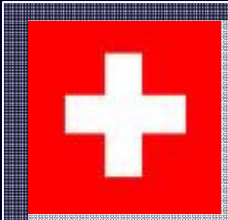
Rotterdam, June 11th 2012

# Safety of Drug-Eluting Stents in Acute Coronary Syndromes

**Stephan Windecker**

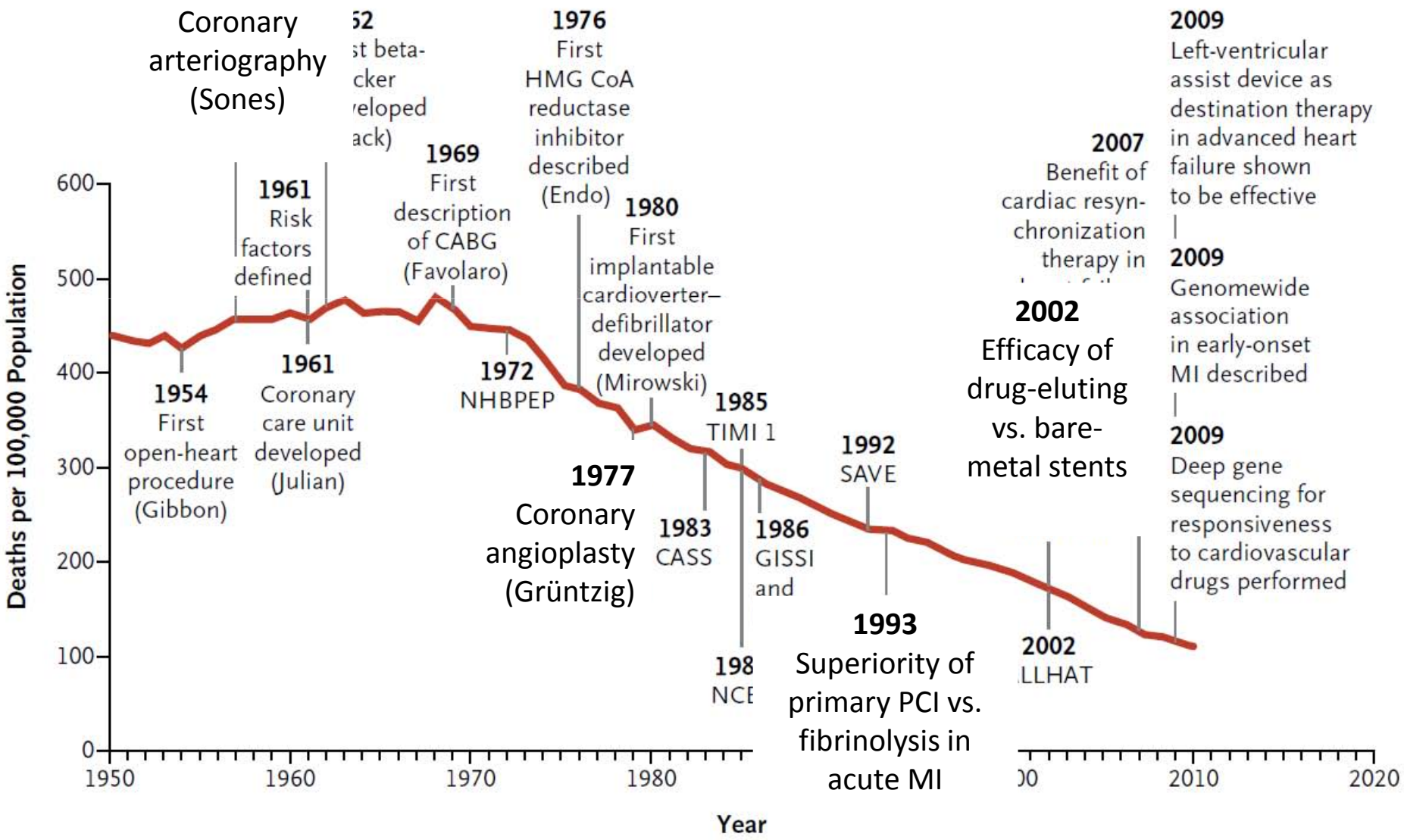
***Department of Cardiology***

***Swiss Cardiovascular Center and Clinical Trials Unit Bern***

***Bern University Hospital, Switzerland***

# Scientific Advances and Cardiovascular Mortality

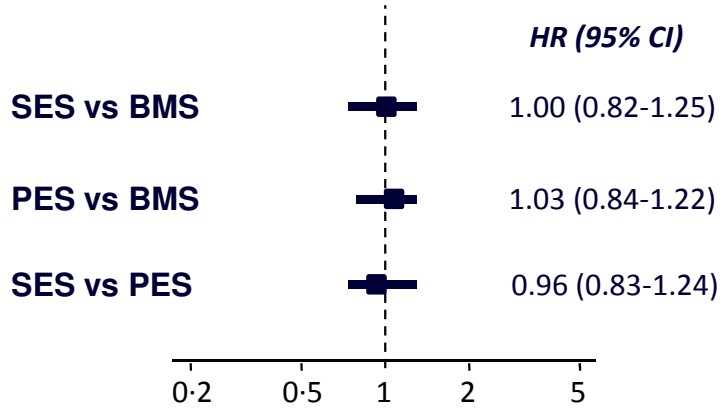
Nabel and Braunwald. *N Engl J Med* 2012;366:54-63



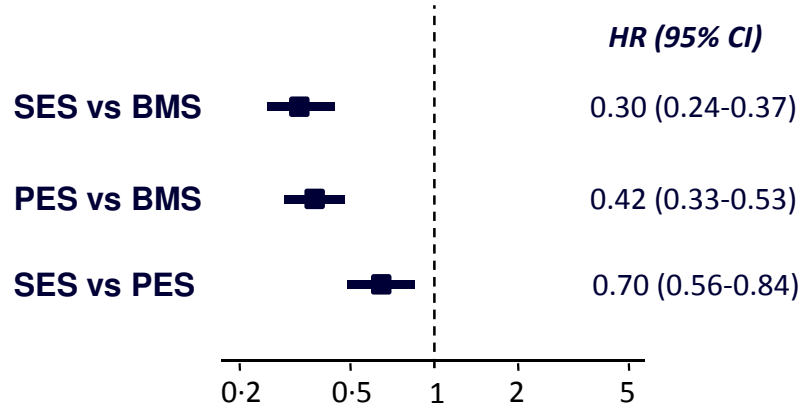
# Mortality and Repeat Revascularization with Early Generation DES versus Bare Metal Stents

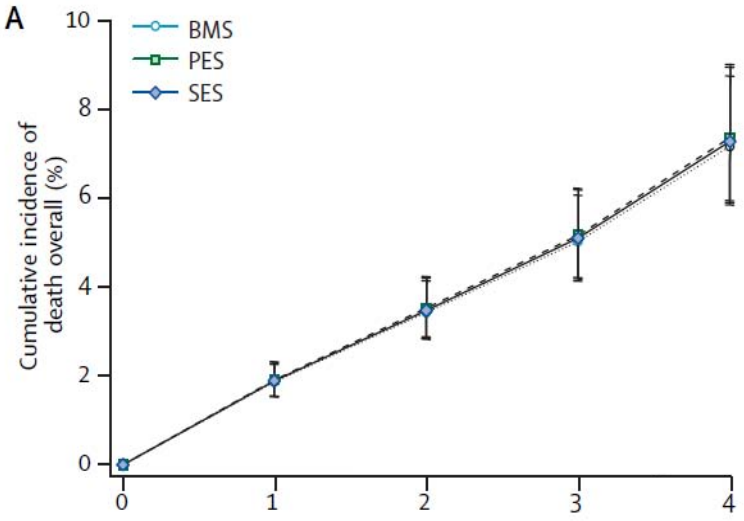
Stettler C et al. *Lancet* 2007;370:937-48

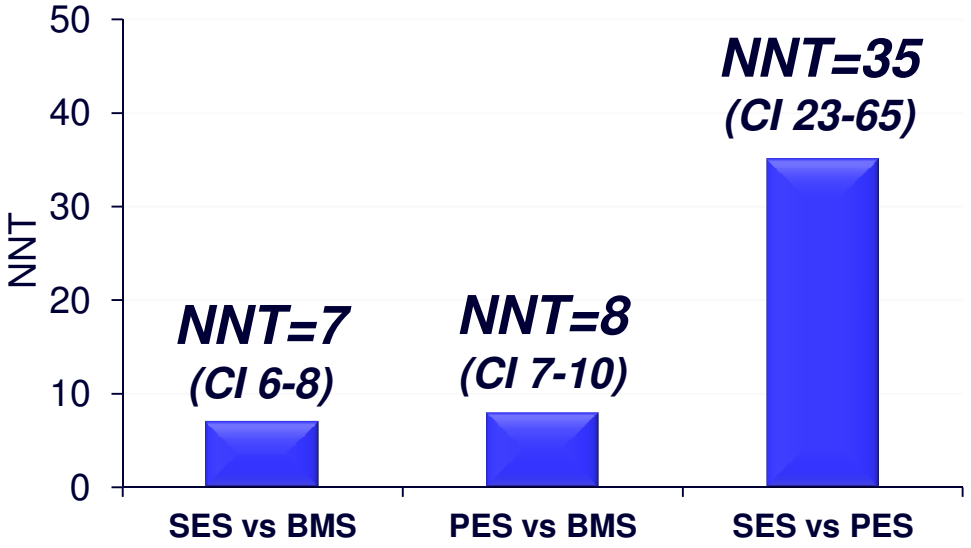
## Mortality




## Repeat Revasc



# Drug-Eluting vs. Bare Metal Stent in Acute MI

Mauri L et al. *N Engl J Med 2008;359:1330-42*

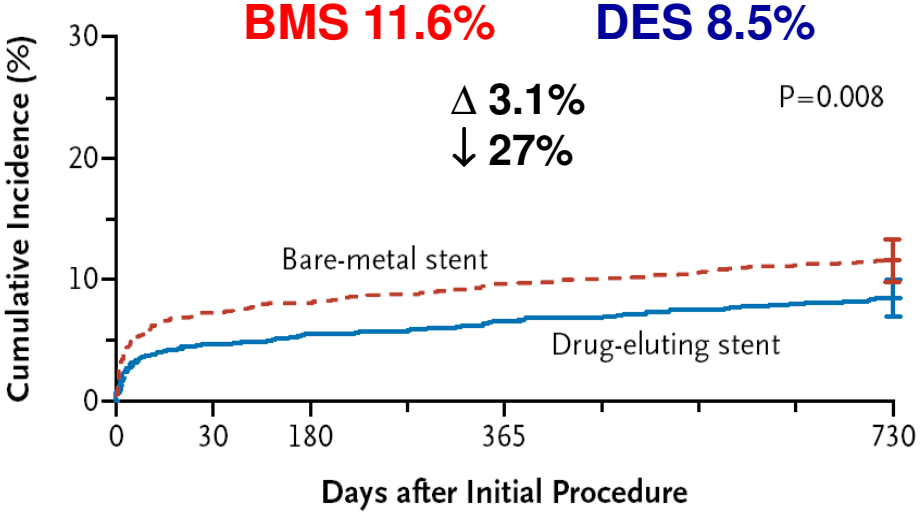
***Propensity Score Matched Pair Comparison of DES and BMS in Patients Undergoing PCI for acute myocardial infarction in Massachusetts***

***N=7,217 Patients (04/2003-09/2004)***

## *Mortality*

**BMS 11.6%** **DES 8.5%**

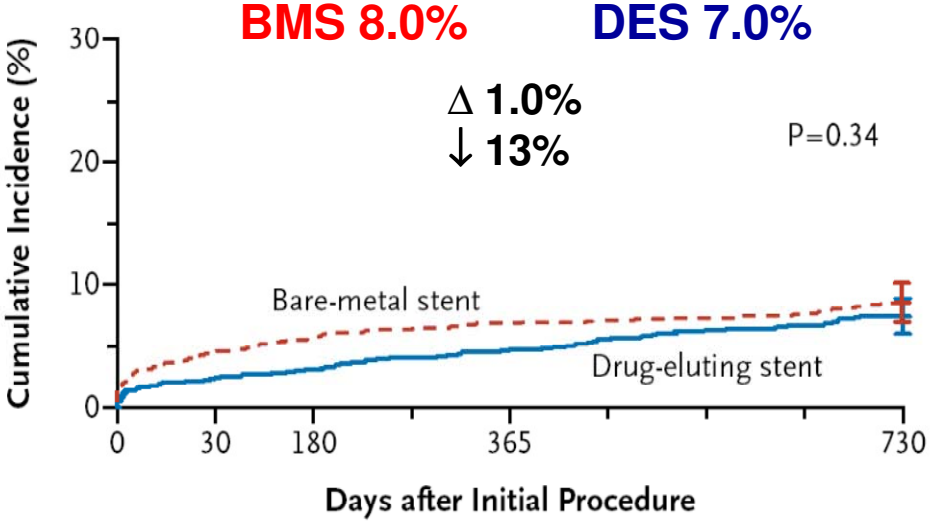
**Δ 3.1%**
**↓ 27%**
P=0.008




## *Recurrent MI*

**BMS 8.0%** **DES 7.0%**

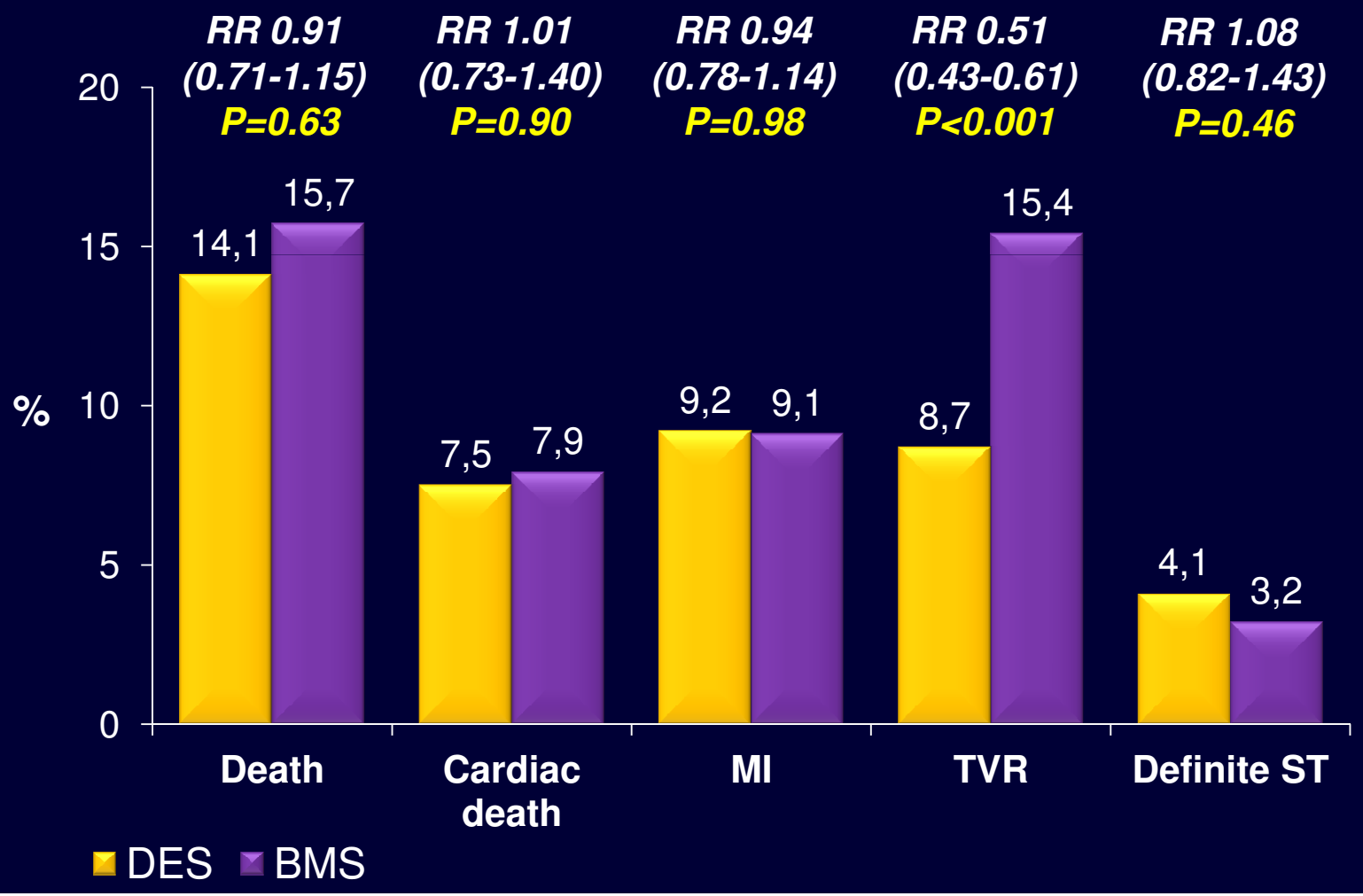
**Δ 1.0%**
**↓ 13%**
P=0.34

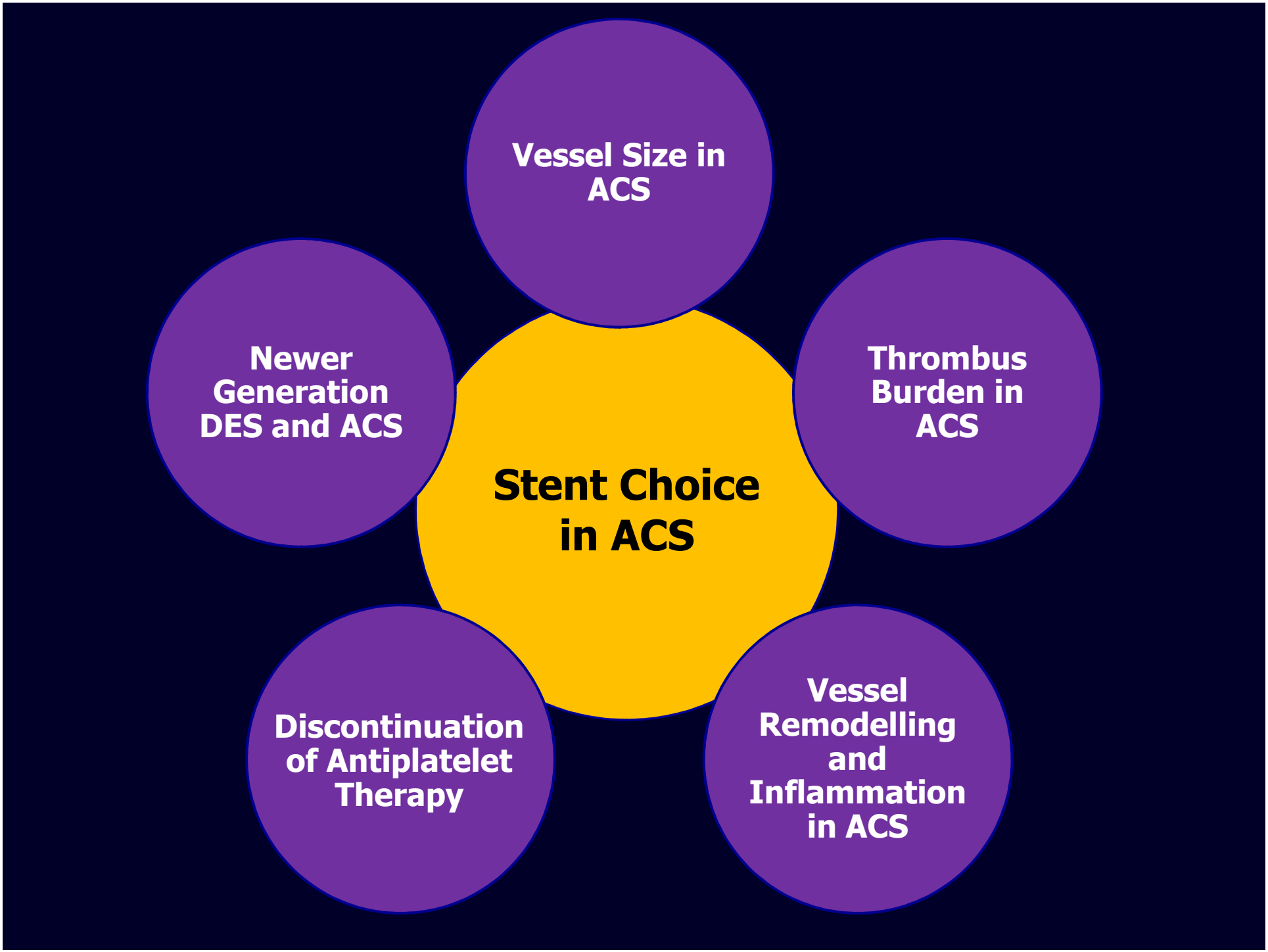


# Early Generation Drug-Eluting Stents versus Bare Metal Stents in Patients With STEMI

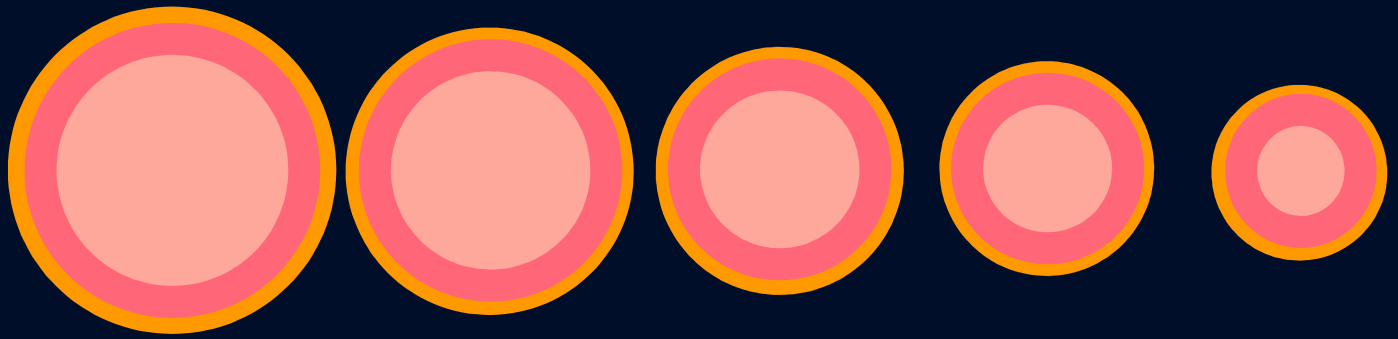
Kalesan B et al. *Eur Heart J* 2012

## *15 RCTs Comparing DES and BMS in 7,843 STEMI Patients*




Vessel Size in ACS
Newer Generation DES and ACS
Thrombus Burden in ACS
Stent Choice in ACS
Discontinuation of Antiplatelet Therapy
Vessel Remodelling and Inflammation in ACS

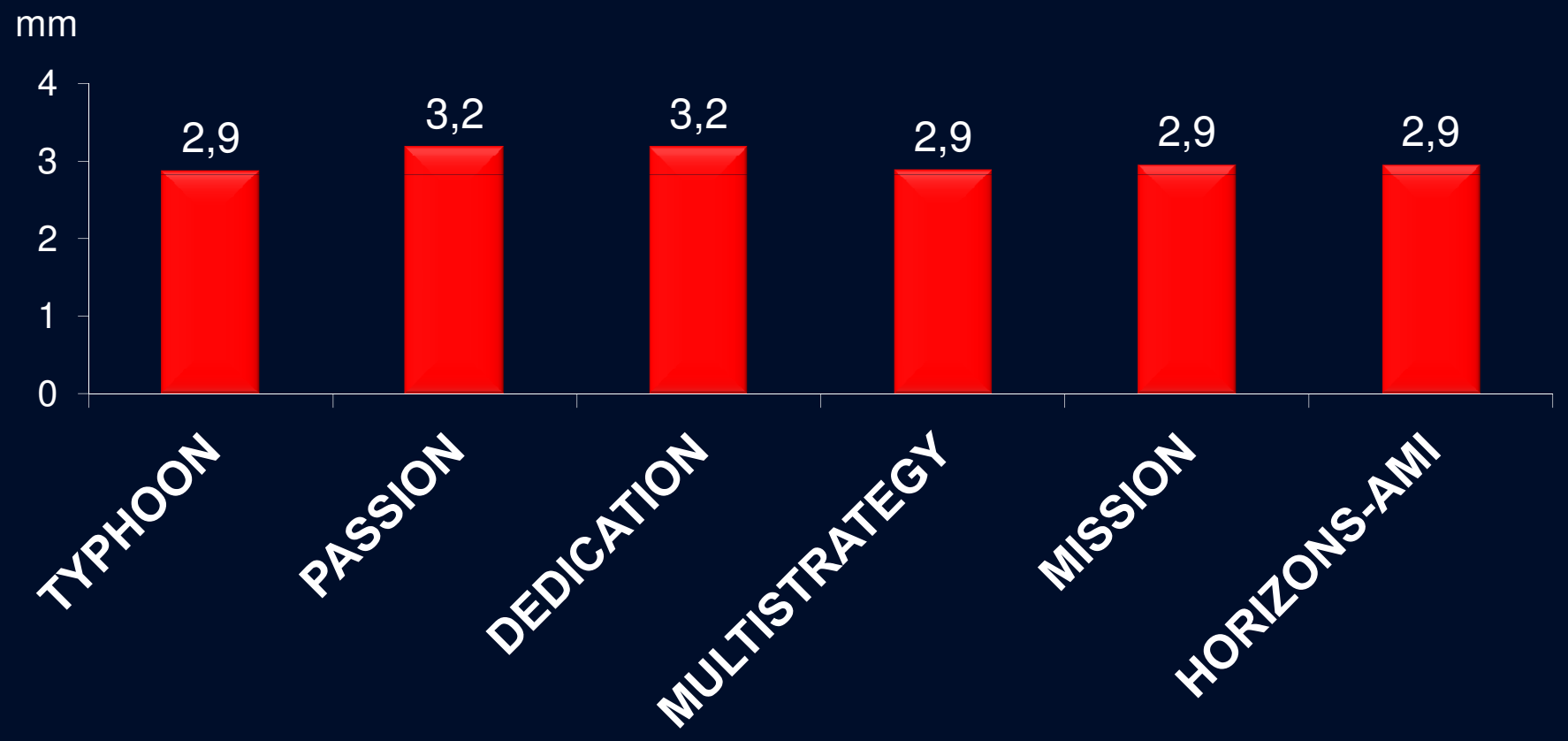
# Impact of Vessel Diameter and Late Loss on Restenosis



| RVD | 4.0 mm | 3.5 mm | 3.0 mm | 2.5 mm | 2.0 mm |
|---|---|---|---|---|---|
| Late loss (BMS) | 0.9 mm | 0.9 mm | 0.9 mm | 0.9 mm | 0.9 mm |
| Diameter stenosis | 23% | 26% | 30% | 36% | 45% |
| Late loss (DES) | 0.2 mm | 0.2 mm | 0.2 mm | 0.2 mm | 0.2 mm |
| Diameter stenosis | 5% | 6% | 7% | 8% | 10% |

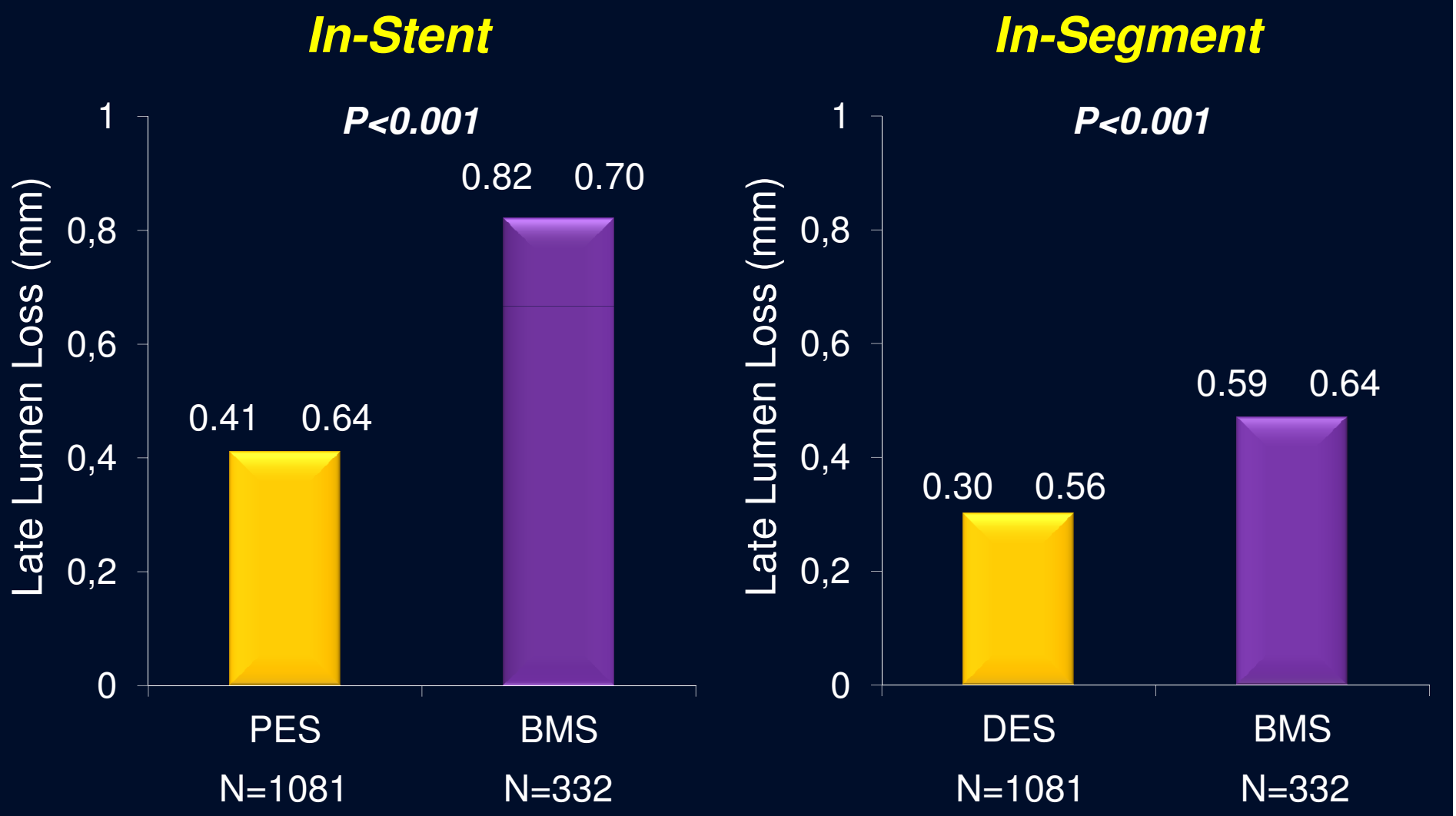
# Vessel Size in Patients With Acute Myocardial Infarction

## *Mean Reference Vessel Diameter (mm)*



# Paclitaxel-Eluting Stents versus Bare-Metal Stents in Acute Myocardial Infarction: HORIZONS-AMI

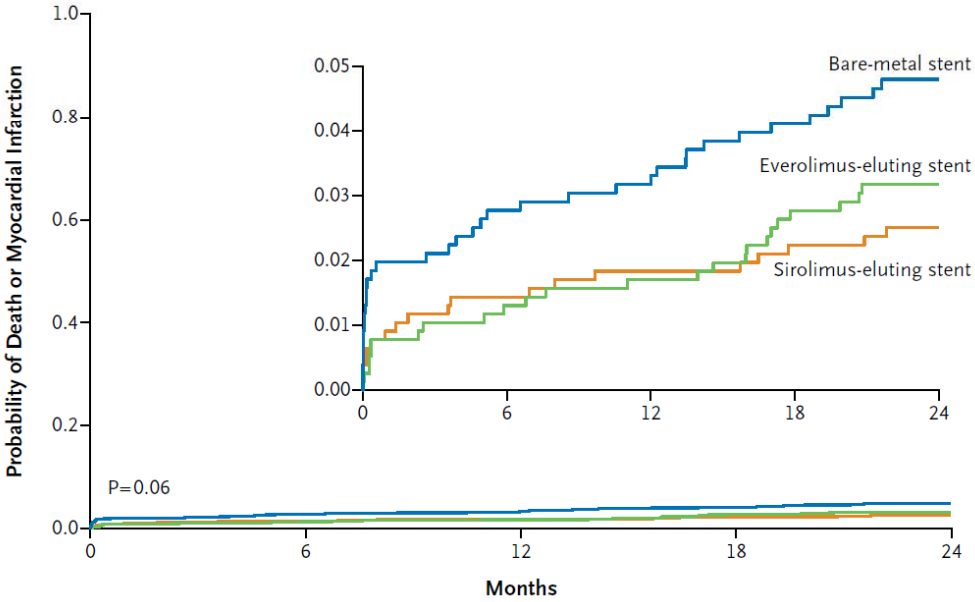
Stone G et al. *N Engl J Med* 2009;360:1946-59



# Drug-Eluting Stent Safety in Large Vessels
# BASKET-PROVE: DES vs BMS

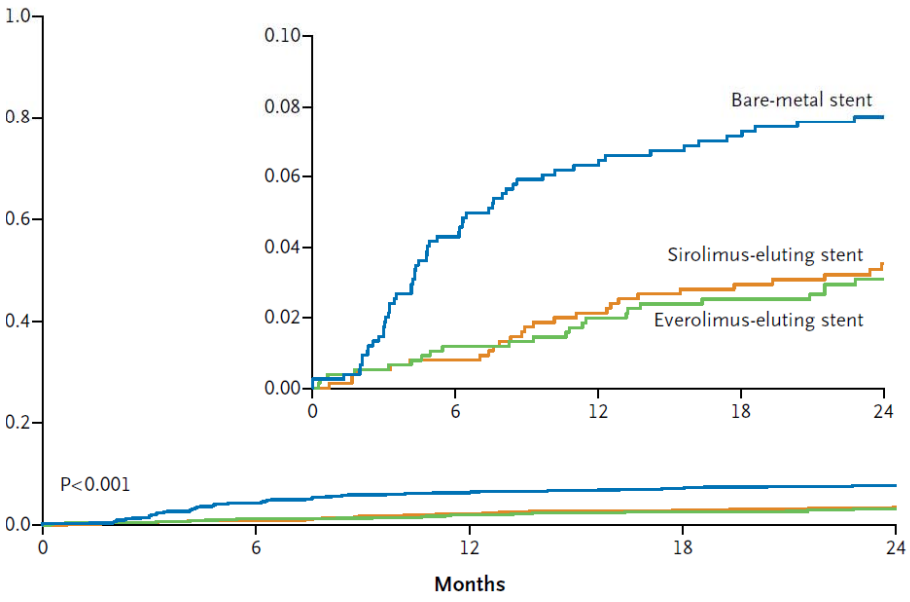
Kaiser C et al. *N Engl J Med* 2010

**Death or MI**




**2,314 Patients**

**Repeat Revasc**

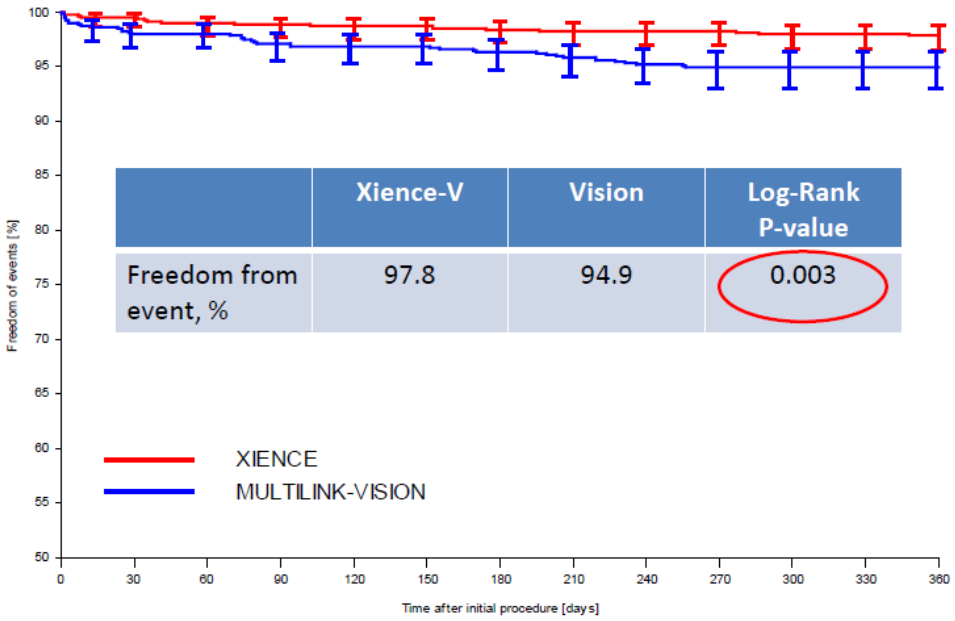



**2,314 Patients**

# Newer Generation Drug-Eluting Stents versus Bare Metal Stents in Patients with STEMI

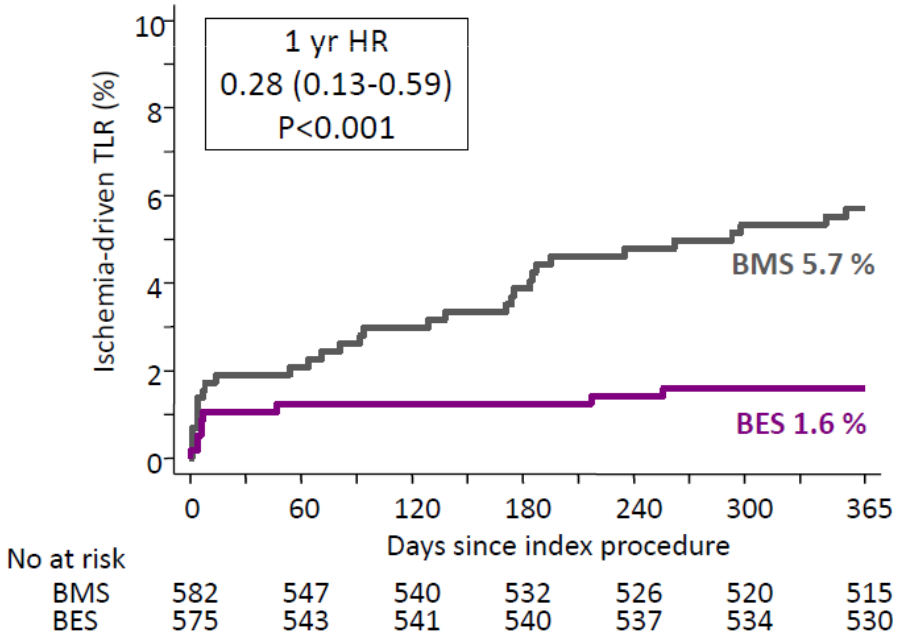
## *Target Lesion Revascularization*

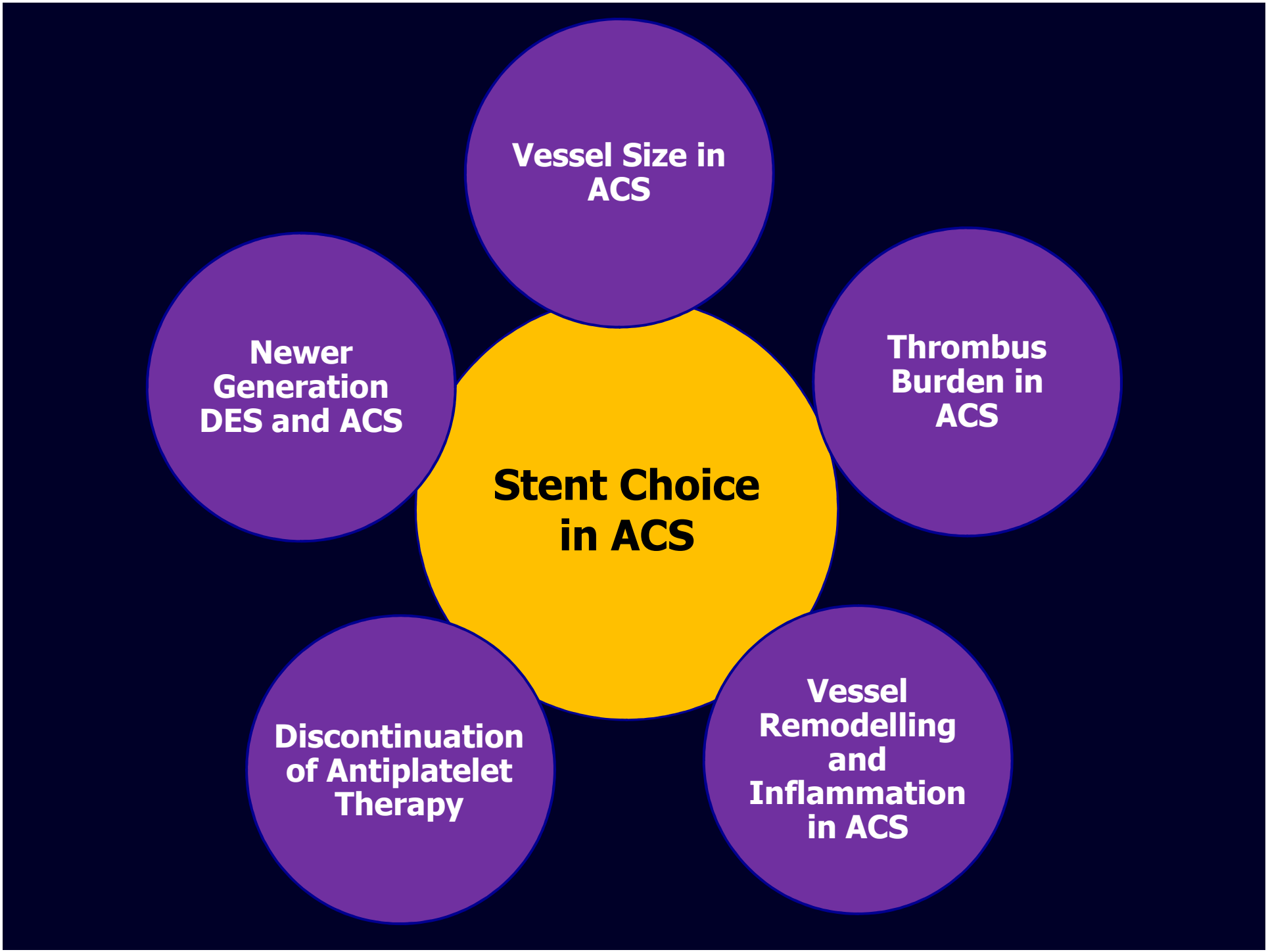
### EXAMINATION
### EES versus BMS




| | Xience-V | Vision | Log-Rank P-value |
|---|---|---|---|
| Freedom from event, % | 97.8 | 94.9 | 0.003 |

### COMFORTABLE AMI
### BES versus BMS

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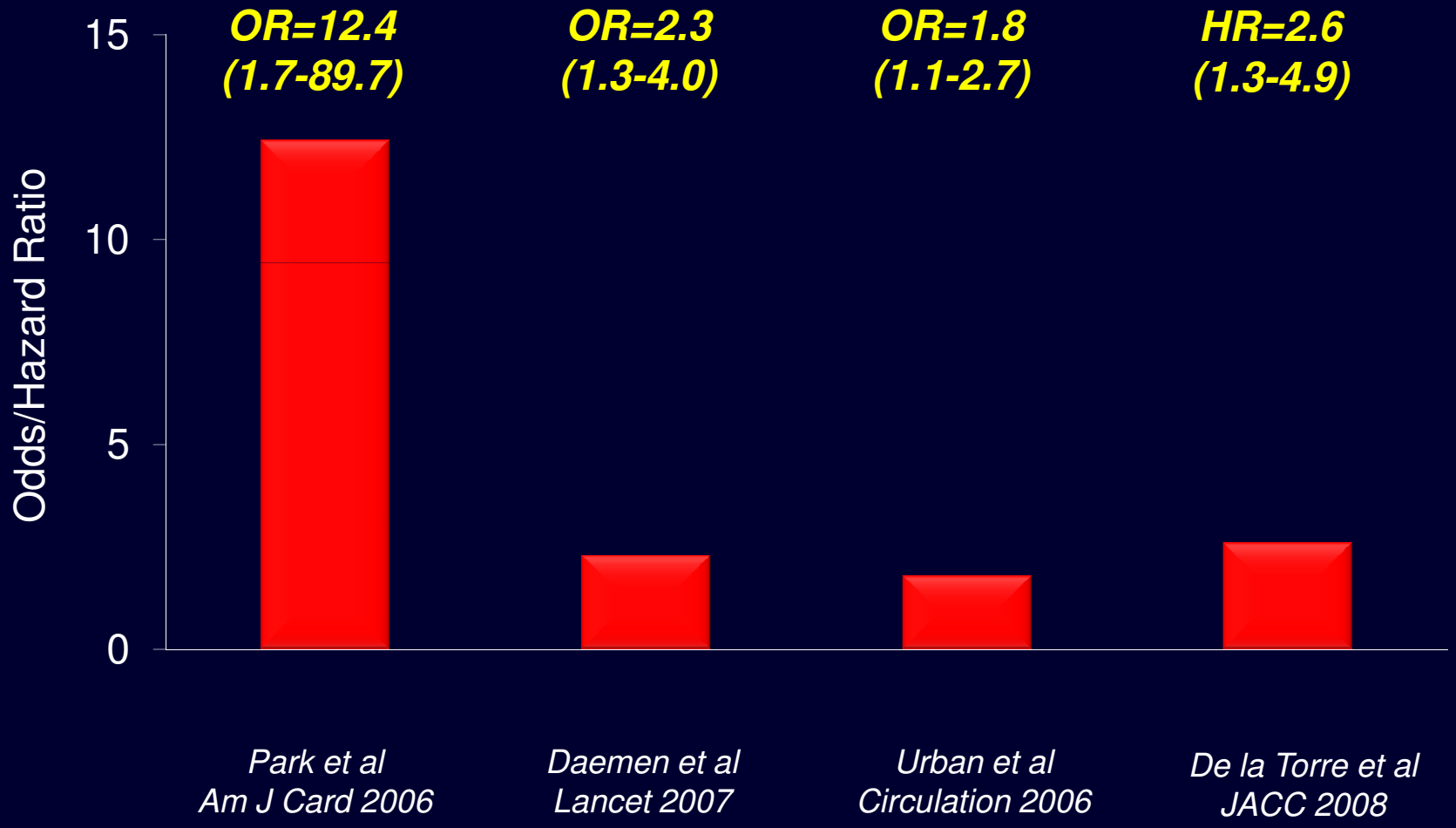
# Acute Coronary Syndrome as Predictor of Stent Thrombosis

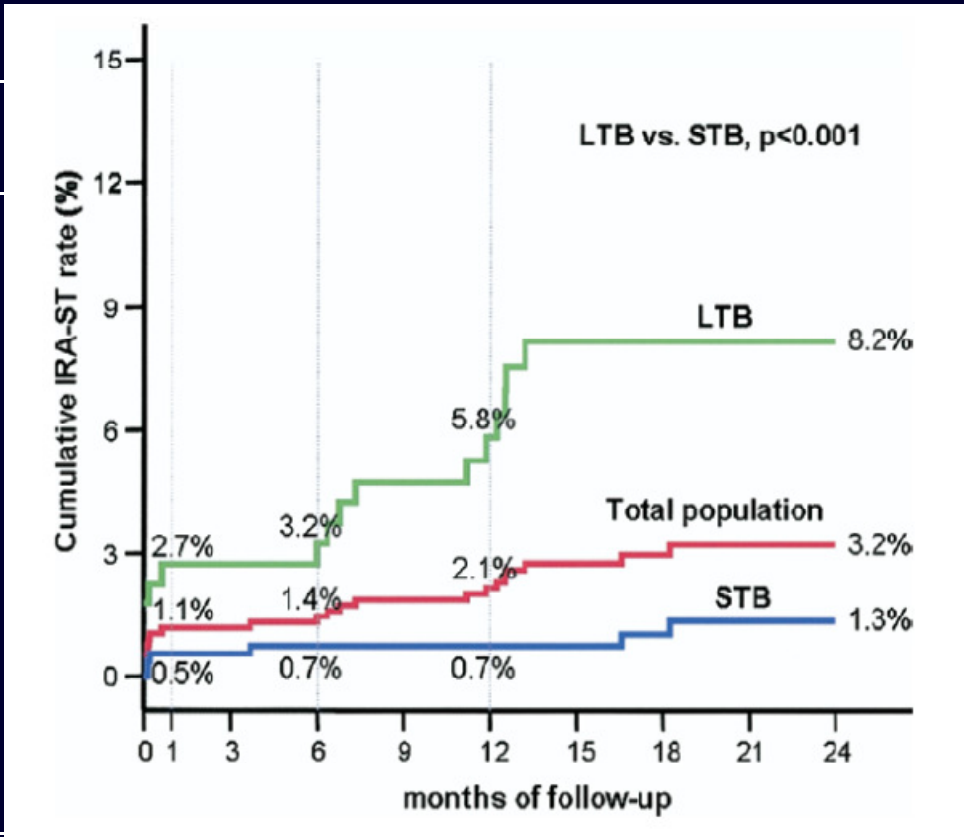


# Impact of Thrombus Burden on Risk of Stent Thrombosis With DES in Patients With STEMI

Sianos G et al. *J Am Coll Cardiol* 2007;50:573-83

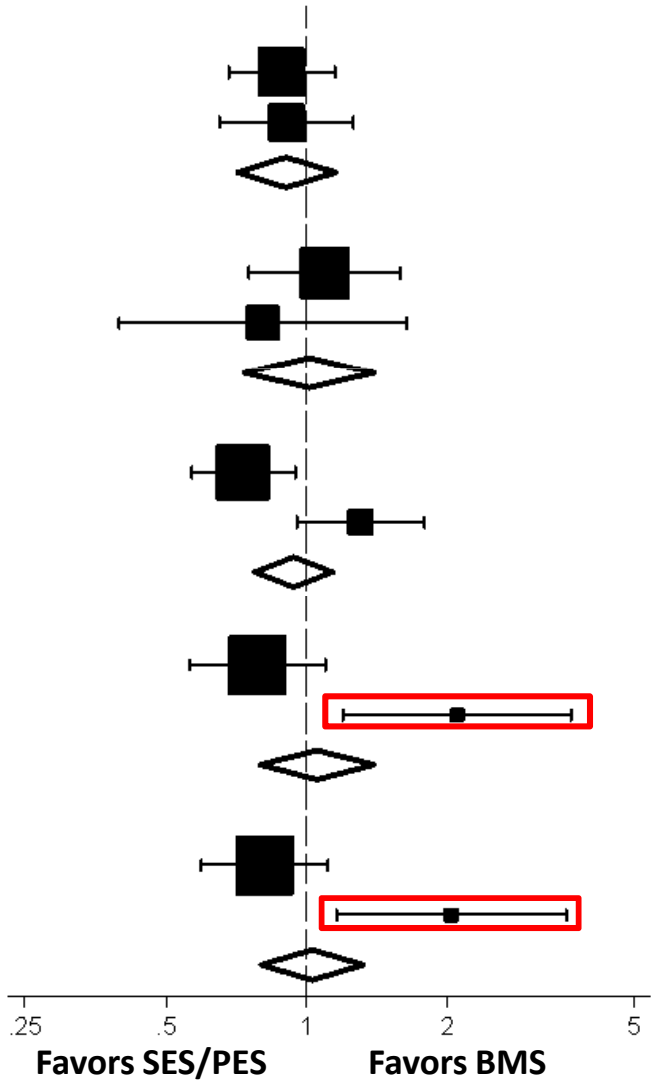
*Independent Predictors of ST*

| Variable | Hazard Ratio | 95% CI |
|---|---|---|
| Age | 0.6 | 0.4-0.8 |
| Index ST | 6.2 | 2.1-18.9 |
| Bifurcation | 4.1 | 1.6-10.0 |
| Thrombectomy | 0.1 | 0.01-0.8 |
| Large thrombus | 8.7 | 3.4-22.5 |



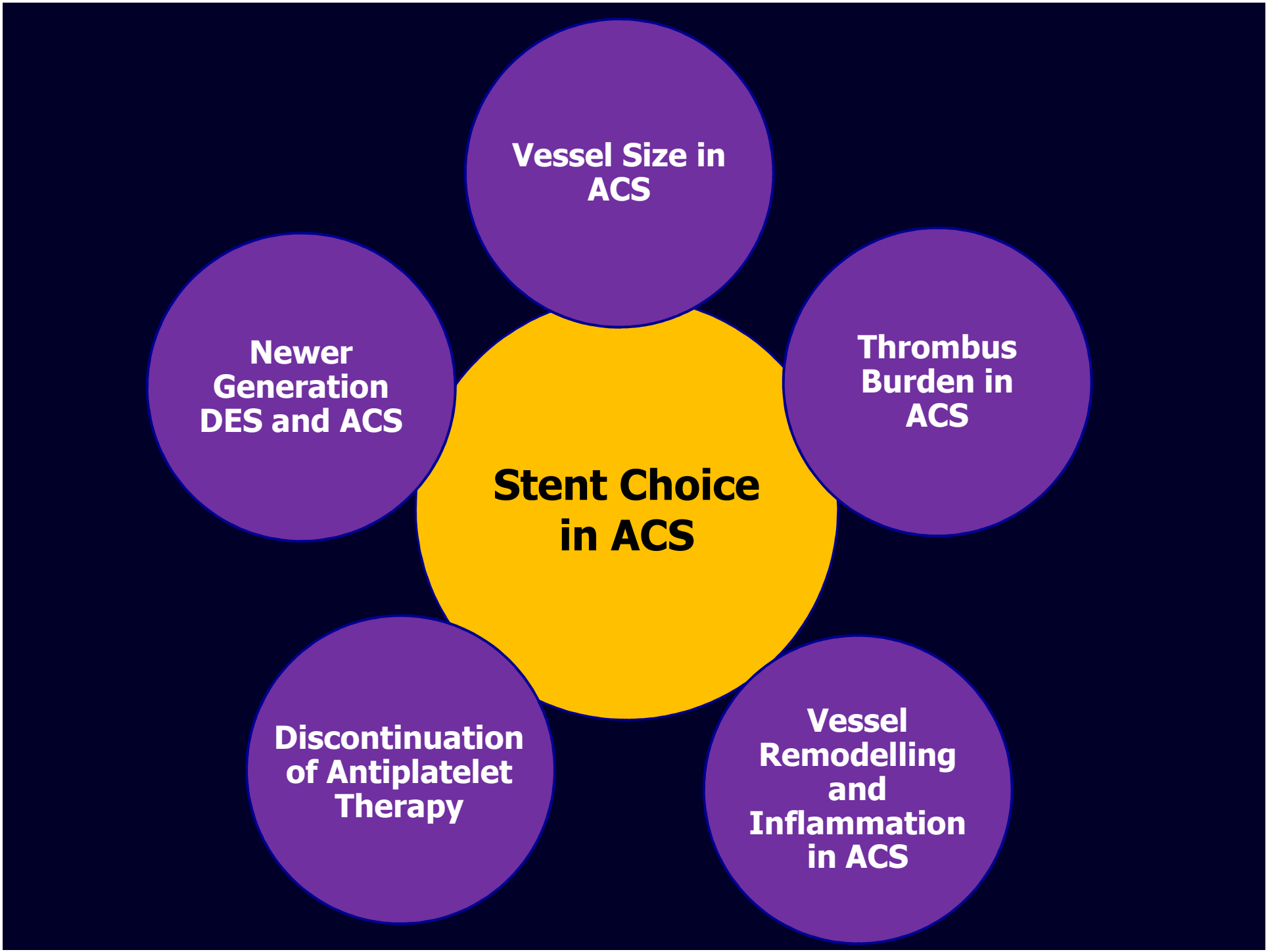
# Risk of Ischemic Events and Stent Thrombosis Stratified According to Time and Stent Type (DES vs BMS) in STEMI

**15 RCTs Comparing DES and BMS in 7,843 STEMI Patients**




| | RR (95% CI) | p-inter |
|---|---|---|
| **Death** | | 0.91 |
| 0 to 1 year | 0.89 (0.68-1.15) | |
| 1 to max FU | 0.91 (0.65-1.26) | |
| 0 to max FU | 0.91 (0.71-1.15) | |
| **Cardiac death** | | 0.46 |
| 0 to 1 year | 1.09 (0.75-1.59) | |
| 1 to max FU | 0.81 (0.40-1.64) | |
| 0 to max FU | 1.01 (0.73-1.40) | |
| **MI** | | 0.006 |
| 0 to 1 year | 0.73 (0.57-0.94) | |
| 1 to max FU | 1.30 (0.95-1.78) | |
| 0 to max FU | 0.94 (0.78-1.14) | |
| **Definite ST** | | 0.0046 |
| 0 to 1 year | 0.79 (0.56-1.10) | |
| 1 to max FU | 2.10 (1.20-3.68) | |
| 0 to max FU | 1.05 (0.79-1.39) | |
| **Definite/ Probable ST** | | 0.0092 |
| 0 to 1 year | 0.81 (0.60-1.11) | |
| 1 to max FU | 2.04 (1.16-3.60) | |
| 0 to max FU | 1.03 (0.80-1.32) | |

*Kalesan, Windecker*


Vessel Size in ACS
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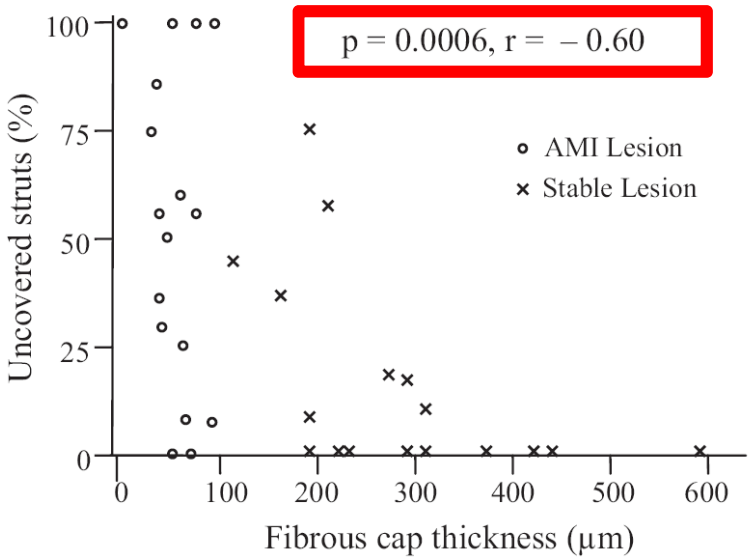
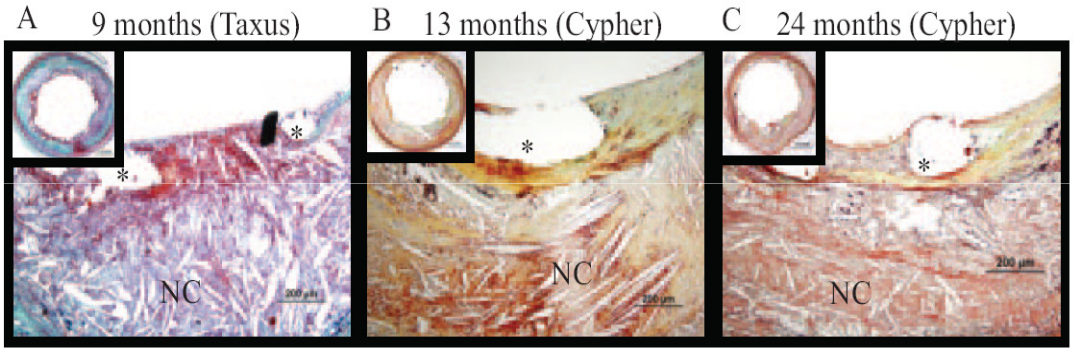
# Arterial Healing at Culprit Sites after DES Implantation in Patients with Acute MI and Stable Angina – An Autopsy Study

Nakazawa et al. *Circulation* 2008; 118:1138-1145

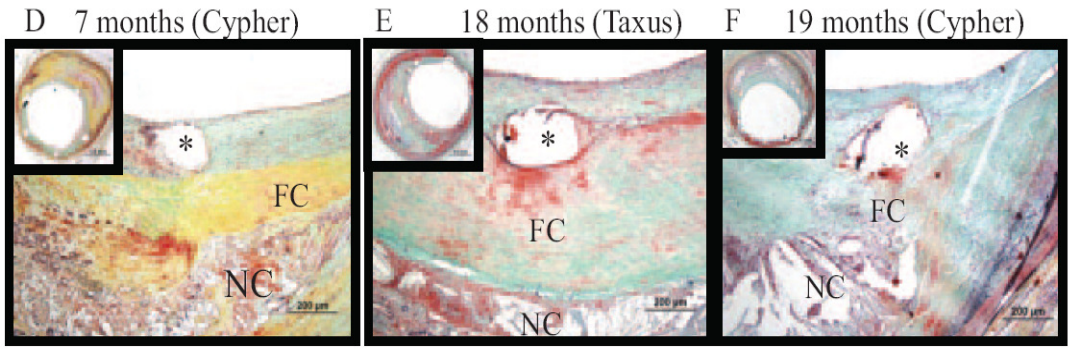
**Correlation between fibrous cap thickness and % uncovered struts**



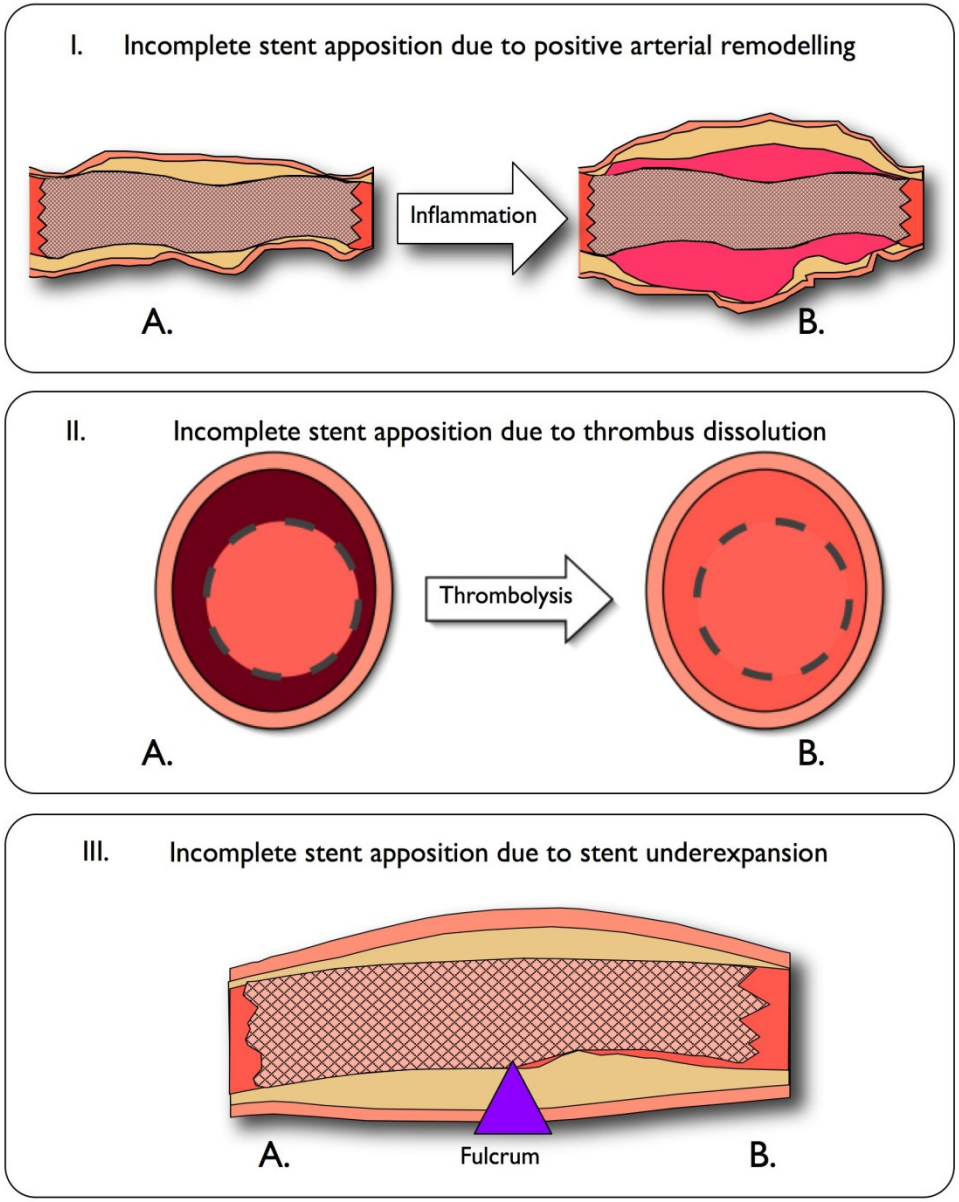

*AMI lesions (with Plaque Rupture)*




*Stable Lesions (with Fibroatheroma and thick cap)*



# Stent Malapposition/Vessel Remodeling




Cook S et al. *Circulation* 2007

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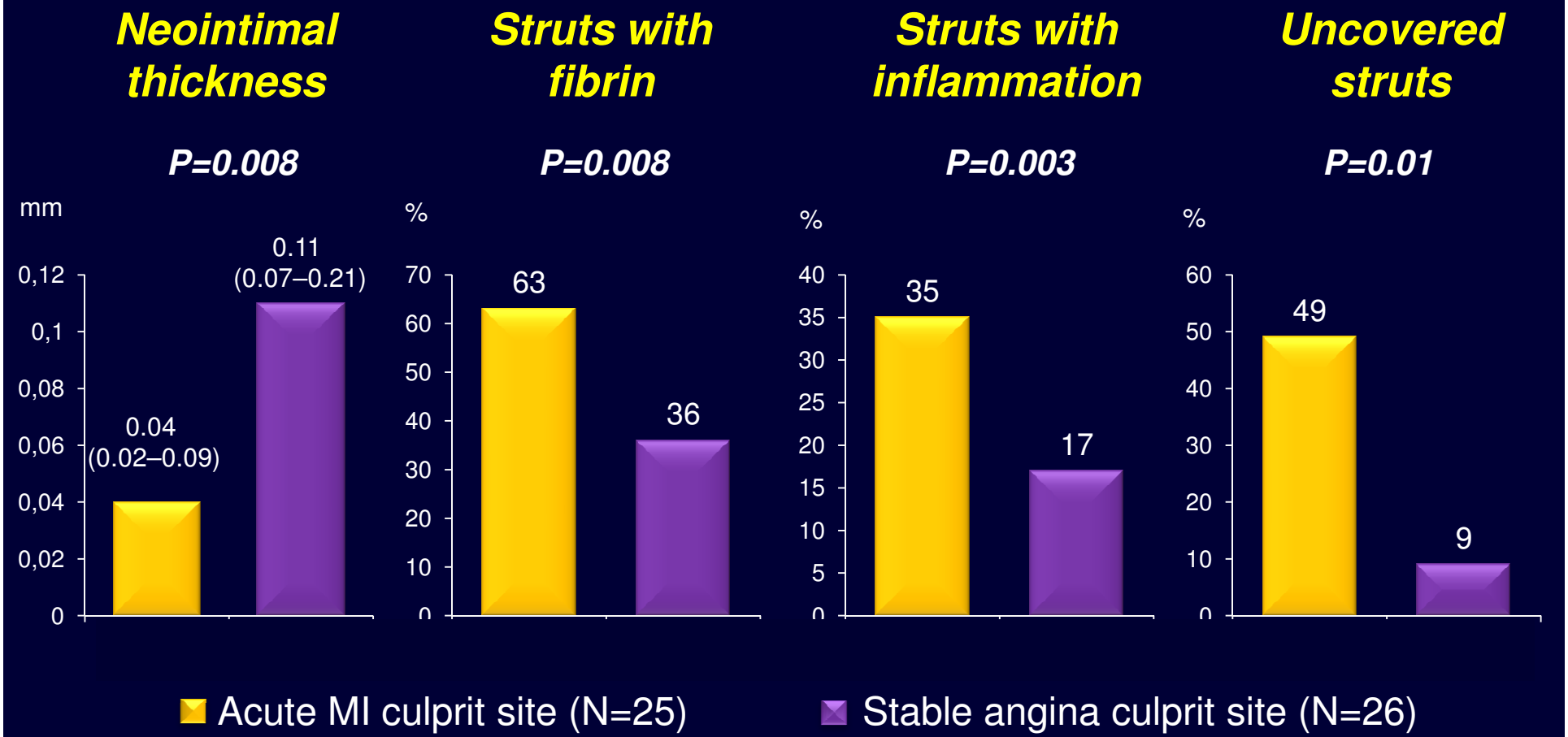
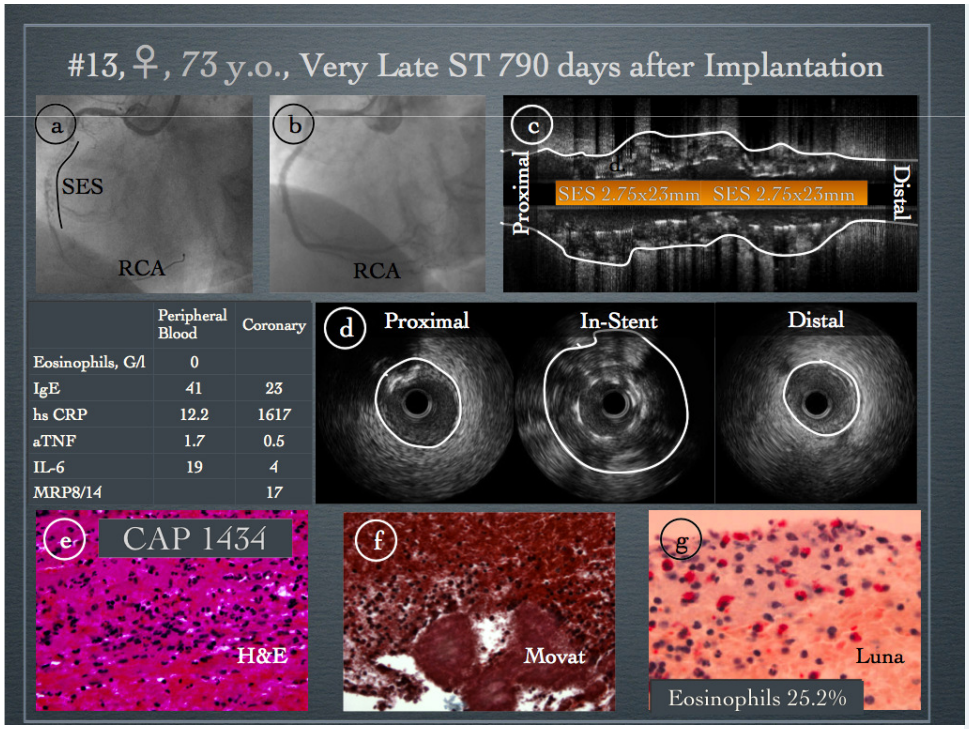
Nakazawa et al. *Circulation* 2008; 118:1138-1145



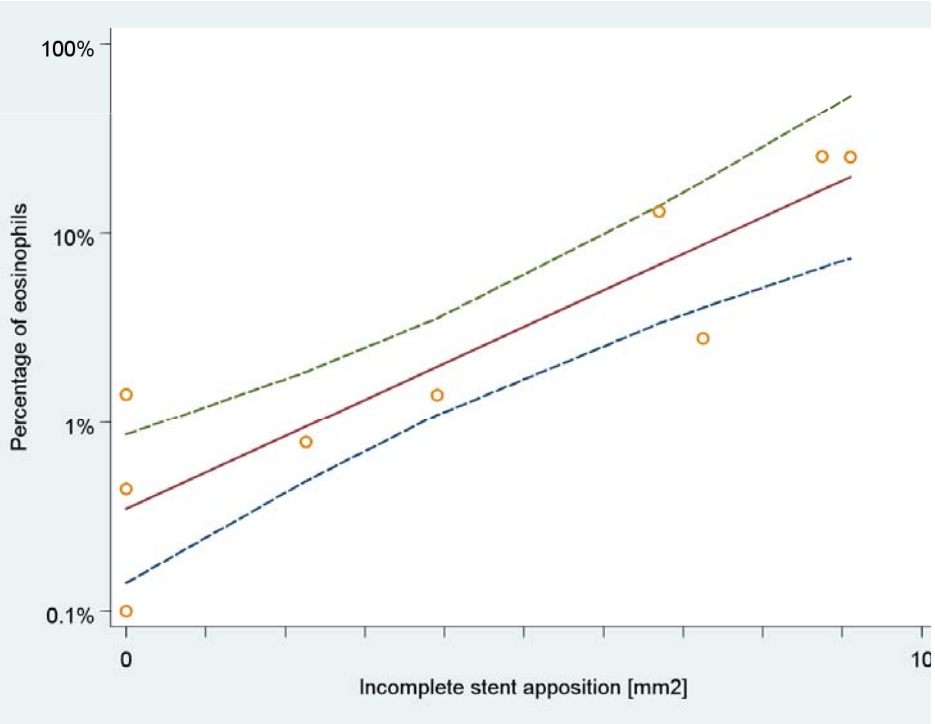
# Association of Eosinophilic Infiltrates of Thrombus Aspirates With Vessel Remodeling

Cook S, Ladich E, Virmani R, Windecker S. *Circulation* 2009

## *Eosinophilic Infiltrates*

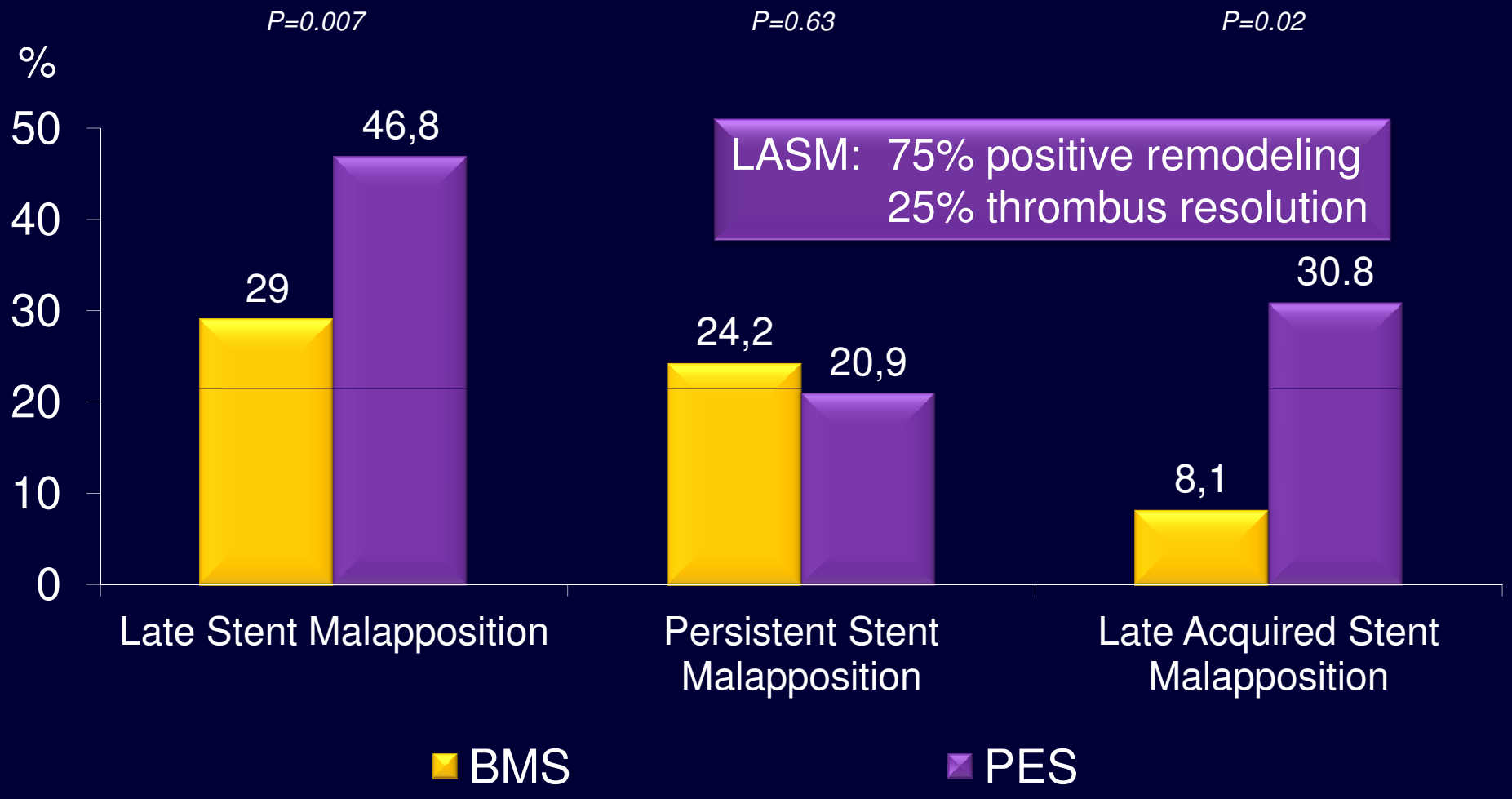



## *Vessel Remodeling*



# Late Acquired Stent Malapposition in HORIZONS-AMI

Guo N et al. *Circulation* 2010;122:1088-84

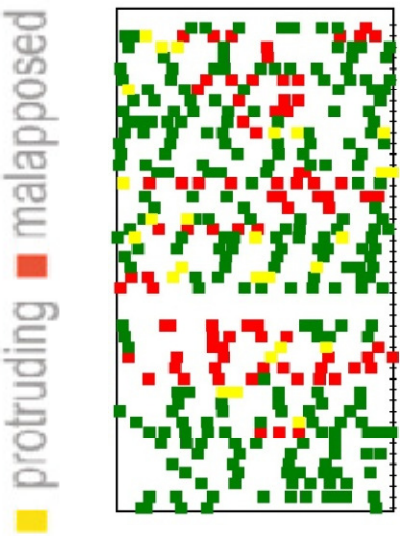


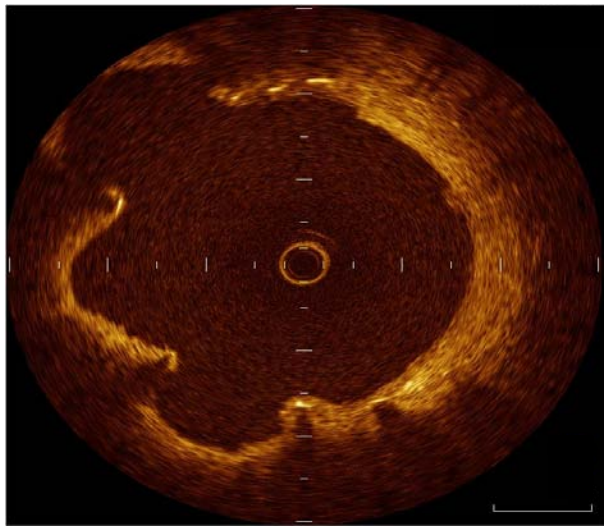

Independent predictors of LASM:

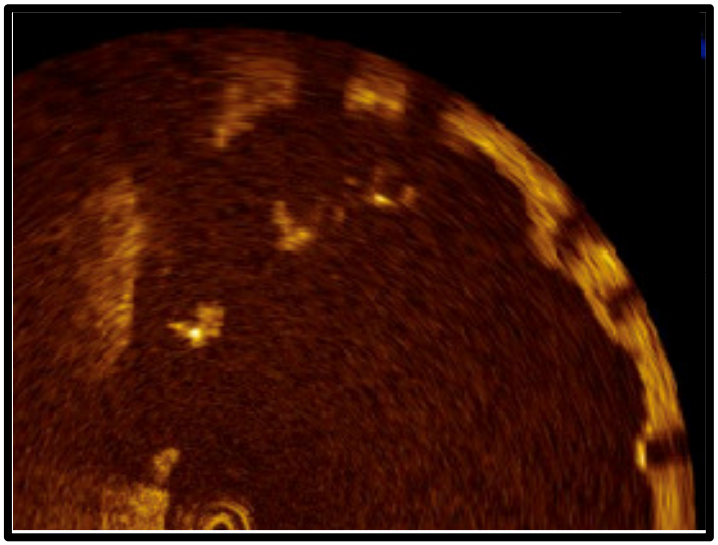
-plaque/thrombus protrusion at baseline (OR=5.6, 95% CI 2.3-13.5)

-PES use (OR=6.3, 95% CI 2.2-18.6)

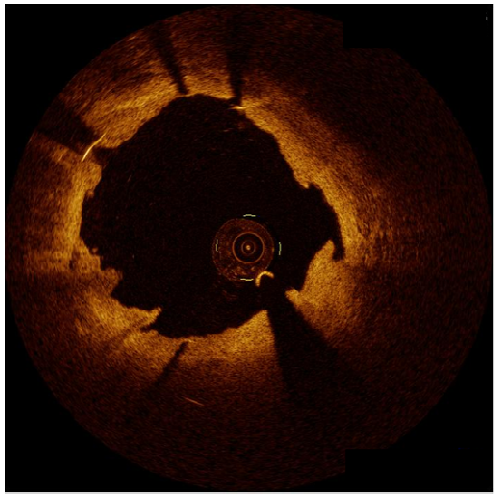
OCT 5 yrs after STEMI

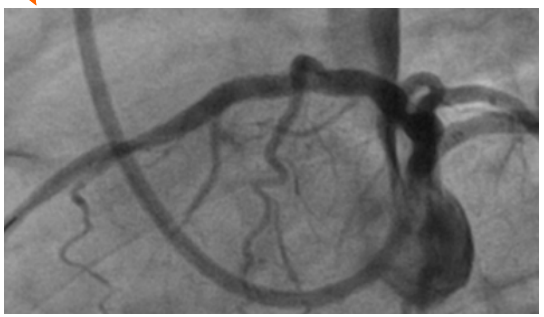


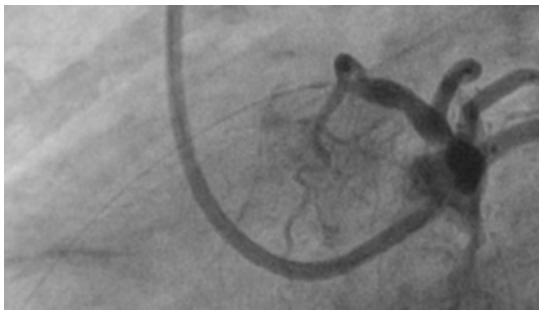





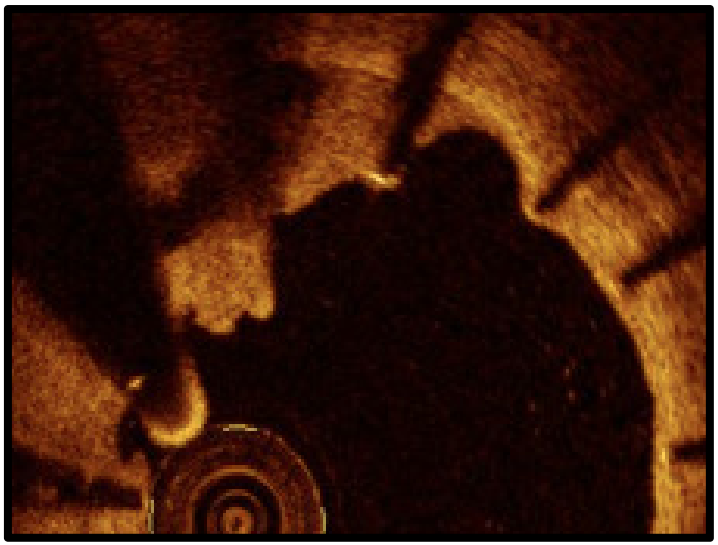
STEMI @ BL







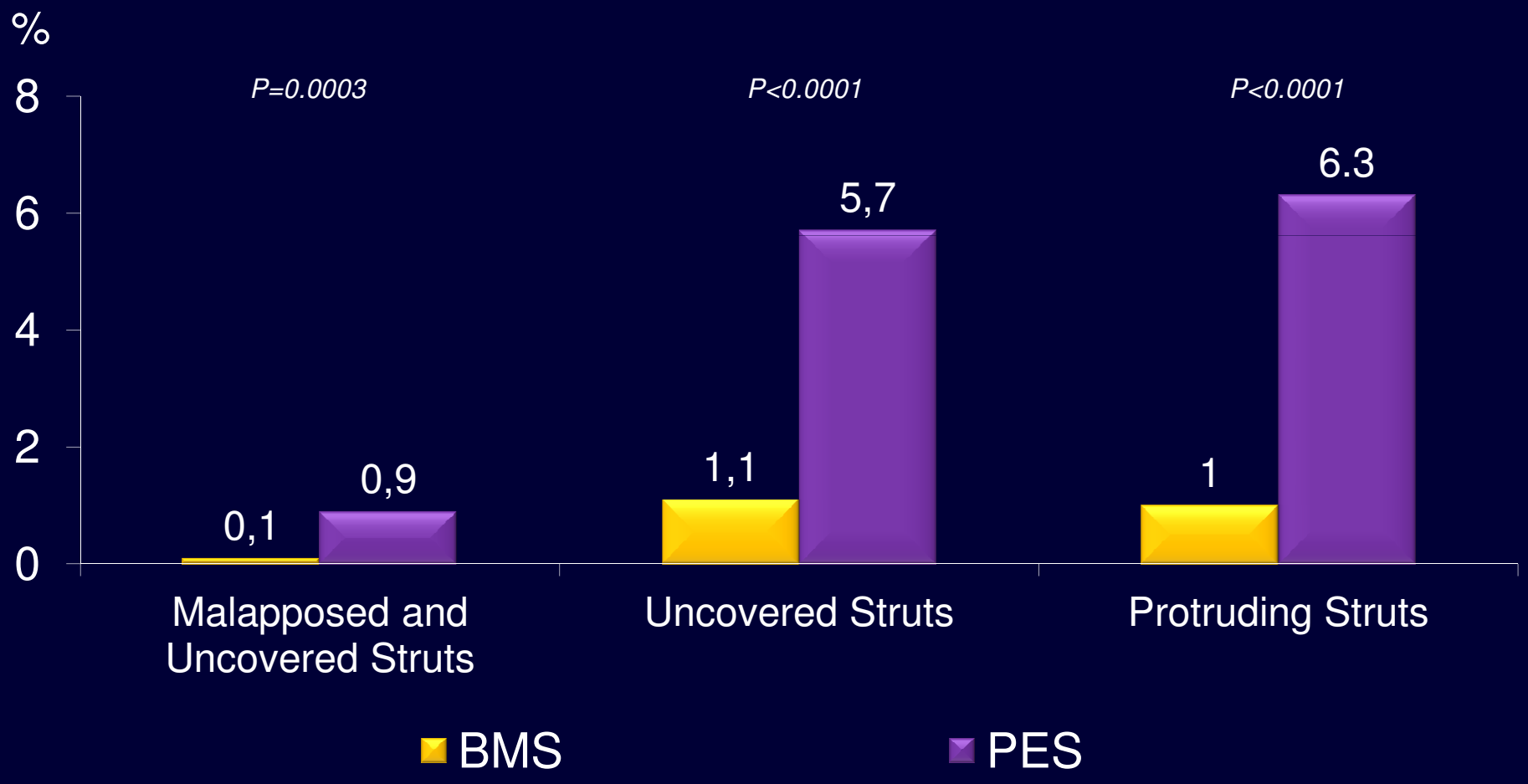
Stent Thrombosis @ 5.5 yrs

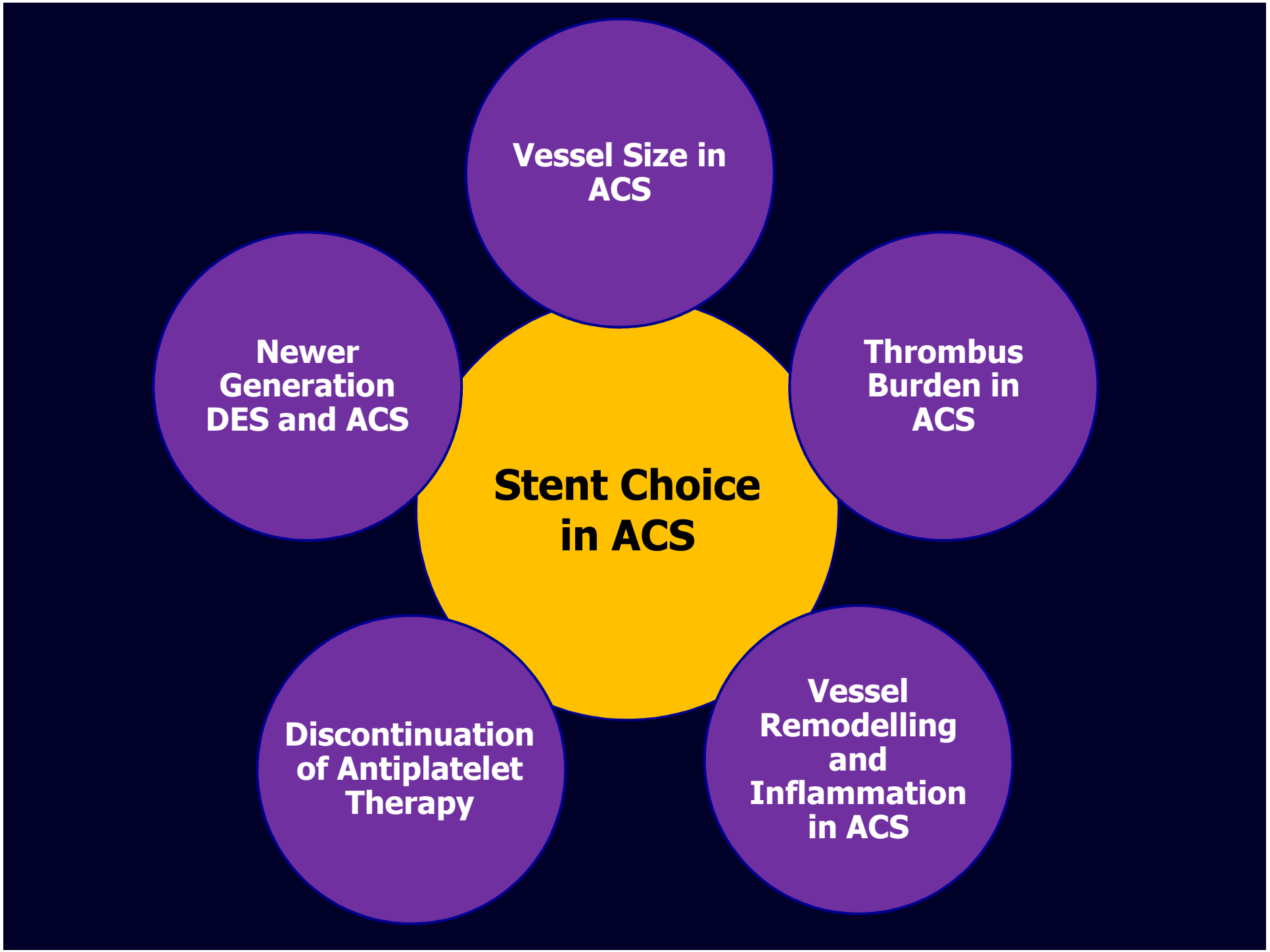


Courtesy Räber/Windecker, SIRTAX OCT

# Strut Coverage, Malapposition and Protrusion in HORIZONS-AMI – OCT Substudy @ 13 Months

Guagliumi G et al. *Circulation* 2010;123:274-81

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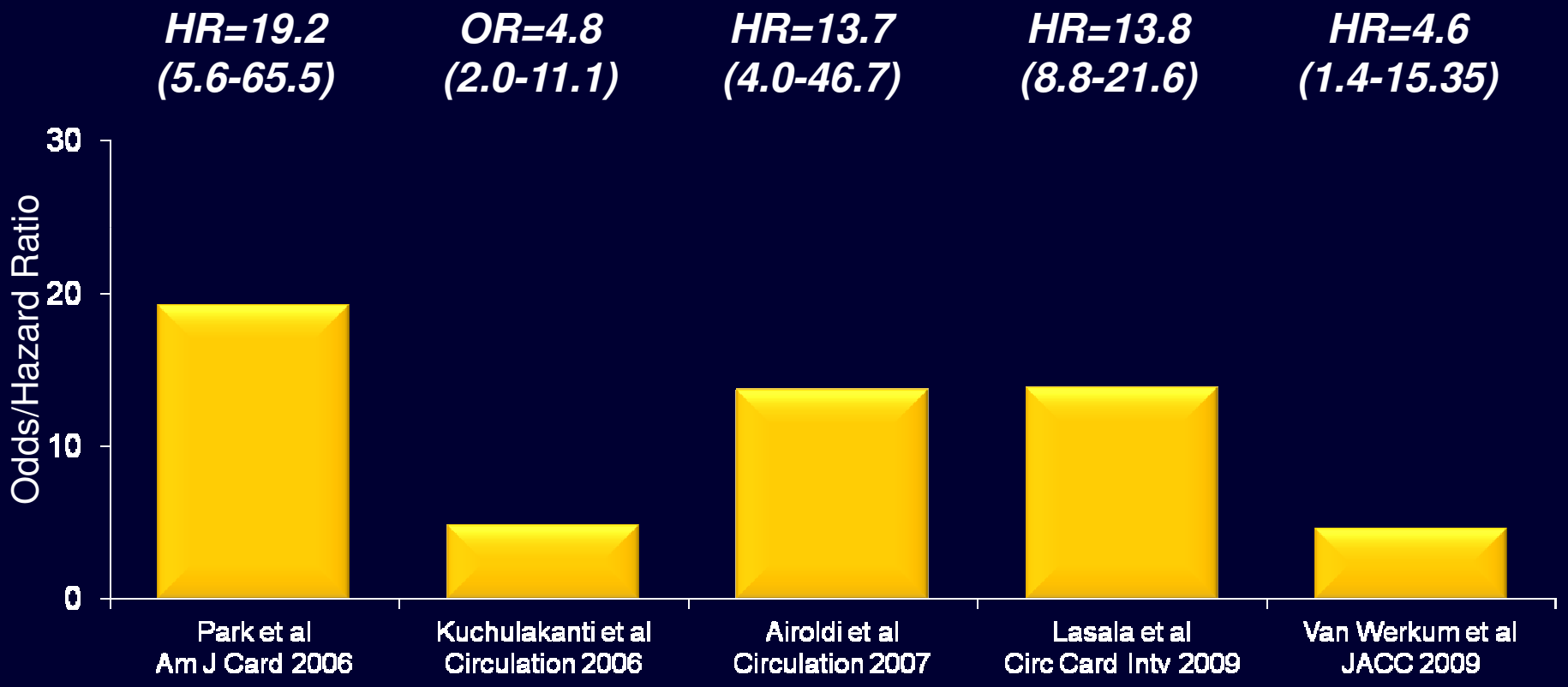
# Discontinuation of Antiplatelet Therapy as Predictor of Stent Thrombosis



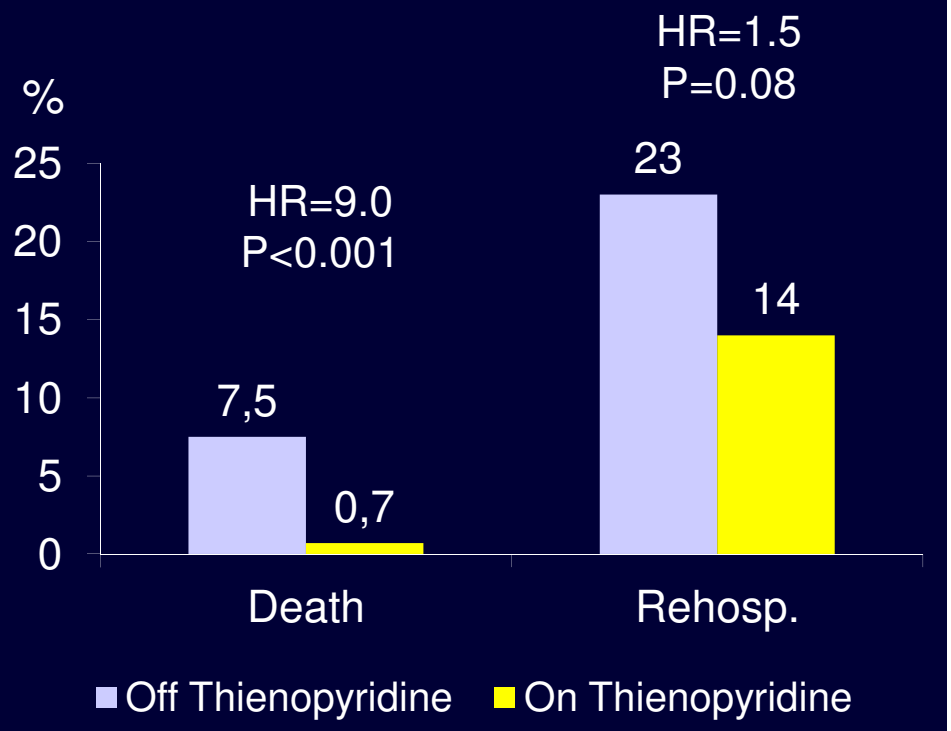
# Premature Discontinuation of Thienopyridine Therapy After DES Implantation

Spertus JA et al. *Circulation* 2006;113:2803-9

Multicenter, prospective PREMIER registry in patients admitted with myocardial infarction
-500 DES patients enrolled at 19 sites
-68 (14%) patients d/c thienopyridine

Factors associated with premature Thienopyridine discontinuation
-older age
-lower socioeconomic status
-preexisting cardiovascular disease
-inadequate discharge instructions
-lack of referral to cardiac rehab

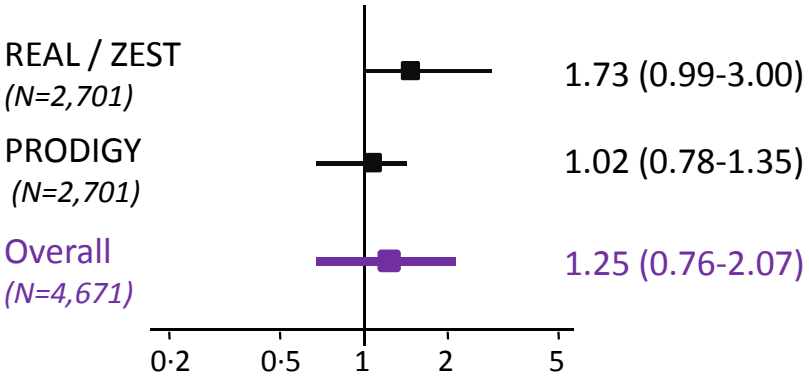
*Mortality Between 30 Days and 1 Year*



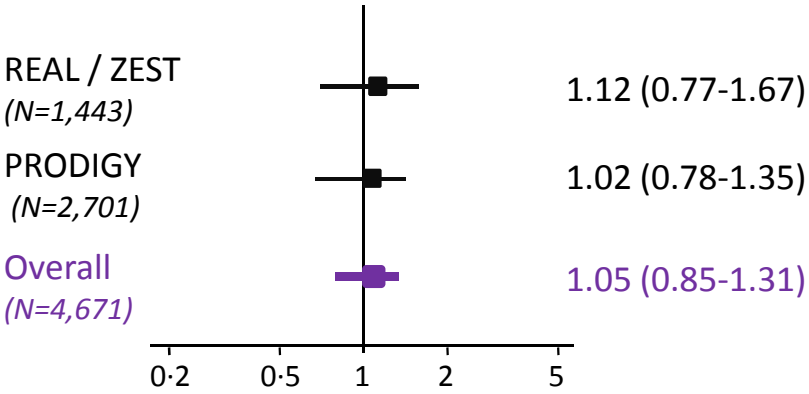
# DAPT Following DES

## Death, MI, or Stroke

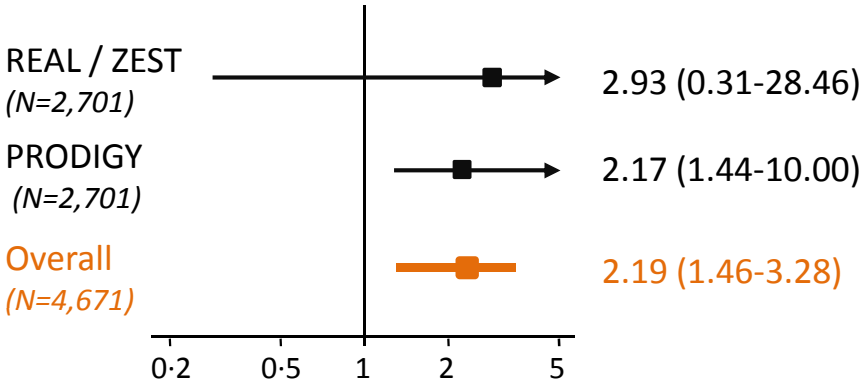
### >1 Year vs. ≤1 Year

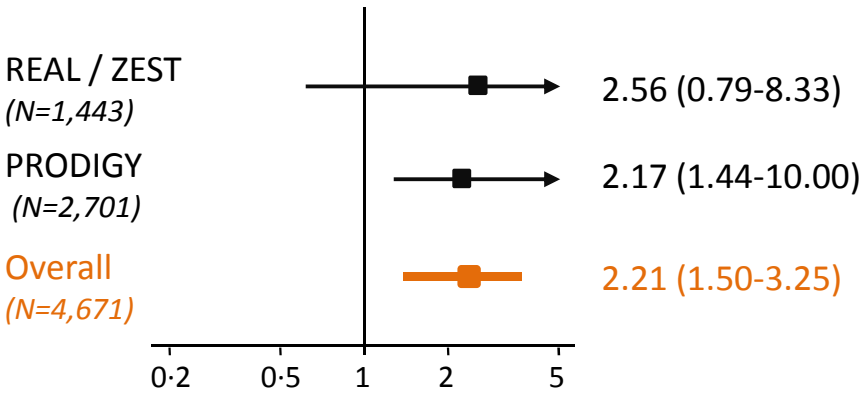



### >6 Months vs. ≤6 Months




## Bleeding

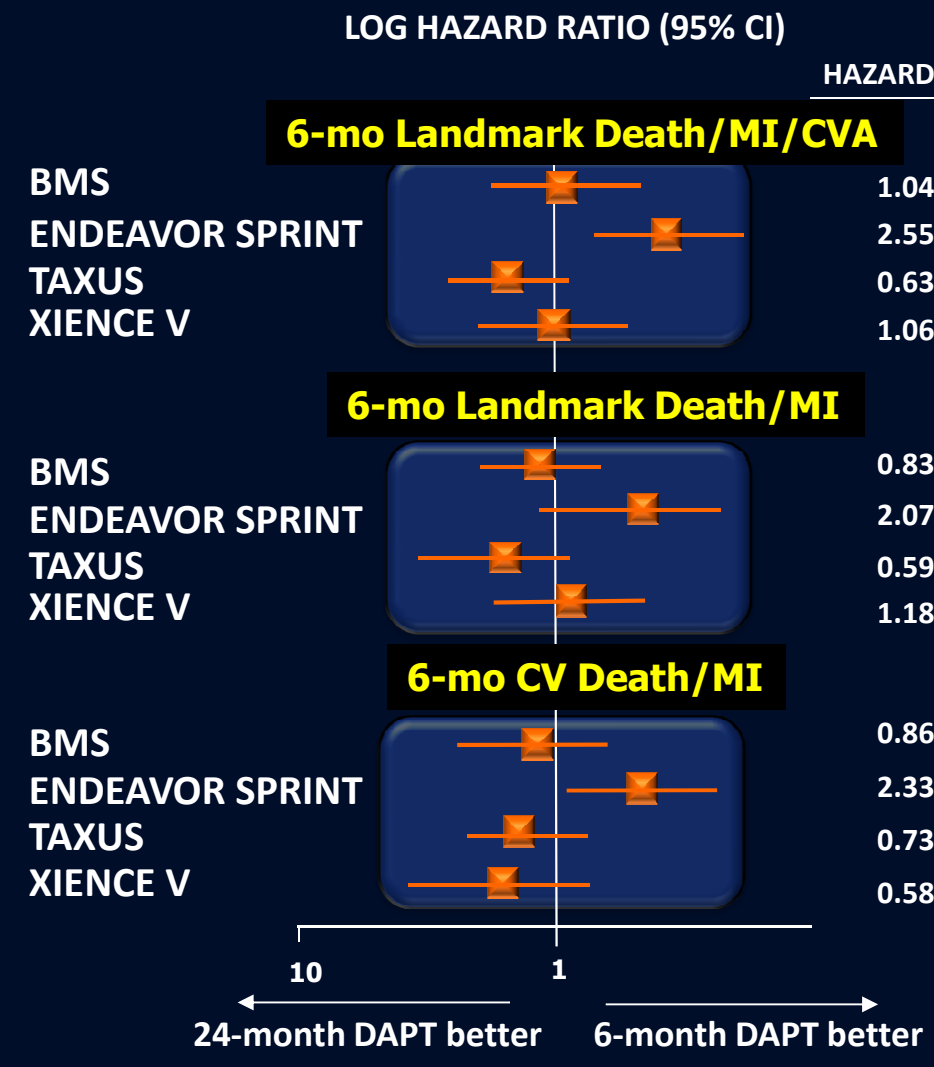



*Adapted from Kastrati A. ESC Congress 2011, Paris*

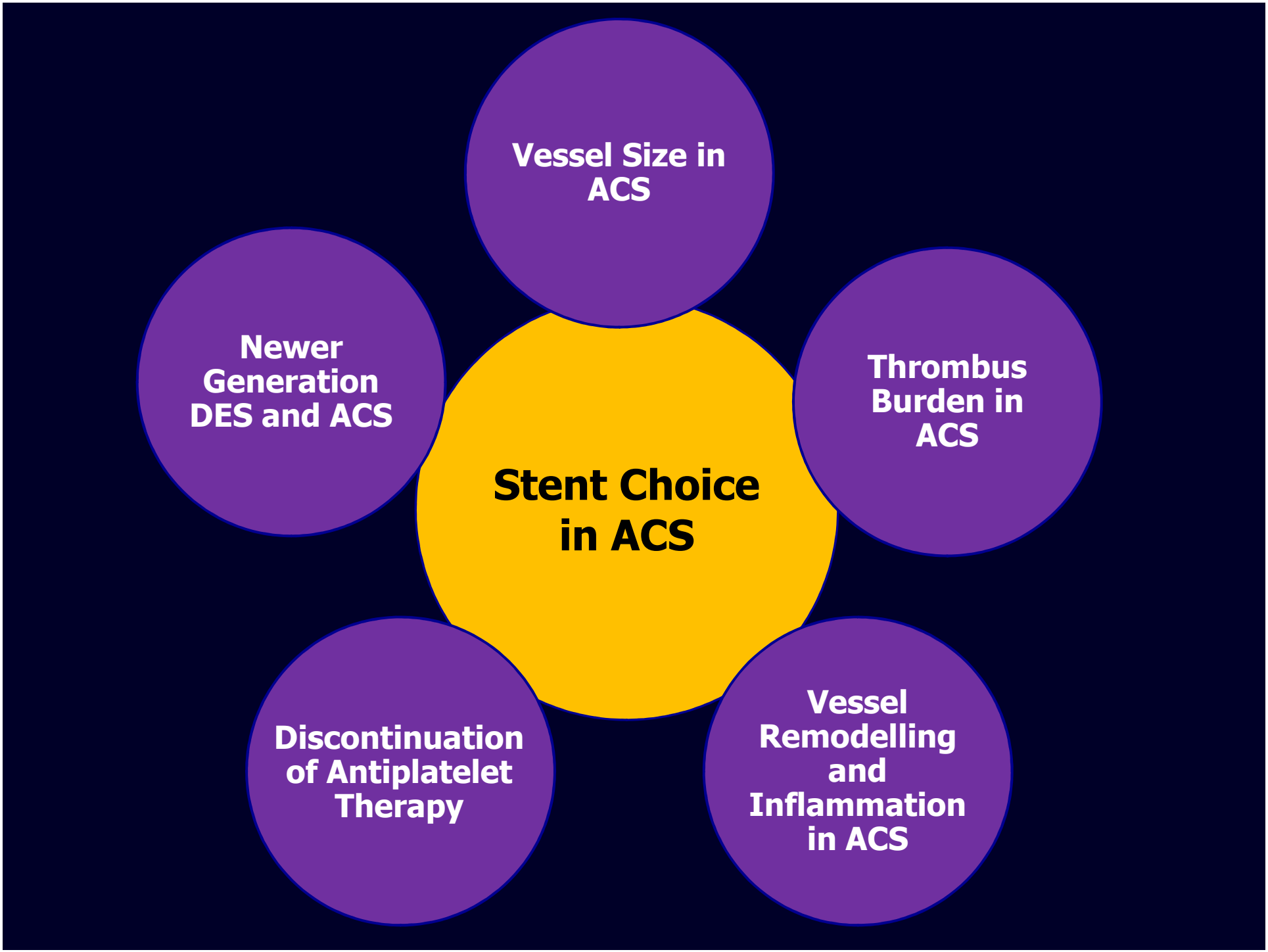
# Pt oriented Outcome stratified by stent

## From 6 up to 24 months



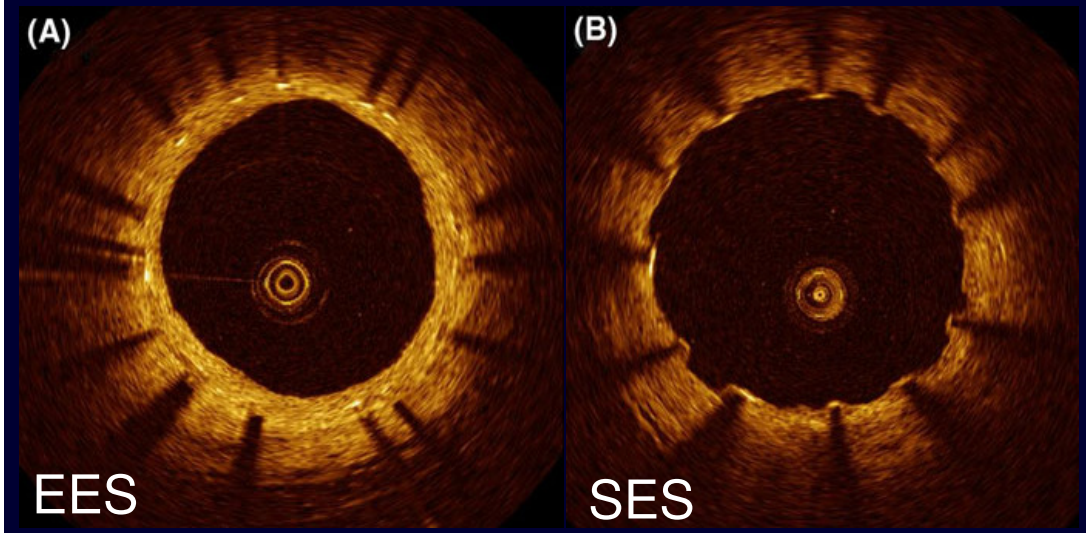

*Courtesy: M Valgimigli*

PRODIGY

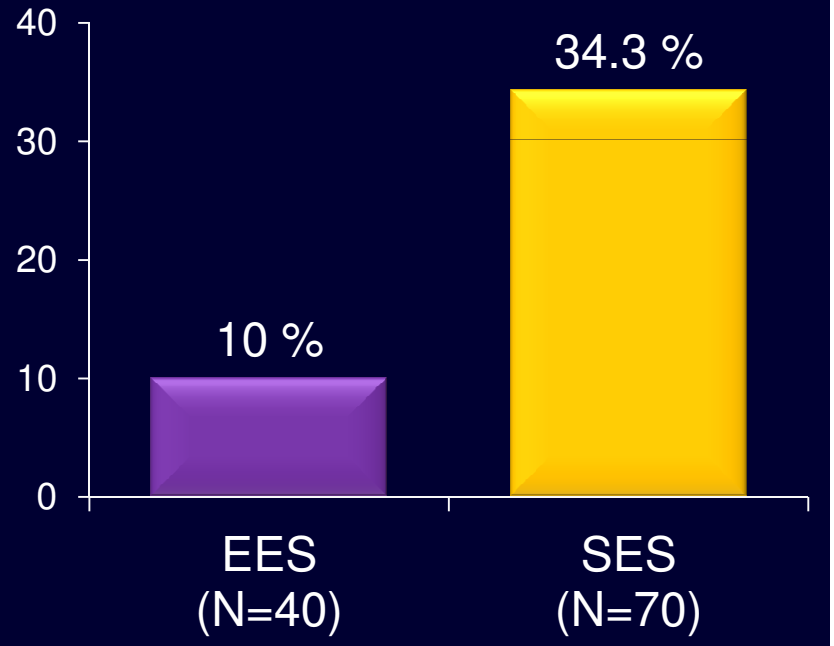

Vessel Size in ACS
Newer Generation DES and ACS
Thrombus Burden in ACS
Stent Choice in ACS
Discontinuation of Antiplatelet Therapy
Vessel Remodelling and Inflammation in ACS

# Struts Coverage 9 Months After Implantation of Everolimus- and Sirolimus-Eluting Stents

Choi et al. *Int J Cardiovasc Imaging* 2011



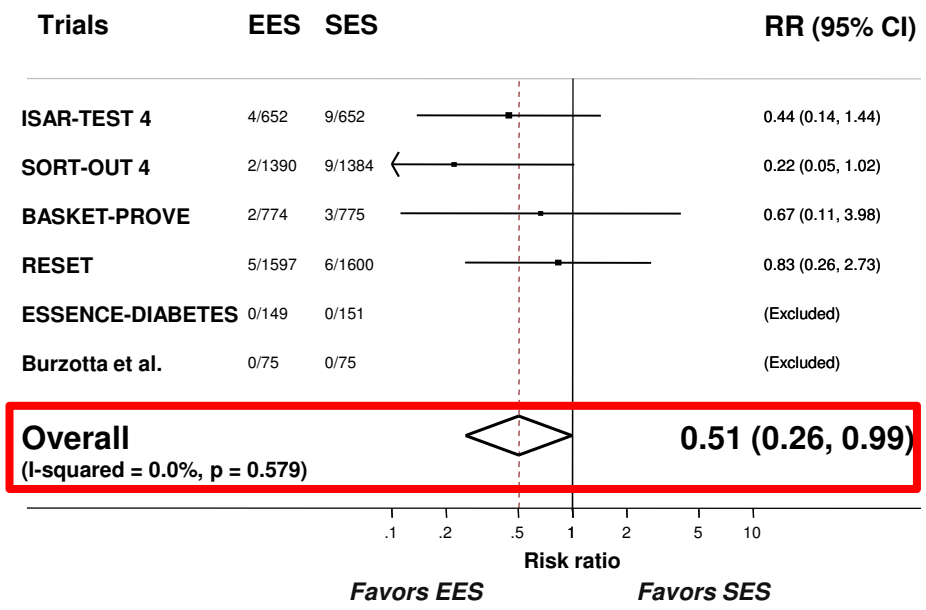

***Lesions With >10% Uncovered Struts***



# Everolimus-Eluting Stent versus Early Generation DES

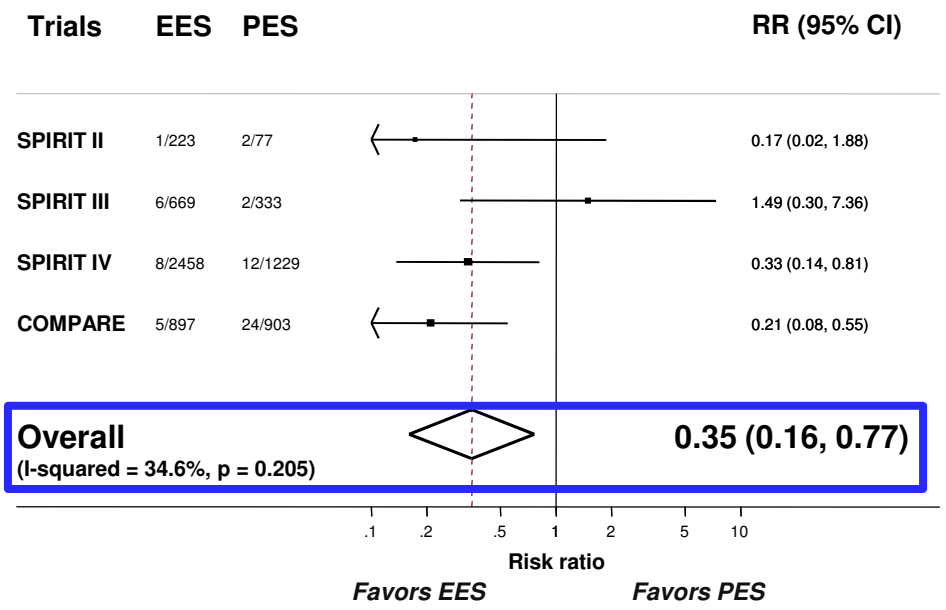
## *DES Safety – Risk of Stent Thrombosis*

**EES vs SES**




**N = 11,167**

**EES vs PES**



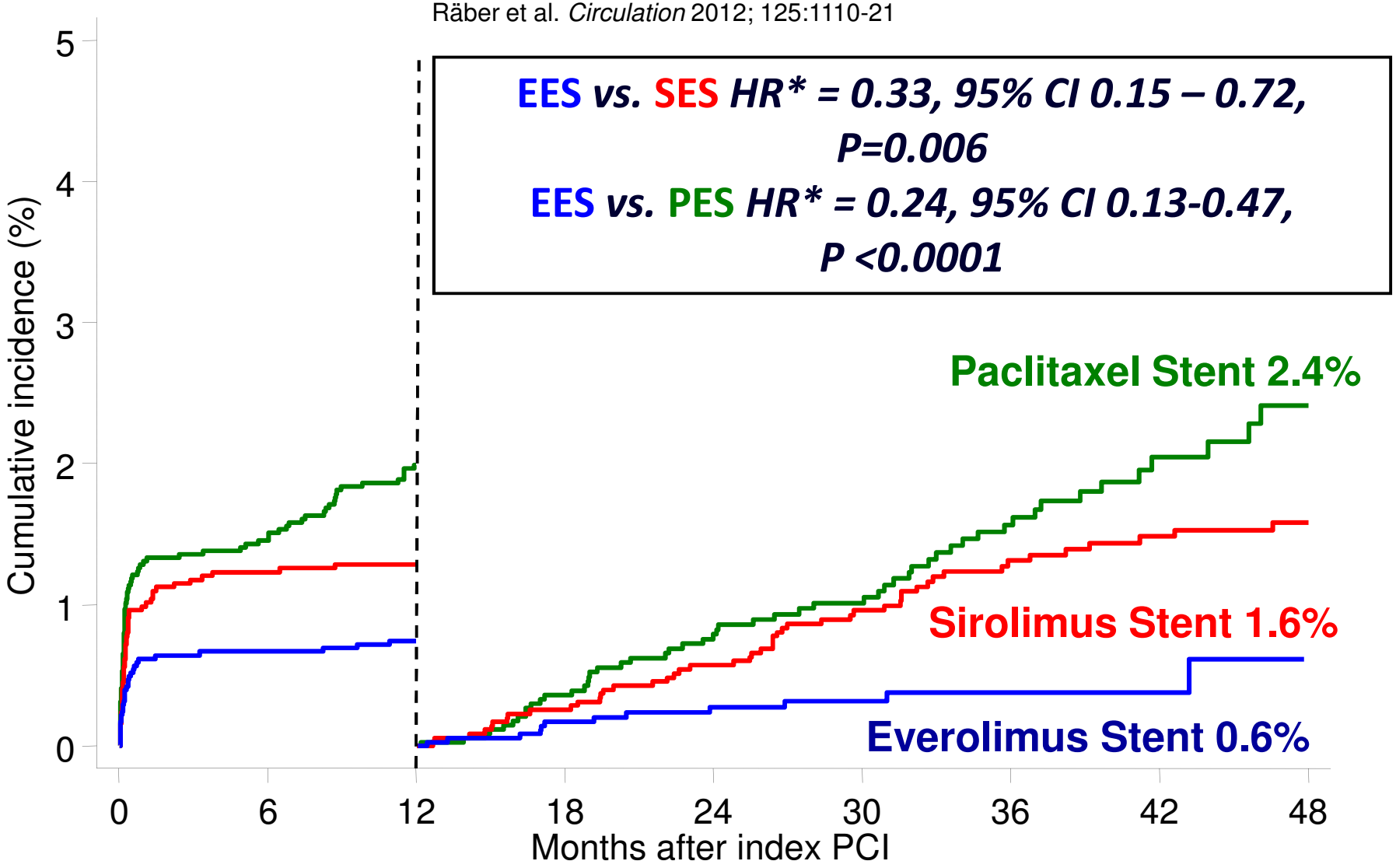

**N = 6,789**

*Kalesan, Windecker*

# Bern-Rotterdam Cohort Study

## *Very Late Definite ST (1-4 yrs)*

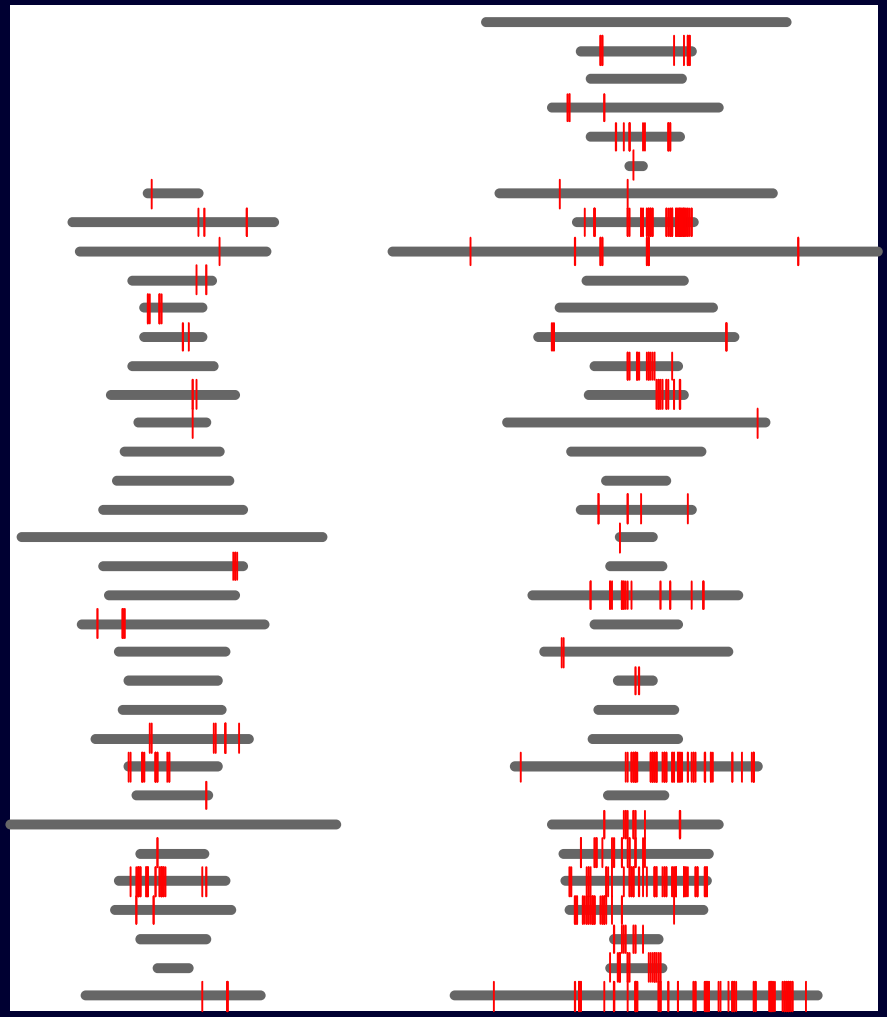
Räber et al. *Circulation* 2012; 125:1110-21




*from Cox proportional hazards model

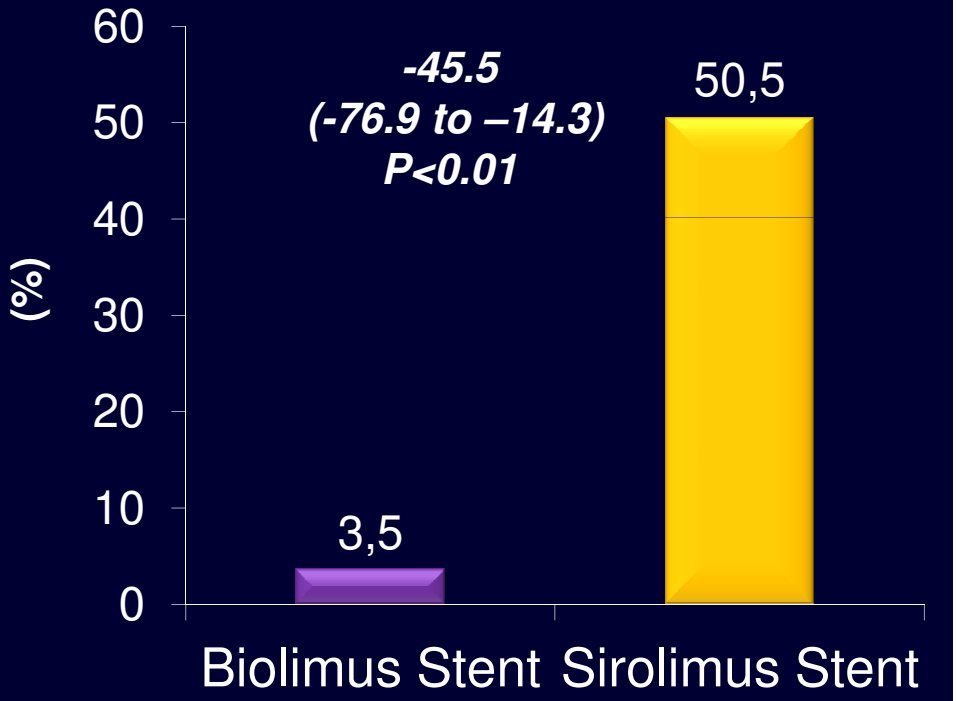
# Biolimus Eluted from Biodegradable Polymer versus Sirolimus Eluted from Durable Polymer

Barlis P et al. *Eur Heart J* 2010



**Biolimus N=29** **Sirolimus N=35**

***Lesions With At Least 5% Uncovered Struts***



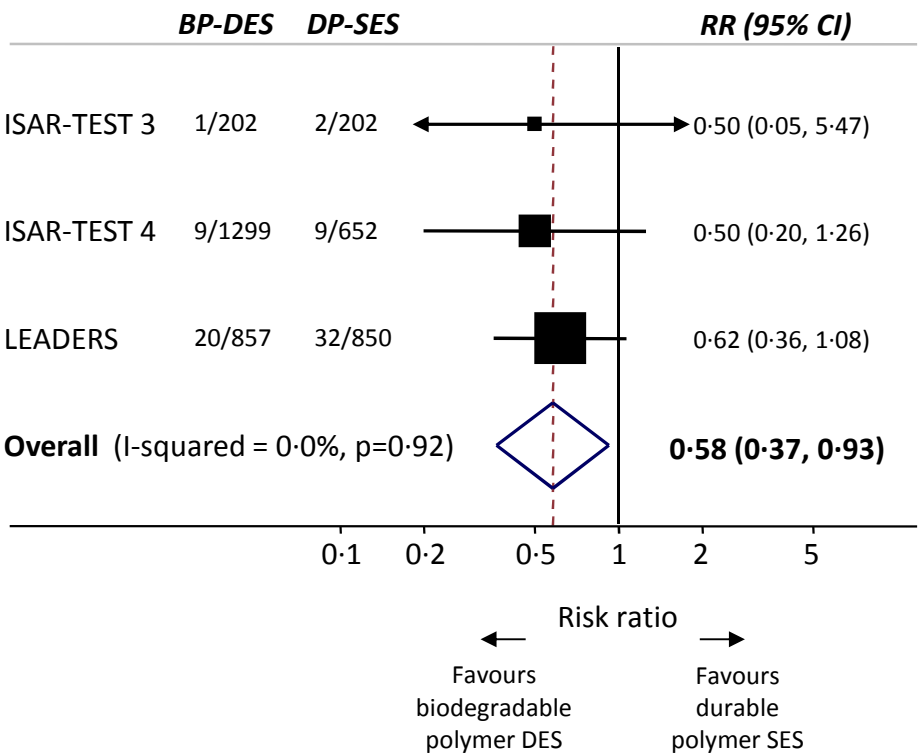

***29 Lesions*** ***35 Lesions***

# Biodegradable Polymer DES versus Durable Polymer Sirolimus Eluting Stents

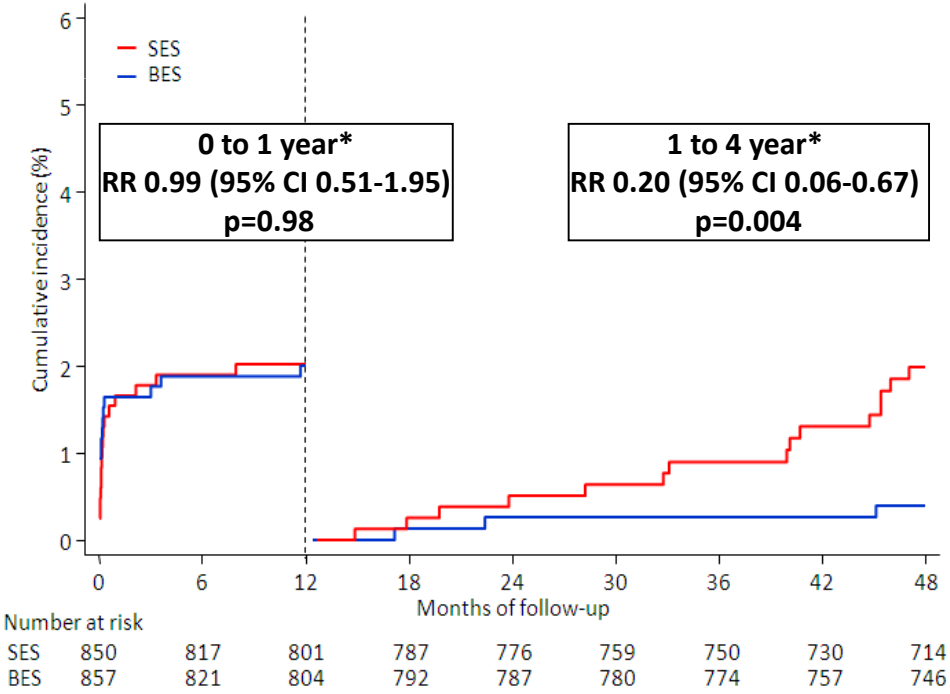
Stefanini G et al. *Lancet* 2011

## *DES Safety – Risk of Stent Thrombosis*

**Definite ST**
**Meta-Analysis**




**Definite ST**
**LEADERS trial @ 4 years**



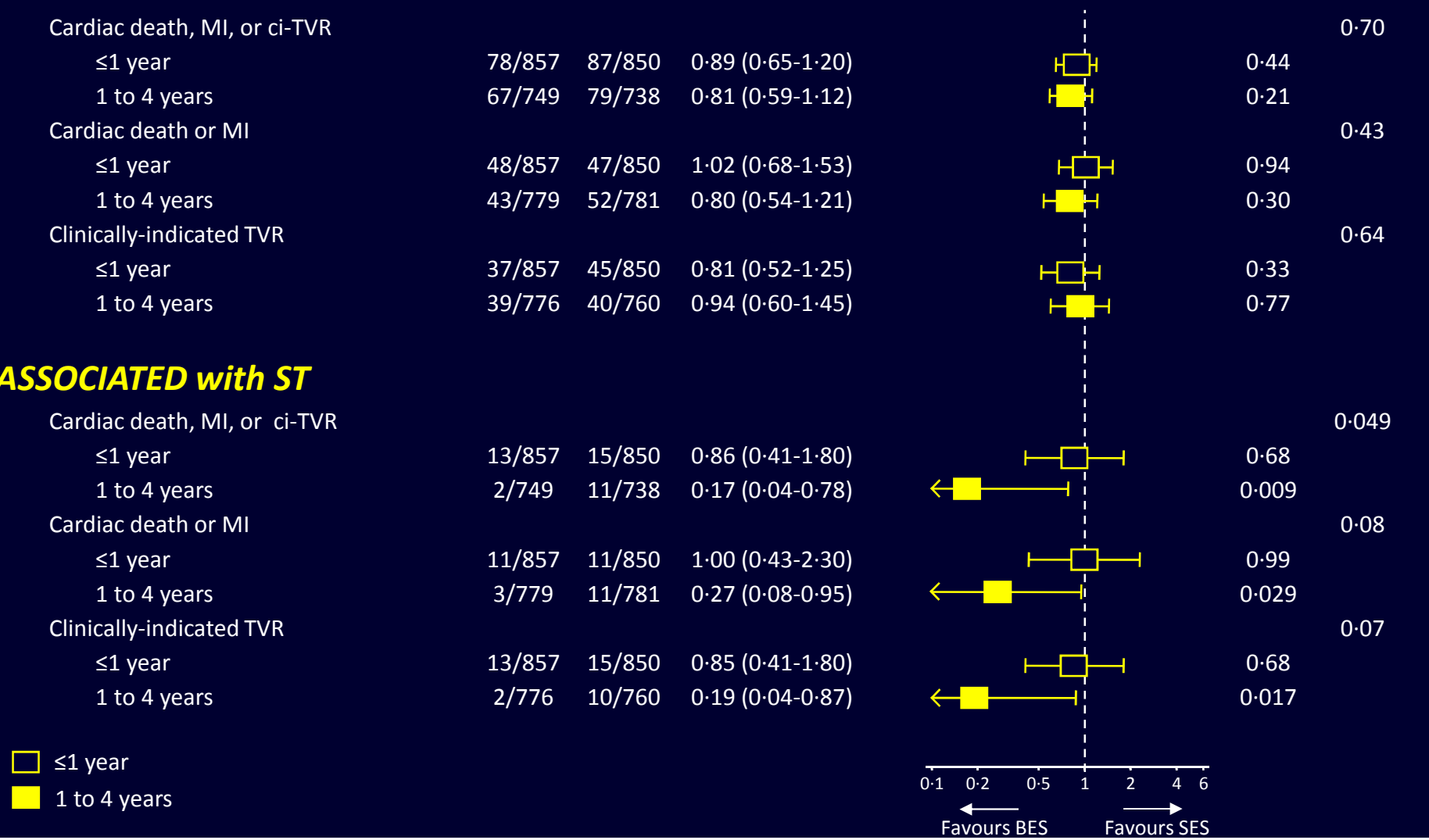

*** RR 0-1 vs RR 1-4 p for interaction=0.017**

# Biodegradable Polymer BES vs Durable Polymer SES

## *Association of Cardiac Events With Definite ST*

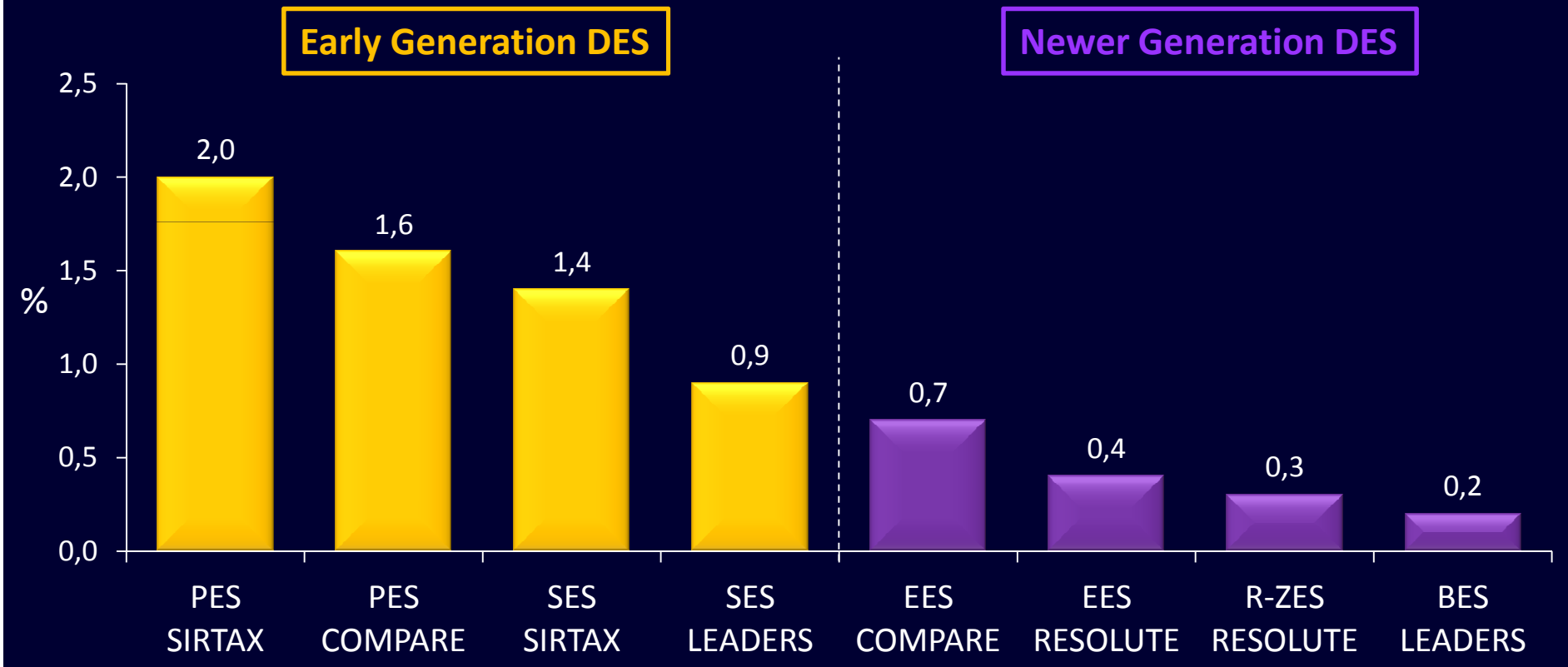
Stefanini G et al. *Lancet* 2011

| | BES | SES | RR (95% CI) | P | P-inter |
|---|---|---|---|---|---|
| ***NOT ASSOCIATED with ST*** | | | | | |
| Cardiac death, MI, or ci-TVR | | | | | 0·70 |
| ≤1 year | 78/857 | 87/850 | 0·89 (0·65-1·20) | 0·44 | |
| 1 to 4 years | 67/749 | 79/738 | 0·81 (0·59-1·12) | 0·21 | |
| Cardiac death or MI | | | | | 0·43 |
| ≤1 year | 48/857 | 47/850 | 1·02 (0·68-1·53) | 0·94 | |
| 1 to 4 years | 43/779 | 52/781 | 0·80 (0·54-1·21) | 0·30 | |
| Clinically-indicated TVR | | | | | 0·64 |
| ≤1 year | 37/857 | 45/850 | 0·81 (0·52-1·25) | 0·33 | |
| 1 to 4 years | 39/776 | 40/760 | 0·94 (0·60-1·45) | 0·77 | |
| ***ASSOCIATED with ST*** | | | | | |
| Cardiac death, MI, or ci-TVR | | | | | 0·049 |
| ≤1 year | 13/857 | 15/850 | 0·86 (0·41-1·80) | 0·68 | |
| 1 to 4 years | 2/749 | 11/738 | 0·17 (0·04-0·78) | 0·009 | |
| Cardiac death or MI | | | | | 0·08 |
| ≤1 year | 11/857 | 11/850 | 1·00 (0·43-2·30) | 0·99 | |
| 1 to 4 years | 3/779 | 11/781 | 0·27 (0·08-0·95) | 0·029 | |
| Clinically-indicated TVR | | | | | 0·07 |
| ≤1 year | 13/857 | 15/850 | 0·85 (0·41-1·80) | 0·68 | |
| 1 to 4 years | 2/776 | 10/760 | 0·19 (0·04-0·87) | 0·017 | |



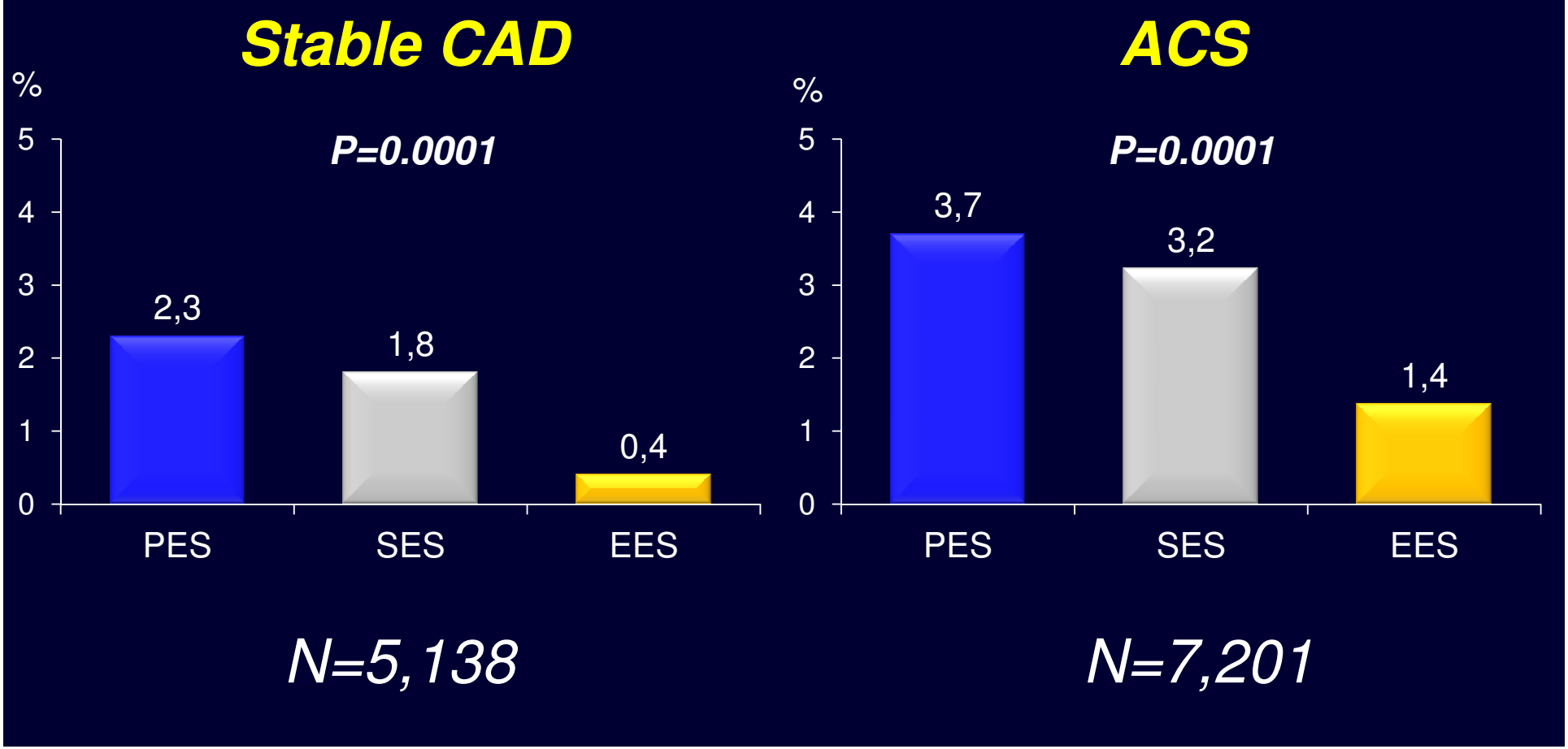
# DES Thrombosis in Perspective

## *Very Late Definite ST in All-Comers Trials @ 3 Years*



# Definite Stent Thrombosis among Patients with Stable Coronary Artery Disease and Acute Coronary Syndromes @ 4 Years

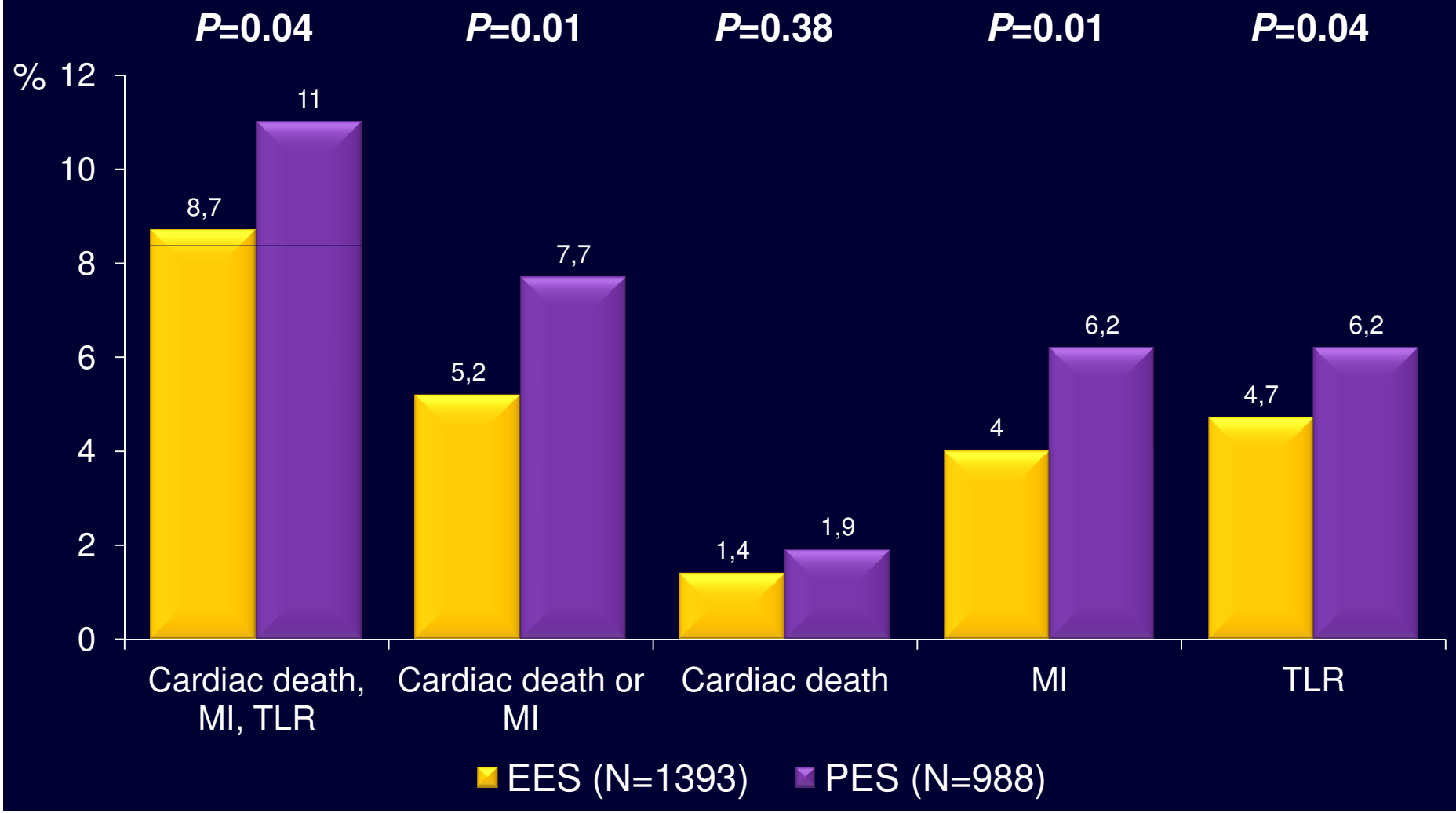
***Bern-Rotterdam Cohort Study***



# Clinical Outcomes With Everolimus- and Paclitaxel-Eluting Stents in Patients With ACS

Planer D et al. *J Am Coll Cardiol Intv* 2011;4:1104–15

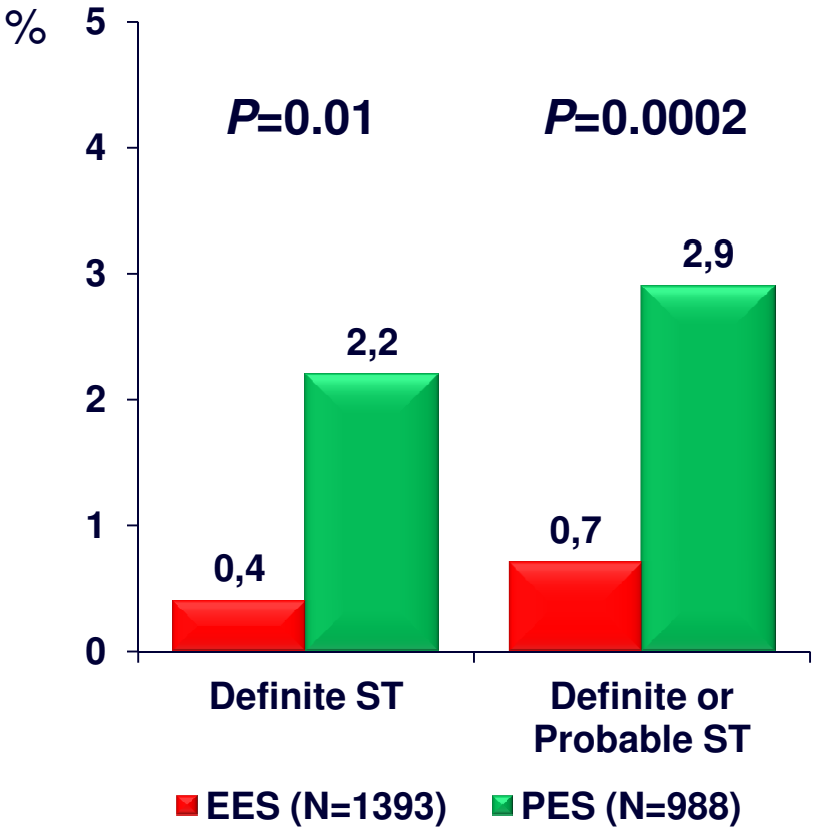
***A Pooled Analysis of SPIRIT II, III, IV, and COMPARE Trials @ 2 Years***

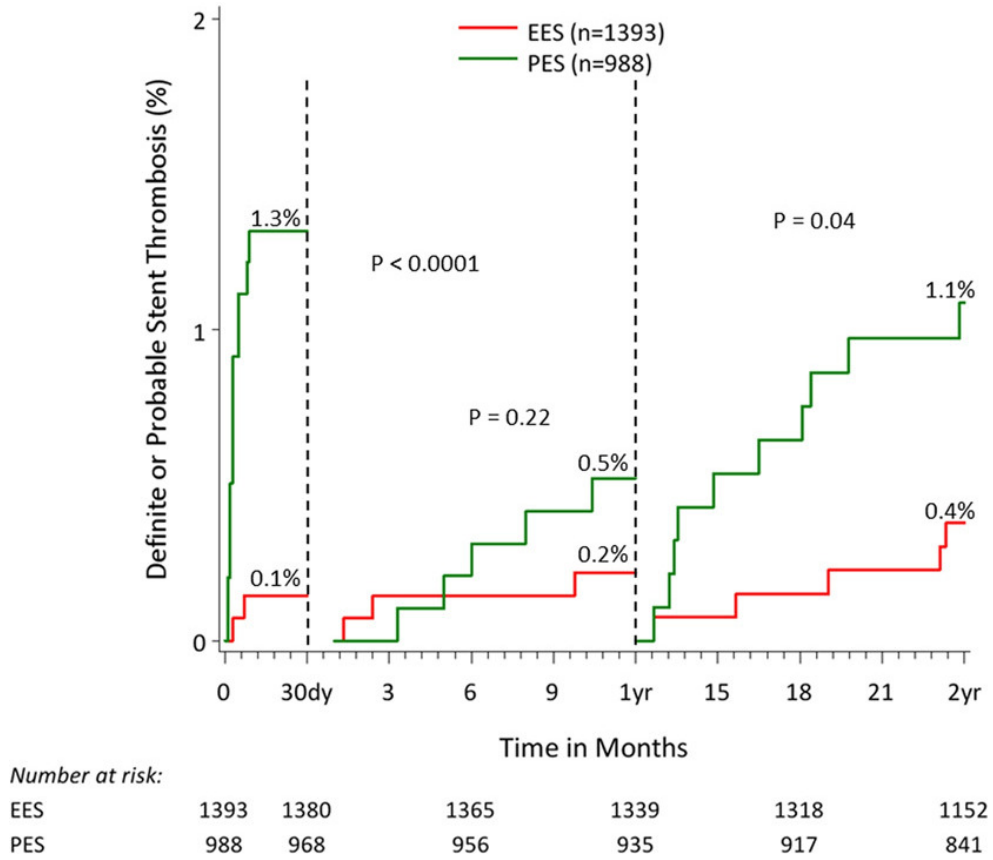


# Stent Thrombosis With Everolimus- and Paclitaxel-Eluting Stents in Patients With ACS

Planer D et al. *J Am Coll Cardiol Intv* 2011;4:1104–15

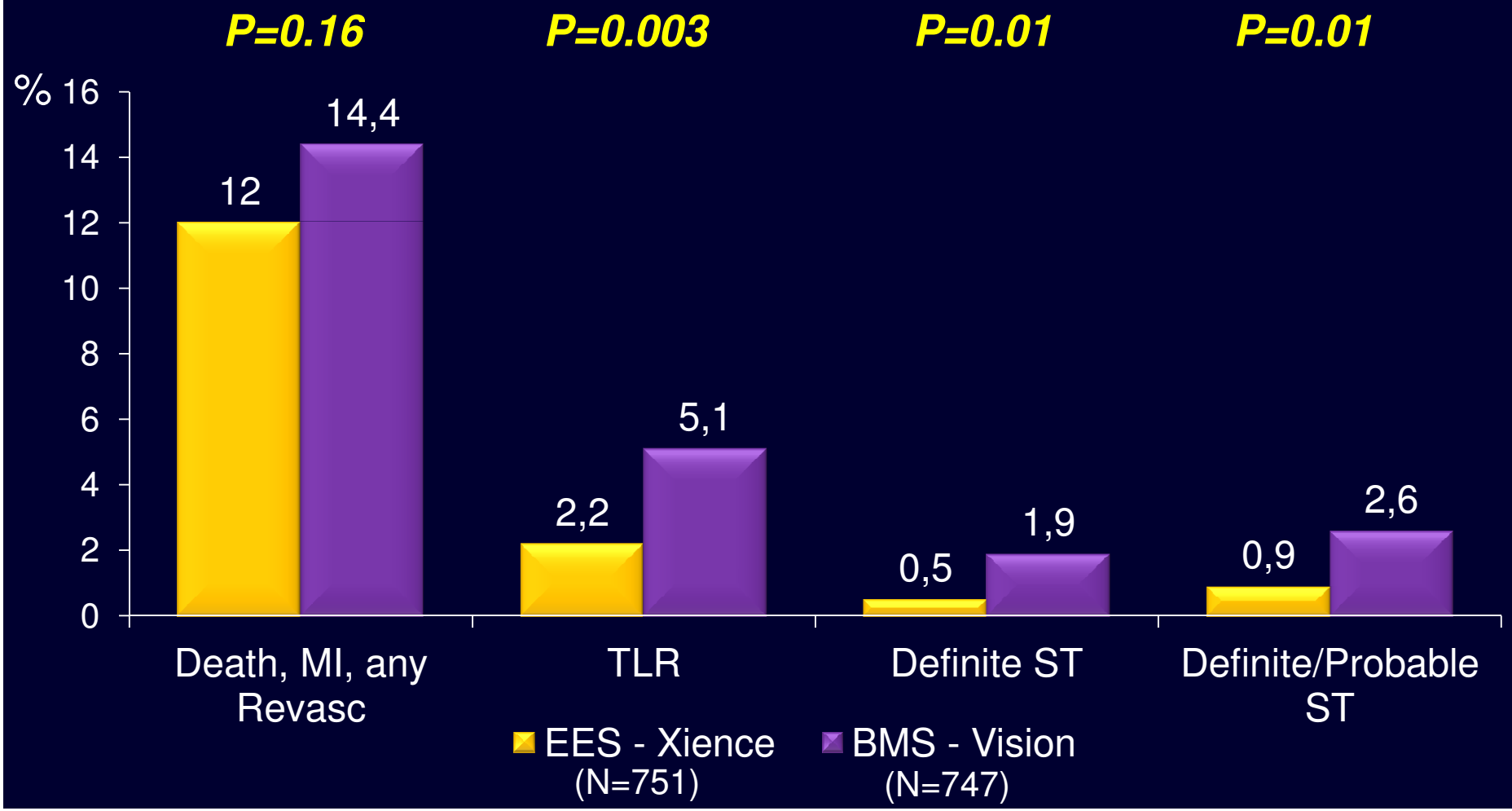
**A Pooled Analysis of SPIRIT II, III, IV, and COMPARE Trials @ 2 Years**



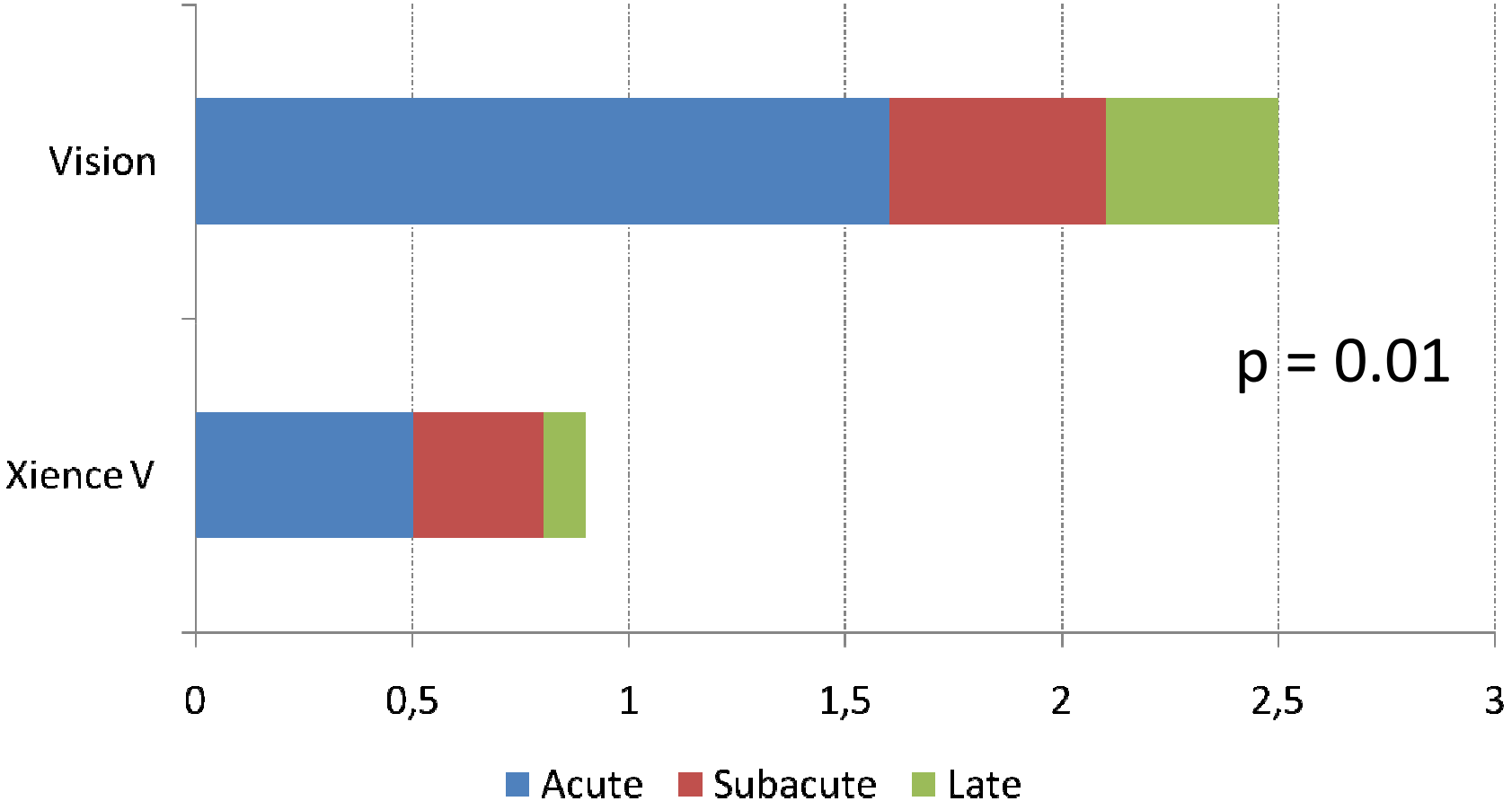
# EXAMINATION Trial - Everolimus-Eluting Stents vs Bare Metal Stents in STEMI @ 12 Months

Sabaté M. *Presented at ESC Congress* 2011



*EXAMINATION trial*

# Definite/Probable Stent Thrombosis

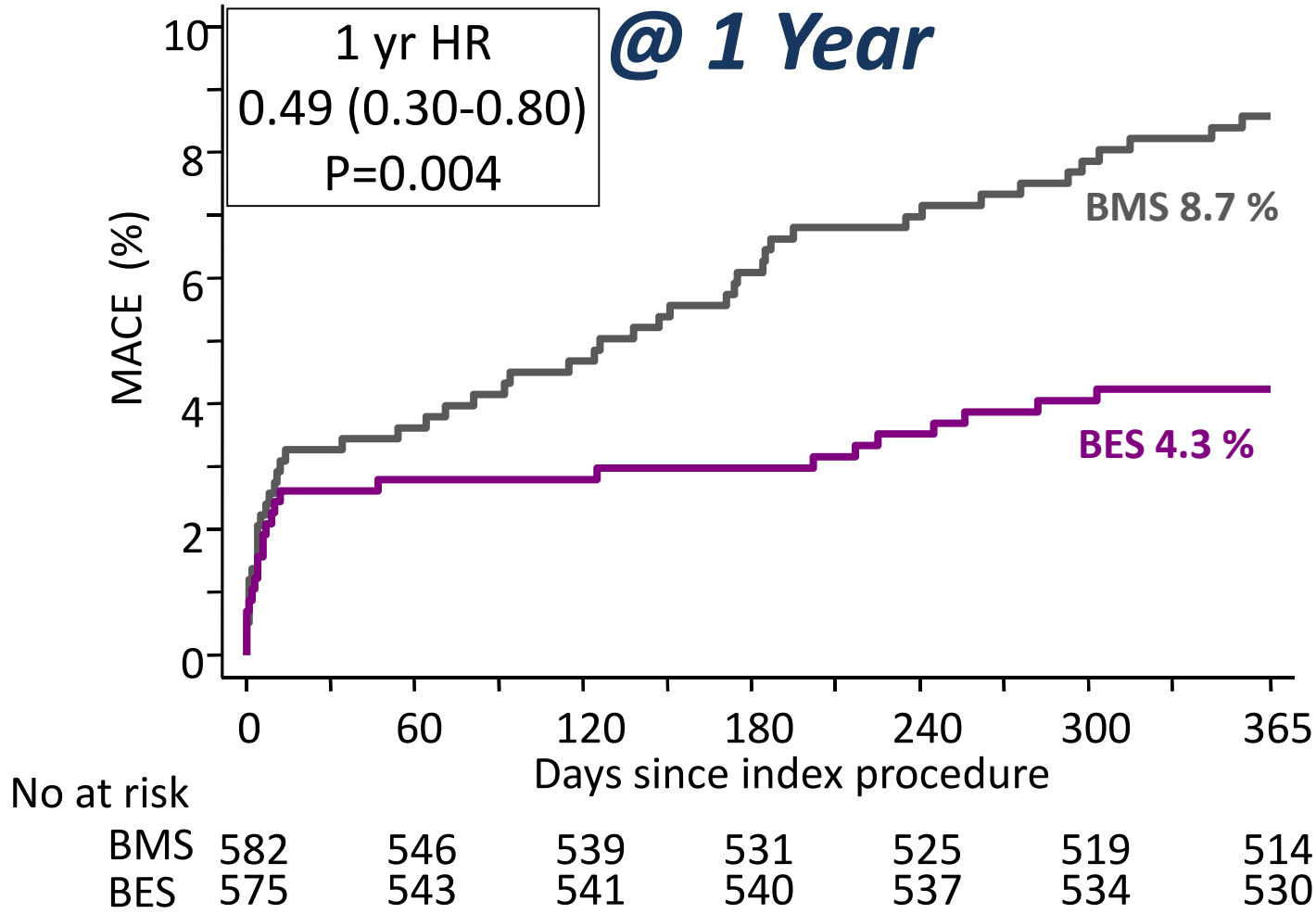



Sabaté M. *ESC Congress* 2011

# COMFORTABLE AMI Trial

## Biolimus-Eluting Stent vs Bare Metal Stent in STEMI

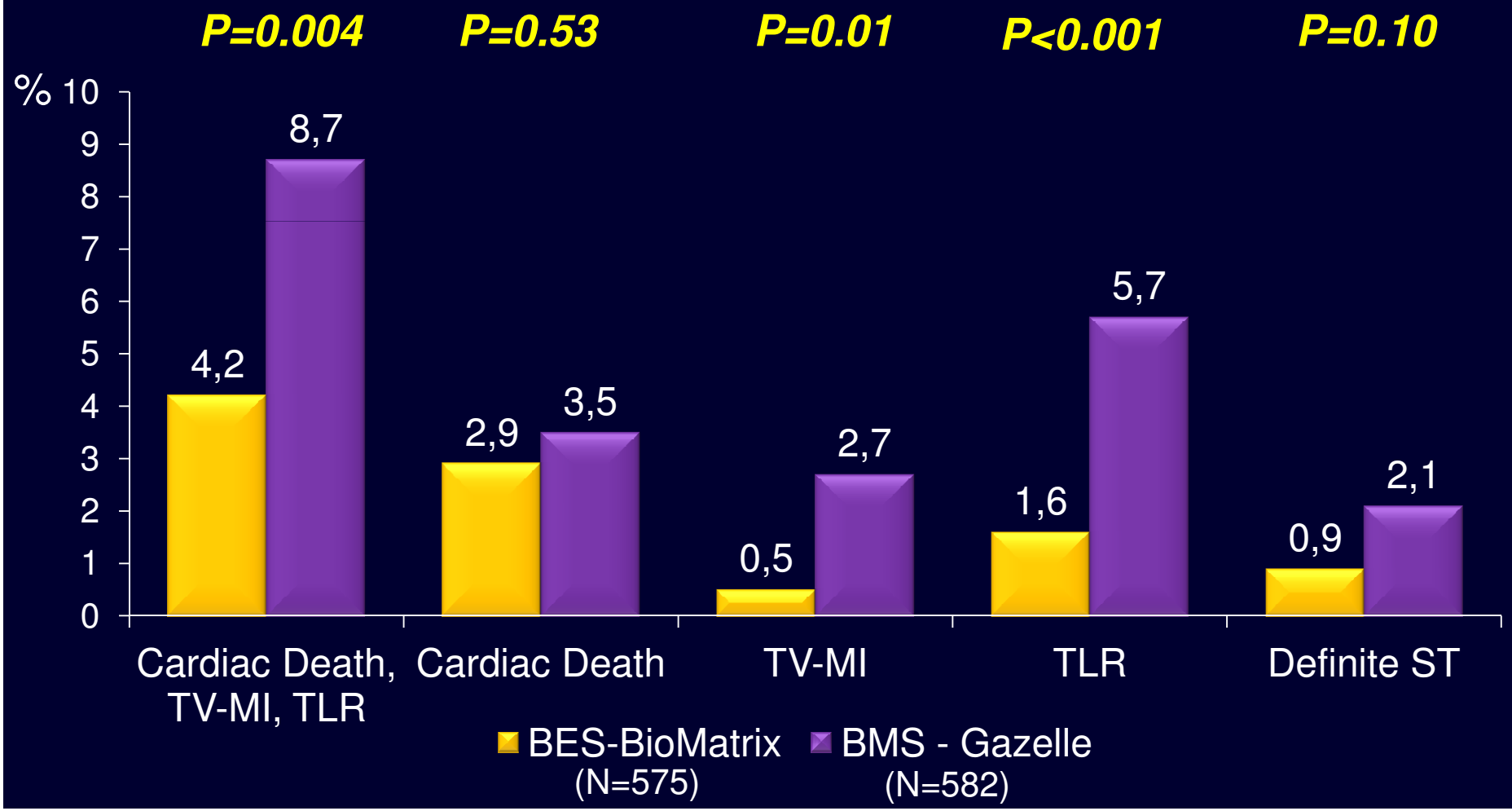
## Primary Endpoint – MACE @ 1 Year




MACE= Cardiac death, TV-MI, ci-TLR – Clinical outcomes were adjudicated by an independent and blinded CEC

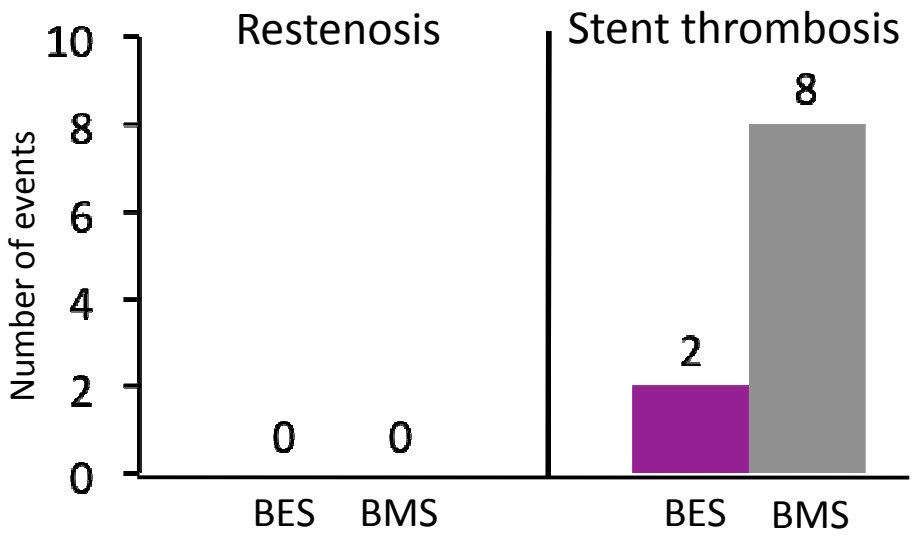
# COMFORTABLE AMI Trial - Biolimus-Eluting Stents vs Bare Metal Stents in STEMI @ 12 Months

Räber L *Presented at EuroPCR 2012*

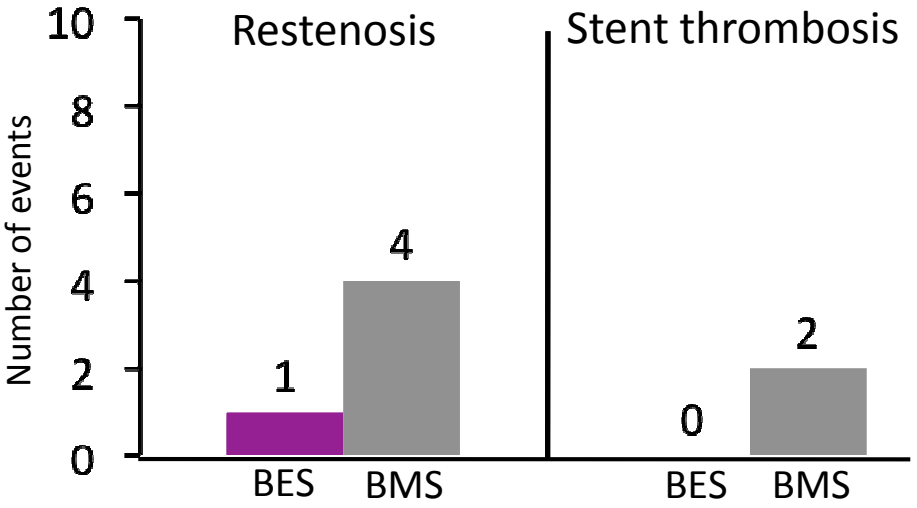


euro PCR 2012

## Target vessel MI up to 30 days



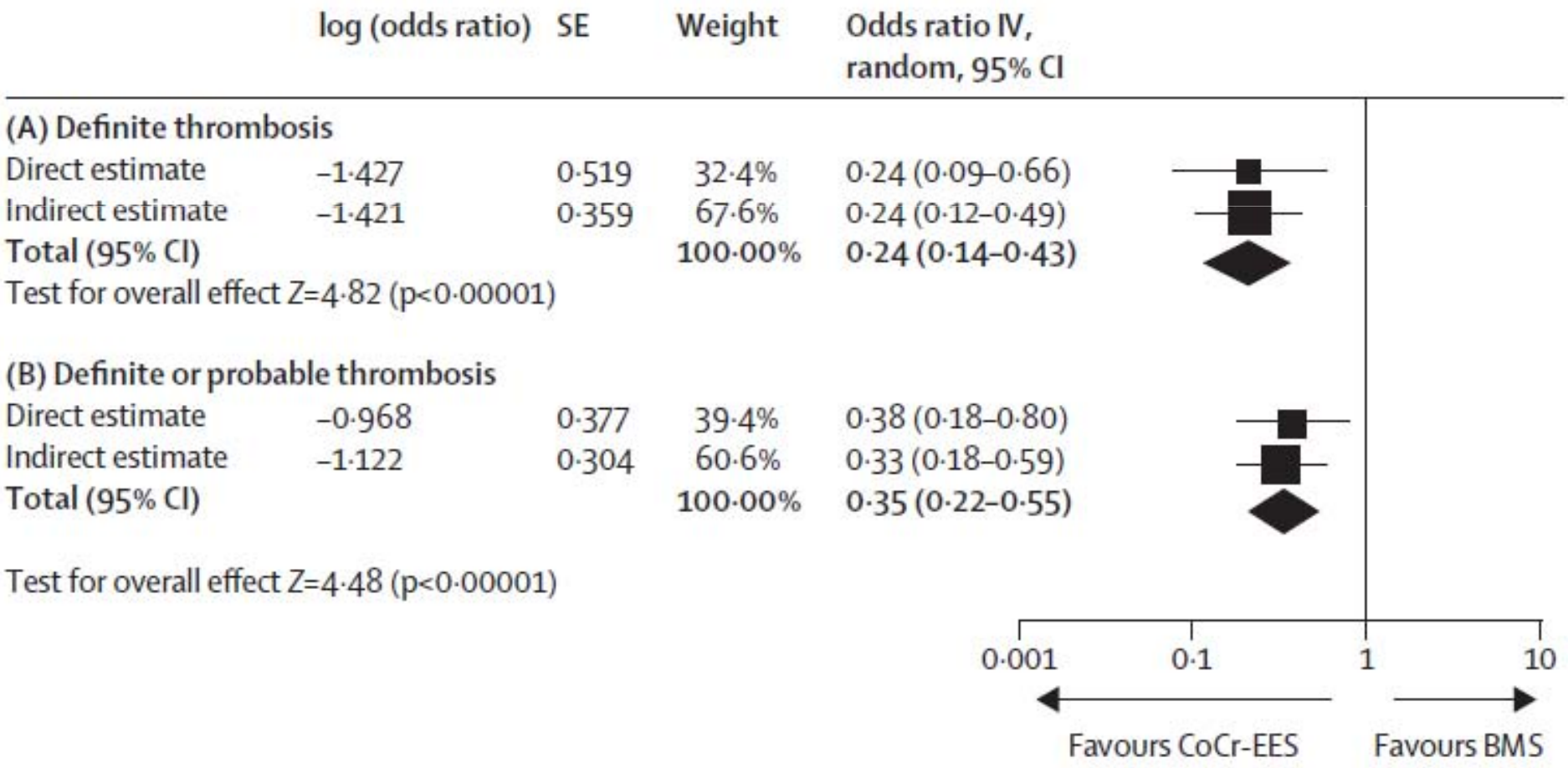

## Target vessel MI between 30 days and 1 year



# Stent Thrombosis With Everolimus-Eluting Stents and Bare Metal Stents

## *A Network Meta-Analysis*

Palmerini T. et al. *Lancet* 2012



# Short and Long-Term Outcomes with Drug Eluting and Bare Metal Stents

## *A Mixed Treatment Comparison of 77 RCTs and 117,762 Patient-Years Fup*

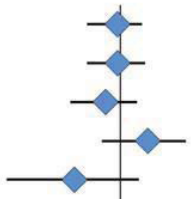
Bangalore S et al. *Circulation 2012*, in press

**Death**

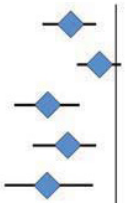
**MI**

### *0 to 1 Year*

| Control | Treatment | Odds Ratio | 95% | CrI |
|---|---|---|---|---|
| BMS (Ref) | | | | |
| | Sirolimus | 0.97 | 0.74 | 1.21 |
| | Paclitaxel | 0.97 | 0.74 | 1.25 |
| | Everolimus | 0.87 | 0.64 | 1.16 |
| | Zotarolimus | 1.28 | 0.85 | 1.80 |
| | Zotarolimus-R | 0.66 | 0.36 | 1.18 |

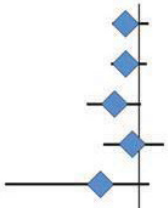


| Control | Treatment | Odds Ratio | 95% | CrI |
|---|---|---|---|---|
| BMS (Ref) | | | | |
| | Sirolimus | 0.67 | 0.53 | 0.84 |
| | Paclitaxel | 0.87 | 0.71 | 1.04 |
| | Everolimus | 0.55 | 0.41 | 0.73 |
| | Zotarolimus | 0.66 | 0.49 | 0.84 |
| | Zotarolimus-R | 0.55 | 0.38 | 0.82 |

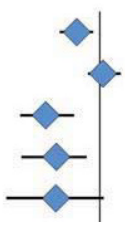


### *Long Term*

| Control | Treatment | Rate Ratio | 95% | CrI |
|---|---|---|---|---|
| BMS (Ref) | | | | |
| | Sirolimus | 0.89 | 0.79 | 1.09 |
| | Paclitaxel | 0.89 | 0.78 | 1.07 |
| | Everolimus | 0.81 | 0.64 | 1.01 |
| | Zotarolimus | 0.94 | 0.73 | 1.24 |
| | Zotarolimus-R | 0.71 | 0.31 | 1.09 |



| Control | Treatment | Rate Ratio | 95% | CrI |
|---|---|---|---|---|
| BMS (Ref) | | | | |
| | Sirolimus | 0.82 | 0.71 | 0.95 |
| | Paclitaxel | 1.02 | 0.90 | 1.20 |
| | Everolimus | 0.63 | 0.51 | 0.80 |
| | Zotarolimus | 0.69 | 0.52 | 0.89 |
| | Zotarolimus-R | 0.69 | 0.45 | 1.03 |



# Short and Long-Term Outcomes with Drug Eluting and Bare Metal Stents

## *A Mixed Treatment Comparison of 77 RCTs and 117,762 Patient-Years Fup*

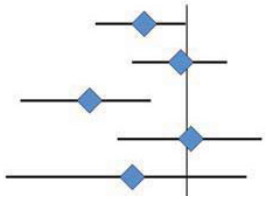
Bangalore S et al. *Circulation 2012*, in press

**Definite or Probable ST**

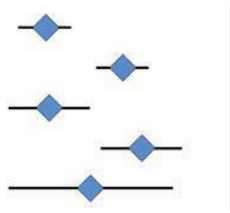
**Target Lesion Revasc**

### *0 to 1 Year*

| Control | Treatment | Treatment | Control | Odds Ratio | 95% | CrI |
|---|---|---|---|---|---|---|
| BMS (Ref) | | | | | | |
| | Sirolimus | | | 0.68 | 0.44 | 0.99 |
| | Paclitaxel | | | 0.95 | 0.61 | 1.44 |
| | Everolimus | | | 0.41 | 0.22 | 0.72 |
| | Zotarolimus | | | 1.04 | 0.53 | 1.98 |
| | Zotarolimus-R | | | 0.61 | 0.19 | 1.72 |

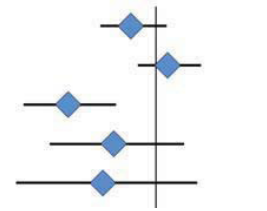


| Control | Treatment | Treatment | Control | Odds Ratio | 95% | CrI |
|---|---|---|---|---|---|---|
| BMS (Ref) | | | | | | |
| | Sirolimus | | | 0.20 | 0.16 | 0.25 |
| | Paclitaxel | | | 0.39 | 0.31 | 0.49 |
| | Everolimus | | | 0.21 | 0.14 | 0.29 |
| | Zotarolimus | | | 0.46 | 0.32 | 0.65 |
| | Zotarolimus-R | | | 0.29 | 0.15 | 0.60 |

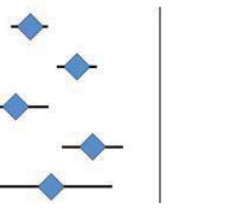


### *Long Term*

| Control | Treatment | Treatment | Control | Rate Ratio | 95% | CrI |
|---|---|---|---|---|---|---|
| BMS (Ref) | | | | | | |
| | Sirolimus | | | 0.80 | 0.61 | 1.10 |
| | Paclitaxel | | | 1.11 | 0.85 | 1.49 |
| | Everolimus | | | 0.46 | 0.31 | 0.70 |
| | Zotarolimus | | | 0.69 | 0.39 | 1.28 |
| | Zotarolimus-R | | | 0.62 | 0.29 | 1.44 |



| Control | Treatment | Treatment | Control | Rate Ratio | 95% | CrI |
|---|---|---|---|---|---|---|
| BMS (Ref) | | | | | | |
| | Sirolimus | | | 0.32 | 0.27 | 0.38 |
| | Paclitaxel | | | 0.48 | 0.41 | 0.58 |
| | Everolimus | | | 0.28 | 0.22 | 0.38 |
| | Zotarolimus | | | 0.56 | 0.43 | 0.72 |
| | Zotarolimus-R | | | 0.39 | 0.23 | 0.66 |



## Table 35 Relative clinical contraindications to the use of drug-eluting stents

| |
|---|
| • Clinical history difficult to obtain, especially in the setting of acute severe clinical conditions (STEMI or cardiogenic shock). |
| • Expected poor compliance with DAPT, including patients with multiple comorbidities and polypharmacy. |
| • Non-elective surgery required in the short term that would require interruption of DAPT. |
| • Increased risk of bleeding. |
| • Known allergy to ASA or clopidogrel/prasugrel/ticagrelor. |
| • Absolute indication for long-term anticoagulation. |

DES are

A

European Heart Journal
doi:10.1093/eurheartj/ehr236



# ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

**The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)**

## *Use of Drug-Eluting Stents*

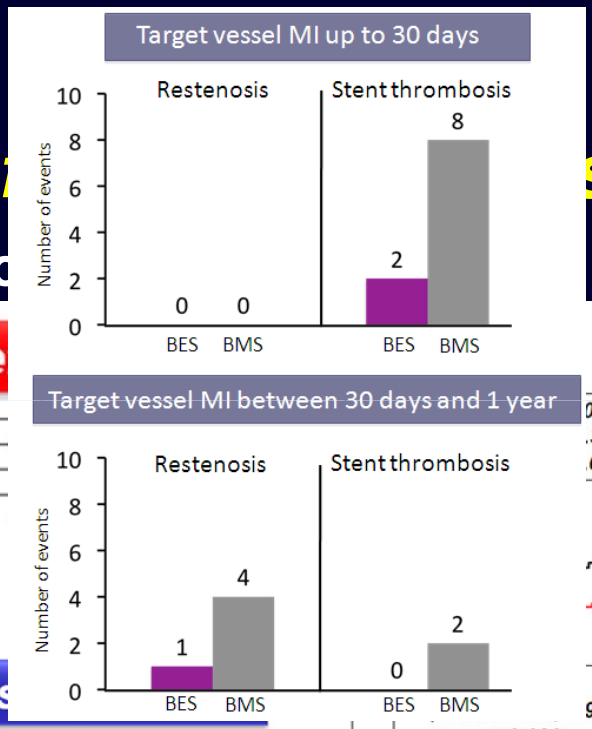
- ***No safety concerns***
- ***Consistent reduction in repeat revascularization with the use of DES***

| | | |
|---|---|---|
| As there are no safety concerns related to the use of DESs in ACS, DESs are indicated based on an individual basis taking into account baseline characteristics, coronary anatomy, and bleeding risk. | I | A |

*Eur Heart J* 2011

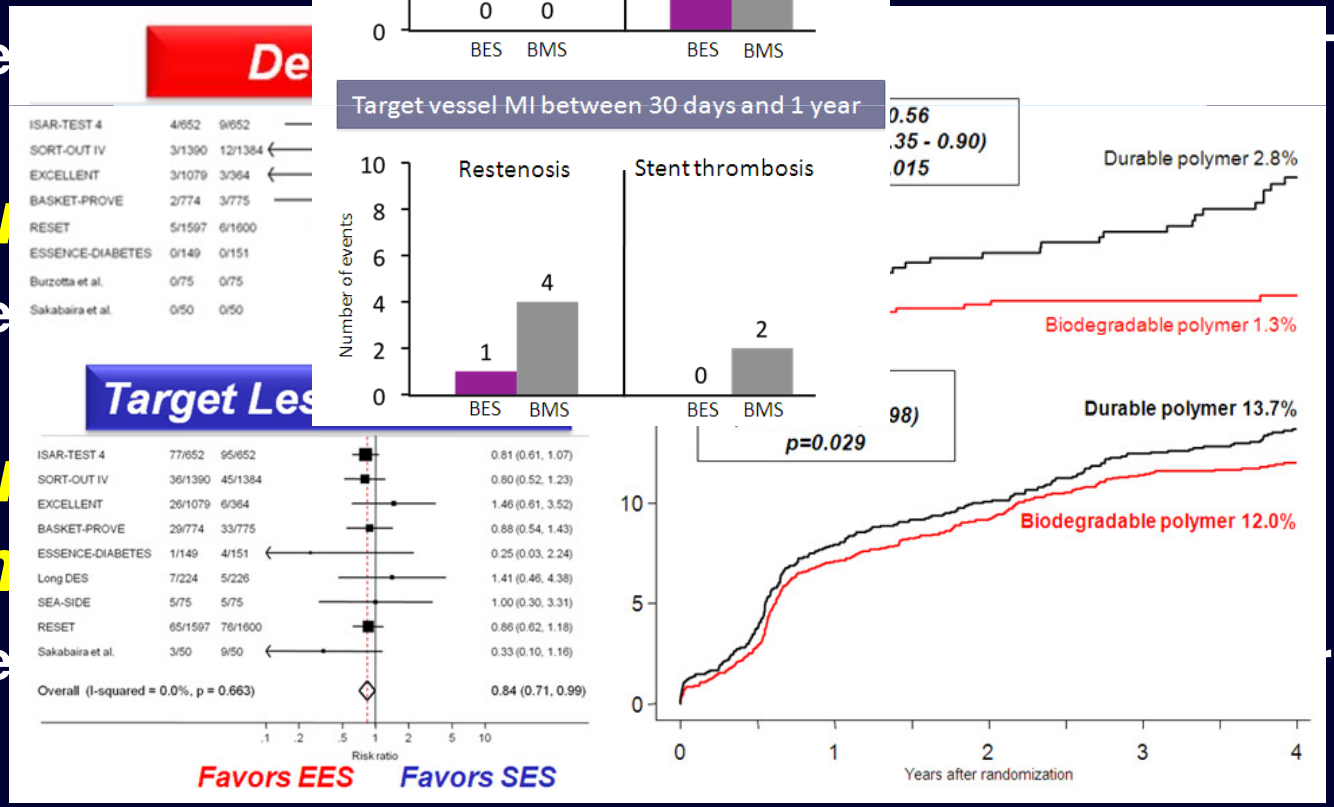
# Newer Generation Drug-Eluting Stents…What Have We Achieved?

- ***Improved sa… …s***
  - **Reduced risk c…**
  - **Re…**
- ***Impr…***
  - **Re…**
- ***Impr… com…***
  - **Re… …risk of MI at …**



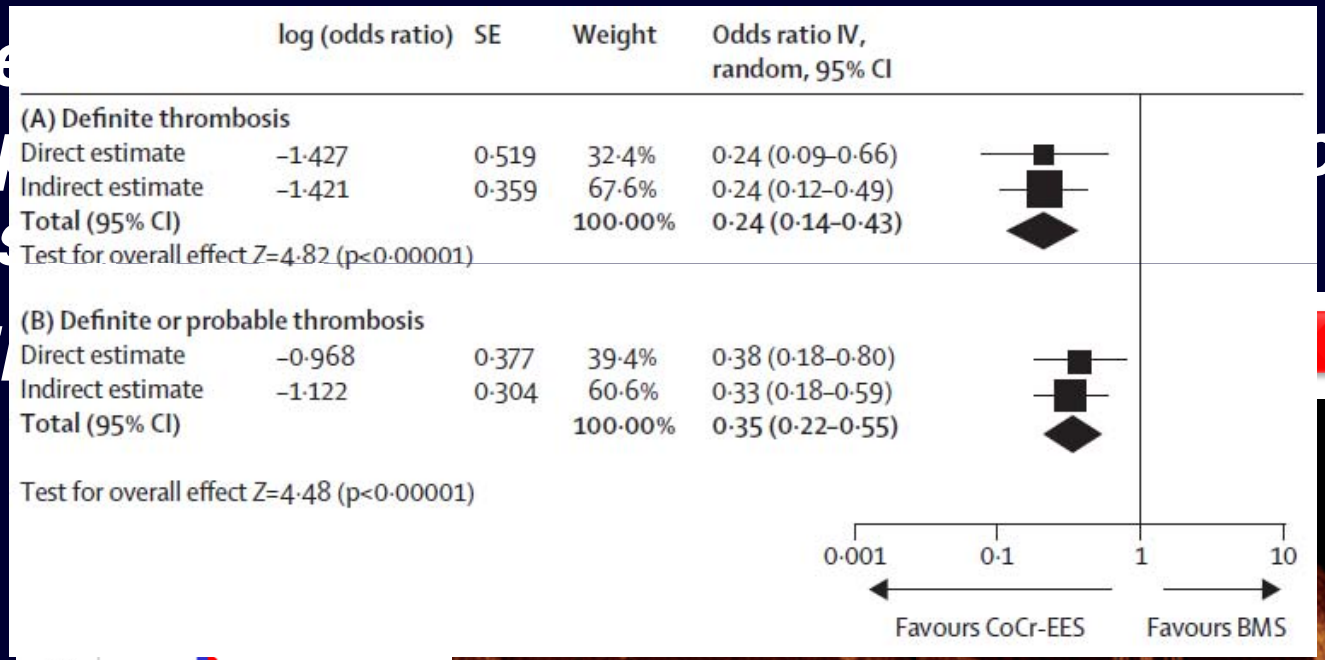






# Questions for Tomorrow

- ***Are newer generation DES safer than BMS during long-term follow-up?***
- ***Are*** ***olymer***
  ***sup***
  ***bas***
- ***Wi*** ***S?***



| | log (odds ratio) | SE | Weight | Odds ratio IV, random, 95% CI |
|---|---|---|---|---|
| (A) Definite thrombosis | | | | |
| Direct estimate | −1·427 | 0·519 | 32·4% | 0·24 (0·09–0·66) |
| Indirect estimate | −1·421 | 0·359 | 67·6% | 0·24 (0·12–0·49) |
| Total (95% CI) | | | 100·00% | 0·24 (0·14–0·43) |
| Test for overall effect Z=4·82 (p<0·00001) | | | | |
| (B) Definite or probable thrombosis | | | | |
| Direct estimate | −0·968 | 0·377 | 39·4% | 0·38 (0·18–0·80) |
| Indirect estimate | −1·122 | 0·304 | 60·6% | 0·33 (0·18–0·59) |
| Total (95% CI) | | | 100·00% | 0·35 (0·22–0·55) |
| Test for overall effect Z=4·48 (p<0·00001) | | | | |