

Overview of DES Safety in Diabetic Patients

David E. Kandzari, MD, FACC, FSCAI

Chief Medical Officer

Cordis Corporation, a Johnson & Johnson Company

dkandzari@crdus.jnj.com

Diabetes: An Emerging Global Epidemic

- › Prevalence increasing worldwide, developing countries > industrialized
- › Heterogeneous sub-population with varied therapies
- › Additive contribution to comorbidity (eg, CAD, chronic kidney disease, retinal disease, PAD)
- › Association with increased systemic pro-inflammatory and pro-thrombotic markers
- › CAD population: ↑ death/MI/stroke, ↑ systemic disease burden
- › PCI population in DES era: ↑ death, MI, restenosis, repeat revascularization, progression of disease

DES in Diabetes: Therapeutic Challenge

› FEW randomized trials exclusive to diabetic PCI population

BMS vs SES

DECODE

SCORPIUS

DIABETES

DESSERT

SES vs PES

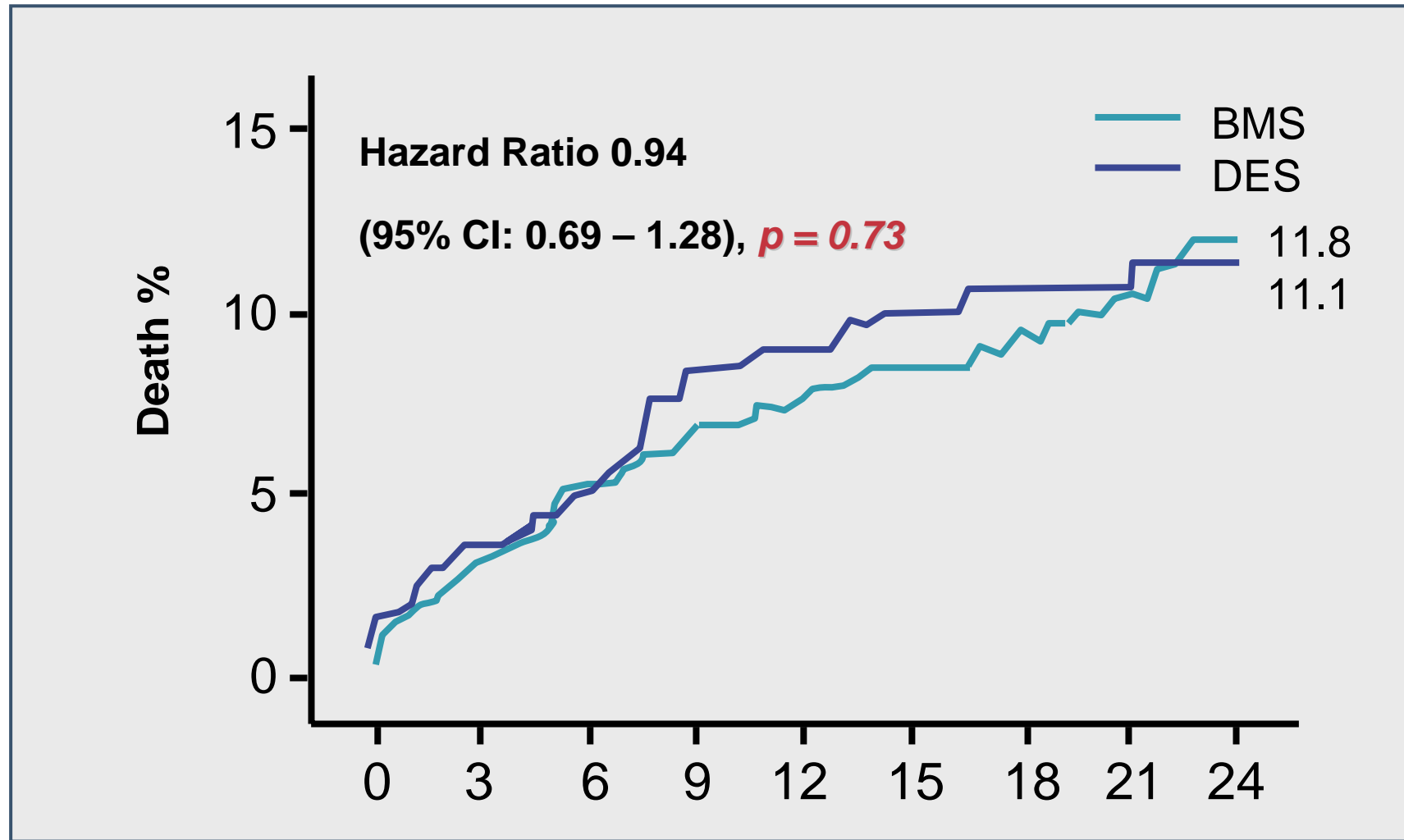
ISAR-DIABETES

› MANY subgroup analyses from both registries and RCTs

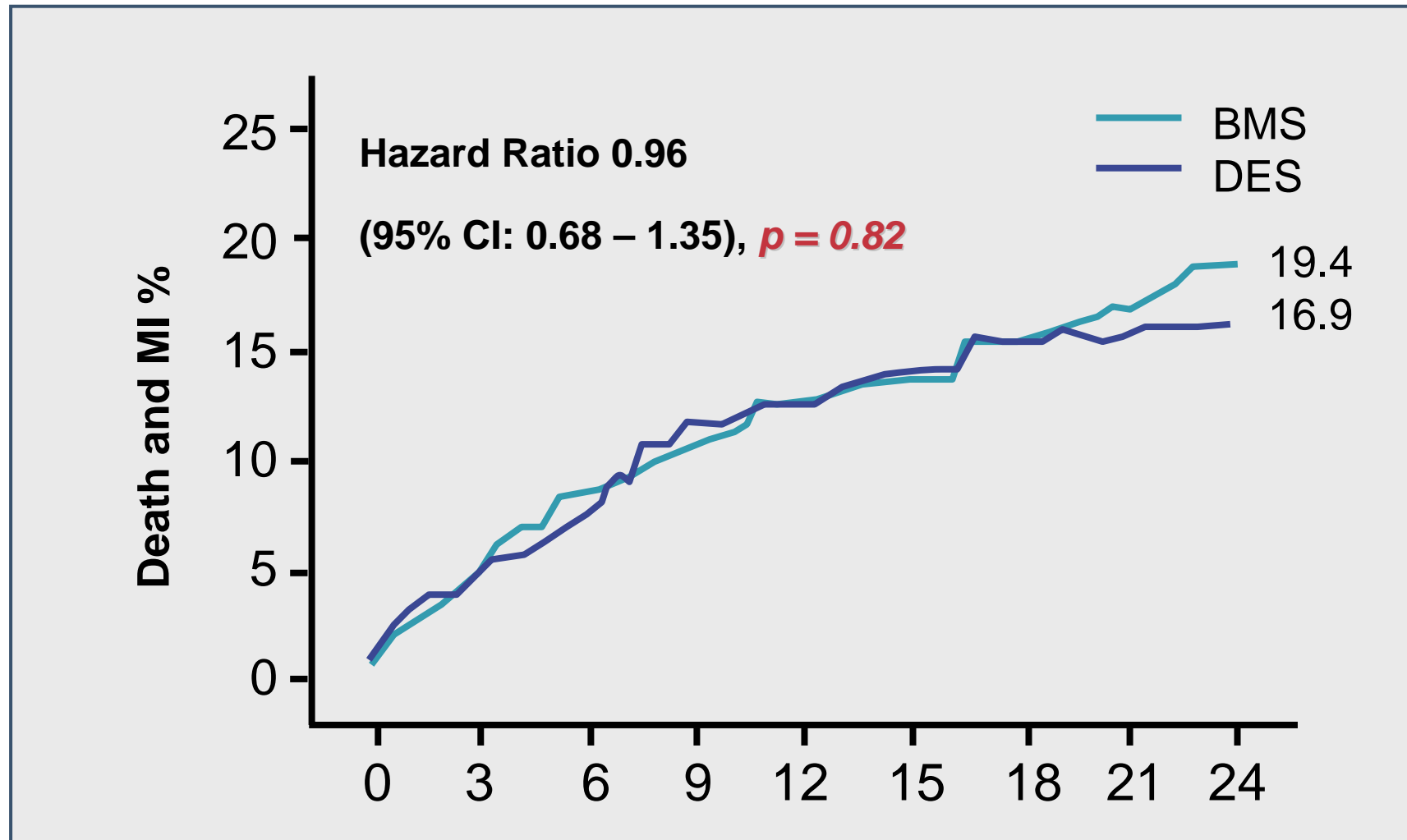
› Sheer number of diabetic analyses enables variable and unexpected results

REAL Registry: BMS and DES in DM

BMS:1,089 DES:559 (70% SES)

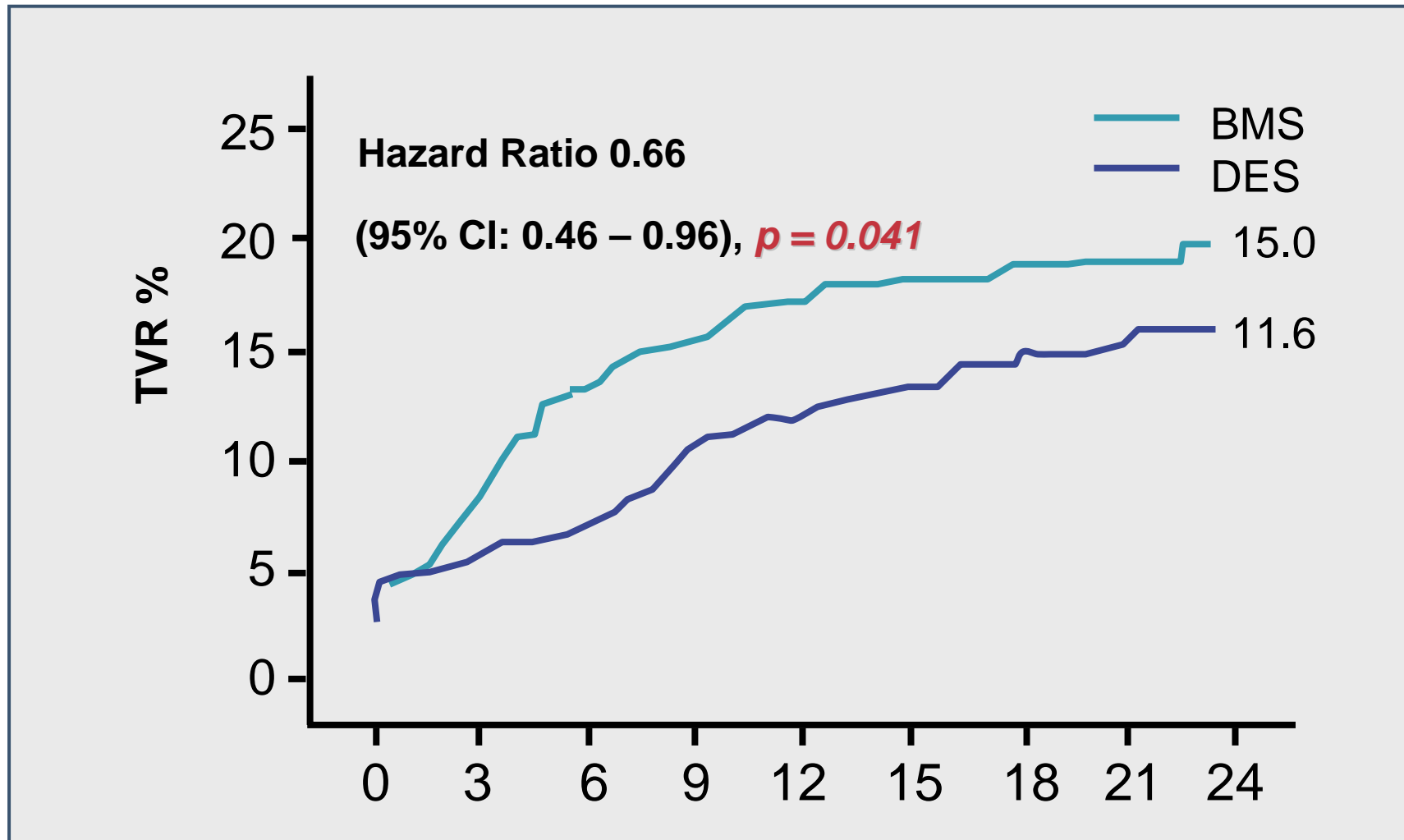


REAL Registry



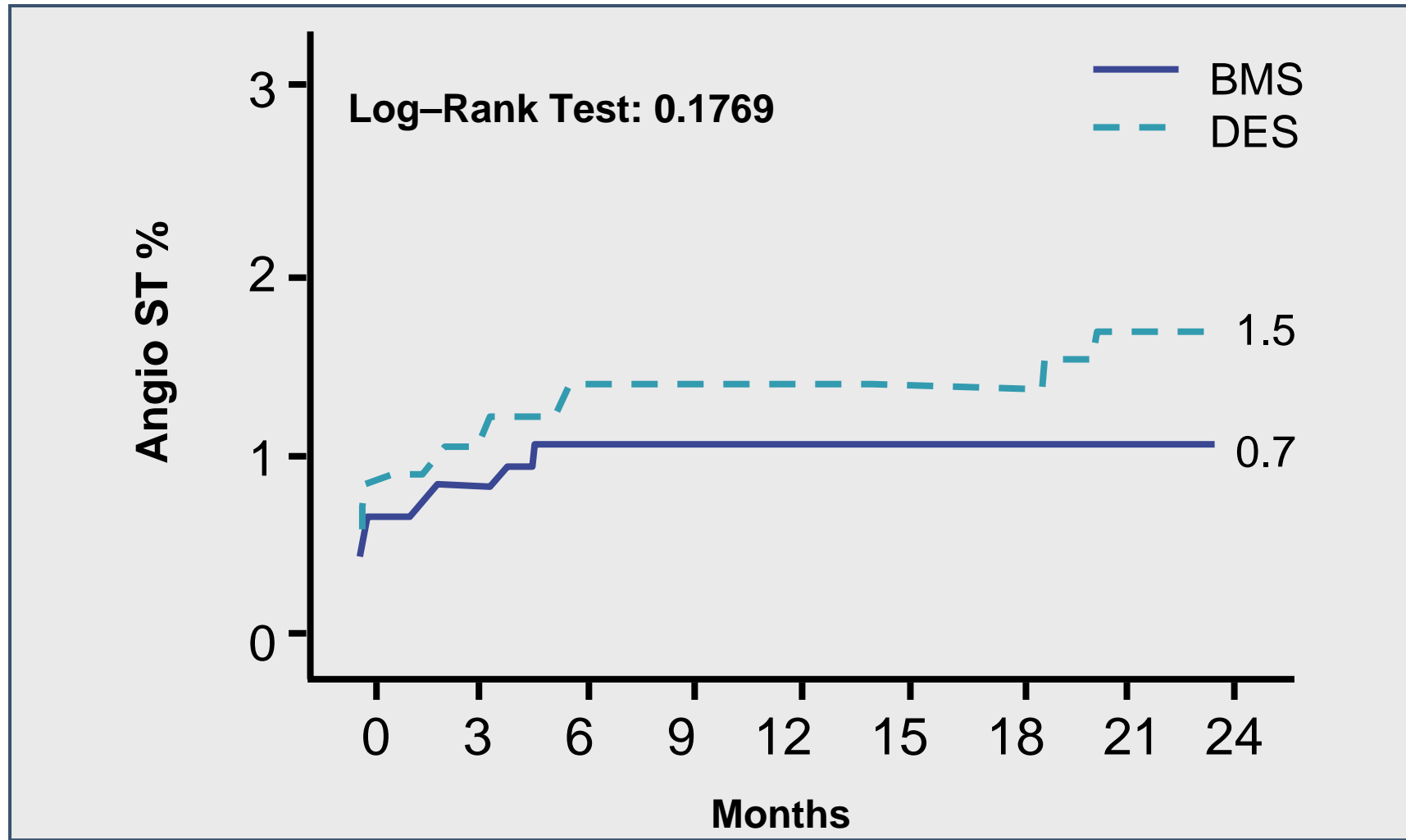
Ortolani et al, *Circ* 2008;117:923-930

REAL Registry



Ortolani et al, *Circ* 2008;117:923-930

REAL Registry

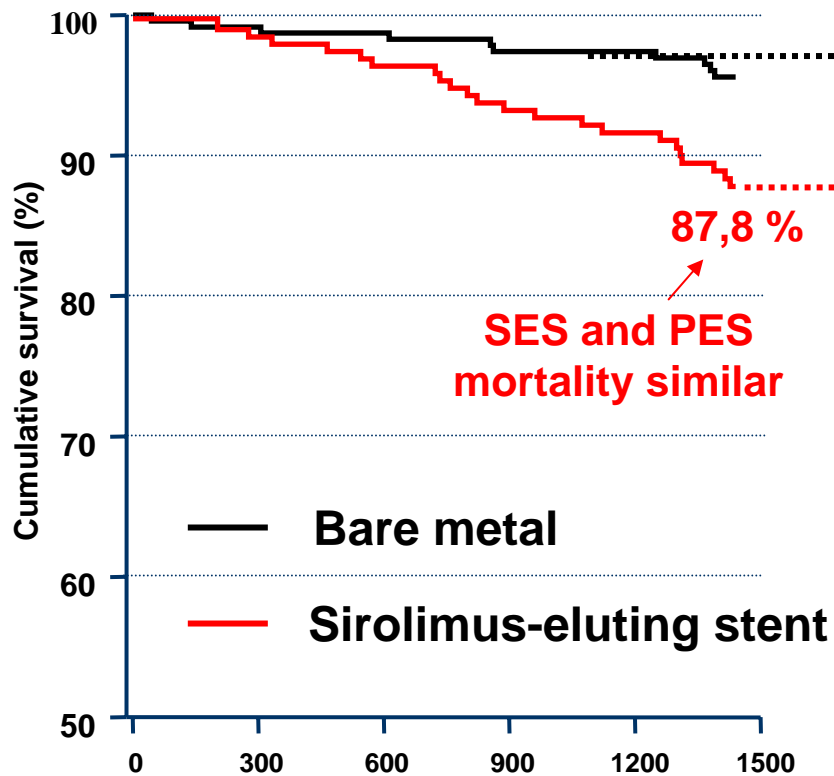


Ortolani et al, *Circ* 2008;117:923-930

Mortality in pooled DES vs BMS analyses: Diabetic subset

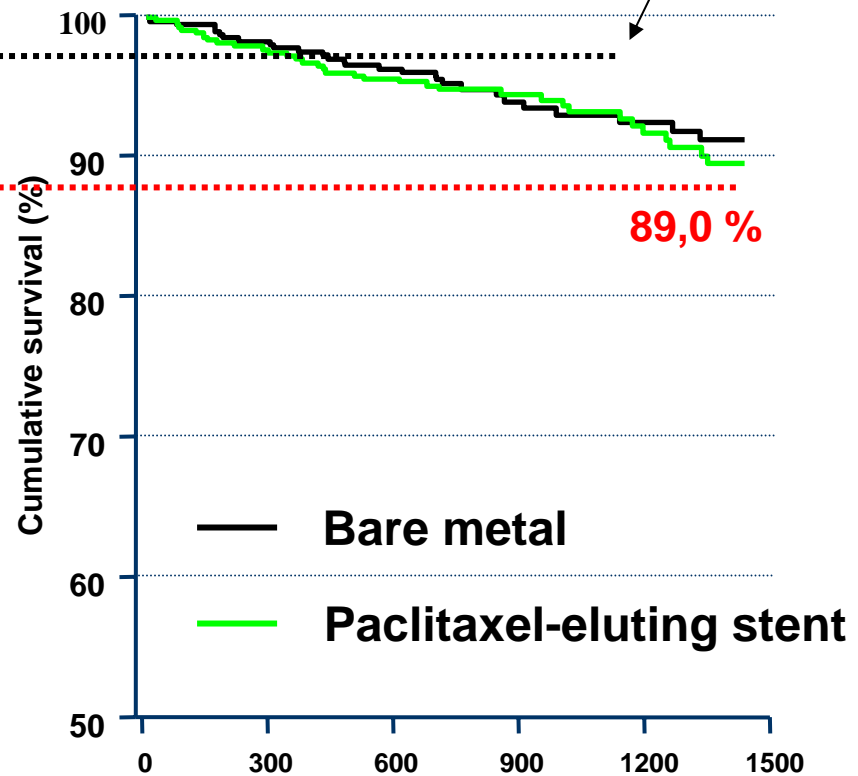
BMS mortality in the
SES trials
exceptionally low

Cypher trials (n=428)



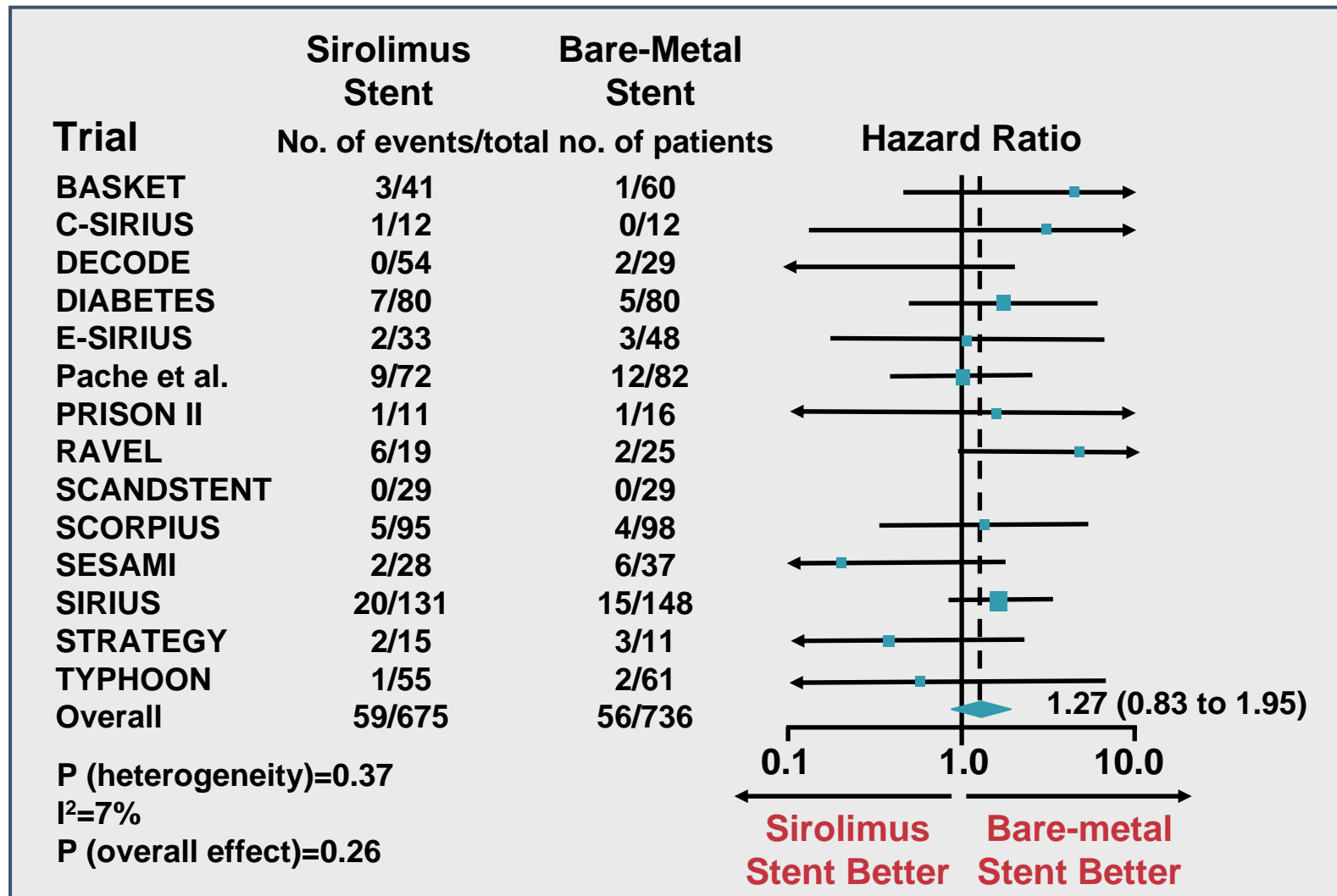
Pooled patient level based analysis of 4-year
f/u of RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS

TAXUS trials (n=814)



Pooled patient level based analysis of TAXUS II (4
yr) , IV (4 yr), V (2yr), VI (3 yr)

Hazard Ratios for Death in Patients with Diabetes Summary of 14 BMS vs SES RCTs

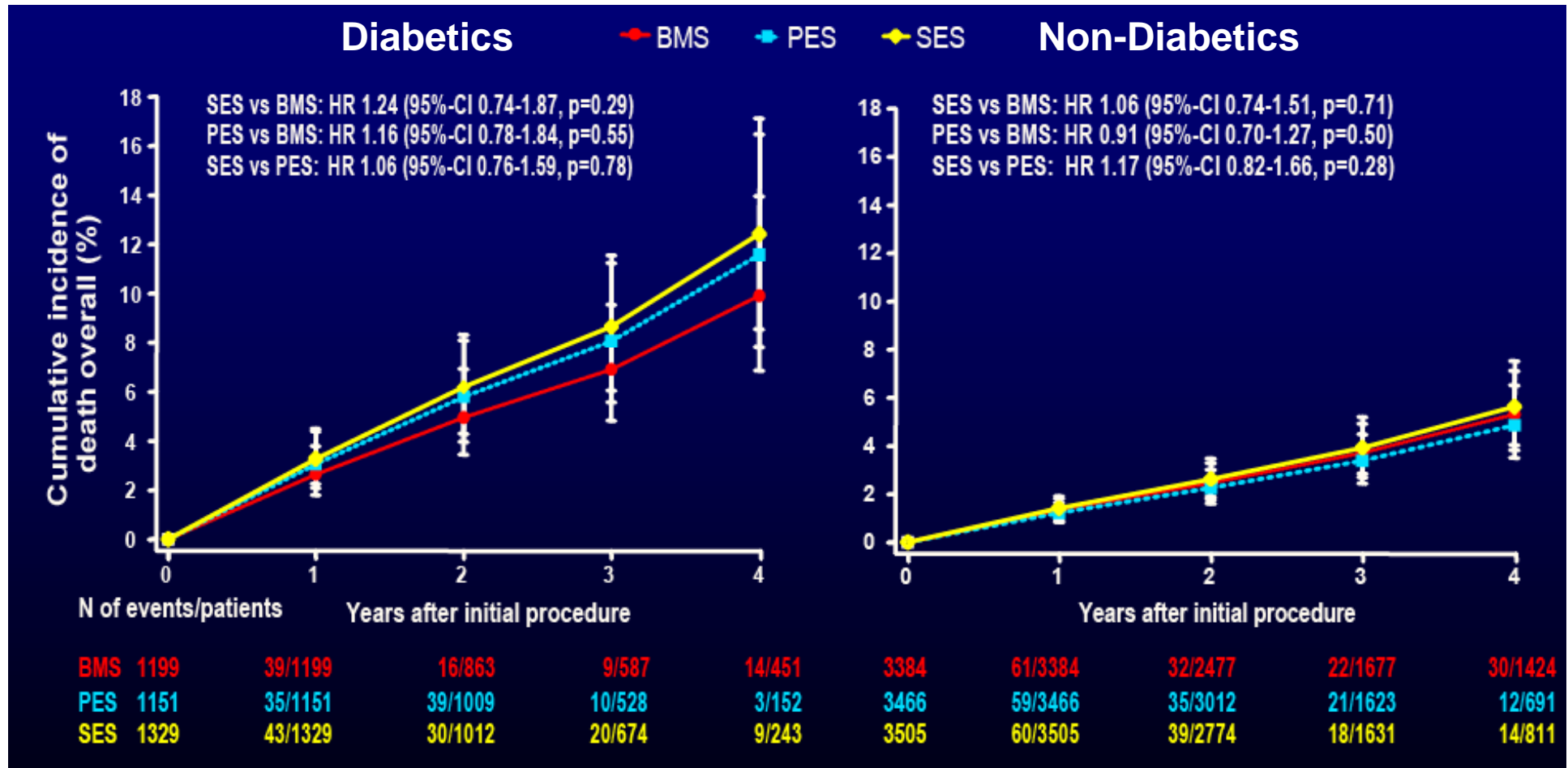


Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis

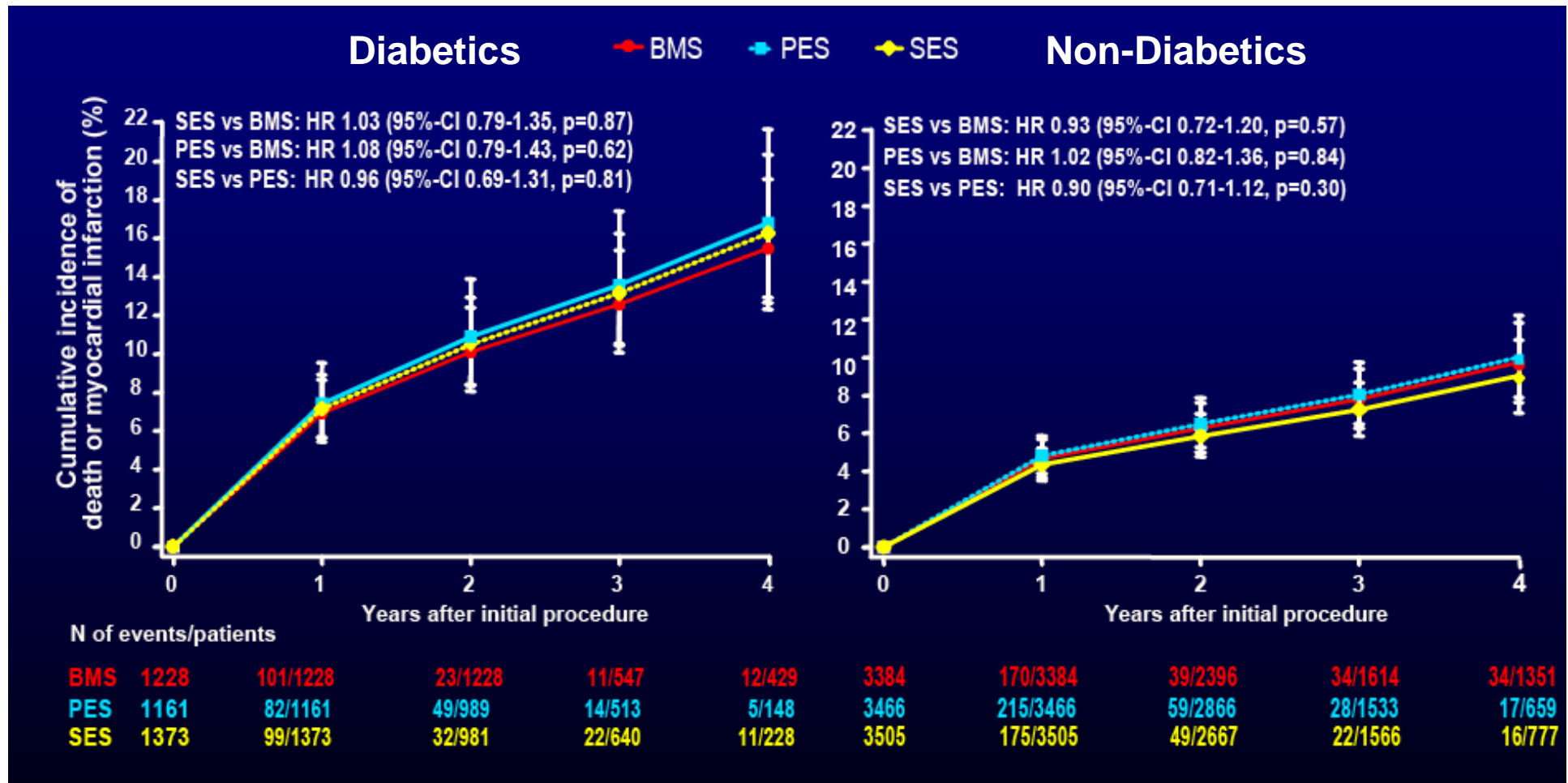
Christoph Stettler, Simon Wandel,* Sabin Allemann, Adnan Kastrati, Marie Claude Morice, Albert Schömig, Matthias E Pfisterer, Gregg W Stone, Martin B Leon, José Suarez de Lezo, Jean-Jacques Goy, Seung-Jung Park, Manel Sabaté, Maarten J Suttorp, Henning Kelbaek, Christian Spaulding, Maurizio Menichelli, Paul Vermeersch, Maurits T Dirksen, Pavel Cervinka, Anna Sonia Petronio, Alain J Nordmann, Peter Diem, Bernhard Meier, Marcel Zwahlen, Stephan Reichenbach, Sven Trelle, Stephan Windecker, Peter Jüni*

Stettler C., et al., Lancet 2007;370:937-48.

Cumulative Incidence of Overall Death: DM vs. Non-DM (N=3,762)

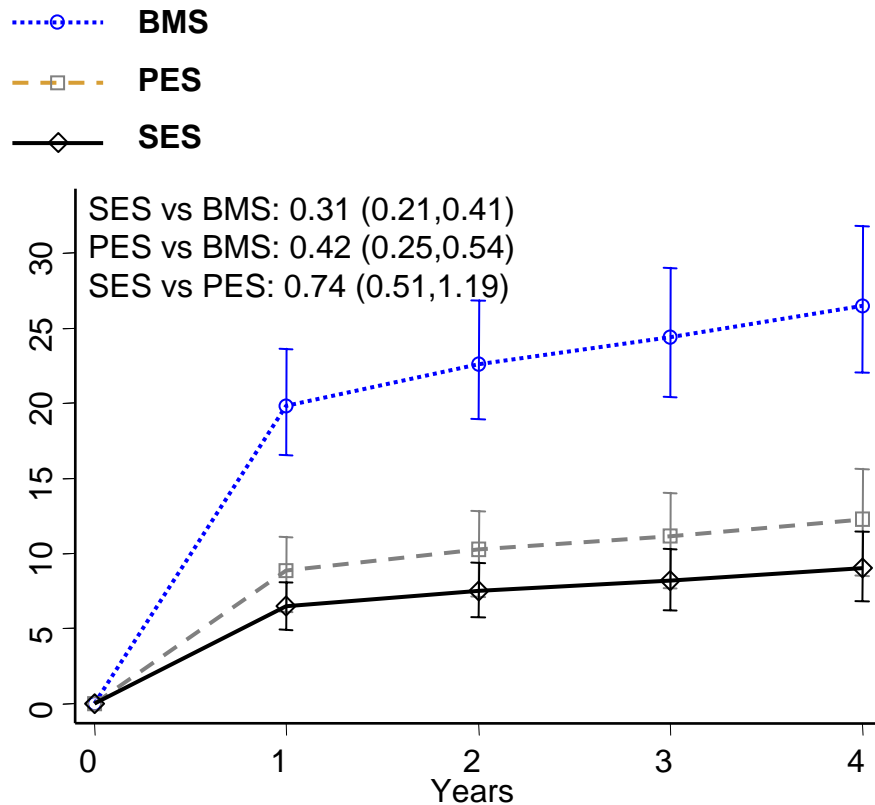


Cumulative Incidence of Overall Death or MI: DM vs. Non-DM (N=3,762)



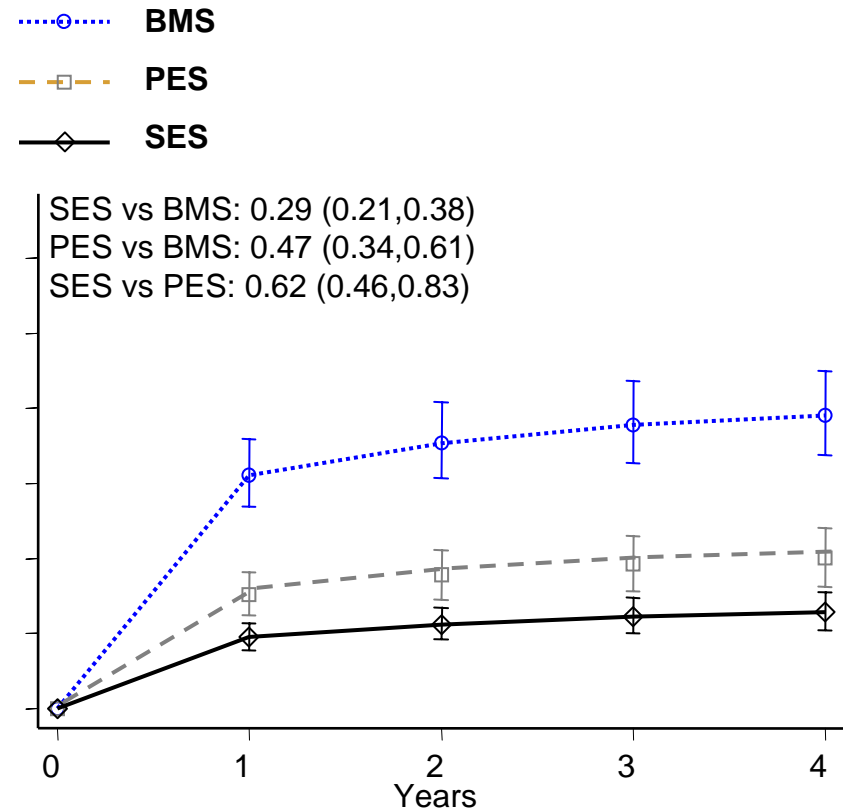
Target Lesion Revascularization

Diabetic Patients



| | | | | | |
|------------|------|------|-----|-----|-----|
| BMS | 1228 | 1228 | 667 | 451 | 348 |
| PES | 1161 | 1161 | 942 | 486 | 146 |
| SES | 1373 | 1373 | 947 | 606 | 219 |

Non-Diabetic Patients

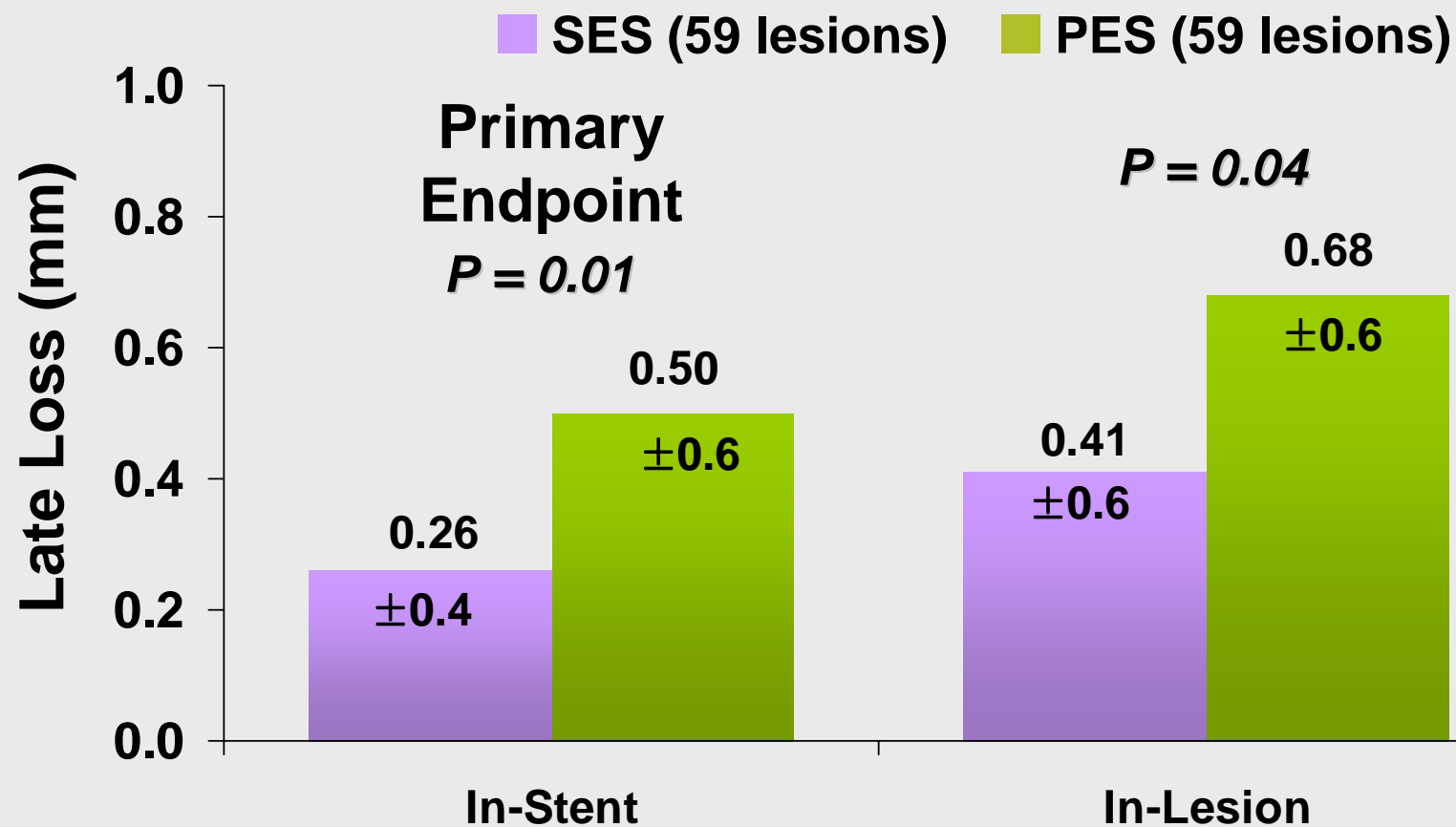


| | | | | | |
|------------|------|------|------|------|------|
| BMS | 3384 | 3384 | 2128 | 1420 | 1195 |
| PES | 3466 | 3466 | 2776 | 1477 | 660 |
| SES | 3505 | 3505 | 2614 | 1512 | 753 |

Comparison of Both TAXUS and Cypher in Same Diabetic Patients

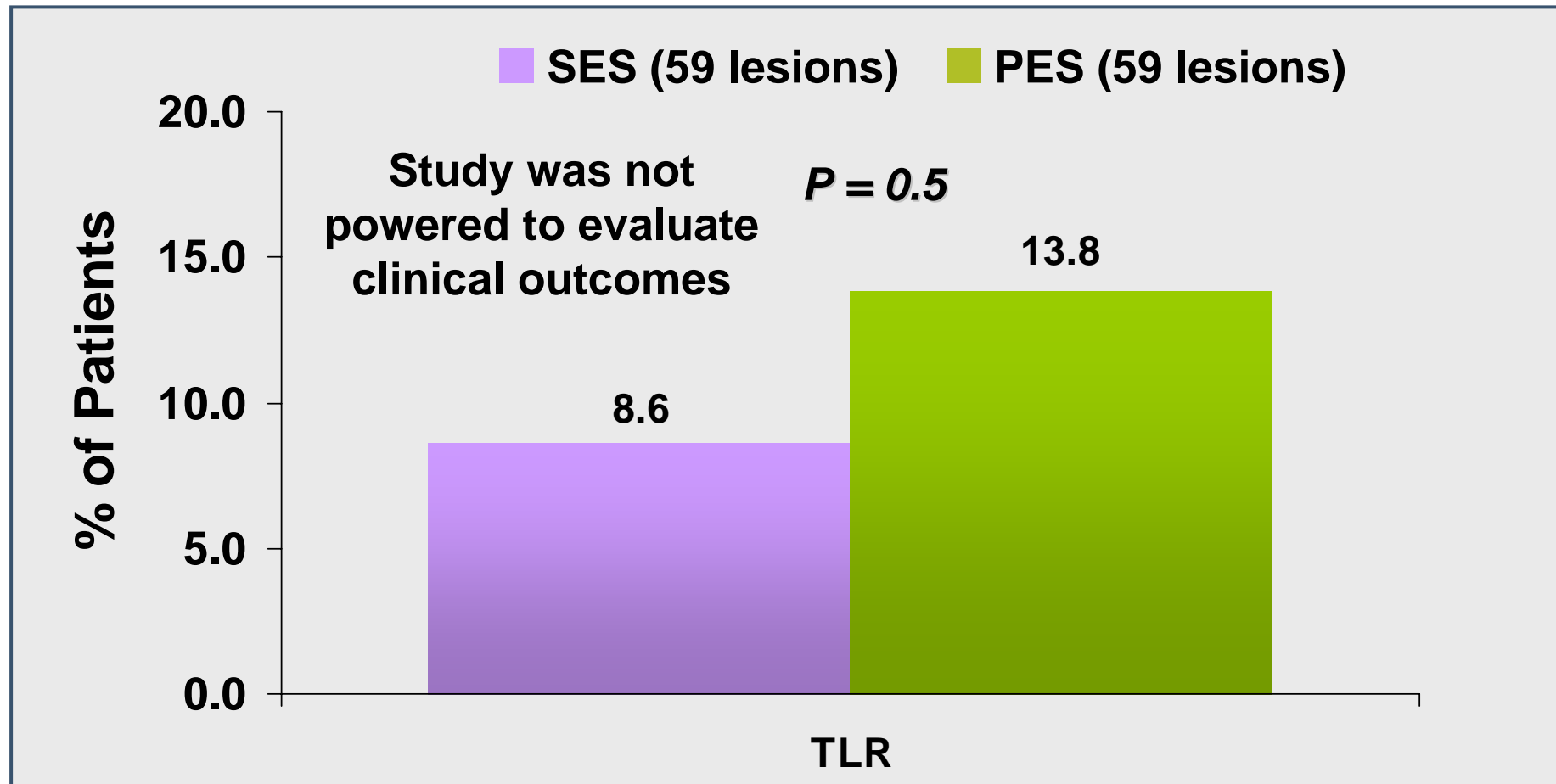
- › Prospective, multi-center (5 Italian centers) randomized study
- › Purpose:
 - Compare the efficacy in prevention of restenosis of SES and PES, both implanted in the same diabetic patient with multiple de novo coronary artery lesions undergoing elective PCI
- › 60 patients with diabetes with ≥ 2 significant de novo stenoses in different coronary segments
- › Primary end point:
 - In-stent late luminal loss (LLL) at 8-month angiographic follow-up

Late Loss at 8-Month Follow-up in Lesions Treated with either SES or PES in the Same Diabetic Patients with Multi-Vessel Disease



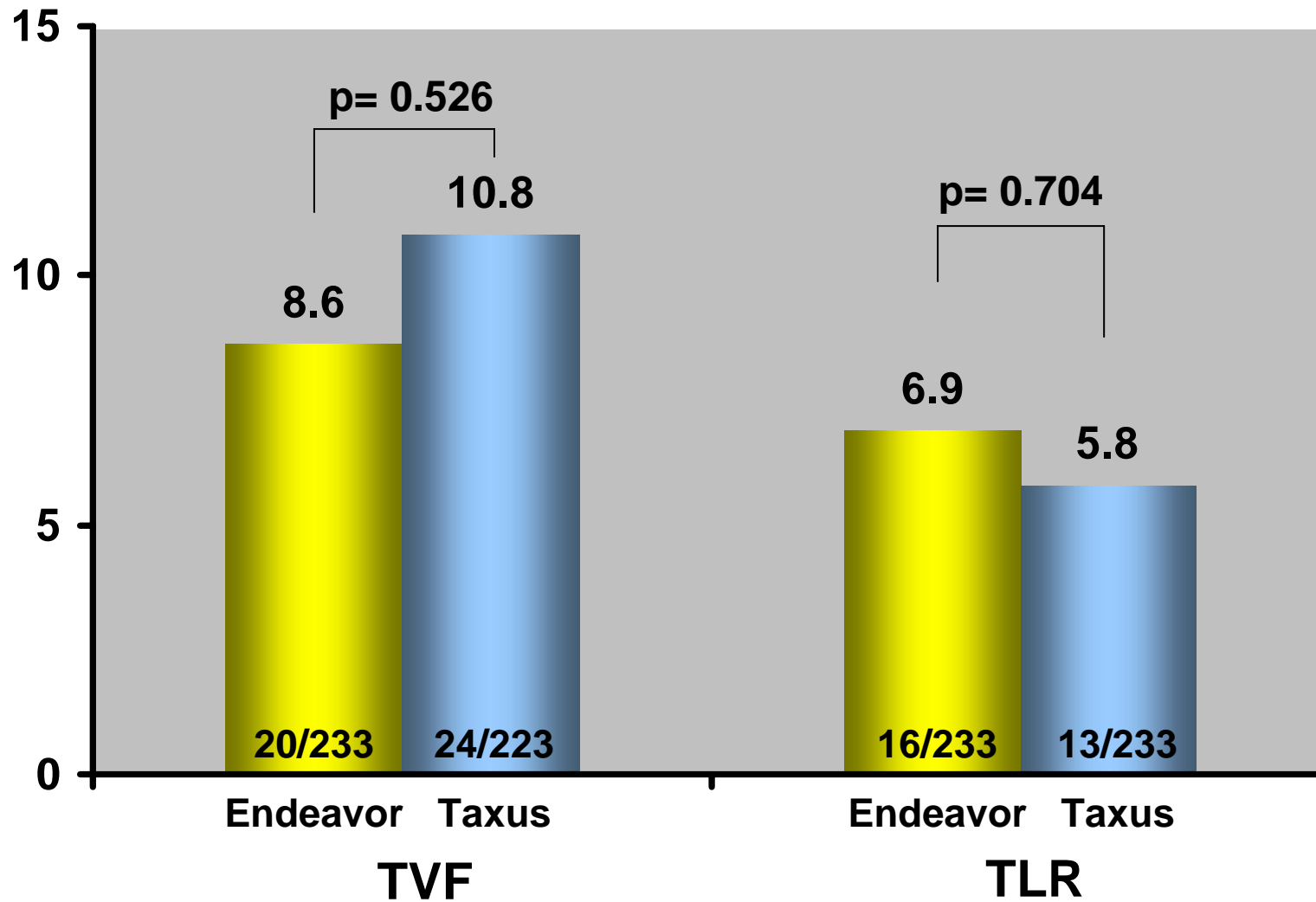
At multivariable analysis, type of DES implanted was the only independent predictor of in-stent LLL (odds ratio 2.3 [95% CI 1.1–5.0]; $P = 0.03$)

TLR at 8-Month Follow-up in Lesions Treated with either SES or PES in the Same Diabetic Patients with Multi-Vessel Disease



ENDEAVOR IV

TVF and TLR at 12 Months: Diabetes Subgroup

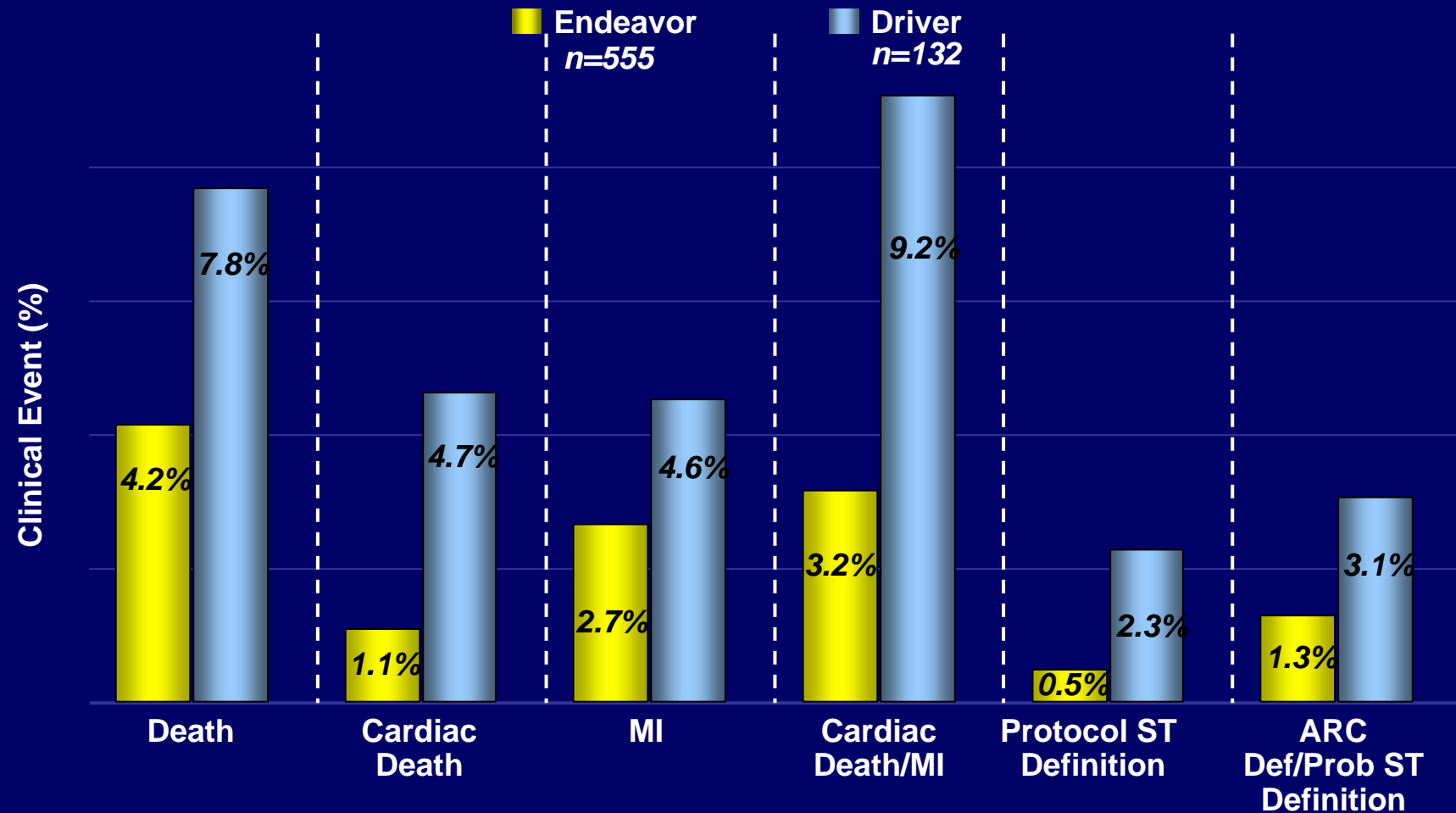


477 diabetic patients (30.8%)

Leon M. et al., Oral Presentation, *TCT 2007*.

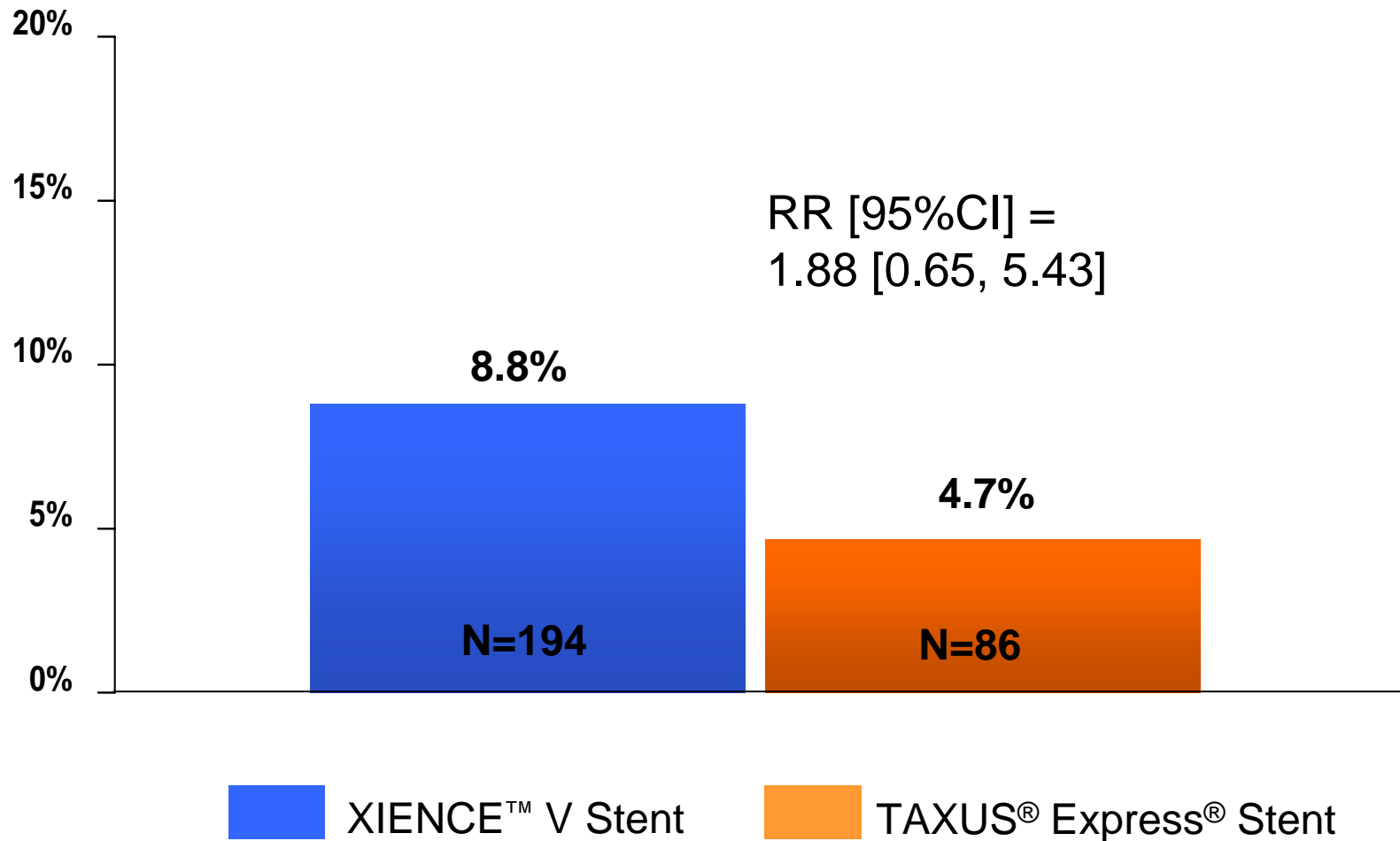
Endeavor Safety Summary: Diabetics

Cumulative Incidence of Safety Endpoints to 1080 Days



SPIRIT III

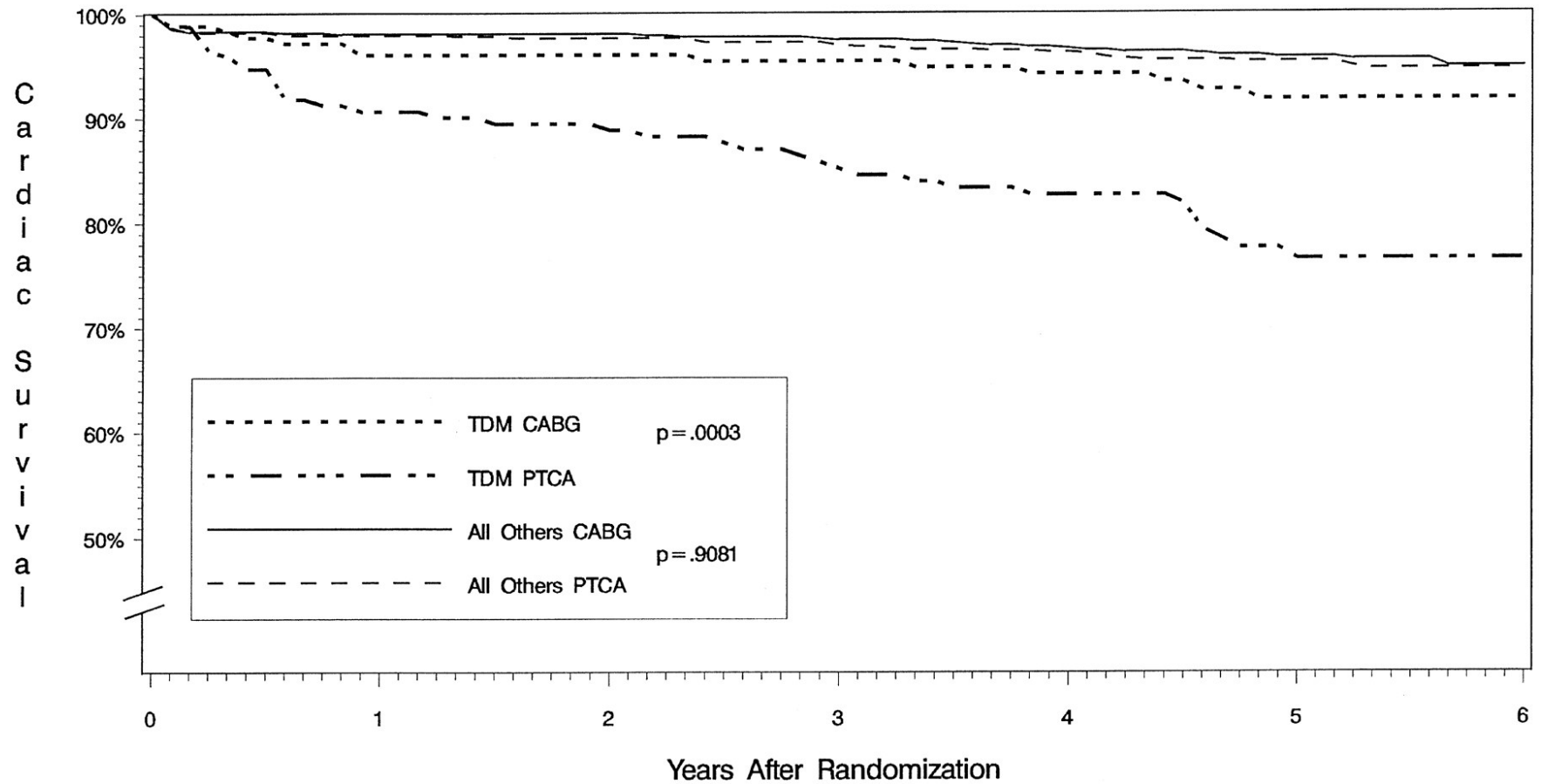
1-Year MACE in Diabetic Subgroup



Presented by Gregg W. Stone MD, TCT 2007. * = Median; single lesion subgroup. Caution – XIENCE V Stent is an investigational Device. Limited by federal law to investigational use. Not available for sale in the U.S. The safety and effectiveness of the TAXUS® Stent have not been established in patients presenting with diabetes, with reference vessel diameters < 2.5 mm, or in lesions longer than 28mm in length. MACE = cardiac death, MI, or ischemia-driven TLR

BARI: CABG vs PTCA

Long-term Survival in Diabetes Following Revascularization



BARI Investigators, T. B.
Circulation 1997;96:1761-1769

ARTS II Diabetic Population

| Hierarchical MACCE (3 years) | ARTS II N=159 patients | ARTS I (CABG) N=96 patients | ARTS I (PCI) N=112 patients |
|---------------------------------|---------------------------|-----------------------------------|--------------------------------|
| Death | 8 (5%) | 5 (5.2%) | 8 (7.1%) |
| Stroke* | 4 (2.5%) | 5 (5.2%) | 5 (4.5%) |
| Myocardial Infarction** | 3 (1.9%) | 3 (3.1%) | 8 (7.1%) |
| CABG*** | 6 (3.8%) | 0 (0.0%) | 11 (9.8%) |
| Repeat PCI**** | 23 (14.5%) | 4 (4.2%) | 21 (18.8%) |
| MACCE | 44 (27.7%) | 17 (17.7%) | 53 (47.3%) |
| Stent Thrombosis | 2 (1.3%) | – | 8 (7.1%) |

*Without Death**

*Without Death & Stroke***

*Without Death, Stroke & AMI****

*Without Death, Stroke, AMI or CABG*****

Figures in Red indicate statistical difference (95% CI) between ARTS II and ARTS I groups

Ongoing DES vs. CABG Randomized Trials

› SYNTAX

1,500 pts with 3 vessel CAD and/or LM disease

Randomization: Surgery vs. PCI (Taxus); nested PCI and CABG registries

Primary Endpoint: Noninferiority 1y MACCE

Estimated presentation: ESC 2008

› CARDIA

512 Diabetics with multivessel coronary disease

Randomization: Surgery vs. PCI (Cypher)

Primary Endpoint: Noninferiority 1y MACCE

Estimated presentation: ESC 2008

› FREEDOM

2,058 (~1200 2/2008) Diabetics with multivessel coronary disease

Randomization: Surgery vs. PCI (Cypher, Taxus)

Primary Endpoint: Superiority ~3y (5y duration) MACCE

Summary

Safety of DES in Diabetes

- › DES does not exclude a higher risk among diabetics of death, MI, restenosis and stent thrombosis c/w non-DM
- › There are multiple local and systemic mechanisms that account for these higher risks
- › Compared with BMS, use of DES has clearly reduced the risk of restenosis but not consistently decreased risk of death, MI or ST
- › Comparisons between DES overall suggest no significant differences in safety or efficacy metrics due to flawed trial design, errors in multiple comparisons and limited sample size
- › Considering emerging diabetes epidemic in PCI population, a DES with clear superiority in diabetes would have tremendous impact