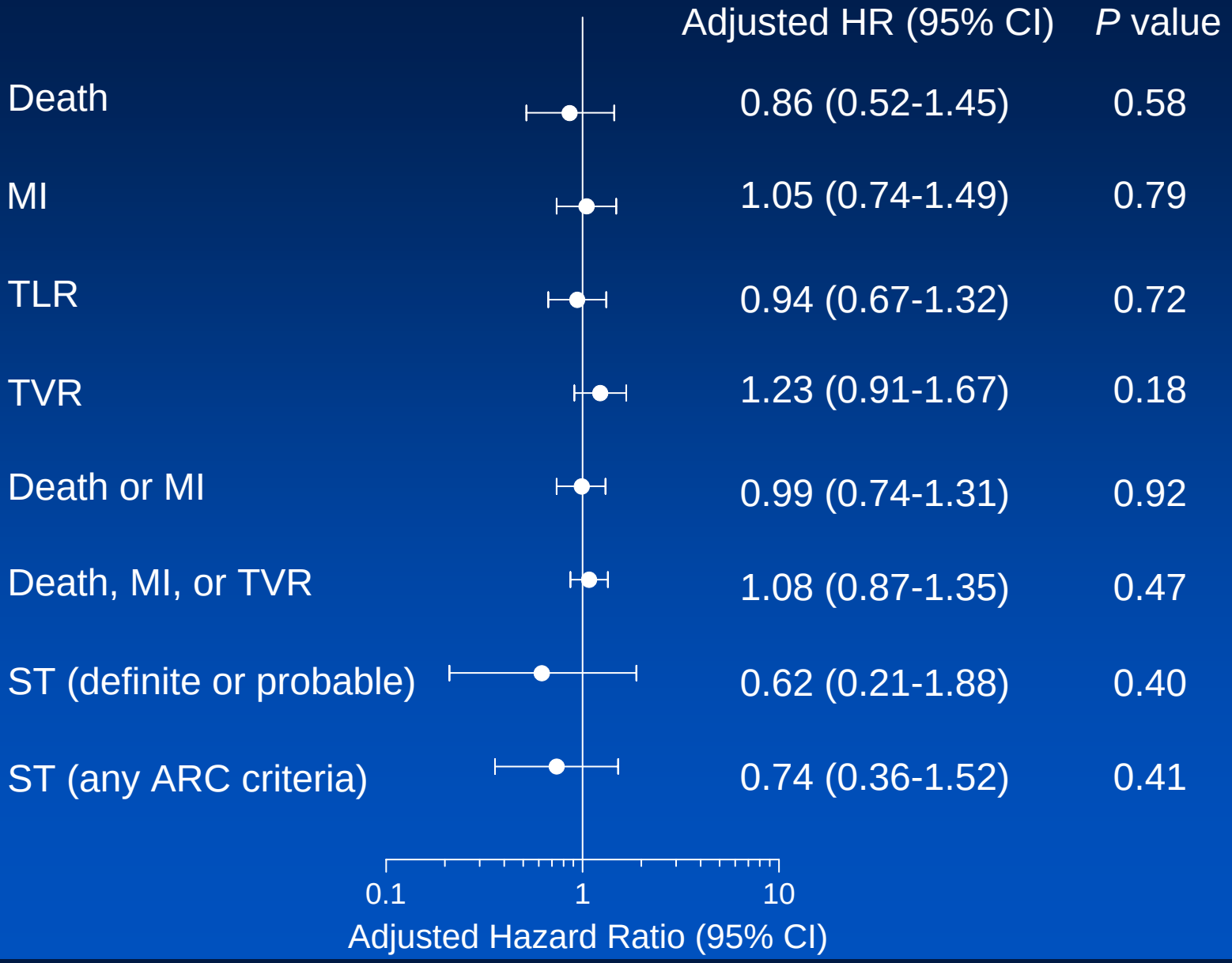


No. at Risk				
Diabetes	865	842	561	247
Non-diabetes	2295	2248	1521	674

Non-diabetes vs. **Insulin-treated diabetes**



Non-diabetes vs. **Non-insulin-treated diabetes**



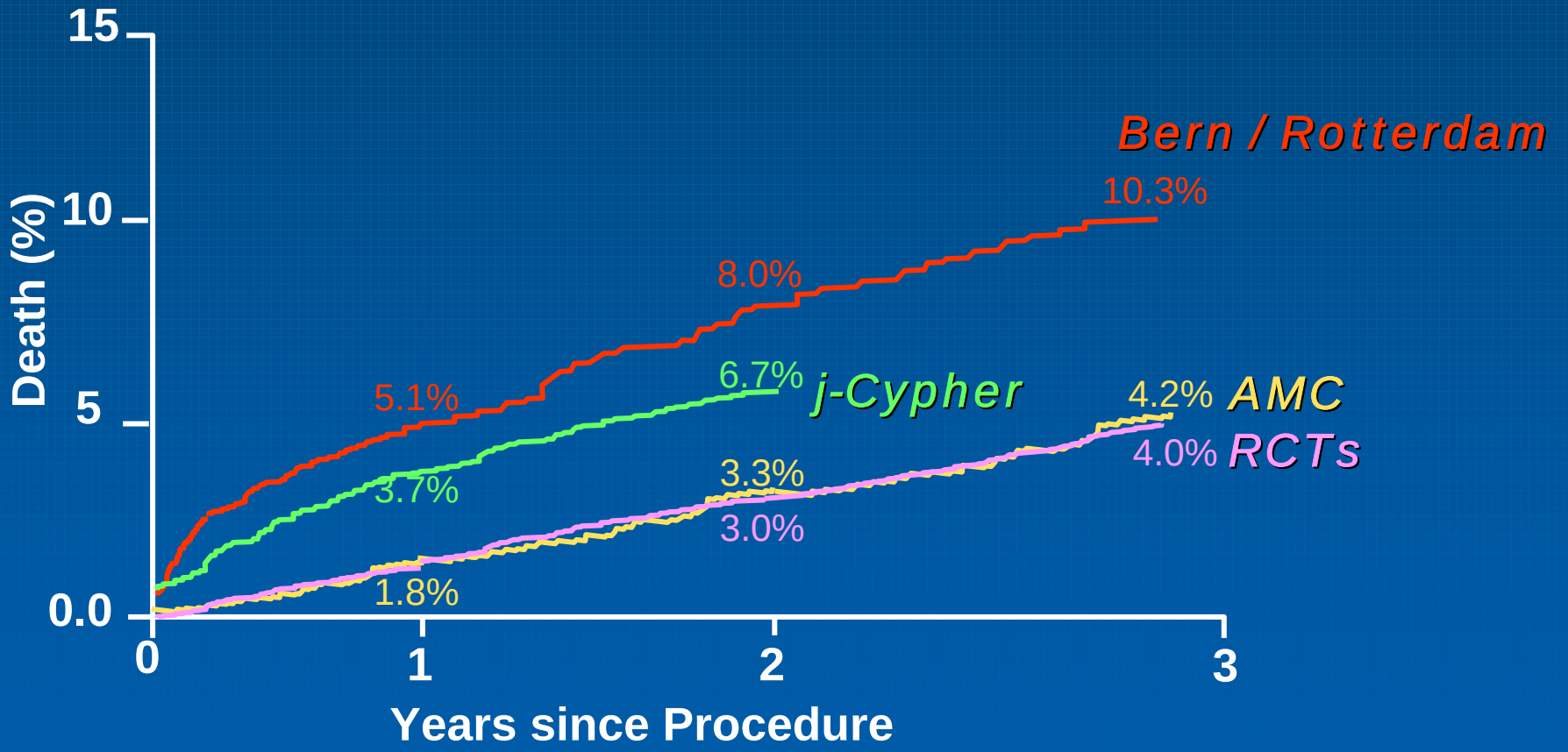
Summary:
Diabetic Impact in Asian Patients

- The overall mortality rate was similar in diabetic and non-diabetic patients
- Diabetic patients have a higher incidence of TVR, without a significantly increased rate of TLR
- There was no significant association between increased risk of stent thrombosis, whether insulin-dependent or not
- Insulin-treated diabetes was independently associated with increased risk of death/MI/or TVR

Any Differences of Mortality and Stent Thrombosis after DES Implantation in Asian vs. Western Patients ?

All-Cause Mortality

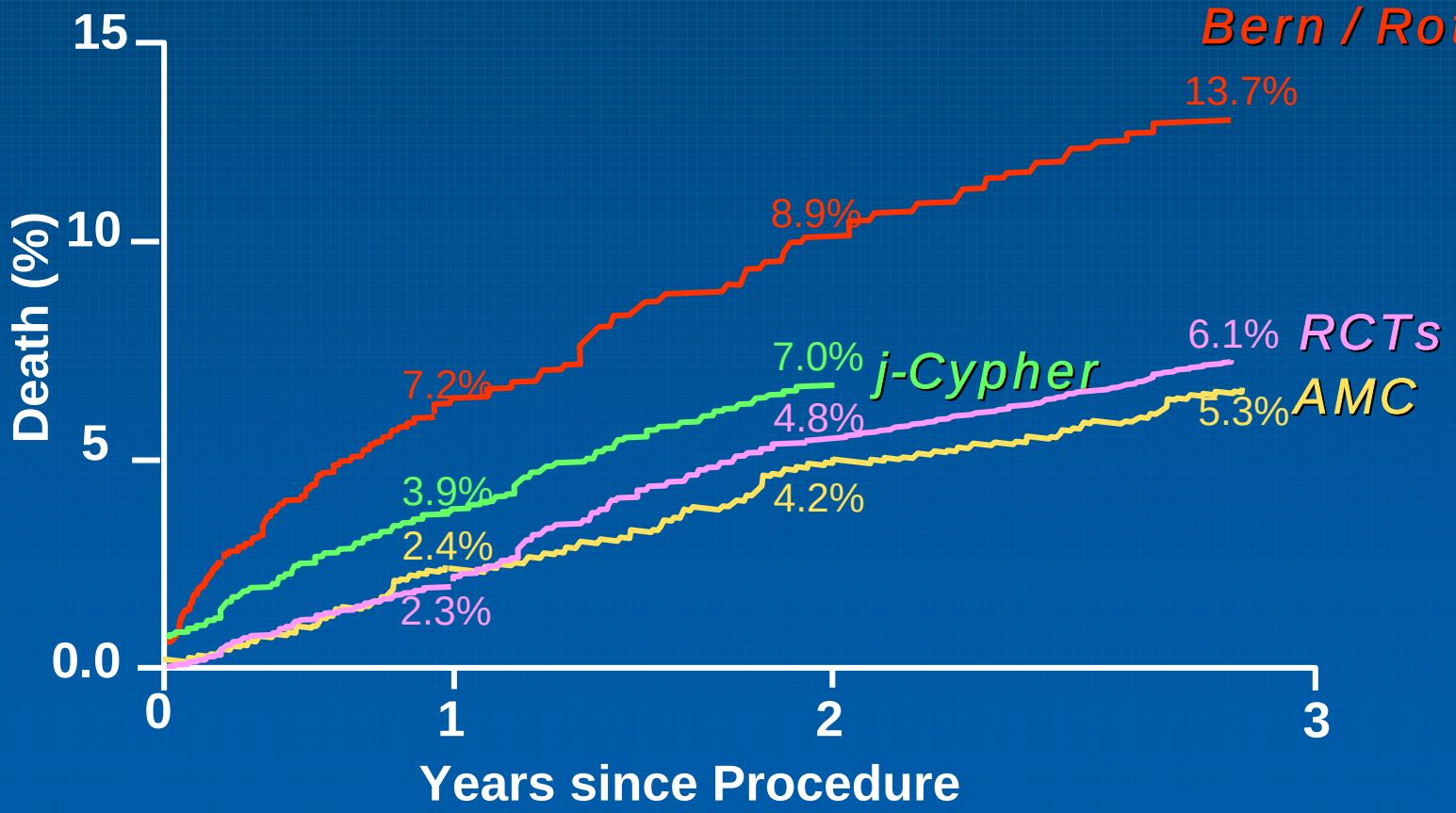
All-cause mortality of Asian Registry is similar
to Western RCT Results, but lower than Western Registry data



Park et al. *JACC:Cardiovascular Interventions* 2008

Death or MI

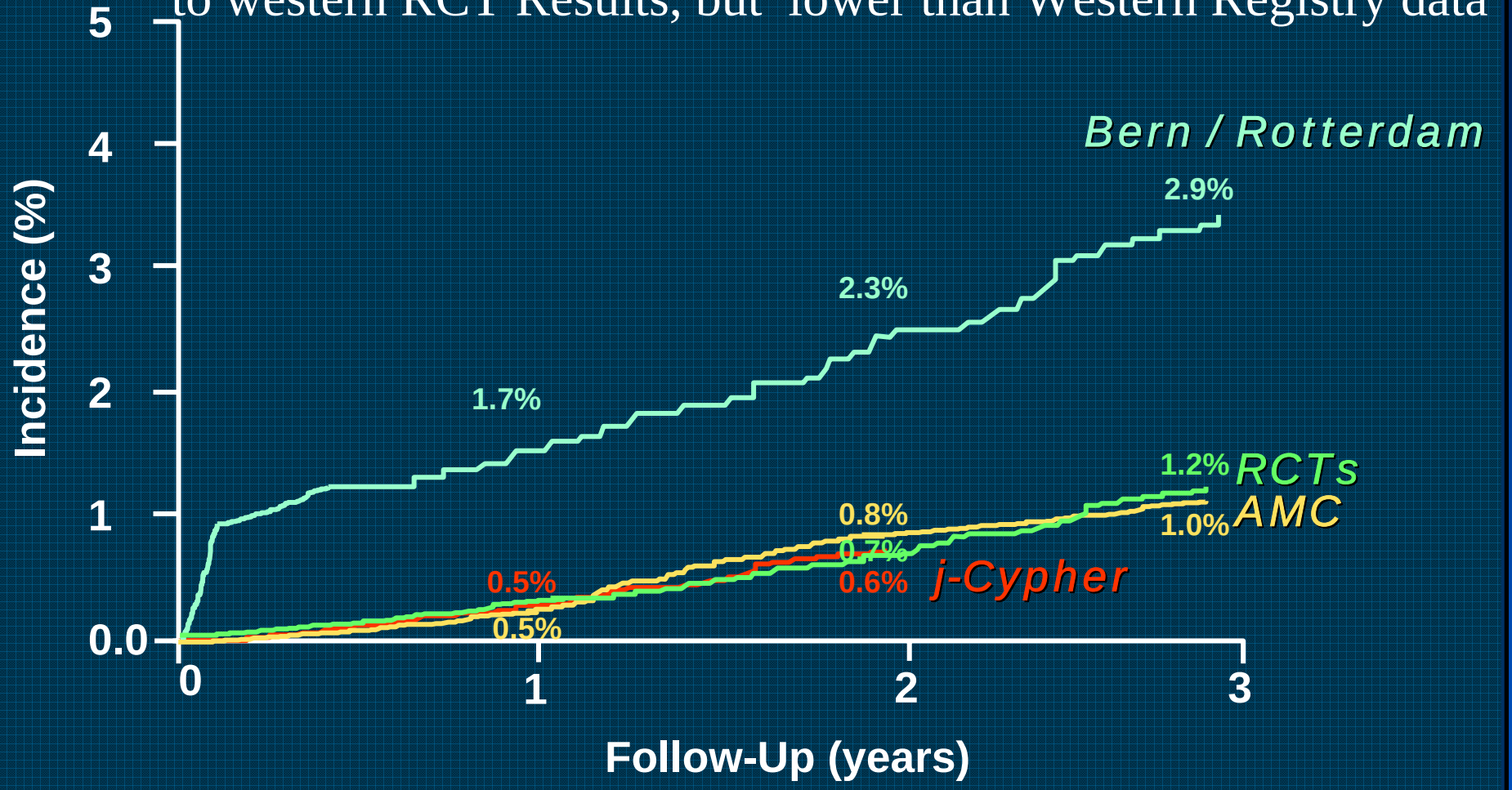
All-Death or MI of Asian Registry is similar
to Western RCT Results, but lower than Western Registry data



Park et al. *JACC:Cardiovascular Interventions* 2008

Incidence of Angiographic ST

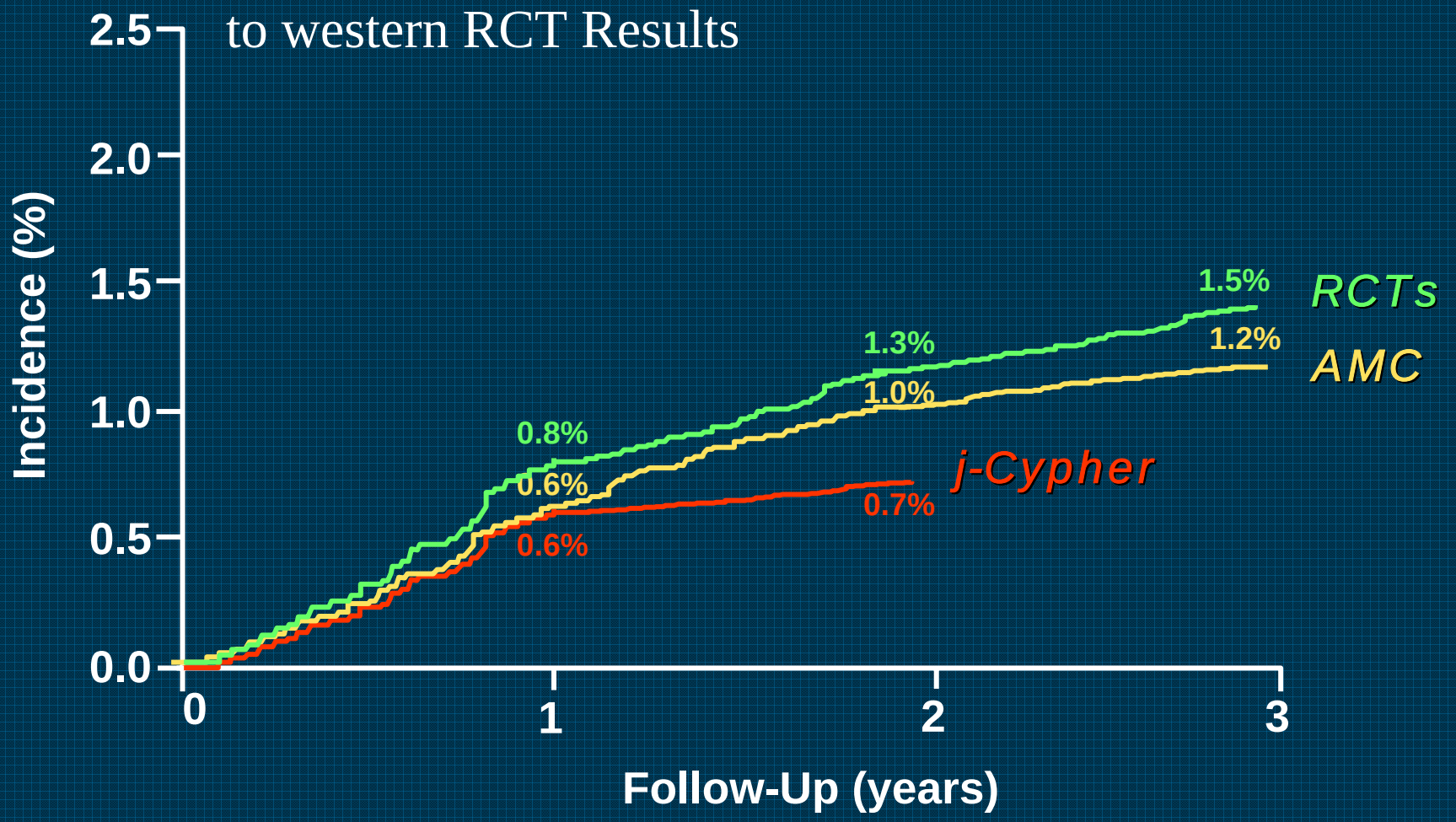
Incidence of ST of Asian Registry is similar
to western RCT Results, but lower than Western Registry data



Park et al. *JACC:Cardiovascular Interventions* 2008

Incidence of ST (Definite+Probable)

Incidence of ST of Asian Registry is similar to western RCT Results



Park et al. *JACC:Cardiovascular Interventions* 2008

Independent risk factors of ST

- Acute coronary syndrome
- Diabetes

Bern / Rotterdam

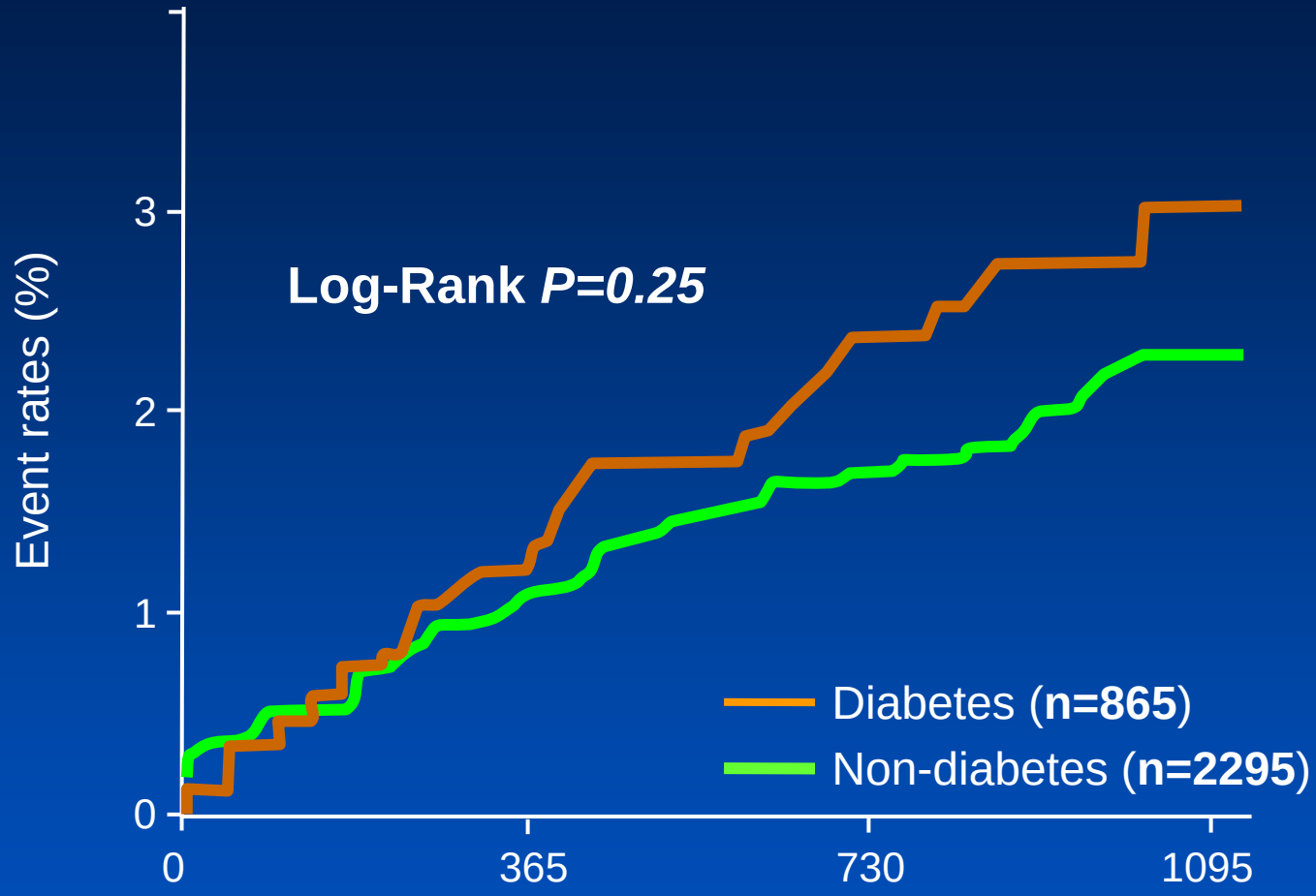
- Lower ejection fraction
- Renal failure
- Stent length

AMC Registry

Patient's factors may be more involved in development of ST in the DES era.
Diabetics is independent predictor in western study

AMC Data

Stent Thrombosis

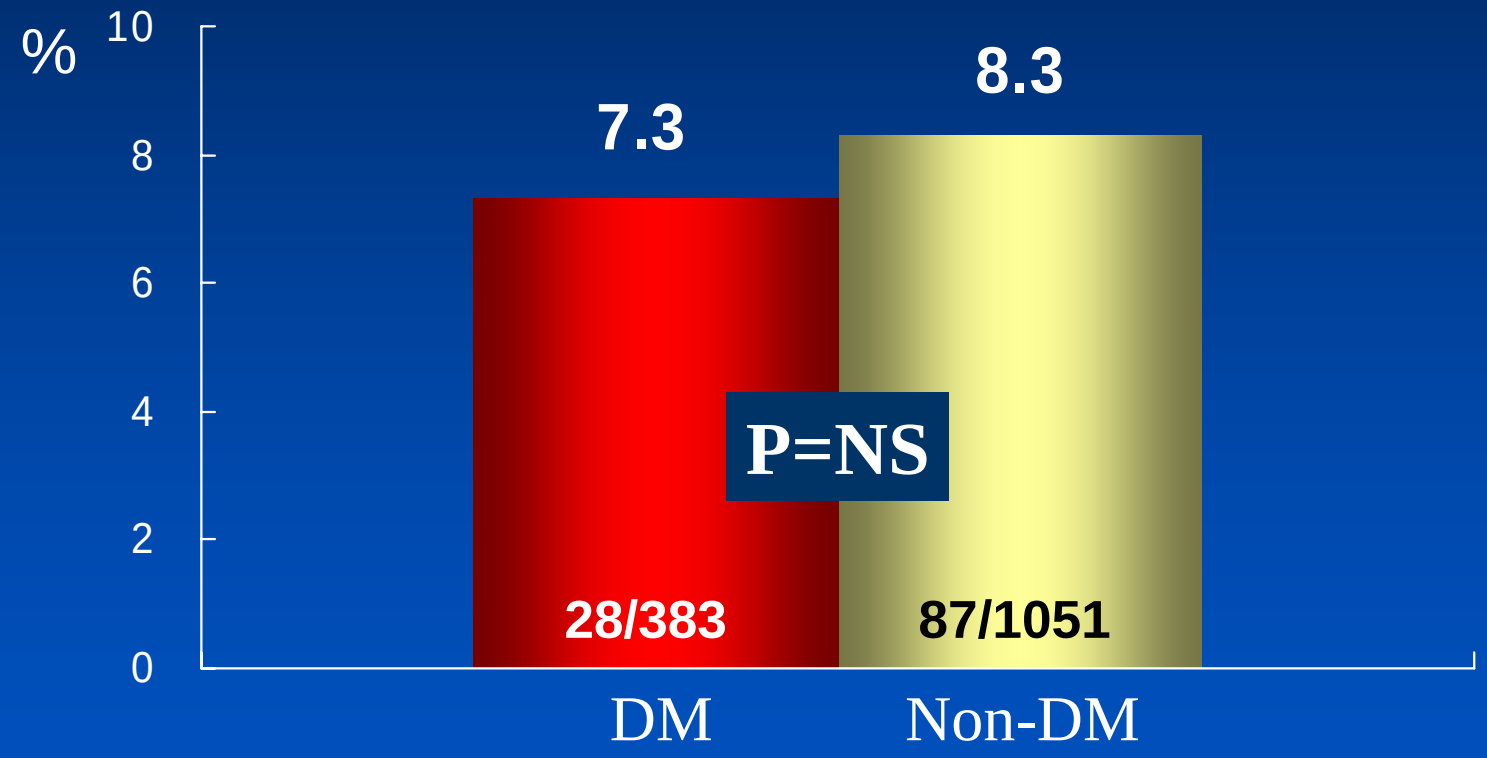


No. at Risk				
Diabetes	865	842	561	247
Non-diabetes	2295	2248	1521	674

AMC Data

Impact of DM on Restenosis after DES Implantation

1126 Cypher lesions and 308 Taxus lesions



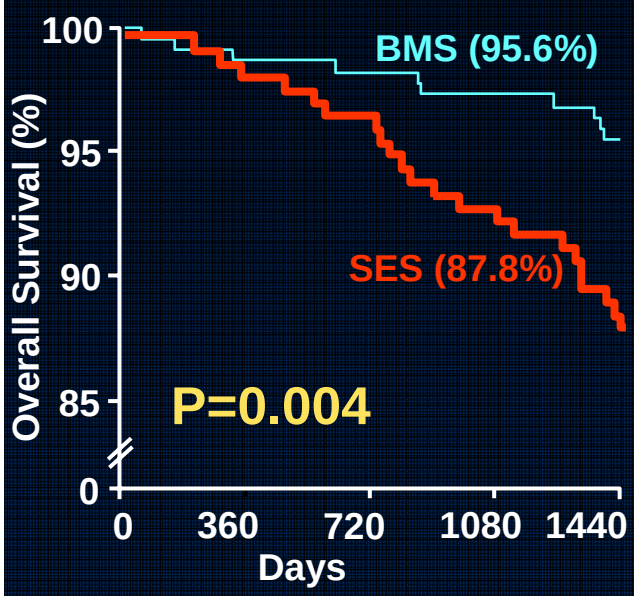
TH Y et al. Am J Cardiol 2005;96:1389

Impact of Diabetes

All-Cause Mortality

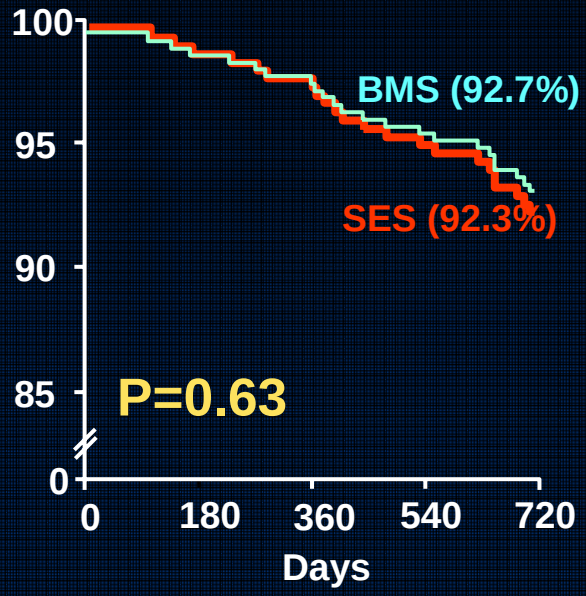
Death at 4 yr F/U

Patients with Diabetes



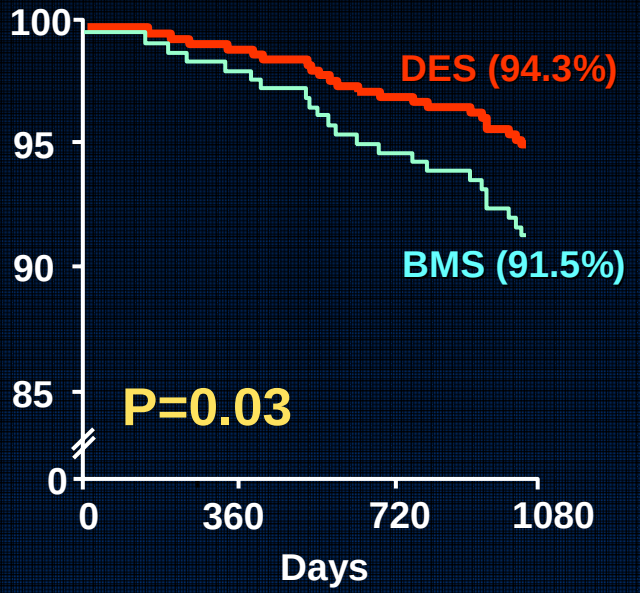
Death at 2 yr F/U

Patients with Diabetes



Death at 3 yr F/U

Patients with Diabetes



RCTs
(RAVEL, SIRIUS,
E-SIRIUS, C-SIRUS)

J-Cypher

AMC Registry

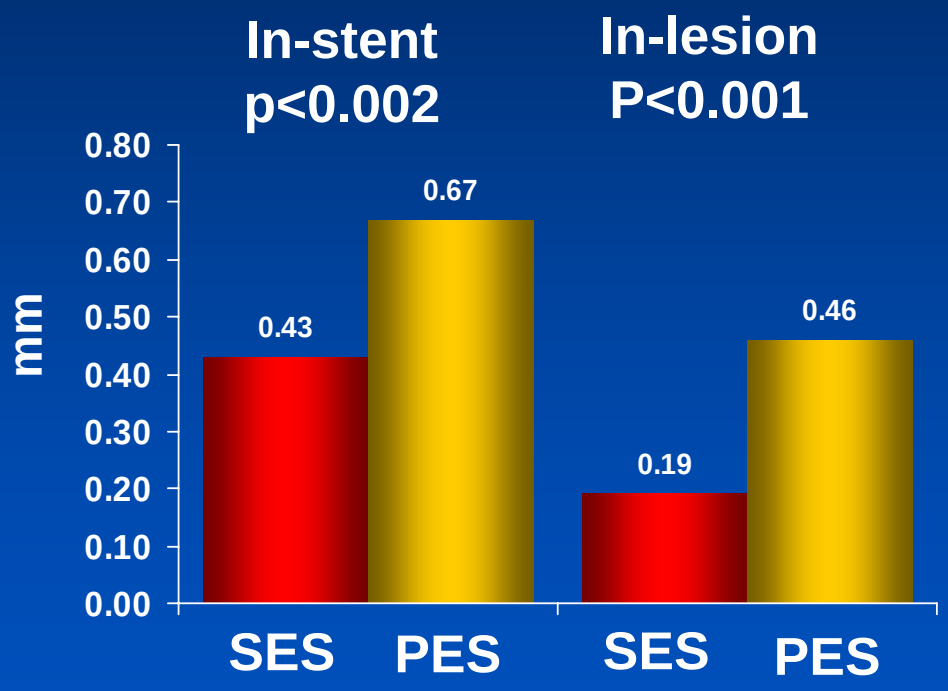
Summary

- Incidence of ST and all-cause mortality of Asian registry was similar to those of western RCT, but lower than results of western registry
- Important predictors of ST was mainly due to patient's clinical factors.
- Impact of diabetes on the long-term outcomes in Asia was very modest, compared to the features from Western data.

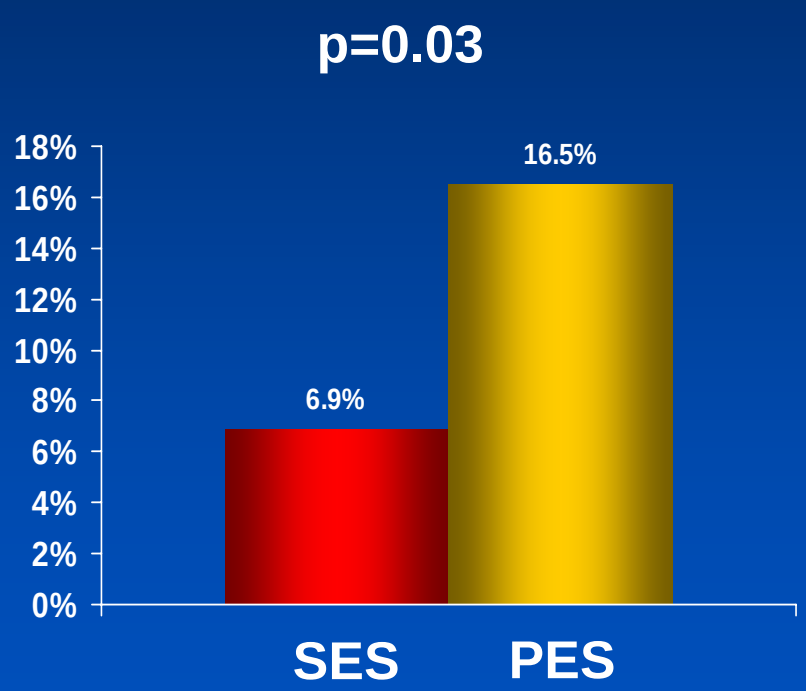
Diabetes
; CYPHER vs. TAXUS

ISAR-DIABETES Trial

Late Lumen Loss

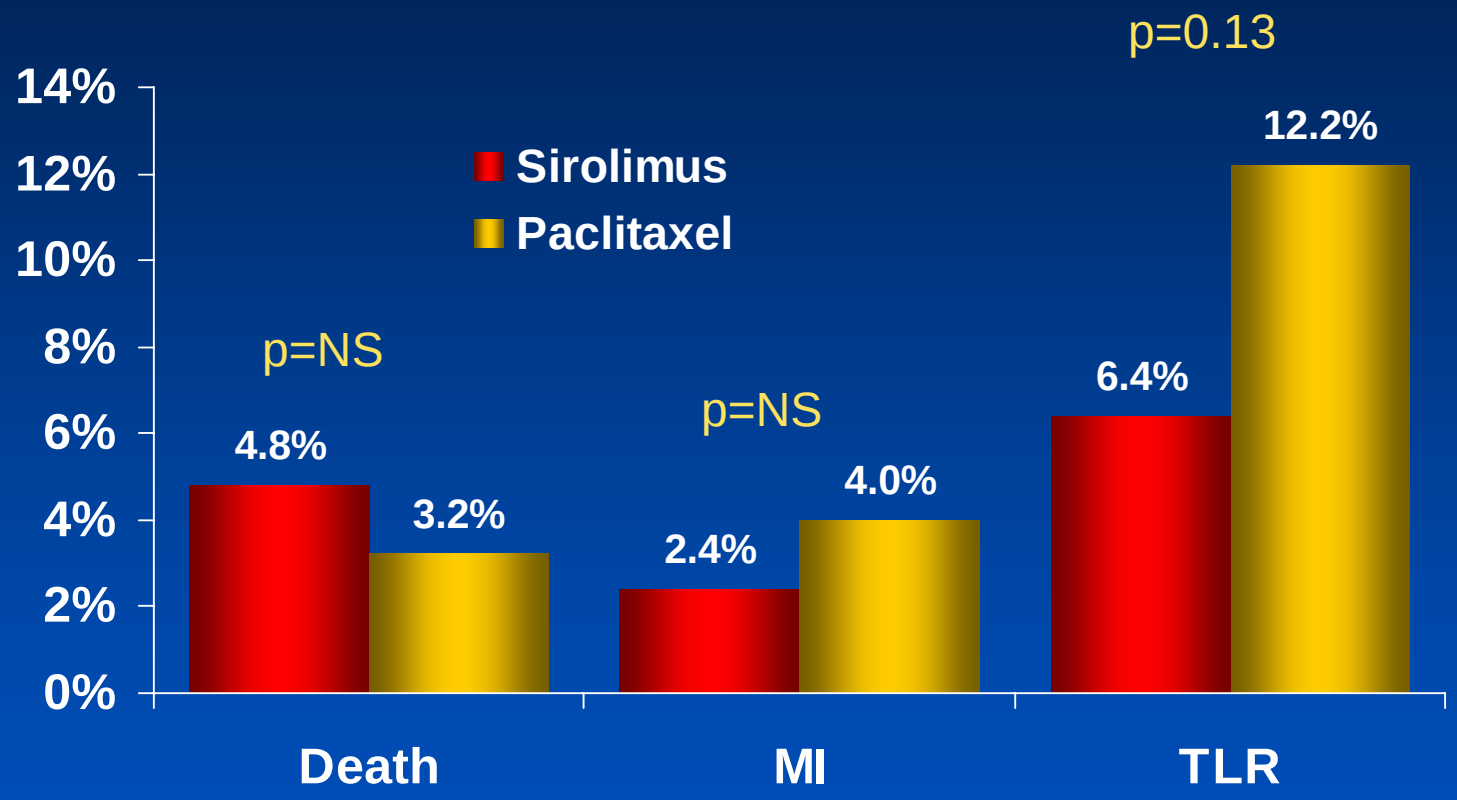


Re-stenosis



Kastrati et al., NEJM 2005;353:663-70

ISAR-DIABETES Trial



There was a trend towards a reduction in TLR (p=0.13)

Kastrati et al., NEJM 2005;353:663-70

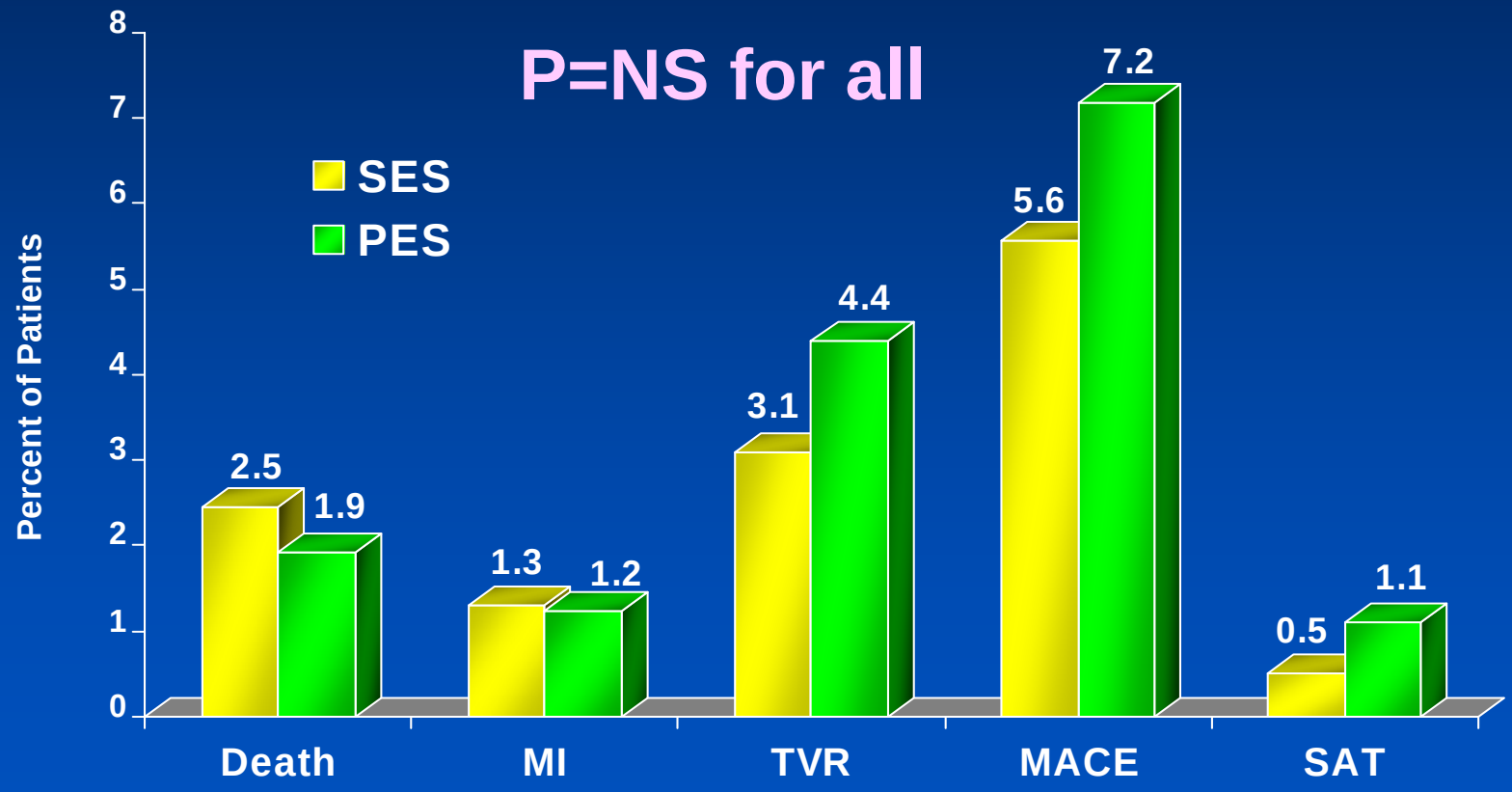
CYPHER vs. TAXUS in Diabetic Patients:

Data from the Strategic Transcatheter Evaluation of New Therapies (STENT) Group Registry

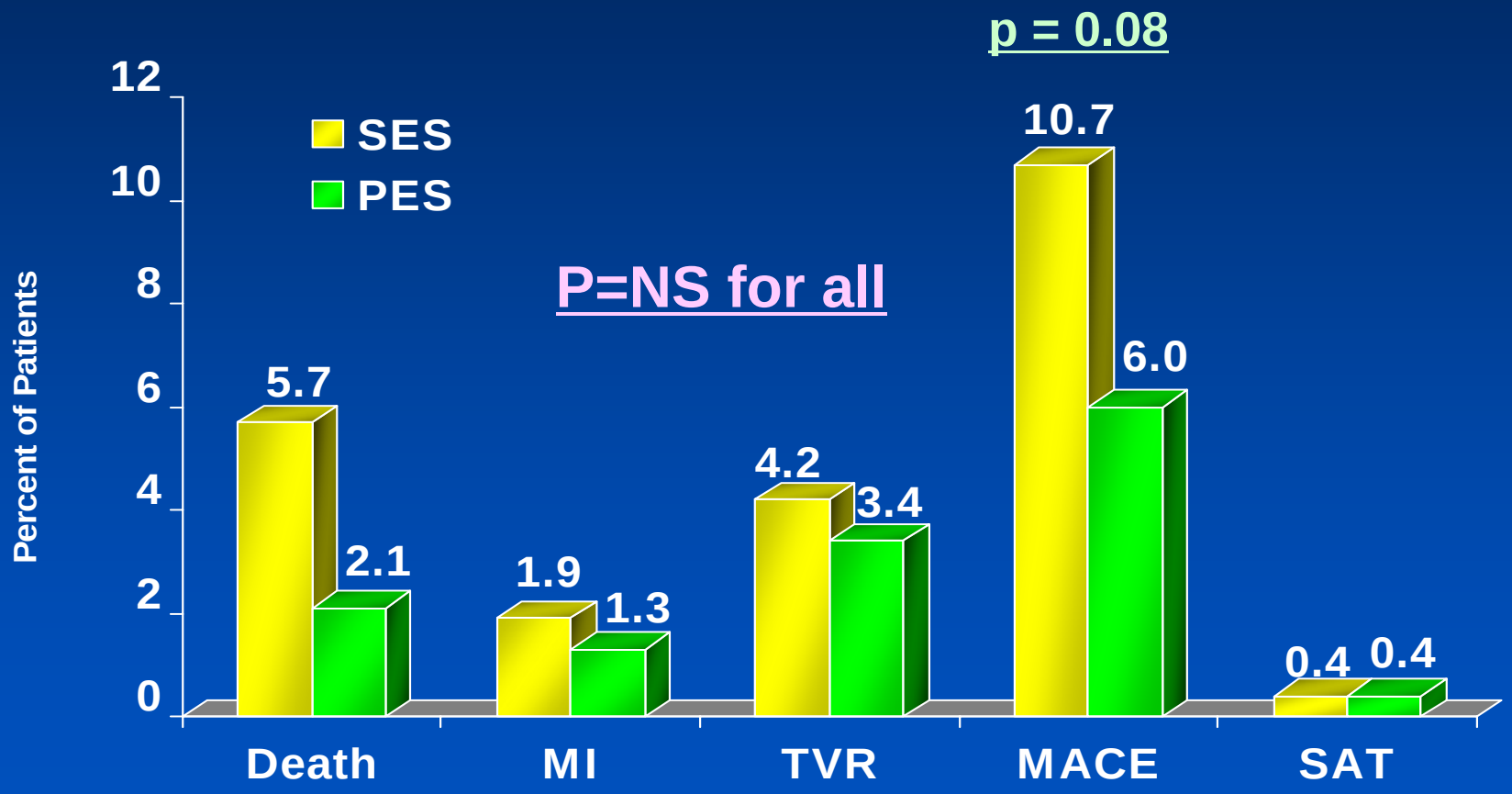
DES Only Patients with Completed 9 Month Follow-Up
Patient Level Analysis

PES or SES *Patients* with 9 mo F/U	n = 5566		
All Diabetic Patients	1680	30.2%	
Sirolimus Eluting Stent Only		875	52.1%
Paclitaxel Eluting Stent Only		805	47.9%
Non-Insulin Treated Diabetics		1182	
Sirolimus Eluting Stent Only		612	51.8%
Paclitaxel Eluting Stent Only		570	48.2%
Insulin-Treated Diabetics		498	
Sirolimus Eluting Stent Only		263	52.8%
Paclitaxel Eluting Stent Only		235	47.2%

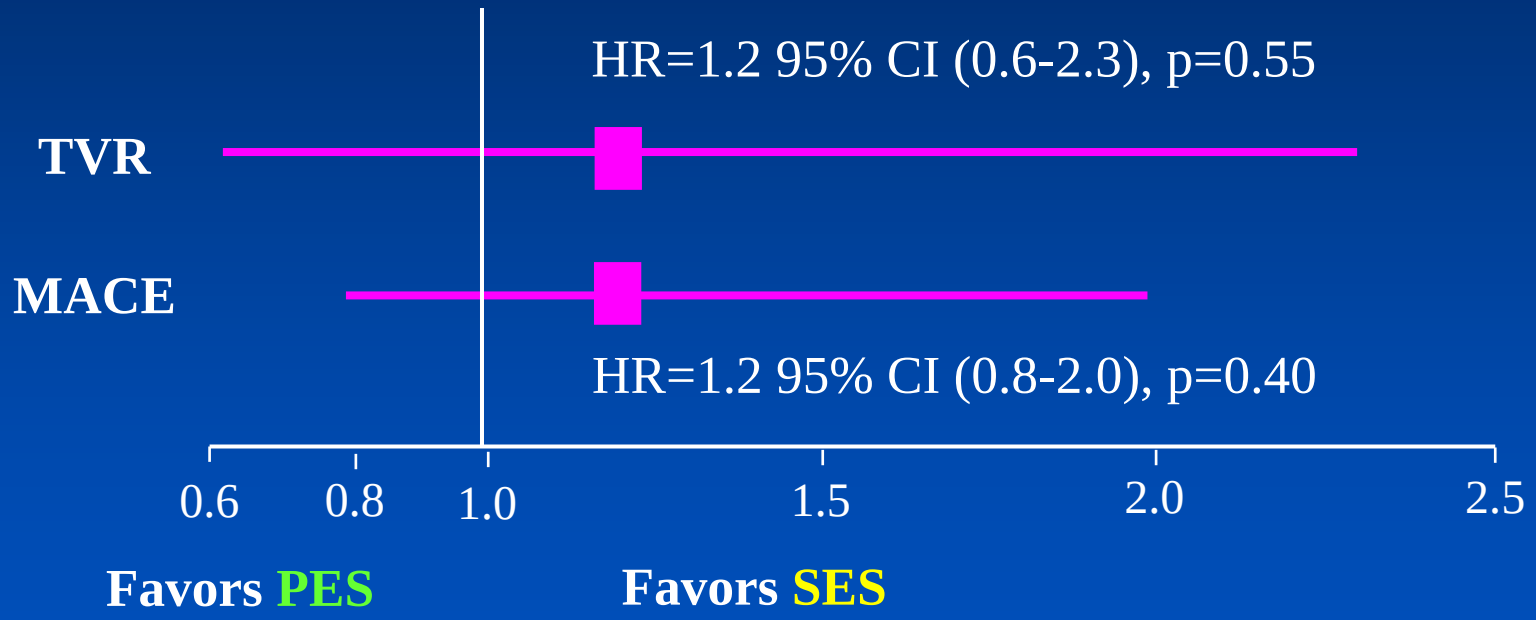
9 Month Clinical Outcomes:
Non-Insulin Treated Diabetics
(unadjusted)



9 Month Clinical Outcomes:
Insulin Treated Diabetics
(unadjusted)

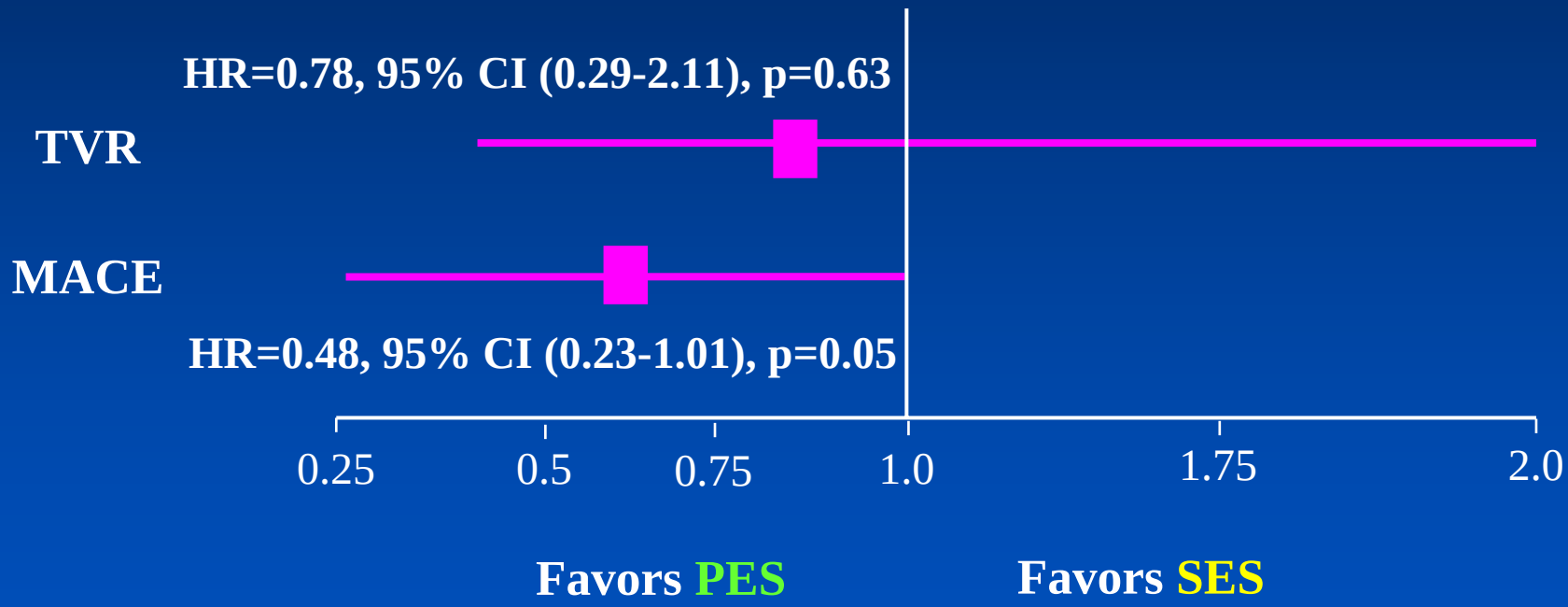


Adjusted Hazard Ratios for Time to Event Comparing PES- and SES-Only **Non-Insulin Treated Patients**



Note: Reference group for HR is SES group

Adjusted Hazard Ratios for Time to Event Comparing PES- and SES-Only **Insulin Treated Patients**



Note: Reference group for HR is SES group

Conclusions: STENT Registry

- PES and SES procedures show similar and very favorable late clinical outcomes in diabetic patients, similar to that reported in prior studies for non-diabetics
- The insulin-treated diabetic group shows a trend favoring PES over SES for late MACE, but needs to be confirmed by further studies

Summary (1)
PCI in Diabetics

- Aggressive revascularization strategy improves the survival in diabetic patients compare to medical treatment.
- Diabetic patients treated with DES bring a reduced risk of TLR,TVR,TVF and MACE compared with BMS
- Diabetics still have higher TVR and Death/MI/TVR especially, insulin treated diabetics have a clear trend of poor clinical outcomes (Death, TVR and Death/MI/TVR) compared to non-diabetics even in the era of DES

Summary (2)
PCI in Diabetics

- According to the ISAR-DIABETES and DECLARE-DIABETES Trial, SES appears to be more effective than PES in preventing restenosis in on-label lesions. However, in real practice, two stent had similar outcomes.
- Adjunctive pharmacologic therapy (Cilostazol, GP IIb/IIIa, Thiazolidinediones, ACEI, strict glycemic control) is likely to further improve PCI outcomes
- Efficacy concerns of DES compare to surgery should be evaluated in the future.