Are DES safer than BMS?

Evidence from a Network Meta-Analysis

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Disclosures

I, Kyung Woo Park, **DO NOT** have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Remember the days of restenosis?

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association. Learn and Live.

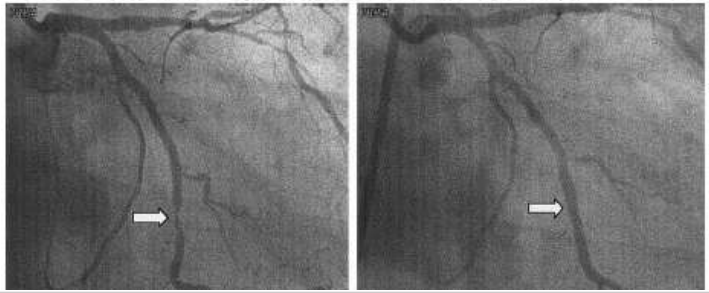
YEAR

2001

Clinical Investigation and Reports

Sustained Suppression of Neointimal Proliferation by Sirolimus-Eluting Stents

One-Year Angiographic and Intravascular Ultrasound Follow-Up

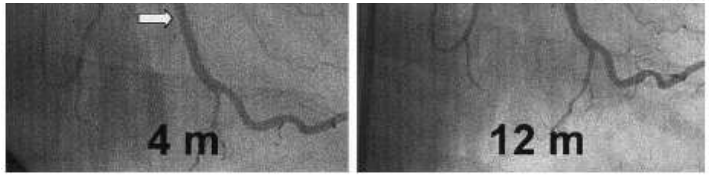


Patrick Serruys – "If I am in a dream, please don't wake me"

Editorial

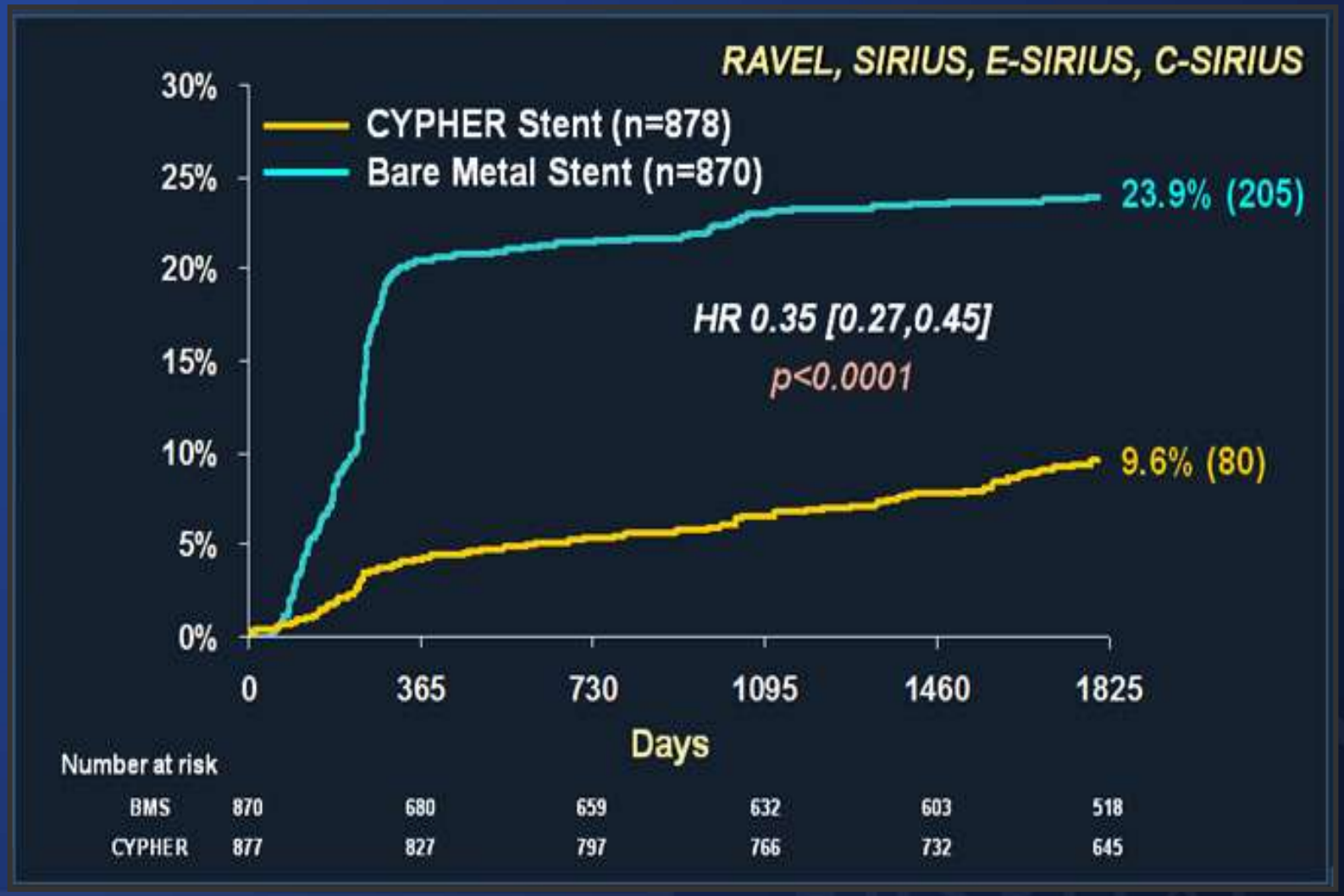
Living the Dream of No Restenosis

Paul S. Teirstein, MD



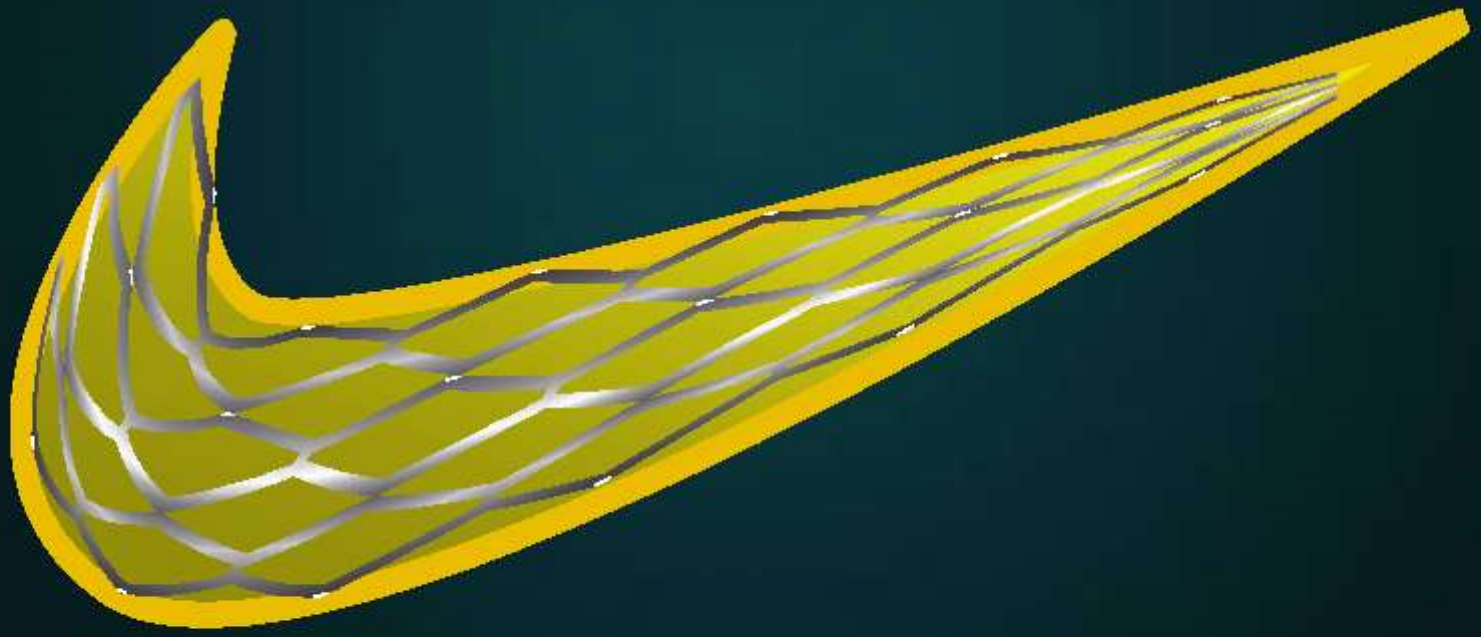
CYPHER vs. BMS : Pooled Analysis

TLR rate from 4 RCTs



Intervention 2003

Just DES It!

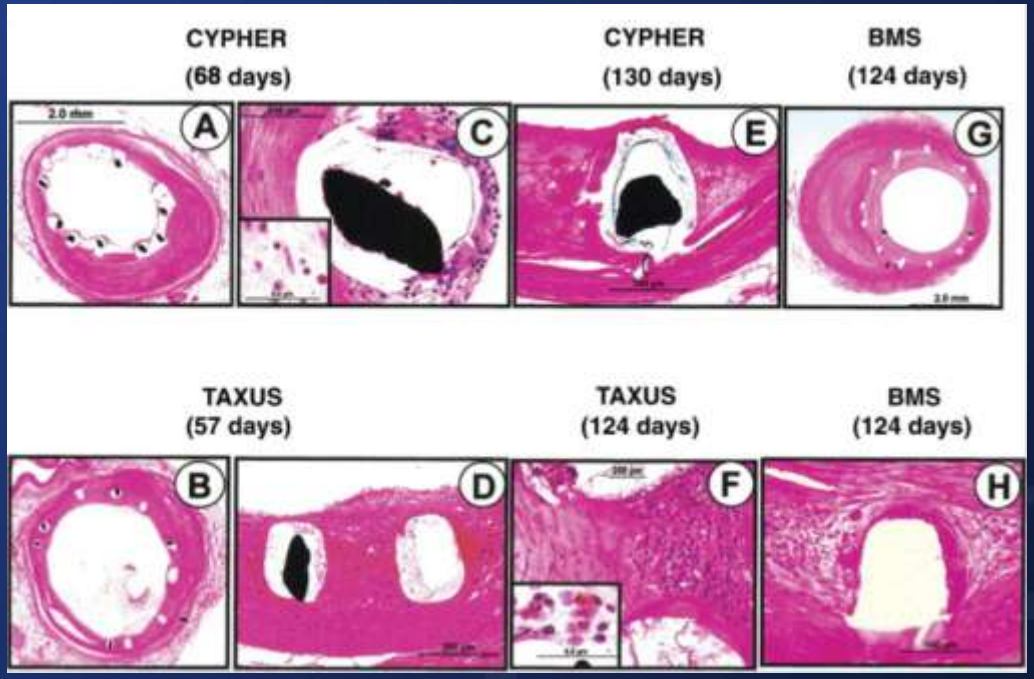


The “Camenzind” Shock – ESC 2006

Do DES kill patients?
Unsafe in the long term compared with BMS

DES and Late Stent Thrombosis

- DES reduce the need for repeat revascularization compared with bare metal stents (BMS)
- However, concerns have been raised regarding the potential for late stent thrombosis with DES related to delayed healing of vessel wall.

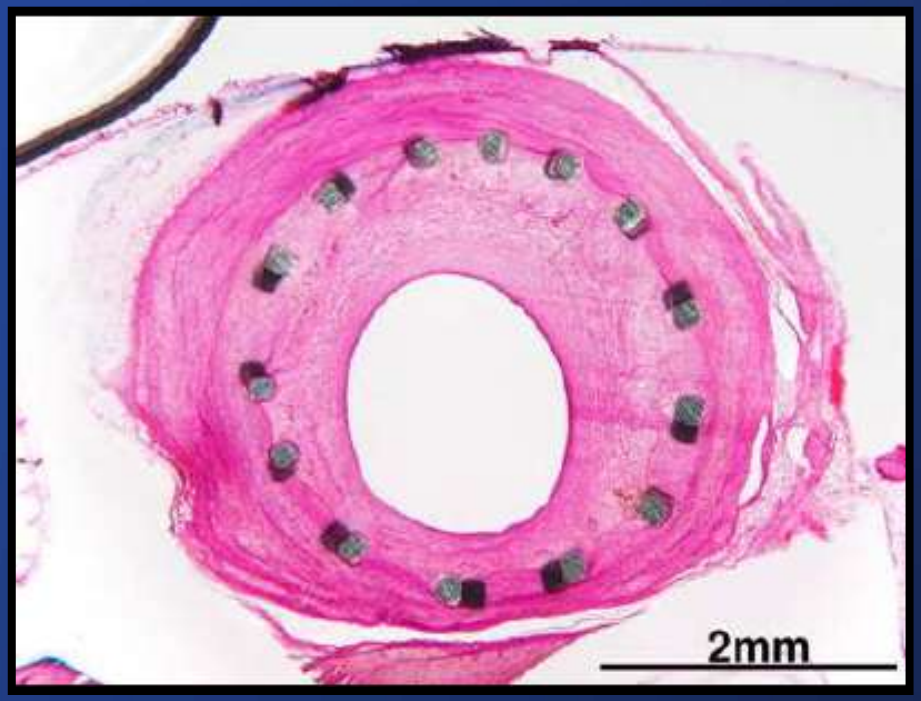


inflammatory infiltrate including eosinophils around Cypher & Taxus struts

Joner et at. JACC. 2006

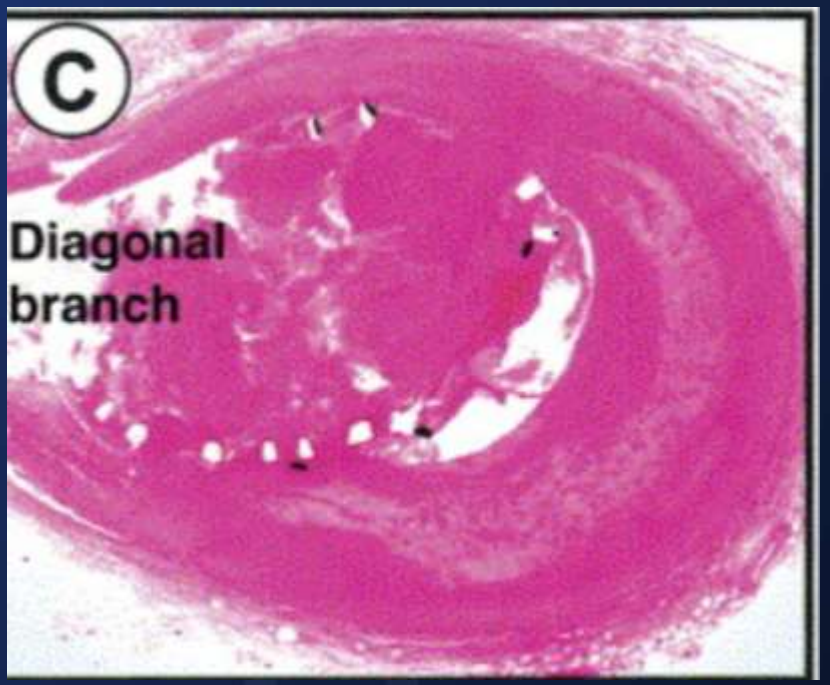
Restenosis

Requiring repeat revascularization
Relatively soft adverse event



Stent Thrombosis

Results in death/MI
Relatively hard adverse event



BMS? vs. DES?

THE LANCET

Articles

Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis

Tullio Palmerini, Giuseppe Biondi-Zoccai, Diego Della Riva, Christoph Stettler, Diego Sangiorgi, Fabrizio D'Ascenzo, Takeshi Kimura, Carlo Briguori, Manel Sabatè, Hyo-Soo Kim, Antoinette De Waha, Elvin Kedhi, Pieter C Smits, Christoph Kaiser, Gennaro Sardella, Antonino Marullo, Ajay J Kirtane, Martin B Leon, Gregg W Stone

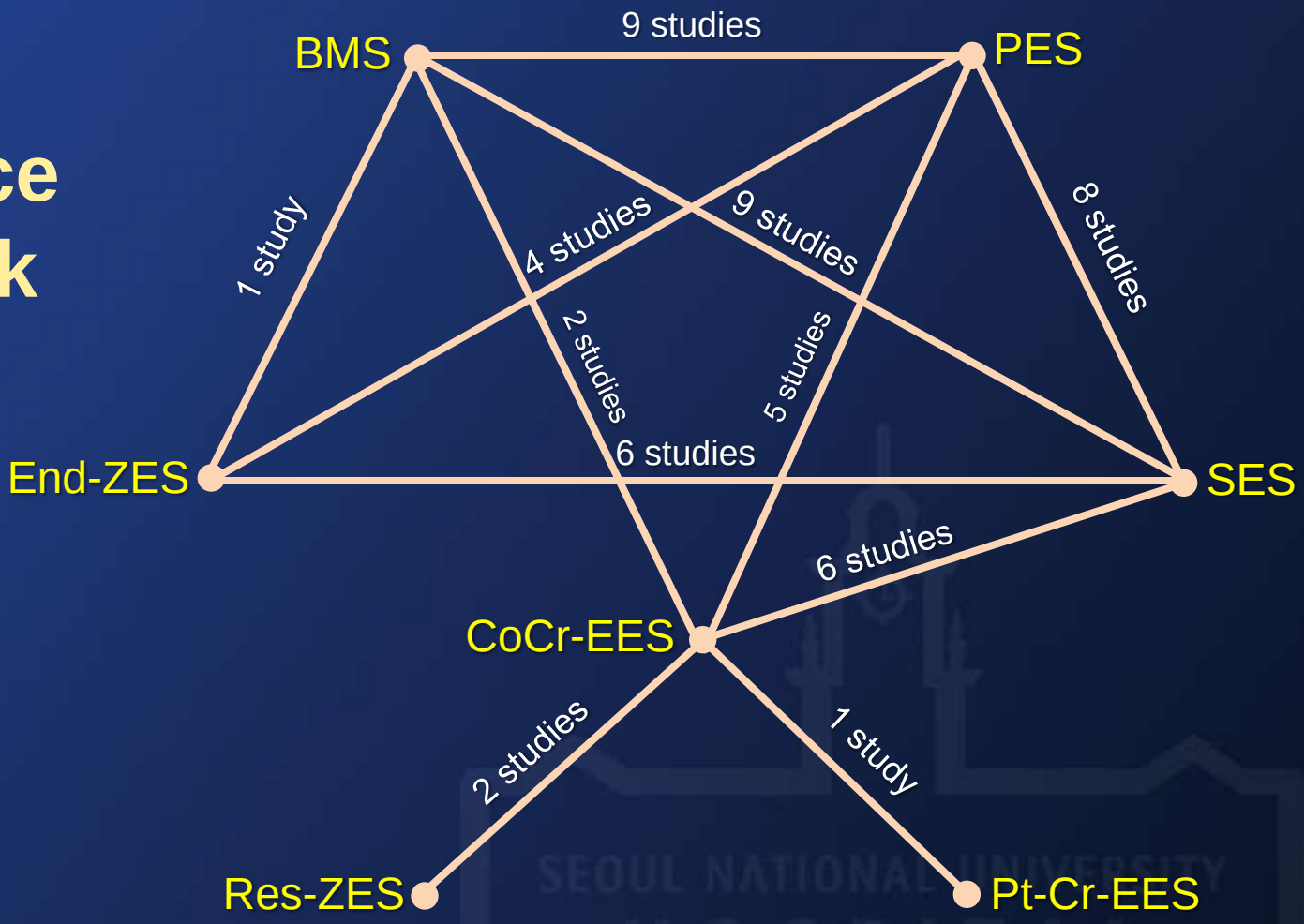
Lancet 2012; 379: 1393–402

Tullio Palmerini et at. Lancet 2012

Stent Thrombosis Network Meta-analysis
Primary EP: ARC Definite ST (FU through 2 years)

49 RCTs, 50,844 pts

Evidence network



Palmerini T et al. Lancet 2012

Stent Thrombosis Network Meta-analysis

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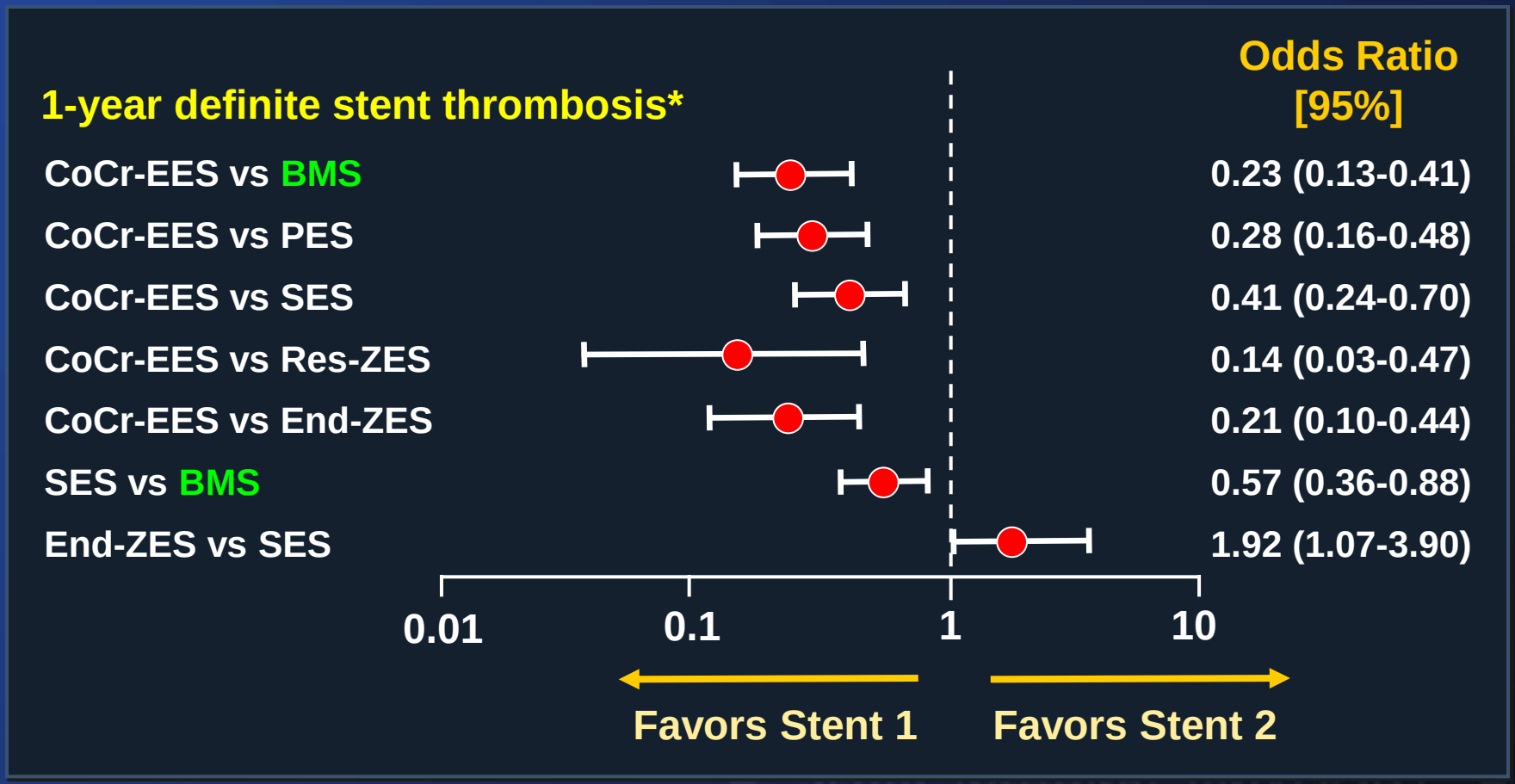


Palmerini T et al. *Lancet* 2012

Interventional Cardiology

Short- and Long-Term Outcomes With Drug-Eluting and Bare-Metal Coronary Stents

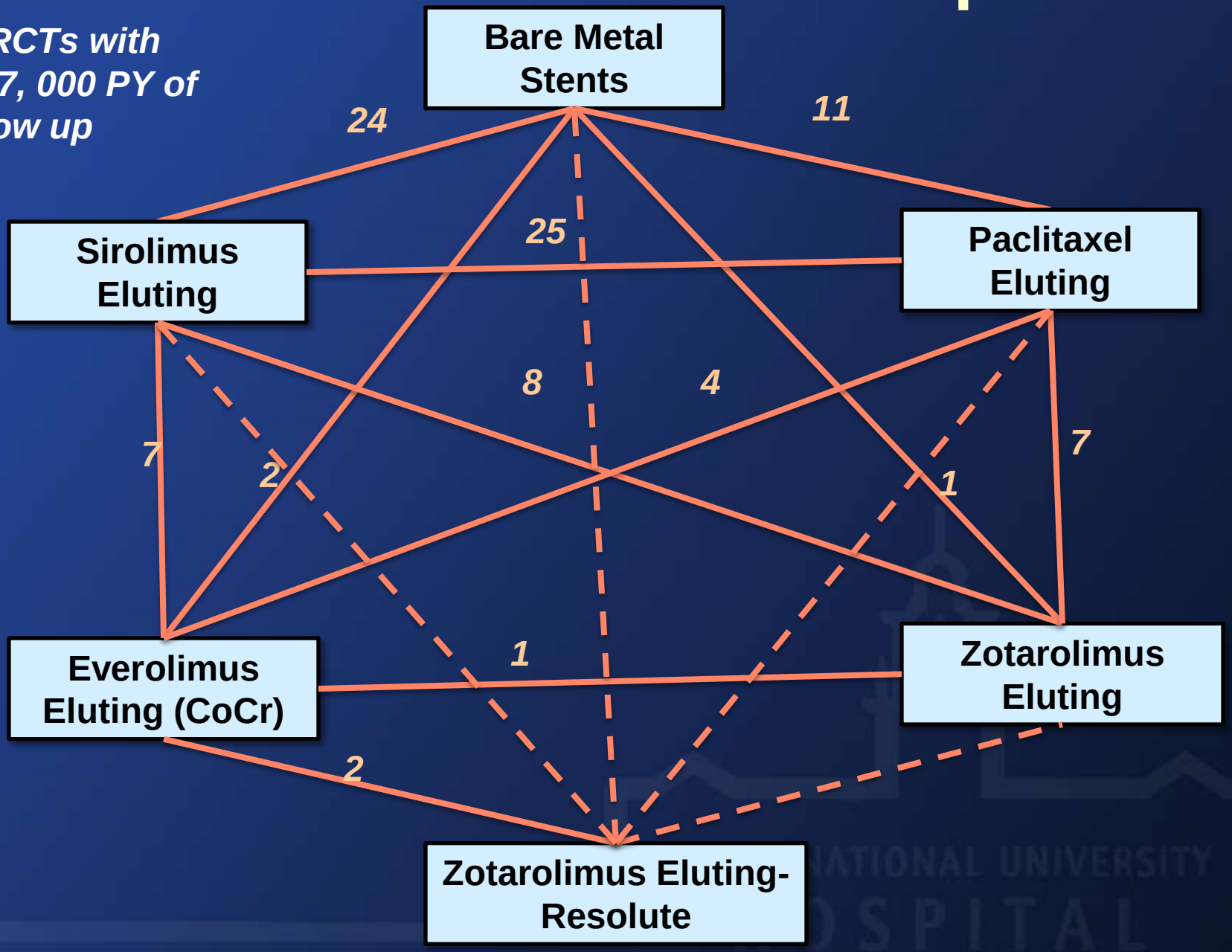
A Mixed-Treatment Comparison Analysis of 117 762 Patient-Years of Follow-Up From Randomized Trials

Sripal Bangalore, MD, MHA; Sunil Kumar, MD; Mario Fusaro, MD; Nicholas Amoroso, MD; Michael J. Attubato, MD; Frederick Feit, MD; Deepak L. Bhatt, MD, MPH; James Slater, MD

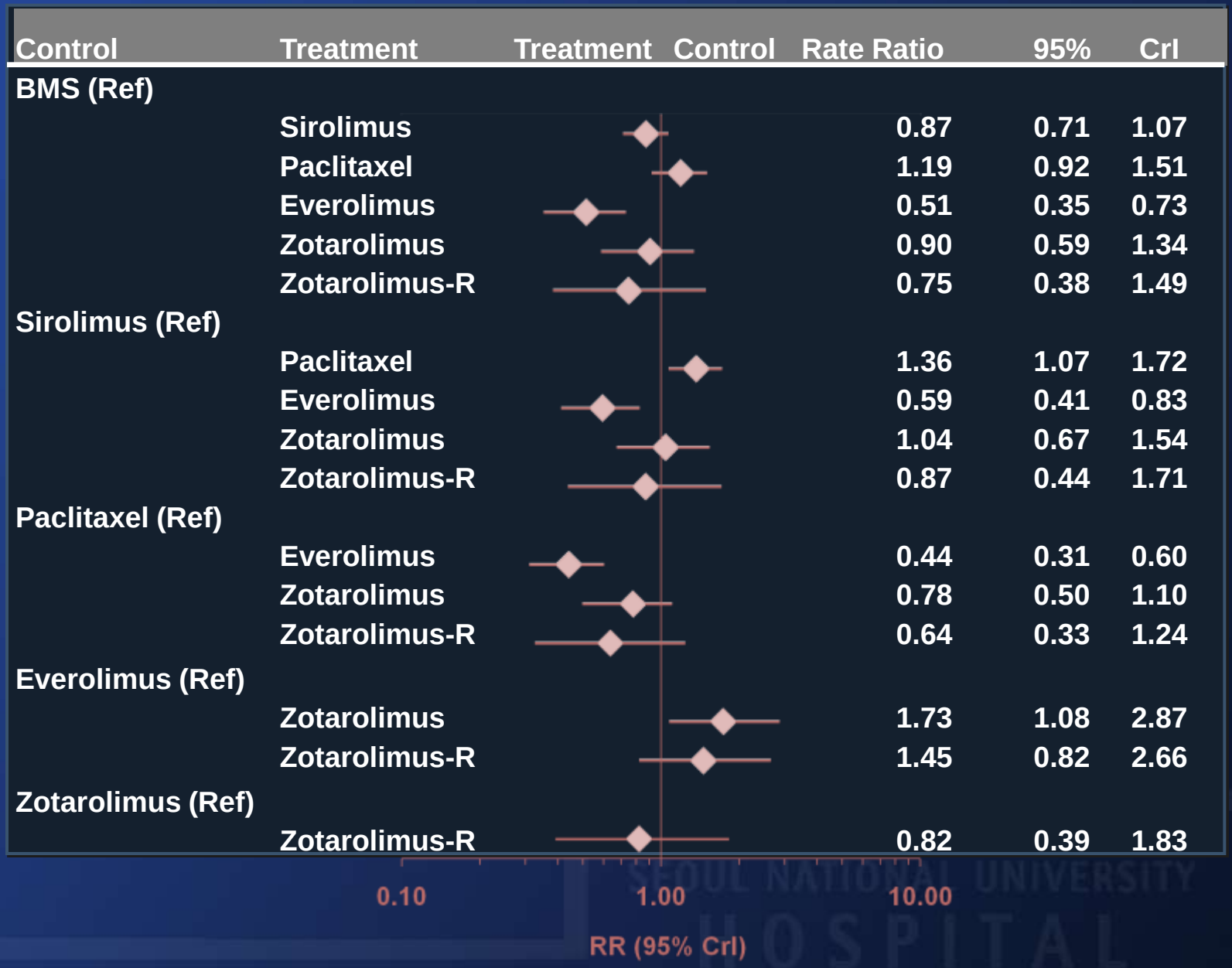
Bangalore et at. Circulation 2012

Network of Treatment Comparisons

76 RCTs with >117, 000 PY of follow up



Any Stent Thrombosis



Bangalore et al. *Circulation*. 2012;125:2873-2891

Background

- Biodegradable-polymer (BP) DES has been developed with an aim to reduce the risk of late stent thrombosis.

- While BP-DES have yet to receive approval in the United States, they are widely used across the world including Asia and Europe.

- Recent meta-analyses (Palmerini et al. Lancet 2012; Bangalore et al. Circ 2012) have shown improved safety as well as efficacy of newer-generation DES.

- However, they have limitations in that the number of patients with newer-generation DES was relatively small and that BP-DES were not included in the analyses.

Background

- Recent meta-analyses (Palmerini et al. Lancet 2012; Bangalore et al. Circ 2012) have shown improved safety as well as efficacy of newer-generation DES.

- Biodegradable-polymer (BP) DES has been developed with an aim to reduce the risk of late stent thrombosis.

- However, they have limitations in that the number of patients with newer-generation DES was relatively small and that BP-DES were not included in the analyses.

- While BP-DES have yet to receive approval in the United States, they are widely used across the world including Asia and Europe.

Aim of Study

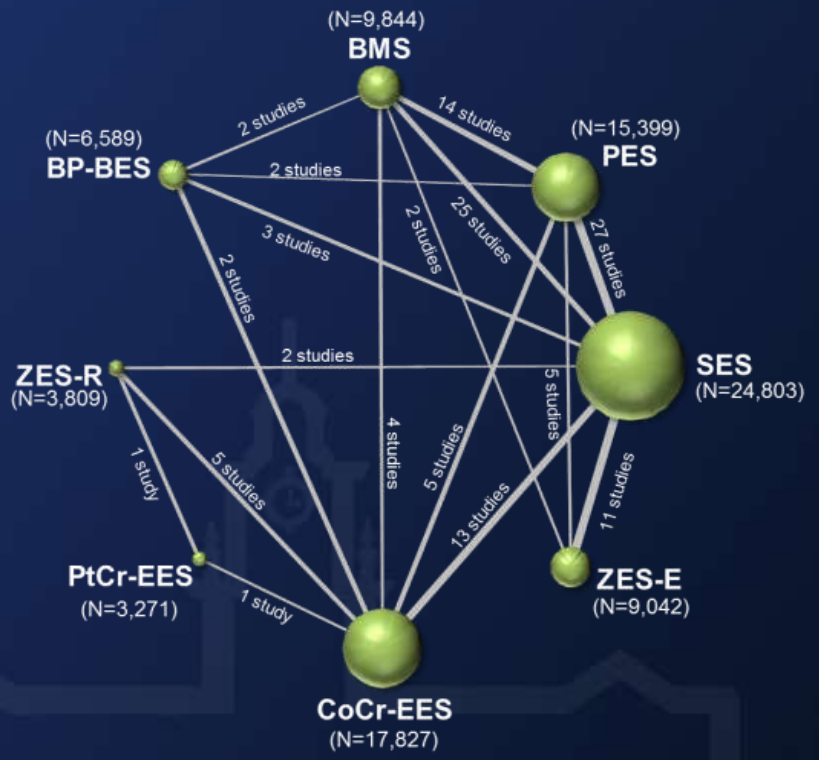
- We sought to compare the clinical outcome of various types of coronary stents including all second-generation DES (including BP-DES) with all available data up to now).

- A systematic literature review of randomized controlled trials comparing coronary stents was performed, and the data from the review was the basis of a multiple-treatments network meta-analysis using a Bayesian framework.

Aim of Study

- In this study, we sought to compare the clinical outcome of various types of coronary stents including **BMS**, **durable-polymer DES (DP-DES)**, and **biodegradable-polymer DES (BP-DES).**

- A **systematic literature review** of randomized controlled trials comparing coronary stents was performed, and the data from the review was the basis of a **multiple-treatments network meta-analysis** using a **Bayesian framework**.



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Eligible Study Criteria

- **Inclusion criteria**
  - RCT comparing 2 or more coronary stents in patients undergoing PCI
  - Study stents
    (1) BMS
    (2) Paclitaxel-eluting stents (PES, Boston Scientific)
    (3) Sirolimus-eluting stent (SES, Cordis)
    (4) Endeavor zotarolimus-eluting stents (ZES-E, Medtronic)
    (5) Cobalt-chromium everolimus-eluting stents (CoCr-EES, Abbott Vascular and Boston Scientific)
    (6) Platinum-chromium everolimus-eluting stents (PtCr-EES, Boston Scientific)
    (7) Resolute zotarolimus-eluting stents (ZES-R, Medtronic)
    (8) BP biolimus A9-eluting stents (BP-BES, Biosensors and Terumo)

- **Exclusion criteria**
  1) Studies comparing two stents with different stent design within the same category described above,
  2) Studies in which specific type of DES was not predefined and the choice among available DES was left to the investigators' discretion (for example, BMS versus any DES)
  3) Stuides published in a language other than English.

  ※ No restrictions were imposed on study period, sample size, or publication status as well as patient or lesion criteria.

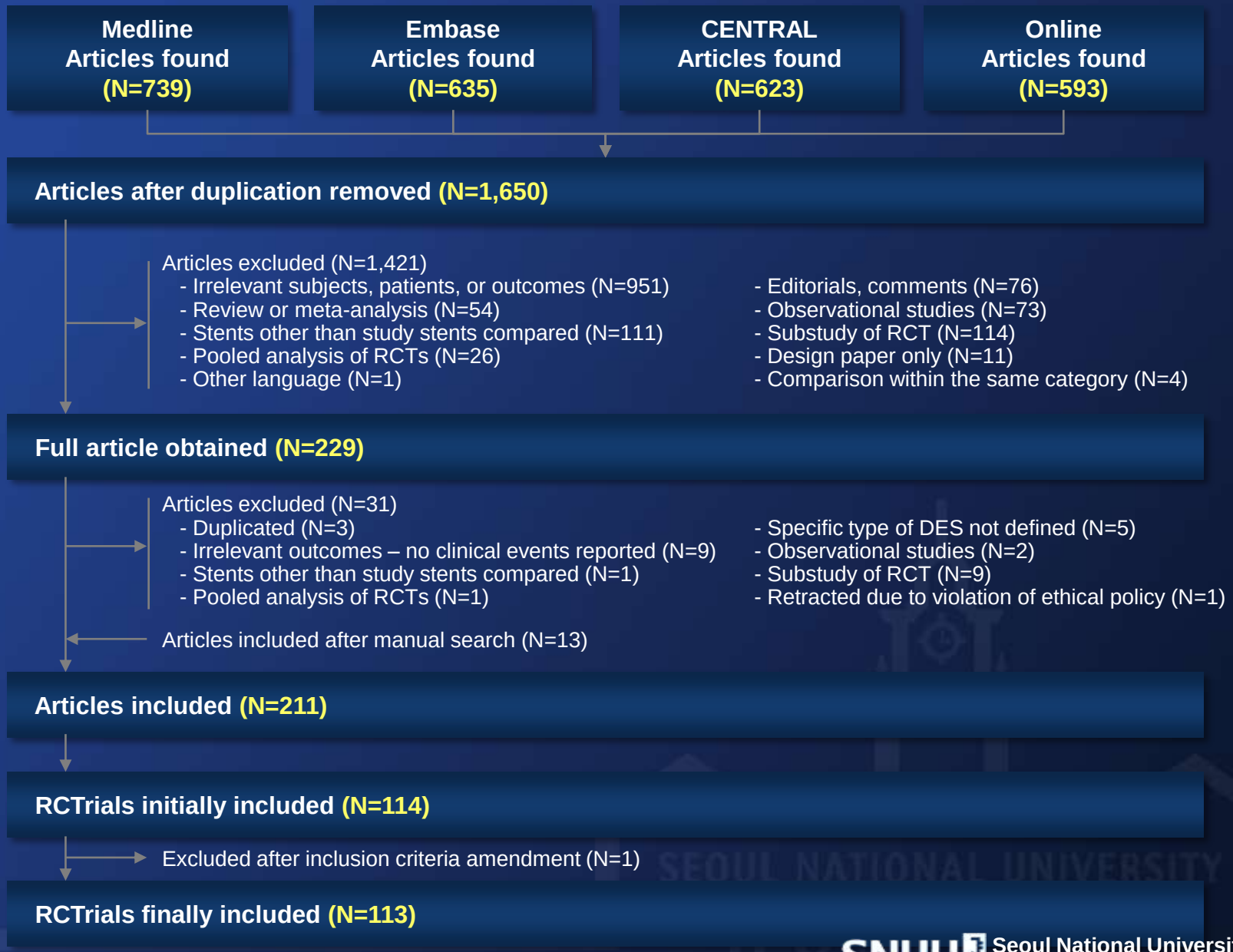
Data Sources

- **Electronic search** (from the inception to March 2013)
  - PubMed
  - Embase
  - Cochrane Central Register of Controlled Trials (CENTRAL)
  - Relevant websites (www.crtonline.org, www.clinicaltrialresults.com, www.tctmd.com, www.cardiosource.com, and www.pcronline.com)

Study Outcomes

- Principal safety endpoint: **definite or probable ST** (ARC ≤ 1 year)
- Other safety endpoints
  - definite ST
  - all-cause death
  - cardiac death
  - myocardial infarction
- Efficacy endpoints
  - TLR
  - TVR

Flow Diagram of Systematic Review



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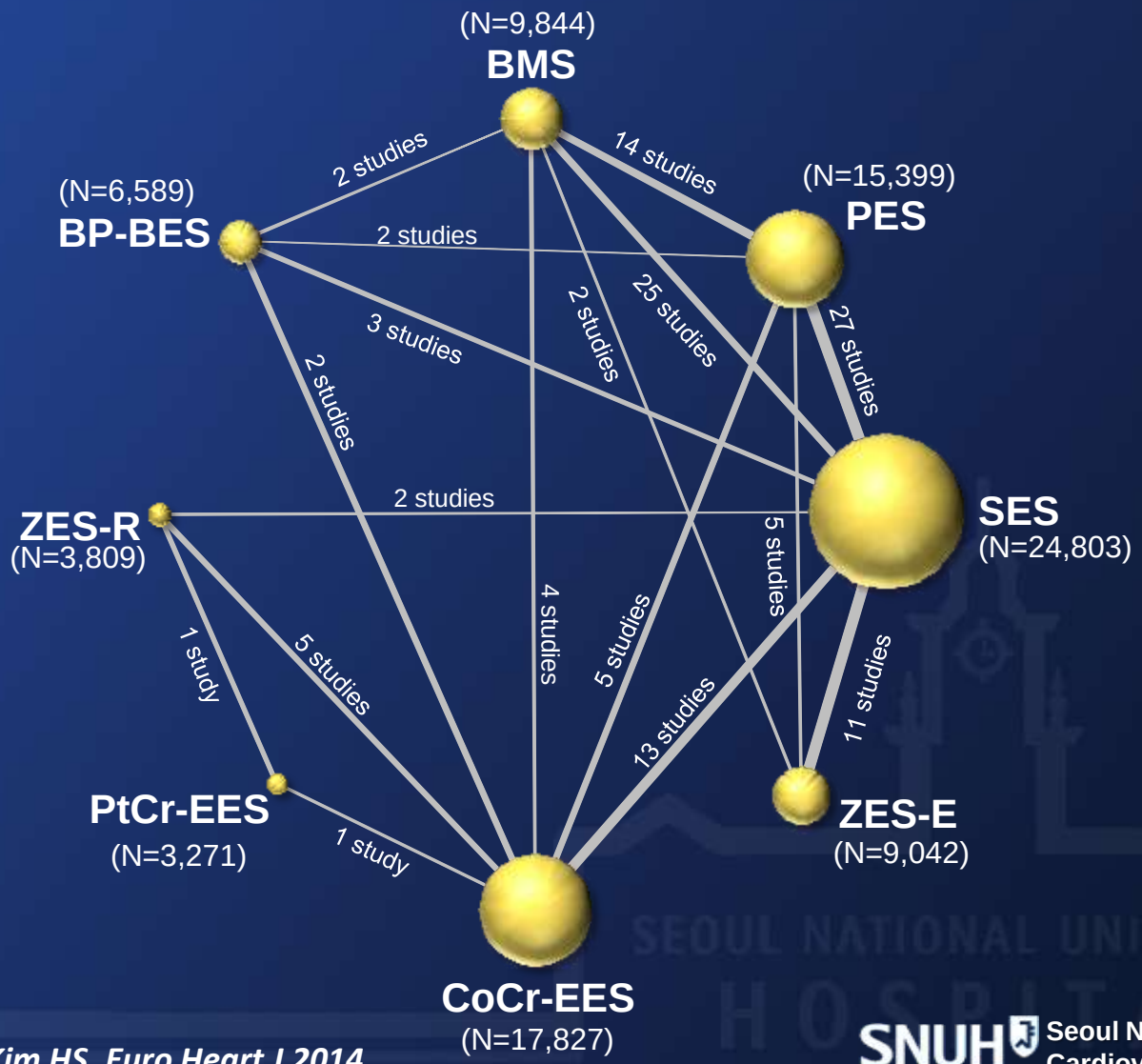
Network Plot of Included Trials

- Polygonal network configuration with mixed connections
- Almost fully closed loops with limited comparisons of PtCr-EES and ZES-R



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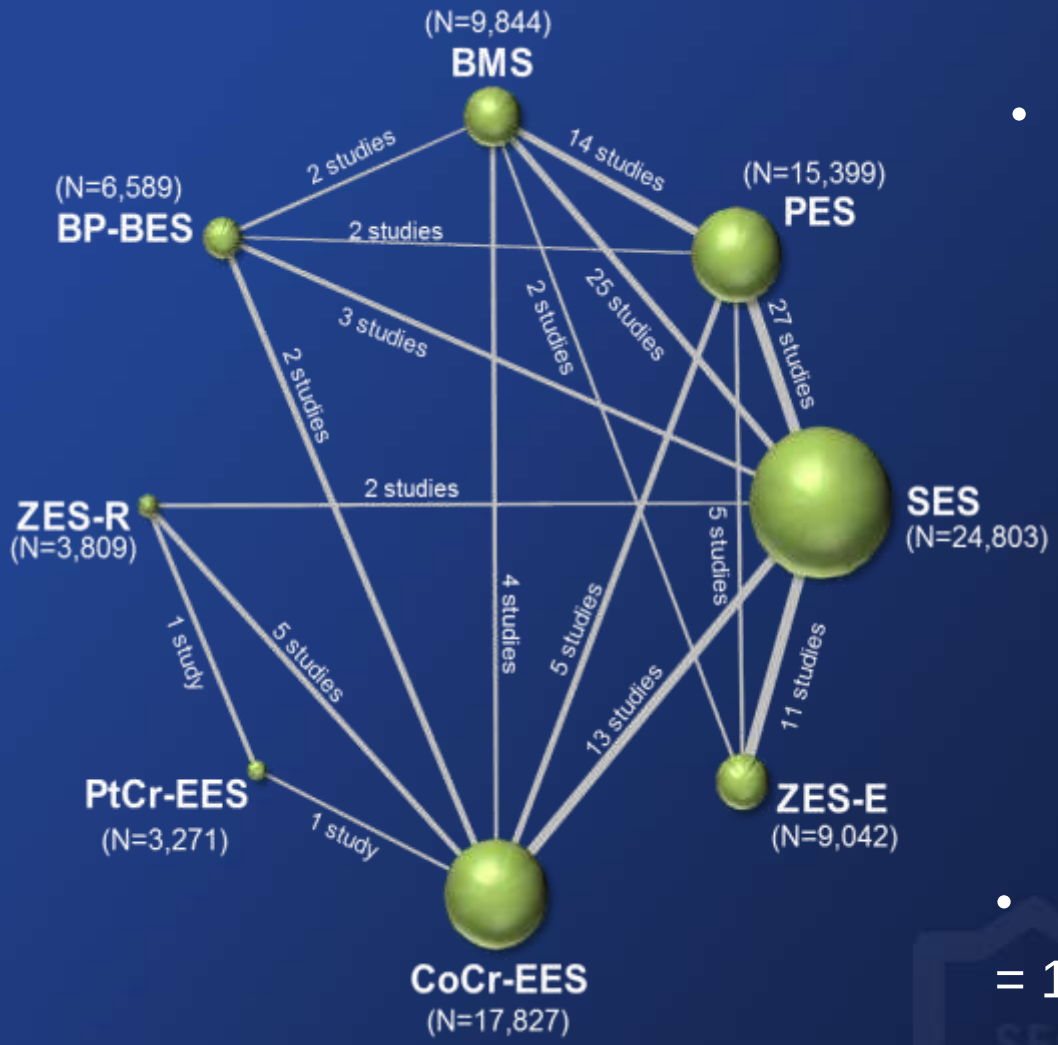
Study Characteristics



- A total of 113 trials with 90,584 patients
  - 6 studies: 3-arm design
  - 1 study: 2-phase enrollment
  - 10 studies: DM
  - 21 studies: STEMI
  - 5 studies: CTO
  - 3 studies: uLMCA disease
  - 3 studies: in-stent restenosis
  - 2 studies: bypass graft

- Estimated median F/U duration = 19.1 months (3 months - 5 years)

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Main Characteristics of Included Trials

Trials	Stent Comparison (Patient Number)	Primary Endpoint	Design	Major Inclusion Criteria	Main Results	Follow-Up
Published in 2002						
RAVEL	SES vs. BMS (120:118)	In-stent LL at 6 months	Multicenter, superiority	Stable or unstable angina	SES superior to BMS	5 years
Published in 2003						
ASPECT	PES vs. BMS (117:58)	% stenosis at 4-6 months	Three-center, superiority	Stable or unstable angina	PES superior to BMS	6 months
E-SIRIUS	SES vs. BMS (175:177)	MLD at 8 months	Multicenter, superiority	Stable or unstable angina	SES superior to BMS	9 months
SIRIUS	SES vs. BMS (533:525)	TVF at 9 months	Multicenter, superiority	Stable or unstable angina	SES superior to BMS	5 years
TAXUS I	PES vs. BMS (31:30)	MACE (death Q-wave MI, TVR, ST) at 30 days	Three-center, feasibility	Stable or unstable angina	Promising results of PES	2 years
TAXUS II	BMS vs. PES (270:266)	%NIH by IVUS at 6 months	Multicenter, superiority	Stable or unstable angina	PES superior to BMS	5 years
Published in 2004						
C-SIRIUS	SES vs. BMS (50:50)	MLD at 8 months	Multicenter, superiority	Stable or unstable angina	SES superior to BMS	9 months
SES-SMART	SES vs. BMS (129:128)	In-segment binary restenosis at 8 months	Multicenter, superiority	Stable angina, ACS	SES superior to BMS	2 years
TAXUS IV	BMS vs. PES (652:662)	TVR at 9 months	Multicenter, superiority	Stable or unstable angina	PES superior to BMS	5 years
Published in 2005						
BASKET	SES vs. PES (264:281)	Cost-effectiveness after 6 months	Single-center, superiority	All-comer design	DES (SES and PES) not superior to BMS	18 months
DIABETES	SES vs. BMS (80:80)	in-segment LL at 9 months	Multicenter, superiority	Diabetes	SES superior to BMS	5 years
ISAR-[illegible]RE	SES vs. PES [illegible]	Binary restenosis at 6 months	Multicenter, superiority	ISR	DES superior to balloon angio	1 year

Continued…

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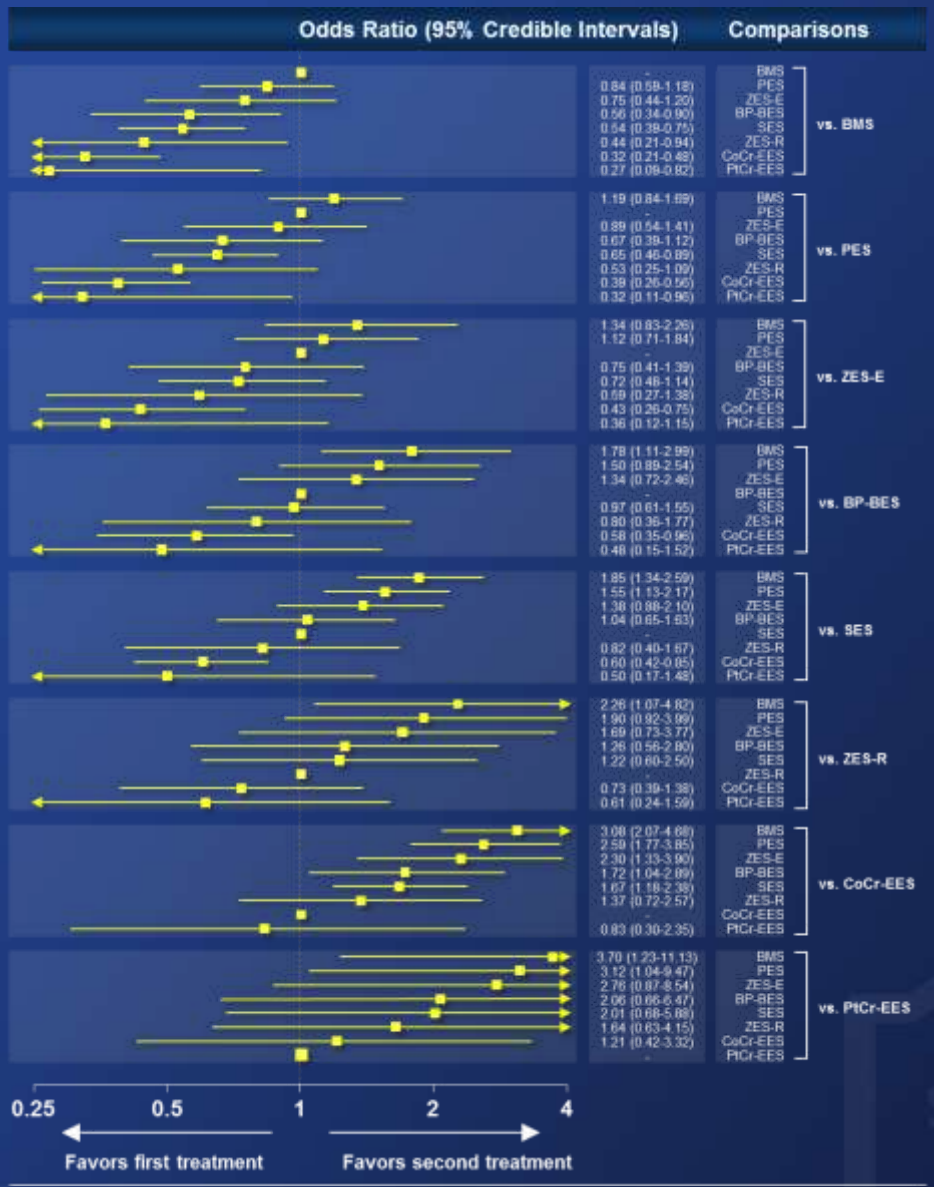
Definite or Probable ST Within 1 Year



vs. BMS

vs. PES

vs. ZES-E

vs. BP-BES

vs. SES

vs. ZES-R

vs. CoCr-EES

vs. PtCr-EES

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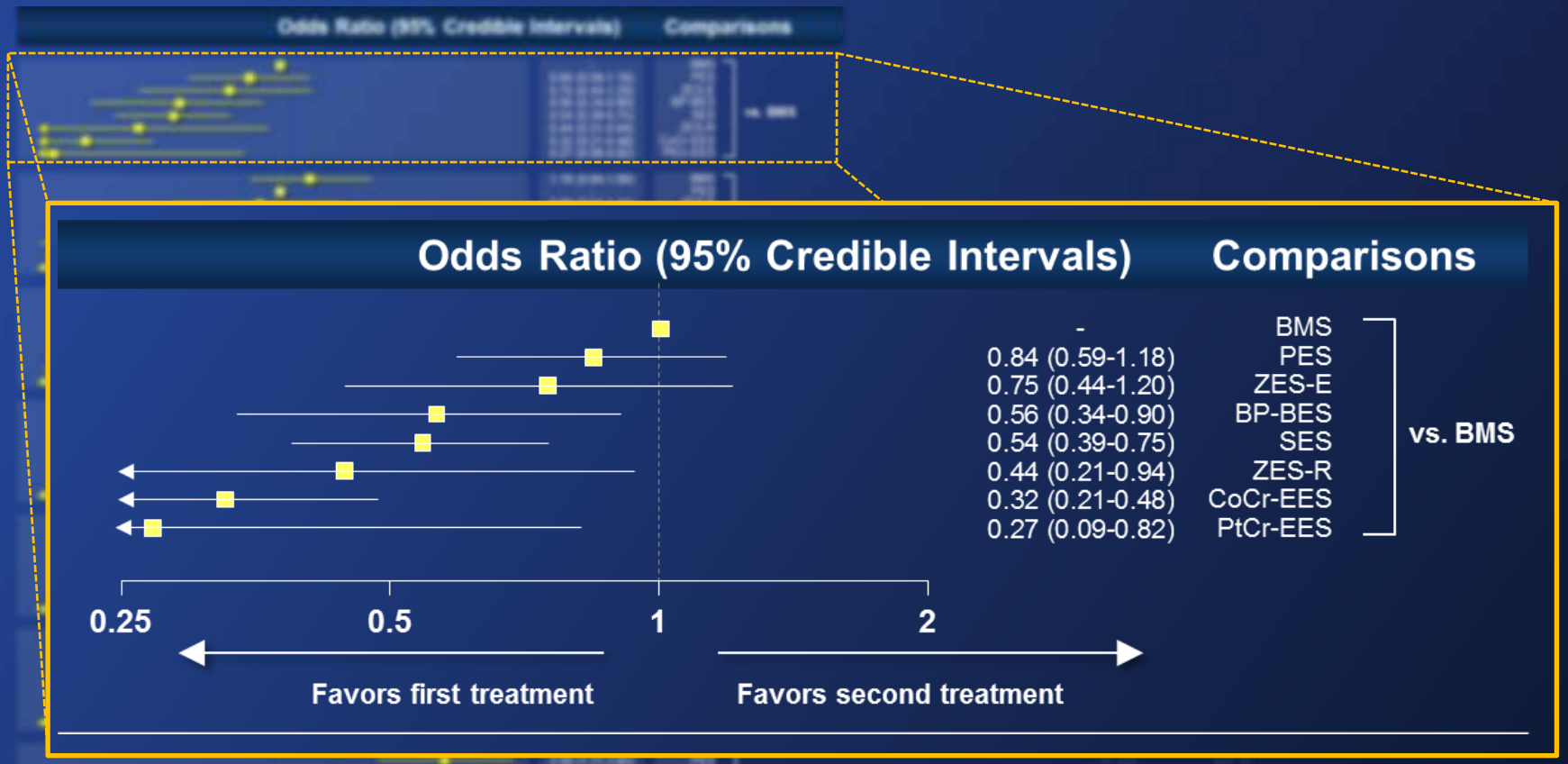
Definite or Probable ST Within 1 Year



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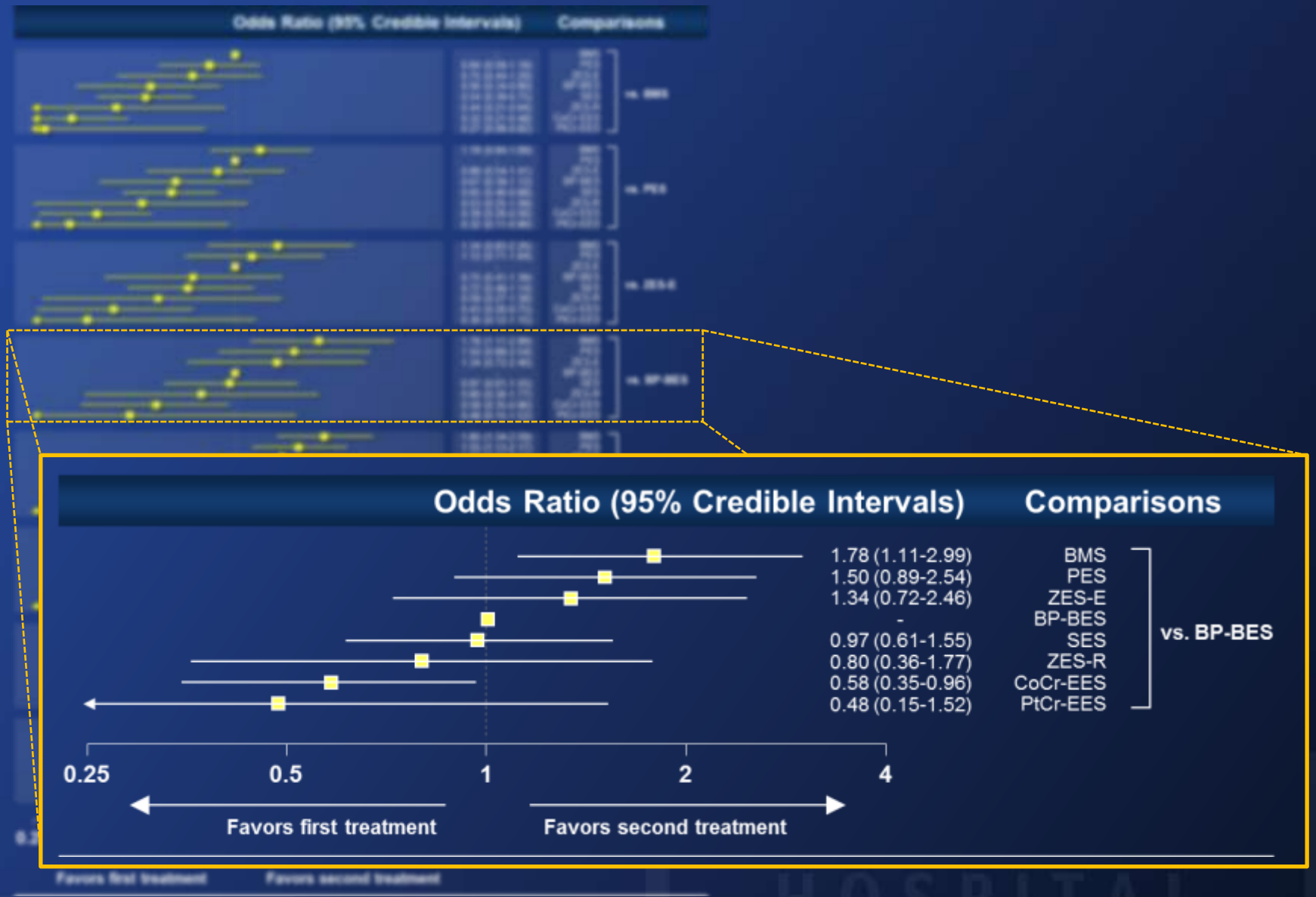

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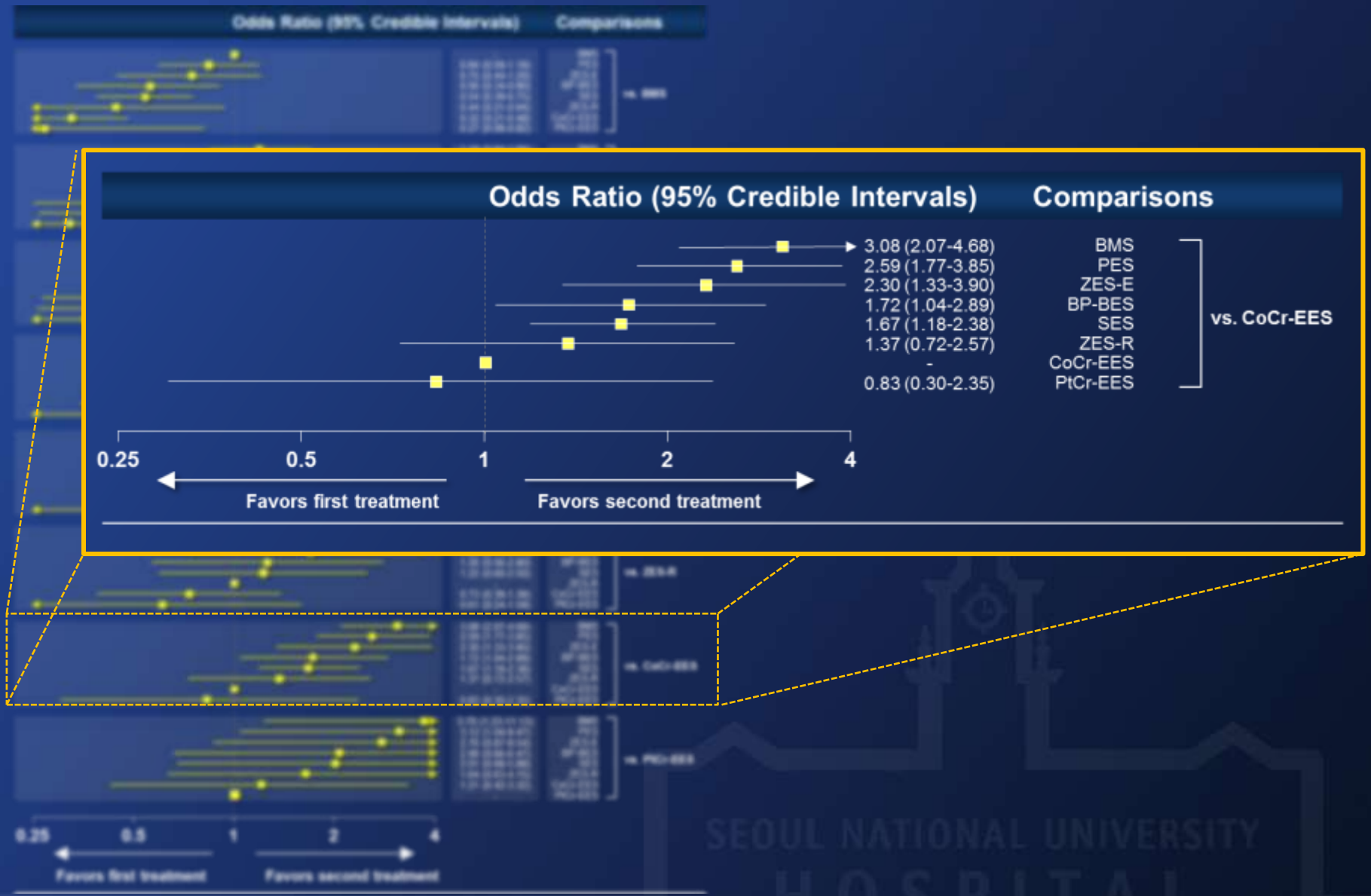

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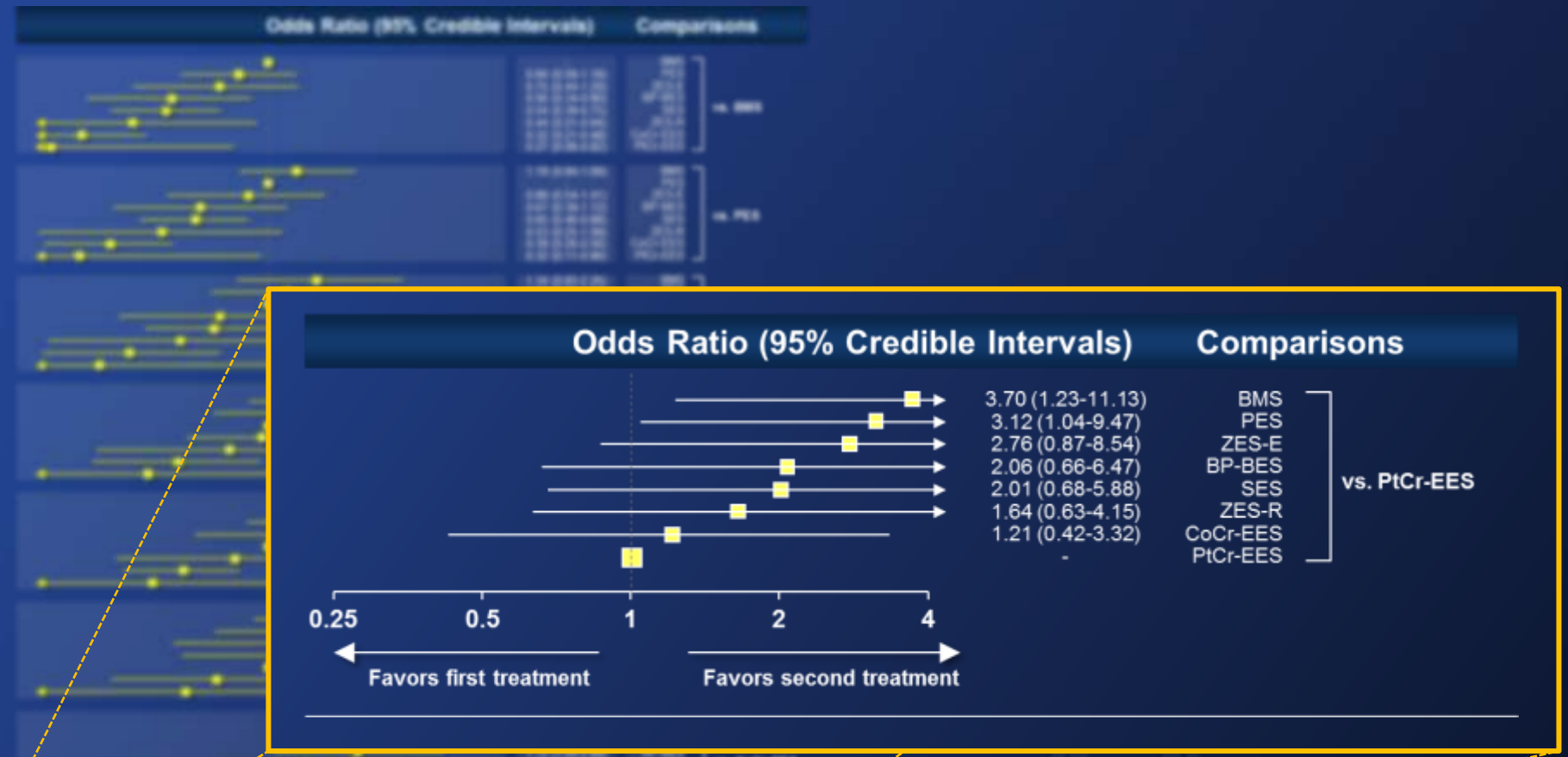

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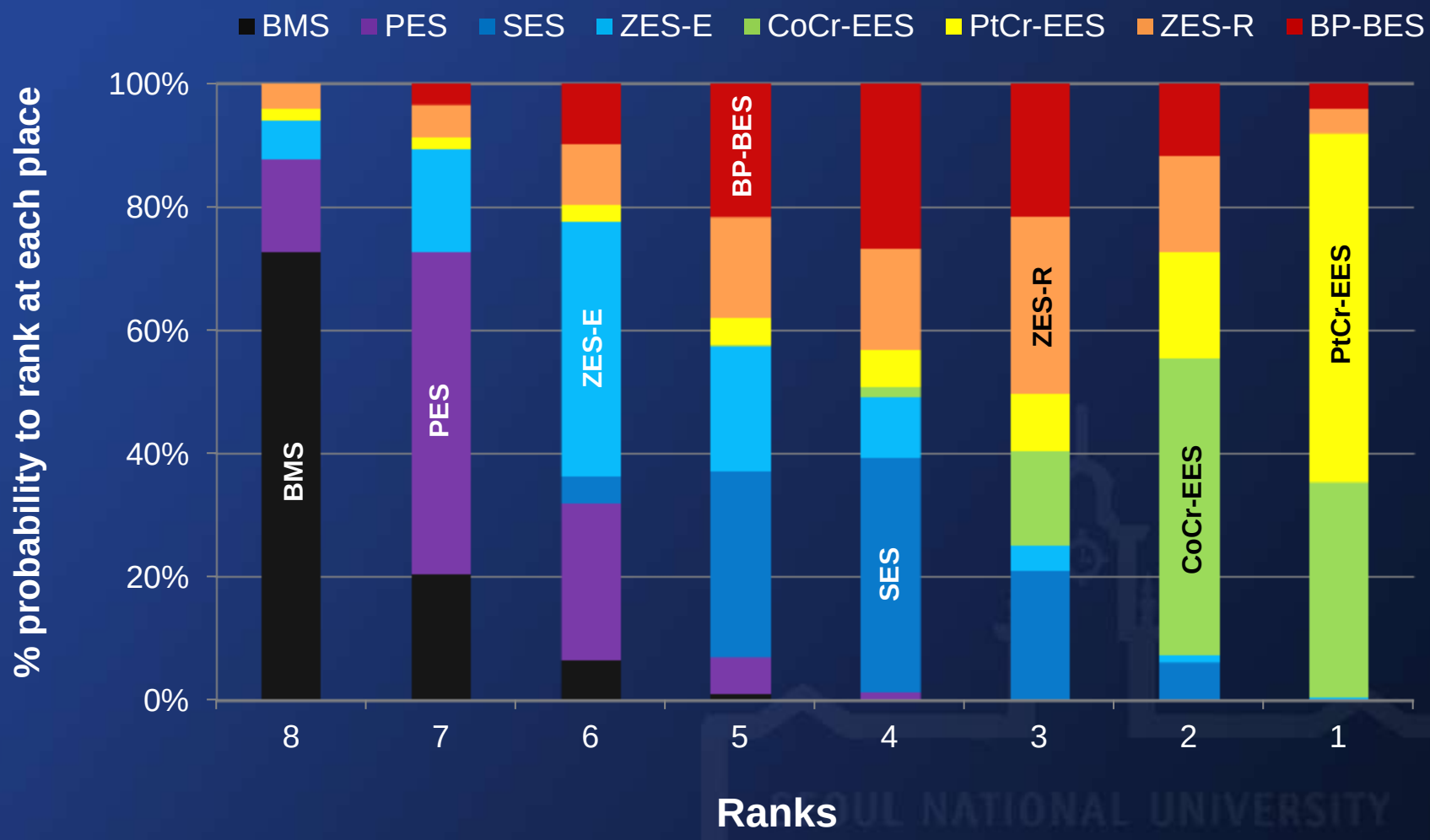
Rankogram

Definite or Probable ST within 1 Year



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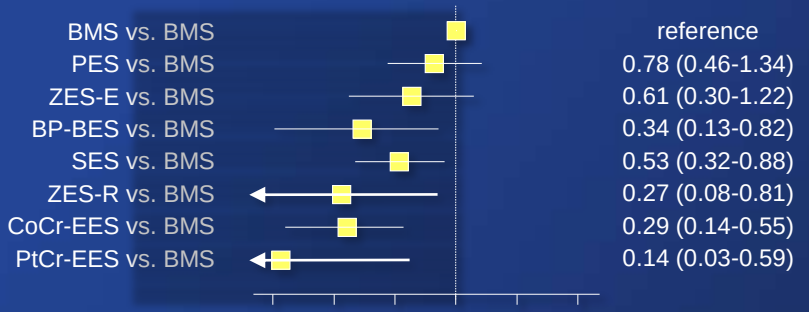
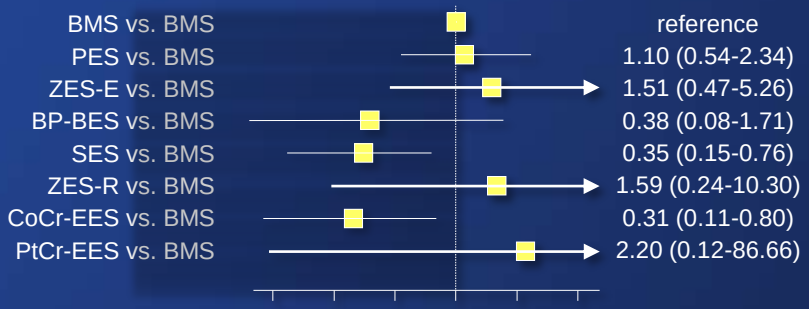
Definite or Probable ST of DES with Reference to BMS

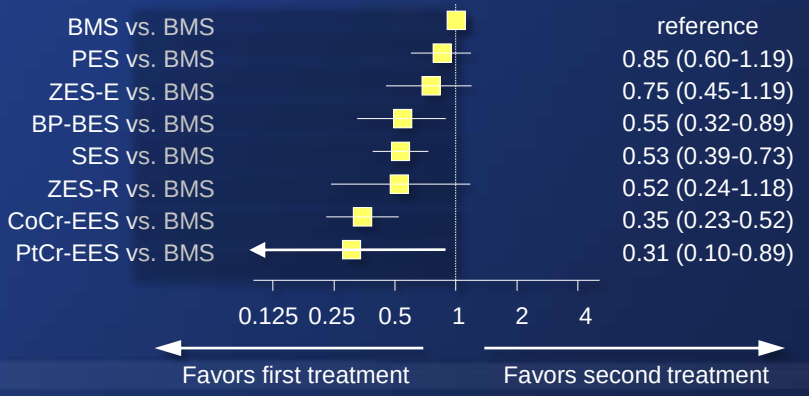
(A) Early ST (≤ 30 days)



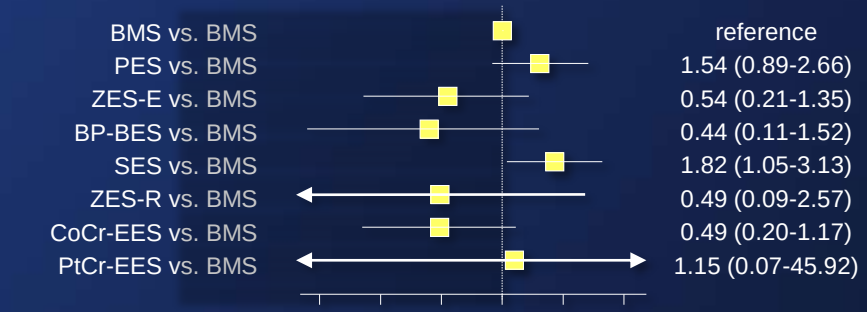
(B) Late ST (31-365 days)



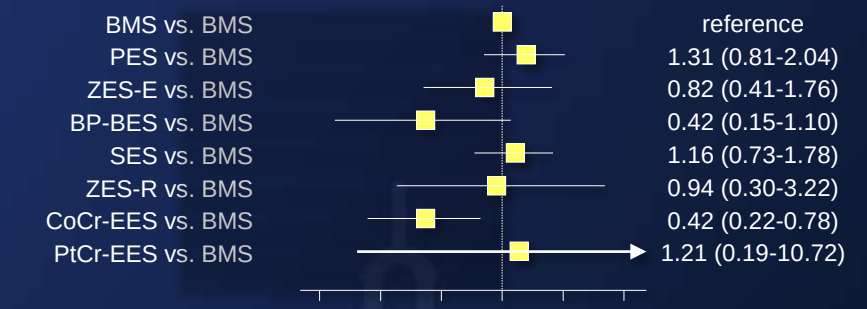
(C) ST within 1 Year (-365 days)



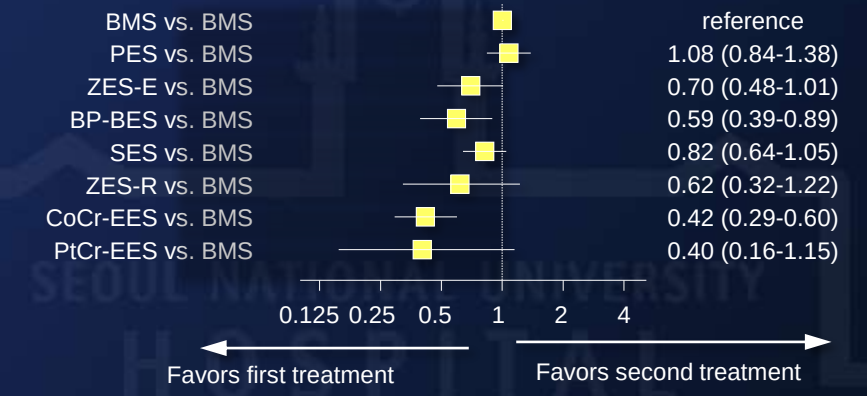
(D) Very Late ST (>365 days)

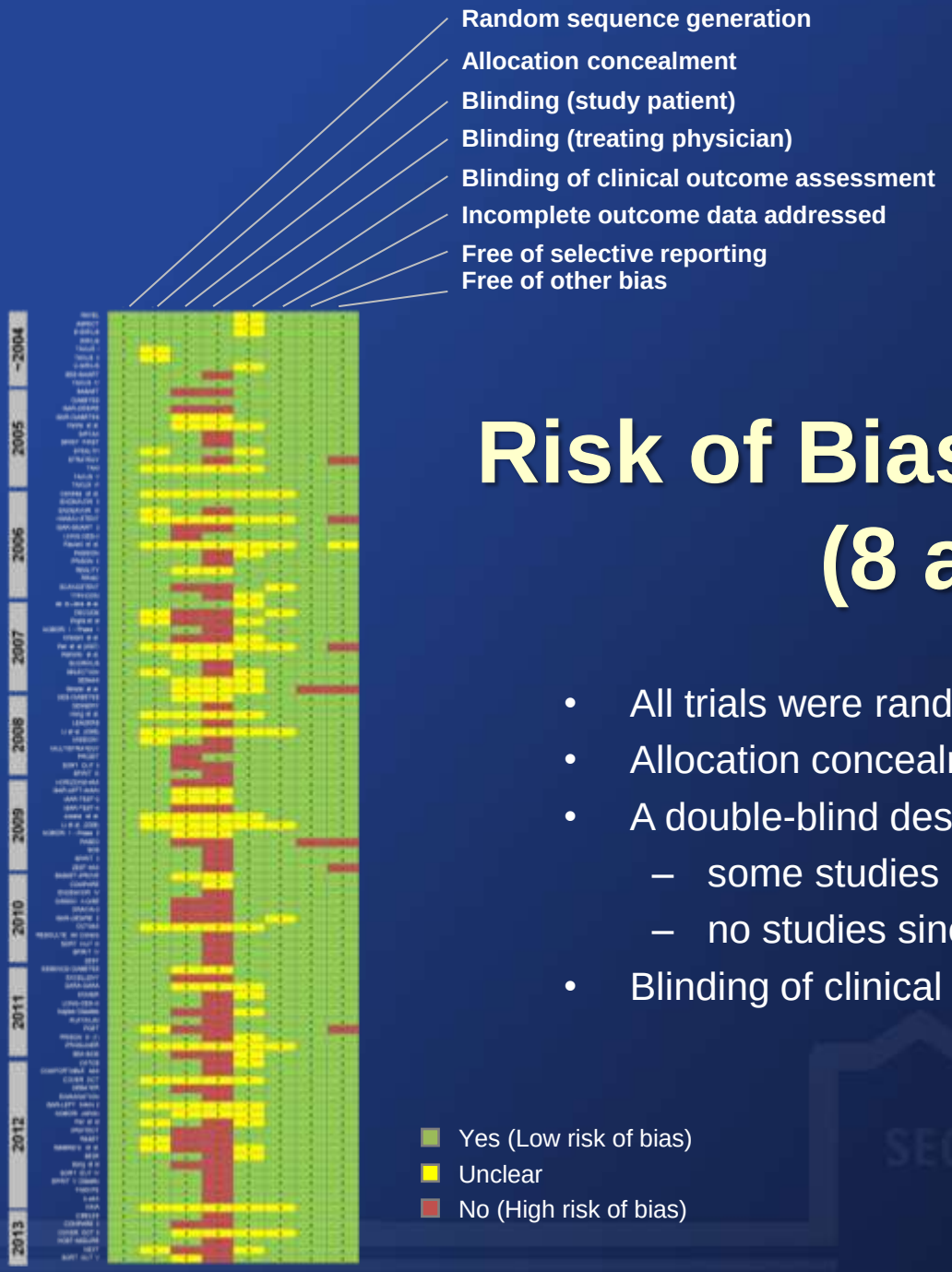


(E) Late and Very Late ST (>30 days)



(F) ST at the Longest Follow-Up



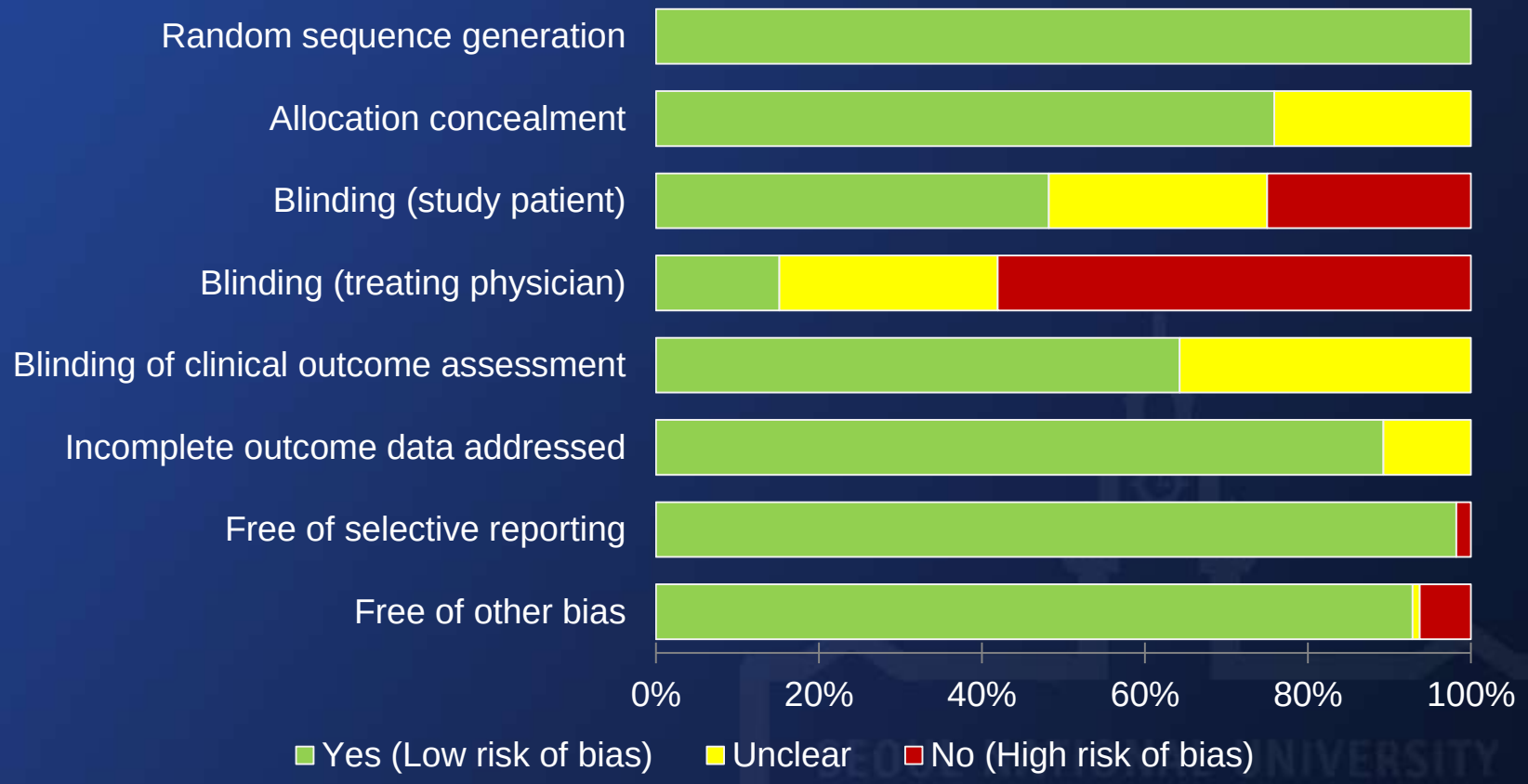


Risk of Bias in all 113 RCTs (8 aspects)

- All trials were randomized controlled trials
- Allocation concealment: adequate in 86/113 trials
- A double-blind design
  - some studies in early period (2003-2006)
  - no studies since 2007
- Blinding of clinical event adjudication: adequate in 2/3

Risk of Bias from 8 Aspects

- Among a total of 113 trials included
- Proportion of studies with each of the judgments for each entry (according to the Cochrane Collaboration's tool)



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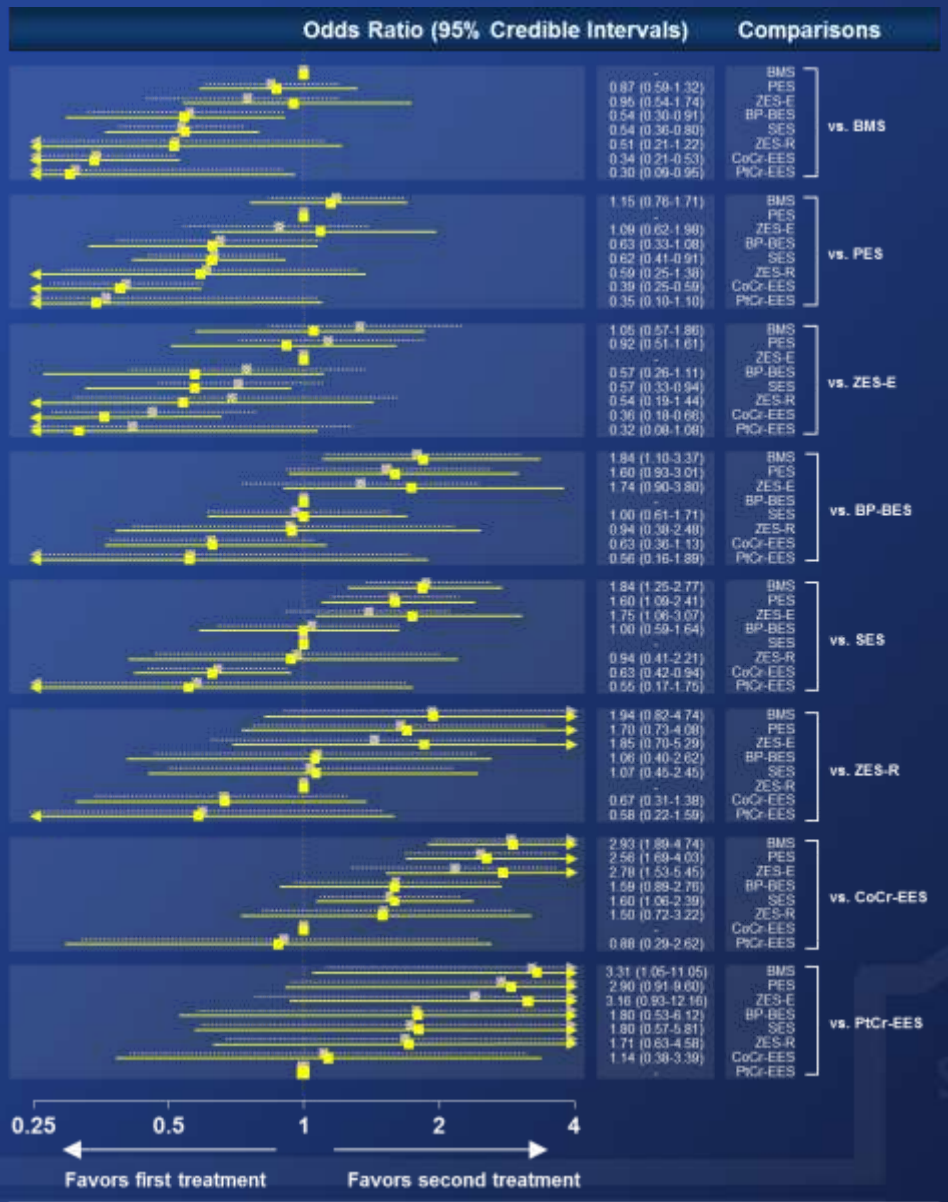
Sensitivity Analysis

Definite or Probable ST within 1 Year



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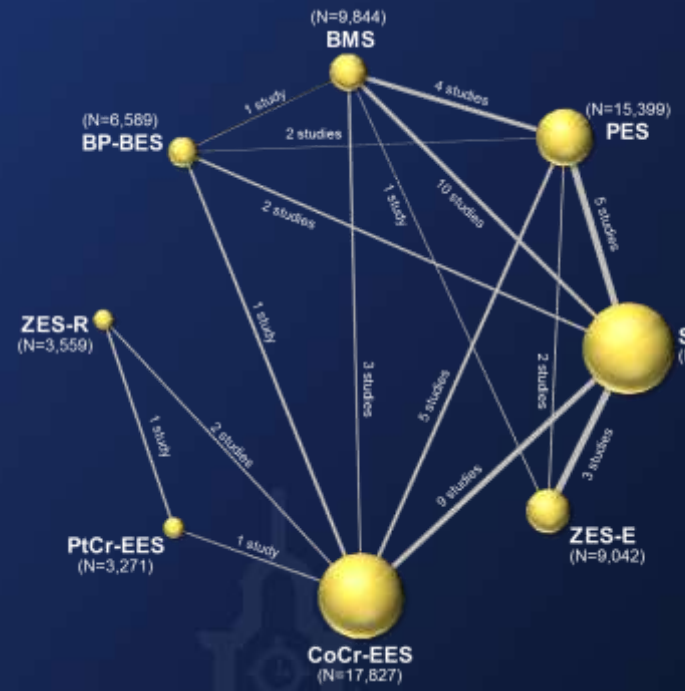
- **Studies with Low Risk of Bias : 48 Trials; 60,911 Patients**



All trials

Trials with low risk of bias only

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Definite ST Within 1 Year

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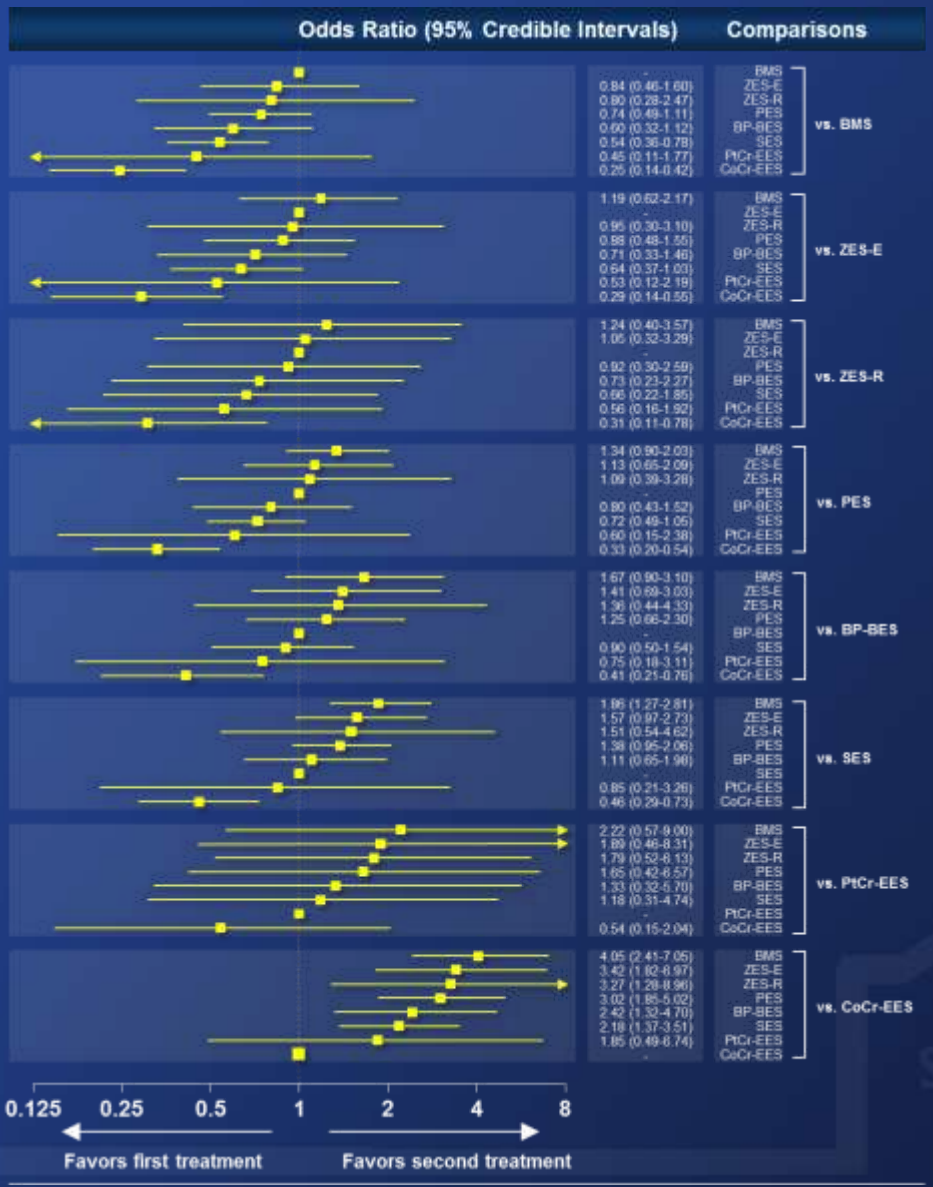
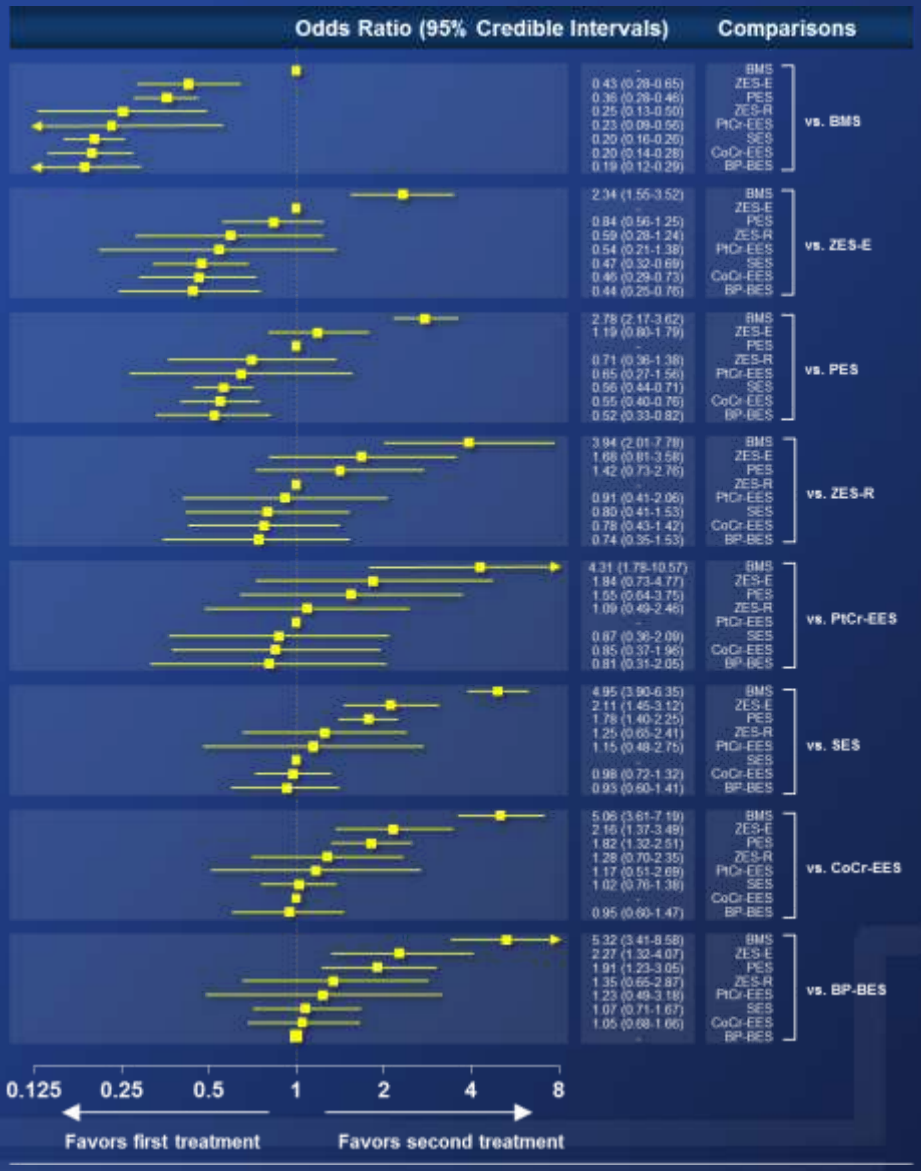
CoCr-EES > (PtCr-EES ≥ SES ≥ BP-BES ≥ PES ≥ ZES-R ≥ ZES-E ≥ BMS)



- CoCr-EES superior to BMS, ZES-E, ZES-R, PES, BP-BES, and SES
- SES superior to BMS
- SES tended to be superior to ZES-E and PES

TLR Within 1 Year

(BP-BES ≥ CoCr-EES ≥ SES ≥ PtCr-EES ≥ ZES-R) > (PES ≥ ZES-E) > BMS



- All DES superior to BMS
- BP-BES, CoCr-EES and SES superior to ZES-E and PES

All-Cause Death in 1 Year

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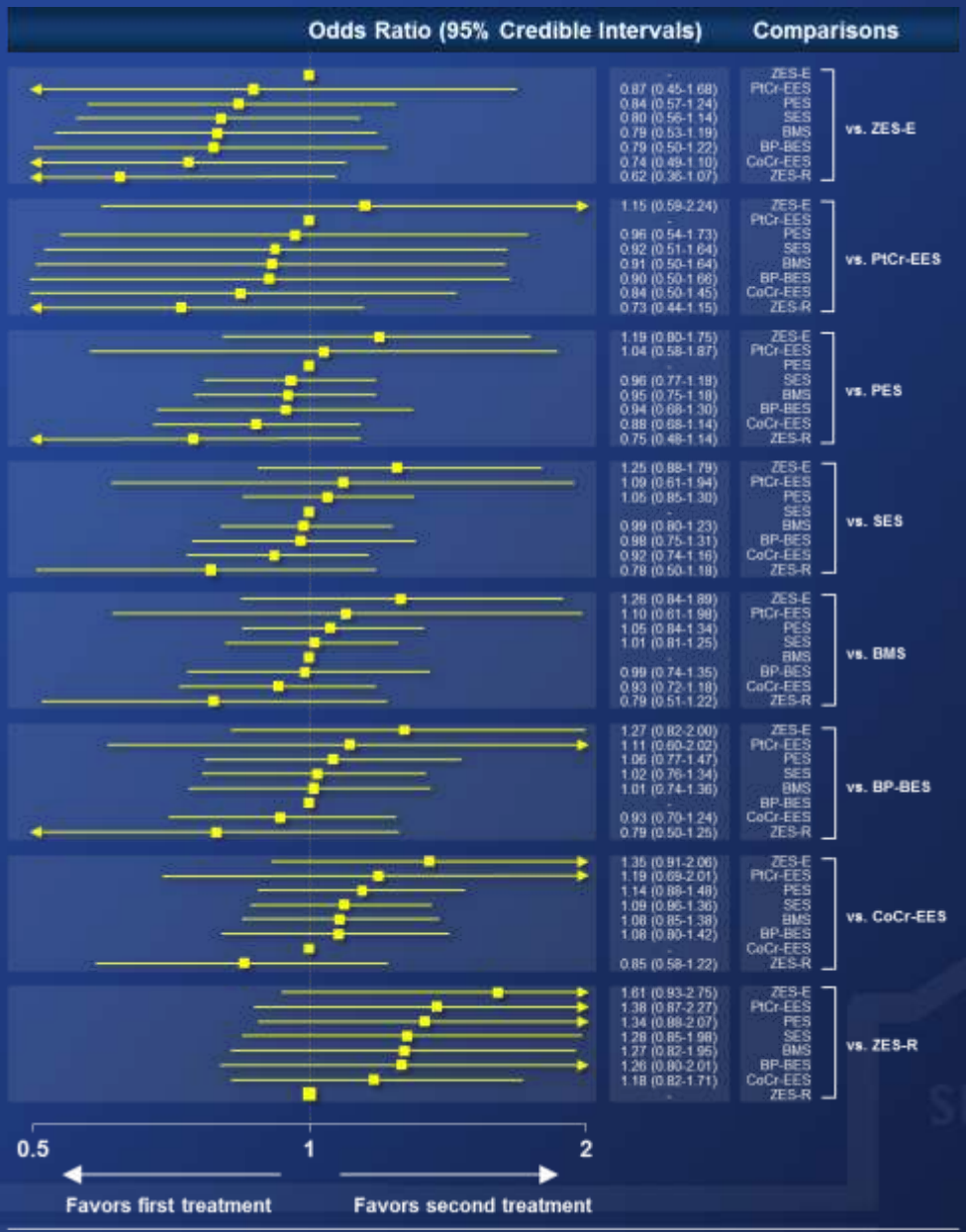

- No significant difference between any comparisons

Conclusions

- All DESs but PES and ZES-E were superior to BMS in terms of ST within 1 year.
- CoCr EES (in large sample size) was superior to any DES even including BP-BES in terms of ST.
- PtCr EES (in small sample size) showed a promising tendency to be superior to any DES in terms of ST.
- Our results suggest that not only the biodegradability of polymer, but the optimal combination of stent alloy, design, strut thickness, polymer, and drug all combined determine the safety of DES.

Kang SH, Park KW,, Kim HS. Euro Heart J 2014

Are DES safer than BMS?

YES!

Thank you for your attention!