

DES in Diabetic Patients

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Why do diabetics have worse outcome after PCI?

- More extensive atherosclerosis and diffuse disease
- Increase prevalence of multivessel disease
- Smaller vessel and longer lesions
- More highly stenotic lesions and higher plaque burden
- Higher incidence of left main disease

Why does Diabetes increase restenosis after PCI?

- Increase insulin
- Increase oxidative stress and inflammation (Fibrinogen and C reactive protein expression)
- Impaired vasomotor activity and increase smooth muscle cell proliferation
- Proatherogenic protein glycation
- Altered coagulation / fibrinolysis (Prothrombotic and increased PAI-1)
- Increased IIa / IIIb receptor numbers

Impact of DES vs BMS in Diabetic Patients

Issues concerning DES in Diabetic Patients

- Diabetic patients: Heterogenous population i.e insulin/non-insulin, large / small vessels, focal / diffuse disease
- None of the randomized Cypher & Taxus trials were designed or powered to prospectively assess the comparative efficacy of DES in DM and non-DM patients

Randomized Controlled Trials Designed To Evaluate Efficacy in Patients with Diabetes

- RCTs – CYPHER[®] Stent vs. BMS
 - DIABETES Trial
 - DECODE Trial
 - SCORPIUS Trial
- RCTs – Taxus Stent vs. BMS
 - None currently exist
- RCTs and Meta-Analysis– CYPHER[®] Stent vs. Taxus Stent
 - ISAR-DIABETES
 - SIRTAX Trial (Pre-specified sub-analysis)

The DECODE Study: 12-Month Analysis

A RANDOMIZED STUDY WITH THE SIROLIMUS-
ELUTING BX VELOCITY™ BALLOON-
EXPANDABLE STENT IN THE TREATMENT OF
DIABETIC PATIENTS WITH NATIVE CORONARY
ARTERY LESIONS

Charles Chan, Robaayah Zambahari, Upendra Kaul,
Sidney A. Cohen, Maurice Buchbinder,
on behalf of the DECODE Study Investigators

Study Design

Multi-center, Open-label, Prospective, randomized controlled trial
200 diabetic patients (100 in US and 100 in Asia/Pacific) undergoing
multi-lesion/multi-vessel PCI

Randomize 2:1
(Stratification by pre-PCI prediction of IIb/IIIa use)

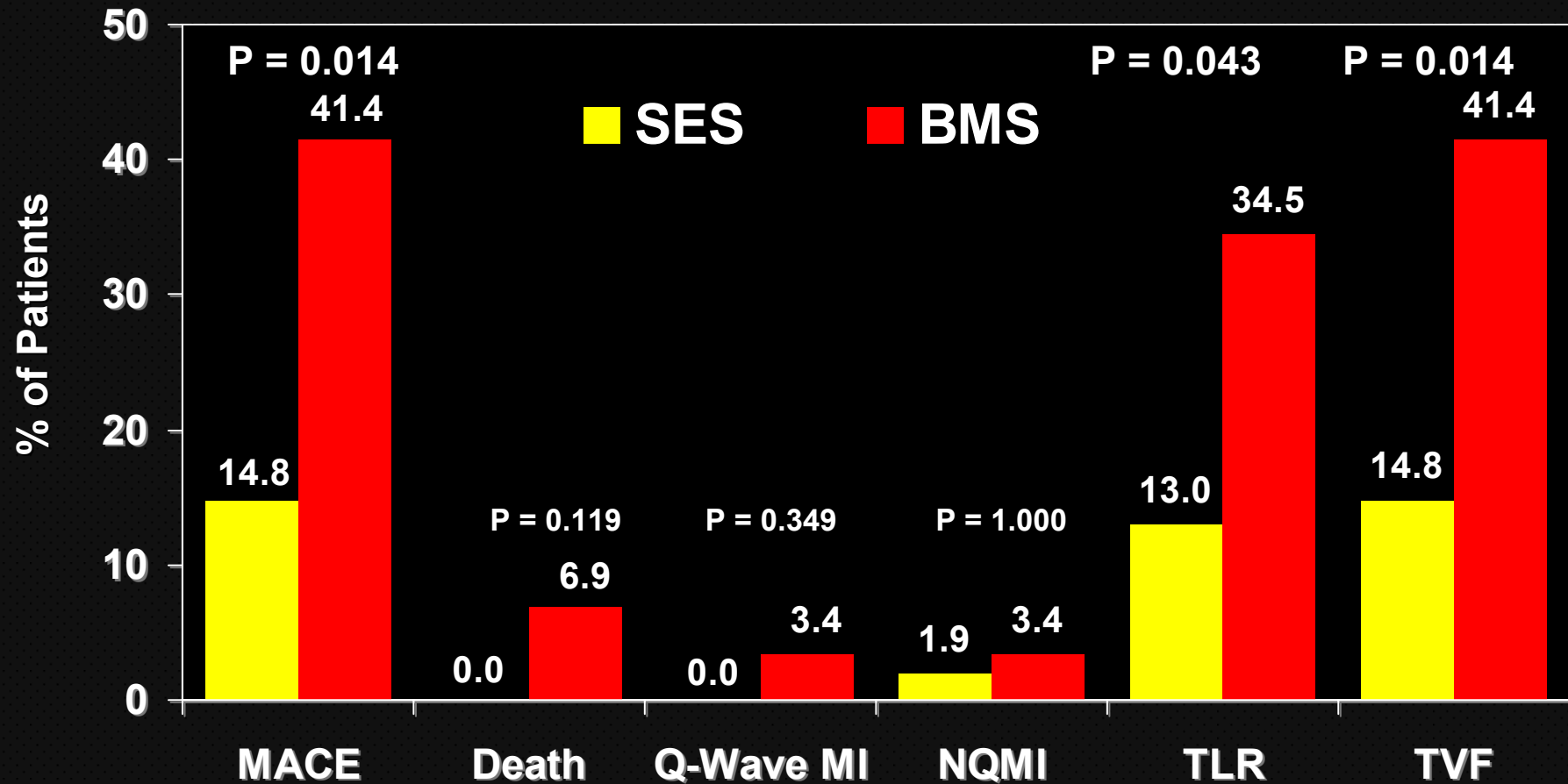
Sirolimus-eluting Stent
(SES)

Bare-Metal Stent
(BMS)

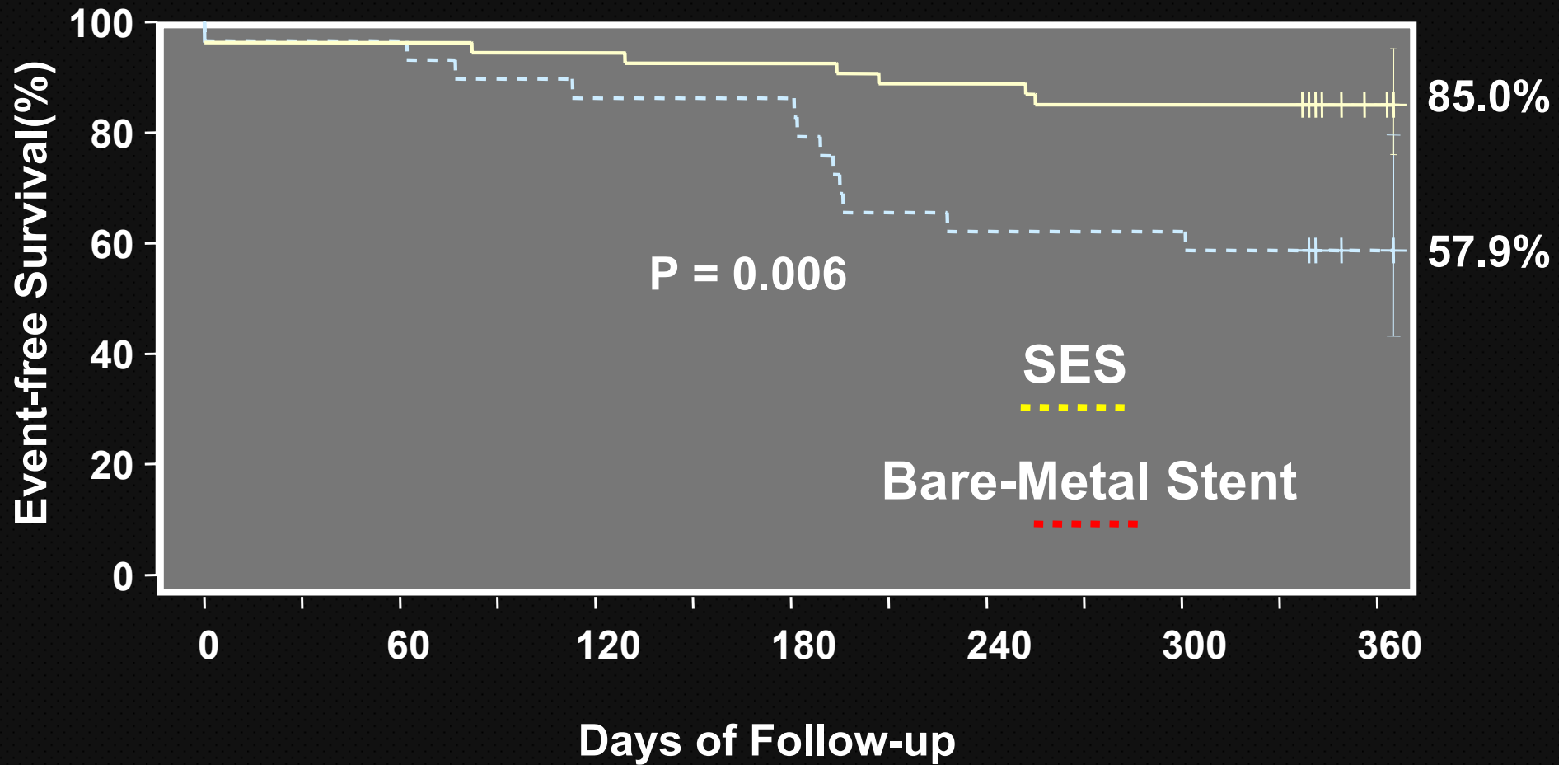
Clinical Evaluations at 30 days, 6 months and 1 year post-PCI
Repeat angiography at 6 months post-PCI
Primary Endpoint: Angiographic In-stent Late Loss at 6 months

Clinical Outcomes Through 12 Months (N=120)

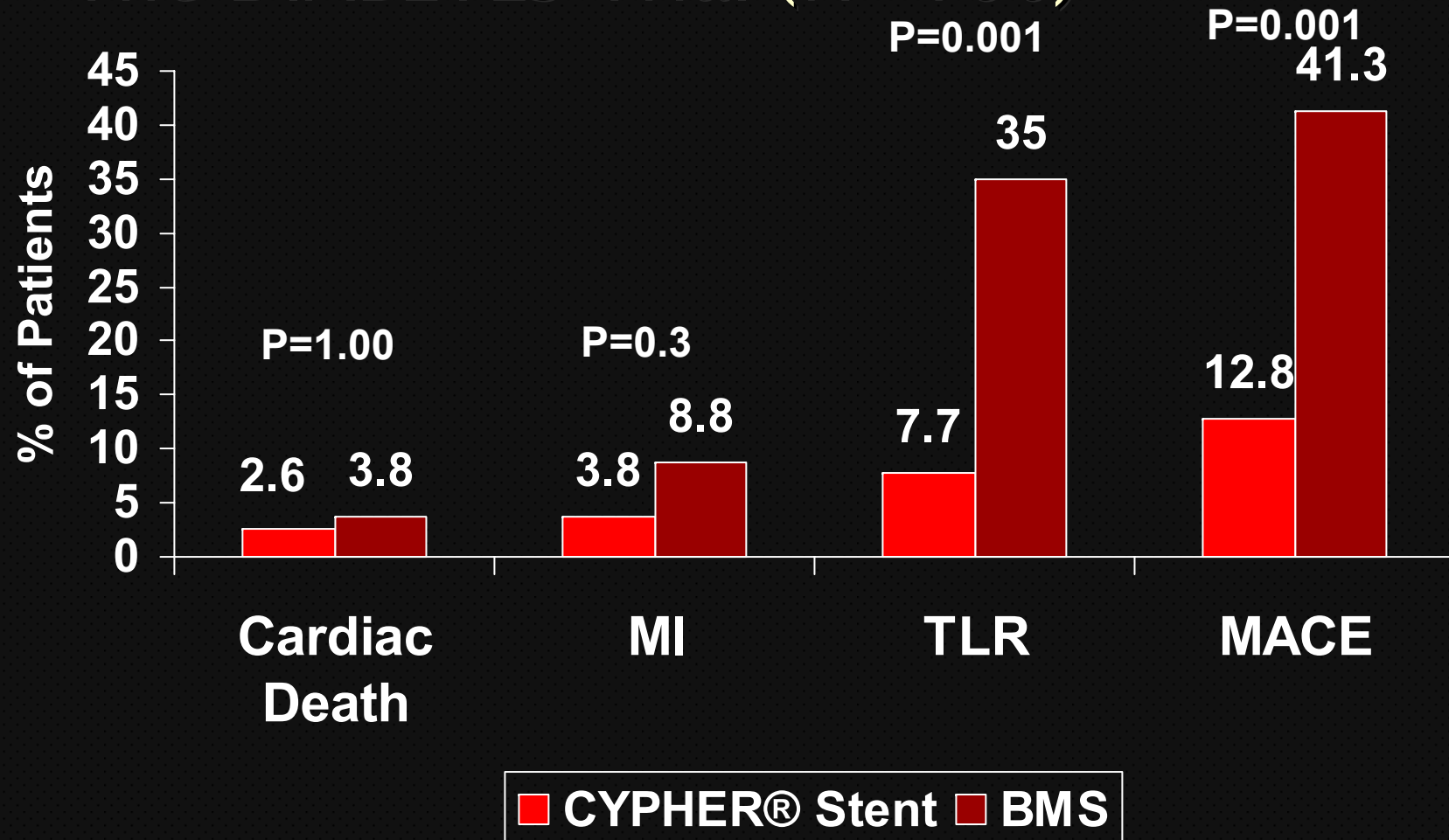
There was no stent thrombosis in either treatment group



Freedom From MACE Through 12 Months (N=120)

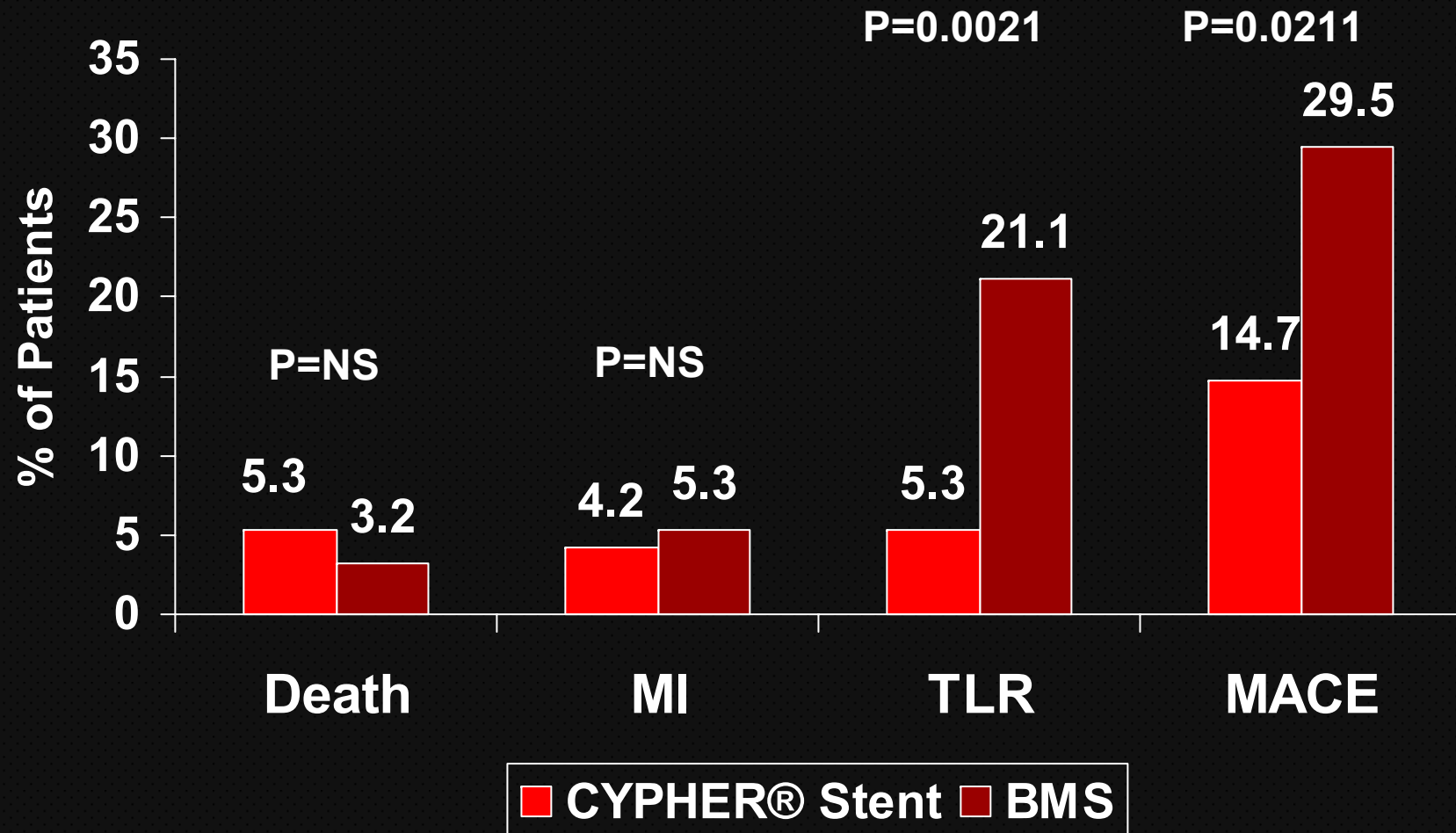


MACE at 24 Month Follow-up The DIABETES Trial (N=160)



The CYPHER® Stent Demonstrated Comparable Safety and Superior Efficacy in Diabetic Patients vs. BMS

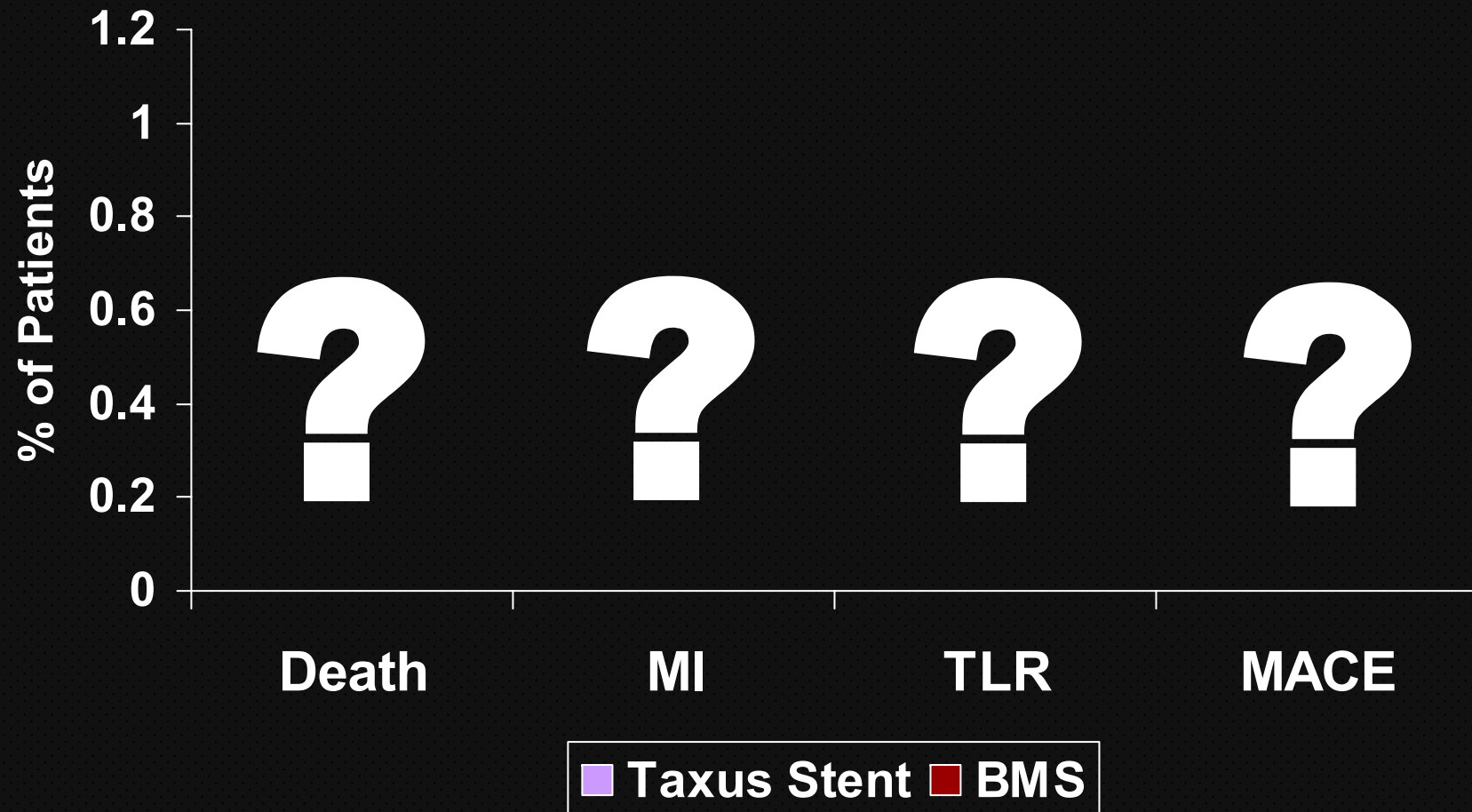
MACE at 8 Month Follow-up The SCORPIUS Trial (N=190)



The CYPHER® Stent Demonstrated Comparable Safety and Superior Efficacy in Diabetic Patients vs. BMS

TCT 2006, Oral Presentation

RCTs Designed To Compare the Taxus Stent vs. BMS in Diabetic Patients (N=0)



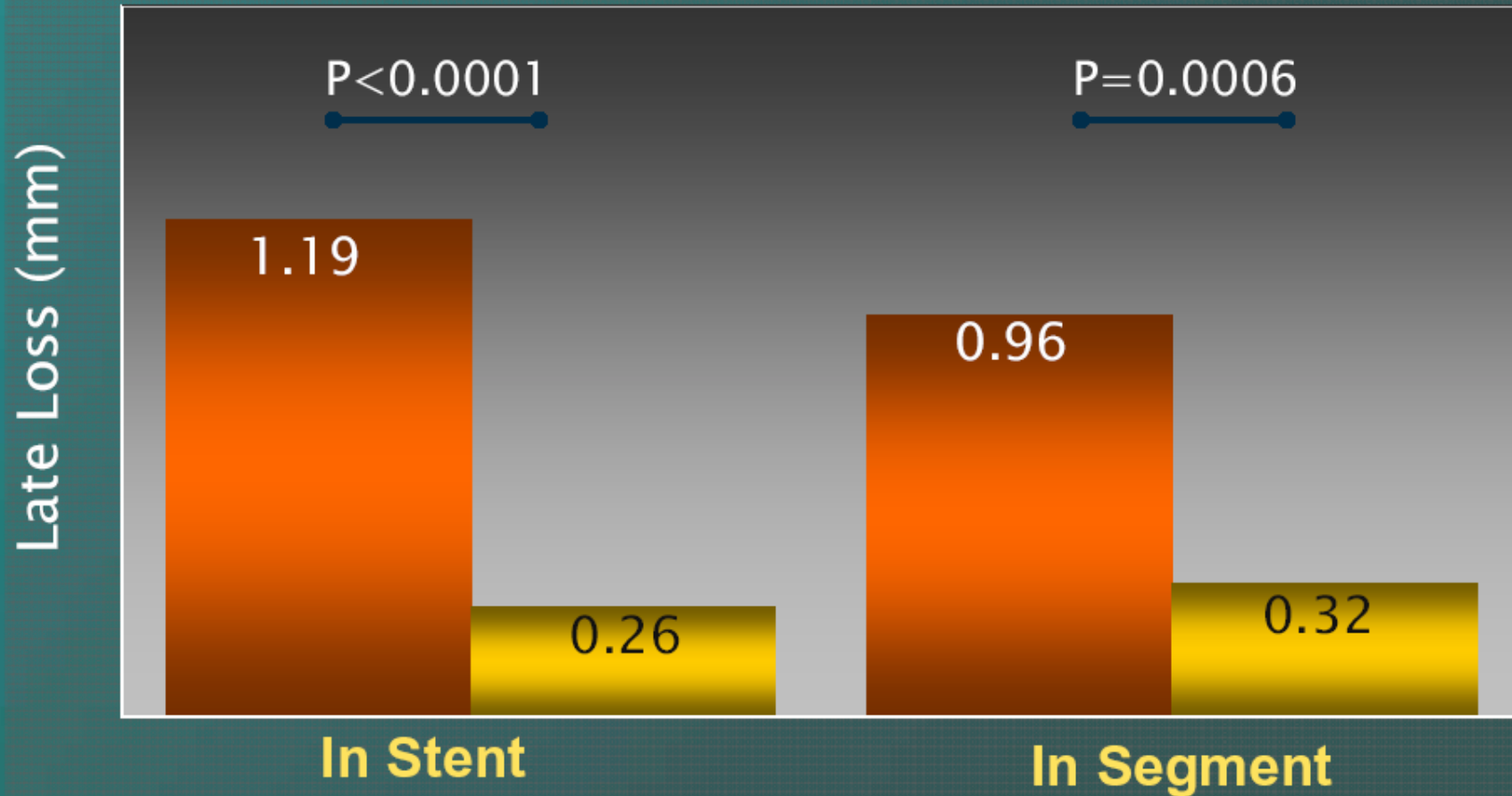
The Taxus Stent Has Not Been Tested in RCTs Designed To Compare Taxus Stent vs. BMS in Diabetic Patients

Meta-analysis of Randomized Cypher & Taxus Trials

Diabetics subgroup analysis
Long-term safety data

CYPHER Trials – Late Loss in DM pts

Control=158 Sirolimus=211



Sirolimus-Eluting stents in Diabetics with Multivessel disease – 1 Yr. Outcomes

	SES 100 pts	BMS 122 pts
Death %	5	4.1
Myocardial infarction %	10	9.8
CVA %	1	1.6
Revascularization %	17	41 *
CABG %	2	5.7
PCI %	15	35 *
MACCE %	25	44 *

Colombo A.

TCT 2004

Events Through 4 Years: Diabetic Subgroups

Diabetic Subgroups	CYPHER® Stent	BMS	p-value*
RAVEL (n=44)	6	2	0.056
SIRIUS (n=279)	14	6	0.037
E-SIRIUS (n=81)	2	2	1.000
C-SIRIUS (n=24)	1	0	1.000
Mortality	11.8% (23 / 195)	4.3% (10 / 233)	0.006
Myocardial Infarction	6.2% (12 / 195)	8.2% (19 / 233)	0.460

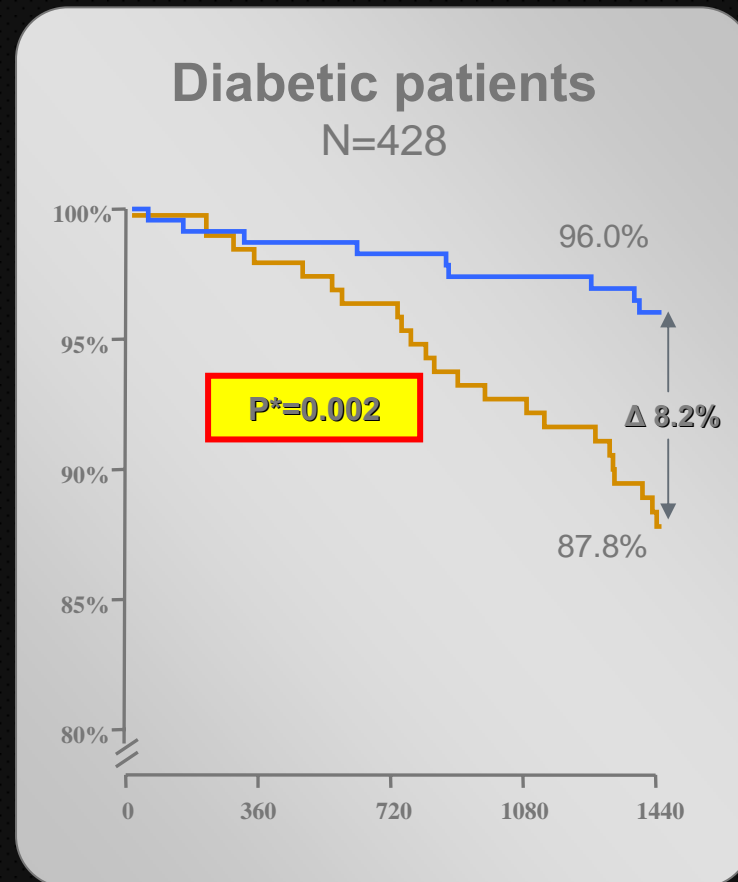
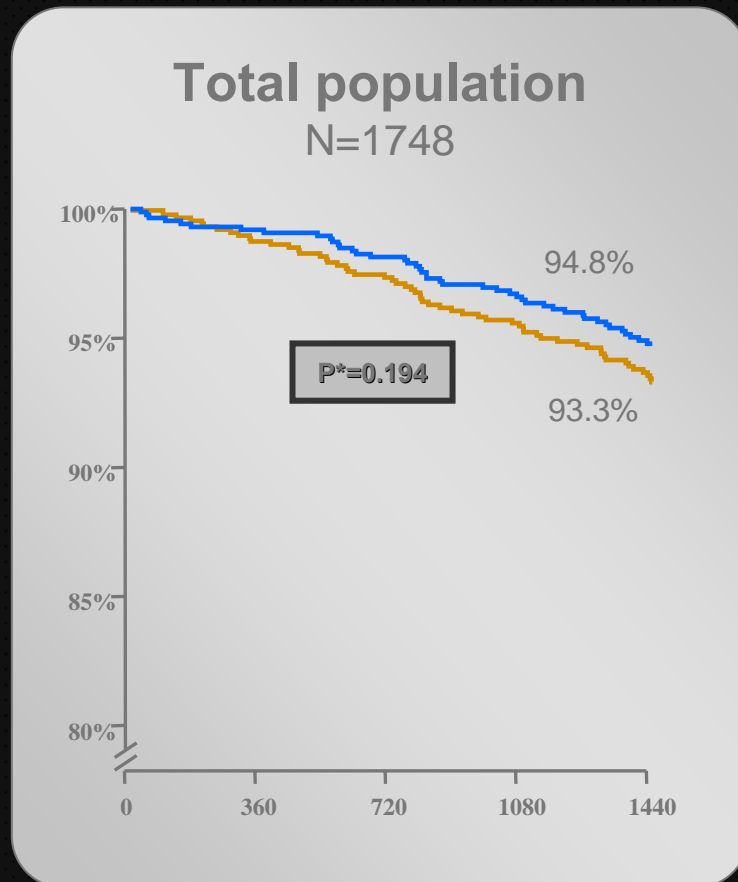
Limitation: Results are derived from post-hoc analyses of non-randomized subgroups

*Fisher's Exact Test p-value

All data are adjudicated by an independent Clinical Events Committee (CEC)

Studies, individually or collectively, were not powered to assess differences in the rates of rare events, such as death, Mi and stent thrombosis

Cypher™ Stent all-cause mortality to 4 years in Diabetic sub-group vs total population



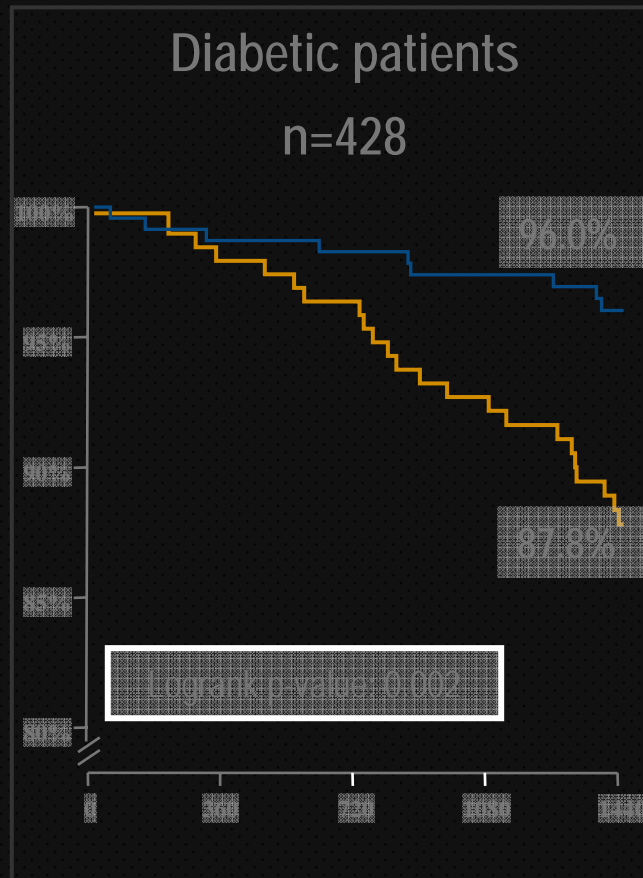
— Cypher Stent

— BMS control

Adapted from Serruys TCT 2006. Serruys independent patient level analysis of the Cypher Stent presented at TCT 2006 Trials included in Cypher Integrated Analysis: RAVEL, SIRIUS, E SIRUS and C SIRIUS all studies sponsored by J&J-Cordis. Cypher is a trademark of J&J/ Cordis Corp. * Log rank p-value

The Difference in Diabetic Mortality is More Apparent in Cardiac Death

RAVEL, SIRIUS, E-SIRIUS and C-SIRIUS



	Sirolimus N=195	Control N=233
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All Death	23 (11.8%)	9 (3.9%)
Cardiac	14 (7.2%)	5 (2.1%)
Non-Cardiac	9 (4.6%)	4 (1.7%)

The Mortality Rate of the BMS Group is lower than predicted

Published data suggest the 5-year mortality rate for the treatment of diabetics with single vessel de novo lesions should be twice as high as that seen in the BMS treatment group in the SIRIUS, E-SIRIUS, C-SIRIUS & RAVEL Trials

Mortality	BMS 4RCTs (n=233)	BMS (5 yrs F/U) n=263)
Total	4.3%	9.6%

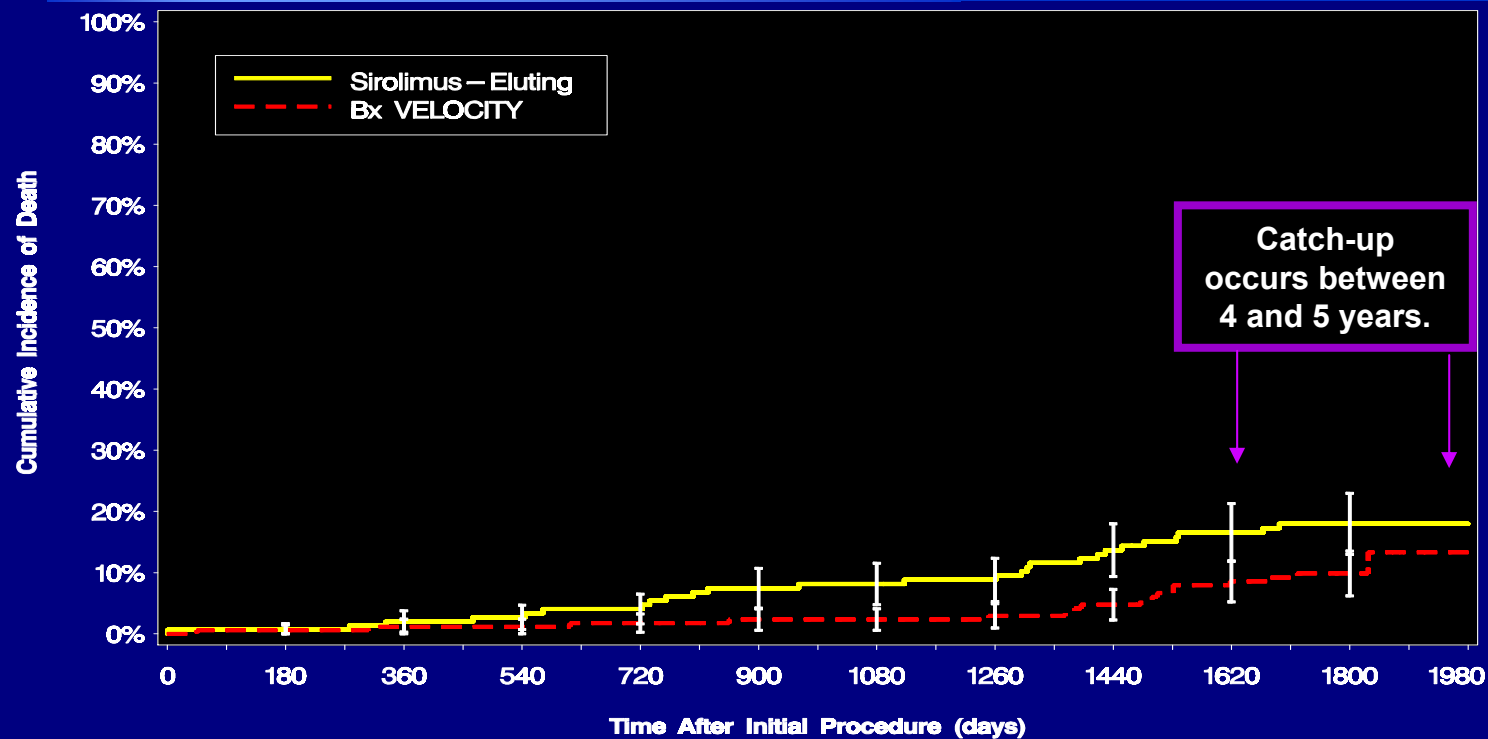
* Lee T et al., AJC, 2006; 98:718-721

Studies, individually or collectively, were not powered to assess differences in the rates of rare events, such as death, Mi and stent thrombosis

SIRIUS and RAVEL Kaplan–Meir Curve

Pooled Data from SIRIUS, RAVEL (Diabetic Patients)

Cumulative Incidence of Death: 0 – 1,980 Days



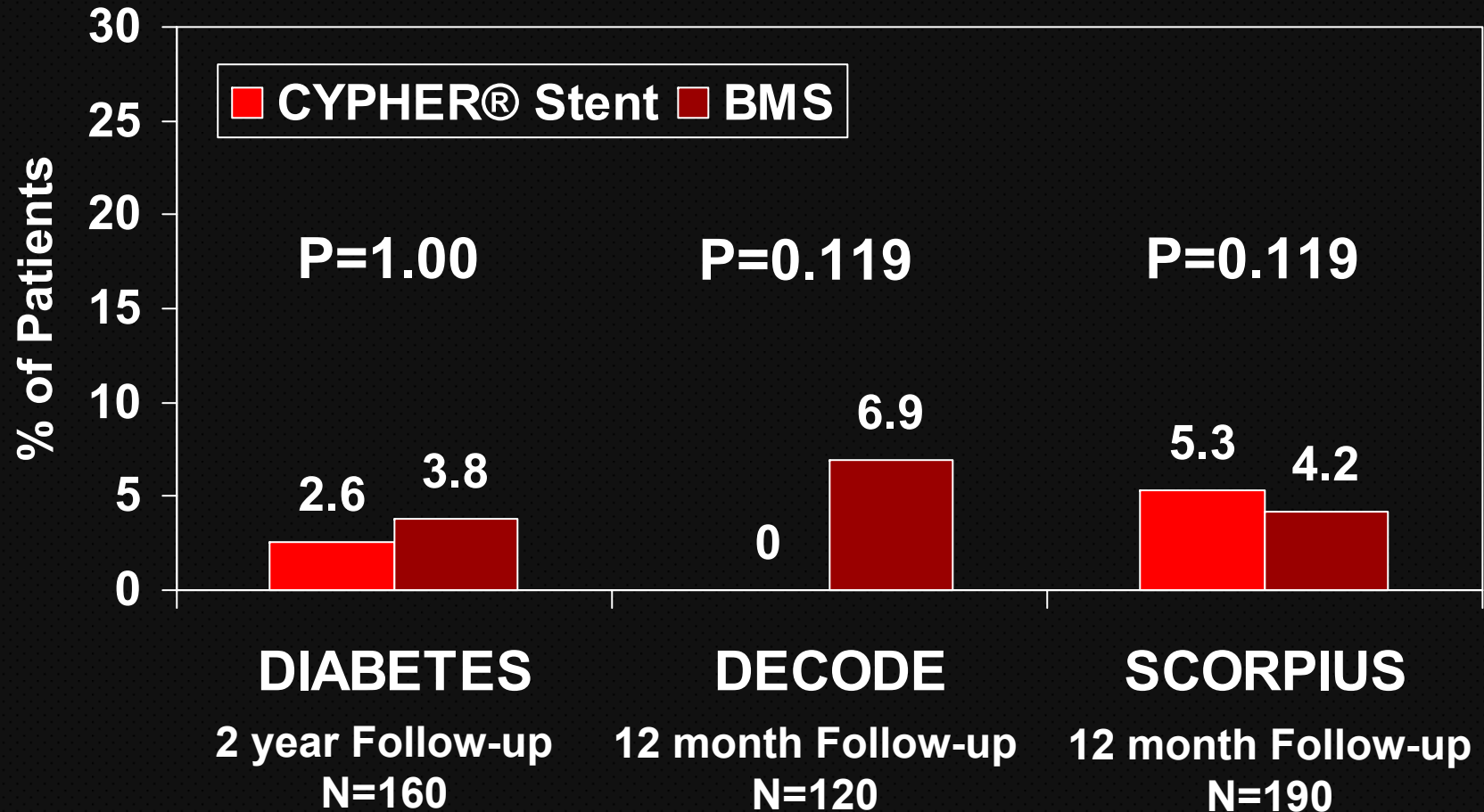
# Entered	0 D	180 D	360 D	720 D	1080 D	1440 D	1800 D
Sirolimus	150	147	145	142	134	124	110
Bx Velocity	173	172	171	169	164	157	136

* Data from RAVEL and SIRIUS

Internal Data, Cordis.

Mortality Rates

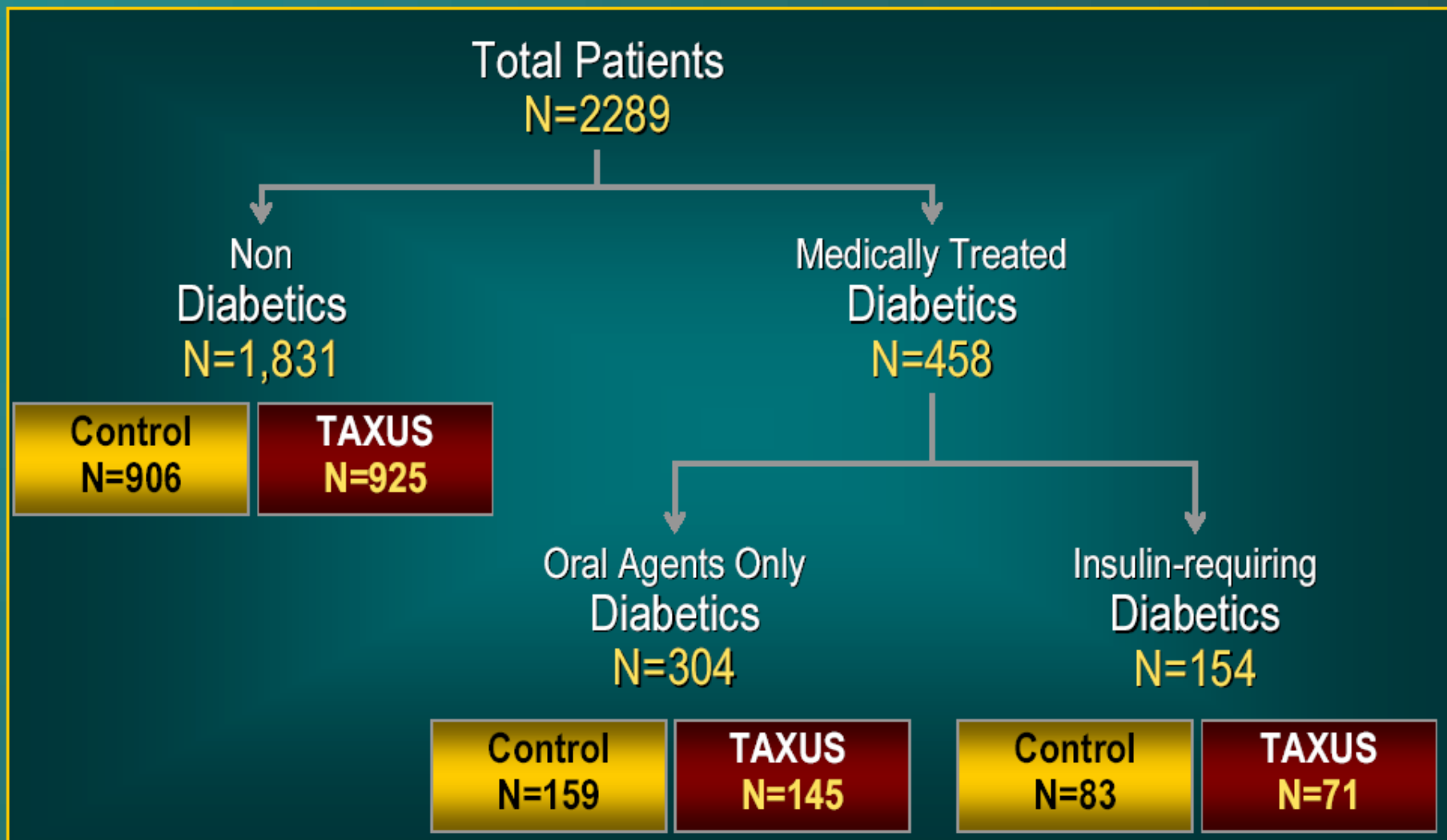
RCTs Designed To Evaluate Diabetic Patients



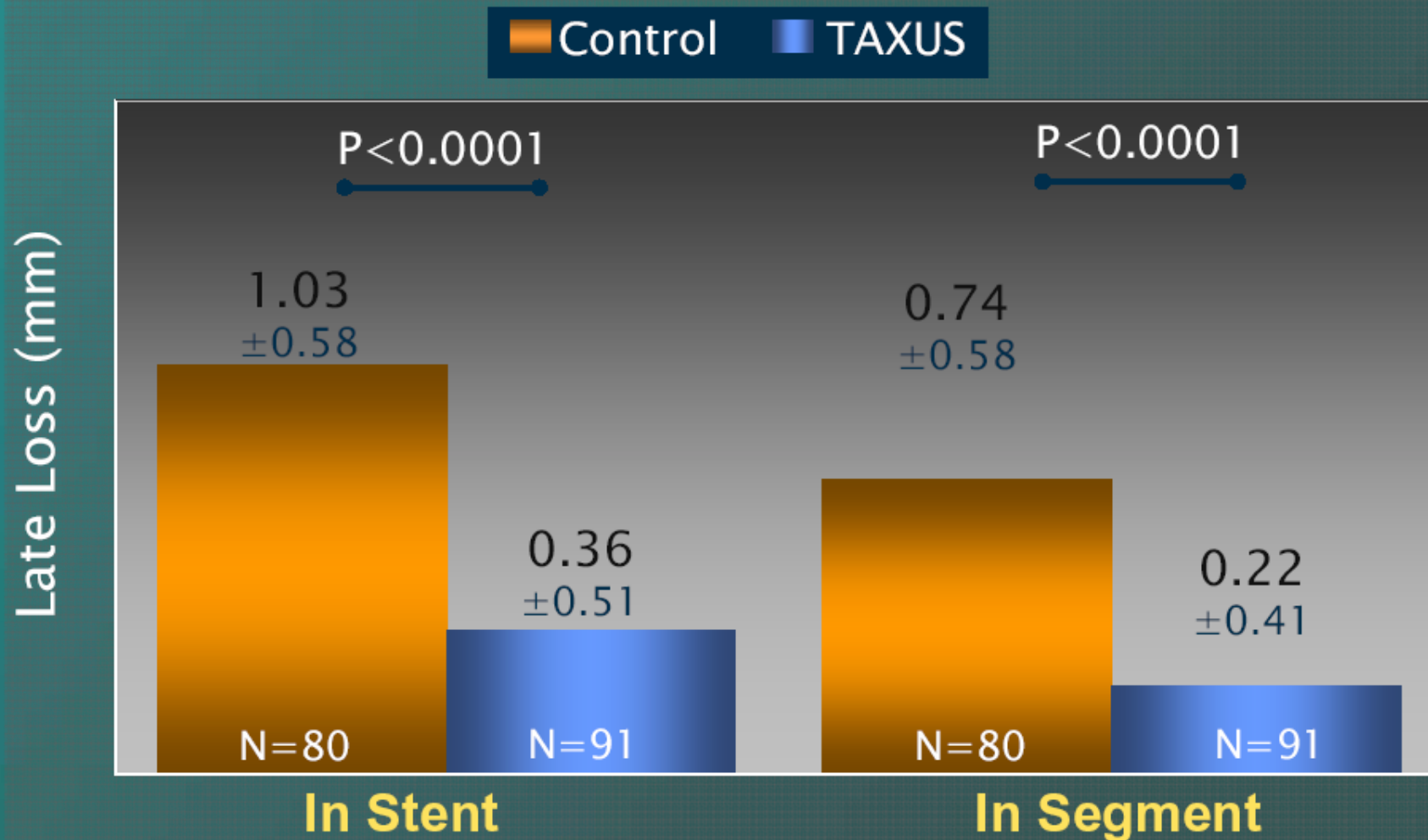
**No Significant Difference in Mortality Rates Across Trials
Designed To Assess The Efficacy of the CYPHER® Stent vs. BMS
Patients With Diabetes**

Studies, individually or collectively, were not powered to assess differences in the rates of rare events, such as death, Mi and stent thrombosis

Diabetics in TAXUS Trials Meta-Analysis

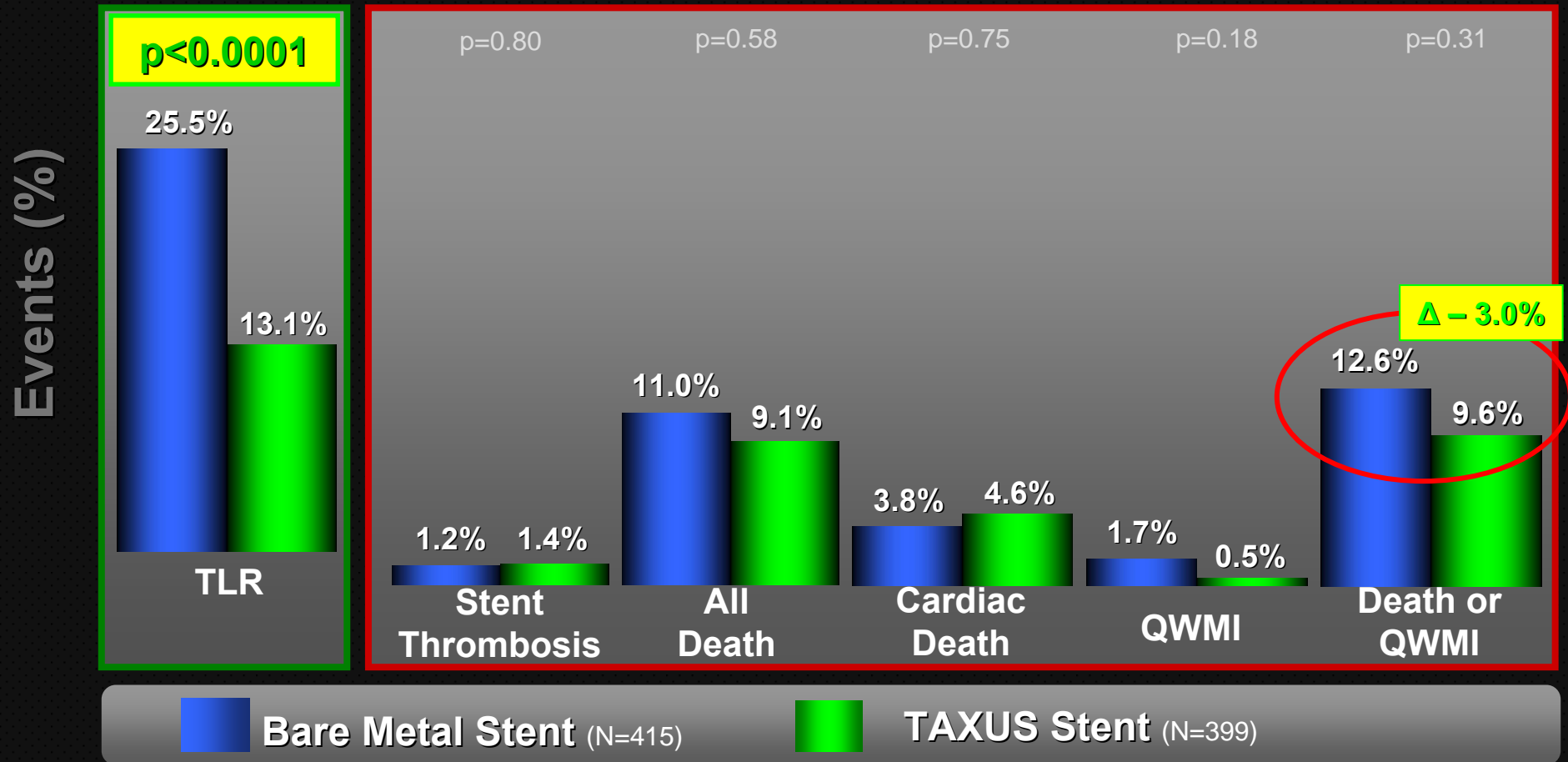


TAXUS Trials – Late Loss in NIDDM pts



TAXUS™ Stent: Significantly lower TLR and as safe -- or safer -- than a BMS in diabetics

TAXUS Stent 4 yr meta-analysis: All Diabetics
 TAXUS II¹ (4 yr) , IV² (4 yr), V³ (2yr), VI⁴ (3 yr) studies (N=814)



TAXUS 4 year meta-analysis, presented by Dr. Baim, TCT 2006. 1. Colombo et al. Circulation. 2003;108:788; 2. Stone et al. N Engl Med. 2004;350:221; 3. Stone et al. JAMA. 2005;294:1215; 4. Dawkins et al. Circulation. 2005;112:3306. Paclitaxel-Eluting NIR Stent and TAXUS Express Stent are investigational devices only.

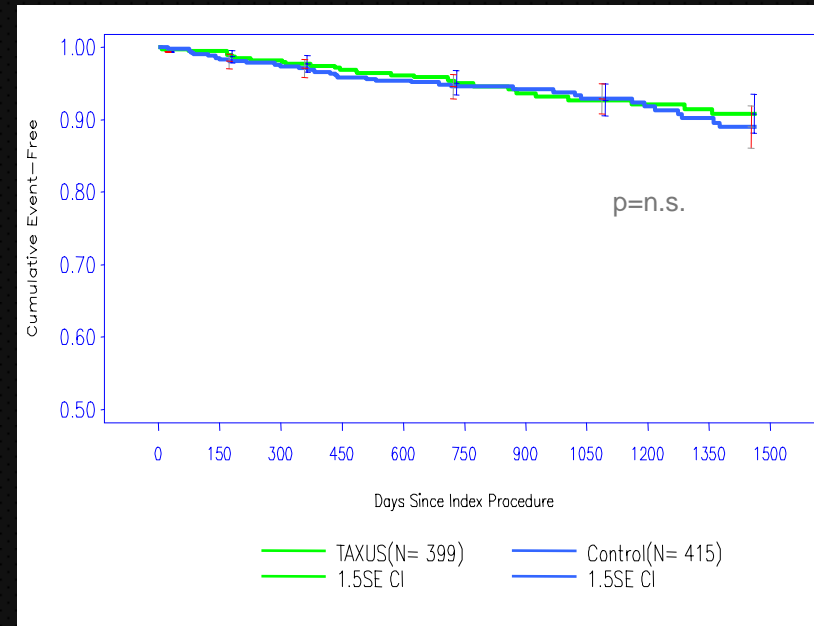
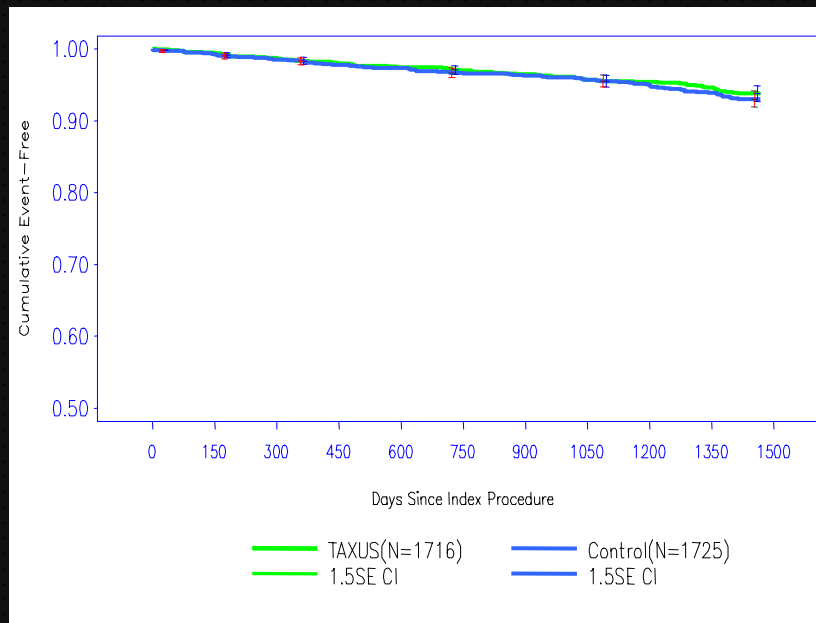
TAXUS™ Stent 4-Year Meta-Analysis Diabetic Sub-Group

TAXUS All-Cause Mortality to 4 Years by Diabetic Sub-Group

Total Population
n=3441

**No Statistical
Difference**

All Diabetics
n=814

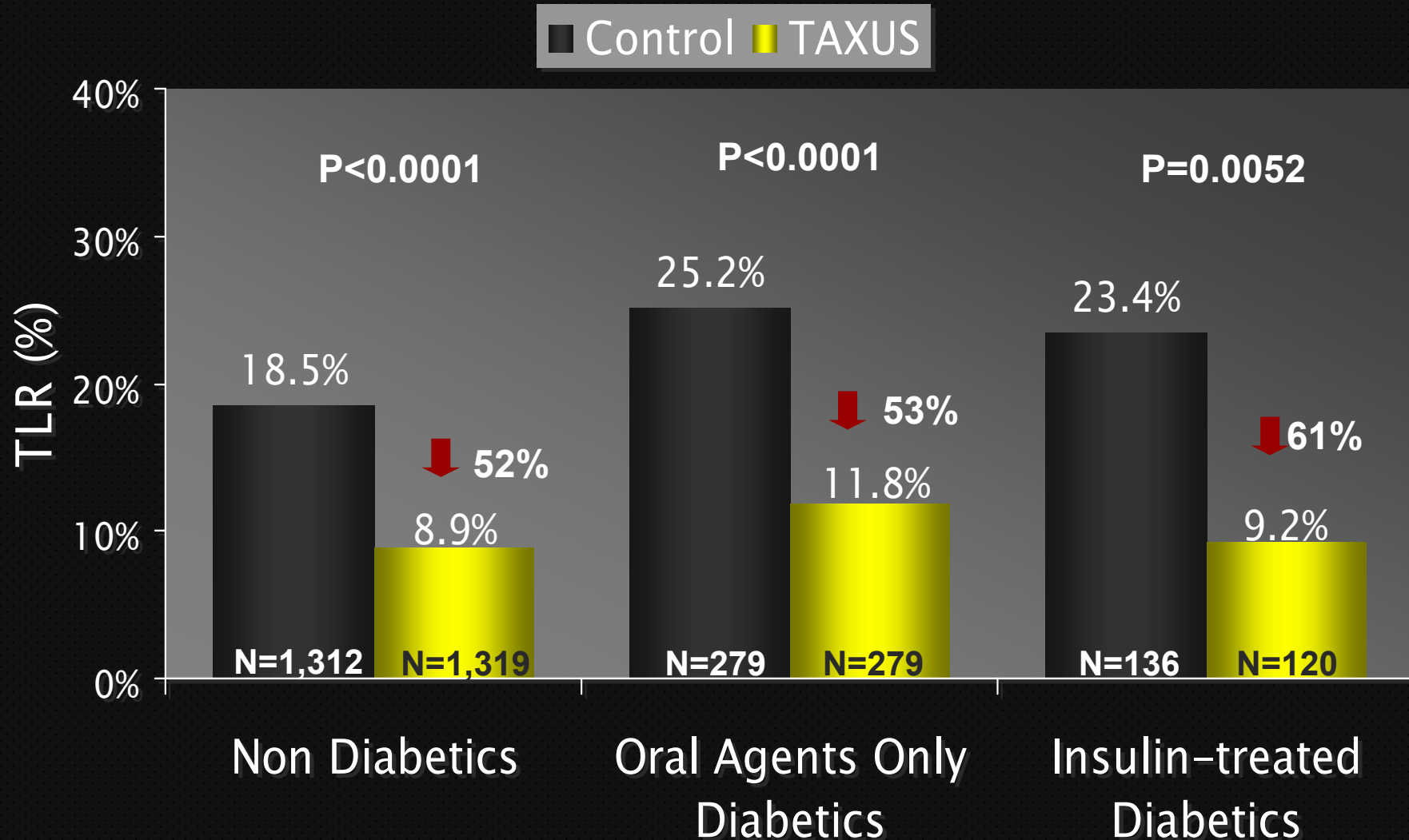


TAXUS 4-year meta-analysis (All Diabetics) presented by Dr. Stone, TCT 2006. TAXUS Stent meta-analysis (all diabetics): TAXUS II1 (4 yr), IV2 (4 yr), V3 (2yr), VI4 (3 yr) (N=3445). 1. Colombo et al. *Circulation*. 2003;108:788; 2. Stone et al. *N Engl Med*. 2004;350:221; 3. Stone et al. *JAMA*. 2005;294:1215; 4. Dawkins et al. *Circulation*. 2005;112:3306. TAXUS™ Stents include the Paclitaxel-Eluting NIR™ Stent (NIR is a trademark of Medinol, Ltd, Jerusalem) in the TAXUS II study, the TAXUS™ Express™ Stent in the TAXUS IV and VI studies and the TAXUS™ Express2™ Stent in the TAXUS V study. BMS Control includes the NIR in the TAXUS II study, Express™ Stent in the TAXUS IV and VI studies and Express2 Stent in the TAXUS V study. Paclitaxel-Eluting NIR Stent and TAXUS Express Stent are investigational devices only.

Impact of DES in Diabetics Subgroups

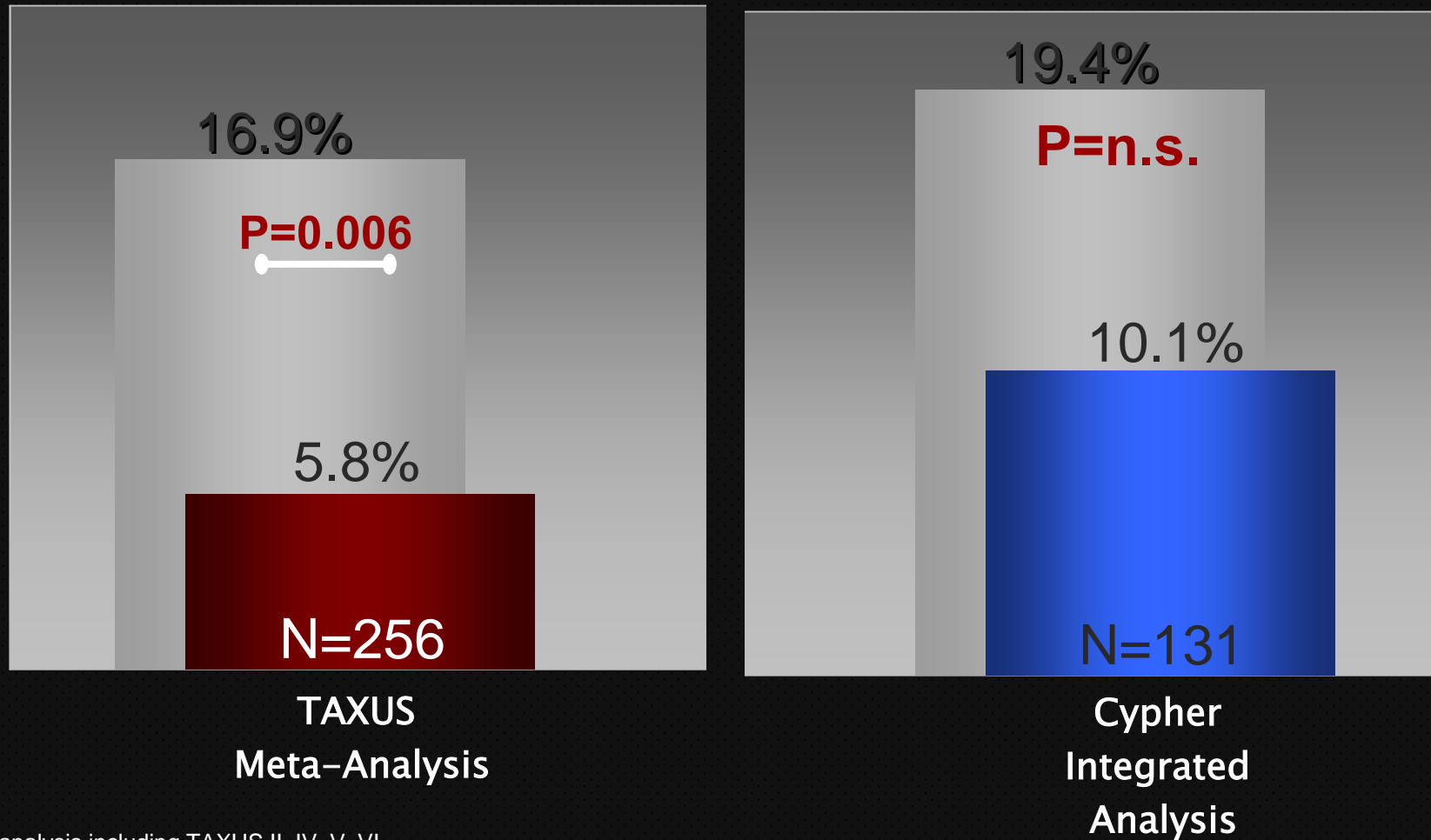
Diabetic Patients in TAXUS Trials

3-year Target Lesion Revascularization



→ *Equal benefit across patients*

DES in Insulin-Requiring Diabetics



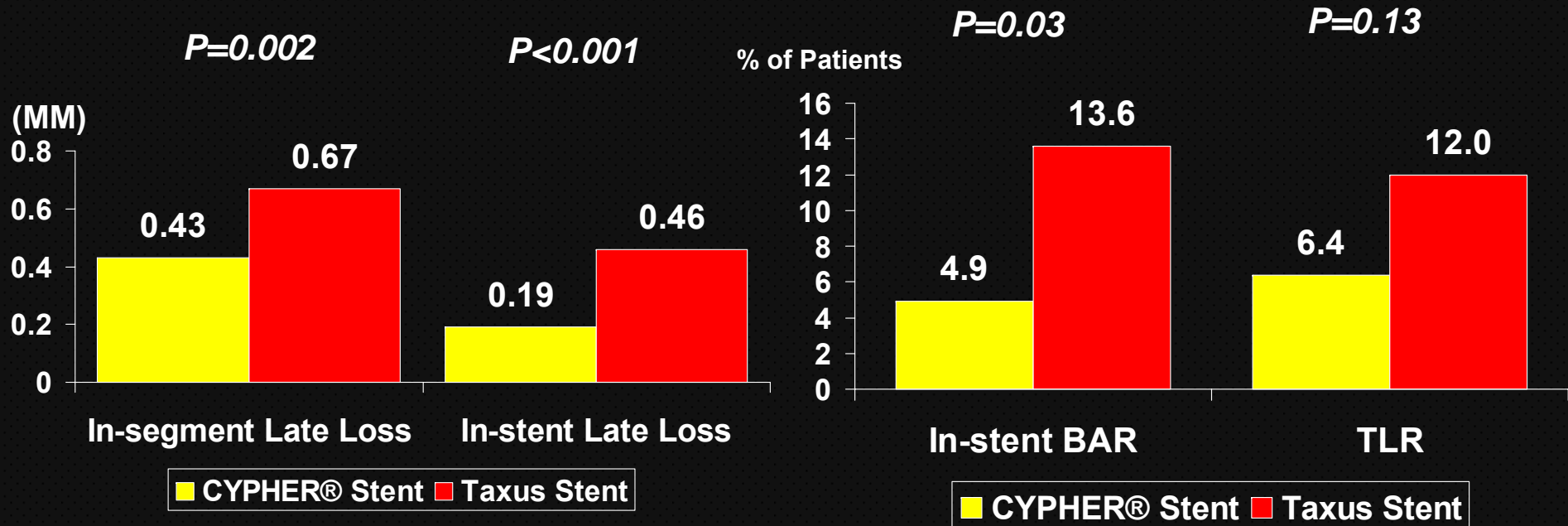
TAXUS metaanalysis including TAXUS II, IV, V, VI

CYPHER integrated analysis including RAVEL, SIRIUS, E- and C-SIRIUS, DIRECT, SVELTE presented at ACC 2005 by Dr. W. Wijns.

The Cypher Stent vs the Taxus Stent: RCT's in diabetic patients

- There is one trial (ISAR-Diabetes) designed to compare the Cypher Stent vs the Taxus stent in diabetics and one pre-specified sub-analysis of diabetic patients in the Sirtax Trial

The ISAR-DIABETES Trial - 9-month Follow-up (N=250)



**Significantly Less Late Lumen Loss
Almost Half the TLR (Difference Is Not Statistically Significant)**

Summary of Outcomes Through 9 Months: The ISAR-DIABETES Trial

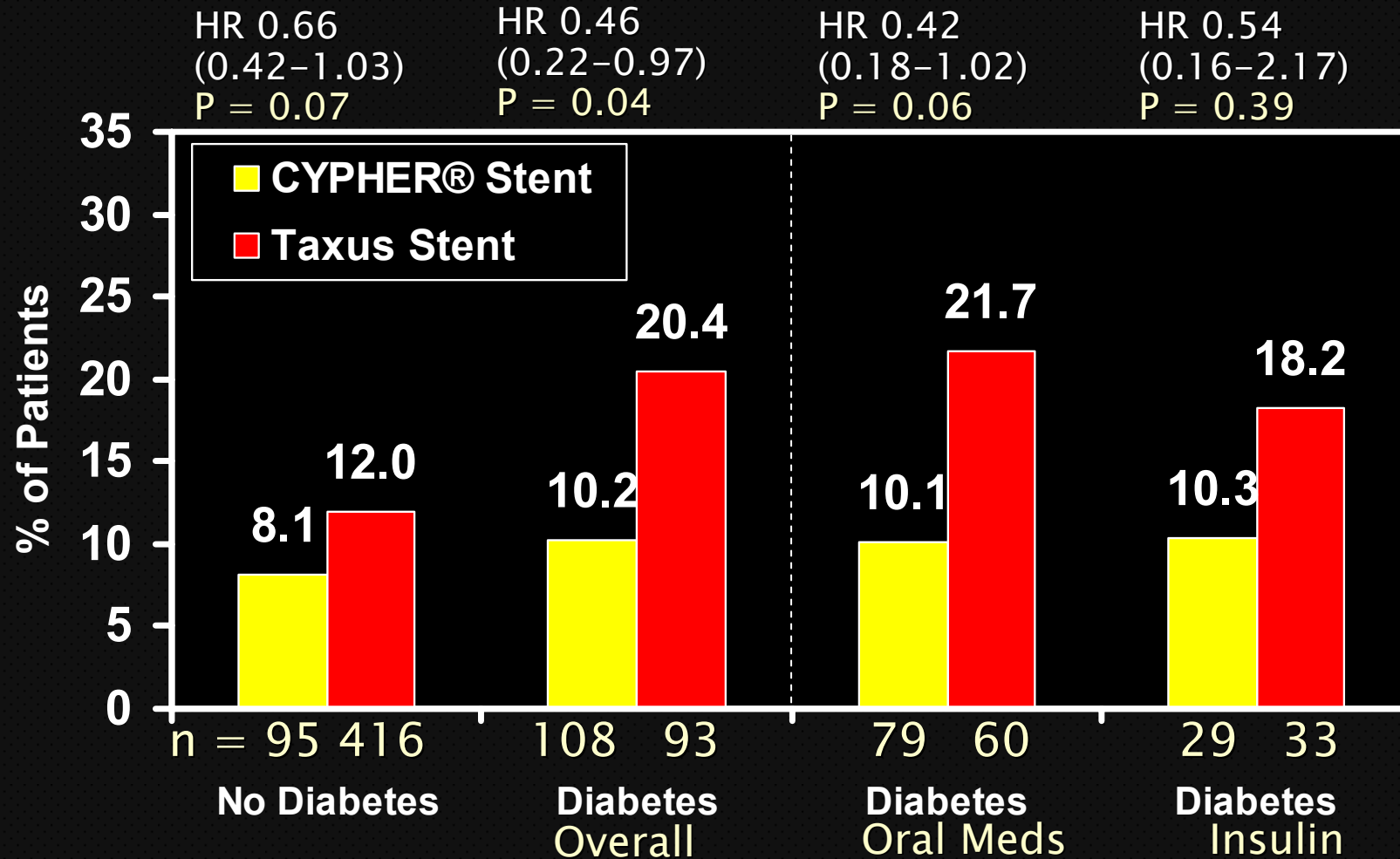
	CYPHER [®] Stent (N=125)	Taxus Stent (N=125)	P-Value
Death, n (%)	4 (3.2%)	6 (4.8%)	0.52
MI, n (%)	5 (4.0%)	3 (2.4%)	0.72
TLR, n (%)	8 (6.4%)	15 (12.0%)	0.13

Limitation: Results are from a randomized, controlled trial powered for binary angiographic restenosis

All patients completed clinical follow-up

Dibra A., et al., *N Engl J Med* 2005;353:663-70.

Summary of MACE* Through 1 Year: Pre-specified SIRTAX Trial Diabetic Subgroup



Results are from a pre-specified subgroup analysis of a randomized, controlled trial powered for MACE.

Limitation: RCT was not powered for comparisons among diabetic patients on insulin or oral hypoglycemic agents.

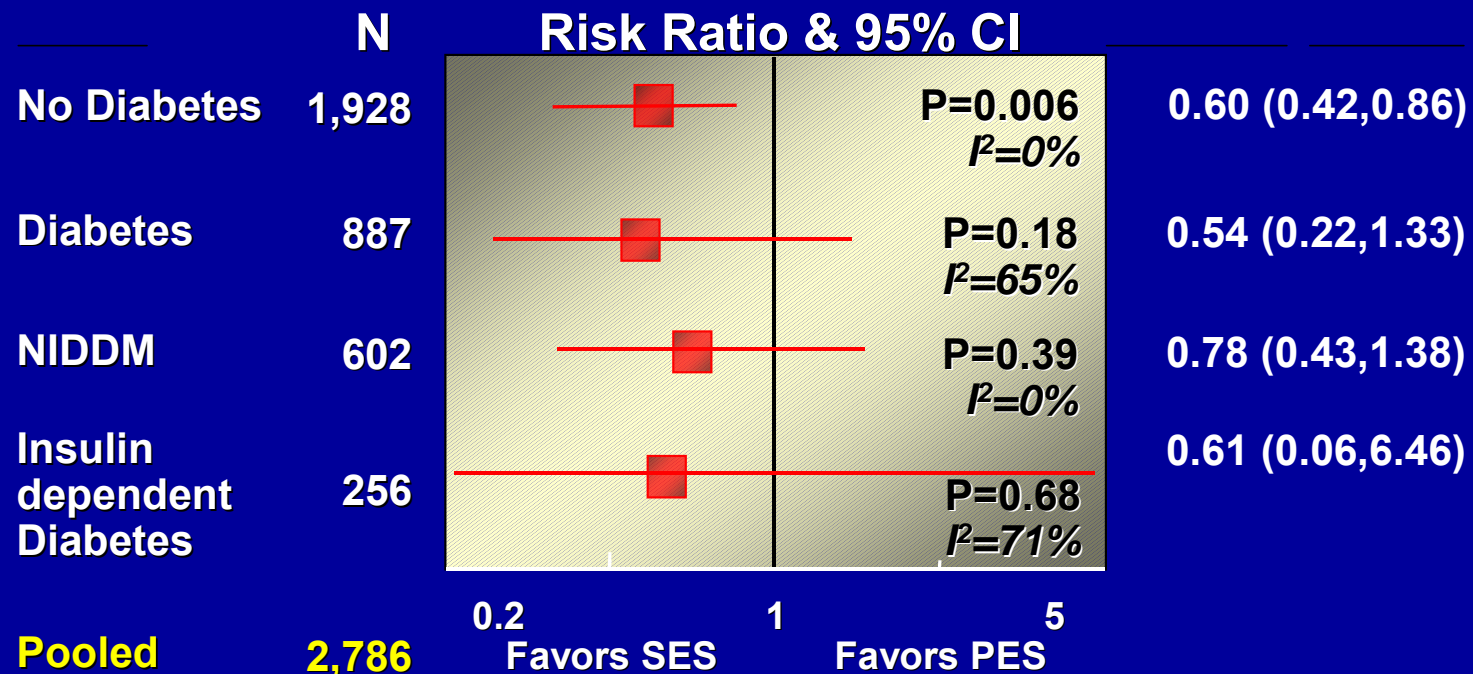
* Cardiac Death, Myocardial Infarction, or Ischemia-driven Target Lesion
Revascularization

Windecker S., et al., *ESC 2006; Poster Presentation.*

Windecker Meta-Analysis

Individual Patient Data Meta-Analysis Risk of TLR and Diabetes

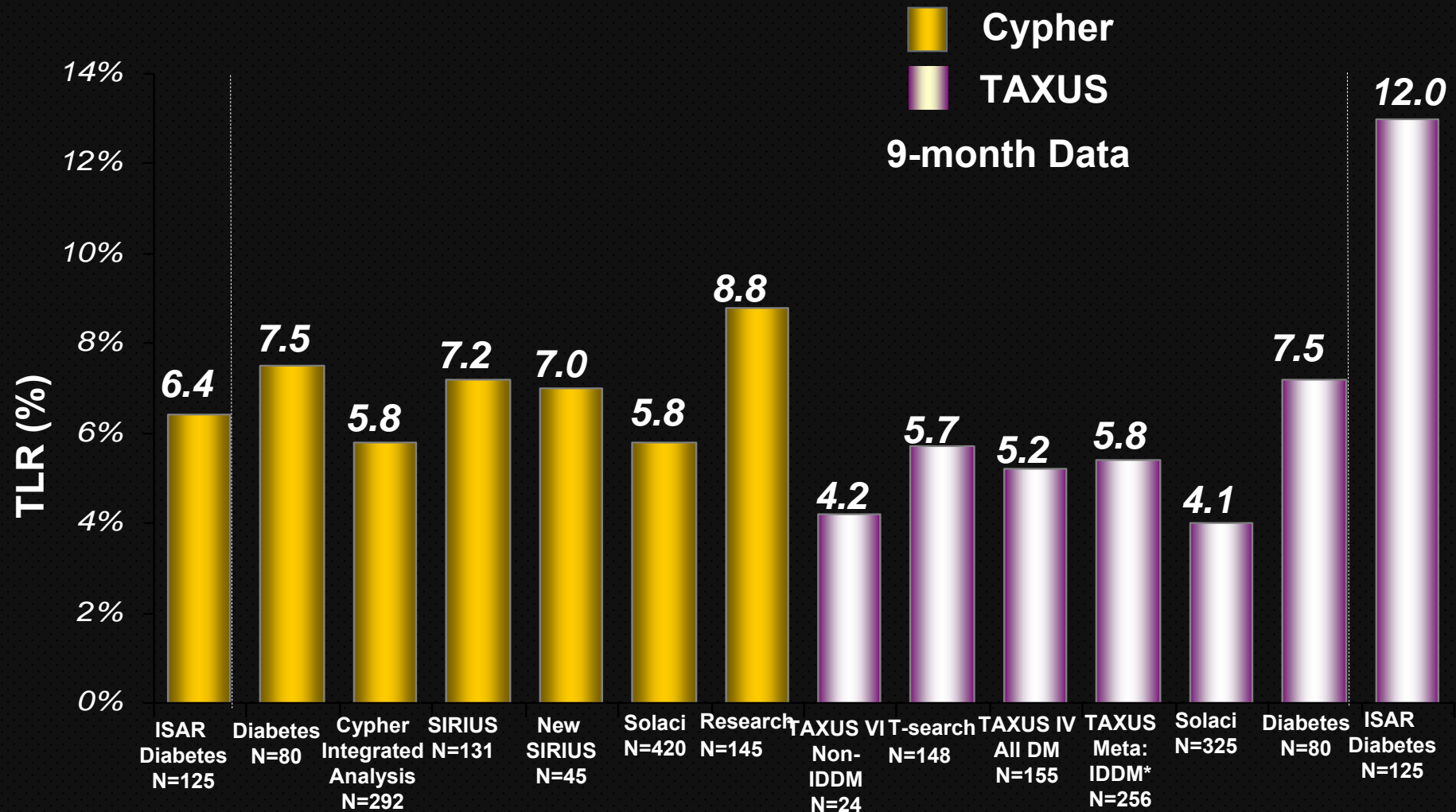
Target Lesion Revascularization



Random Effects Model

Data from ISAR-DESIRE, ISAR-DIABETES, REALITY, SIRTAX

Diabetic Data Across Trials



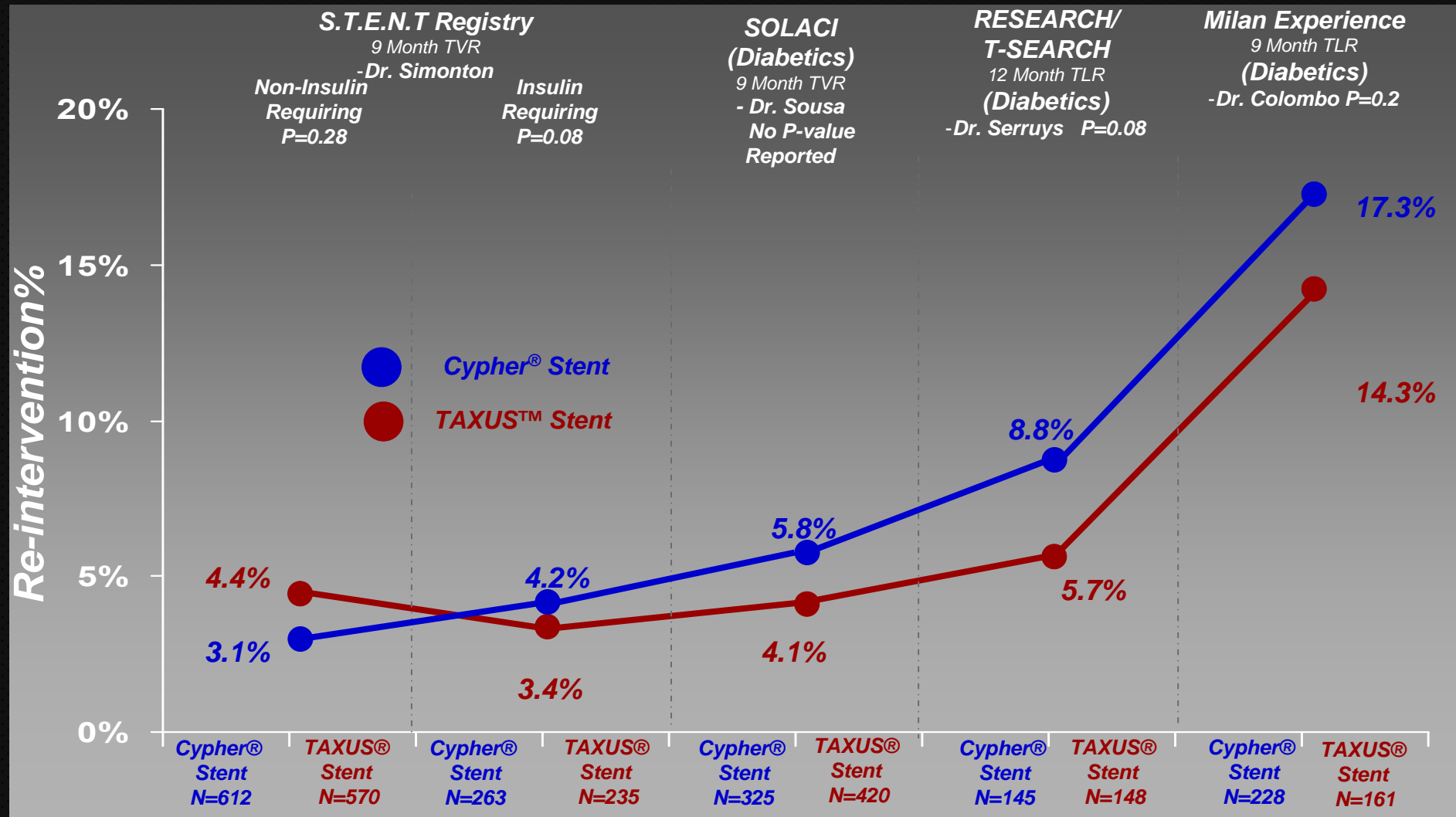
*12-month data
**6-month data

The safety and efficacy of the TAXUS® Express2™ Stent have not been established in patients with diabetics. Data from trials that are not head-to-head are not intended to be comparative.

Real World Diabetic Patients

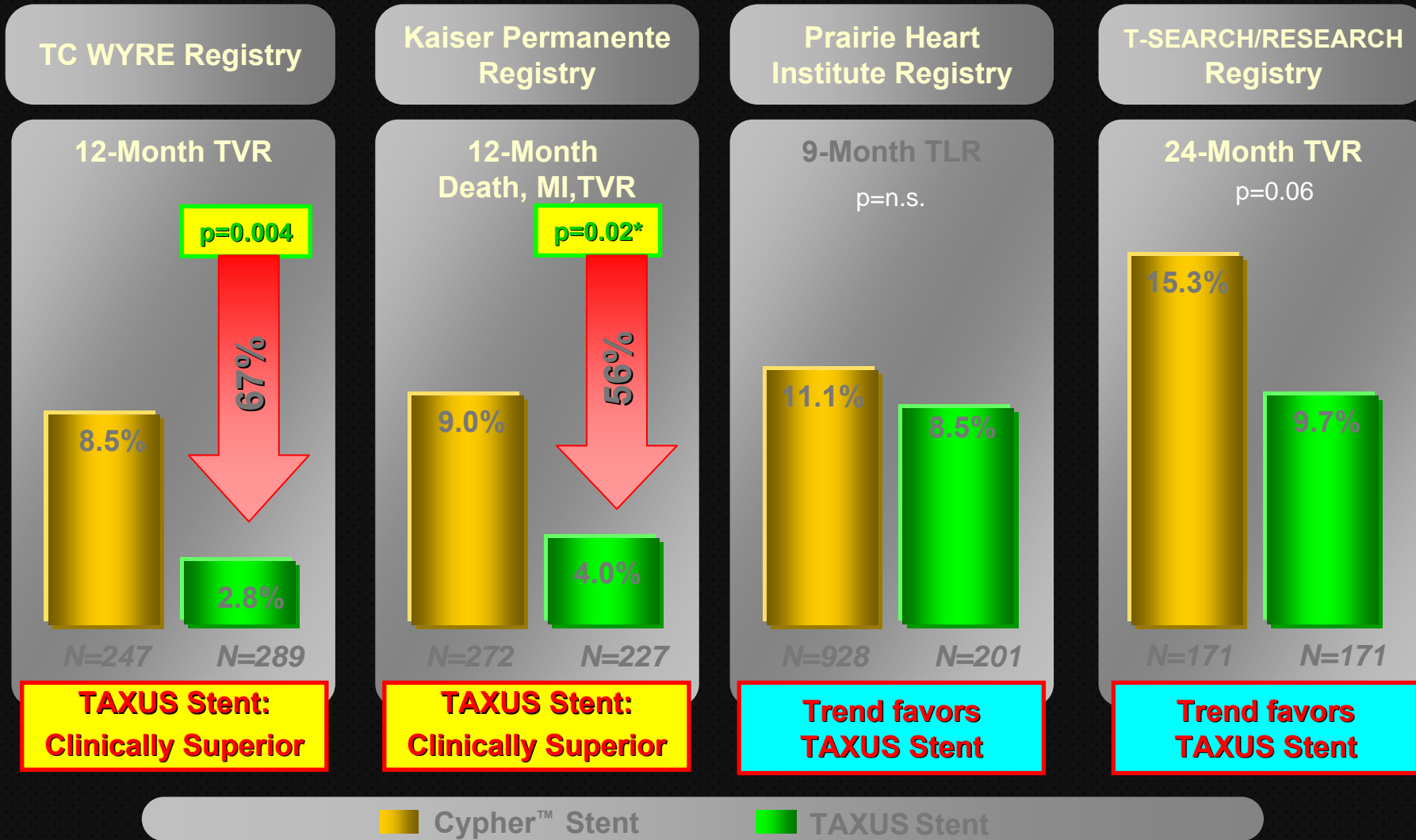
Data from Cypher & Taxus Registries

Comparative Real World Studies & Registries In Diabetics (3,000+ Patients with Clinical Follow-up Only)



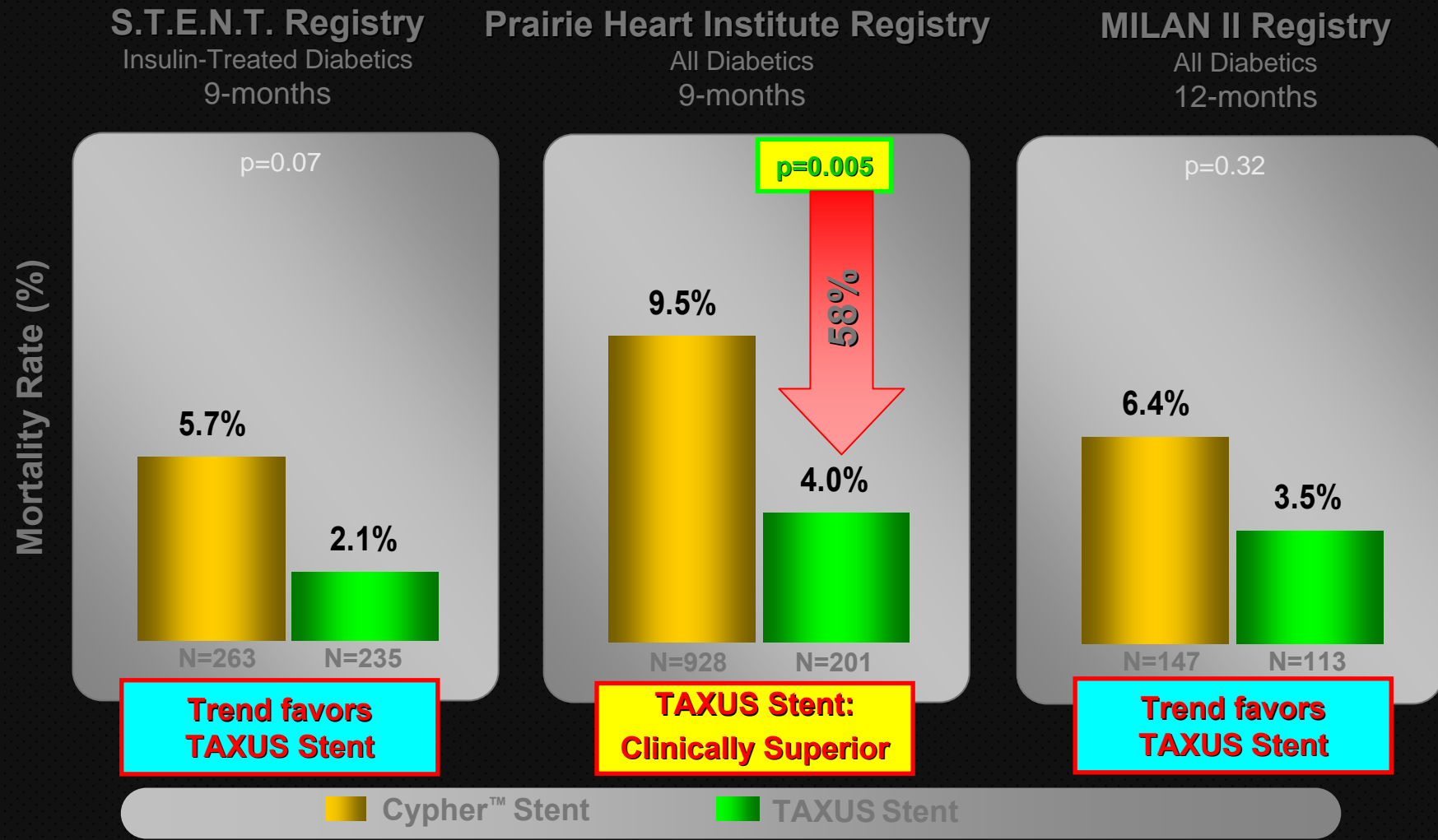
Increasing Lesion Length

New registries confirm that the TAXUS™ Stent is Superior in Diabetics



TC WYRE registry data presented by Dr. Kandzari and Dr. O'Neill at TCT 2006. Kaiser Permanente registry data presented by Dr. Brar at TCT 2006. Prairie Heart Institute registry data presented by Dr. Mishkel et al. TCT 2006. T-Search/Research registry presented by Dr. Daemen at AHA 2006. Cypher is a registered trademark of J&J/ Cordis Corp. * Log-Rank p-value.

TAXUS™ Stent: Mortality rates better in Diabetic patients



S.T.E.N.T. Registry presented at ACC 2006 by Dr. Simonton. *Prairie Heart Institute study presented by Dr. Mishkel et al. TCT 2006. Centro Cuore Columbus (Milan II) data presented by Dr. Cosgrave at TCT 2006. Cypher is a registered trademark of J&J/ Cordis Corp.

Conclusions

- Does DES improve outcome of PCI in DM? → Yes
- Is there a difference in response to DES between insulin and non-insulin required DM? → Perhaps
- Does DES eliminate DM as a predictor of restenosis? → No
- Is there compelling evidence to establish the comparative efficacy of Sirolimus vs Paclitaxel stent in DM? → There is no significant difference in clinical outcomes and neither in NIDDM which are hypothesized to be better off with PES although there is a trend in more favourable outcome in PES especially in Real World Registries