Established and Emerging Differences in DES

An Interplay of Clinical Trials, Public Opinion and Physician Perceptions

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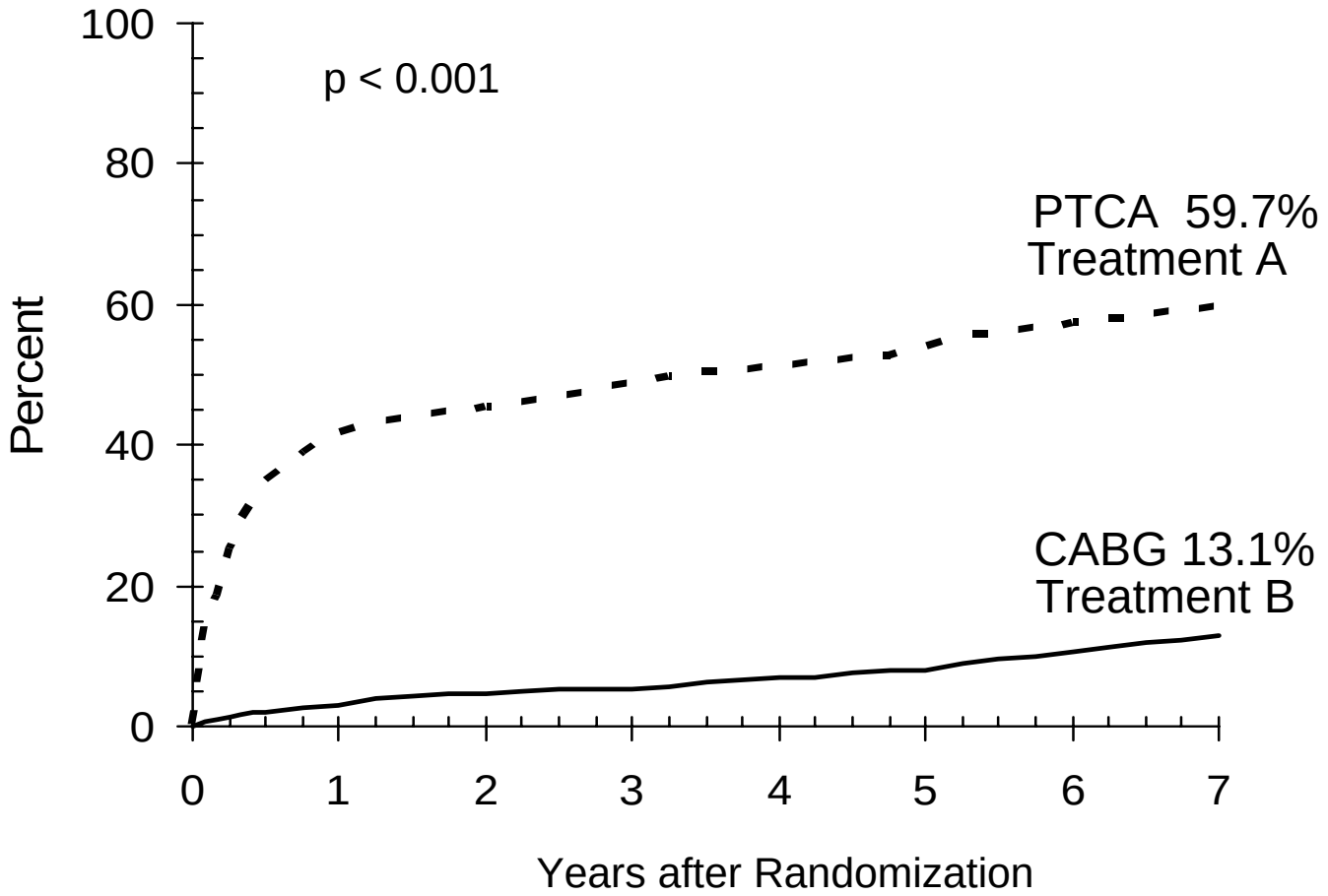
Does the Interventional Community Adhere to Clinical Trial Results?



Source: BARI Trial Investigators

Does the Interventional Community Adhere to Clinical Trial Results?

Influence of the Bypass Angioplasty Revascularization Investigation National Heart, Lung, and Blood Institute Diabetic Clinical Alert on Practice Patterns

Results from the National Cardiovascular Network Database

Darren K. McGuire, MD, MHSc; Kevin J. Anstrom, PhD; Eric D. Peterson, MD, MPH

Background—In 1995, the Bypass Angioplasty Revascularization Investigation (BARI) found that patients with diabetes had a survival benefit when treated with surgical revascularization versus balloon angioplasty, prompting a National Heart Lung and Blood Institute (NHLBI) "Clinical Alert." The influence of the BARI findings and of the Clinical Alert on practice patterns is unknown.

Methods and Results—The practice patterns of coronary revascularization among patients with diabetes and multivessel coronary artery disease (CAD) were analyzed using data collected in 1994 to 1997 from 13 centers participating in the National Cardiovascular Network. The study population included patients with diabetes and multivessel CAD who underwent elective coronary revascularization (n=9619). Over the 4 years of the study, the Clinical Alert had no significant impact on the proportion of diabetic patients undergoing percutaneous revascularization (28.6% before versus 26.8% after the Clinical Alert; $P=0.06$). Among individual hospitals, the probability of diabetic patients receiving percutaneous revascularization varied by >13-fold (4.3% to 56.6%). Adjusting for clinical factors and the BARI Clinical Alert did not alter this variability. Among the investigators surveyed, although 91% were aware of the Clinical Alert and 76% felt the findings were valid, >50% felt the Clinical Alert had limited or no impact on their personal or institution's care patterns.

Conclusions—Limited consensus exists regarding the most appropriate method of revascularization for diabetic patients with multivessel CAD. The results from a large, randomized, clinical trial and subsequent Clinical Alert had no measurable impact on this practice variability. **(*Circulation*. 2003;107:1864-1870.)**

Impact of Clinical Trials Often Exceeds Conclusions from the Study Results Alone

- Sheer number of clinical trials
- Market potential of new device approval
- Industry competitive landscape
- Personalities involved

  Physicians (Non-interventionalists)

  Professional societies (ACC, SCAI, AHA, ESC)

  Regulatory bodies (FDA Panel 12/2006, NICE)

  Political interest groups (Waxman)

  Pharmaceutical and device industry

“Intent to Treat”
Knowing the Evidence but Not Applying It

Coming Full Circle in Understanding DES
ESC 2006 ⇒ TCT 2007

What a difference a year makes

TUESDAY

ESC Congress News

WORLD HEART FEDERATION

World Congress of Cardiology 2006

The unique meeting of the European Society of Cardiology Congress 2006 and the World Heart Federation's XVth World Congress of Cardiology

Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session I, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year's meeting.

"Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is unknown," said Yusuf. "I've a feeling the data we're seeing today is only the tip of the iceberg. We need to encourage more public access to the data."

obtain this data from the manufacturer," said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). "The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed," he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

"There's no beneficial influence on mortality – PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest pain. It's not re-stenosis that kills but the

TCT2007 TRANSCATHETER CARDIOVASCULAR THERAPEUTICS

CARDIOVASCULAR RESEARCH FOUNDATION

TCT DAILY

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Wednesday • October 24, 2007 WASHINGTON, DC

INSIDE

AMIHOT II
Saturated oxygen is beneficial after acute anterior MI when PCI is initiated within 6 hours of symptom onset.
page 3

CAREER RECOGNIZED
Barry T. Katzen, MD, awarded the TCT 2007 Career Achievement Award.
page 6

OPTIMA
Higher rate of MI after immediate vs. deferred PCI in patients with high-risk non-ST-segment elevation acute coronary syndrome.
page 14

COLLABORATION

Do Drug-eluting Stents Decrease Mortality?

Registry data from real-world practice with DES are showing consistently positive safety, efficacy data

According to reports presented at TCT 2007, DES have improved outcomes and done so safely, in some cases reducing mortality.

"It is encouraging that these data so consistently show safety and efficacy. The challenge will be synthesizing the data from so many different areas into information for clinical practice," **Gregg Stone, MD**, Chairman of the Cardiovascular Research Foundation, said during the session.

In addition to moderating, Stone presented landmark results of the TAXUS registry concerning the impact of long-term clopidogrel use on death, MI and stent thrombosis. The data do not support routinely extending thienopyridine treatment beyond one year in patients who were event-free after either treatment with DES or bare-metal stents in single, de novo lesions in native coronary arteries.

Gregg Stone, MD

Tudor D. Vagaonescu, MD, a cardiologist at the University of Medicine and Dentistry of New Jersey, presented MIDAS registry data on 11,118 patients who were treated with either a single bare-metal stent (n = 5,399) or a single DES (n = 5,719) in the years 2003 and 2004.

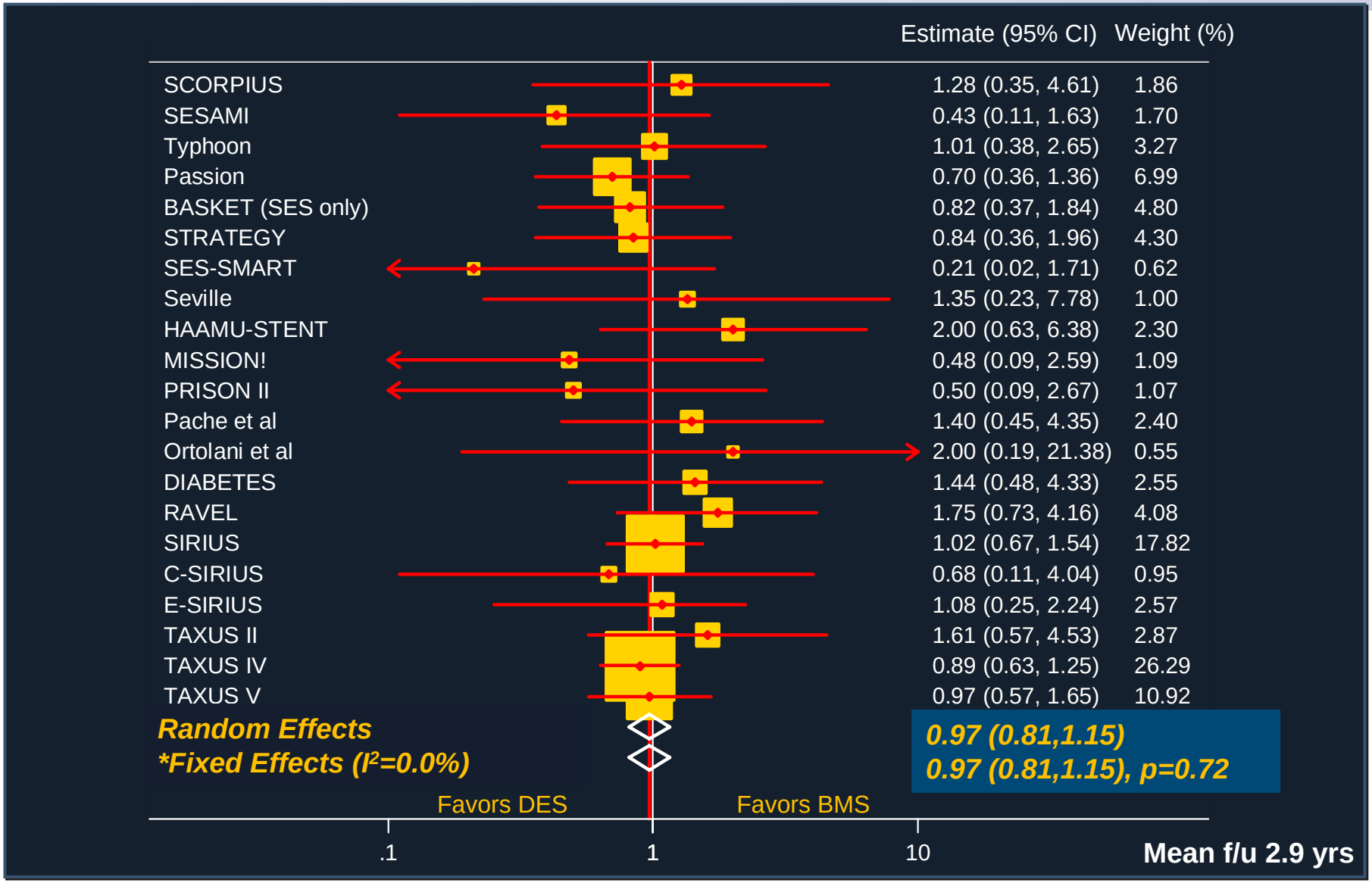
Vagaonescu concluded that the use of a single DES in the setting of AMI was associated with a significant reduction of two-year all-cause mortality and cardiovascular mortality when compared with the use of a single bare-metal stent.

For complete coverage see Emerging DES Data articles inside.

Cardiologist Discusses Army Career

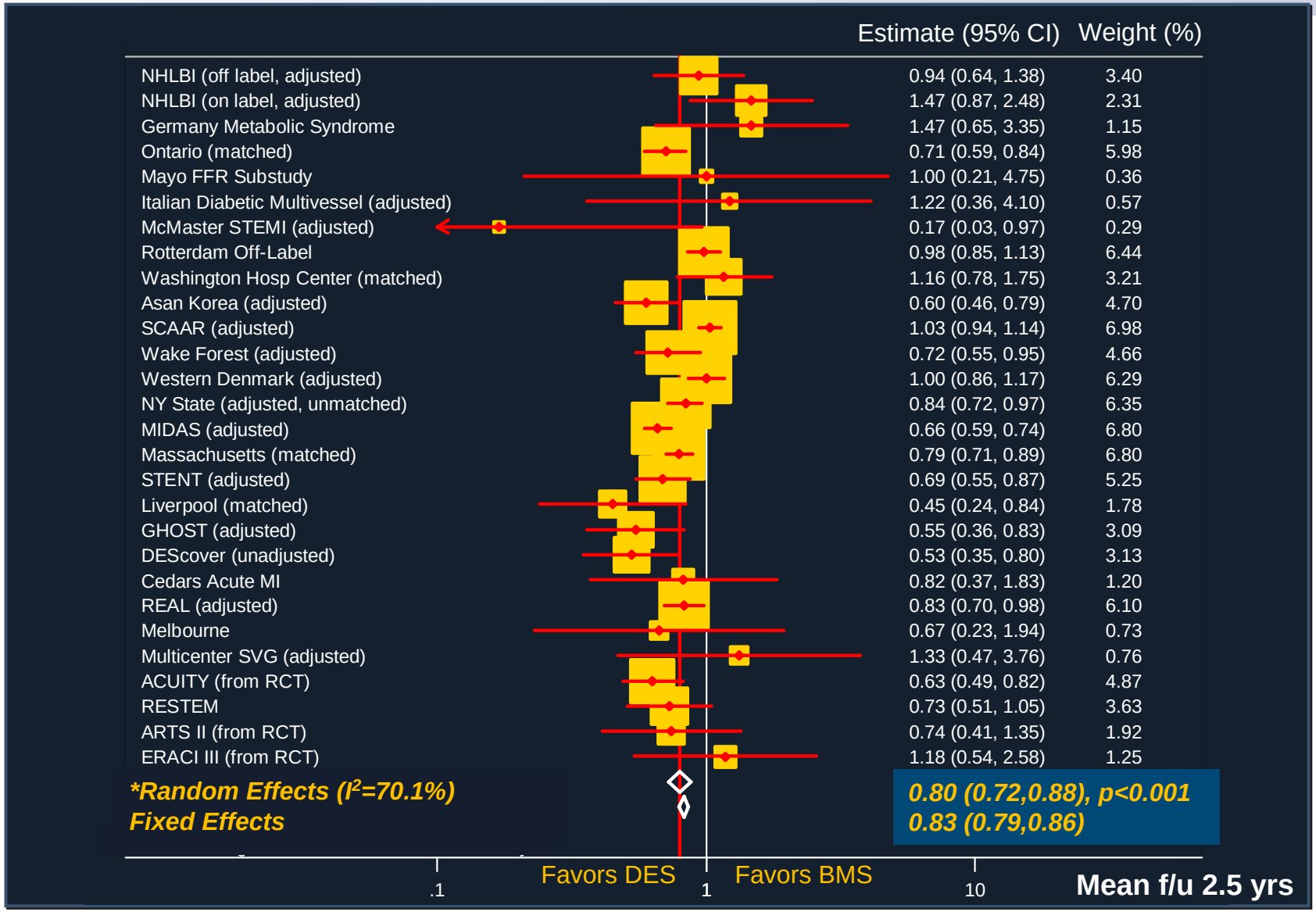
Casscells invited attendees to contribute.

All-Cause Mortality:
All RCTs (*8,867 patients, 21 trials*)



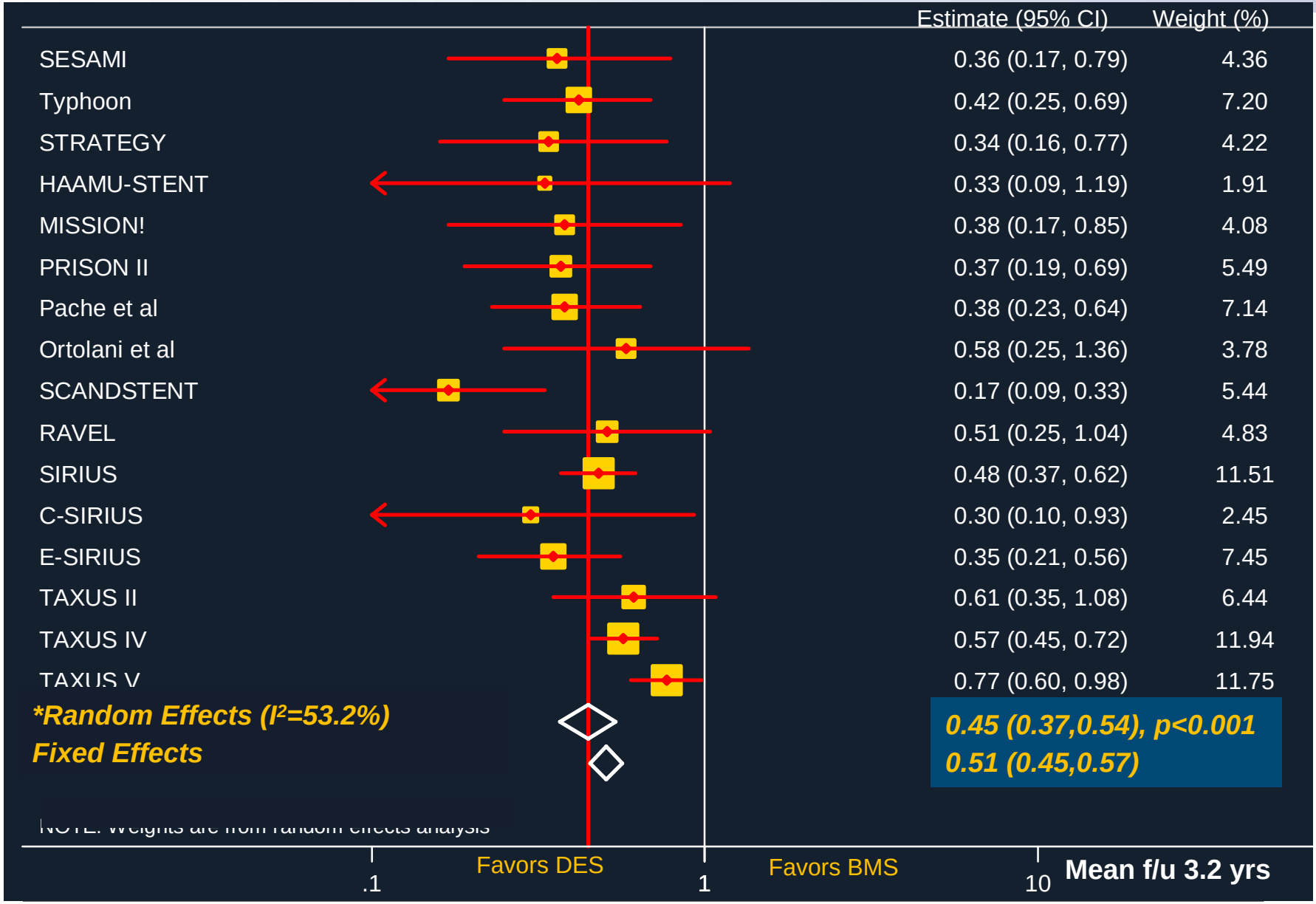
Kirtane A., Stone G., ACC Oral Presentation; 2008

All-Cause Mortality:
All Registries (*161,232 patients, 28 registries*)

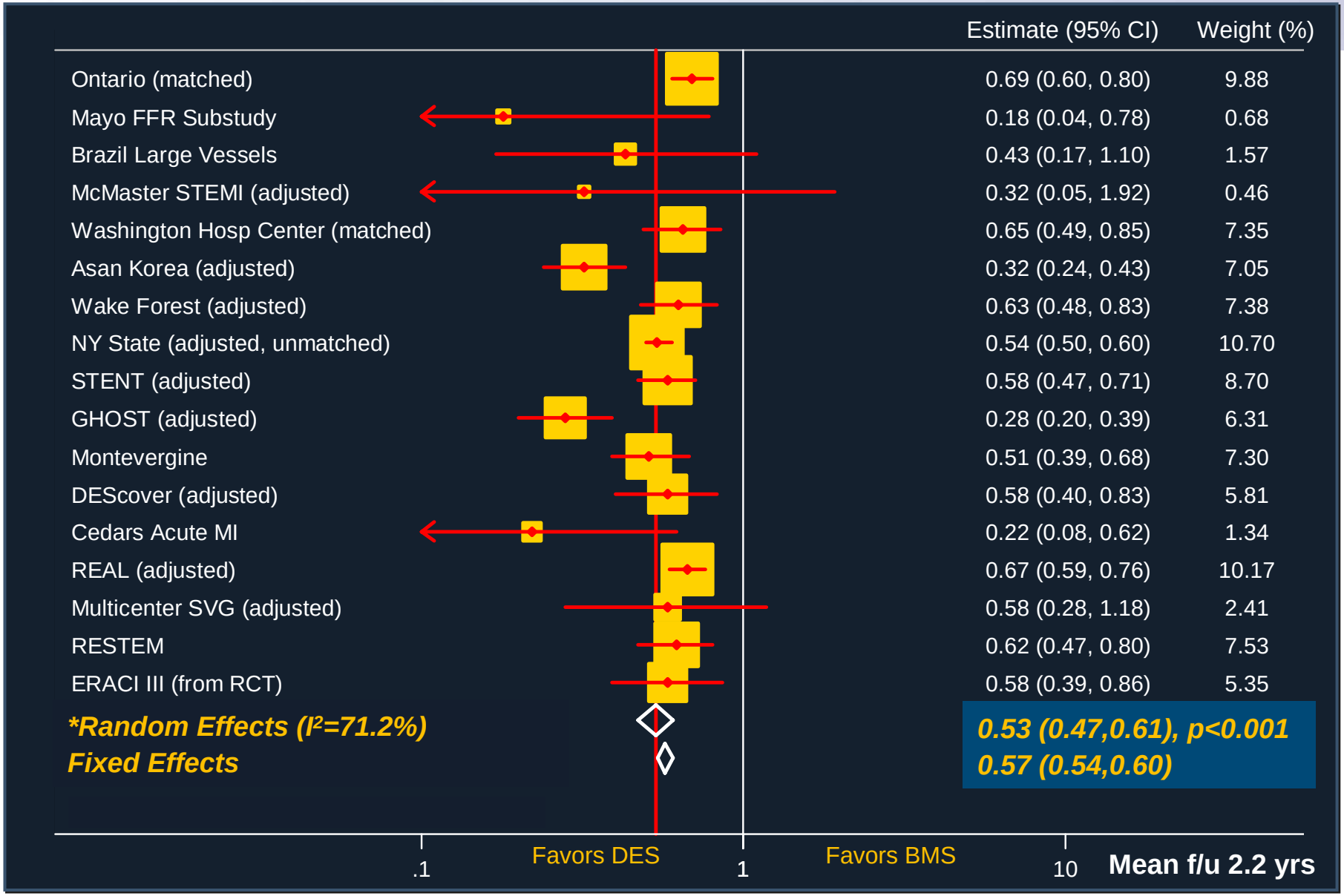


Kirtane A., Stone G., ACC Oral Presentation; 2008

TVR
All RCTs (*7,291 patients, 16 trials)*



TVR
All Registries (*73,819 patients, 17 registries)*



What Do We Know About DES in 2008?

- Profound, durable reduction in need for repeat revascularization
- From RCTs, no overall differences in D/MI/ST, now entering 6th year of follow-up
- Possibly lower MI and death compared with bare metal stents
- ‘Off Label’ does not mean ‘Unstudied’

  Majority of data support no difference in off-label safety metrics between DES and BMS

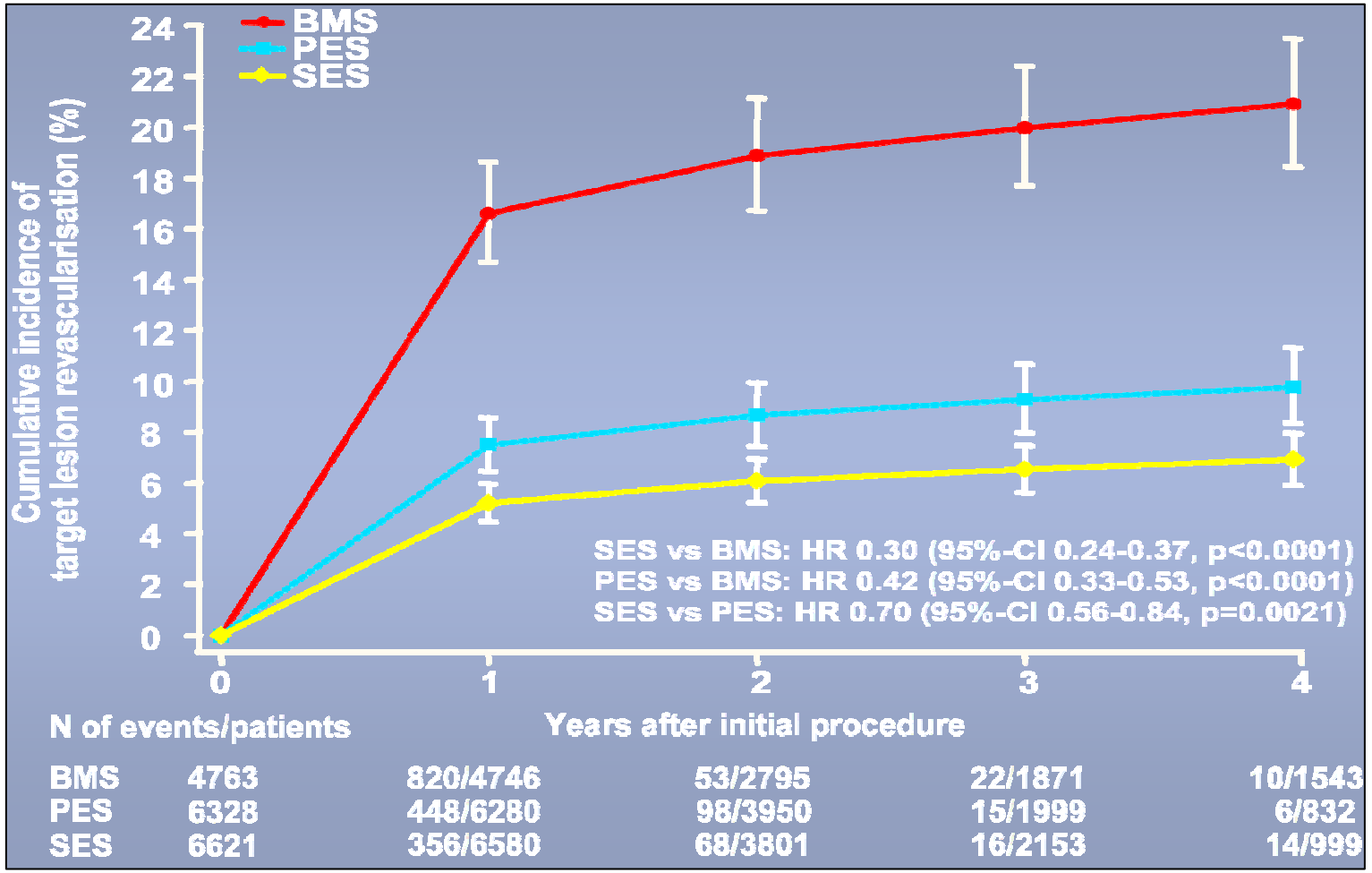
- Emerging differences in efficacy and safety endpoints between DES, no ‘class effect’

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.

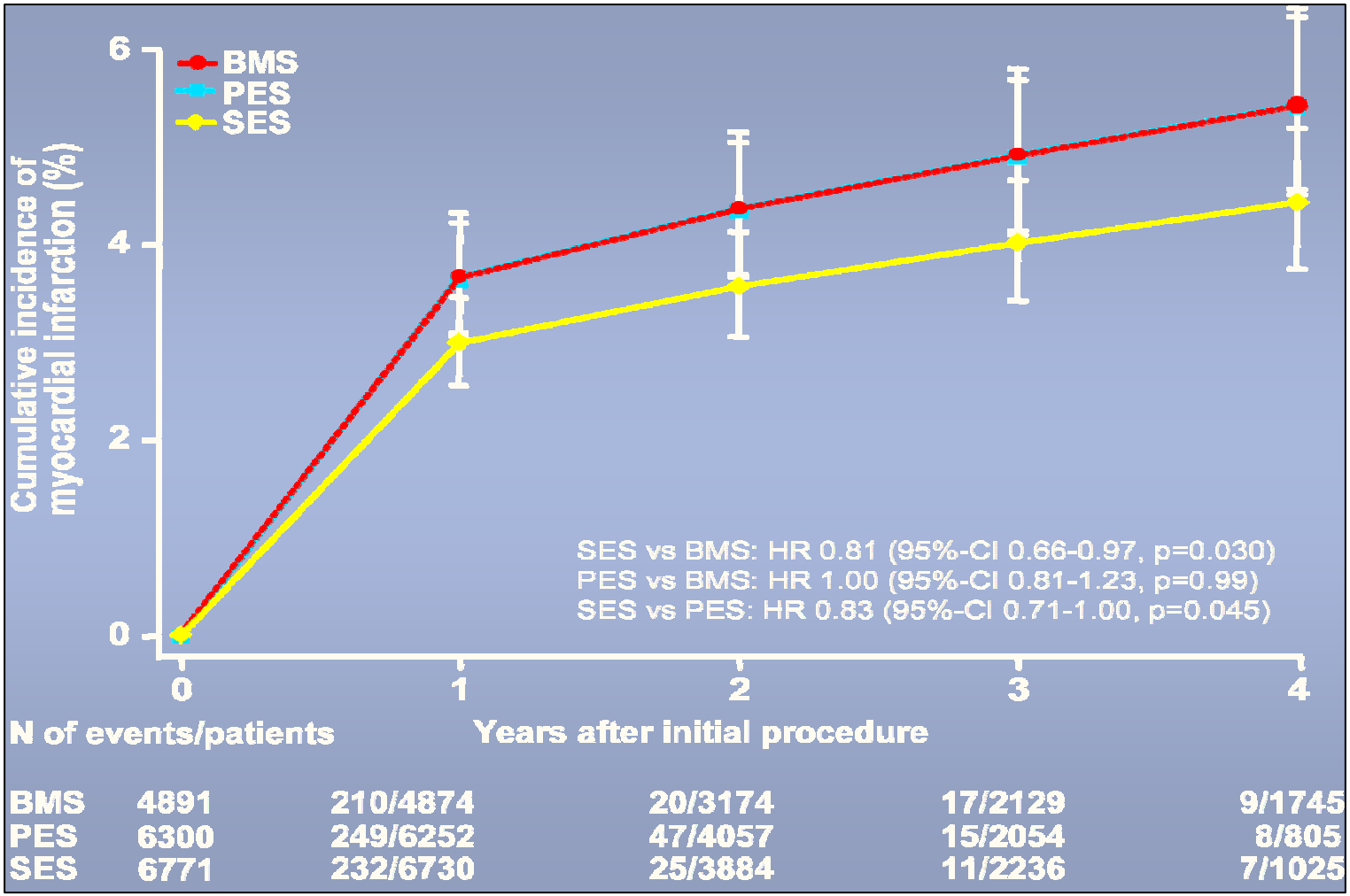
Cumulative Incidence of TLR
38 RCTs, 18,023 patients



**** TVR was used as a proxy for 3 studies***

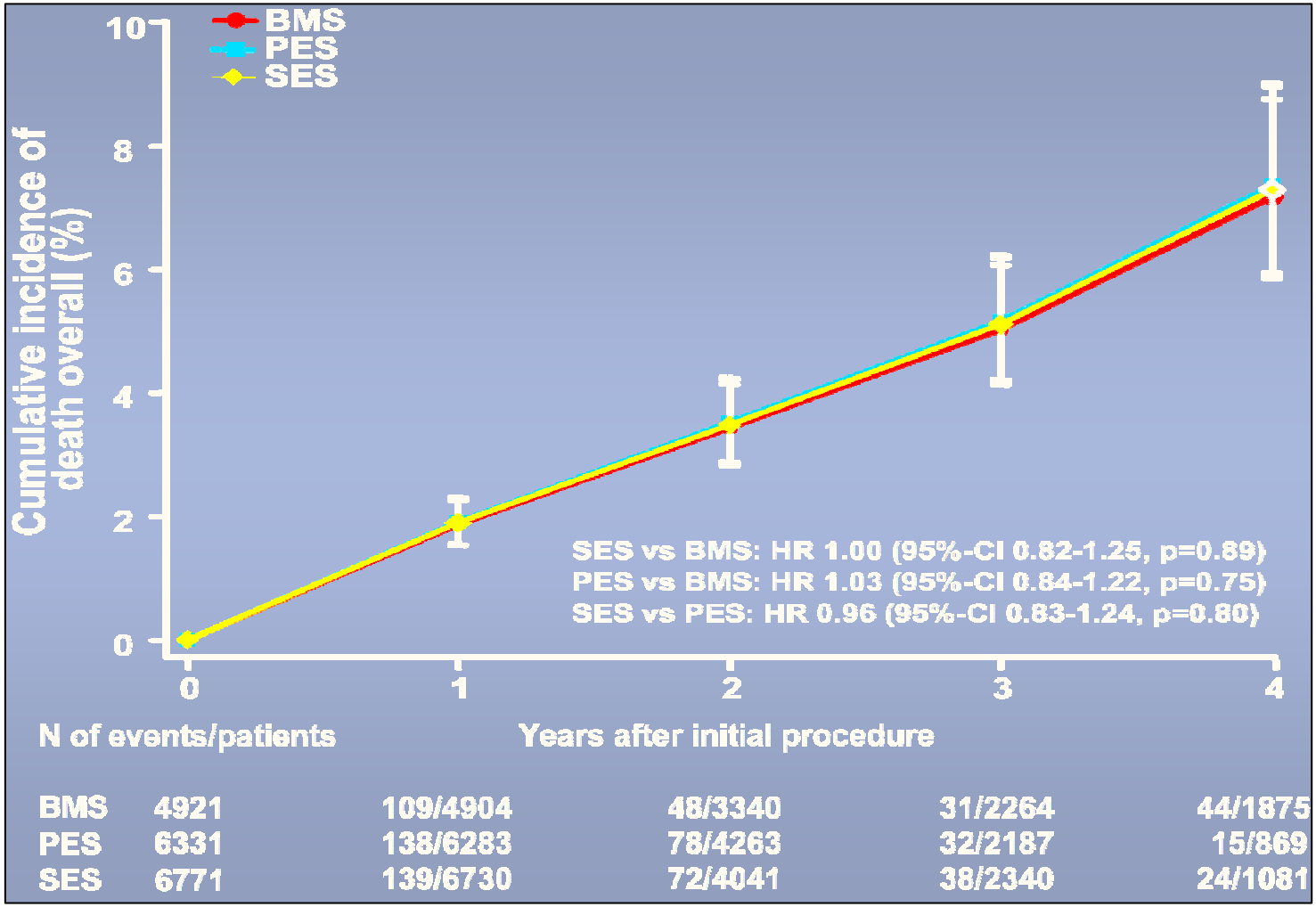
Stettler C., et al., *Lancet* 2007;370:937-48.

Cumulative Incidence of Myocardial Infarction 38 RCTs, 18,023 patients



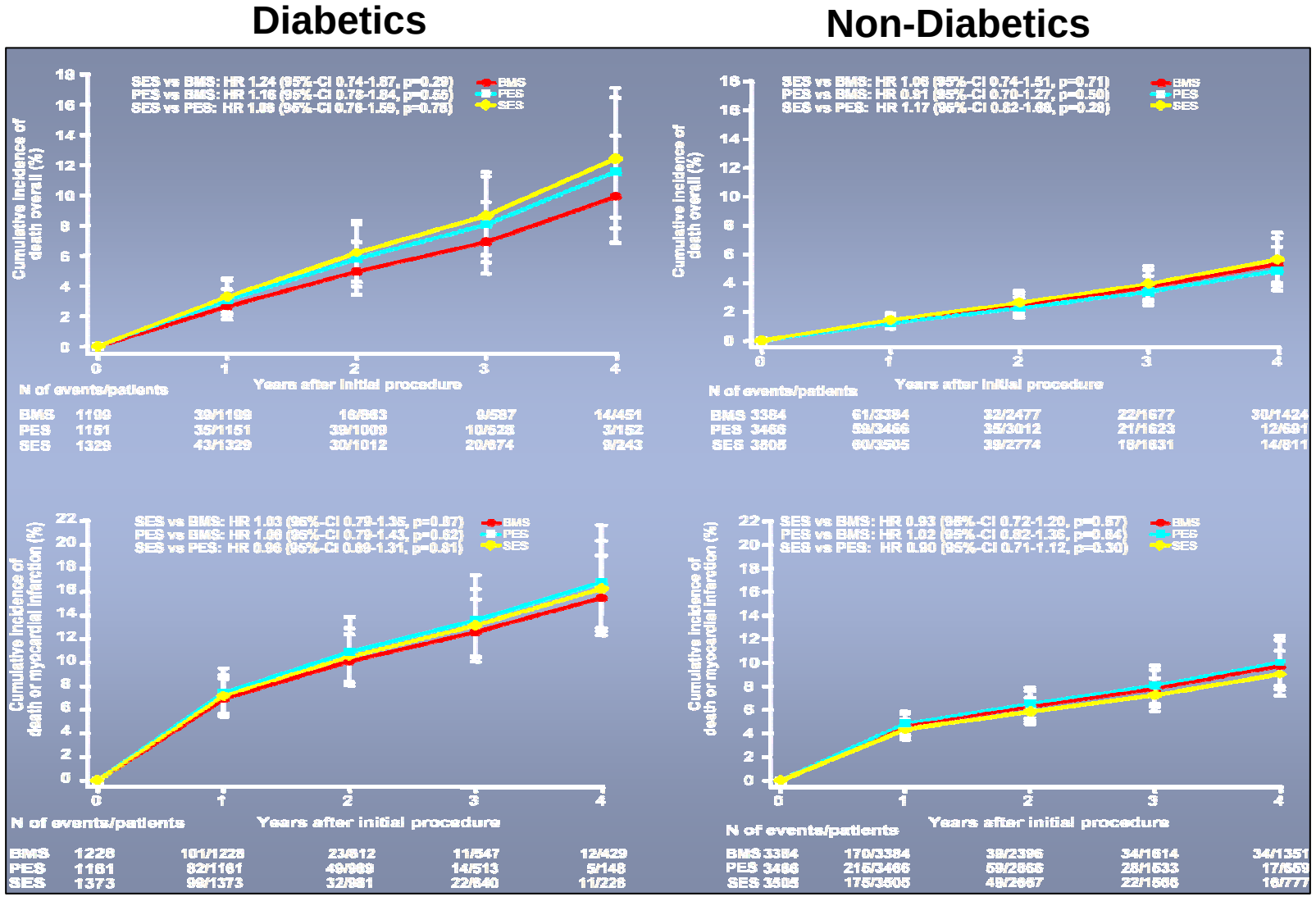
Stettler C., et al., *Lancet* 2007;370:937-48.

Cumulative Incidence of All-Cause Mortality 38 RCTs, 18,023 patients



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

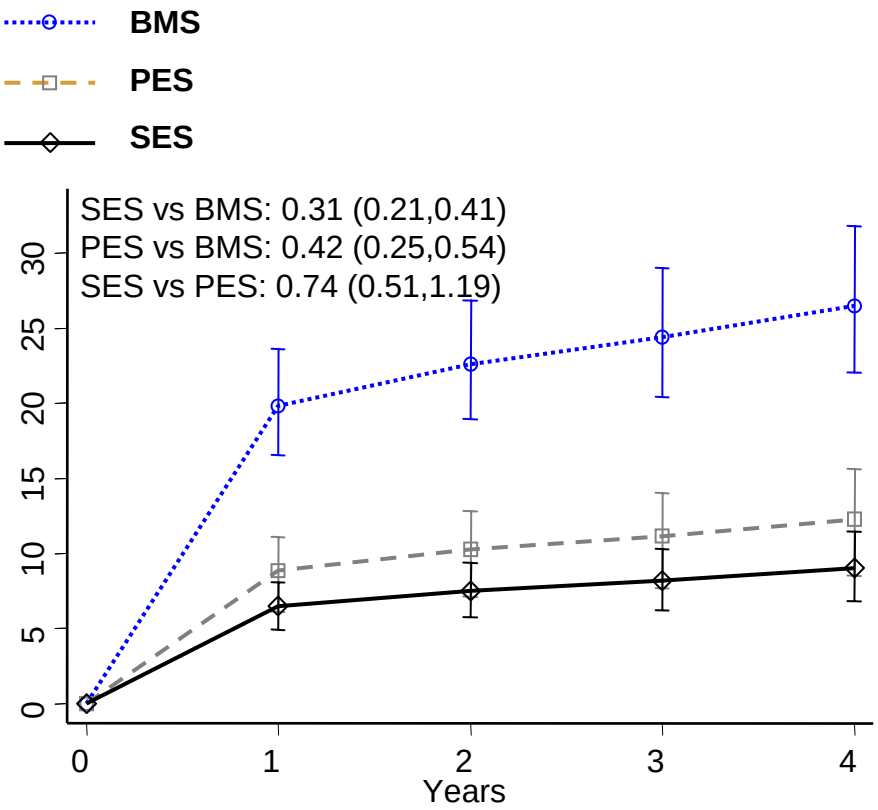
Cumulative Incidence of Overall Death and Death/MI: DM vs. Non-DM (N=3,762)



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

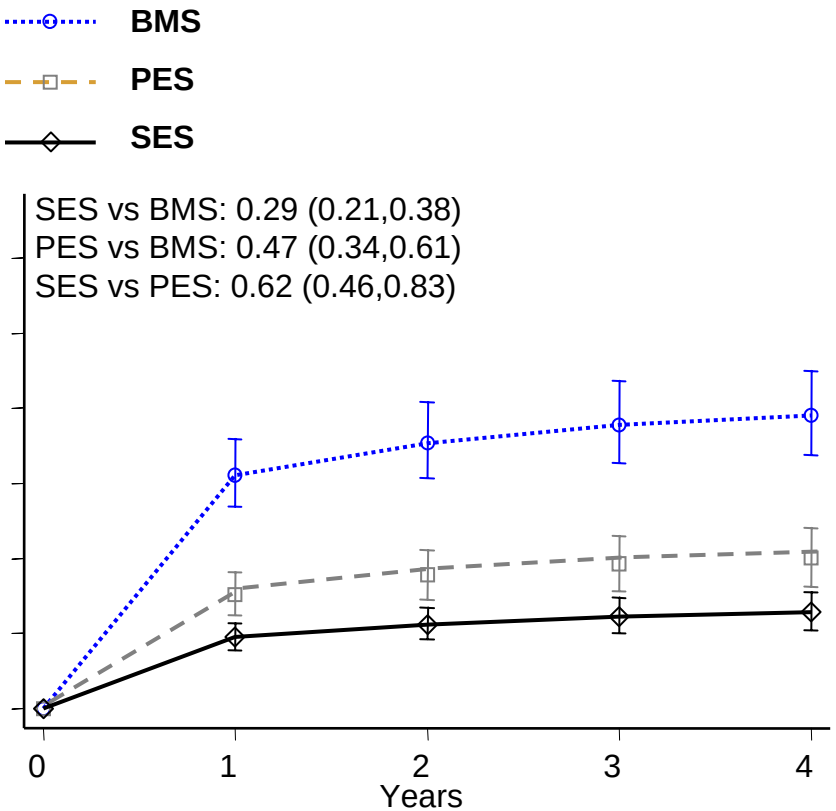
Target Lesion Revascularization

Diabetic Patients



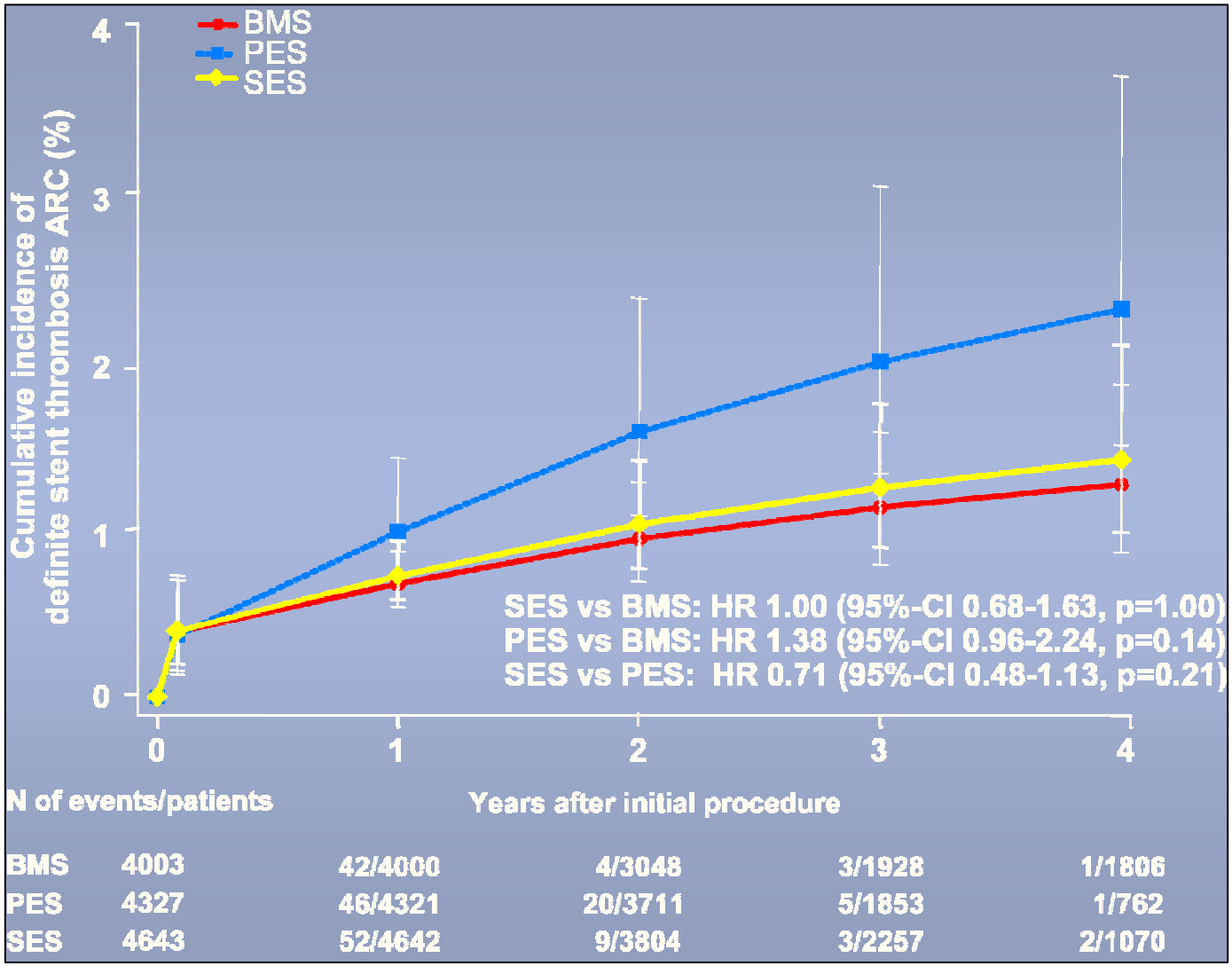
BMS	1228	1228	667	451	348
PES	1161	1161	942	486	146
SES	1373	1373	947	606	219

Non-Diabetic Patients



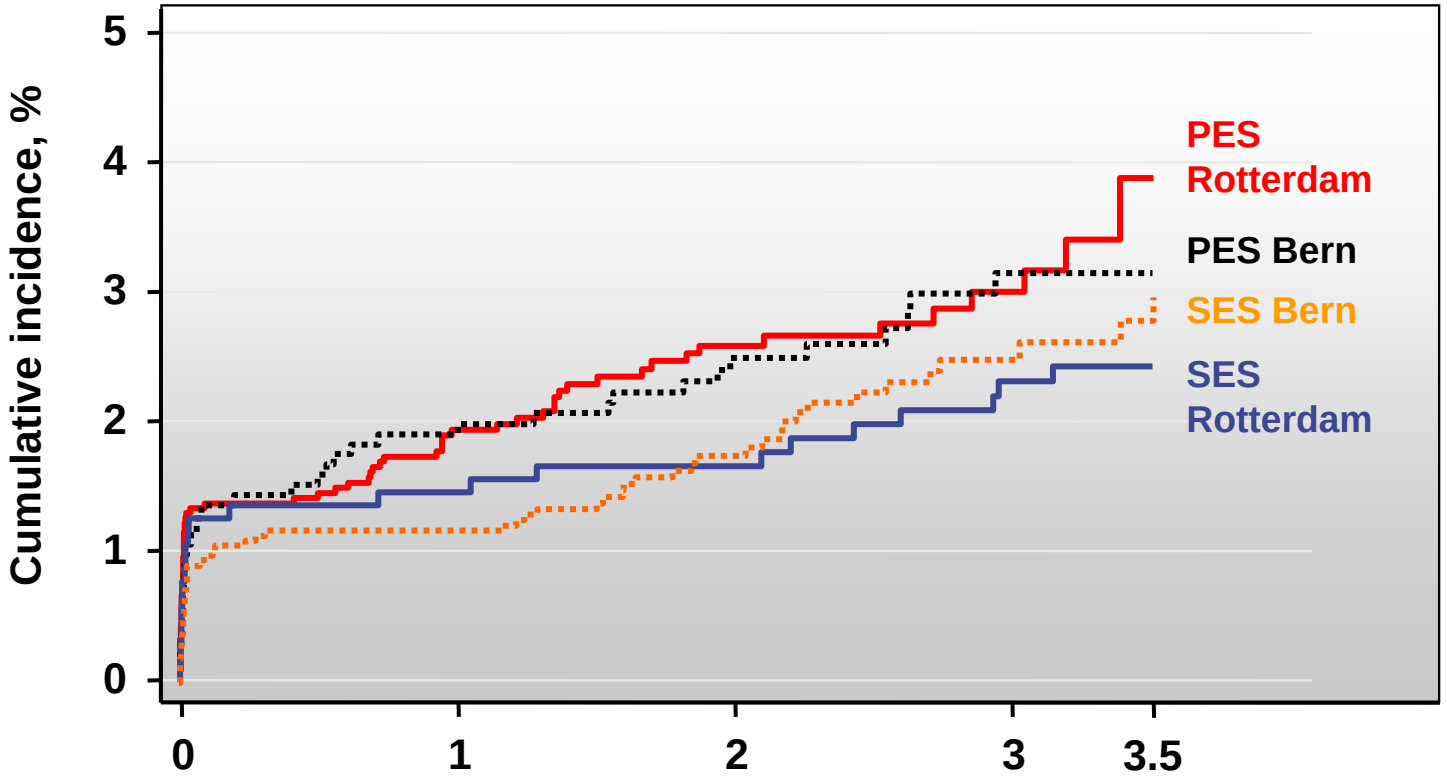
3384	3384	2128	1420	1195
3466	3466	2776	1477	660
3505	3505	2614	1512	753

Cumulative Incidence of ARC Definite ST
38 RCTs, 18,023 Patients



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

Definite Stent Thrombosis and Stent Type
Bern - Rotterdam Cohort Study



PES: 3.6%

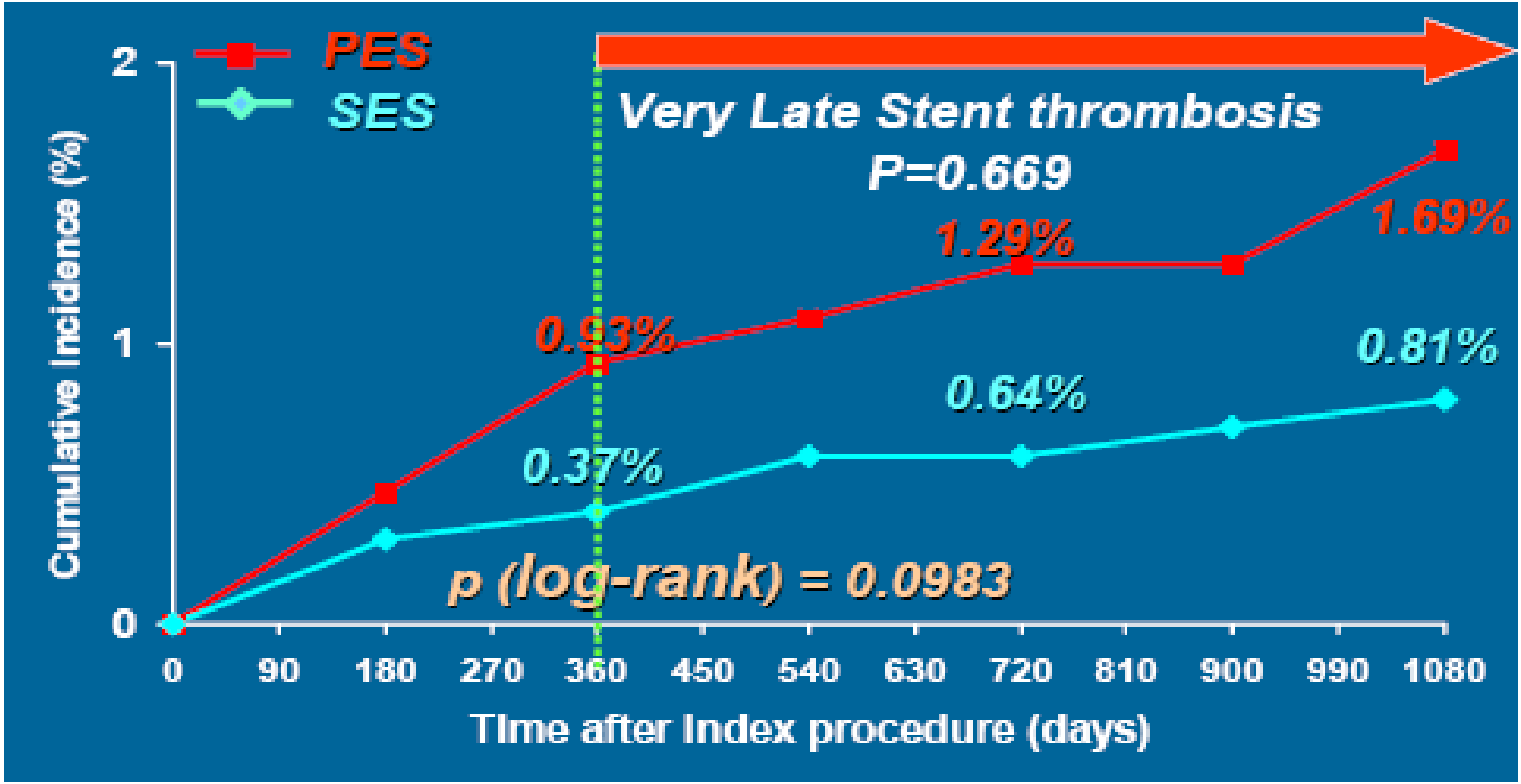
SES: 2.7%

HR=0.71
(0.53-0.95)
P=0.019

Months	1	12	24	36	42
Cumulative incidence SES, %	1.0	1.2	1.7	2.4	2.7
Cumulative incidence PES, %	1.3	1.9	2.5	3.1	3.6

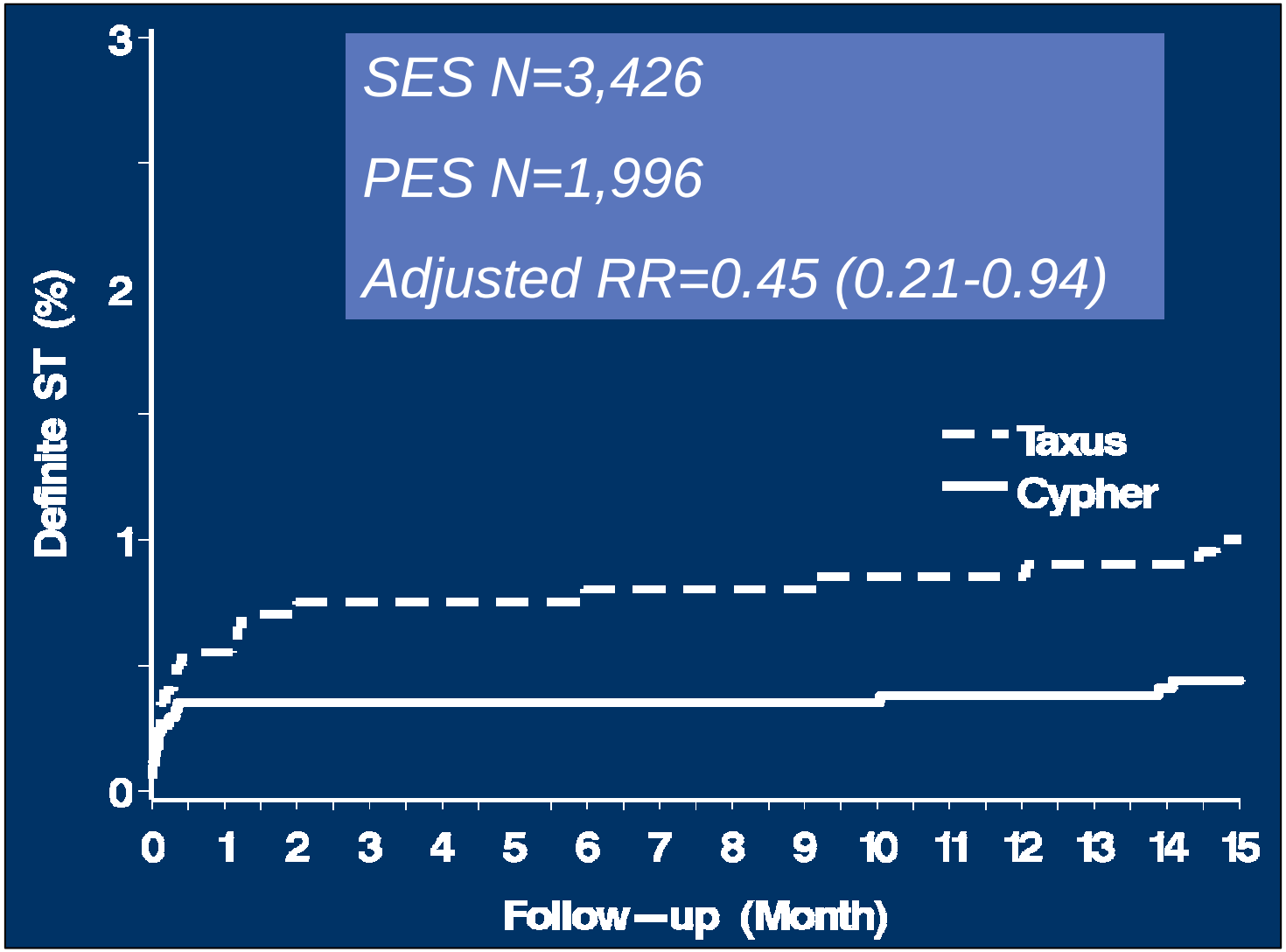
Daemen et al. ESC2007

ASAN:
ARC Definite ST up to 3 Years



Park SJ et al. TCTSummit, Seoul April 2007; TCT2007

Western Denmark Heart Registry
Definite Stent Thrombosis (ST)



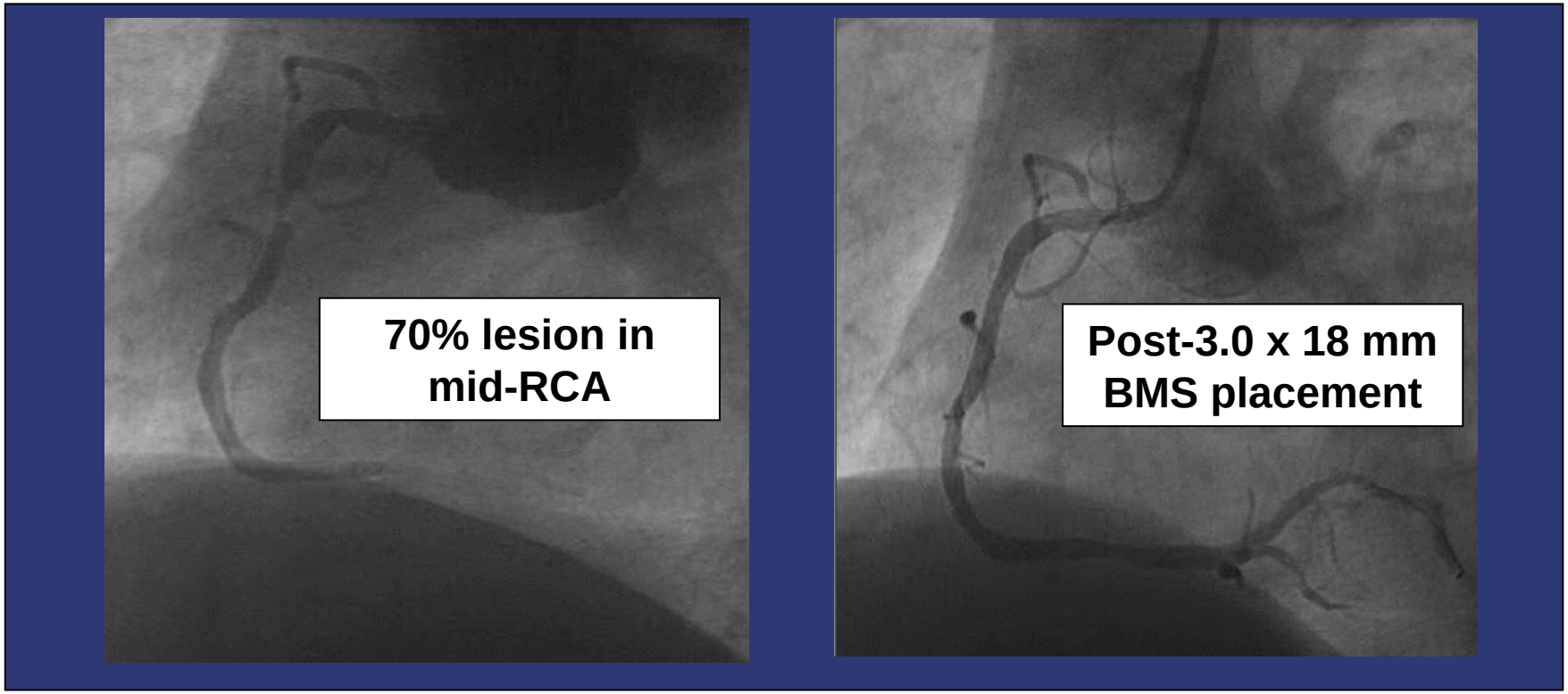
M. Maeng TCT2007

Lessons Learned From DES Trials
2002 to Today

1. Angiographic Endpoints Alone are Insufficient
2. There is not one ‘end all, be all’ trial
3. Look for consistency across trial designs
4. We never followed patients treated with BMS so systematically and over long-term until DES

Very Late Stent Thrombosis in RAVEL Trial

- 60 year old man with diabetes, hypertension, dyslipidemia, gout and tobacco use presented with angina in 2000
- After angiography, patient randomized in RAVEL trial

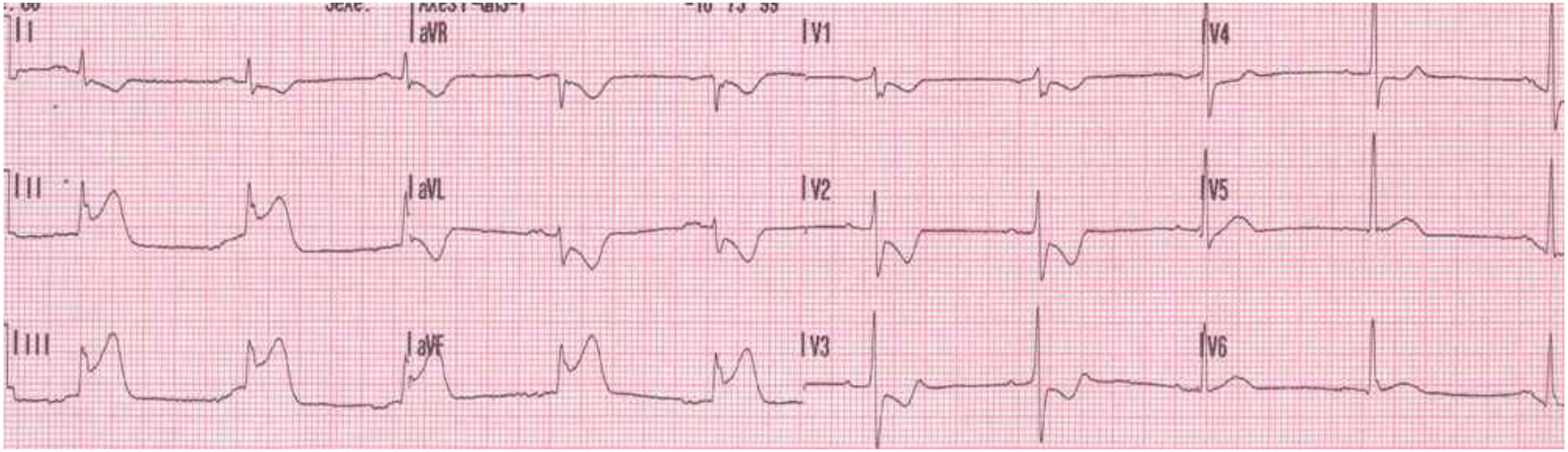


- *ASA, clopidogrel for 2 months upon discharge*

Zajarias A, et al.,http://www.europcronline.com/eurointervention/12th_issue/case1.

Very Late Stent Thrombosis in RAVEL Trial

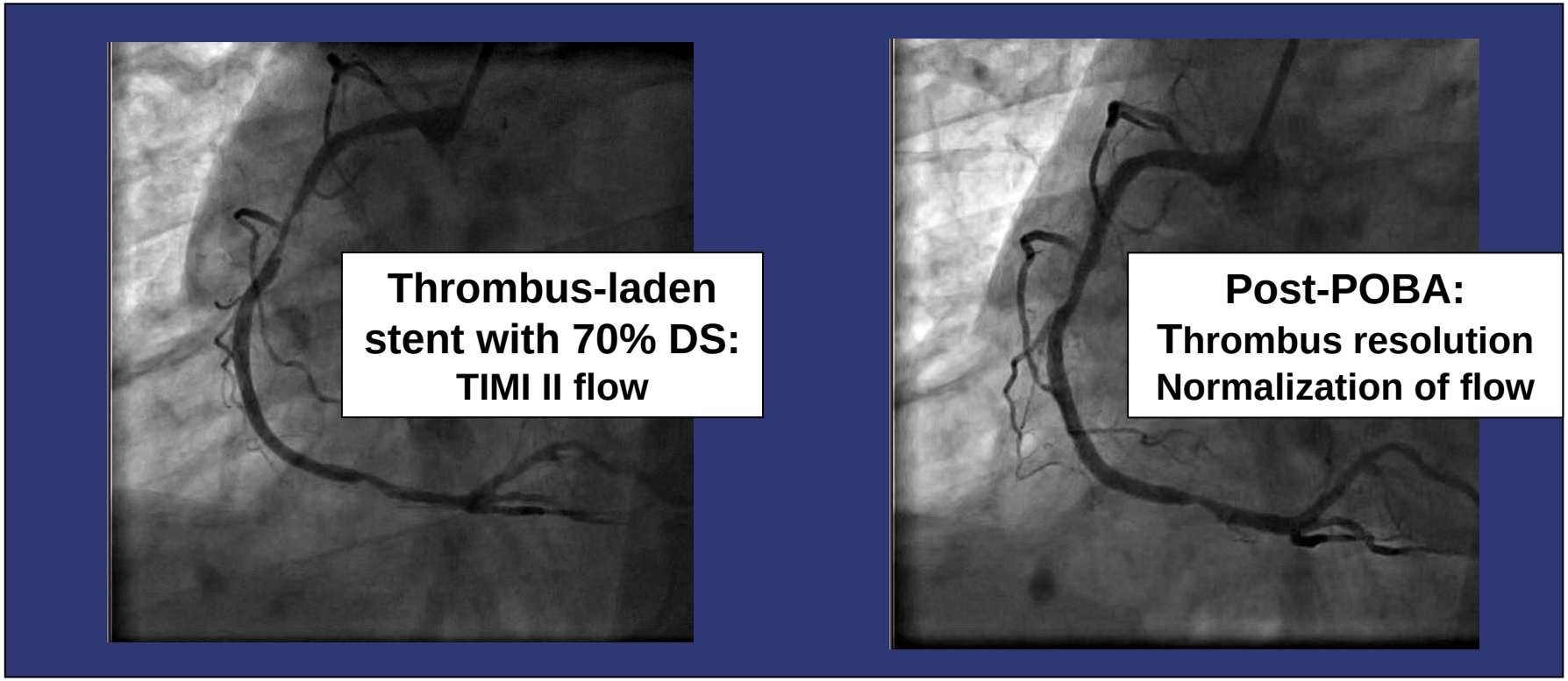
- 50% diffuse ISR noted at 6-month angiographic F/U
- Treated medically; annual follow-up with an exercise stress test revealed no symptoms or inducible ischemia for 6 years
- 7 years post-PCI:
  - Patient has an inferior STEMI while still on ASA



Zajarias A, et al.,http://www.europcronline.com/eurointervention/12th_issue/case1.

Bare Metal Stent VLST in RAVEL

- Fibrinolytic therapy, then emergency rescue PTCA due to persistence of symptoms and lack of ST resolution



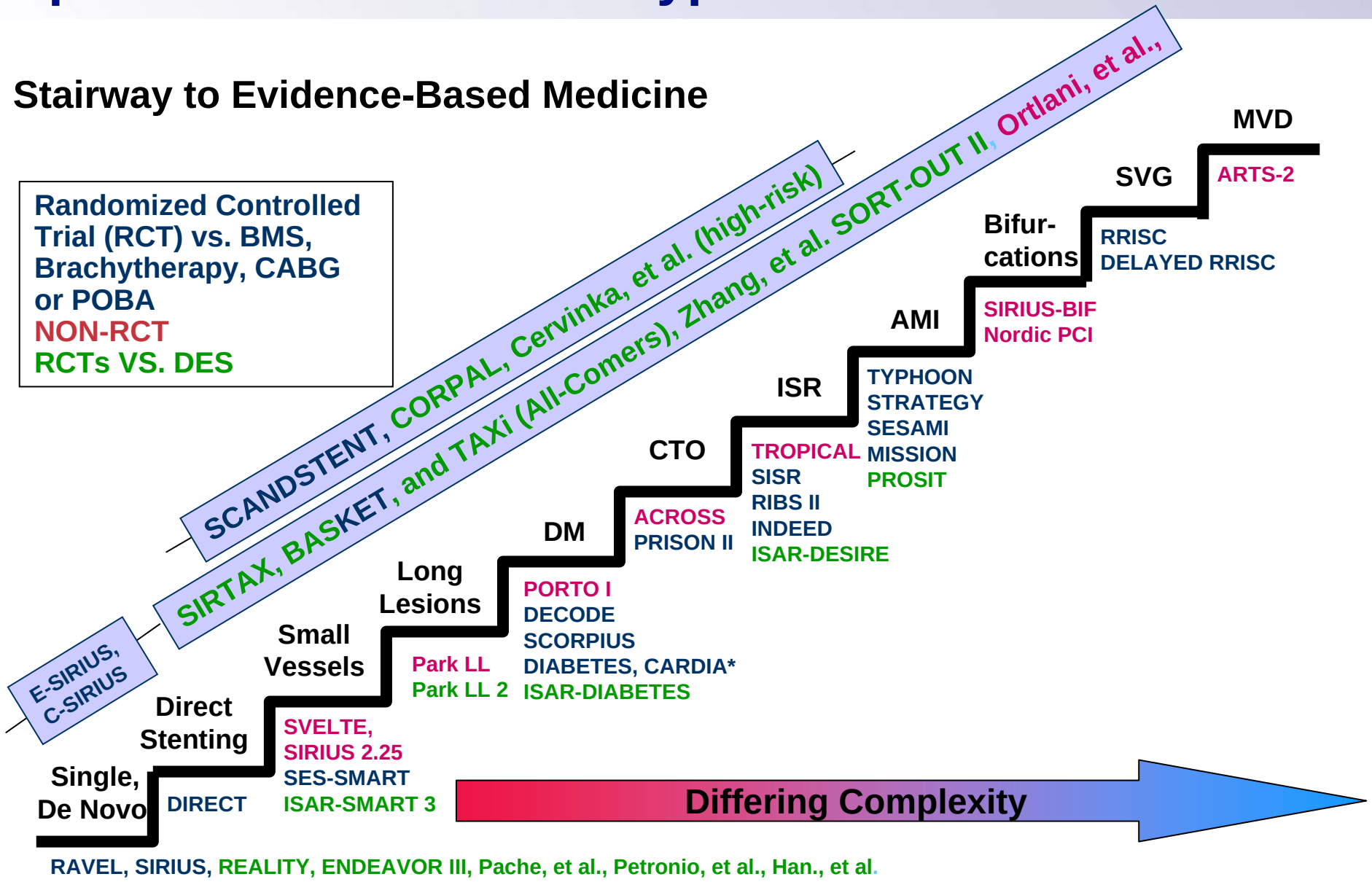
- Discharged on ASA/Clopidogrel

Zajarias A, et al.,http://www.europcronline.com/eurointervention/12th_issue/case1.

Lessons Learned From DES Trials
2002 to Today

1. Angiographic Endpoints Alone are Insufficient
2. There is not one ‘end all, be all’ trial
3. Look for consistency across trial designs
4. We never followed patients treated with BMS so systematically and over long-term until DES
5. When low frequency and late-occurring events are of interest, there is no substitute for large trials, diverse patient populations and long-term follow-up
6. Avoid indirect, cross trial comparisons—randomized trials represent best opportunity for comparison, but what is standard of comparison?

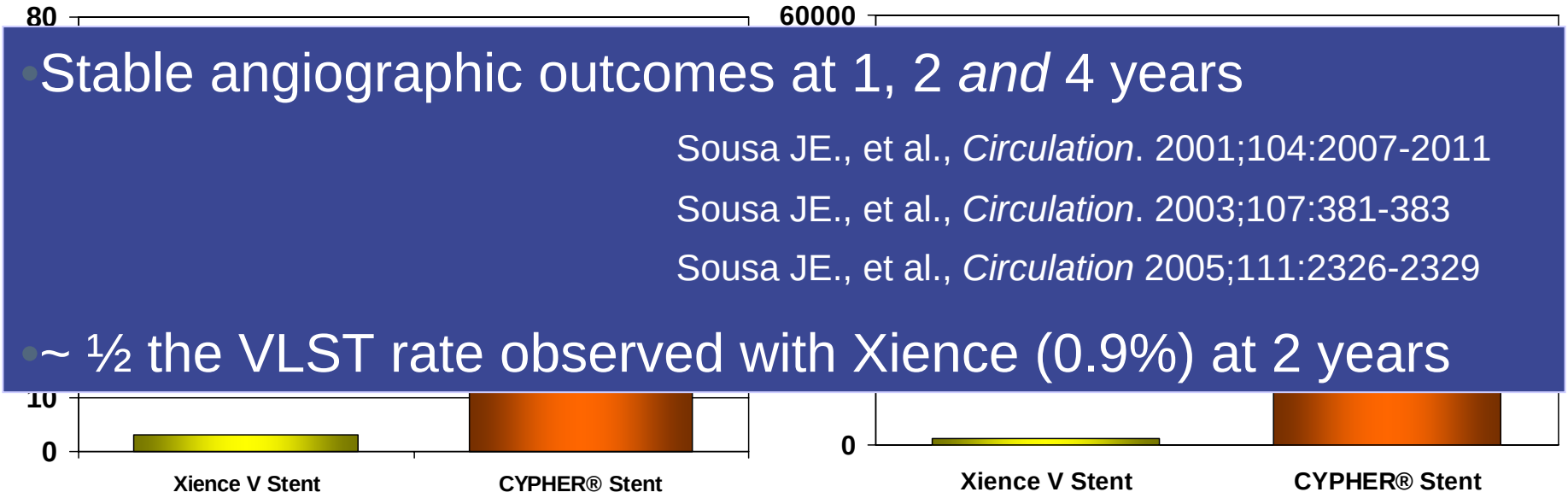
Dedicated Trials with CYPHER® Stent in Specific Patient/Lesion Types



Clinical Trials Experience

Number of Clinical Studies

Number of Patients Studied



- Stable angiographic outcomes at 1, 2 *and* 4 years

  Sousa JE., et al., *Circulation*. 2001;104:2007-2011

  Sousa JE., et al., *Circulation*. 2003;107:381-383

  Sousa JE., et al., *Circulation* 2005;111:2326-2329

- ~ ½ the VLST rate observed with Xience (0.9%) at 2 years

- Xience V (≤2 year follow-up):
  - 3 clinical studies
  - ~ 952 patients
- CYPHER® Stent (5 year follow-up):
  - > 75 clinical studies
  - > 50,000 patients
  - Post-marketing experience: > 3 million patients

Informing Real World Clinical Practice

J-CYPHER Registry

- 12,824 SES patients
- 41% diabetes, 5% hemodialysis
- 55% MVD, 7% Unprotected LM, 9% CTOs
- Successful SES deployment 99.8% (17,545/17,584)
- IVUS 42%, Max inflation pressure 17.8 ATM

  →3% baseline incomplete apposition

- 3 year ARC def/prob ST 1.36% (0.47% at 30 days, 0.74% at 1 year)

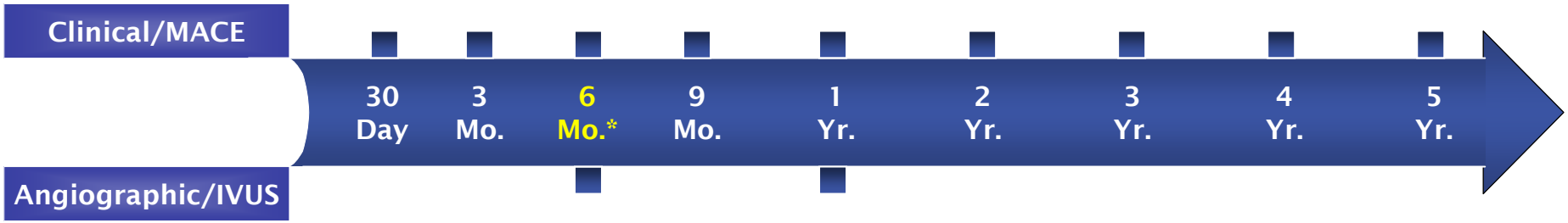
RES-ELUTION Study Design
Multi-center, Prospective, Two-arm, Non-Inferiority, Randomized Control Trial using Conor SES

388 patients randomized for the treatment of
a Single *De Novo* Native Coronary Artery Lesion <28 mm with RVD 3.0-3.5 mm
Conducted at up to 40 Centers Worldwide
Principal Coordinating Investigators: Pr C. Spaulding, Dr. Alexandre Abizaid, Dr. John Ormiston

Investigational Arm
Conor SES

Control Arm
TAXUS Liberté

Primary Endpoint: 6-Month In-Stent Late Loss
Sub-Studies: 6 and 12 Month IVUS (first 50 pts, per treatment arm)
Dual antiplatelet therapy for 6 mo. Minimum
12 mo. Recommended per ESC/ACC/AHA/SCAI guidelines



*Primary Endpoint Analysis

Summary
Impact of Emerging Comparative DES Data

Significant differences exist in both DES safety and efficacy

- Emerging differences in SES/PES safety (ST, MI) against background of disparate efficacy
- Established superiority of –limus agents
- Absence of “class effect” between SES and PES (FDA 12/2006)

2008: Attention to late and low frequency events, yet limited information with new DES technologies

- Differences in outcome relate to specific agent, elution rate, dose and ?polymer
- Introduction of several ‘novel’ DES are outpacing supportive evidence
- Much inferential data (preclinical, etc.) but need trial patient data

What is required for a DES to become the benchmark for safety and efficacy for new comparative DES programs?

- Recent newer DES data leaving us with ore questions than answers
- Systematic, long-term comparative data in large and varied patient population
- Detailed, patient level data represented in all trial designs
- Threshold to improve upon existing data with SES is a challenge for new DES