# The Preponderance of Data Favors CYPHER
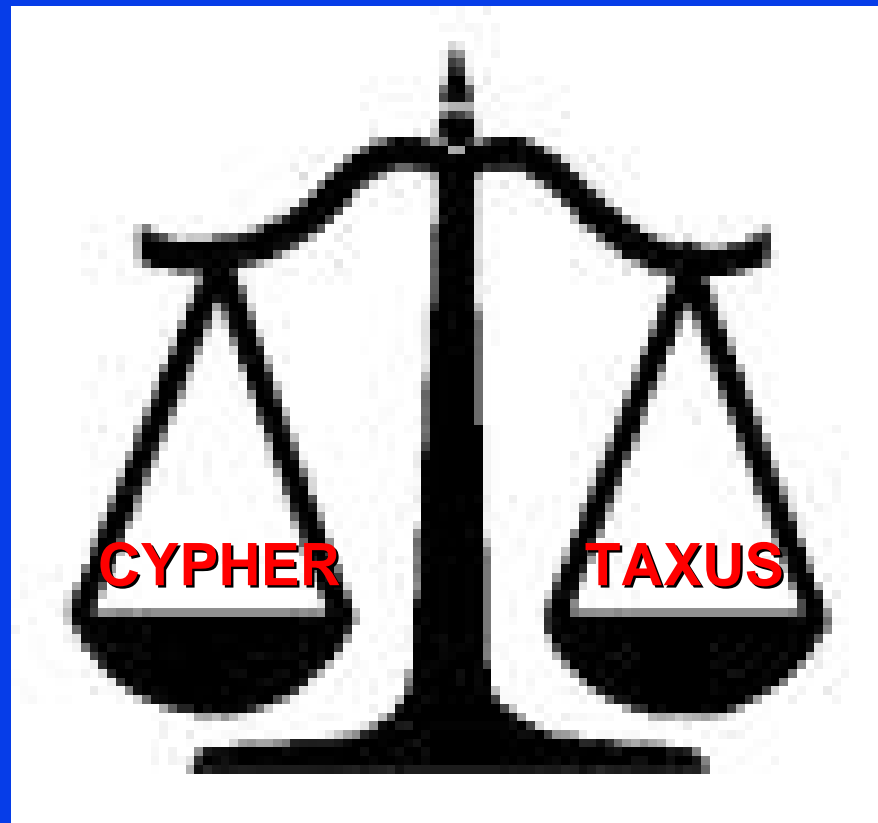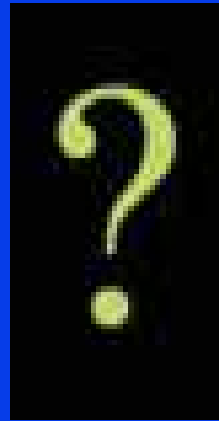
## Angioplasty Summit 2006
## Seoul, Korea

### David R. Holmes, MD
**Mayo Clinic**
**Rochester, MN**

MAYO CLINIC

# How Do We Compare

CYPHER          TAXUS

MAYO CLINIC

# 1 Corinithians

- **If I speak in the tongues of men and angels, but have no love, I am only a resounding gong.**

- **If I speak in the tongues of men and angels but have no RCT data, I am clueless.**

MAYO CLINIC

# How Do We Compare DES
## What Metrics?

**Early**

- Deliverability
- Efficacy
- Safety
- Costs

**Late**

- Physiology, LL
- Angiography, RR
- Efficacy
  Clinical restenosis
  TLR vs TVR
- Safety
- Costs

**Superiority, non-inferiority, concordance?**

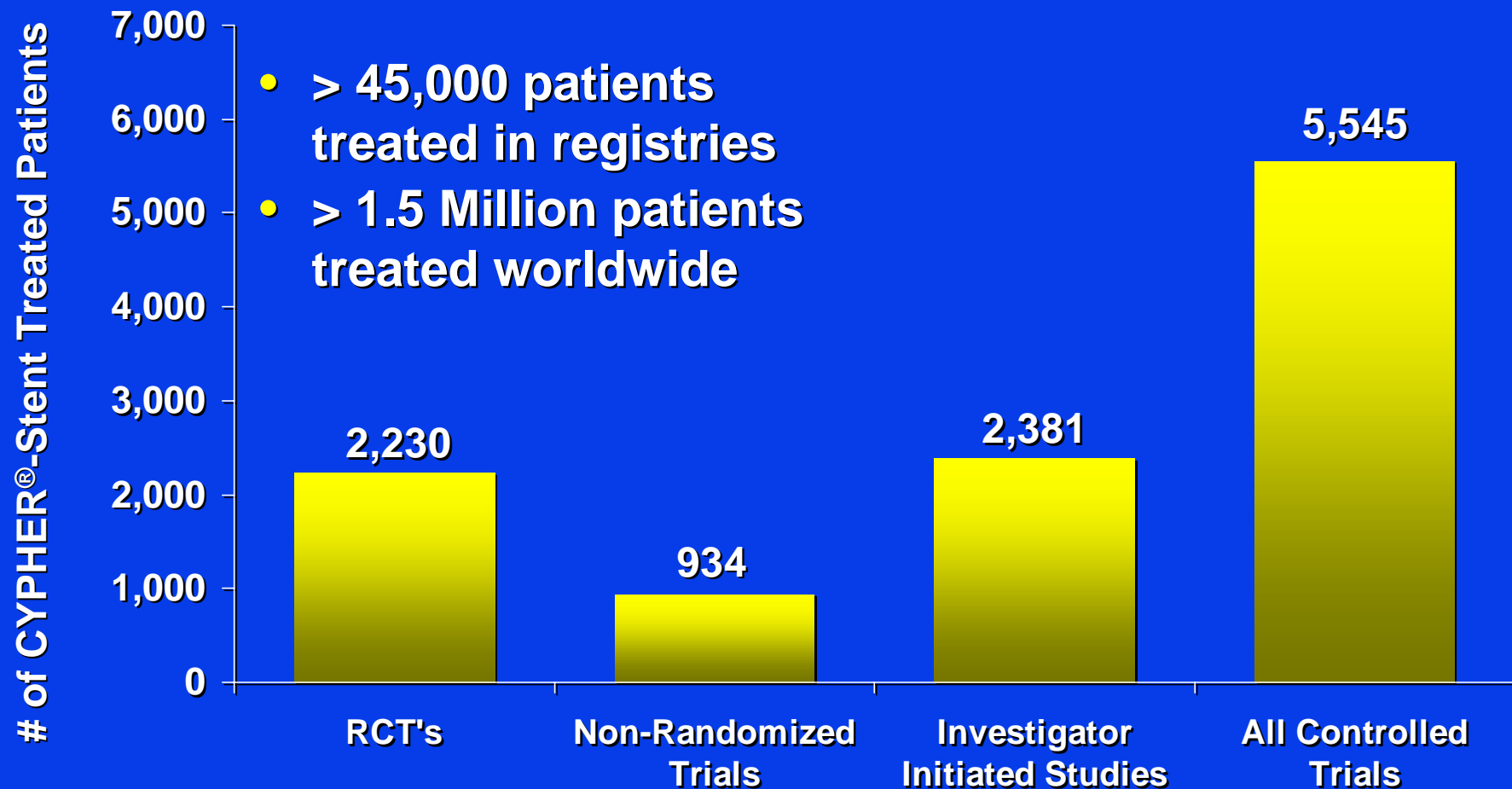MAYO CLINIC

# What Do We Need?

- **1a.  Systematic review RCT's**
- **1b.  Individual RCT's**
- **2a.   Systematic review of cohort studies**
- **2b.  Individual Cohorts**
- **3.    Case control studies, review or single**
- **4.    Case series**
- **5.    Expert opinion**
- **6.    Bah Humbug**

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# A P-value does not substitute for a brain

**Statistics . . . will prove anything, even the truth**

Sir Berkeley Moynihan 1865-1936

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# Number of CYPHER® Stent Treated Patients

- > 45,000 patients treated in registries
- > 1.5 Million patients treated worldwide



Bar chart — # of CYPHER®-Stent Treated Patients:
- RCT's: 2,230
- Non-Randomized Trials: 934
- Investigator Initiated Studies: 2,381
- All Controlled Trials: 5,545

* RCT: RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, REALITY, SISR, DECODE, TYPHOON
NRCT: FIM, SVELTE, SIRIUS 2.25, SIRIUS 4.0, ARTS II
IIS's: SES-SMART, Park LL, DIABetes, TAXi, SIRTAX, ISAR-Diabetes, ISAR-DESIRE, CORPAL, BASKET, RIBS-II, PORTO I, PORTO II, SVELTE
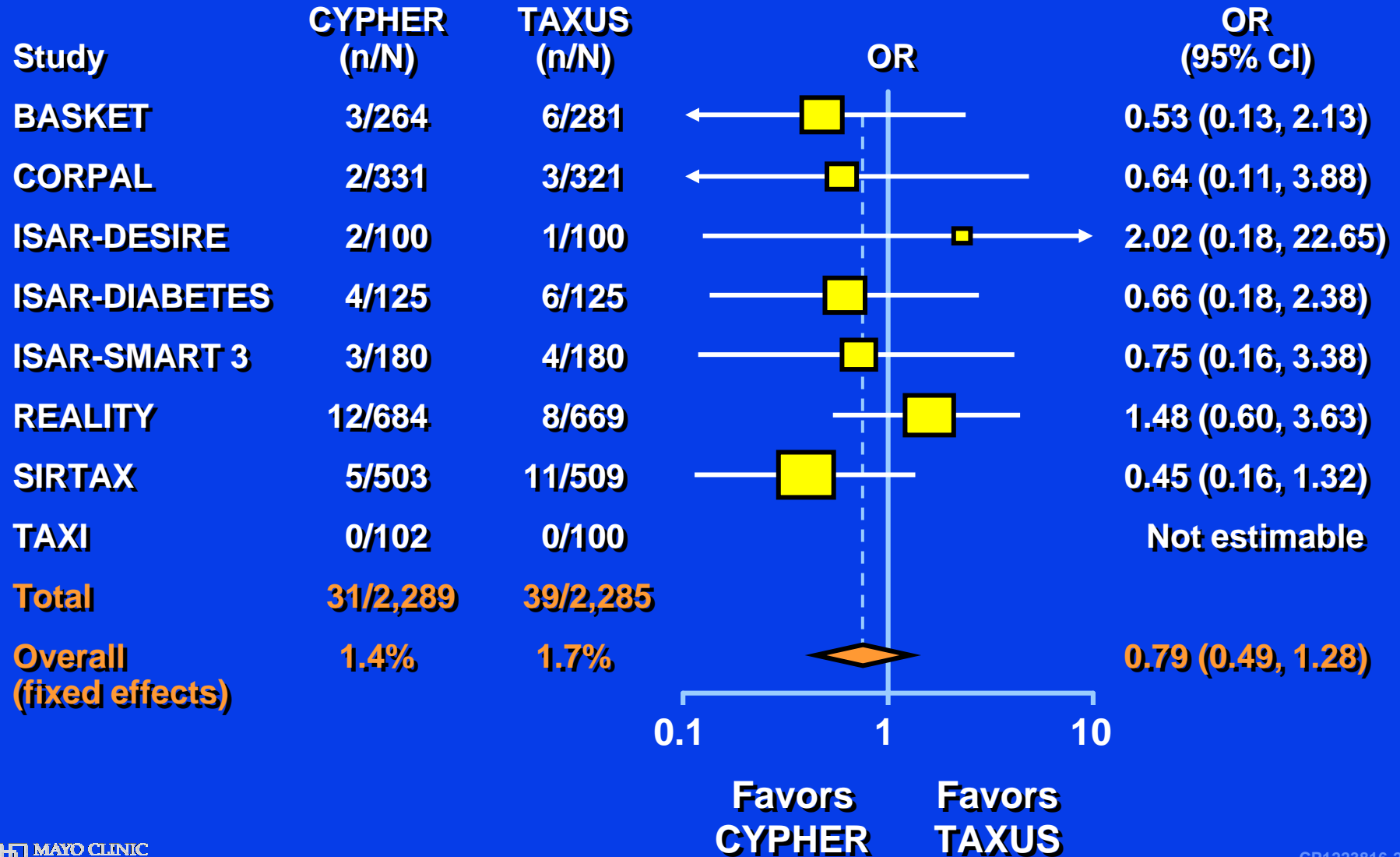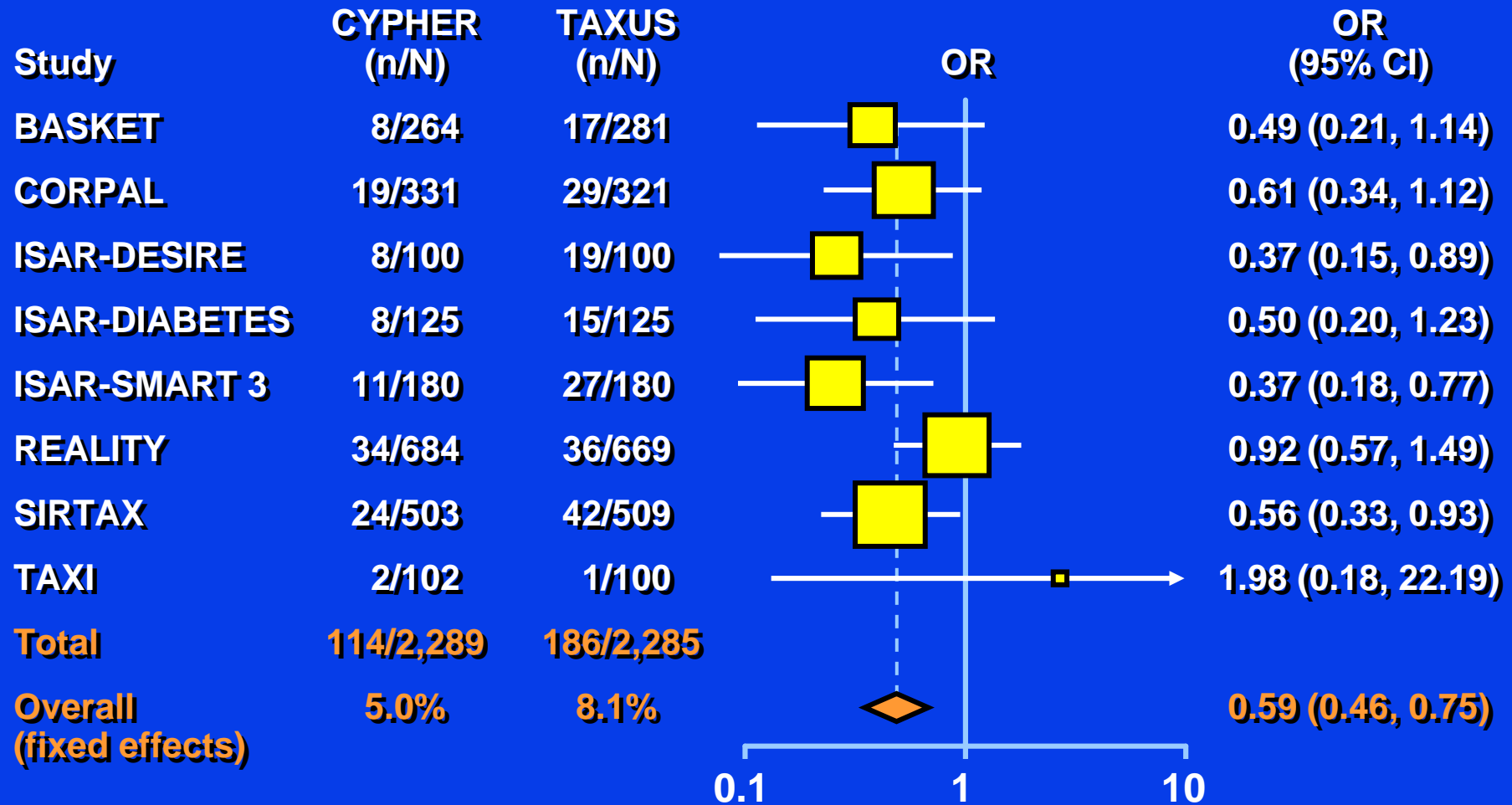
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# Randomized Studies

| Trial | Patients | |
| --- | --- | --- |
| | CYPHER | TAXUS |
| BASKET, Lancet, 2005 | 264 | 281 |
| CORPAL, ACC, 2005 | 331 | 321 |
| ISAR-DESIRE, JAMA, 2005 | 100 | 100 |
| ISAR-DIABETES, NEJM, 2005 | 125 | 125 |
| ISAR-SMART 3, EHJ, 2006 | 180 | 180 |
| REALITY, ACC, 2005 | 684 | 669 |
| SIRTAX, NEJM, 2005 | 503 | 509 |
| TAXI, JACC, 2005 | 102 | 100 |
| Total | 2,289 | 2,285 |

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## Mortality
## Randomized Trials: CYPHER vs TAXUS

| Study | CYPHER (n/N) | TAXUS (n/N) | OR | OR (95% CI) |
|---|---|---|---|---|
| BASKET | 3/264 | 6/281 | | 0.53 (0.13, 2.13) |
| CORPAL | 2/331 | 3/321 | | 0.64 (0.11, 3.88) |
| ISAR-DESIRE | 2/100 | 1/100 | | 2.02 (0.18, 22.65) |
| ISAR-DIABETES | 4/125 | 6/125 | | 0.66 (0.18, 2.38) |
| ISAR-SMART 3 | 3/180 | 4/180 | | 0.75 (0.16, 3.38) |
| REALITY | 12/684 | 8/669 | | 1.48 (0.60, 3.63) |
| SIRTAX | 5/503 | 11/509 | | 0.45 (0.16, 1.32) |
| TAXI | 0/102 | 0/100 | | Not estimable |
| Total | 31/2,289 | 39/2,285 | | |
| Overall (fixed effects) | 1.4% | 1.7% | | 0.79 (0.49, 1.28) |

Favors CYPHER    Favors TAXUS

# Clinical Restenosis – Need for Reintervention
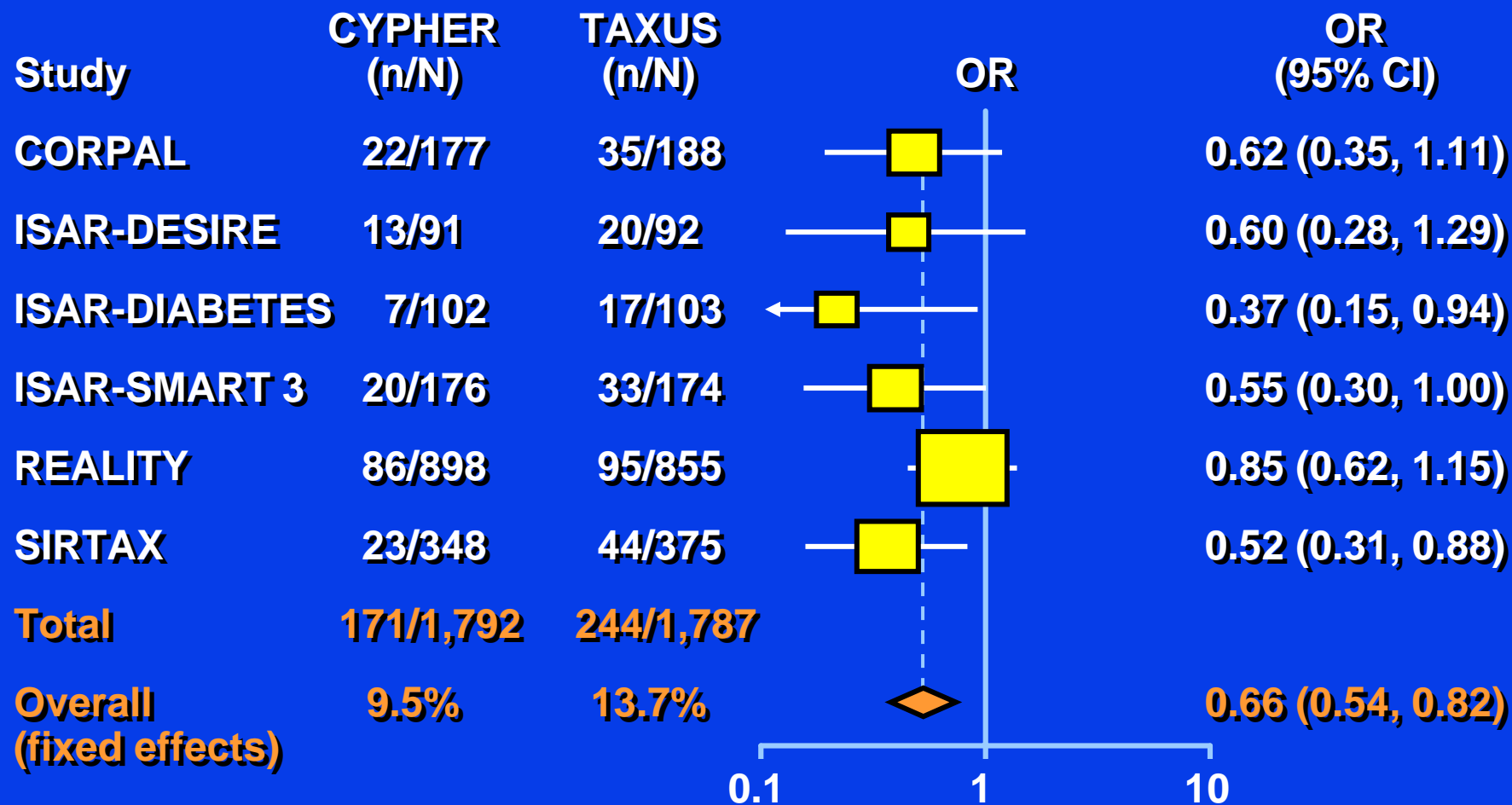
| Study | CYPHER (n/N) | TAXUS (n/N) | OR | OR (95% CI) |
|---|---|---|---|---|
| BASKET | 8/264 | 17/281 | | 0.49 (0.21, 1.14) |
| CORPAL | 19/331 | 29/321 | | 0.61 (0.34, 1.12) |
| ISAR-DESIRE | 8/100 | 19/100 | | 0.37 (0.15, 0.89) |
| ISAR-DIABETES | 8/125 | 15/125 | | 0.50 (0.20, 1.23) |
| ISAR-SMART 3 | 11/180 | 27/180 | | 0.37 (0.18, 0.77) |
| REALITY | 34/684 | 36/669 | | 0.92 (0.57, 1.49) |
| SIRTAX | 24/503 | 42/509 | | 0.56 (0.33, 0.93) |
| TAXI | 2/102 | 1/100 | | 1.98 (0.18, 22.19) |
| Total | 114/2,289 | 186/2,285 | | |
| Overall (fixed effects) | 5.0% | 8.1% | | 0.59 (0.46, 0.75) |

0.1    1    10

Favors CYPHER    Favors TAXUS

JAMA, 2005; Lancet, 2005; EHJ, 2006

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CP1223816-17

# Angiographic Restenosis

| Study | CYPHER (n/N) | TAXUS (n/N) | OR | OR (95% CI) |
|---|---|---|---|---|
| CORPAL | 22/177 | 35/188 | | 0.62 (0.35, 1.11) |
| ISAR-DESIRE | 13/91 | 20/92 | | 0.60 (0.28, 1.29) |
| ISAR-DIABETES | 7/102 | 17/103 | | 0.37 (0.15, 0.94) |
| ISAR-SMART 3 | 20/176 | 33/174 | | 0.55 (0.30, 1.00) |
| REALITY | 86/898 | 95/855 | | 0.85 (0.62, 1.15) |
| SIRTAX | 23/348 | 44/375 | | 0.52 (0.31, 0.88) |
| Total | 171/1,792 | 244/1,787 | | |
| Overall (fixed effects) | 9.5% | 13.7% | | 0.66 (0.54, 0.82) |

Favors CYPHER    Favors TAXUS

JAMA, 2005; Lancet, 2005; EHJ, 2006

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CP1223816-16
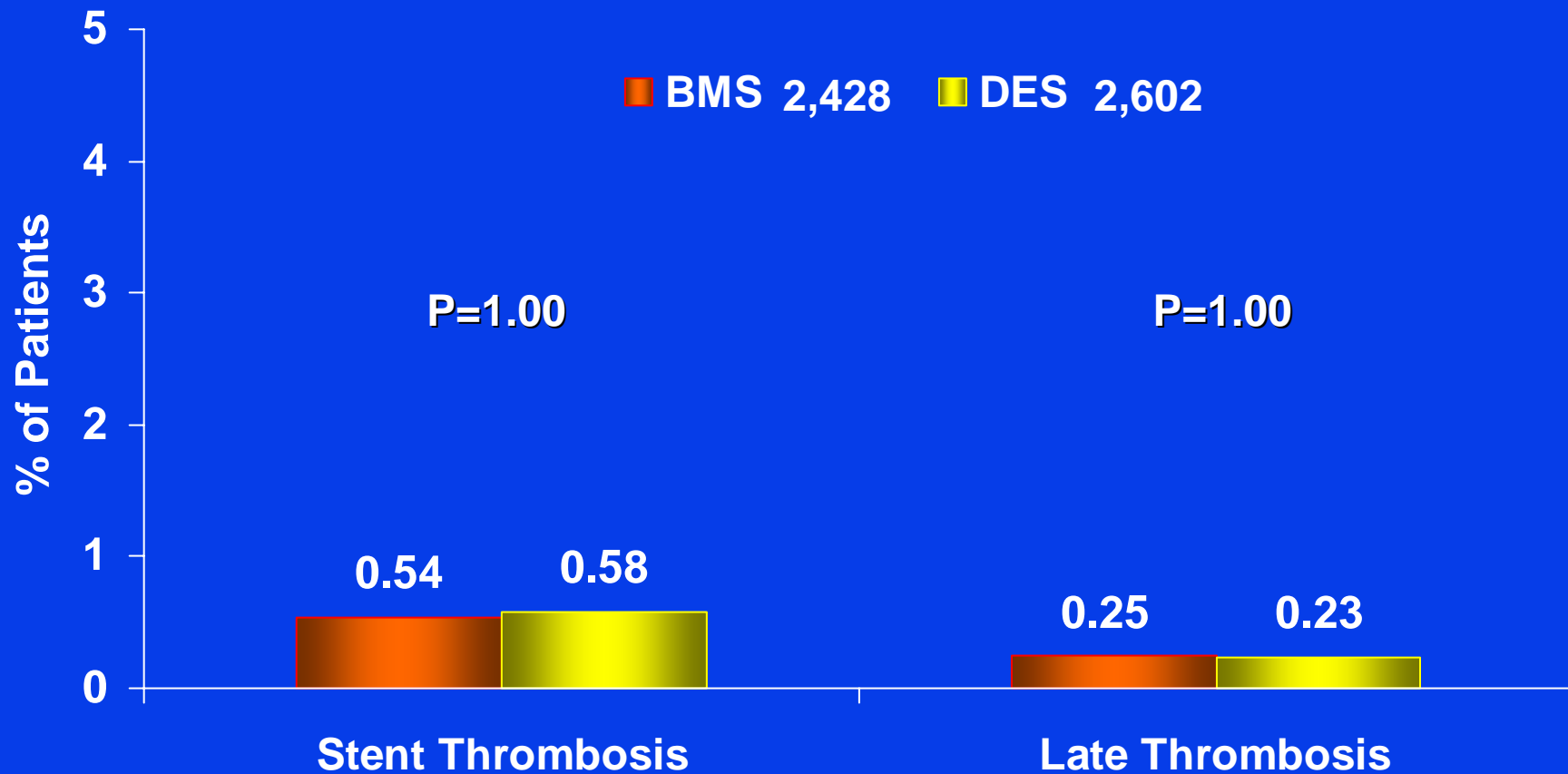
# Stent Thrombosis
## Registry Studies:  CYPHER vs TAXUS

| Study | CYPHER (n/N) | TAXUS (n/N) | OR | OR (95% CI) |
|---|---|---|---|---|
| Iakovou et al | 9/1,062 | 20/1,167 | | 0.49 (0.22, 1.08) |
| Kim et al | 0/184 | 0/166 | | Not estimable |
| RE- and T-SEARCH | 2/508 | 8/576 | | 0.28 (0.06, 1.33) |
| Total | 11/1,754 | 28/1,909 | | |
| Overall (fixed effects) | 0.6% | 1.5% | | 0.43 (0.21, 0.87) |

0.1    1    10

Favors CYPHER    Favors TAXUS

MAYO CLINIC

CP1223816-23
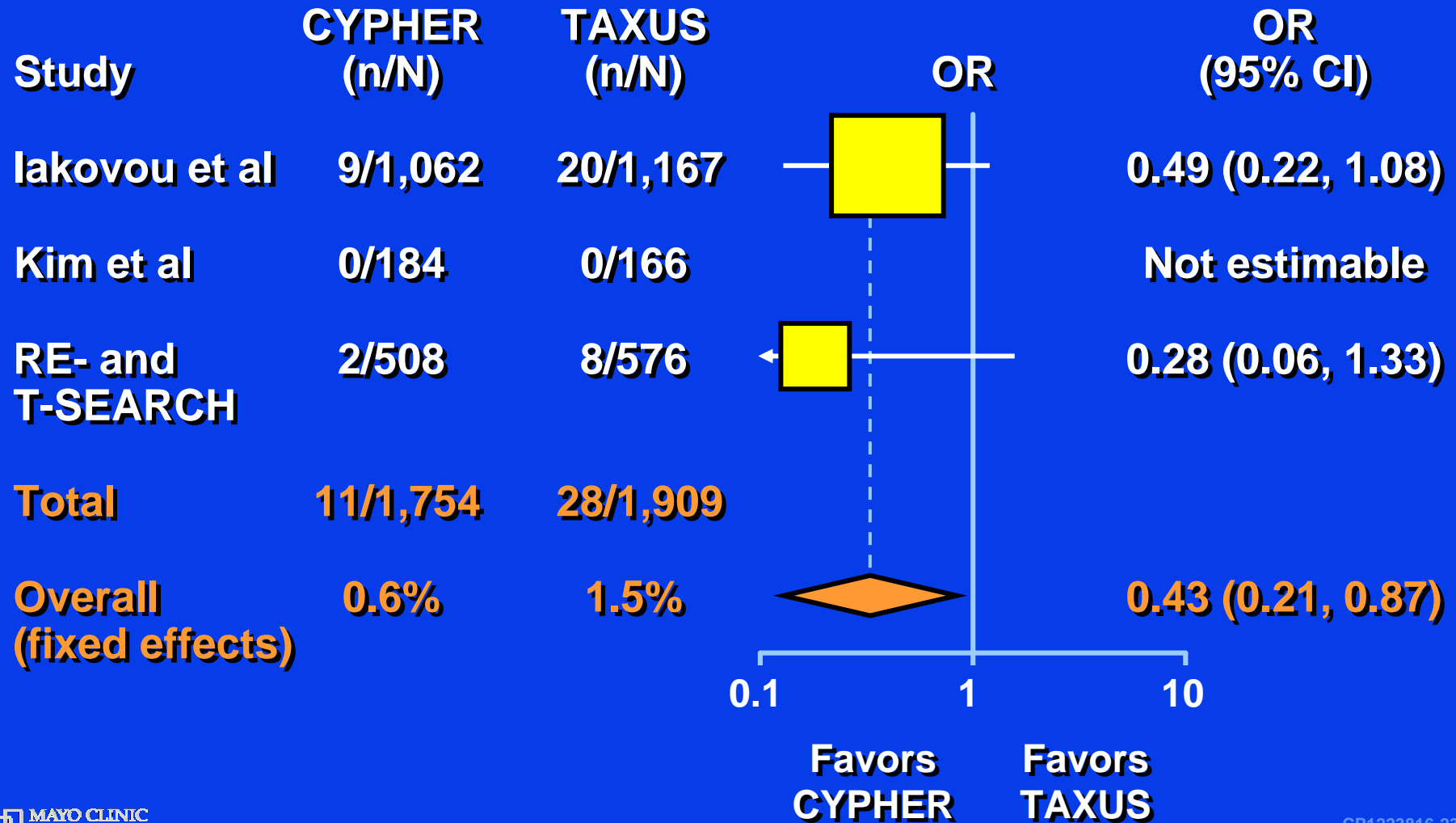
# Stent Thrombosis
## Randomized Trials:  CYPHER vs TAXUS
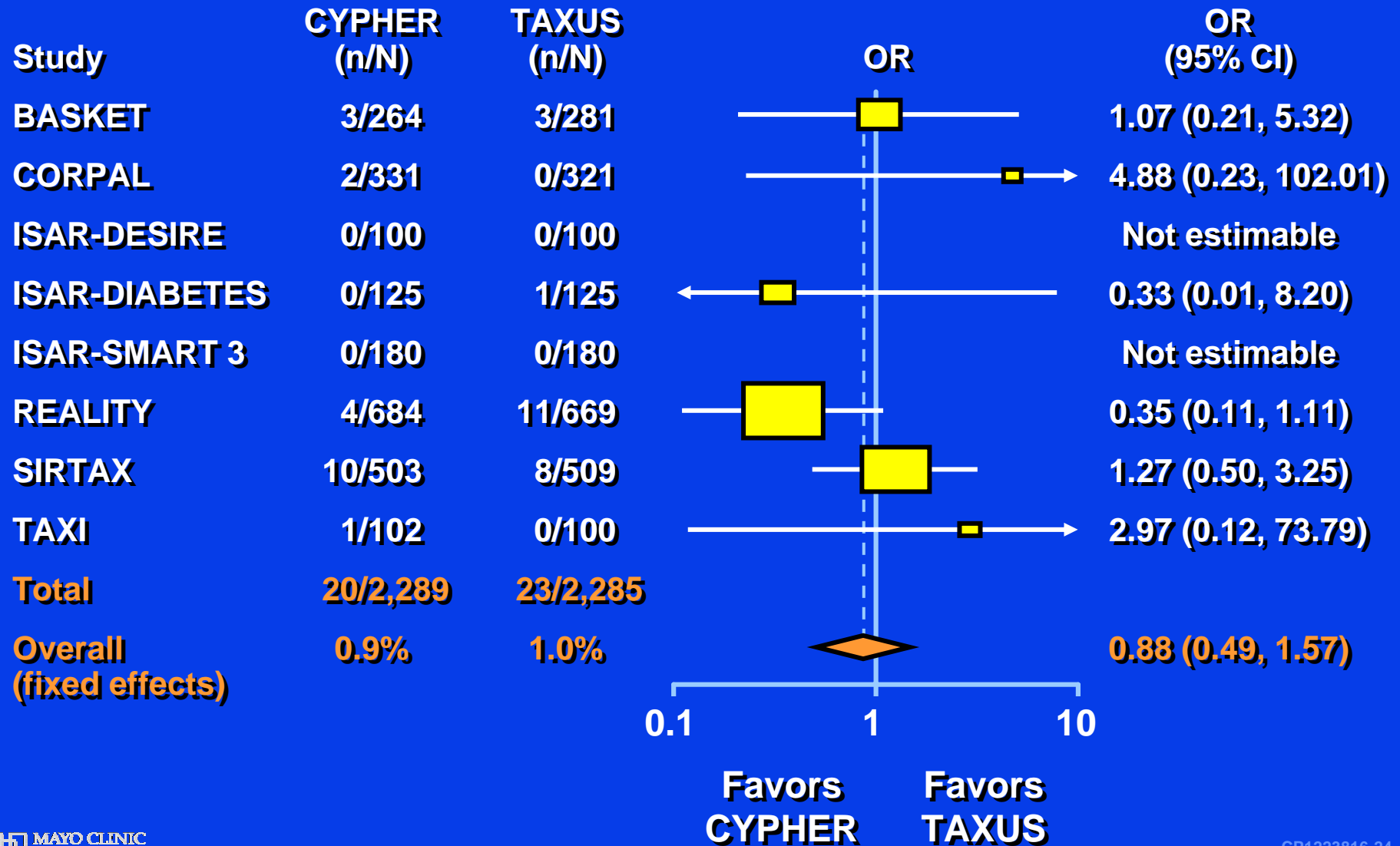
| Study | CYPHER (n/N) | TAXUS (n/N) | OR | OR (95% CI) |
|---|---|---|---|---|
| BASKET | 3/264 | 3/281 | | 1.07 (0.21, 5.32) |
| CORPAL | 2/331 | 0/321 | | 4.88 (0.23, 102.01) |
| ISAR-DESIRE | 0/100 | 0/100 | | Not estimable |
| ISAR-DIABETES | 0/125 | 1/125 | | 0.33 (0.01, 8.20) |
| ISAR-SMART 3 | 0/180 | 0/180 | | Not estimable |
| REALITY | 4/684 | 11/669 | | 0.35 (0.11, 1.11) |
| SIRTAX | 10/503 | 8/509 | | 1.27 (0.50, 3.25) |
| TAXI | 1/102 | 0/100 | | 2.97 (0.12, 73.79) |
| Total | 20/2,289 | 23/2,285 | | |
| Overall (fixed effects) | 0.9% | 1.0% | | 0.88 (0.49, 1.57) |

0.1    1    10

Favors CYPHER    Favors TAXUS

MAYO CLINIC

CP1223816-24
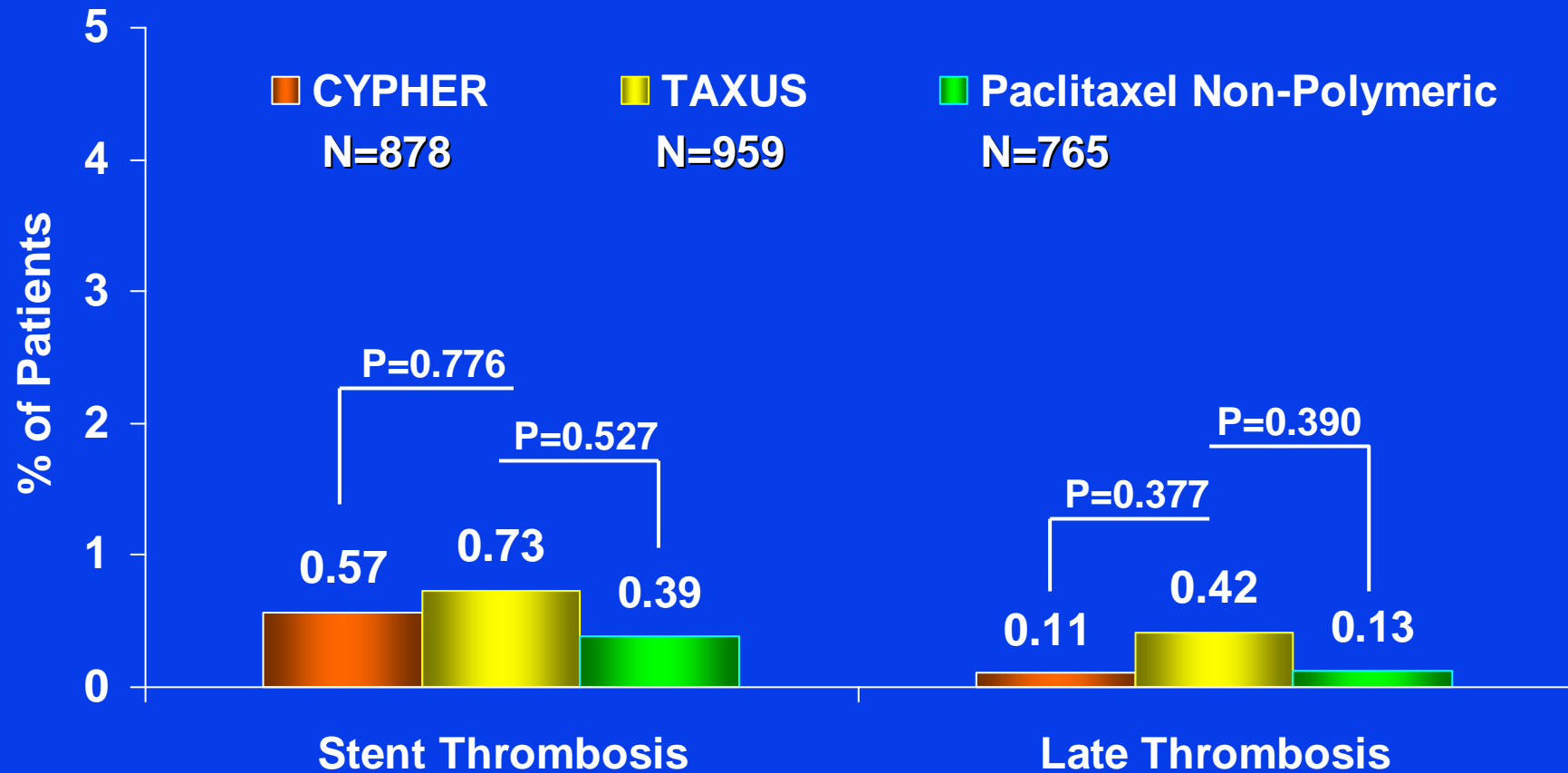
# Late Loss and DES

- **Late loss is measurable, albeit in subsets**
- **There are differences between drugs and devices tested**
- **Facilitates smaller trials**
- **Measures some aspects of physiology**

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# Late Loss is the Preferred Parameter for Evaluating Drug-Eluting Stent Performance

- Drug-eluting stents have reduced angio-graphic restenosis rates by 75% vs BMS

- Late loss enables direct comparison of biological response (suppression of neointimal hyperplasia)

- Late loss is a direct angiographic measure of the absolute amount of renarrowing, independent of vessel diameter

# CYPHER Sirolimus-Eluting Stent
## Consistently Lower Late Loss Than Any Other DES

**In-Stent Late Loss (Noncomparative Studies)**

mm

| Study | Late Loss (mm) |
|---|---|
| RAVEL[1] | 0.00 |
| SIRIUS[2] | 0.17 |
| NEW SIRIUS[3] | 0.18 |
| DIRECT[4] | 0.18 |
| II[5] | 0.31 |
| IV[6] | 0.39 |
| VI[7] | 0.39 |
| I[8] | 0.61 |
| II[9] | 0.62 |

CYPHER     TAXUS     ENDEAVOR
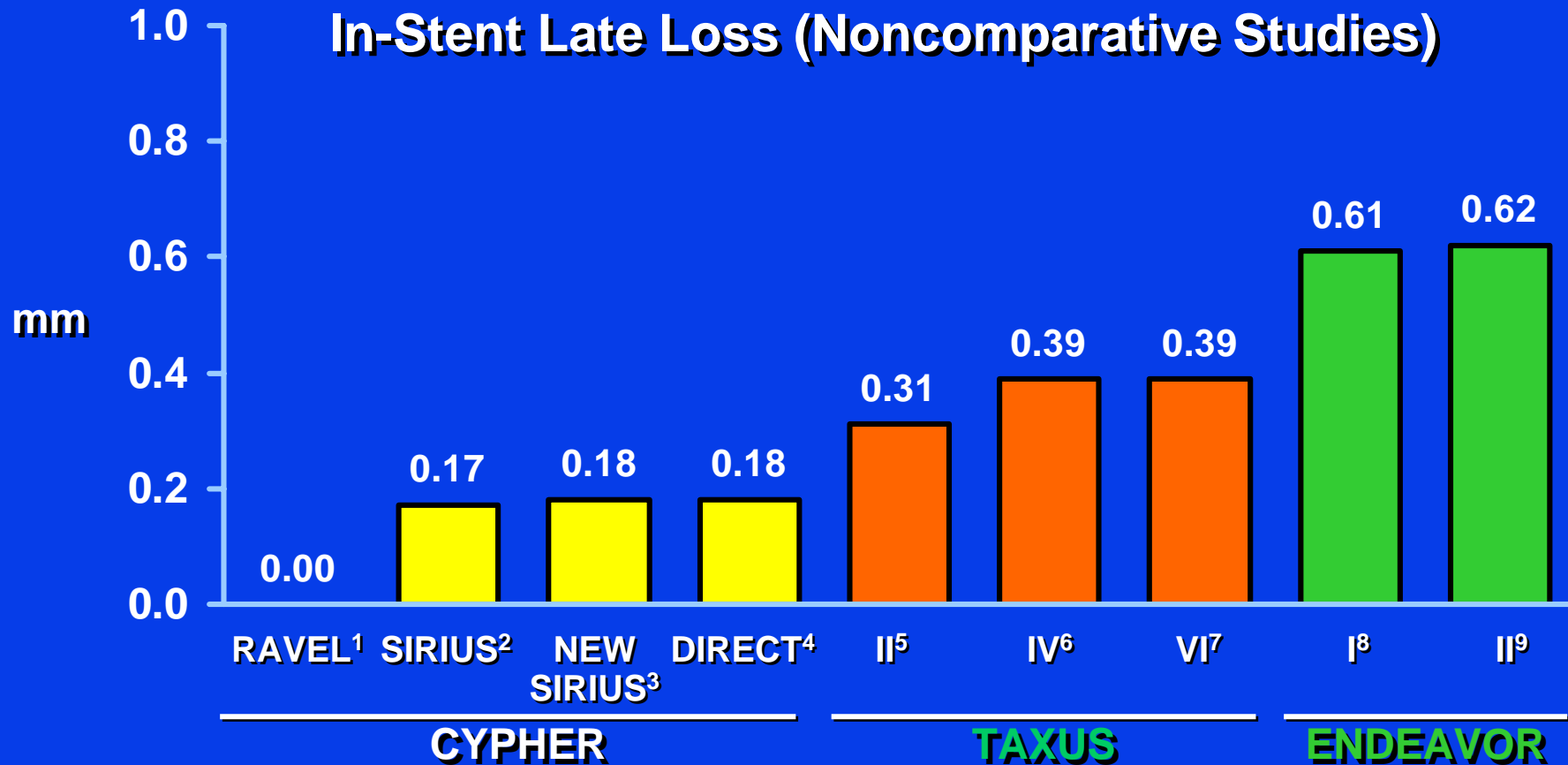
1. Morice MC et al: NEJM 346:773, 2002 2. Moses J et al: NEJM 349:315, 2003
3. Schofer J: ACC, 2004 4. Moses J: ACC, 2004 5. Colombo A: TCT, 2002
6. Stone G et al: NEJM 350:221, 2004 7. Dawkins K: UroPCR, 2004
8. Meredith I: ACC, 2004 9. Wijns W: ACC, 2005

CP1223790-13

# Randomized DES Head-to-Head Studies
## Differences in Mean Late Loss Values are Highly Significant



Legend: CYPHER (yellow), TAXUS (orange), ENDEAVOR (green)

Y-axis: In-stent late loss (mm), scale 0.0 to 1.0

| Study | P-value | CYPHER | TAXUS | ENDEAVOR |
|---|---|---|---|---|
| Endeavor III (8m) | P<0.001 | 0.15 | | 0.60 |
| REALITY[1] (8m) | P<0.001 | 0.09 | 0.31 | |
| SIRTAX[2] (9m) | P<0.001 | 0.13 | 0.25 | |
| ISAR DIABETES[3] (6m) | P<0.001 | 0.19 | 0.46 | |
| ISAR-SMART 3[4] (6-8m) | P<0.001 | 0.25 | 0.56 | |
| ISAR-DESIRE[5] (6m) | P=0.001 | 0.21 | 0.48 | |

Increasing level of complexity of study populations
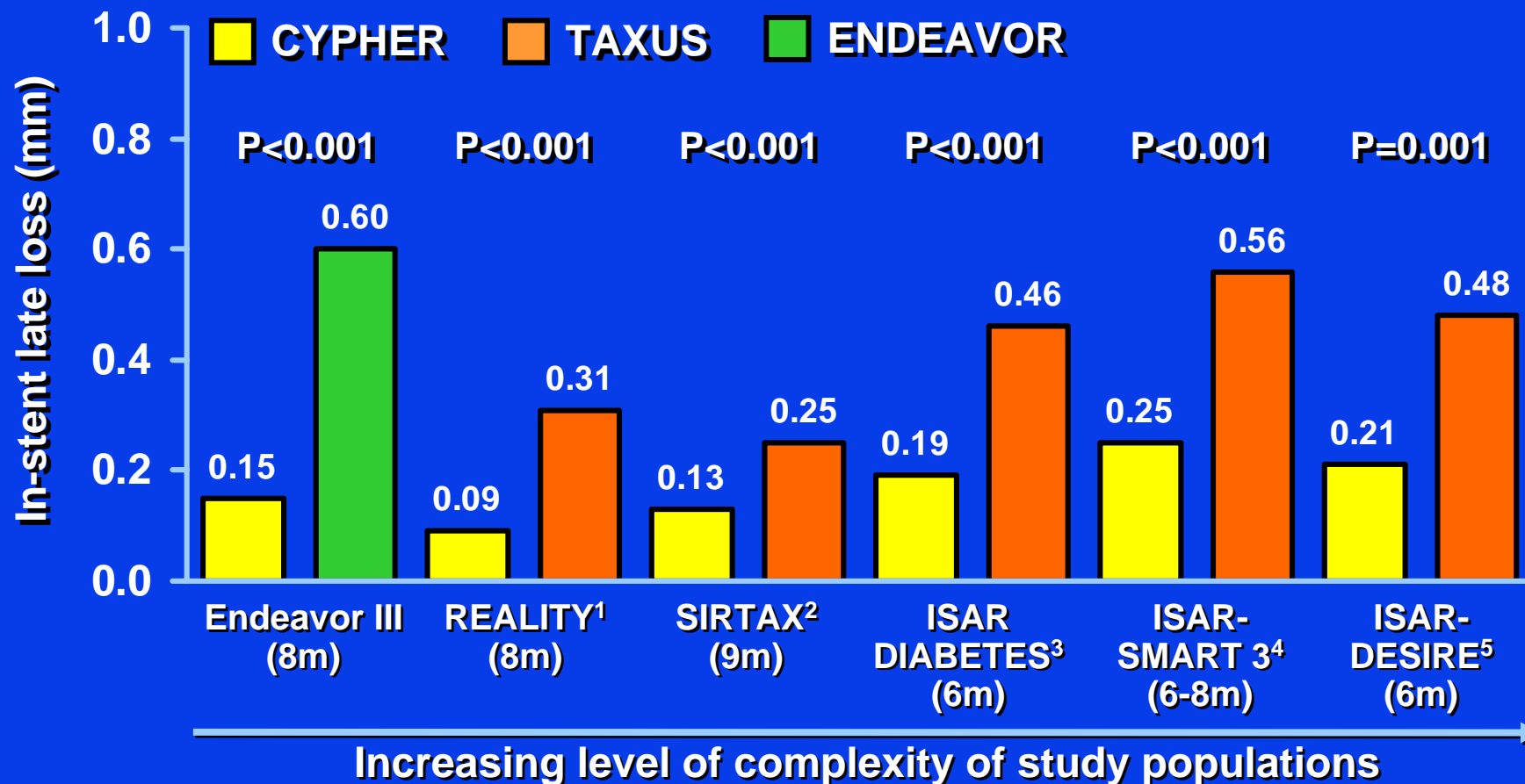
1. Morice MC:  ACC, 2005 2. Windecker et al:  NEJM 355:653, 2005
3. Dibra et al:  NEJM 355:663, 2005 4. Mehili et al:  Eur Heart J 27: 260, 2006
5. Kastrati A., ESC, 2004

# Randomized DES Head-to-Head Studies
## Differences in Mean Late Loss Values are Highly Significant

In-stent late loss (mm)

Legend: CYPHER, TAXUS, ENDEAVOR

| Study | CYPHER | TAXUS | ENDEAVOR | P-value |
|---|---|---|---|---|
| Endeavor III (8m) | 0.15 | | 0.60 | P<0.001 |
| REALITY[1] (8m) | 0.09 | 0.31 | | P<0.001 |
| SIRTAX[2] (9m) | 0.13 | 0.25 | | P<0.001 |
| ISAR DIABETES[3] (6m) | 0.19 | | 0.46 | P<0.001 |
| ISAR-SMART 3[4] (6-8m) | 0.25 | 0.56 | | P<0.001 |
| ISAR-DESIRE[5] (6m) | 0.21 | | 0.48 | P=0.001 |

Increasing level of complexity of study populations
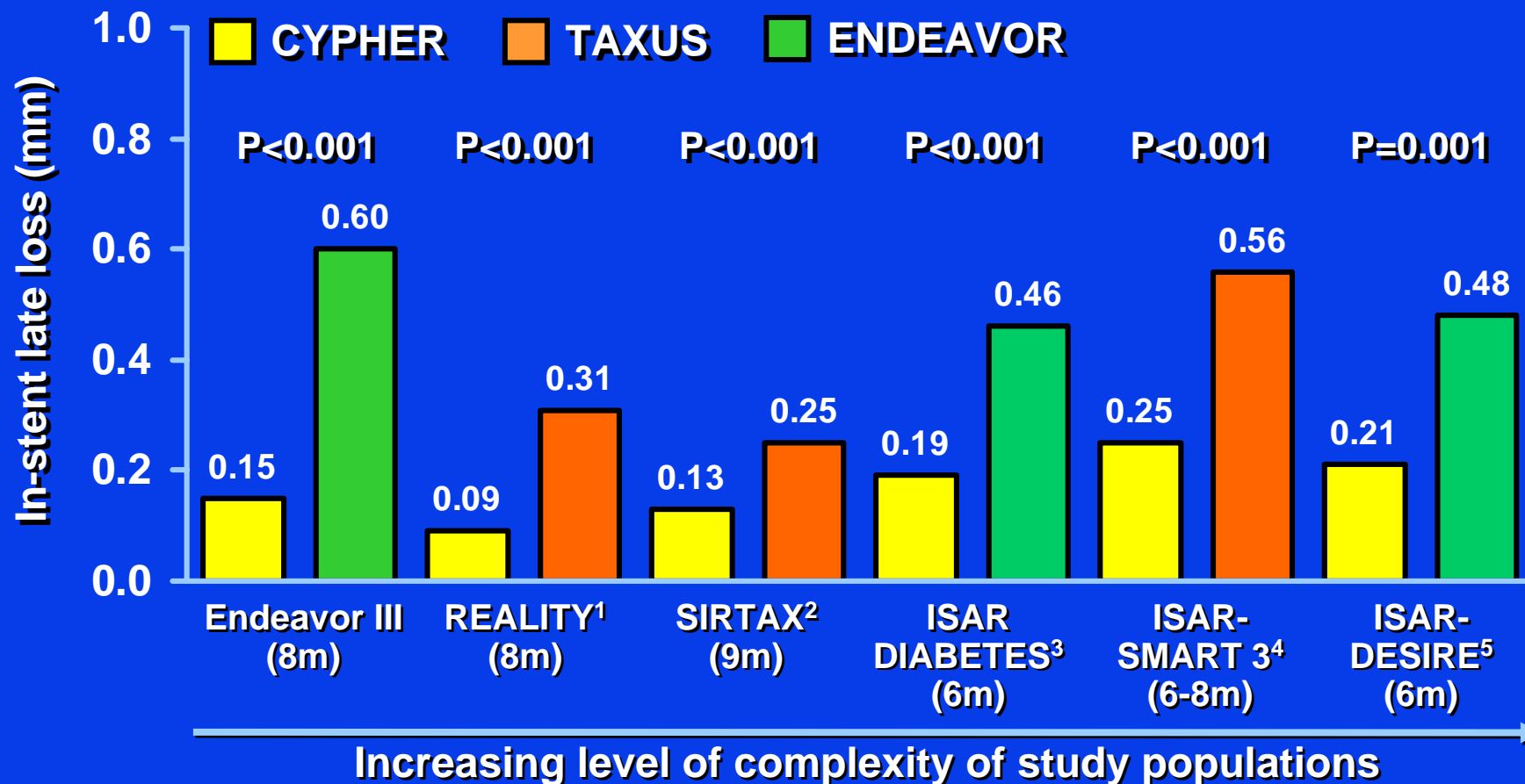
1. Morice MC: ACC, 2005  2. Windecker et al: NEJM 355:653, 2005
3. Dibra et al: NEJM 355:663, 2005  4. Mehili et al: Eur Heart J 27: 260, 2006
5. Kastrati A., ESC, 2004

CP1223790-14

# Superior Outcomes in More Complex Patients and Lesions

## Target Lesion Revascularization

● CYPHER   ● TAXUS   ● ENDEAVOR

| TAXi[7] (6m) | Endeavor III[5] (9m) P=0.34 | REALITY[1] (89m) P=NS | SIRTAX[2] (9m) P=0.025 | ISAR-DIABETES[3] (9m) P=0.13 | ISAR-SMART 3[6] (6m) P=0.008 | ISAR-DESIRE[4] (9m) P=0.02 |

**TLR (%)**

25 —

20 —

**Unknown impact on TLR of ENDEAVOR high late loss in more complex groups** **?**

LL 0.48 mm

LL 0.56 mm

19.0*

15 —

LL 0.45 mm

12.0

10 —

LL 0.60 mm

LL 0.25 mm

LL 0.31 mm

6.3

8.3

LL 0.21 mm

14.7

8.0*

5.4

5 —

3.5

5.0

4.8

6.4

6.0

LL 0.25 mm

1.9

LL 0.19 mm

1.0

LL 0.15 mm

LL 0.09 mm

LL 0.13 mm

0 —

**Increasing level of complexity**

*TLR

1. Morice MC: ACC, 2005 2. Windecker et al: NEJM 355:653, 2005 3. Dibra et al: NEJM 355:663, 2005 4. Kastrati A: ESC, 2004 5. Kandzari D: TCT, 2005 6. Mehili et al: Eur Heart J 27: 260, 2006 7. Goy J: JACC 45:308, 2005

CP1223790-17
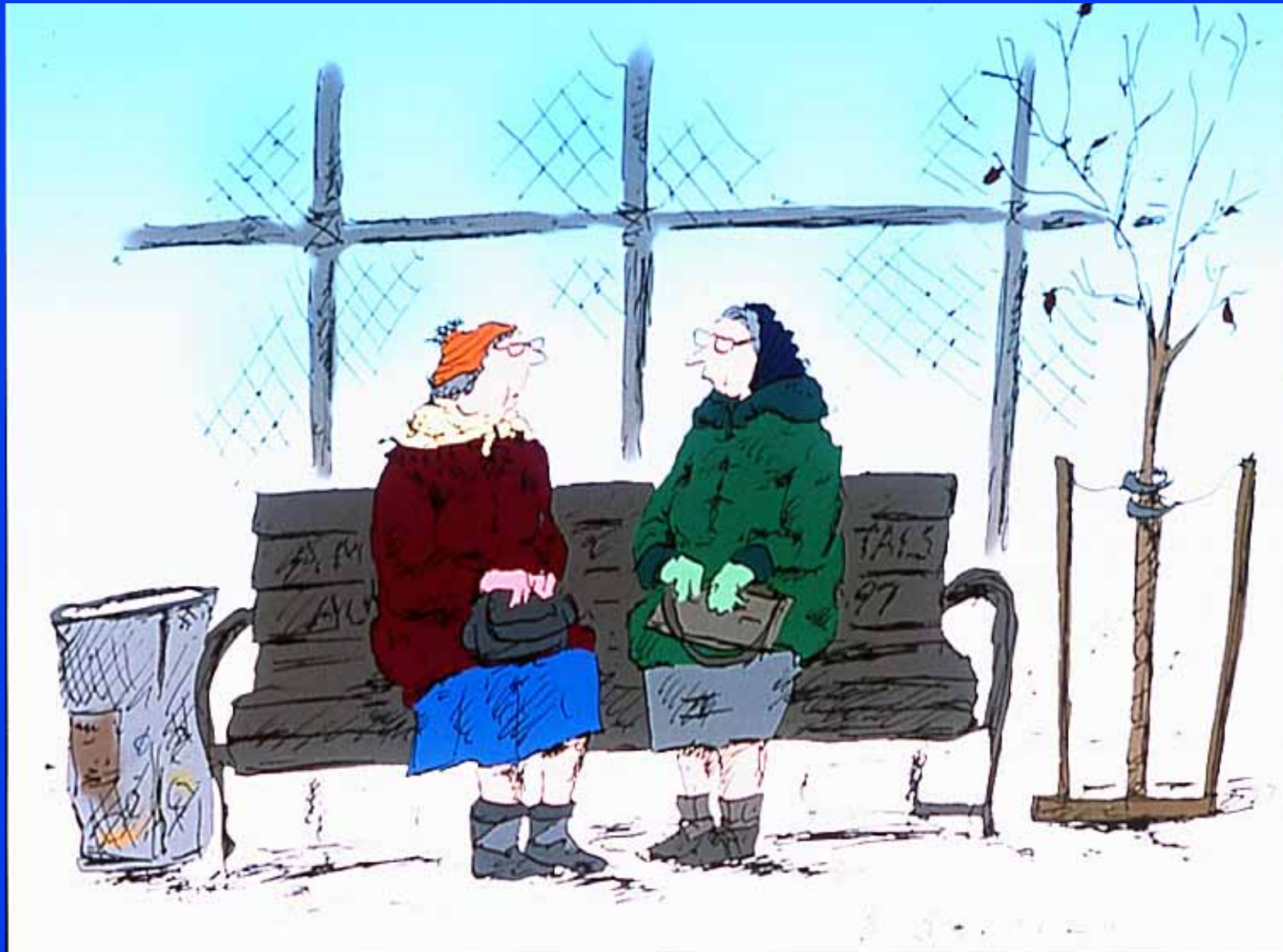
"Am I the smart one and you're the pretty one or is it the other way around?"

# Background: Stent Overlap

Concerns have been raised by the TAXUS V study: Overlapping/multiple TAXUS® stents in a single vessel appear to be associated with a significantly higher 30-day MI rate compared to bare-metal stents (BMS)

The cause of this association is not clear

It is also not clear whether this problem is specific to TAXUS® or is common to drug-eluting stents
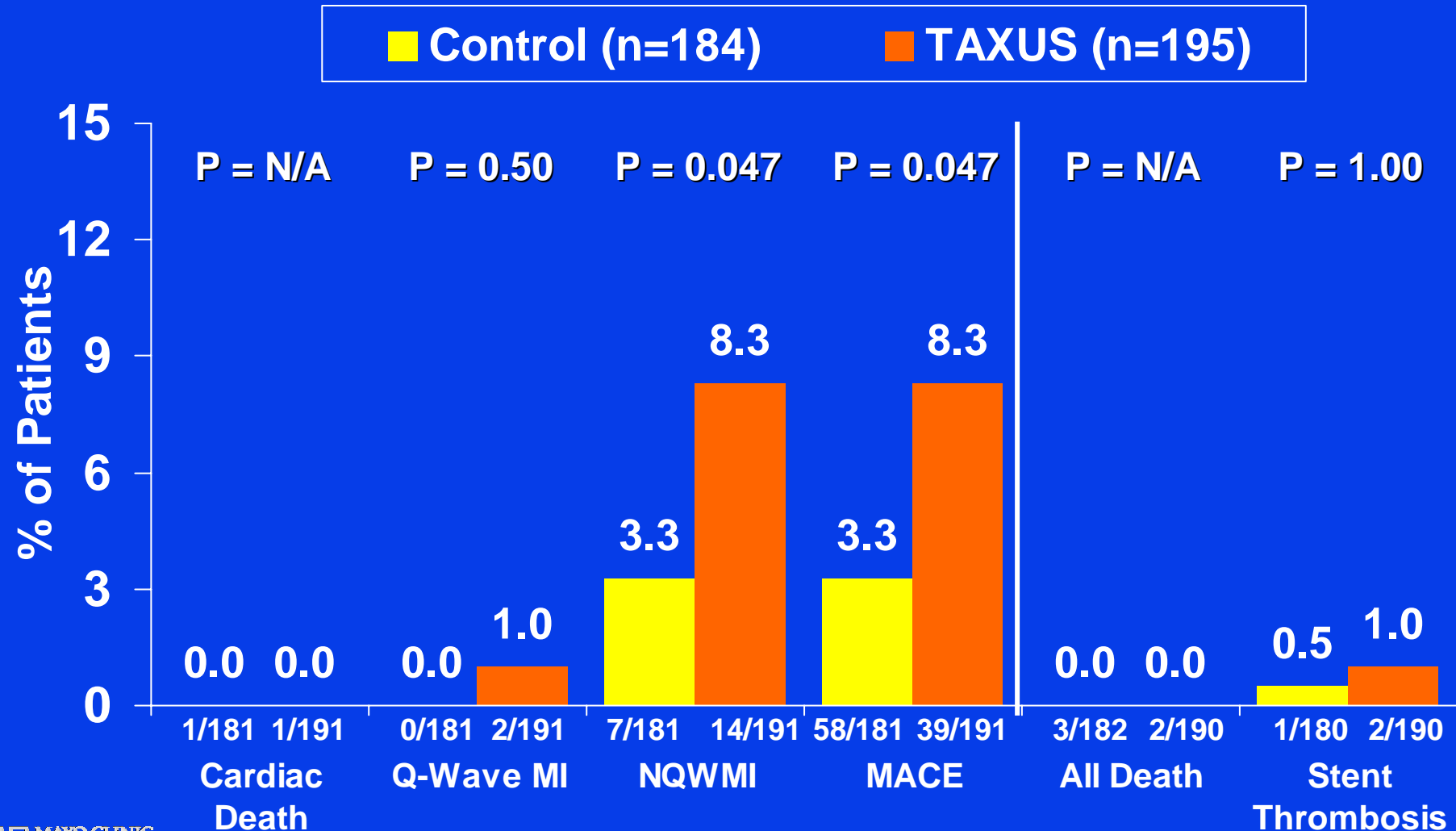
# Effect of Multiple Stenting on 9-Month TLR
## TAXUS II, IV, V, VI Meta-analysis



Single Stent: Control 12.3 (169/1377), TAXUS® 4.9 (67/1360), ↓60%, *P*<0.0001

Multiple Stents: Control 25.7 (85/331), TAXUS® 8.5 (29/343), ↓66%, *P*<0.0001

Patients (%)

■ Control    ■ TAXUS®

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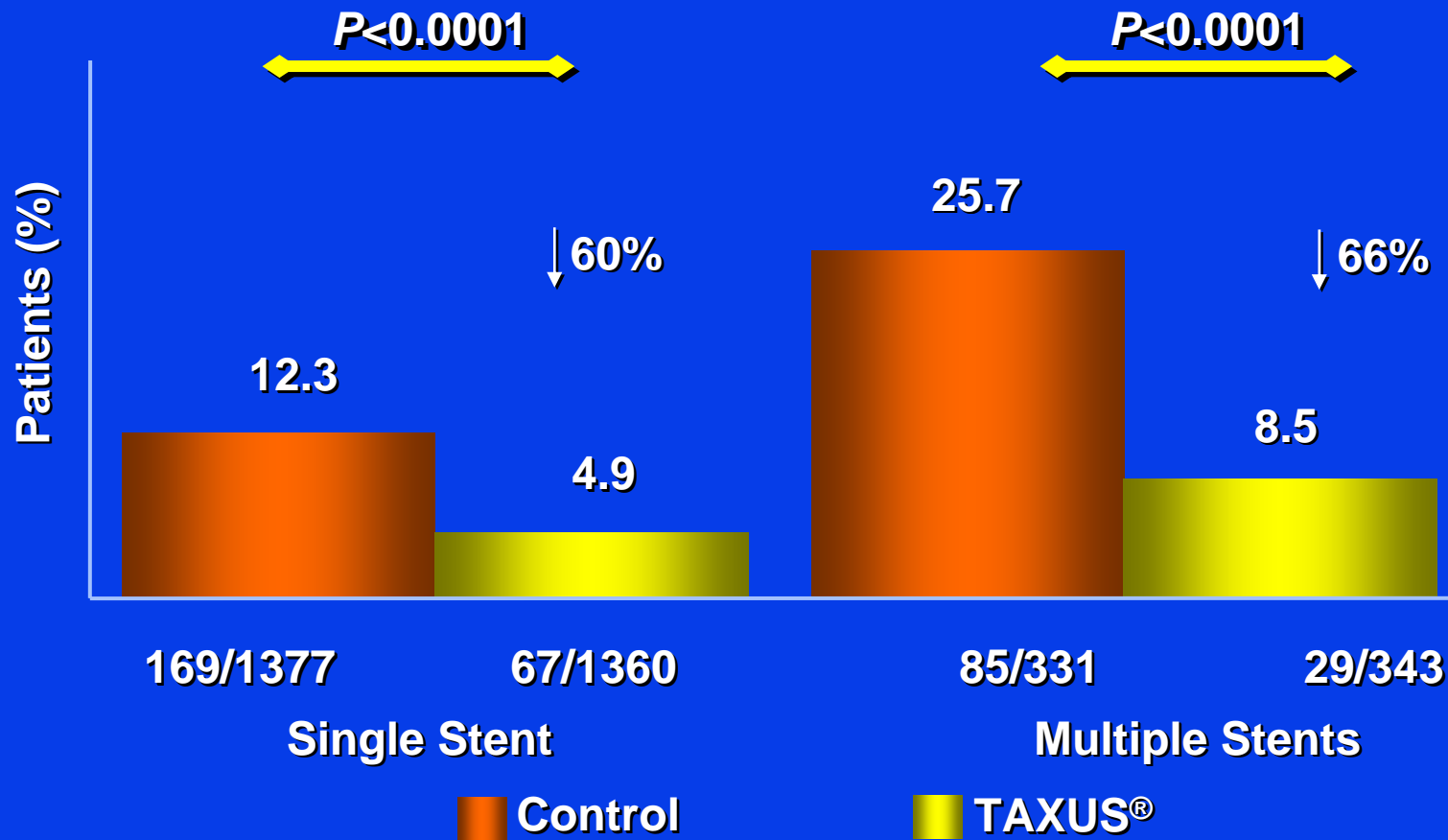
# Methods

- **3 prospective RCTs comparing SES and BMS (SIRIUS, E-SIRIUS, C-SIRIUS) and 1 prospective SES registry (DIRECT)**

- **Patients included in these studies have a single native stenosis between 15-30 mm in length in a vessel between 2.5 and 3.5 mm in diameter**

- **Patients with true bifurcation lesions were excluded, defined as a significant stenosis (>50%) involving the origin of large (≥2.5 mm) branch vessel**

- **Patients with multiple (>2), long (>18 mm) stents were selected for this subset analysis**
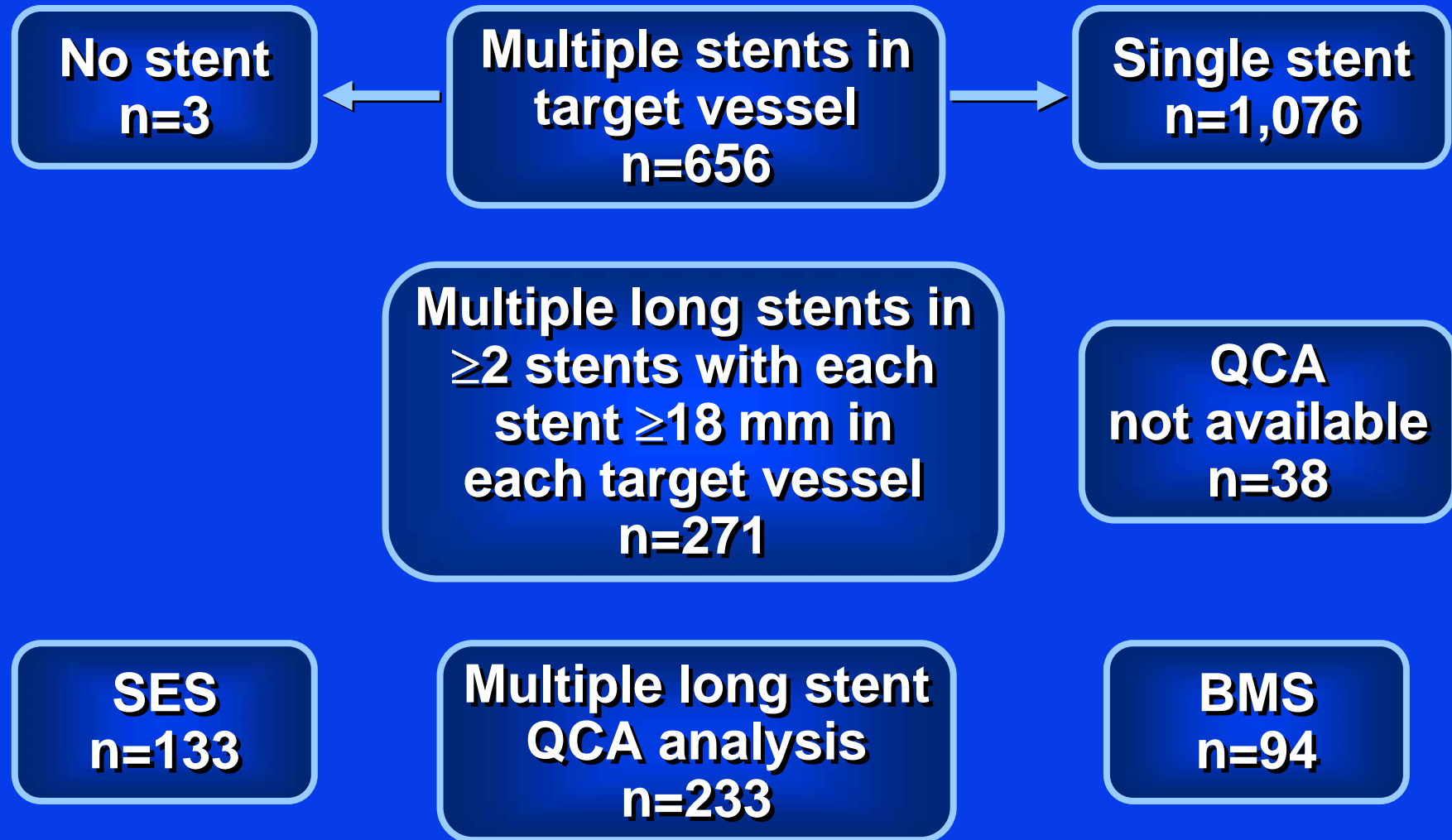
# Stents Implanted

| | CYPHER | BMS | P |
|---|---|---|---|
| Stents (no.) | 369 | 254 | |
| Stent length (mm) | 39.5±8.5 | 39.5±8.2 | 0.99 |
| Stent length | | | |
|   8 mm | 8.8 | 7.5 | 0.633 |
|   18 mm | 90.5 | 91.6 | 0.759 |
| Bailout stent (%) | 2.1 | 6.4 | 0.017 |
| Mean no. stents/pt | 2.32±0.69 | 2.27±0.55 | 0.484 |
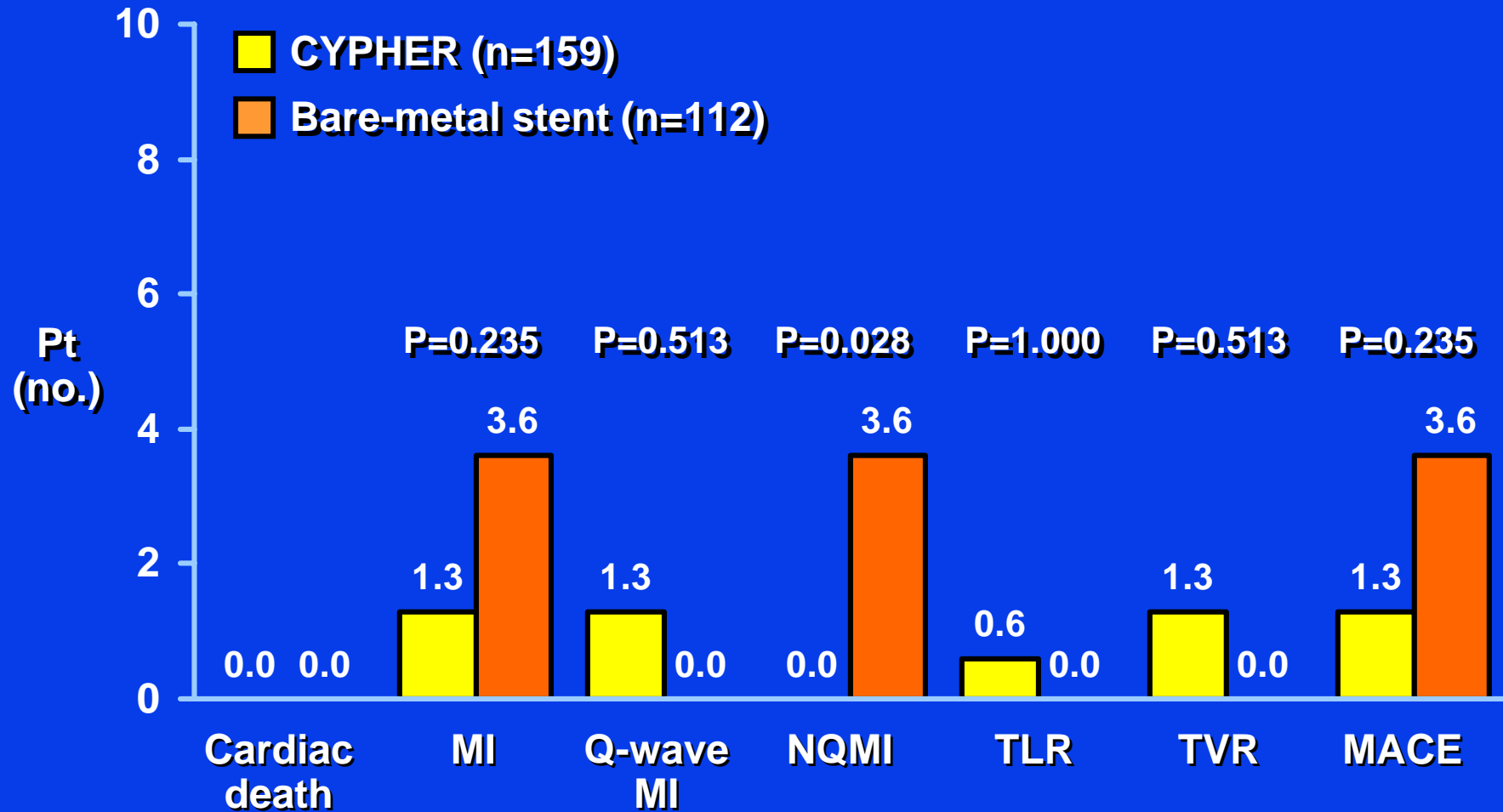
30-Day MI Rates
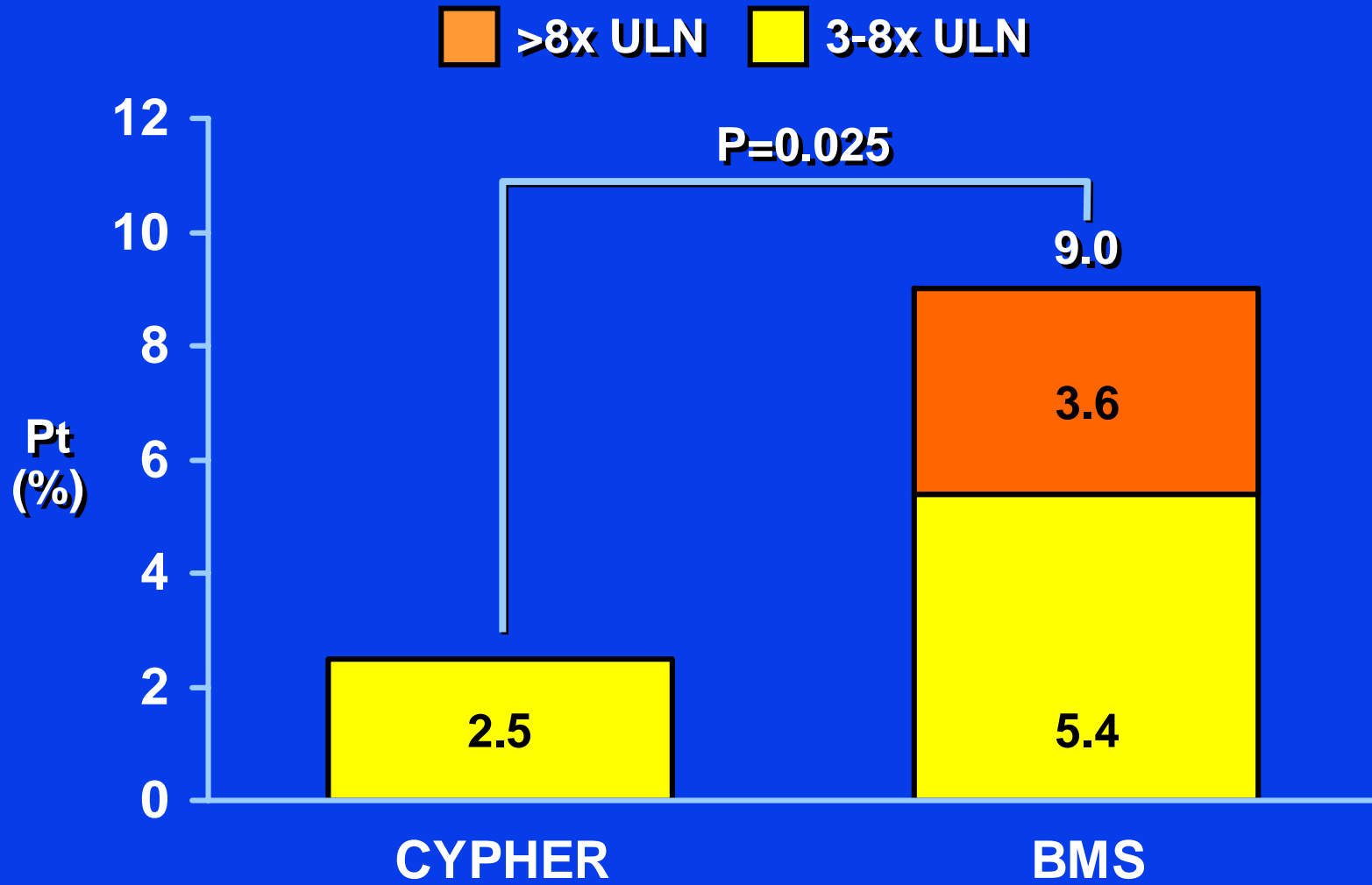
# 9-Month Safety Summary
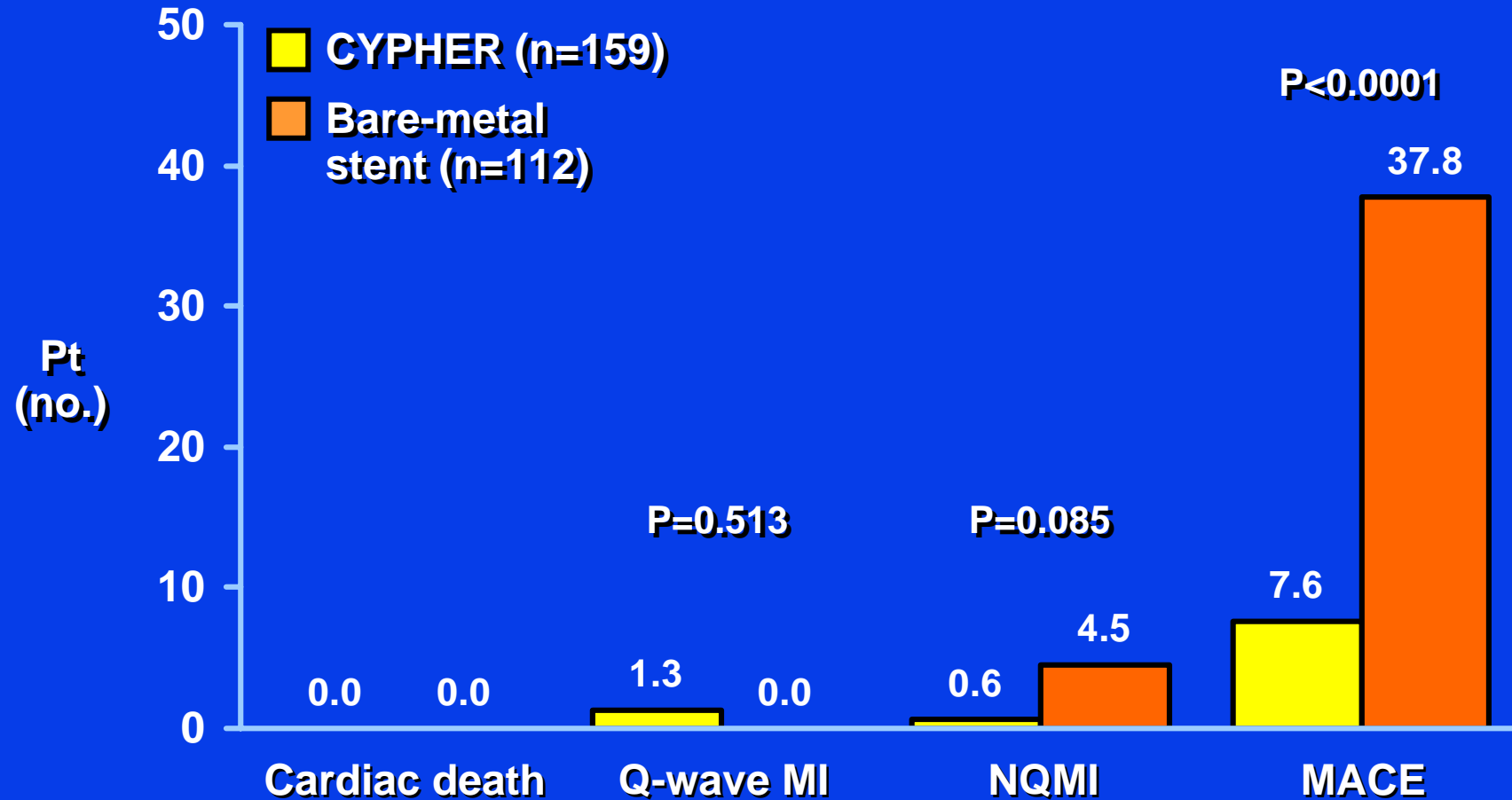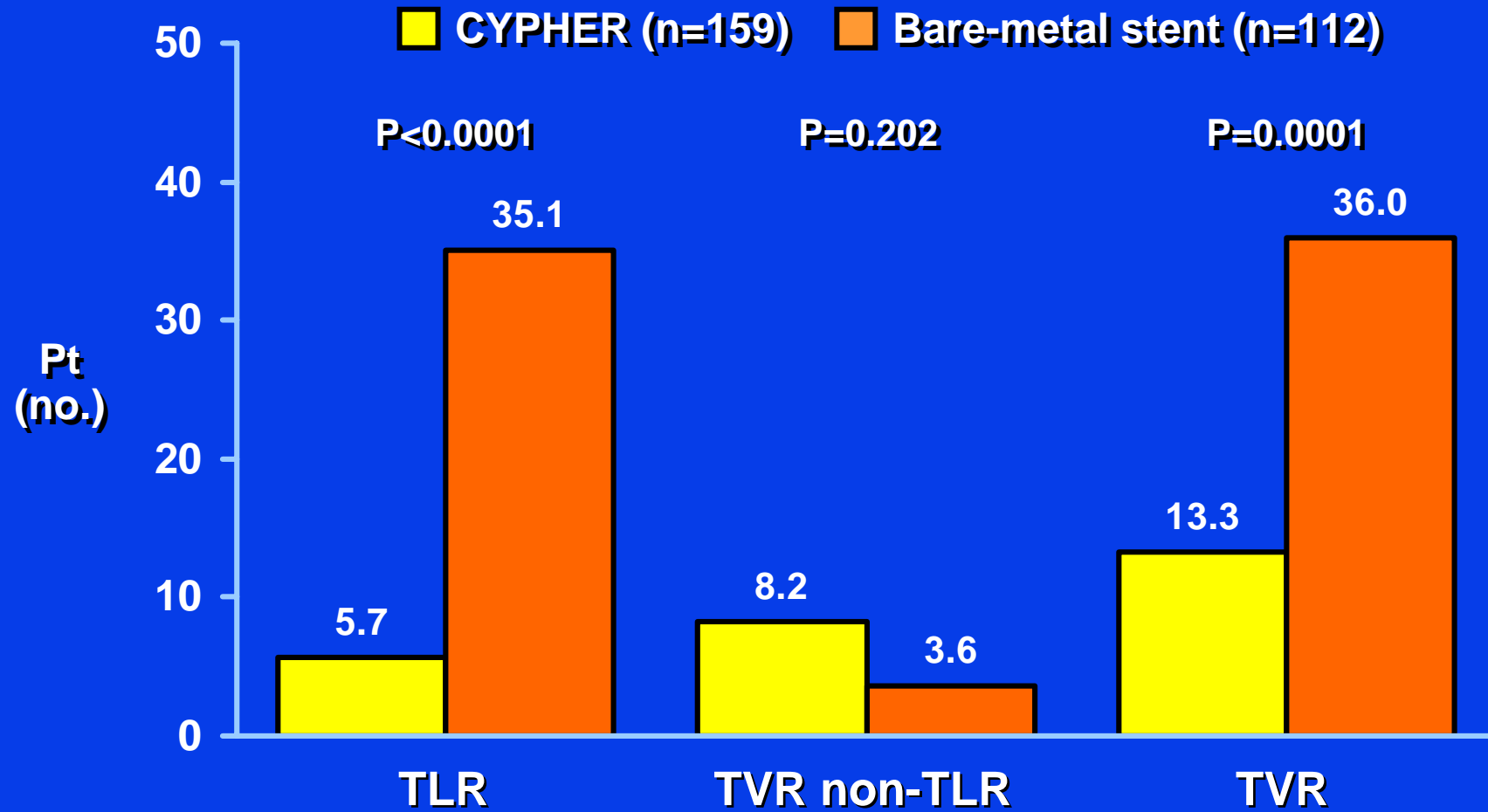


CYPHER (n=159)
Bare-metal stent (n=112)

Pt (no.)

| | Cardiac death | Q-wave MI | NQMI | MACE |
|---|---|---|---|---|
| P-value | | P=0.513 | P=0.085 | P<0.0001 |
| CYPHER | 0.0 | 1.3 | 0.6 | 7.6 |
| Bare-metal stent | 0.0 | 0.0 | 4.5 | 37.8 |
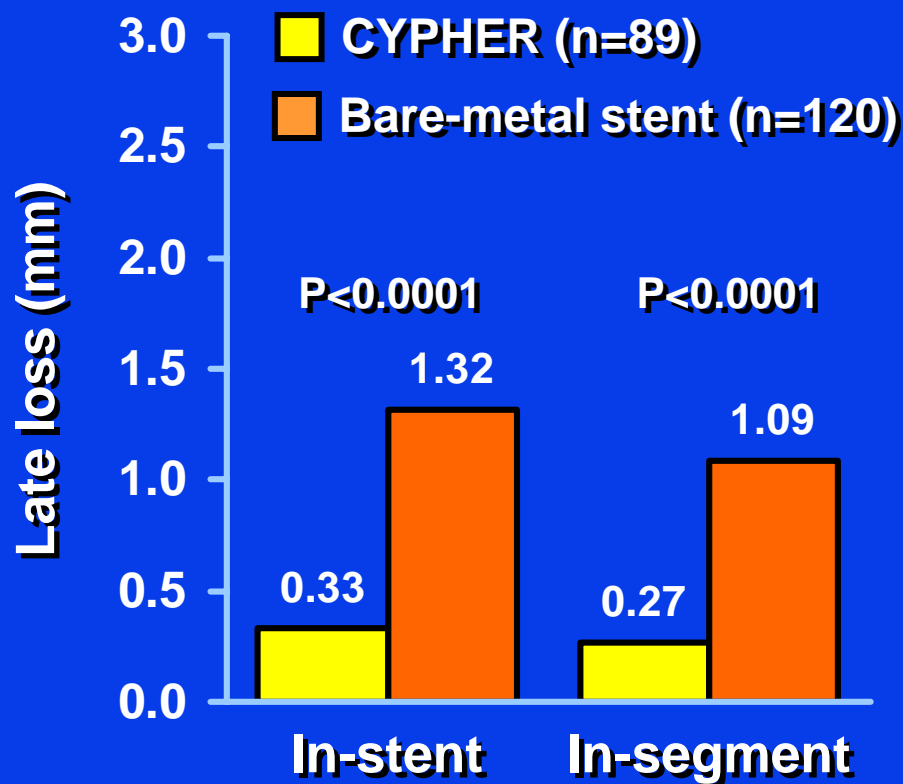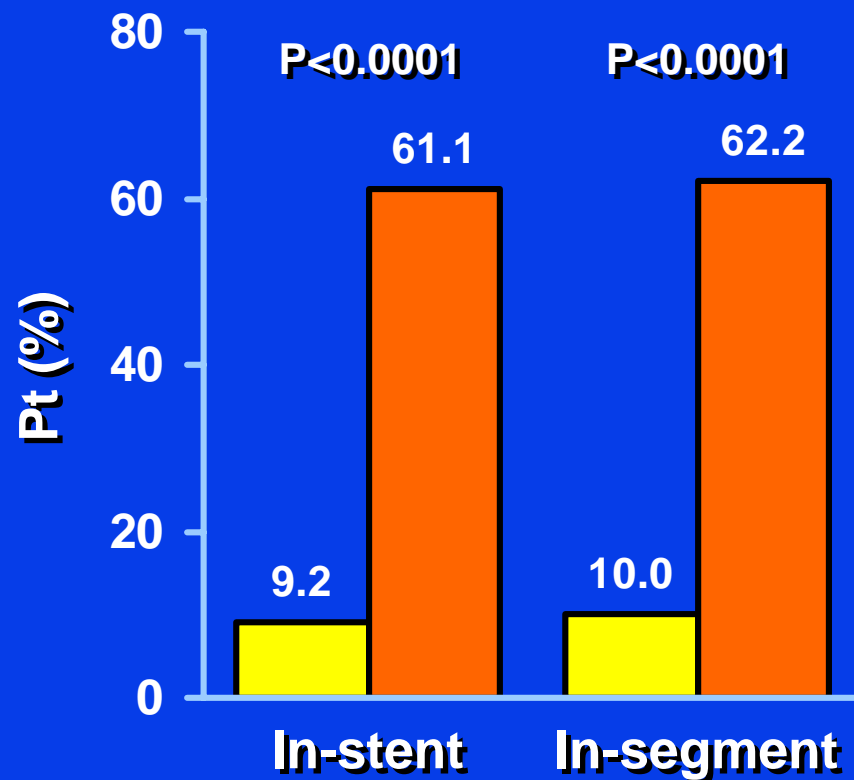
# What Would We Agree On CYPHER vs TAXUS

- **Physiology – specifically late loss is quite different**

- **The link between late loss and clinical outcome may be important in higher risk patients**

- **Although there has been some variability in clinical restenosis, CYPHER is slightly better and never worse than TAXUS**

- **SAT rates are probably similar but still works in progress**

# Title/drp–author:  WT/BK – Holmes, D
# Sub/drp–Job#:  YW105/BK – CP1223793

## Subject:  Cyper Long Stents

**Background:  BU3**

**Banner/brdr:  BU2/BU41**

**Side title:  YW105**

- **/colhdgs:  YW105**

**Text:  WT/BK**

**Highlight:  YO114**

**Subdue:  BU31**

**Footnotes:  BU41**

**Plot/brdr:  open/BU41**
**x, y only**

**PPT shooting instructions**
**PPT File to Server**
**(24 images)**

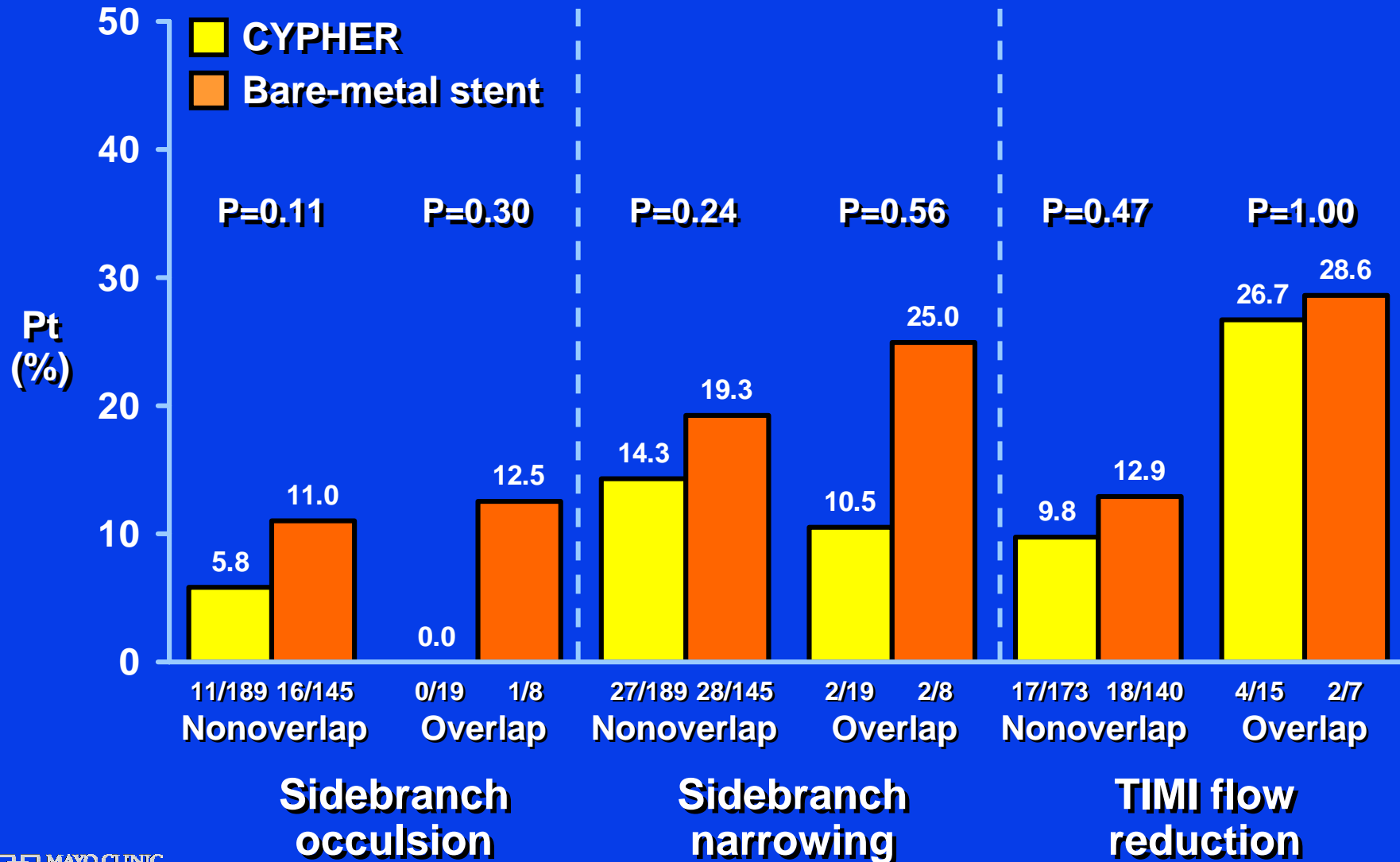## COLOR REFERENCE ONLY
**Match:  Mayo2BU (CP1111378)**

MAYO CLINIC
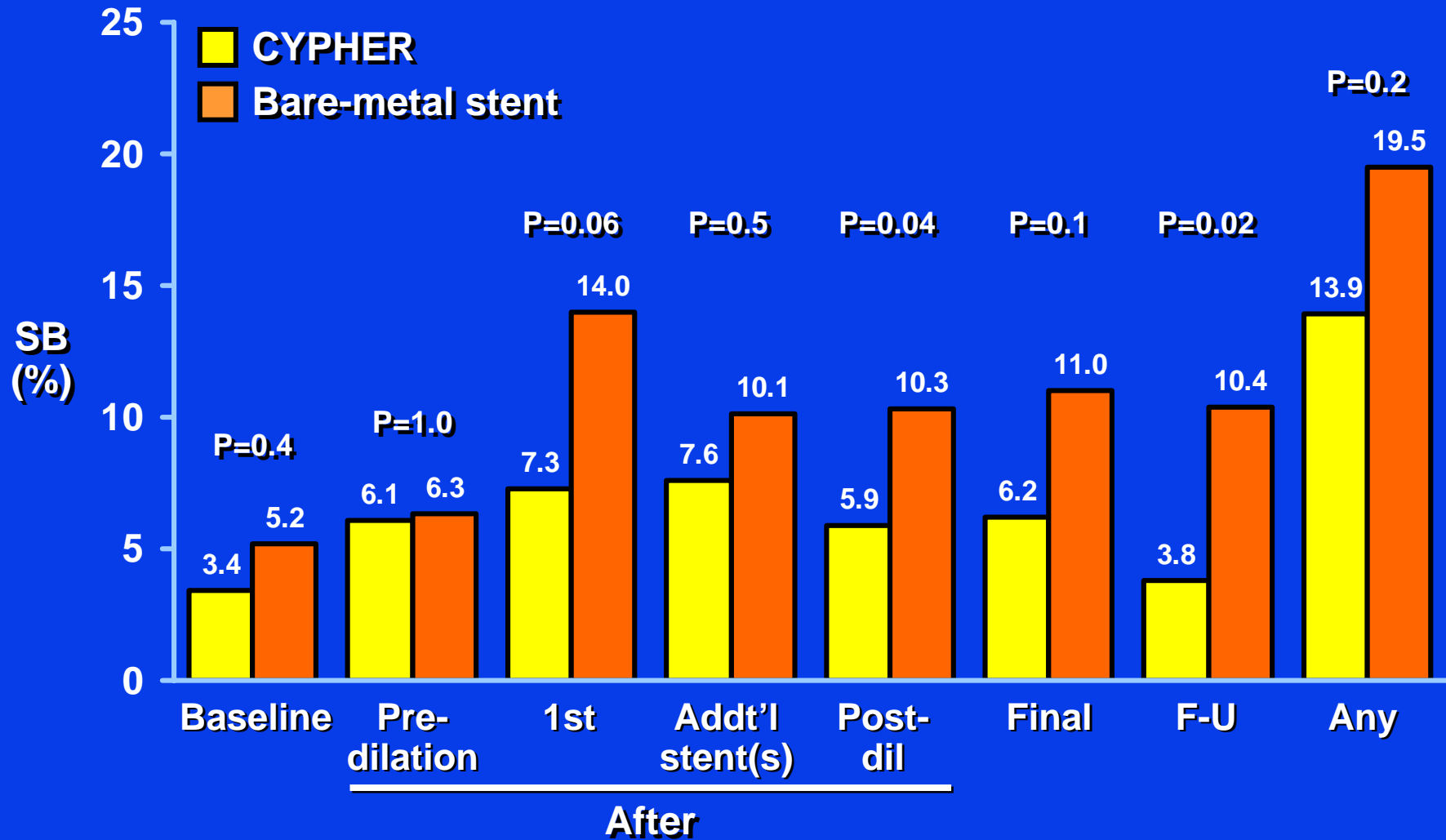
Impact of the Overlap Region (per Sidebranch)

# Association of Sidebranch Flow and MI

| MI (WHO) | With MI (14 branches) | Without MI 414 branches | P |
|---|---|---|---|
| SB occlusion | 0.0 | 7.9 | 1.000 |
| SB reduced flow | 0.0 | 16.7 | 0.377 |
| SB compromise | 10.0 | 12.3 | 1.000 |
| MI (CKMB >3x ULN) | With MI (28 branches) | Without MI (400 branches) | |
| SB occlusion | 27.3 | 6.5 | 0.004 |
| SB reduced flow | 40.9 | 14.7 | 0.004 |
| SB compromise | 19.0 | 11.8 | 0.306 |

# Multiple Logistic Regression Predictors of Myonecrosis (Any CPK-MB >3 x Normal)

|  | Coefficient | SE | OR | P |
|---|---|---|---|---|
| ↓ SB flow | 2.2238 | 0.8197 | 9.2422 | 0.0067 |
| Age (yr) | -0.0911 | 0.0411 | 0.9129 | 0.0265 |
| Treatment group (CYPHER vs control) | -1.4961 | 0.8792 | 0.2240 | 0.0888 |
| Canadian CV Society class III or IV | -1.4319 | 0.8820 | 0.2389 | 0.1045 |

# Conclusions

- In this series of patients treated with multiple, long stents (lesion length 21.1 mm; stent length 39.5 mm), the SES (vs BMS) was associated with

    - Similar rates of 30-day MACE and overall MI

    - Markedly reduced 9-month MACE due to reductions in the need for TLR

- No evidence of enhanced risk of sidebranch compromise with SES compared with BMS

- Overlapped BMS and SES both have more frequent reduction in sidebranch flow than