Why Should Diabetics be Treated Differently?

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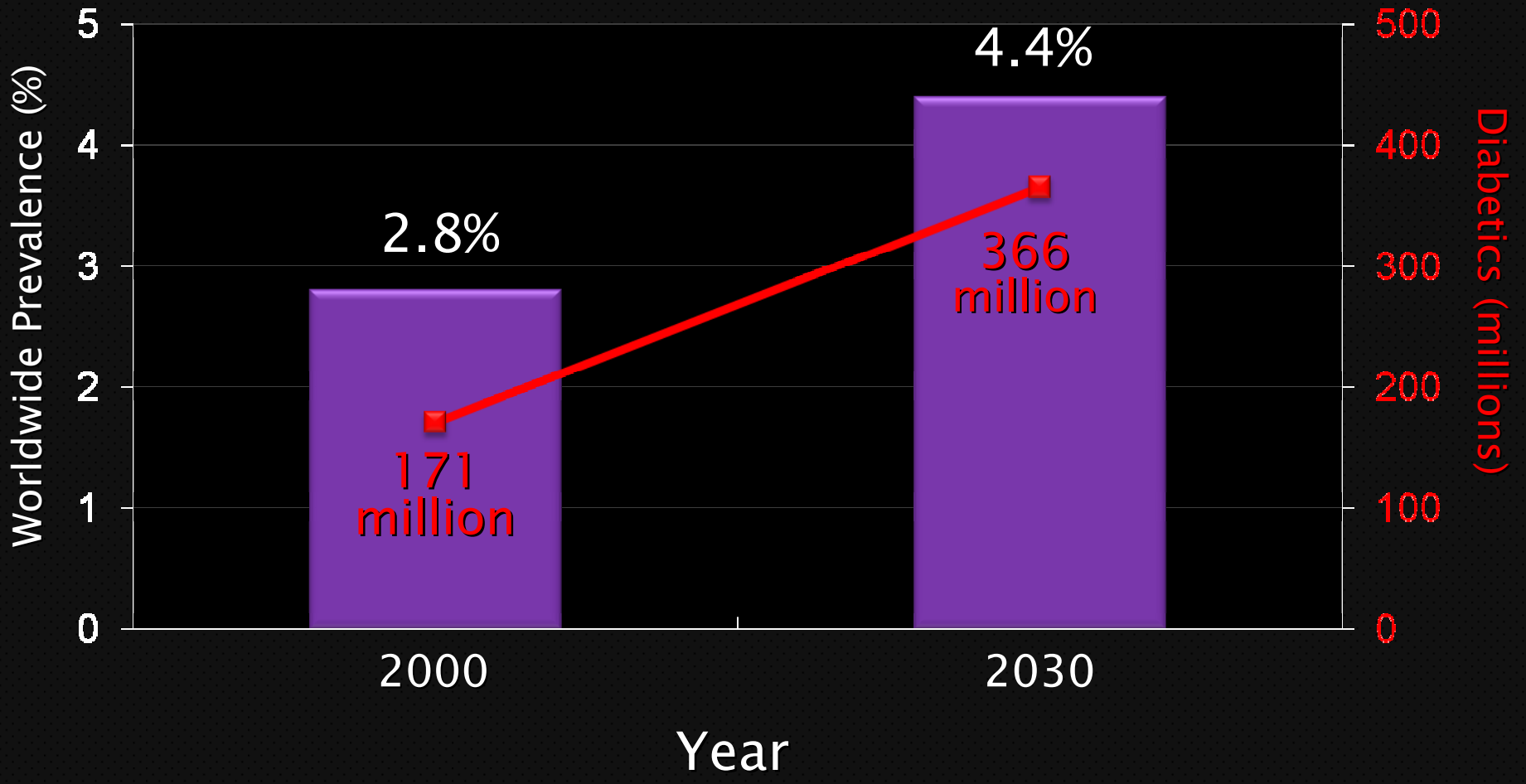
Angioplasty Summit TCT Asia Pacific
3rd APSIC Fellowship Convocation

Conflicts of Interest

- Employee & Stockholder:
  Boston Scientific Corporation
- I intend to reference unlabeled/unapproved uses of products in my presentation

Prevalence of Diabetes Mellitus



Diabetes Care 2004:27:1047-1053

Prevalence of Diabetes Mellitus

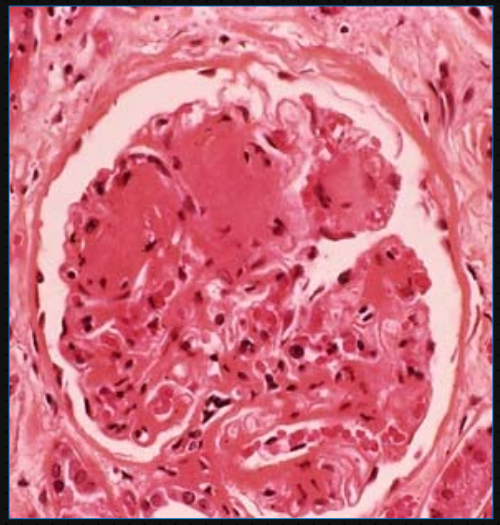
1:3

Diabetes: Collateral Damage in Europe

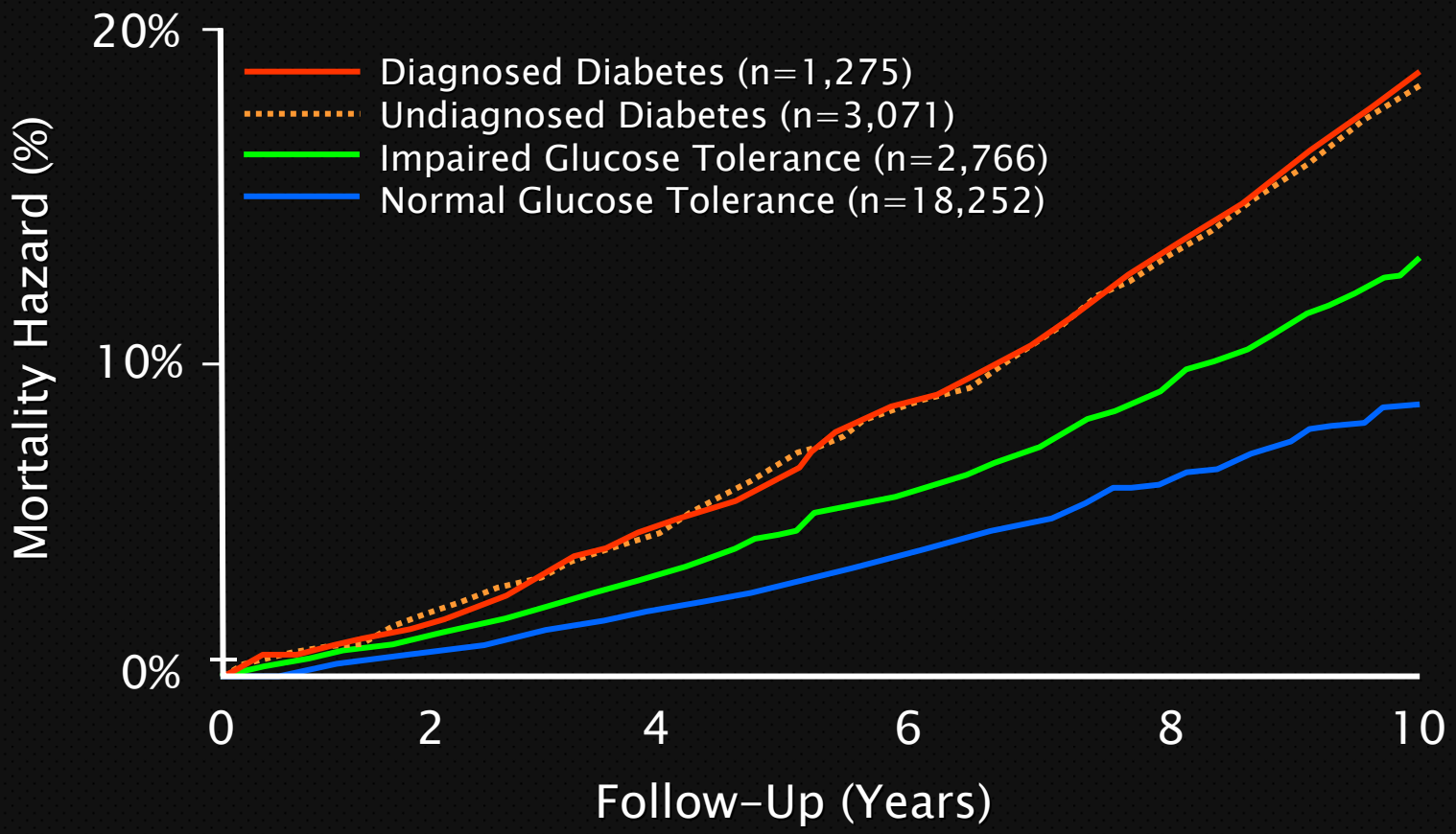
- Every 2 minutes a Stroke
- Every 4 minutes a Myocardial Infarction
- Every 4 minutes an Amputation
- Every 12 minutes a Loss of Kidney Function
- Every 18 minutes a Loss of Eye Sight

CODE-2, Costs of Diabetes in Europe: Type-2-Diabetes (1998)

Diabetic Complications

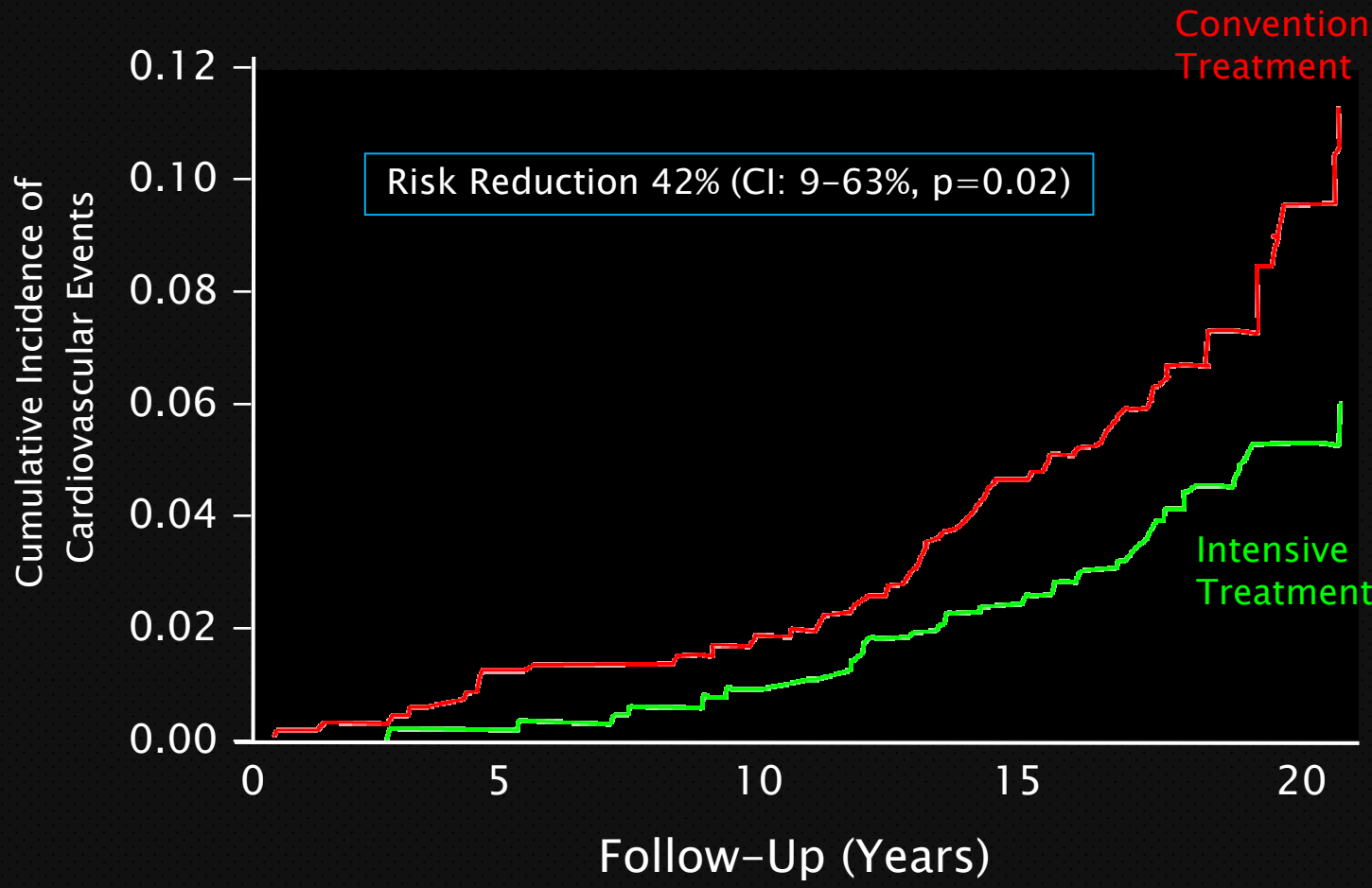


Influence of Glucose Status on Adjusted Mortality Risk



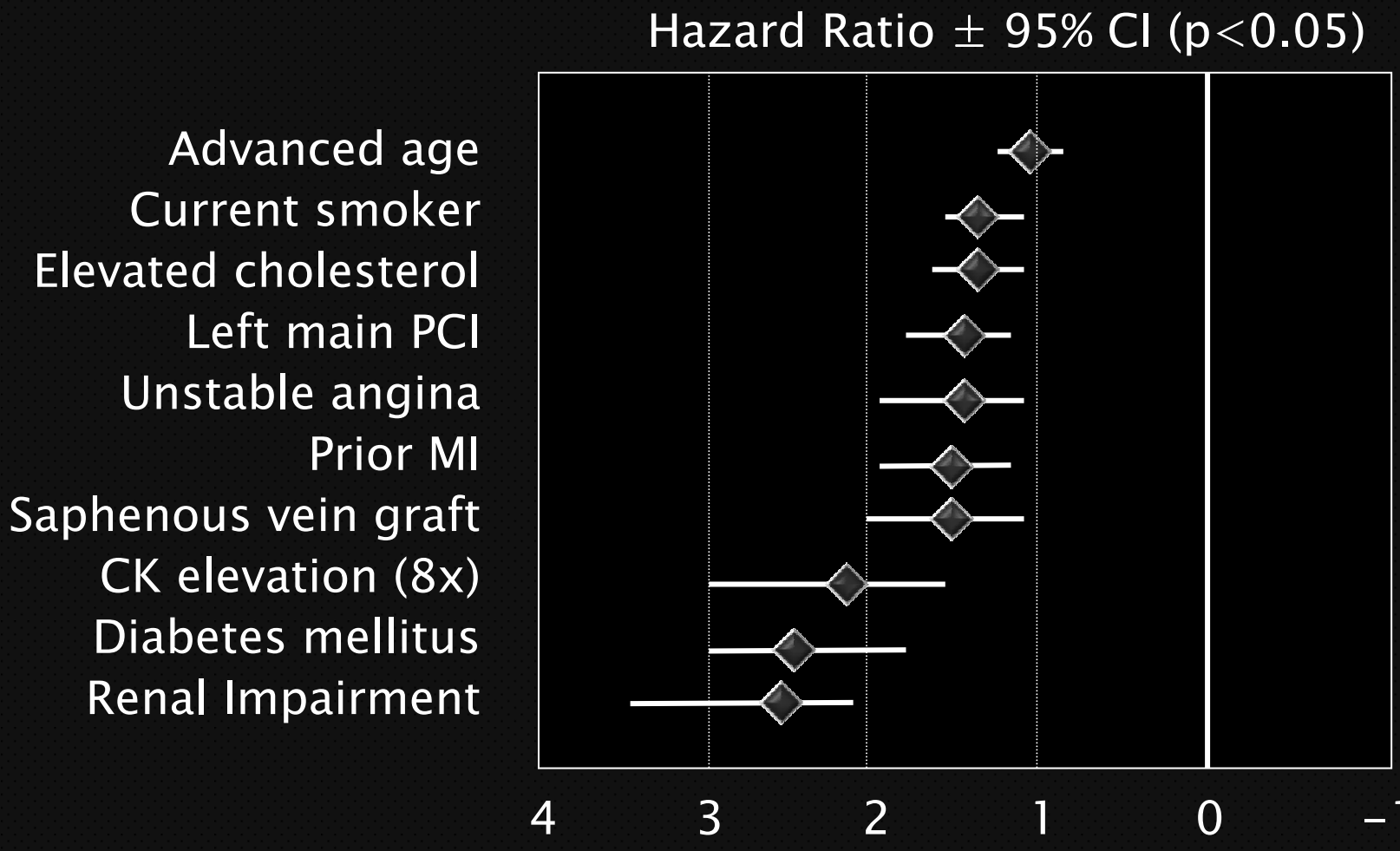
DECODE Study Group. Lancet 1999;354:617-621

Long-term Effects of Intensive Medical Management in Diabetes Mellitus



New Engl J Med 2005;353:2643–2653

Percutaneous Coronary Intervention
Multivariate correlates of cumulative late mortality



Circ 2001;104:642-647

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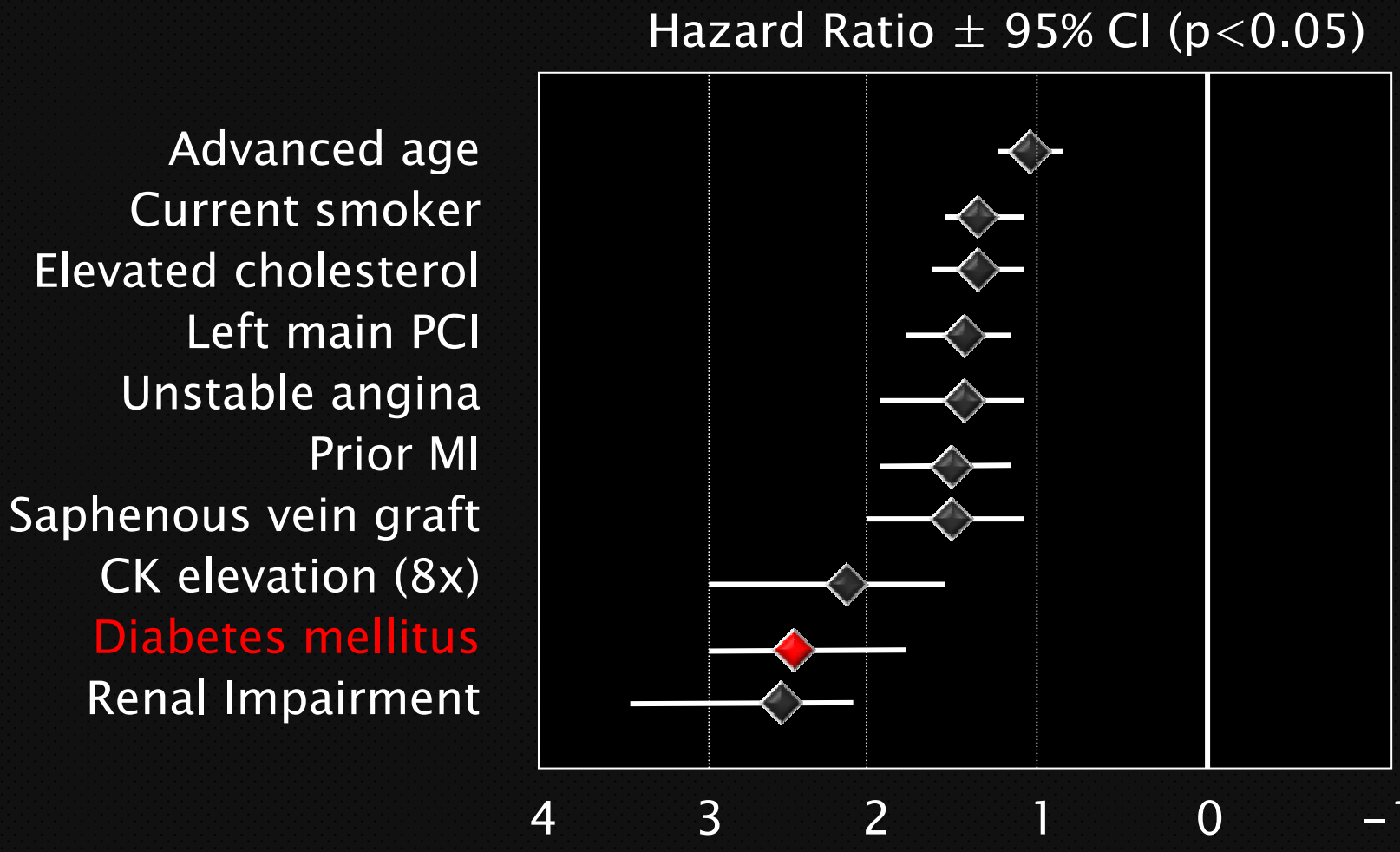
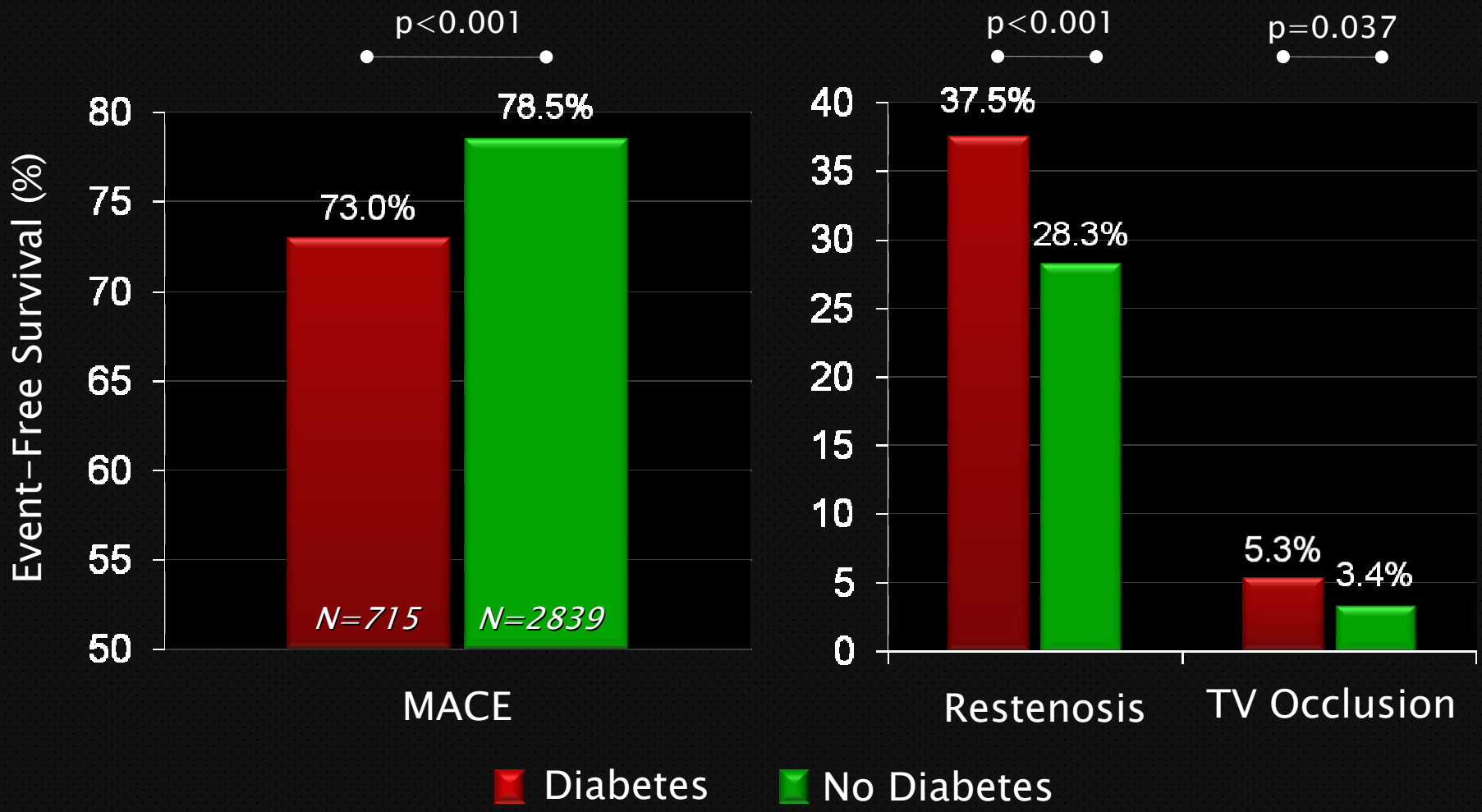


Circ 2001;104:642-647

POBA and Diabetes

J Am Coll Cardiol 1999;34:476-485

Outcomes in Diabetics following BMS

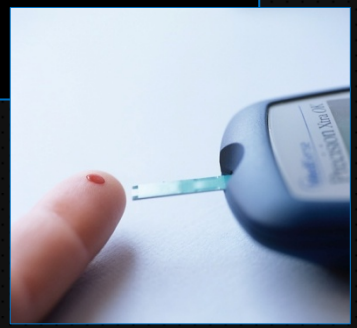


J Am Coll Cardiol 1998;32:1866-1873

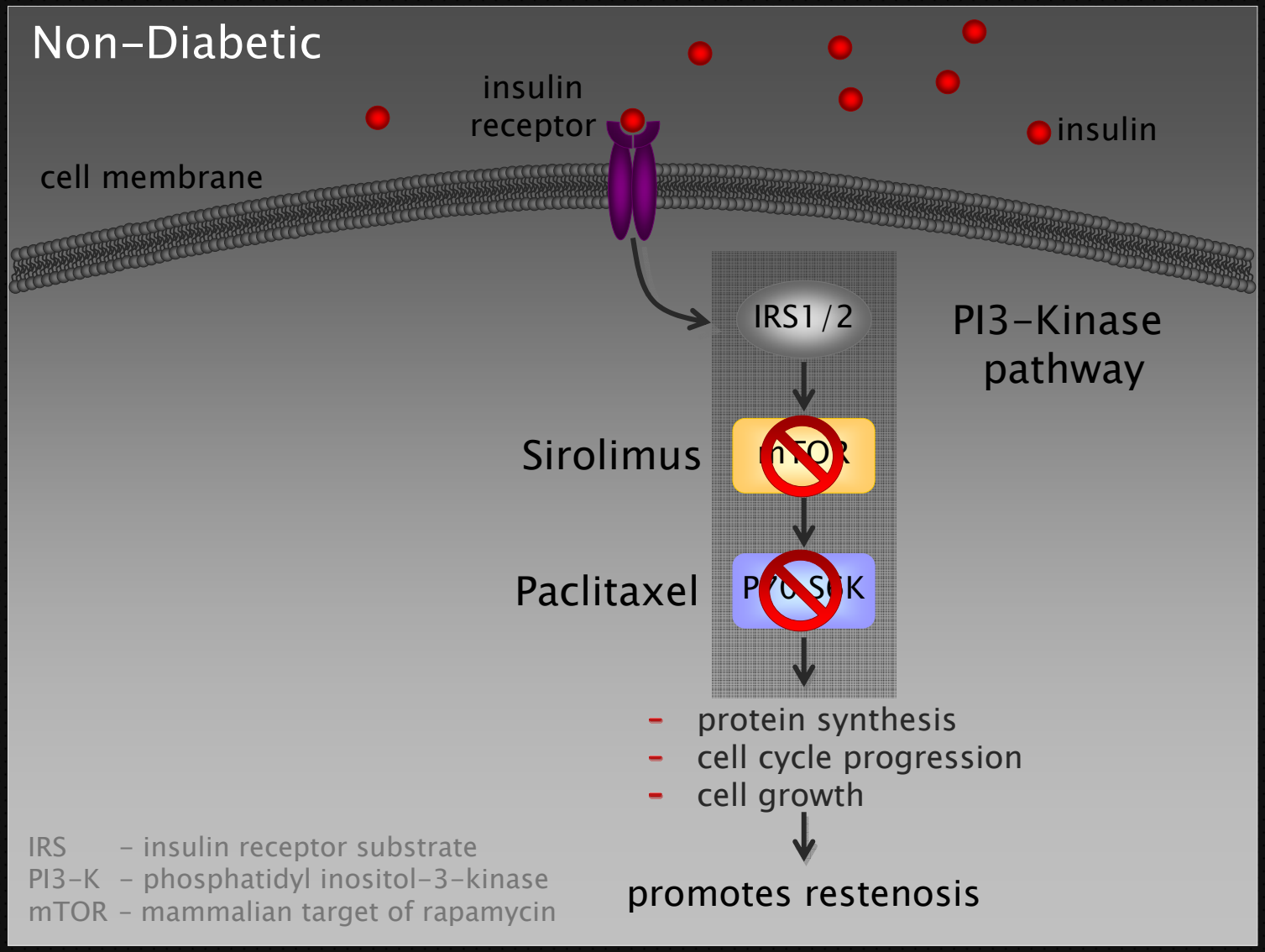
Why are Diabetics different?

- Increased oxidative stress and inflammation (Fibrinogen and C-reactive protein expression)
- Impaired vasomotor activity, increased smooth muscle cell proliferation
- Proatherogenic protein glycation
- Altered coagulation/fibrinolysis (prothrombotic and increased PAI-1)
- Increased platelet IIb/IIIa receptor numbers

Is there a Specific Role for Paclitaxel Elution in the Diabetic Patient?



Insulin & Restenosis



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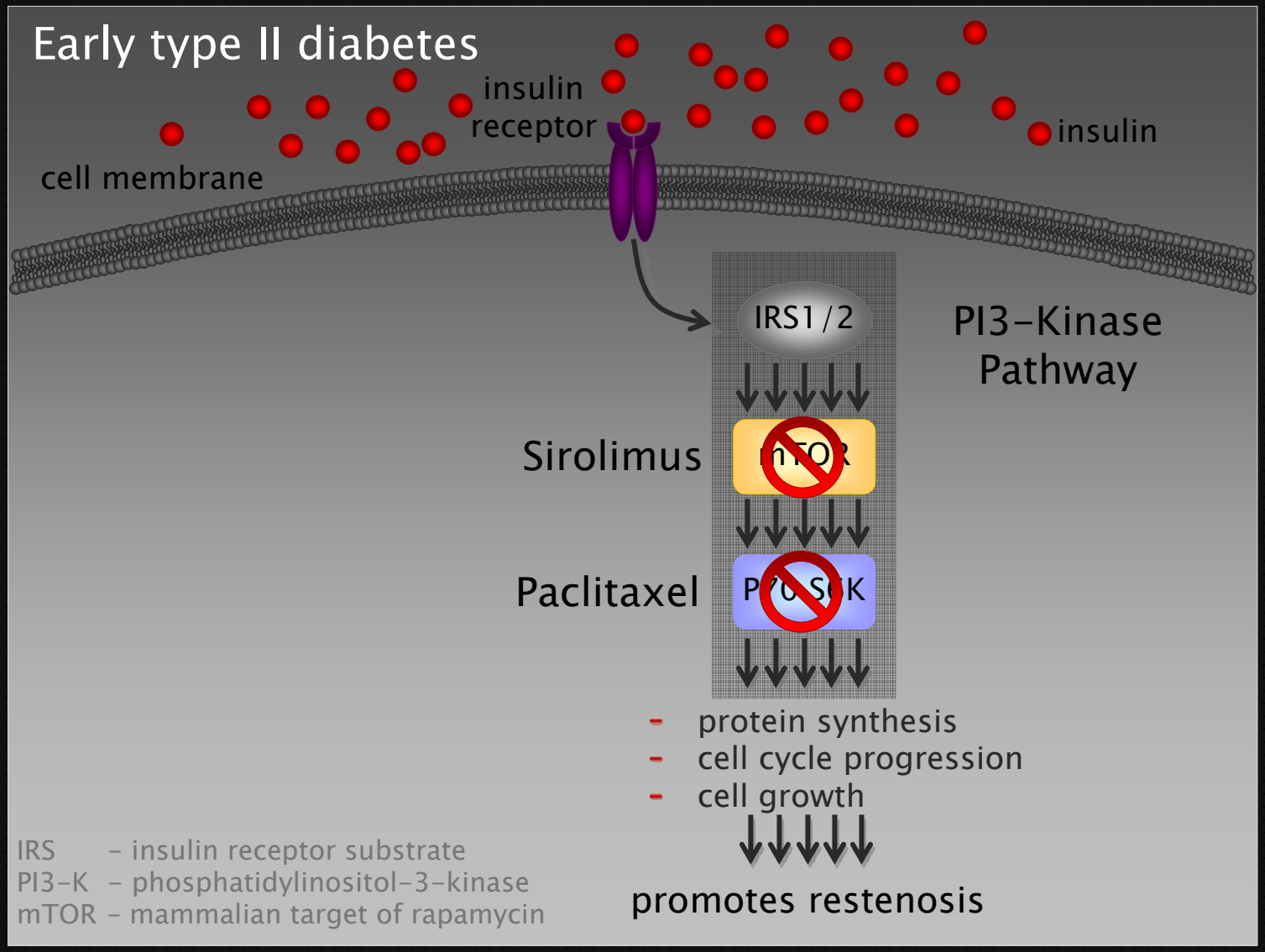

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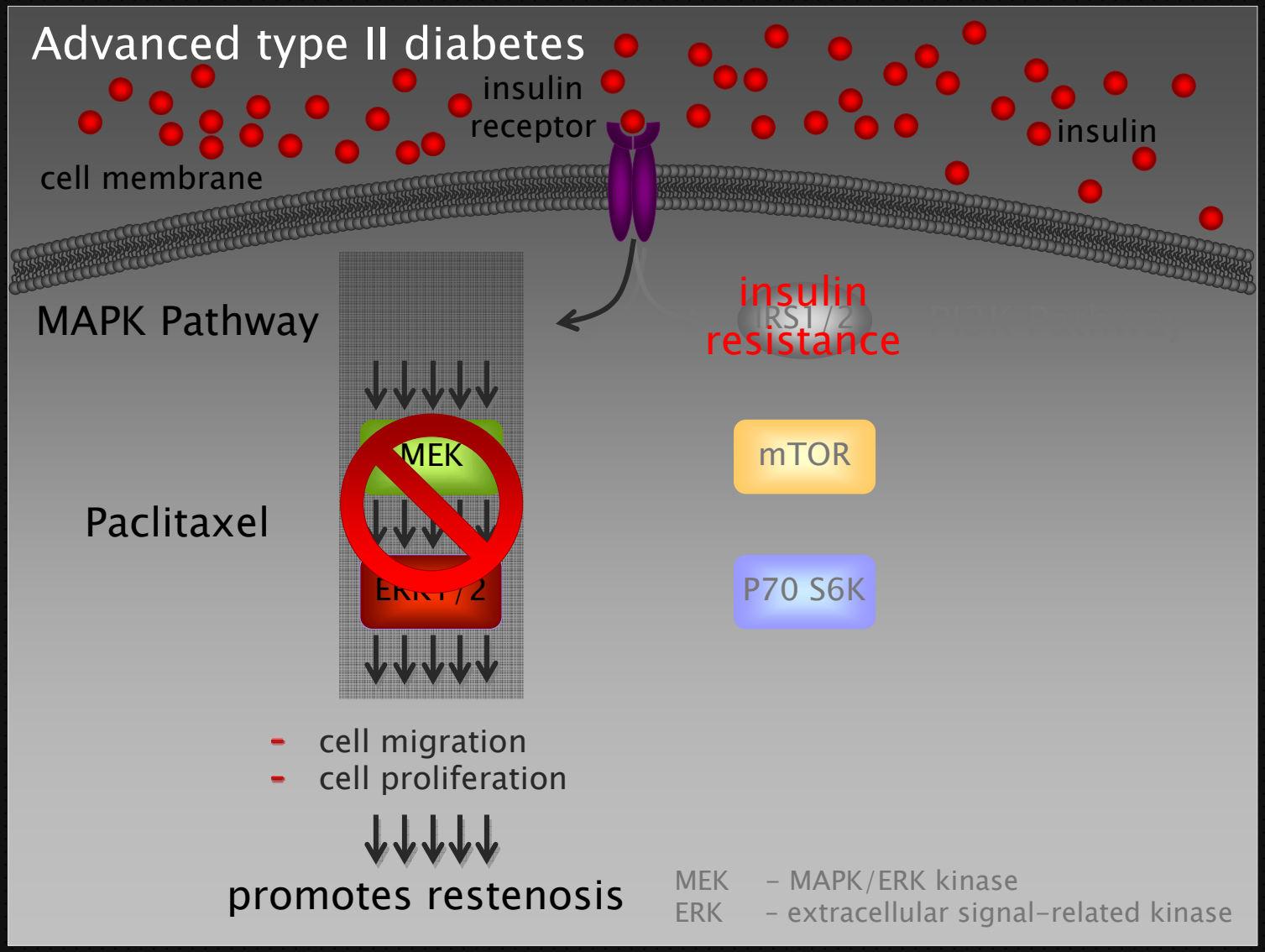


Comparative Effects of Paclitaxel and Rapamycin on Smooth Muscle Migration and Survival

Role of Akt-Dependent Signaling

Cam Patterson, Sabeen Mapera, Hui-Hua Li, Nageswara Madamanchi, Eleanor Hilliard, Rob Lineberger, Robert Herrmann, Peter Charles

Objective—Advances in stent technology have enabled the delivery of drugs to improve outcomes after stent deployment. However, the optimal payloads for stents are not clear, and the appropriate stent-based therapies for high-risk patients, such as diabetics, have not been clearly established.

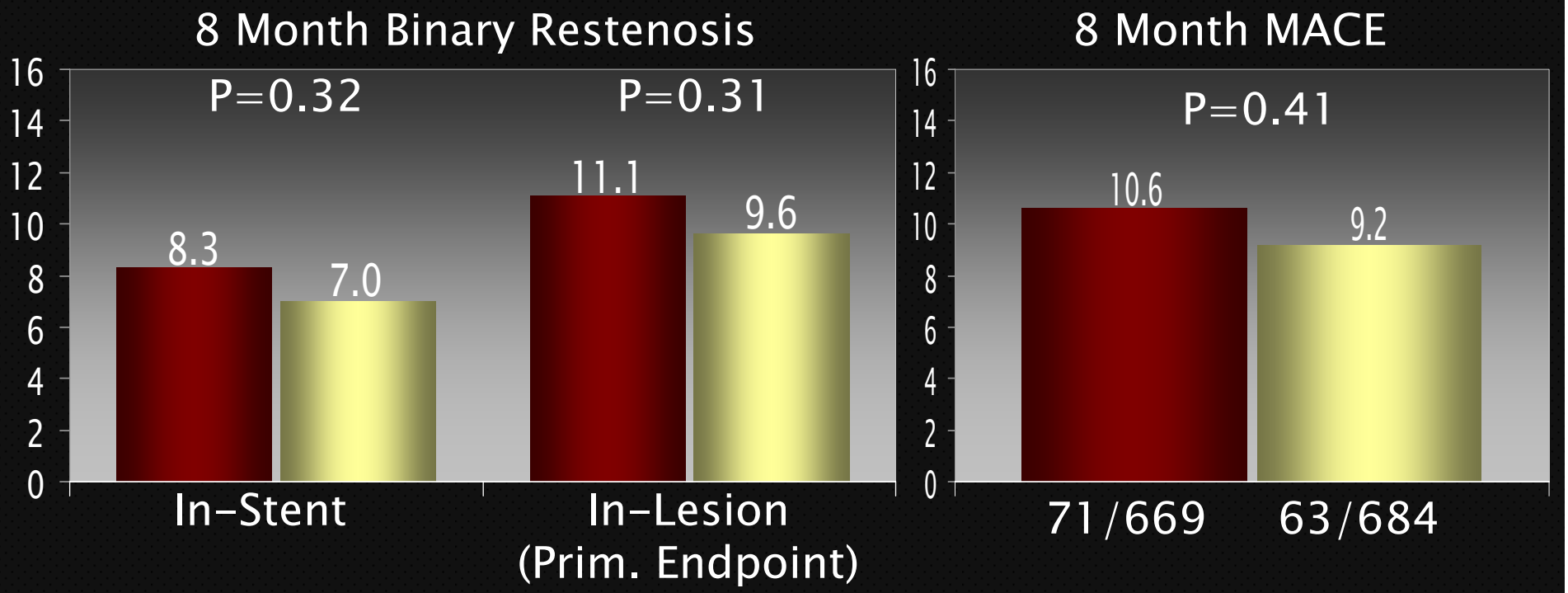
Methods and Results—We used smooth muscle cell culture models to compare the activities of rapamycin and paclitaxel. Smooth muscle cells were grown in normal or high glucose to induce insulin resistance. Both paclitaxel and rapamycin activate mitogen-activated protein kinase pathways similarly. However, rapamycin potently activates AKT-dependent signaling, an effect that overrides the downregulation of this pathway by insulin resistance and that causes phosphorylation of the AKT-dependent transcription factor FOXO1. This effect is associated with attenuation of the anti-migratory effects of rapamycin under high glucose conditions that are not observed with paclitaxel, as well as with increased protection against ceramide-induced cytotoxicity, both of which are dependent on FOXO1 phosphorylation.

Conclusions—Differences between the ability of rapamycin and paclitaxel to activate AKT may account for their differential cell survival and antichemotactic activities. These observations may provide a basis for understanding clinical differences between rapamycin- and paclitaxel-coated stents. The approaches used in these studies can be expanded to other candidate stent payloads as a method for triage in preclinical studies. (***Arterioscler Thromb Vasc Biol.* 2006;26:1473-1480.**)

Arterioscler Thromb Vasc Biol 2006;26:1473-1480

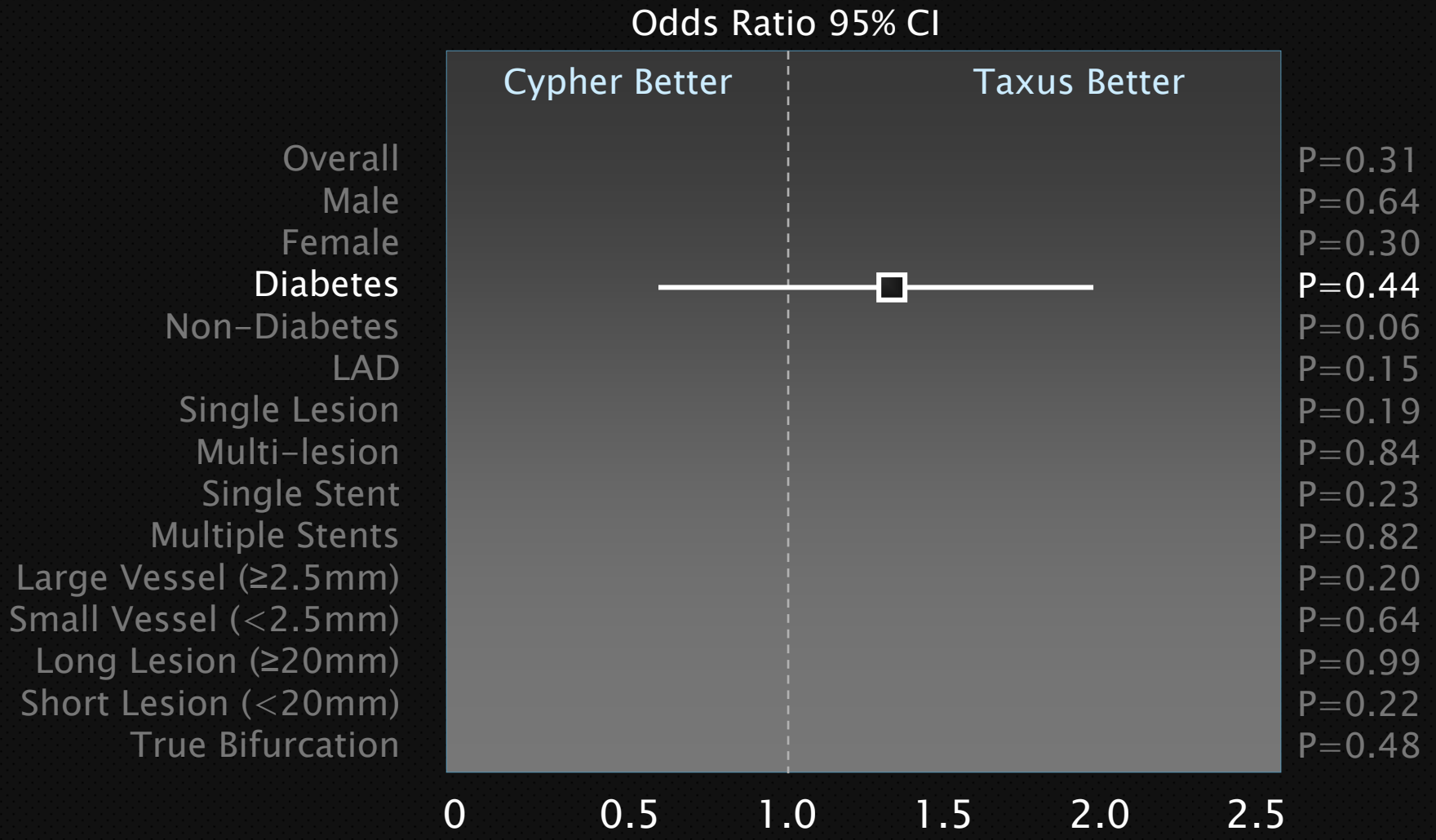
Head to Head Trials
REALITY–Intention to Treat

TAXUS (669 pts; 941 lesions) CYPHER (684 pts; 970 lesions)



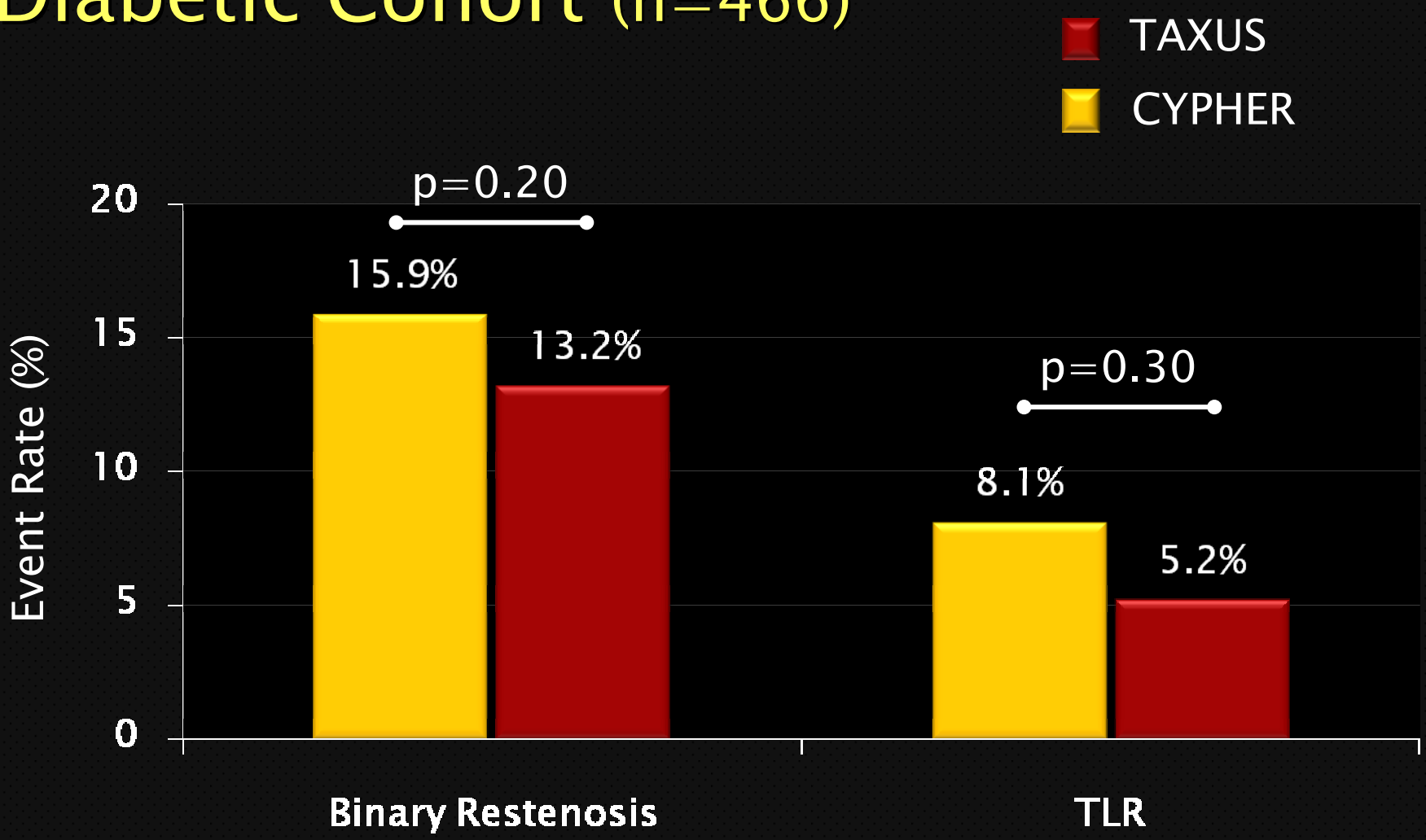
Comparable efficacy and safety results between TAXUS and CYPHER

REALITY: Subgroup Analysis
In-Lesion Restenosis (8 months)



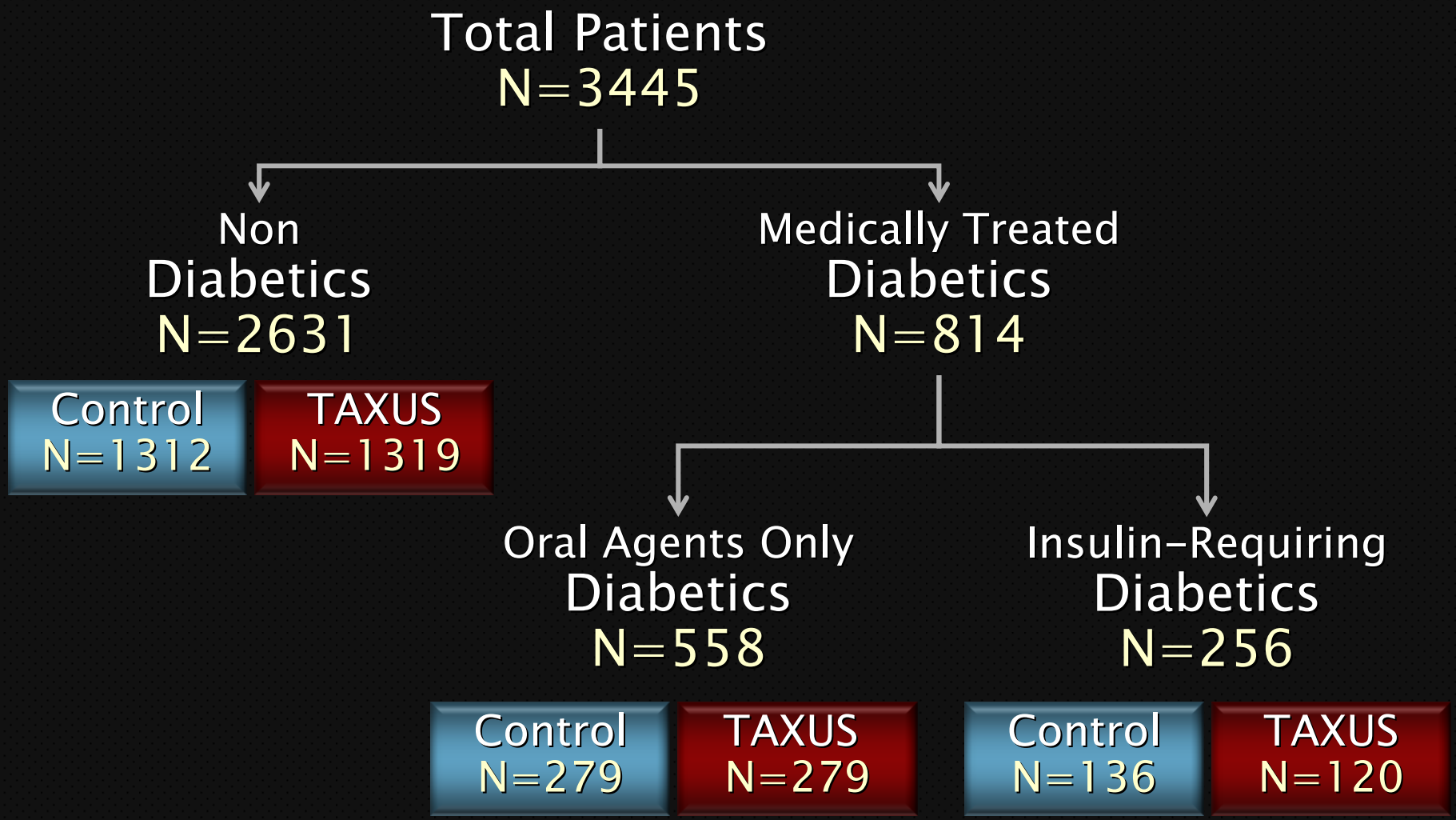
Morice M-C. ACC 2005

REALITY Trial
Diabetic Cohort (n=466)



Kastrati TCT 2006

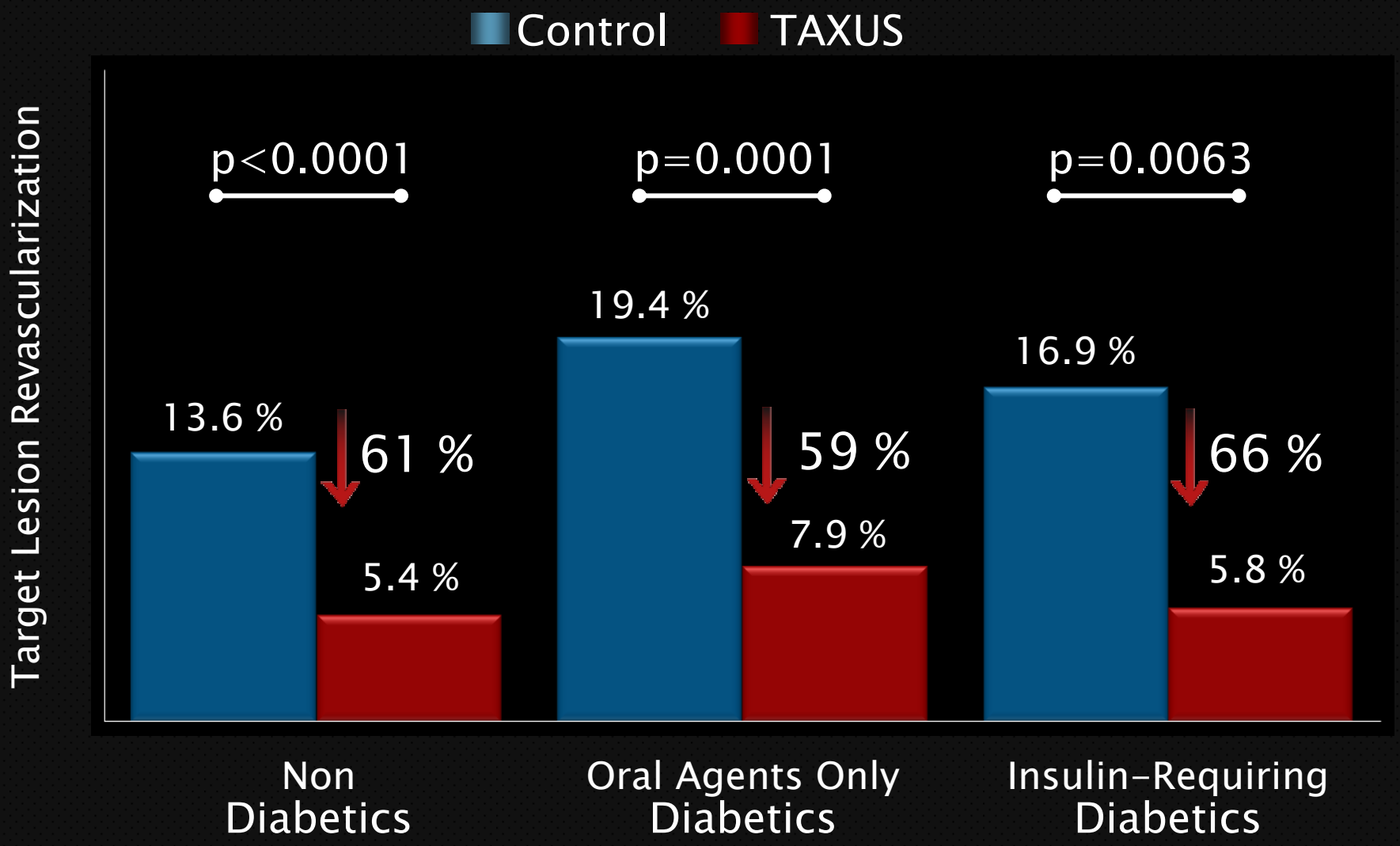
Diabetic Meta-Analysis*



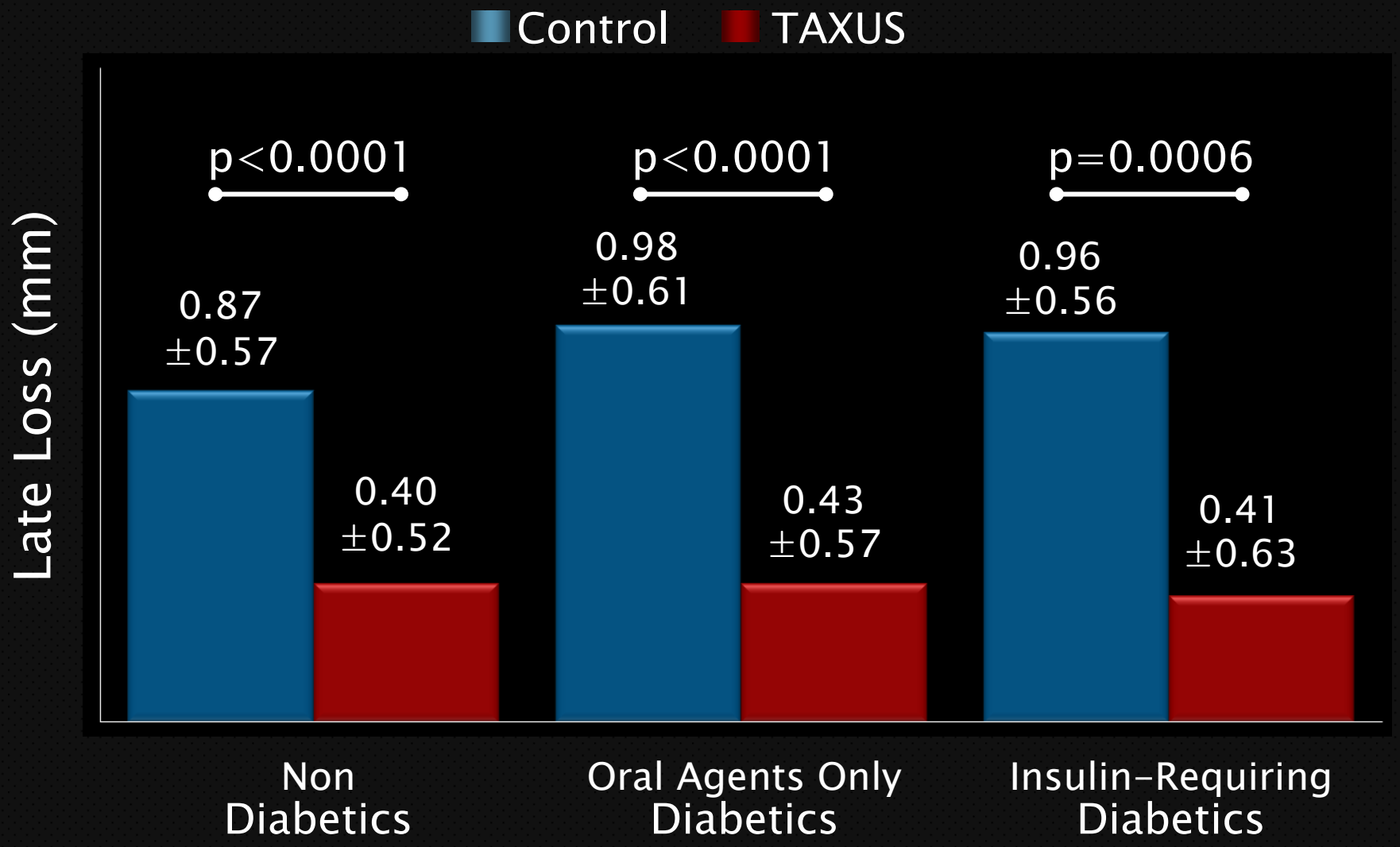
*TAXUS II, IV, V, VI

EuroInterv 2006;2:61-68

Target Lesion Revascularisation (12 months)

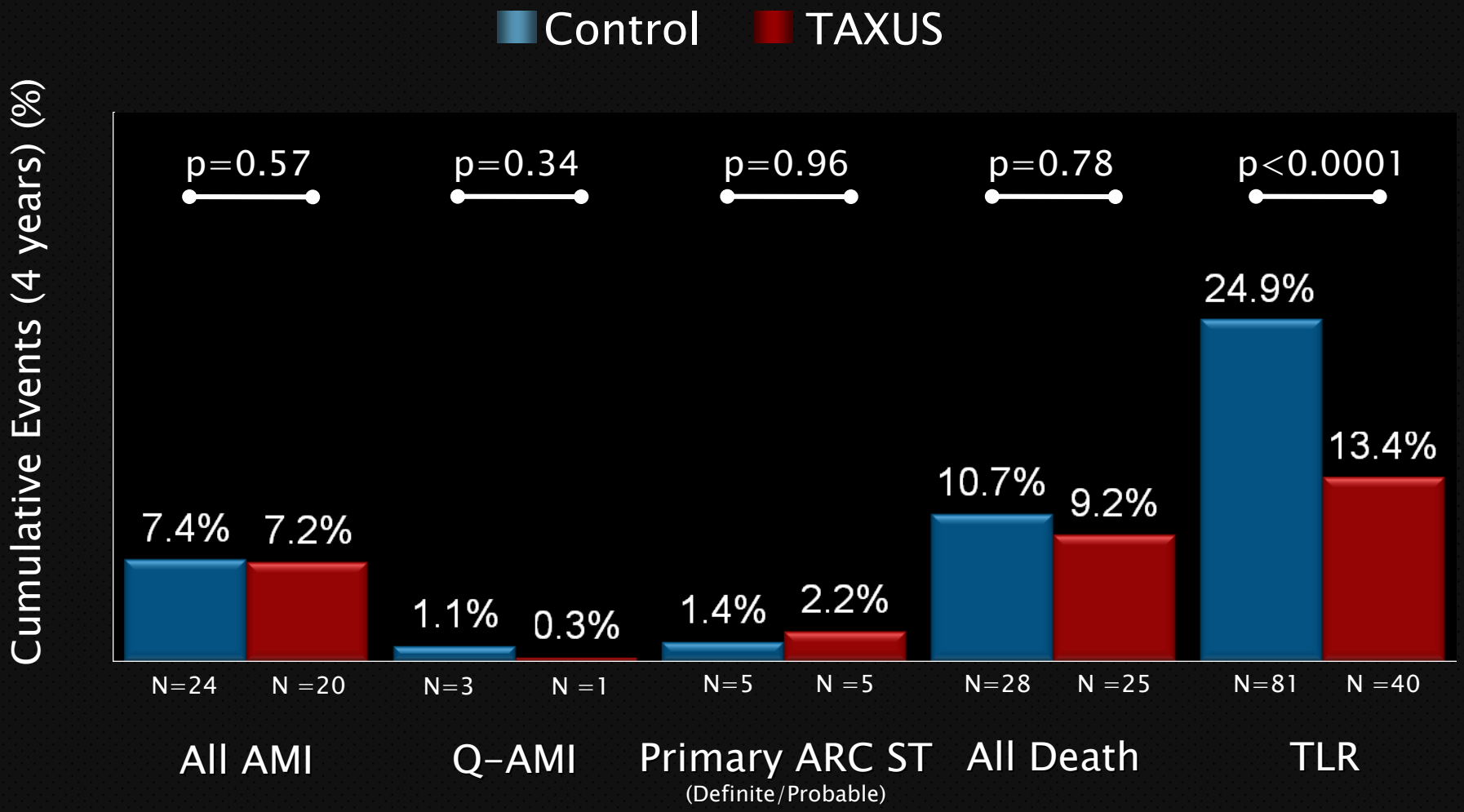


In-Stent Late Loss



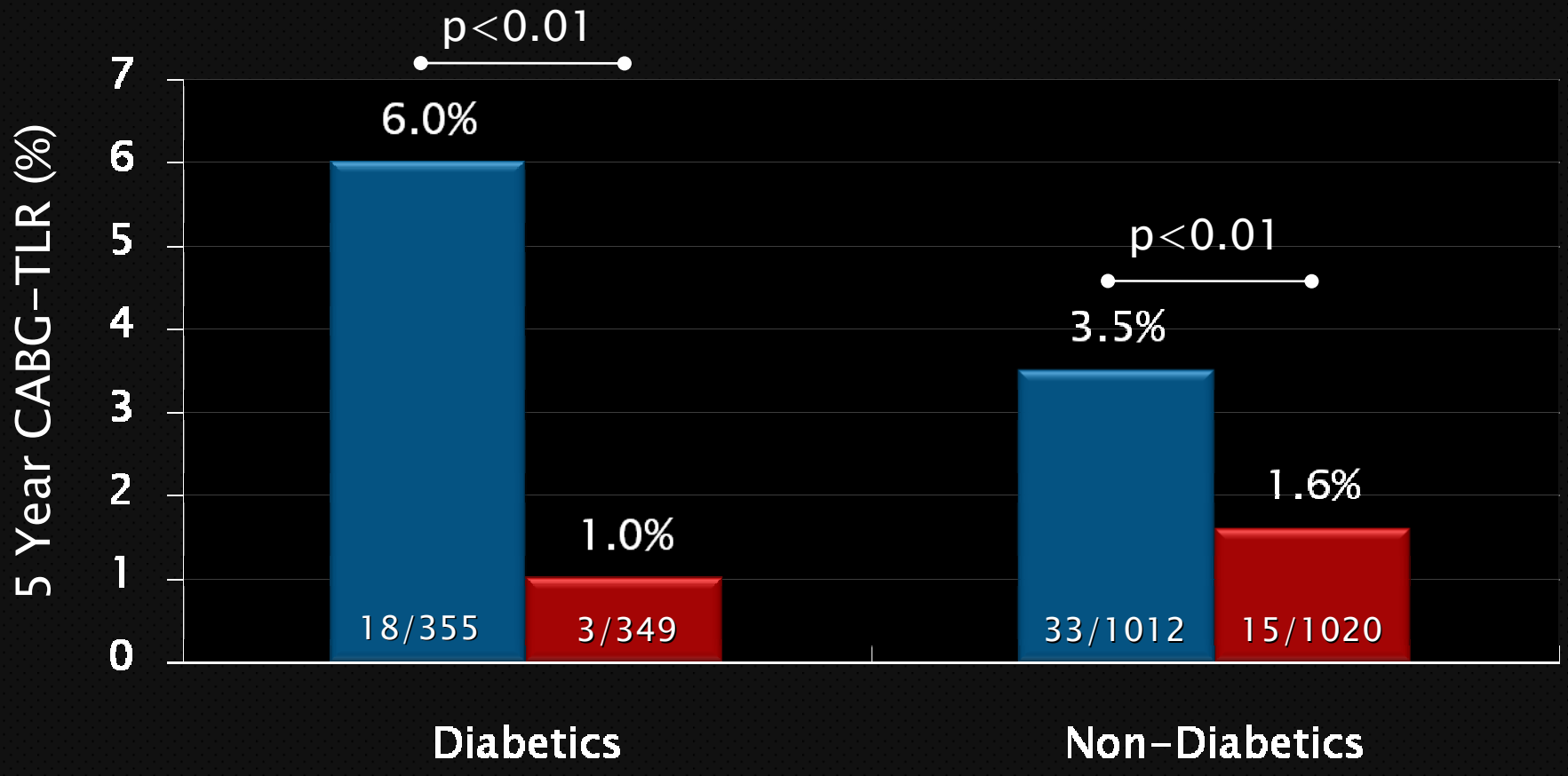
Diabetics: Four Year Event Rates (n=715)

TAXUS I (5y), II-SR (4y), IV (4y), V (2y) Meta-Analysis



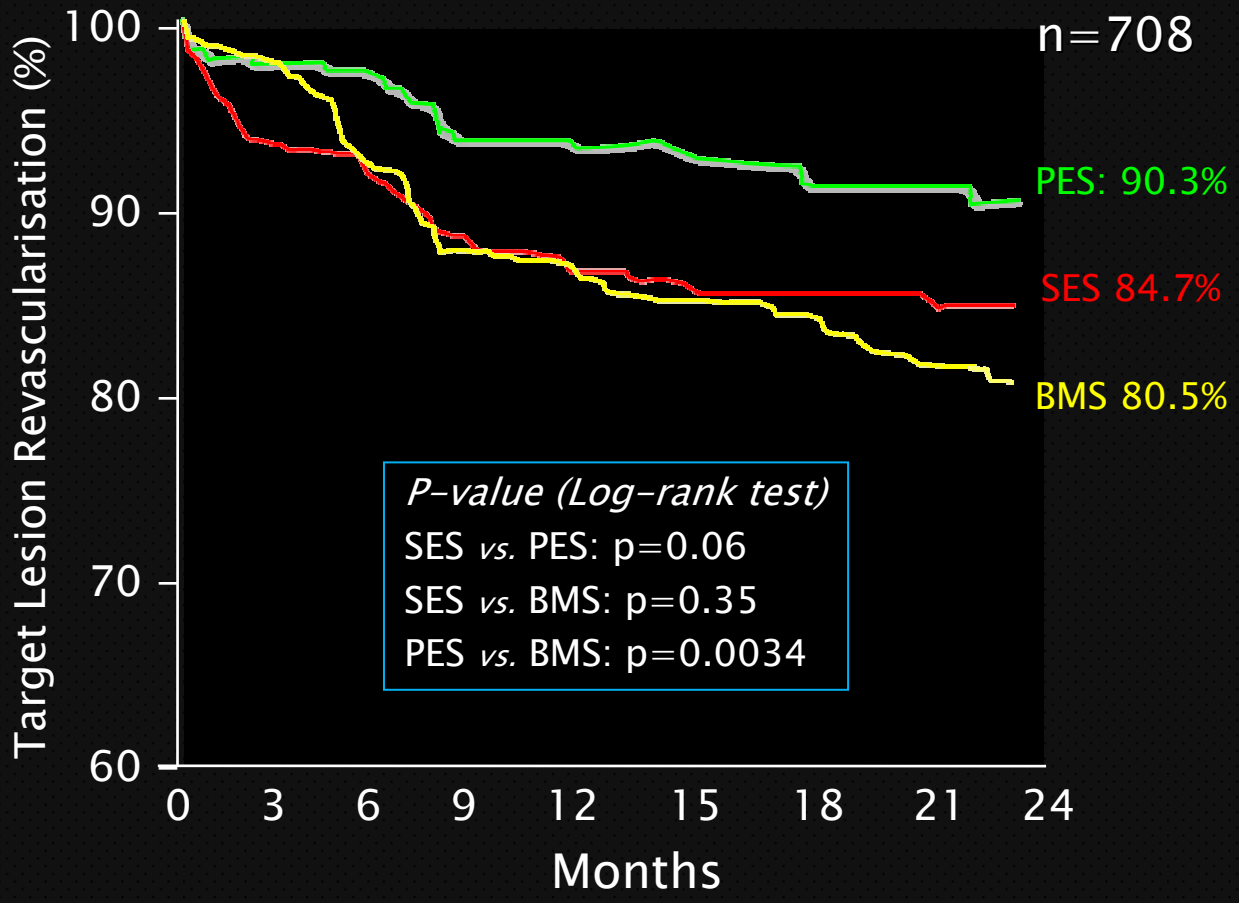
Event rates based on Kaplan Meier Estimate & P-Values from Log Rank

Surgical Revascularisation (CABG) in Diabetics following treatment with the Taxus SR* Stent *vs.* BMS Control (5 Years)



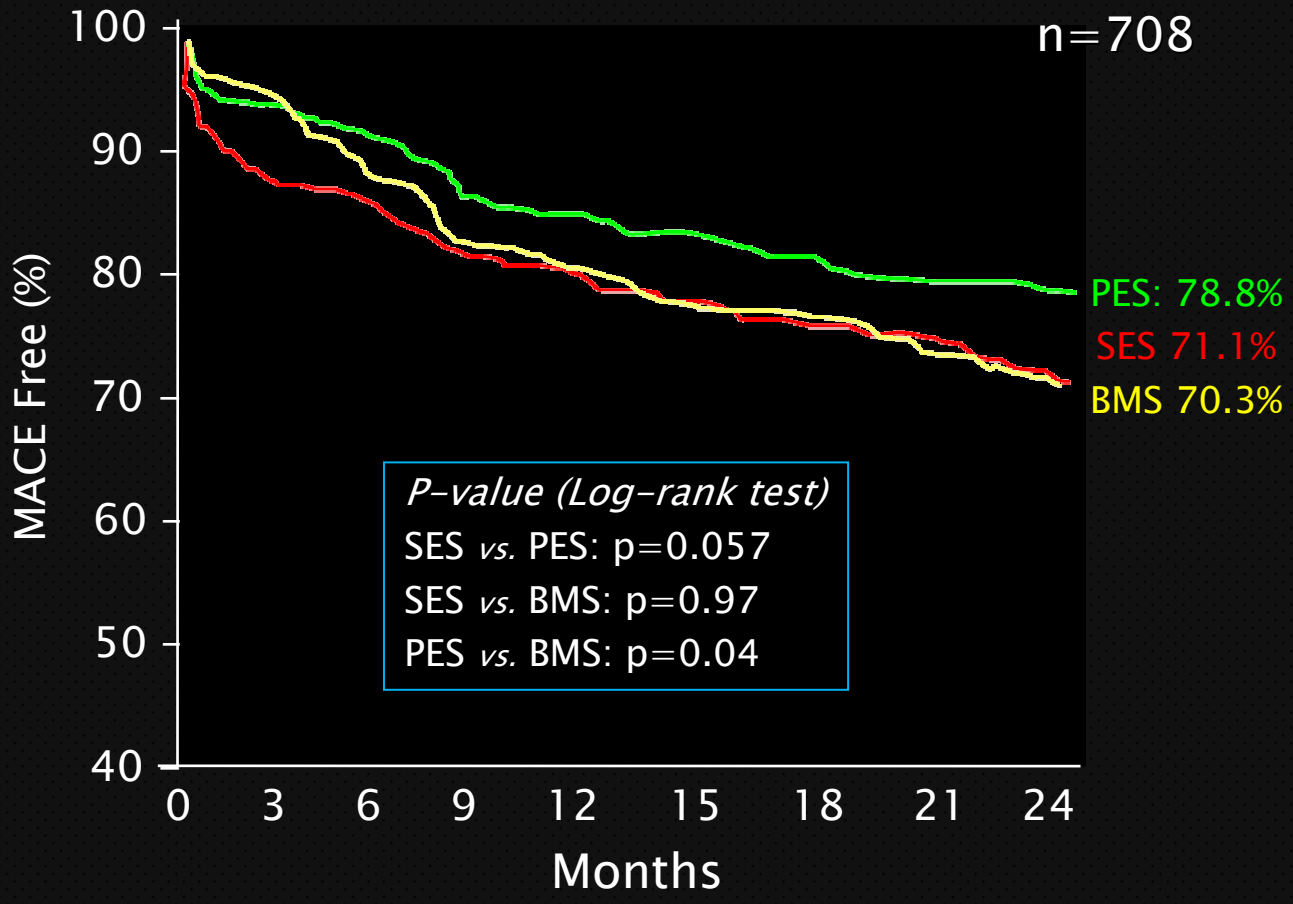
*TAXUS SR II, IV, V Trials (n=2,736)

Diabetes Mellitus: PES *vs.* SES *vs.* BMS (Thoraxcenter)



Eur Heart J 2007;28:26-32

Diabetes Mellitus: PES *vs.* SES *vs.* BMS (Thoraxcenter)



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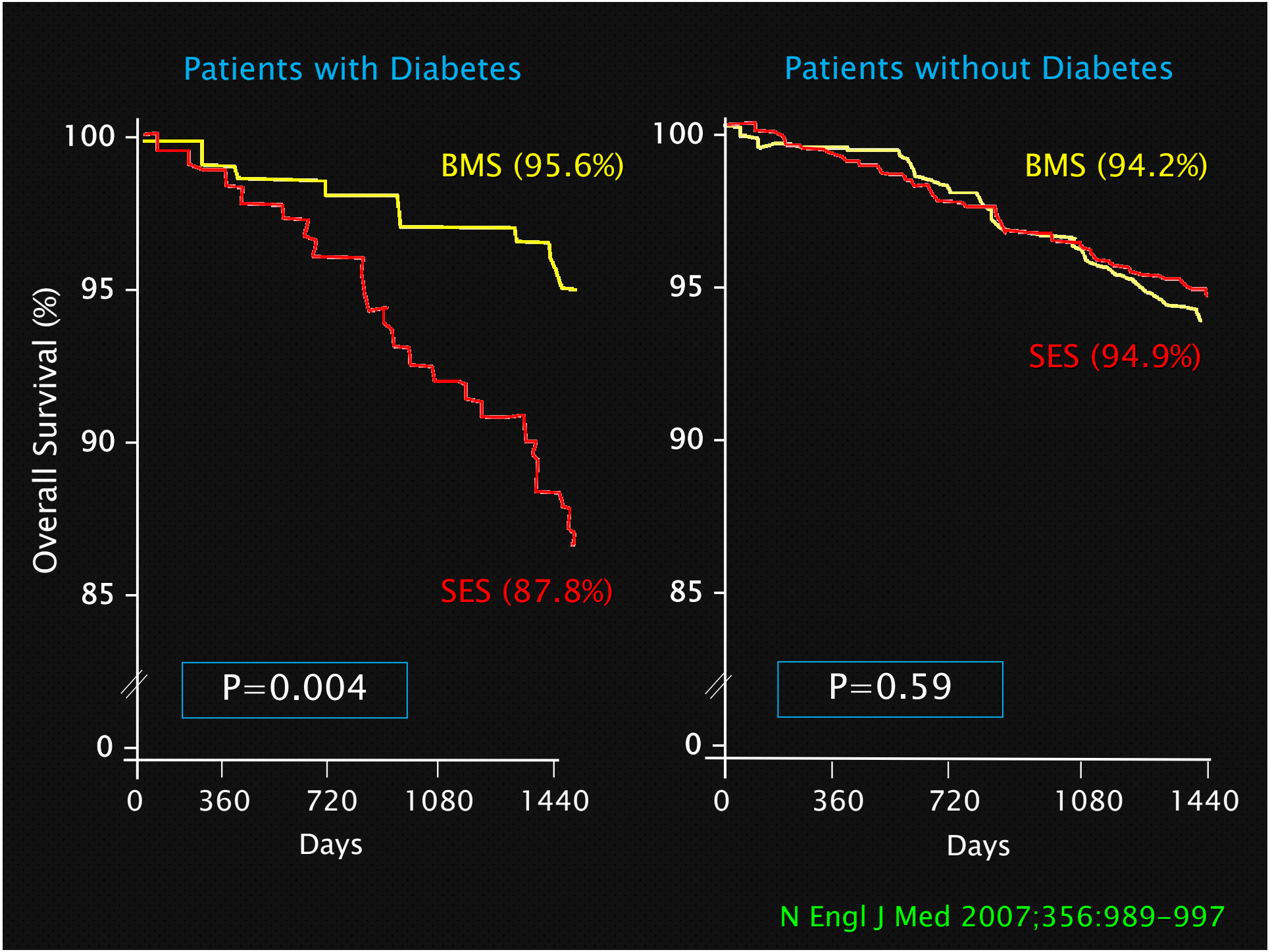
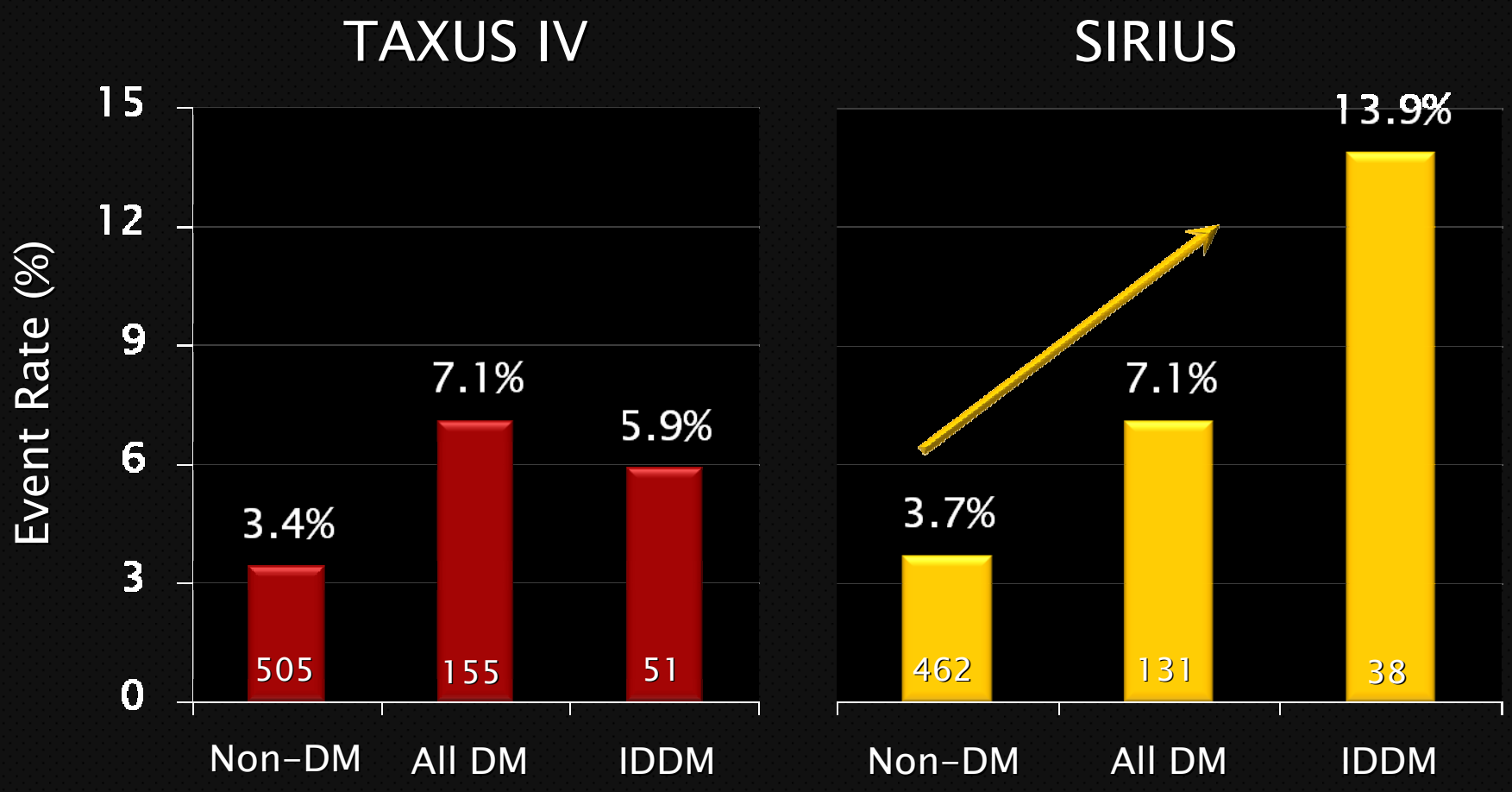
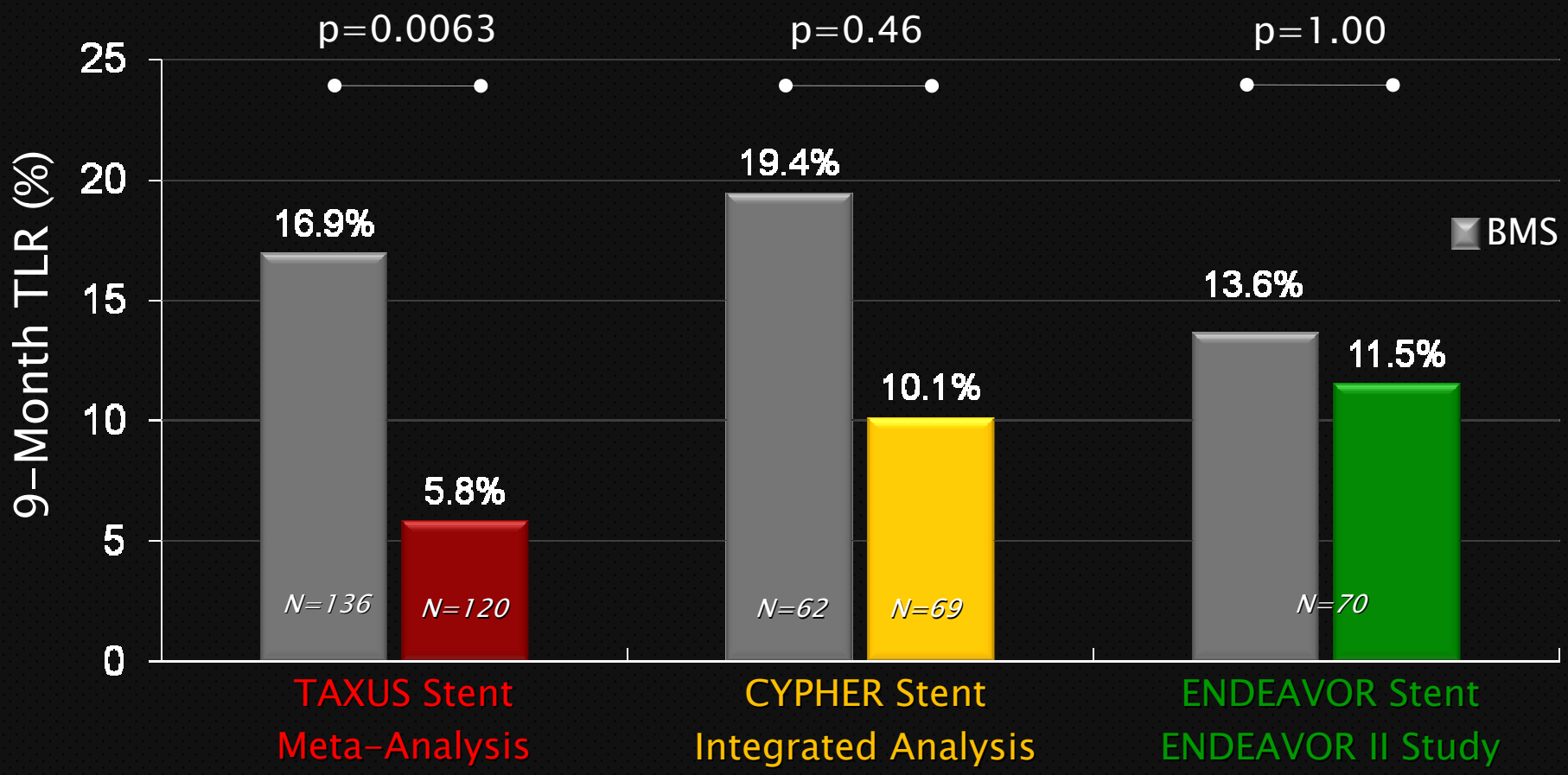

Patients with Diabetes
Patients without Diabetes
Overall Survival (%)
100
95
90
85
0
BMS (95.6%)
SES (87.8%)
P=0.004
BMS (94.2%)
SES (94.9%)
P=0.59
0
360
720
1080
1440
Days
N Engl J Med 2007;356:989-997

TAXUS IV & SIRIUS

Target Lesion Revascularization (12 months)

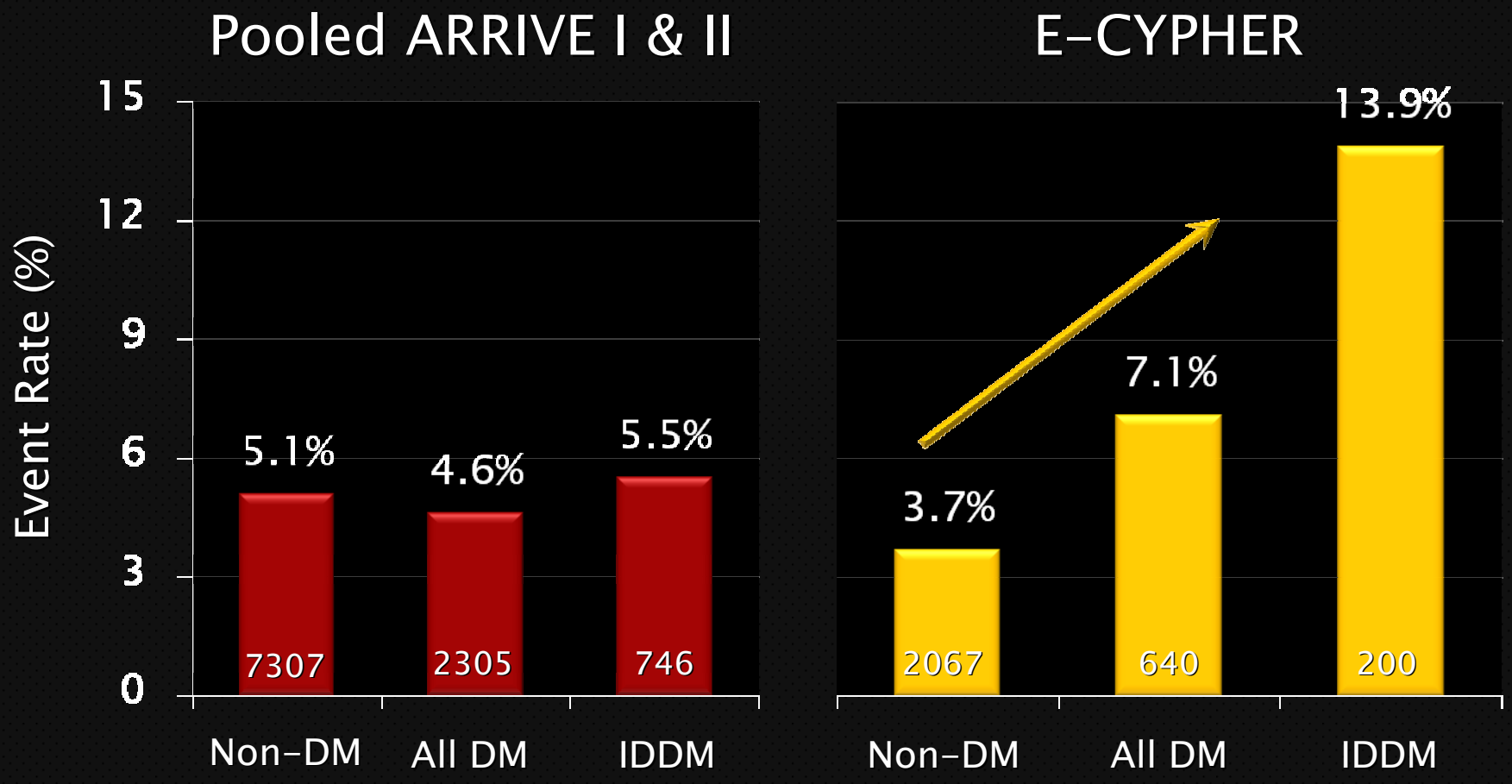


Comparative TLR Reduction with DES Insulin-treated Diabetic Patients

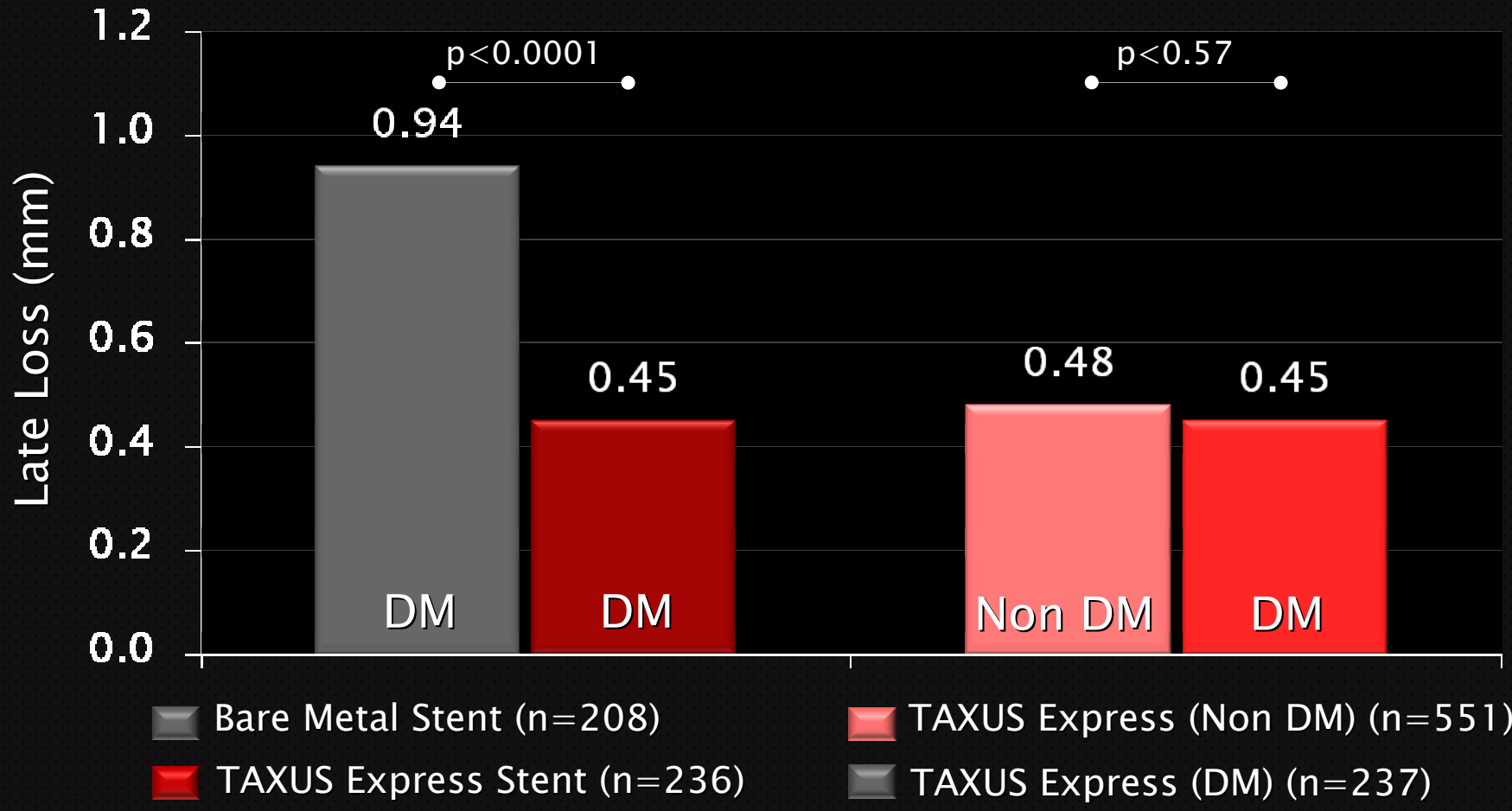


ARRIVE I & II, E-CYPHER Registries

Stent Related Revascularization (12 months)

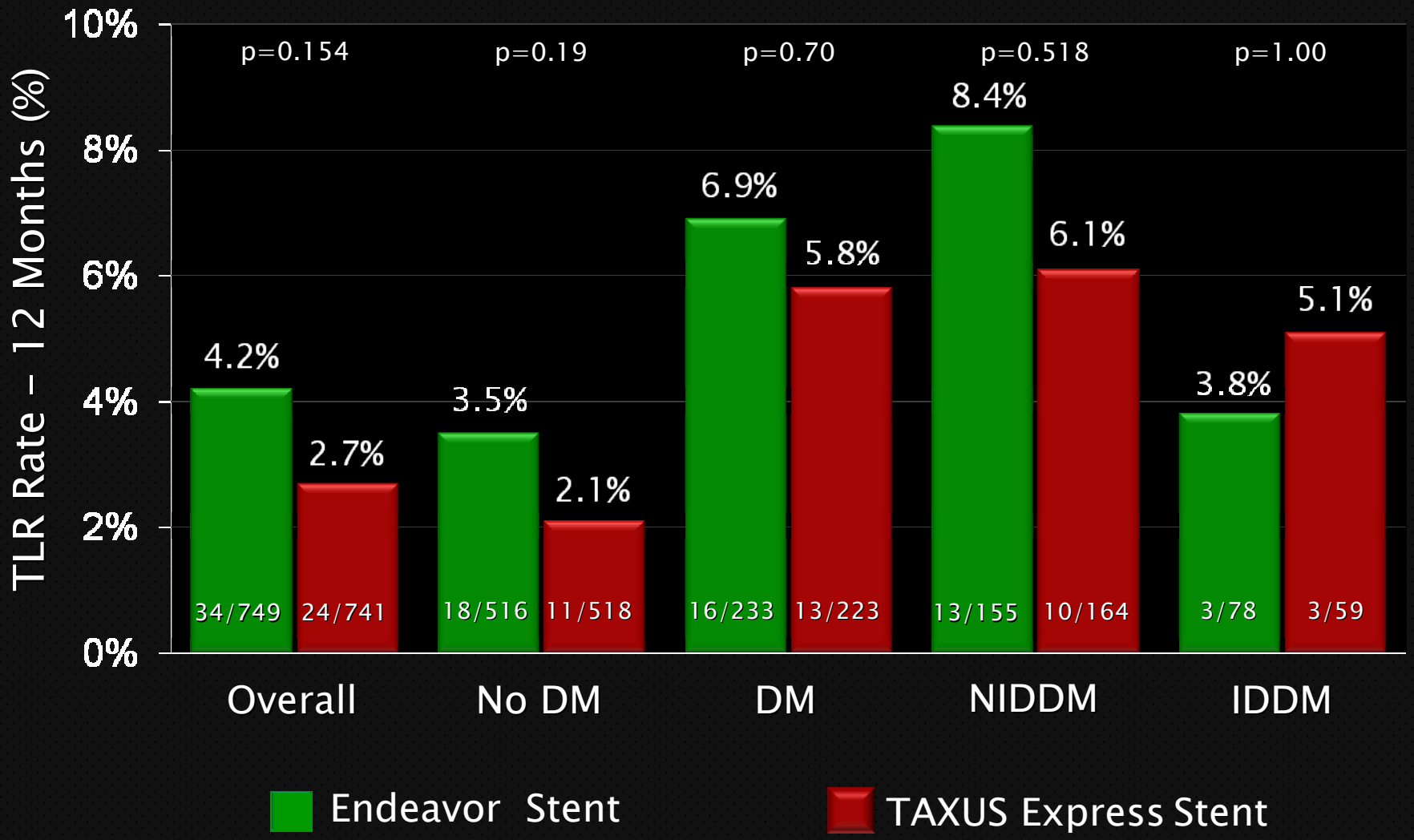


TAXUS IV and V Diabetic Subset 8-Month Angiographic Results



ACC 2008

ENDEAVOR IV
Diabetic Subset Analysis



ACC 2008

TAXUS Stent Diabetic CE Mark
Diabetic Evidence Base

Study	TAXUS (n)	Control (n)
TAXUS IV	155	163
TAXUS V de novo	183	173
TAXUS V ISR	78	61
ATLAS WH, DS, SV, LL	413	517
ARRIVE I	756	–
ARRIVE 2	1549	–
OLYMPIA IC Transitional	264	–
Total Diabetic Patients (n)*	3398	914

**Medically treated Diabetics*

Conclusions:

- The worldwide prevalence of diabetes is increasing
- Patients with diabetic coronary disease present a therapeutic challenge
- Signal pathways confirm the unique effect of paclitaxel in inhibiting smooth muscle cell migration, proliferation and restenosis
- Data from randomized controlled trials, meta-analyses and registries have confirmed the safety, efficacy and superiority of the TAXUS stent in the diabetic patient