Network Meta-Analysis

Durable-Polymer DES
vs.
Biodegradable-Polymer DES
vs.
BMS

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CLINICAL RESEARCH
Interventional cardiology

Biodegradable-polymer drug-eluting stents vs. bare metal stents vs. durable-polymer drug-eluting stents: a systematic review and Bayesian approach network meta-analysis

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Background The aim of this study was to compare the safety and efficacy of biodegradable-polymer (BP) drug-eluting stents (DES), bare metal stents (BMS), and durable-polymer DES in patients undergoing coronary revascularization, we performed a systematic review and network meta-analysis using a Bayesian framework.

Methods and results Study stents included BMS, paclitaxel-eluting (PES), sirolimus-eluting (SES), endeavor zotarolimus-eluting (ZES-E), cobalt–chromium everolimus-eluting (CoCr-EES), platinium–chromium everolimus-eluting (PtCr-EES), resolute zotarolimus-eluting (ZES-R), and BP biolimus-eluting stents (BP-BES). After a systematic electronic search, 113 trials with 90 584 patients were selected. The principal endpoint was definite or probable stent thrombosis (ST) defined according to the Academic Research Consortium within 1 year.

Results Biodegradable polymer-biolimus-eluting stents [OR, 0.56; 95% credible interval (CrI), 0.33–0.90], SES (OR, 0.53; 95% CrI, 0.38–0.73), CoCr-EES (OR, 0.34; 95% CrI, 0.23–0.52), and PtCr-EES (OR, 0.31; 95% CrI, 0.10–0.90) were all superior to BMS in terms of definite or probable ST within 1 year. Cobalt–chromium everolimus-eluting stents demonstrated the lowest risk of ST of all stents at all times after stent implantation. Biodegradable polymer-biolimus-eluting stents was associated with a higher risk of definite or probable ST than CoCr-EES (OR, 1.72; 95% CrI, 1.04–2.98). All DES reduced the need for repeat revascularization, and all but PES reduced the risk of myocardial infarction compared with BMS.

Conclusions All DESs but PES and ZES-E were superior to BMS in terms of ST within 1 year. Cobalt–chromium everolimus-eluting stents was safer than any DES even including BP-BES. 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.

Keywords Bare metal stents • Drug-eluting stents • Biodegradable polymer drug-eluting stents • Meta-analysis

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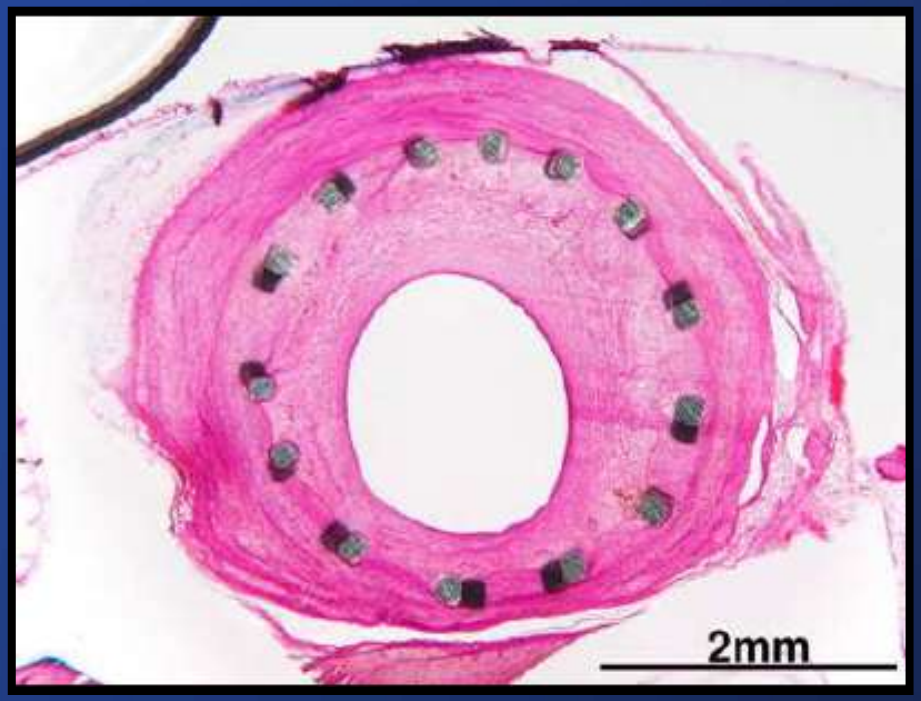
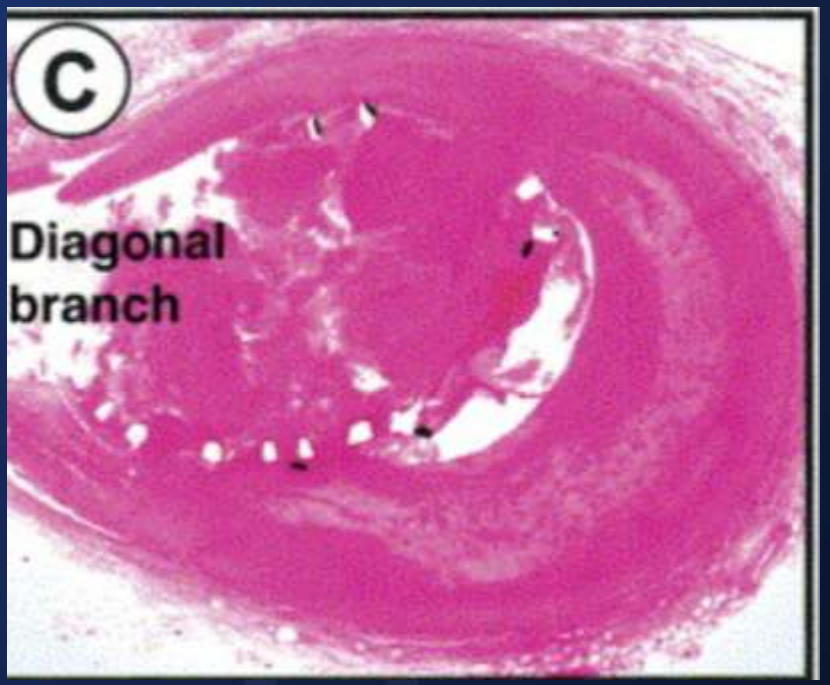
Restenosis

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

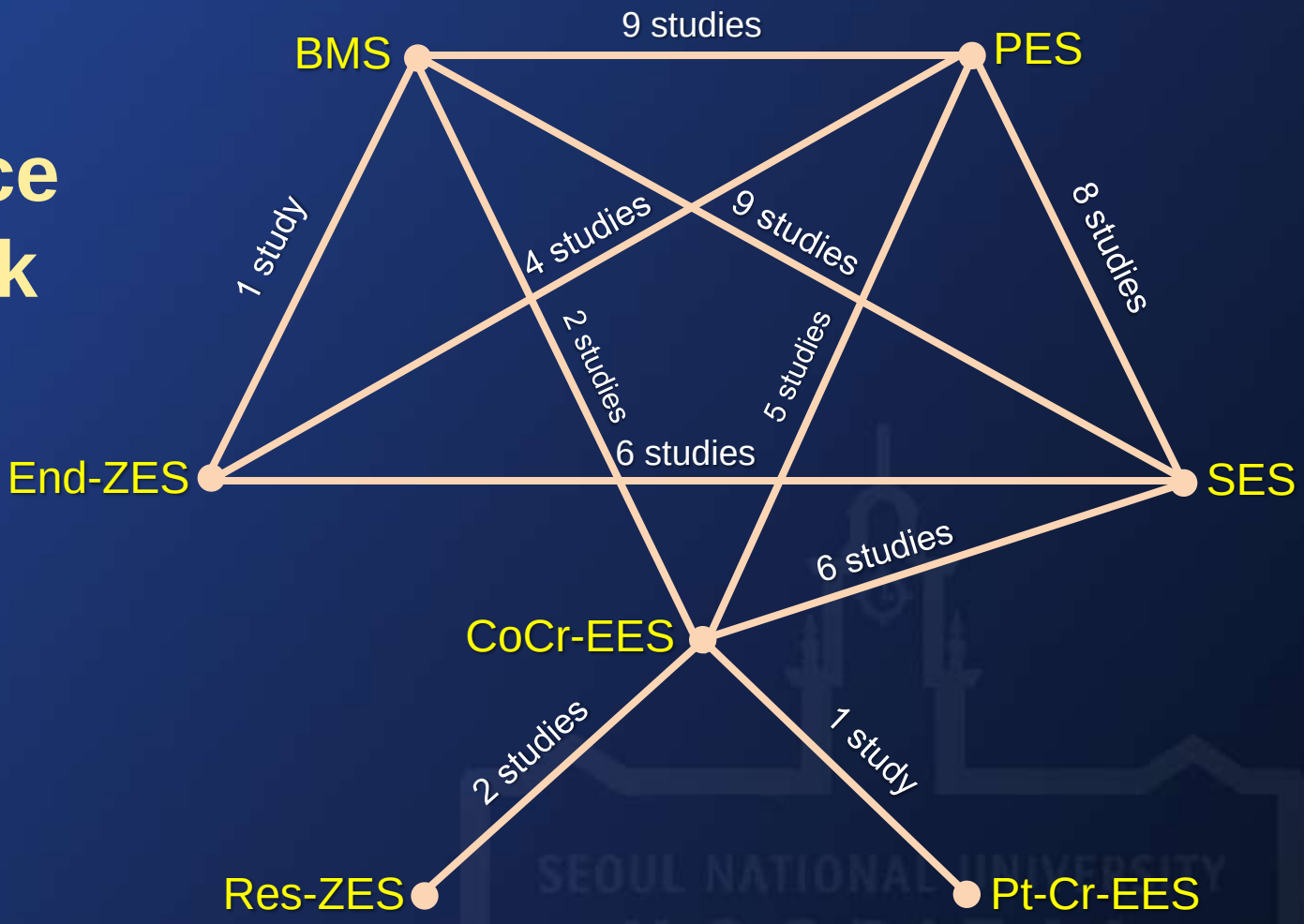
Lancet 2012; 379: 1393–402

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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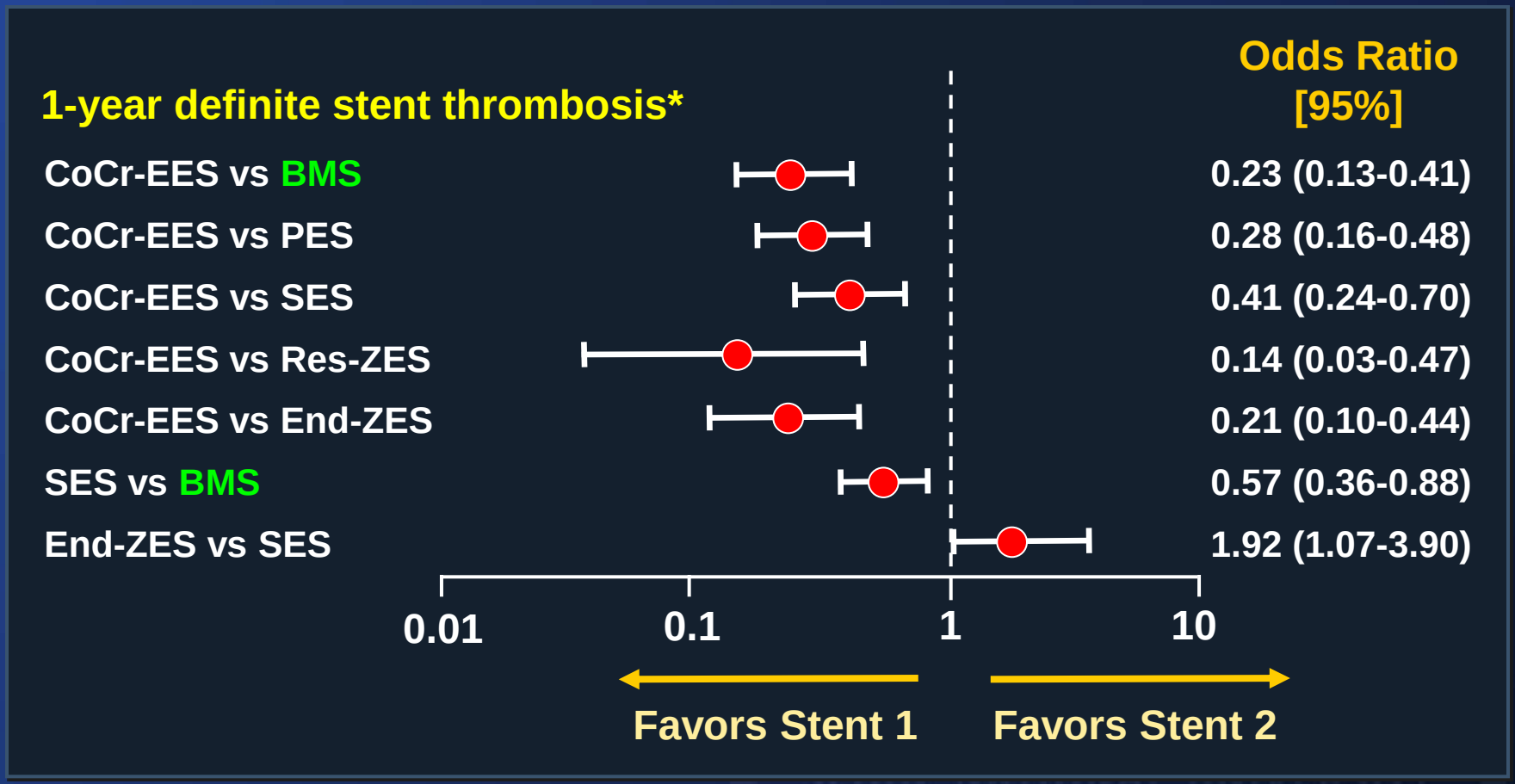


Palmerini T et al. *Lancet* 2012

Interventional Cardiology

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

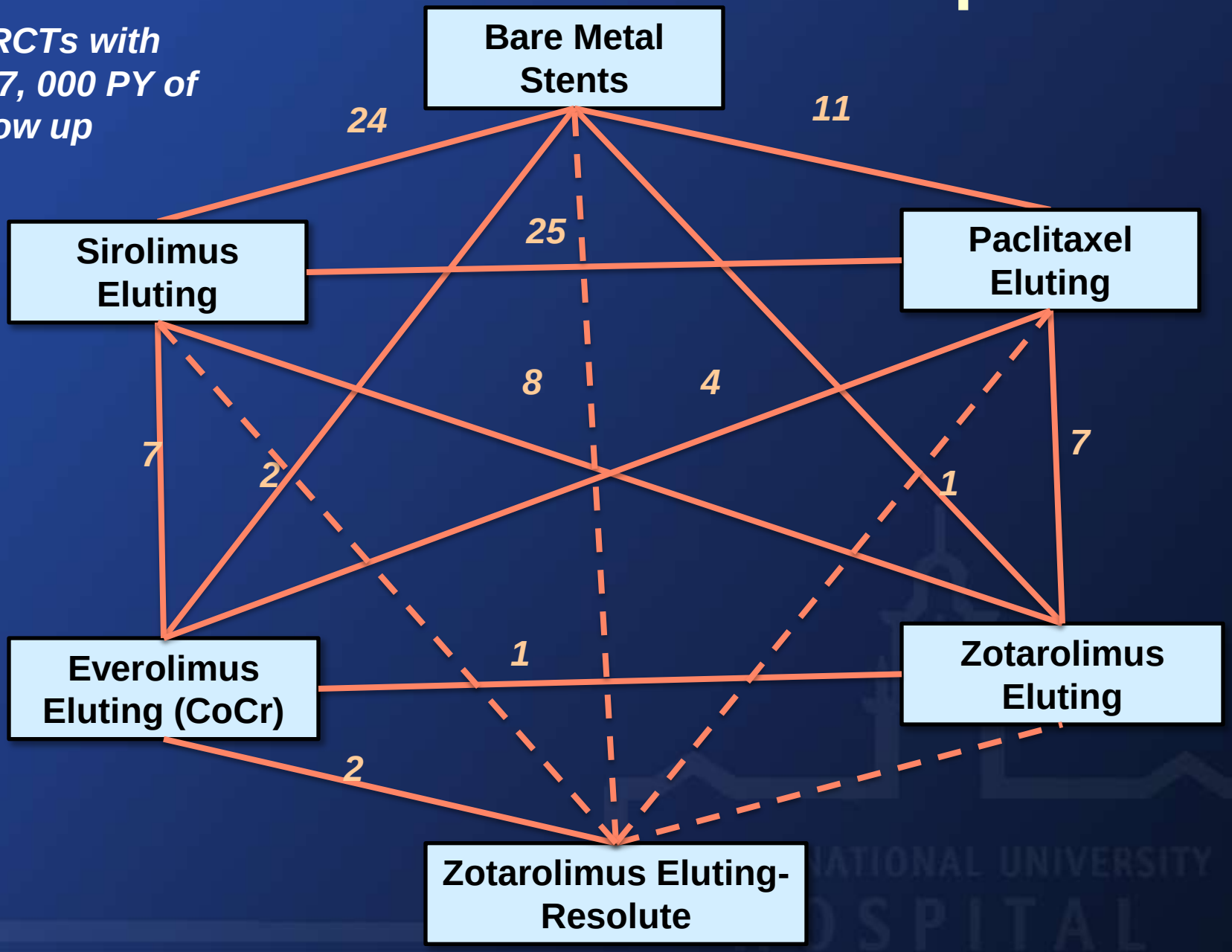
A Mixed-Treatment Comparison Analysis of 117 762 Patient-Years of Follow-Up From Randomized Trials

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

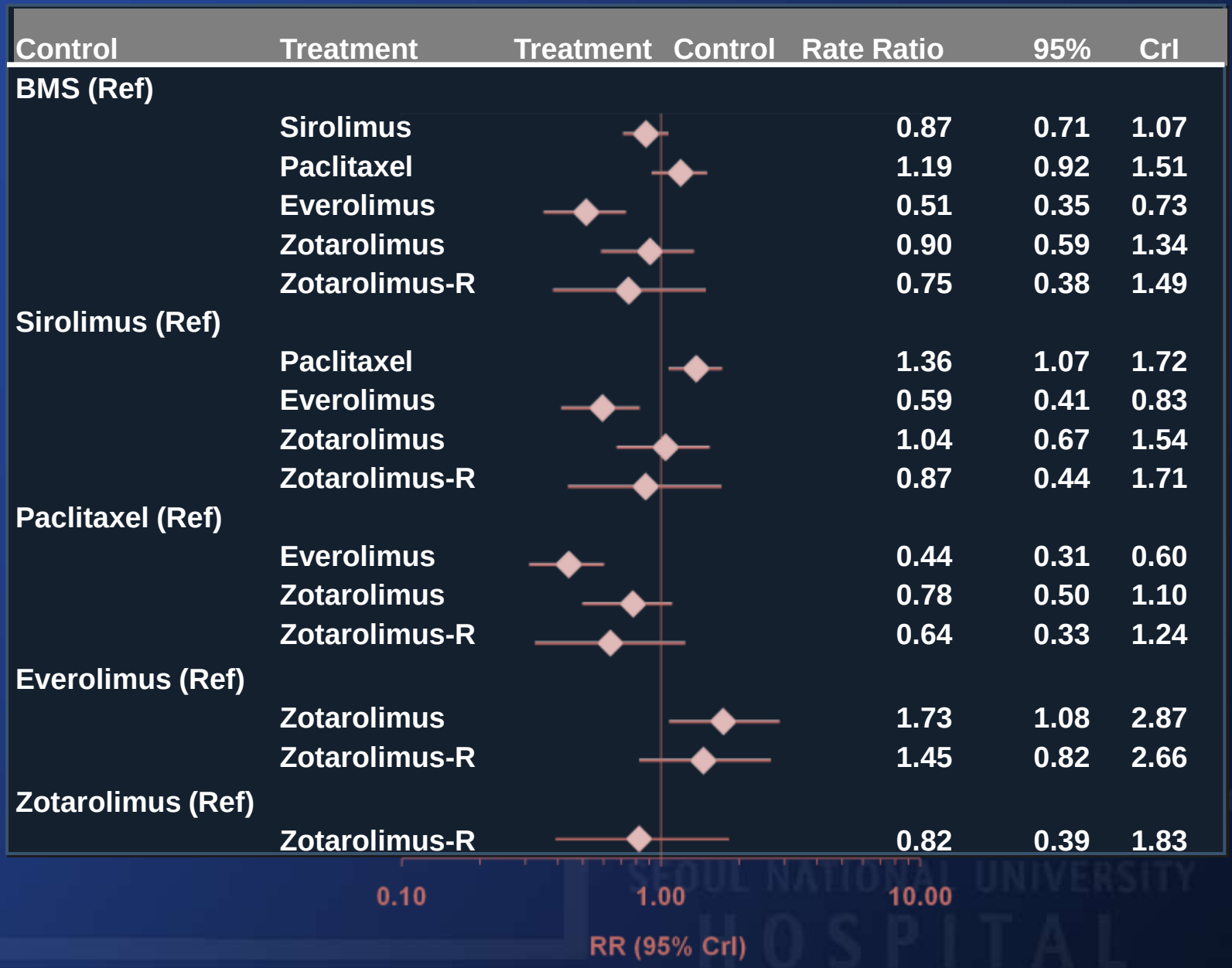
Bangalore et at. Circulation 2012

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.

Biodegradable Polymer DES

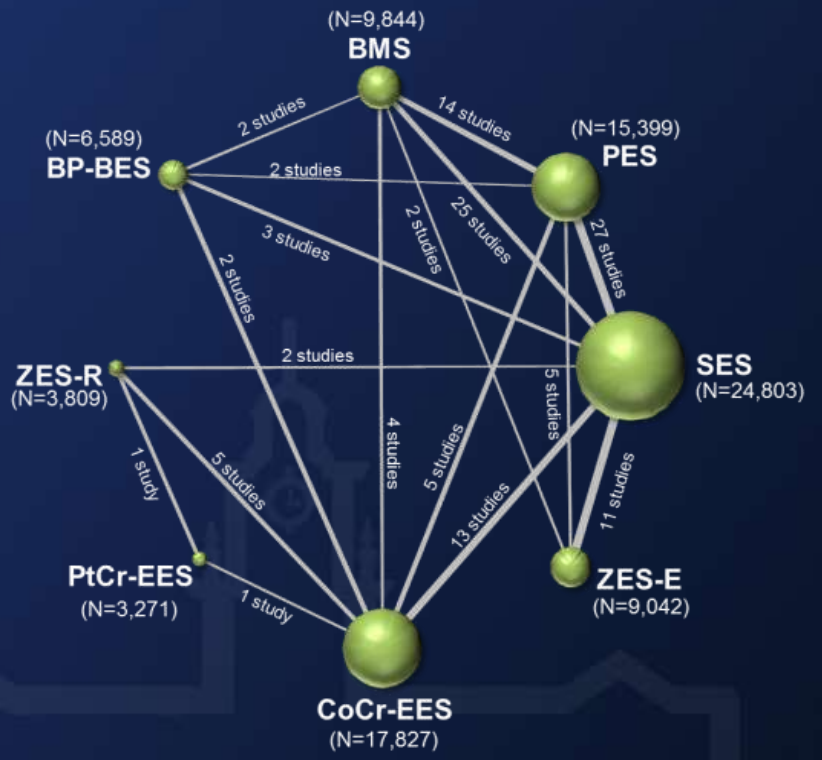
Developed with an aim to reduce the risk of late stent thrombosis

Biodegradable polymer ➔ vanish within 6-9 months

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).**

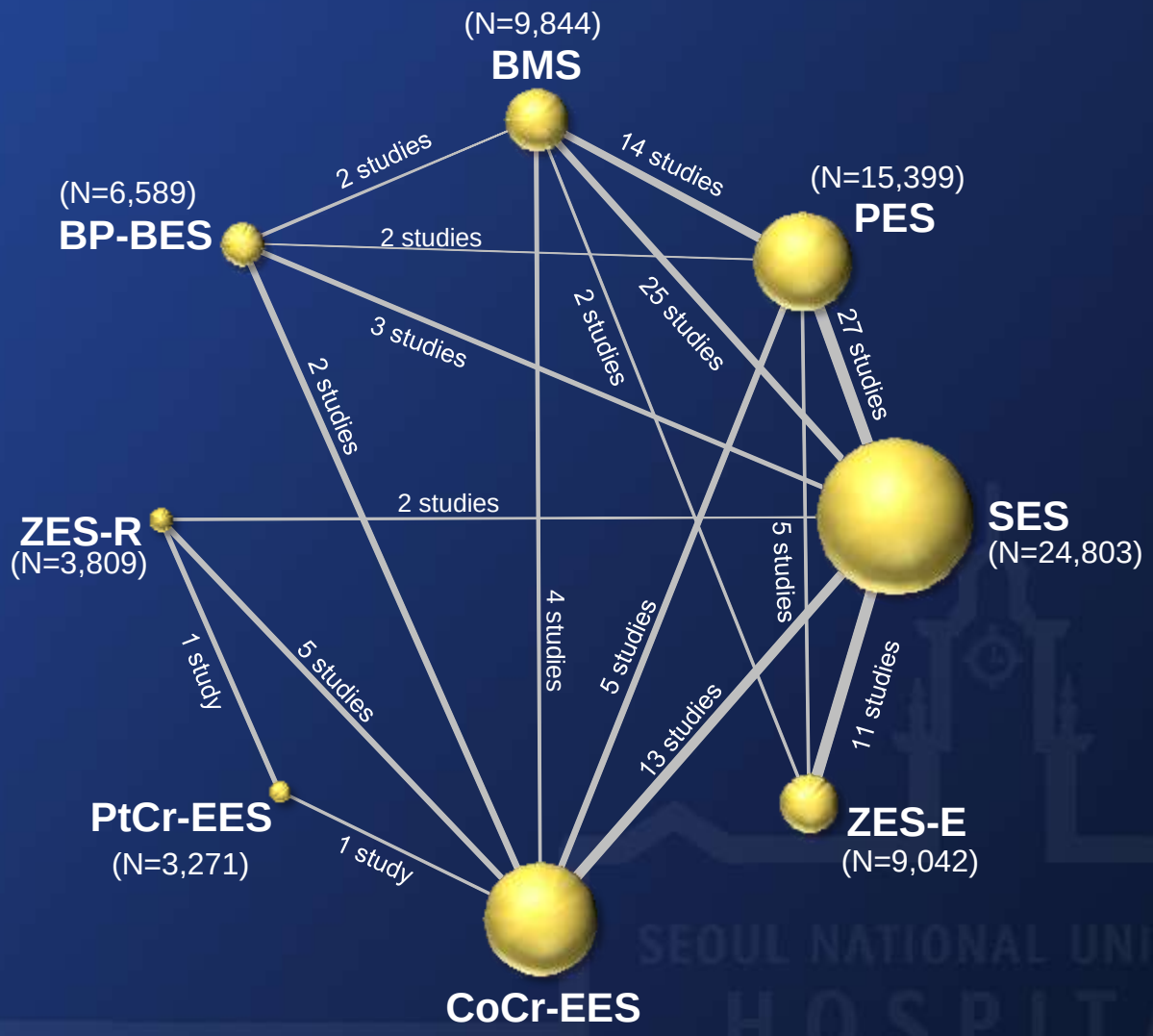
- A **systematic literature review** of randomized controlled trials comparing coronary stents was performed, and the data from the review was the basis of a **multiple-treatments network meta-analysis** using a **Bayesian framework**.



Flow Diagram of Systematic Review

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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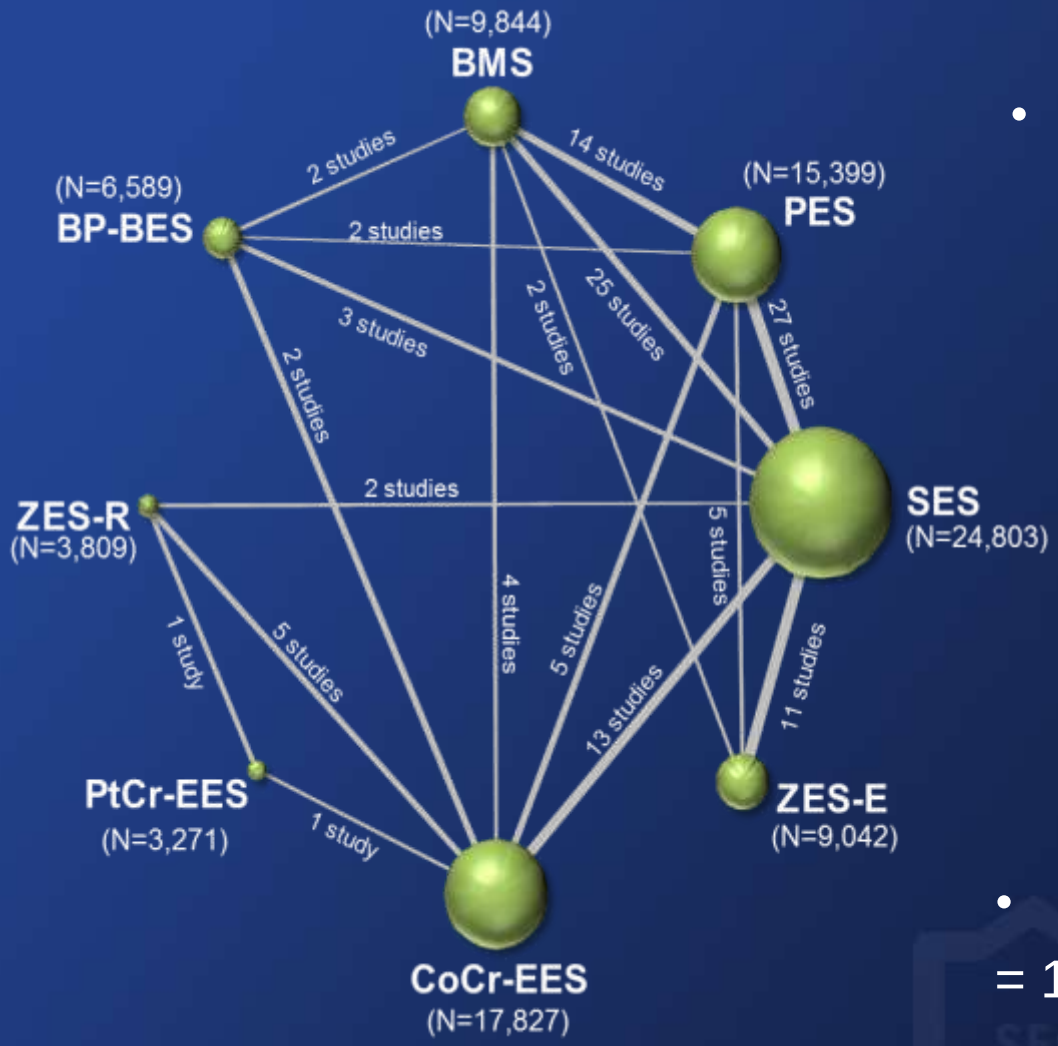
Study Characteristics



- 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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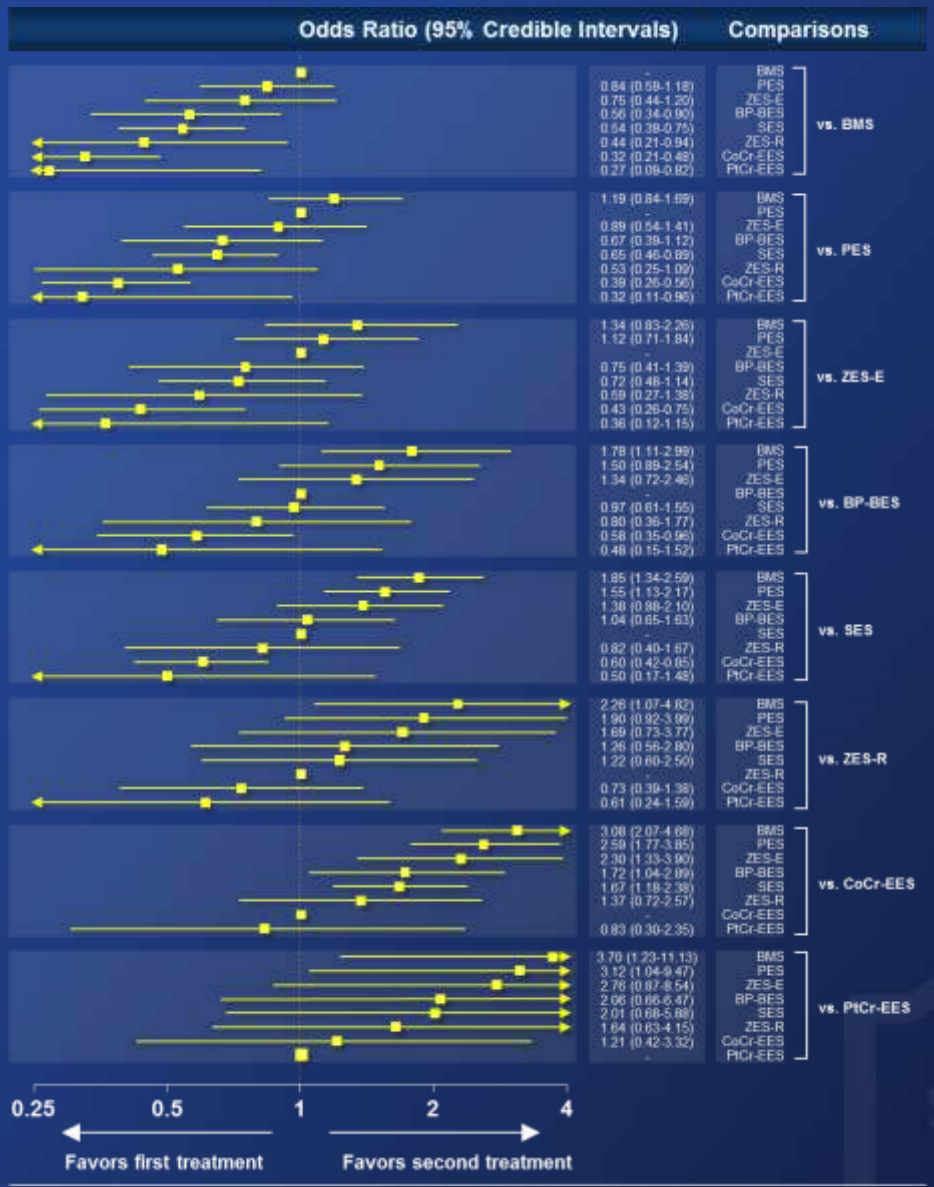
Main Characteristics of Included Trials

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…

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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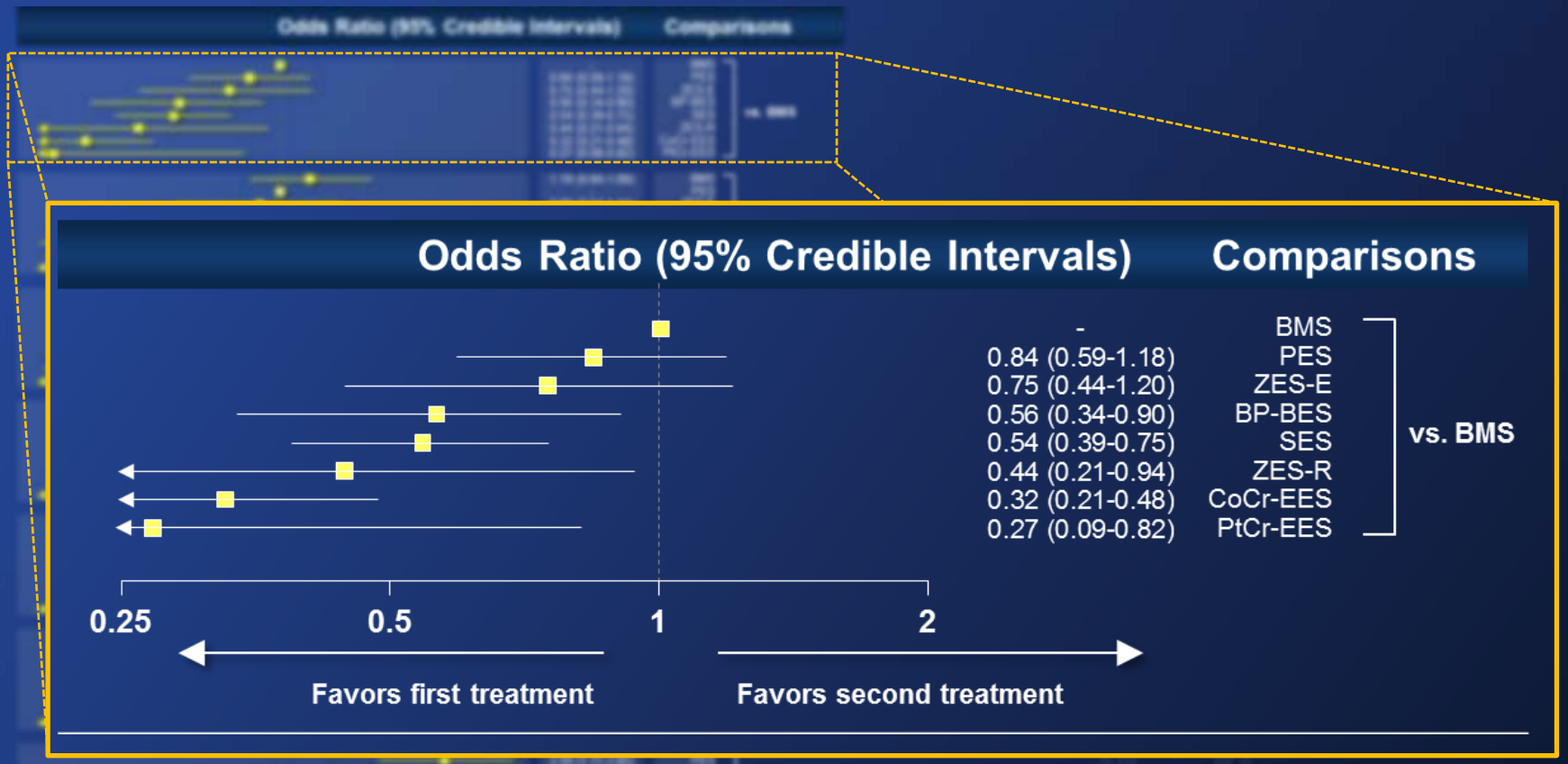
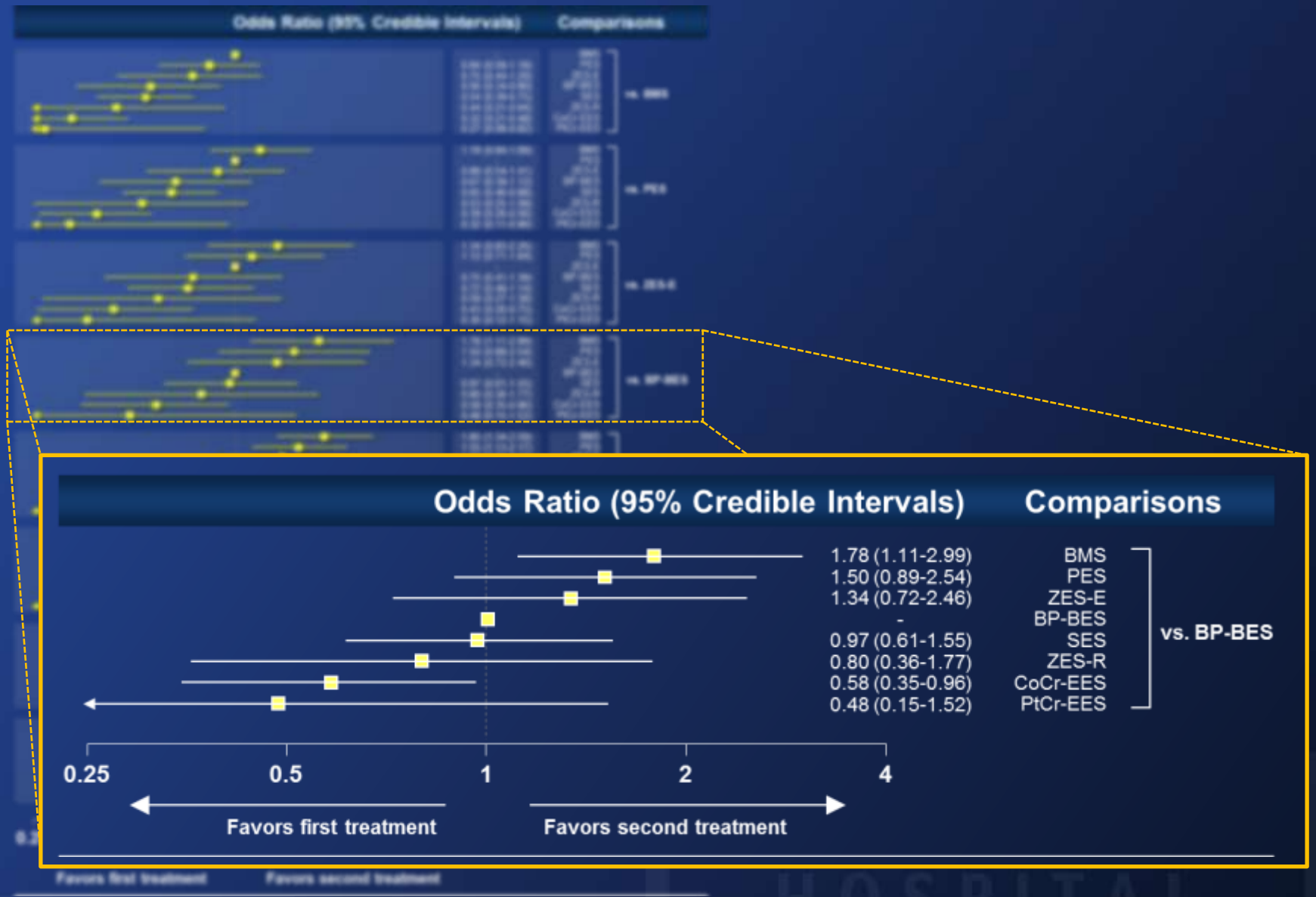
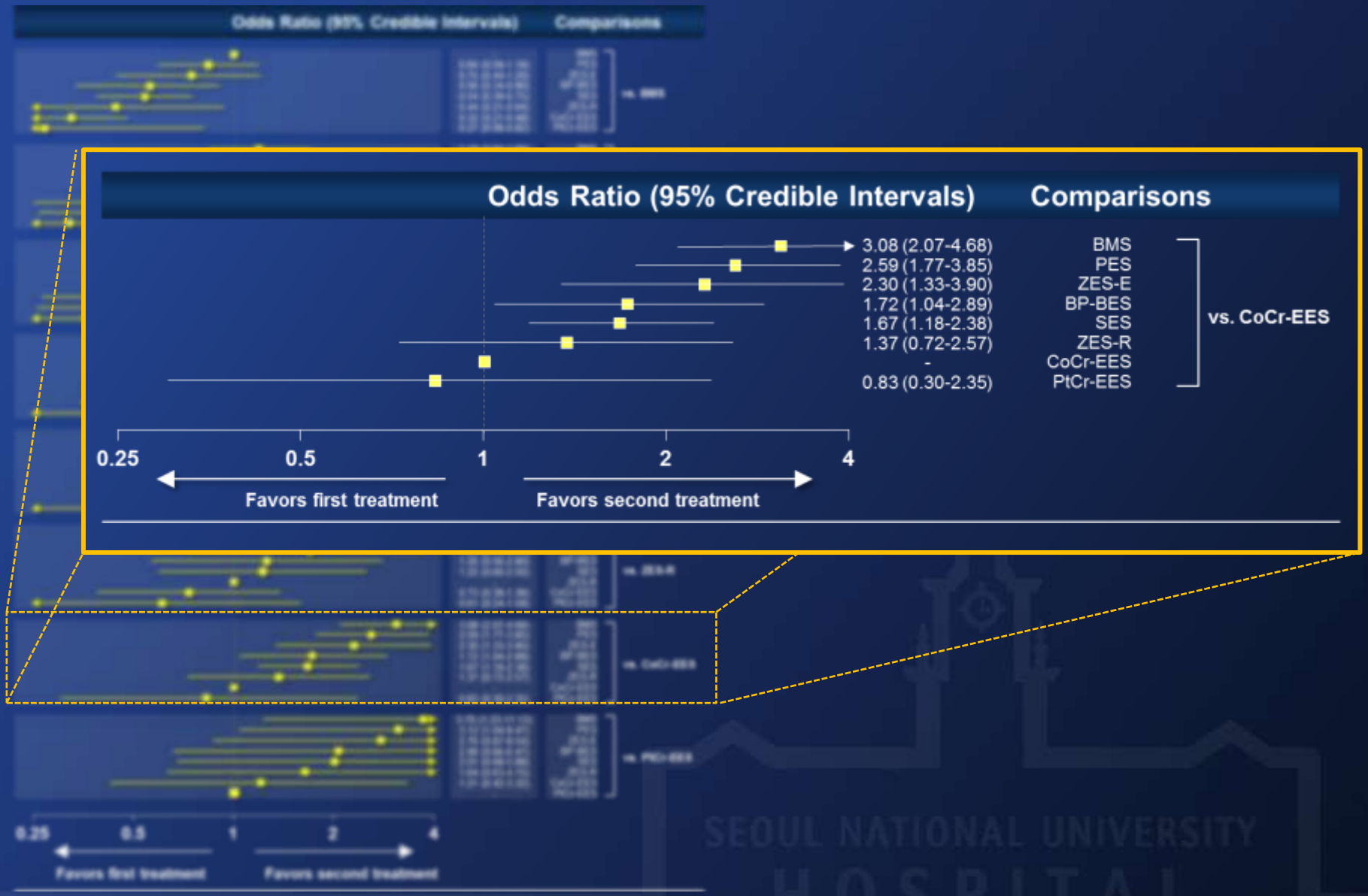
Definite or Probable ST Within 1 Year



Definite or Probable ST Within 1 Year



Definite or Probable ST Within 1 Year



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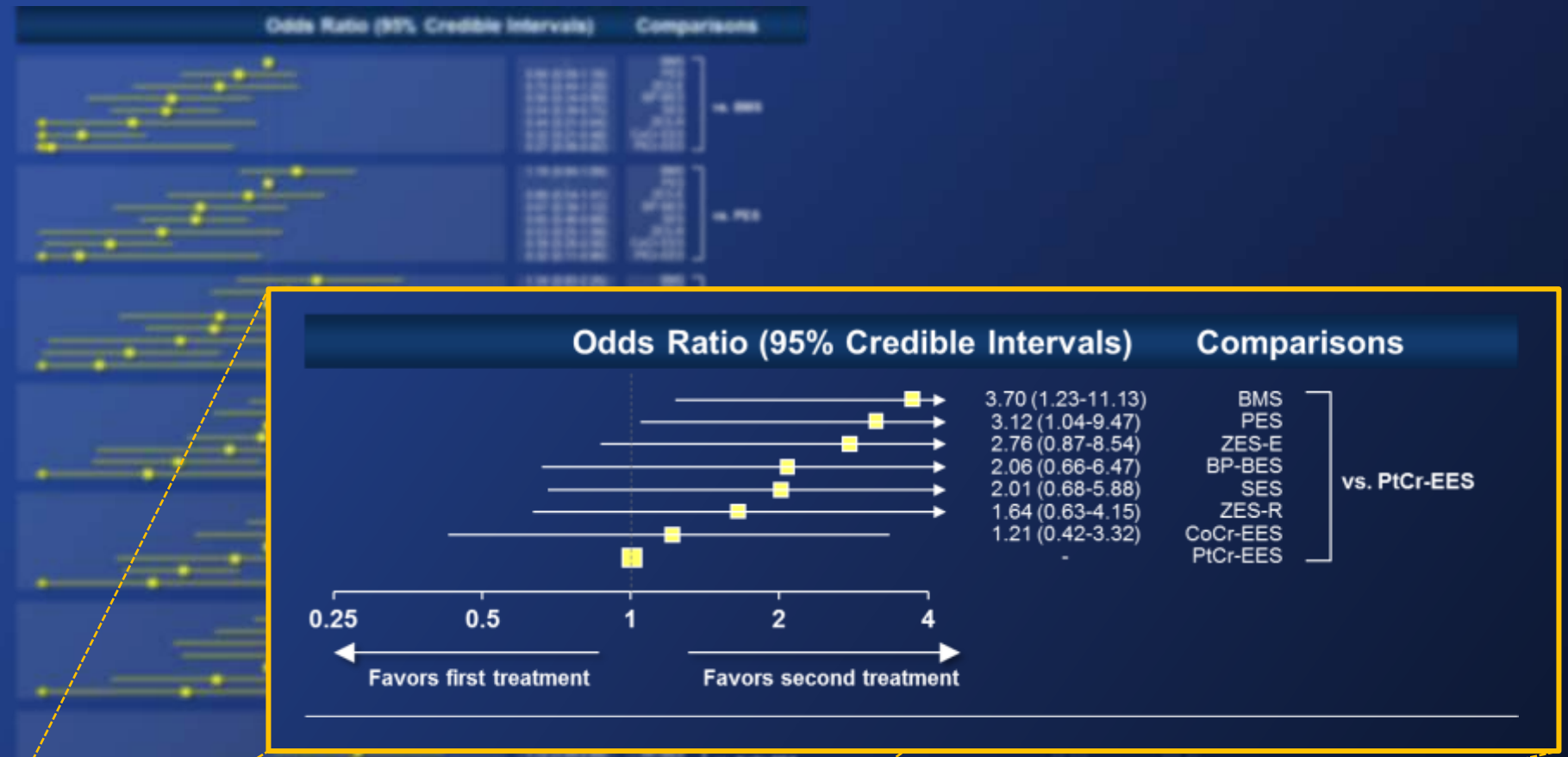
Definite or Probable ST Within 1 Year



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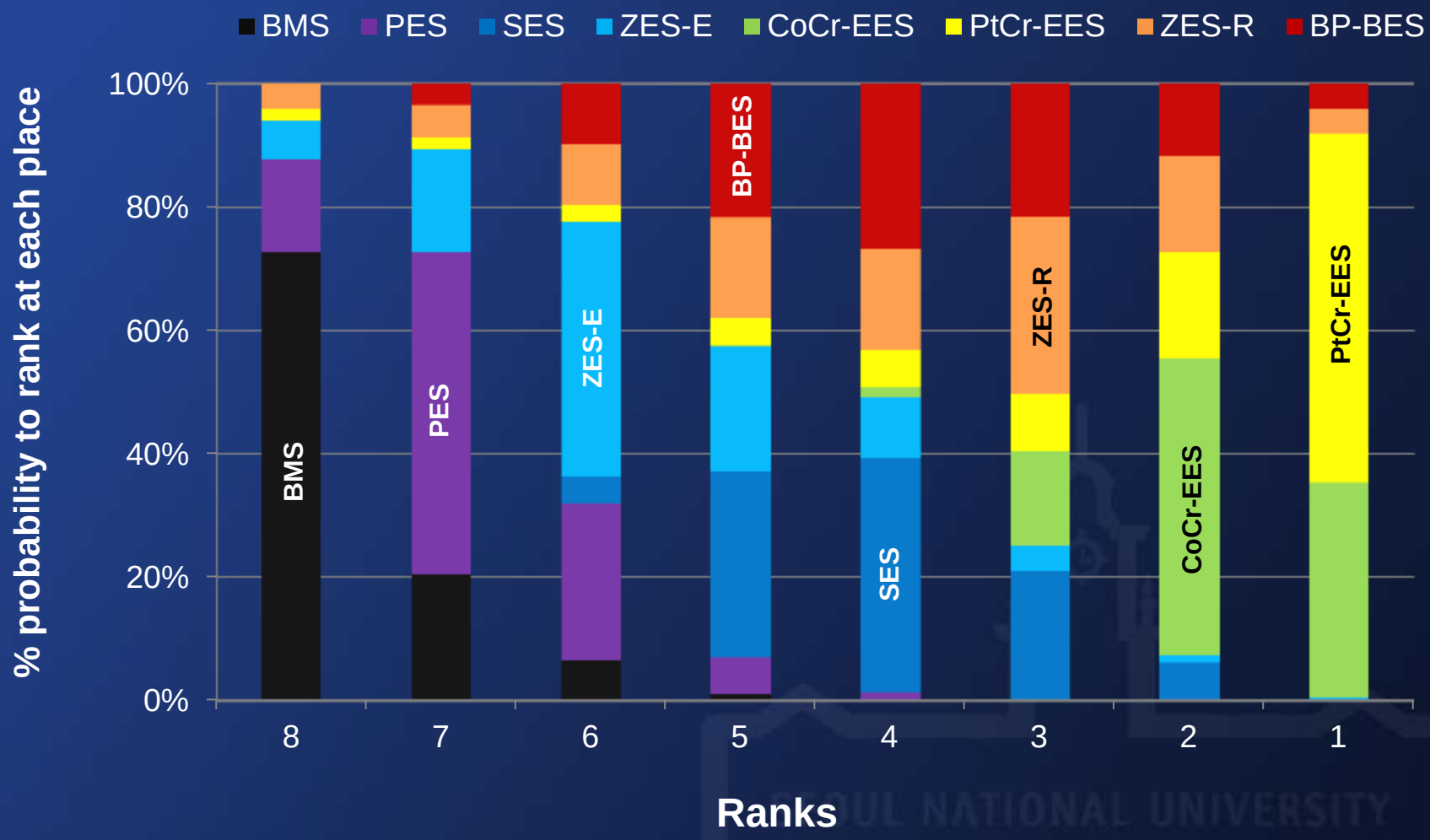
Rankogram

Definite or Probable ST within 1 Year



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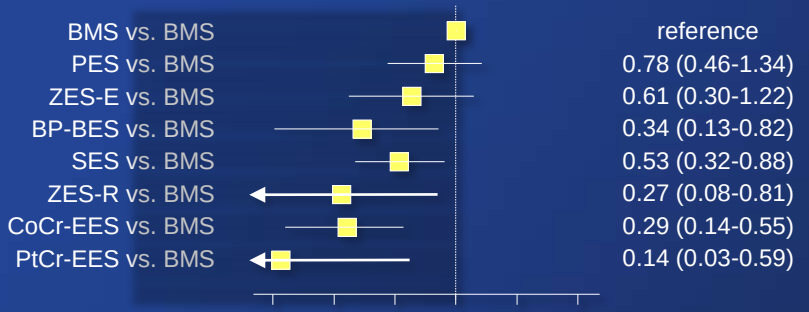
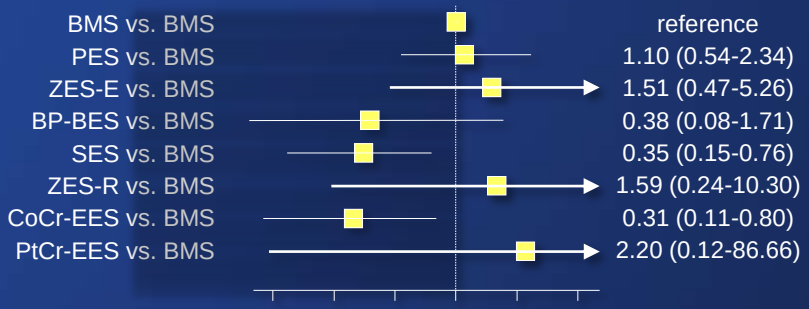
Definite or Probable ST of DES with Reference to BMS

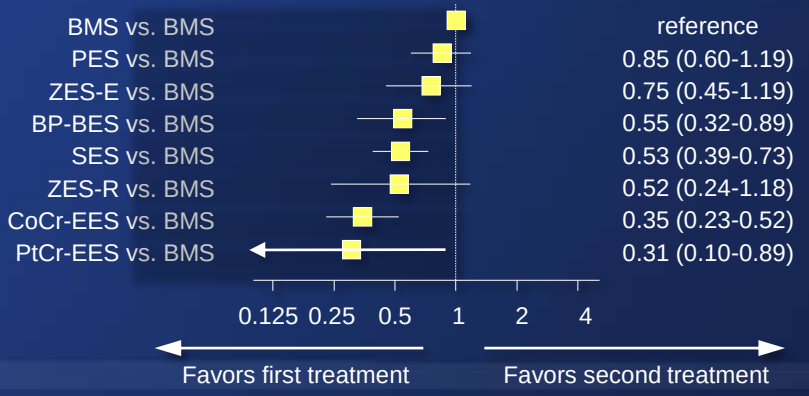
(A) Early ST (≤ 30 days)



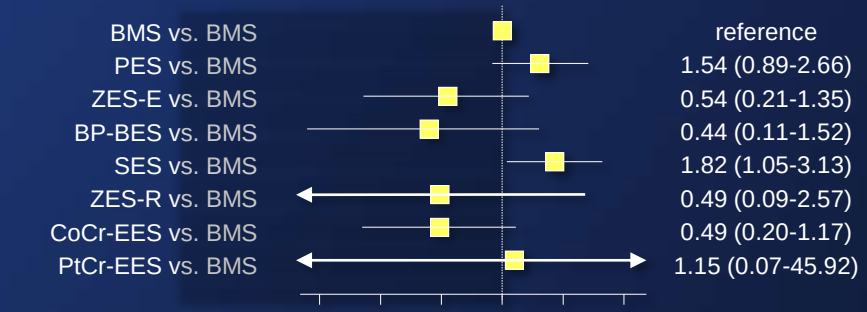
(B) Late ST (31-365 days)



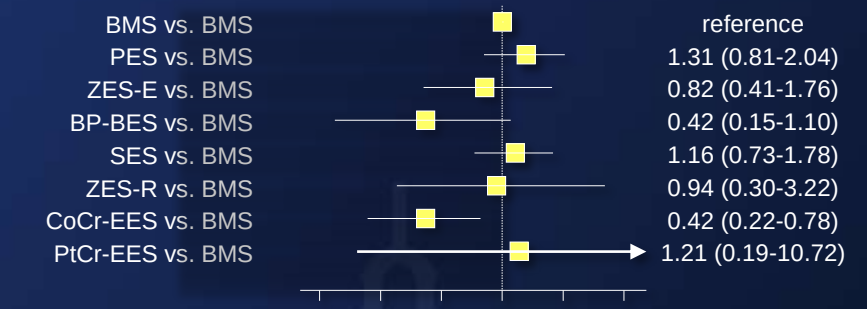
(C) ST within 1 Year (-365 days)



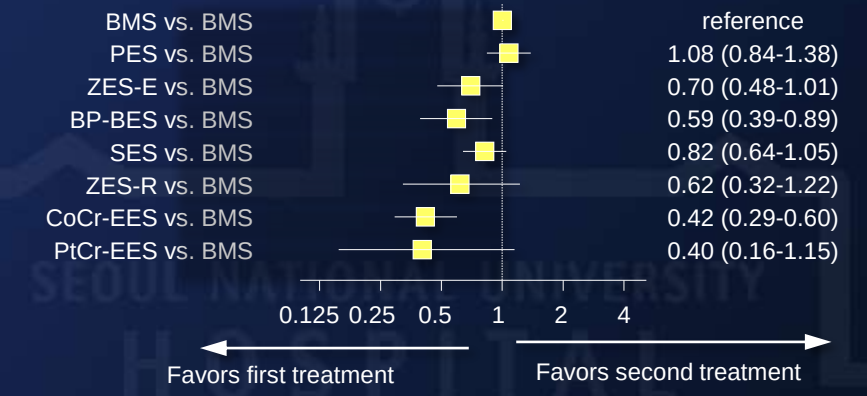
(D) Very Late ST (>365 days)

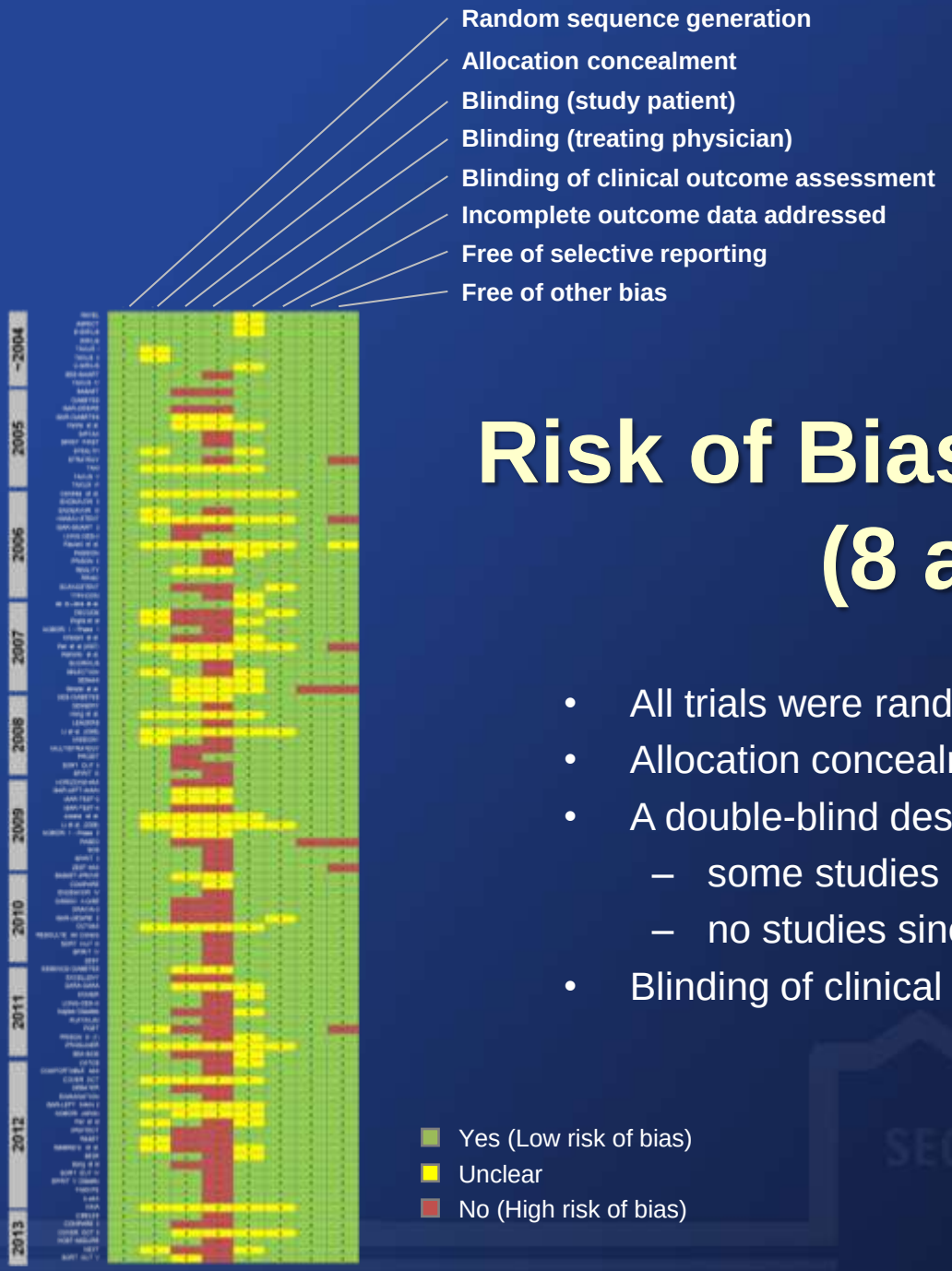


(E) Late and Very Late ST (>30 days)



(F) ST at the Longest Follow-Up



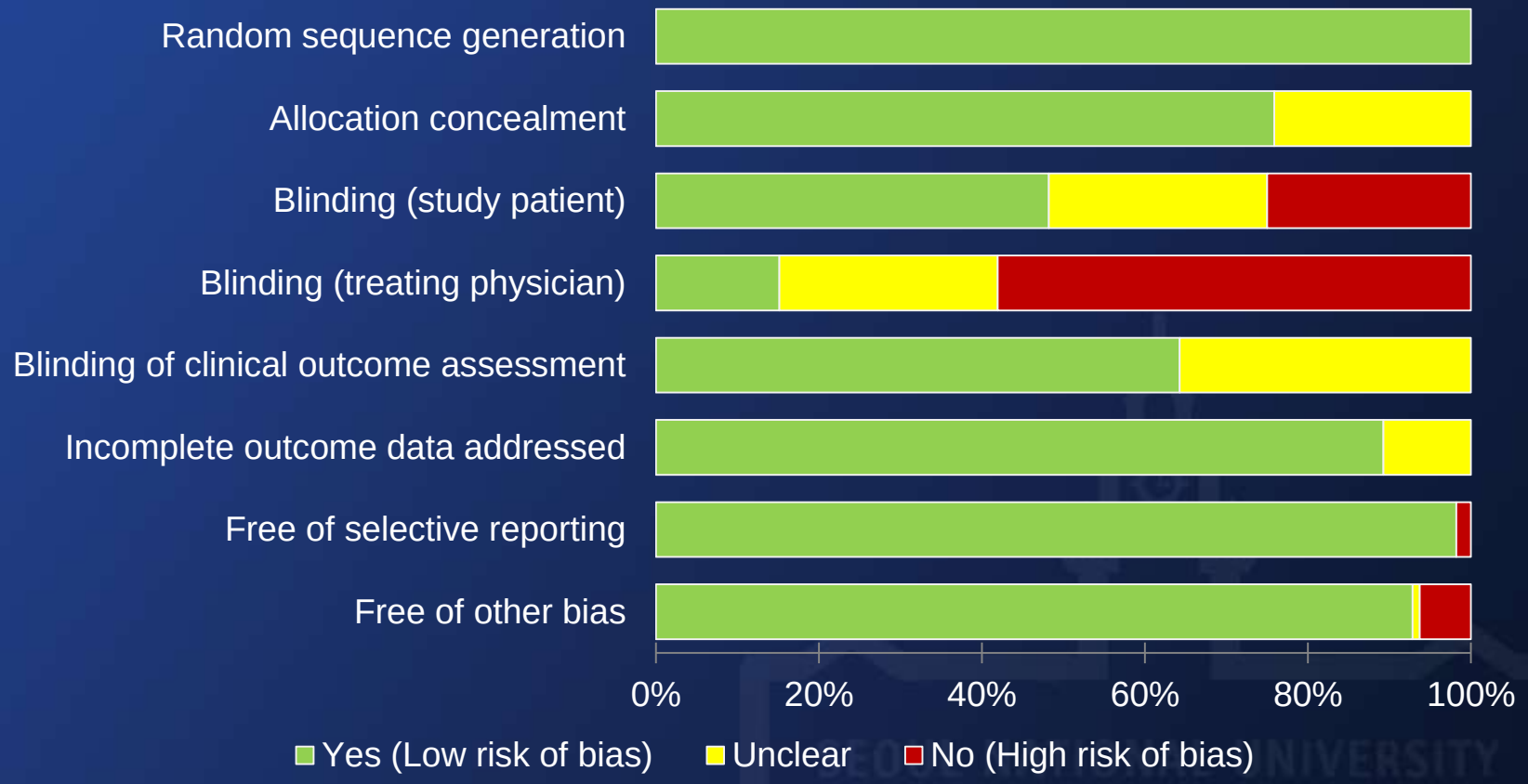


Risk of Bias in all 113 RCTs (8 aspects)

- 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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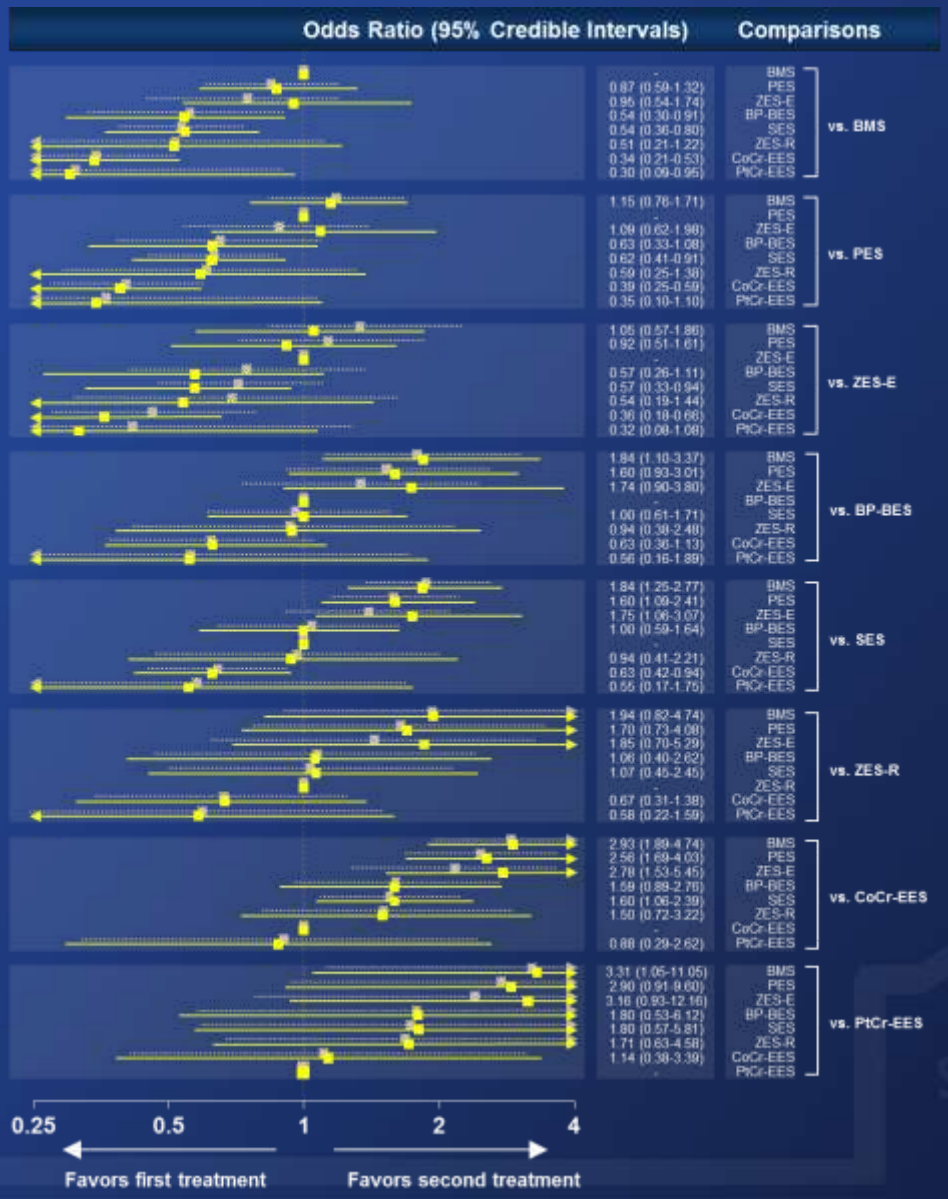
Sensitivity Analysis

Definite or Probable ST within 1 Year



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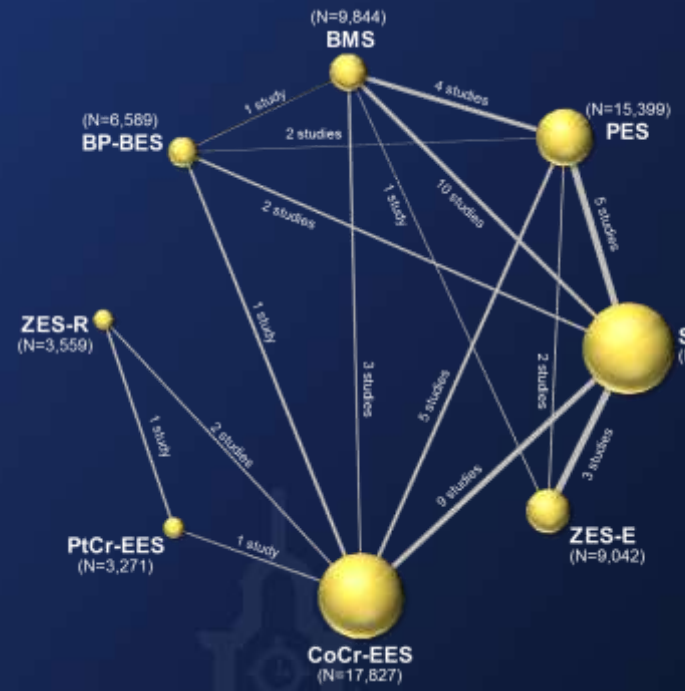
- **Studies with Low Risk of Bias : 48 Trials; 60,911 Patients**



All trials

Trials with low risk of bias only

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Definite ST Within 1 Year

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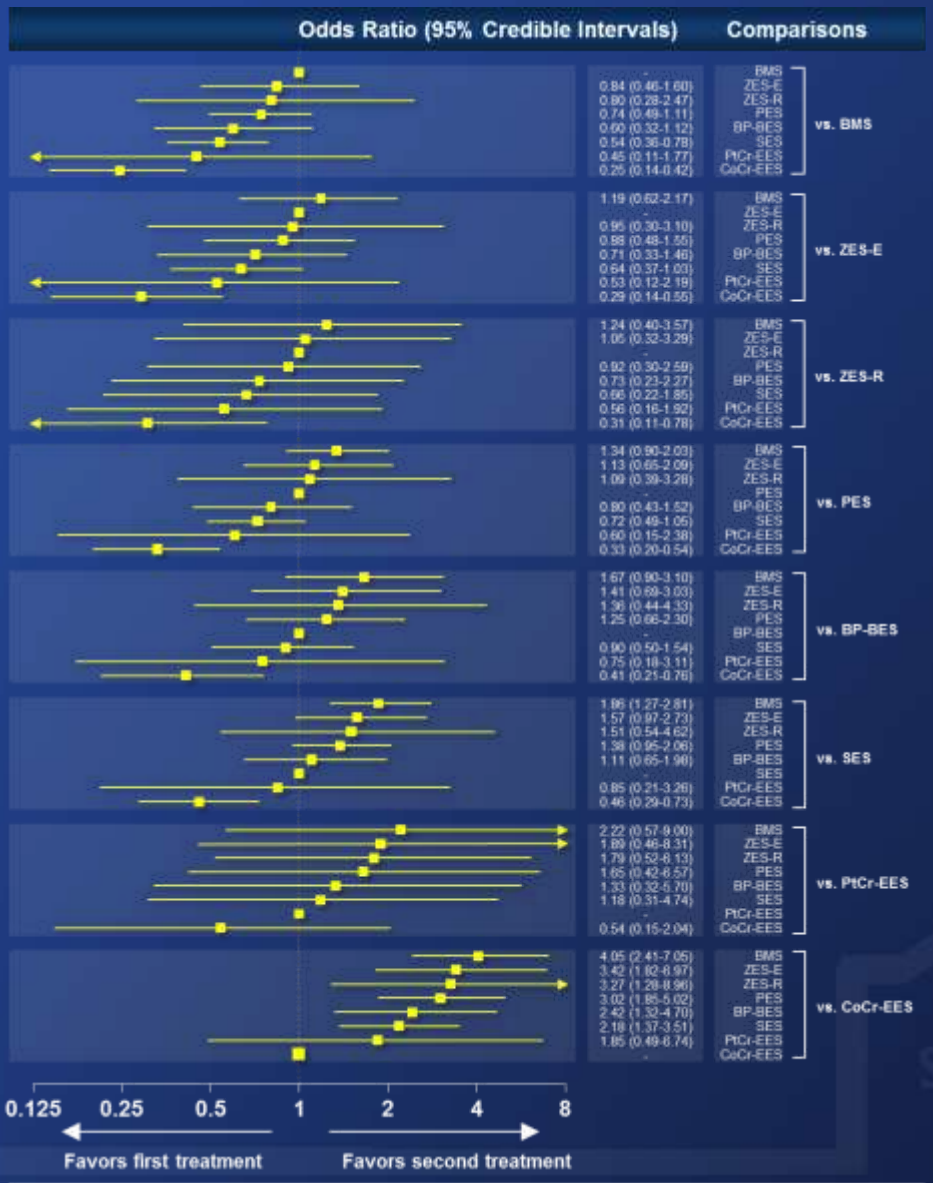
CoCr-EES > (PtCr-EES ≥ SES ≥ BP-BES ≥ PES ≥ ZES-R ≥ ZES-E ≥ BMS)



- 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

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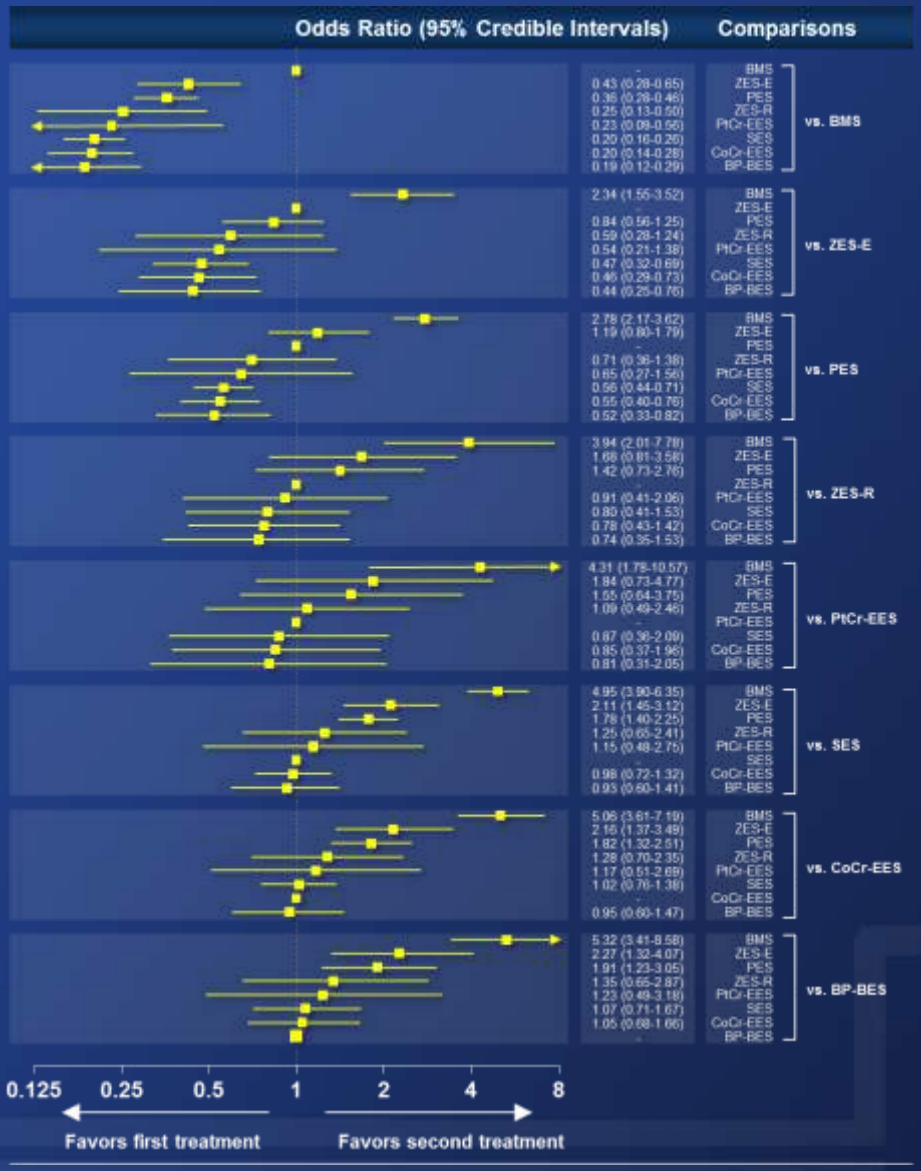
(BP-BES ≥ CoCr-EES ≥ SES ≥ PtCr-EES ≥ ZES-R) > (PES ≥ ZES-E) > BMS



- 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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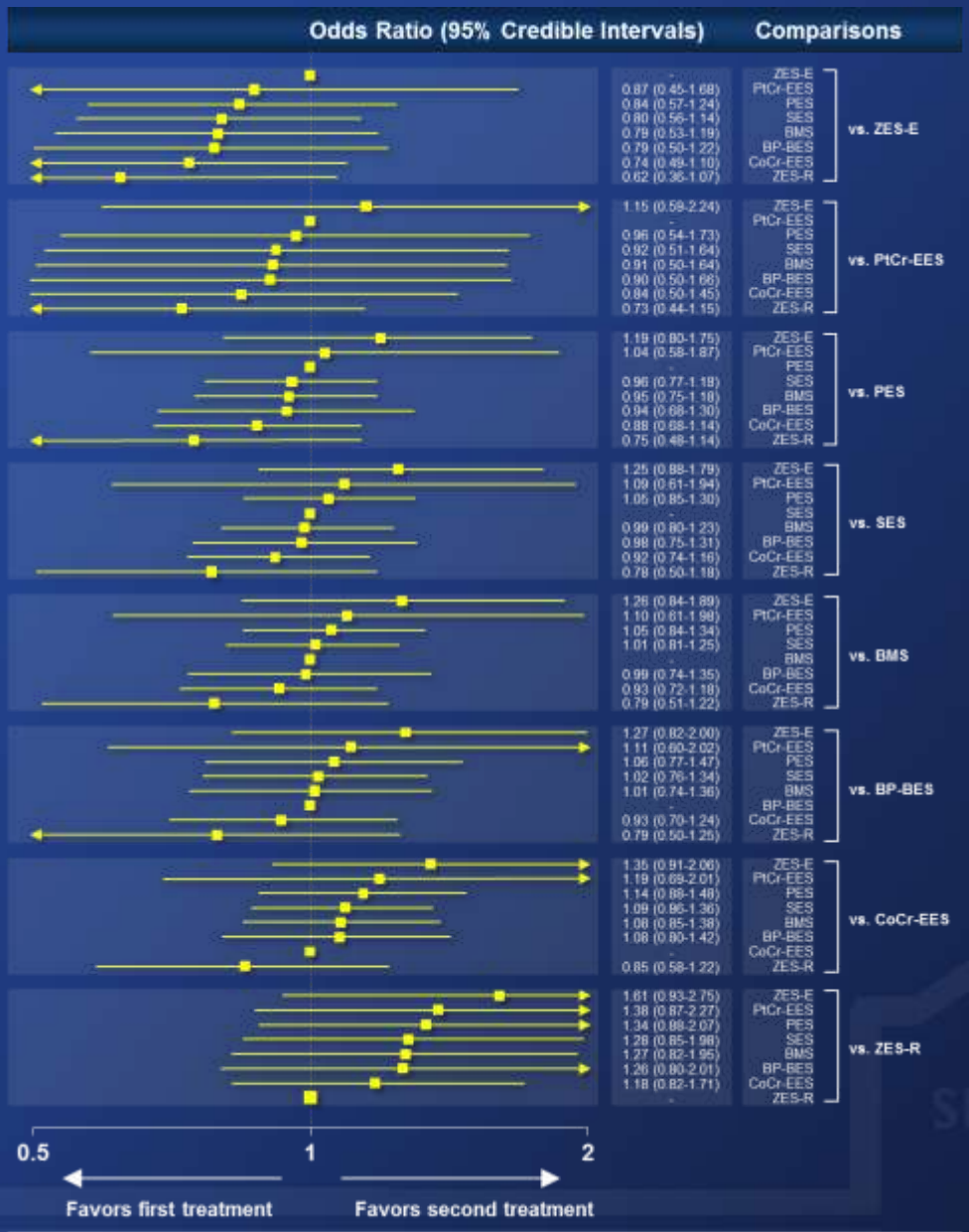

- No significant difference between any comparisons

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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.

Network Meta-Analysis

Durable-Polymer DES
vs.
Biodegradable-Polymer DES
vs.
BMS

Hyo-Soo Kim, MD/PhD/FAHA

Cardiovascular Center,

Seoul National University Hospital (SNUH), Seoul;

Eligible Study Criteria

- **Inclusion criteria**
  - RCT comparing 2 or more coronary stents in patients undergoing PCI
  - Study stents
    - (1) **BMS** (Bare metal stents)
    - (2) **PES** (Paclitaxel-eluting stents, Boston Scientific)
    - (3) **SES** (Sirolimus-eluting stents, Cordis)
    - (4) **ZES-E** (Endeavor zotarolimus-eluting stents, Medtronic)
    - (5) **CoCr-EES** (Cobalt-chromium everolimus-eluting stents, Abbott Vascular and Boston Scientific)
    - (6) **PtCr-EES** (Platinum-chromium everolimus-eluting stents, Boston Scientific)
    - (7) **ZES-R** (Resolute zotarolimus-eluting stents, Medtronic)
    - (8) **BP-BES** (BP biolimus A9-eluting stents, 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) Studies 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 ≤ 1 year (defined according to the ARC consensus)
- Other safety endpoints
  - definite ST - all-cause death
  - cardiac death - myocardial infarction
- Efficacy endpoints
  - TLR - TVR

Data Analysis

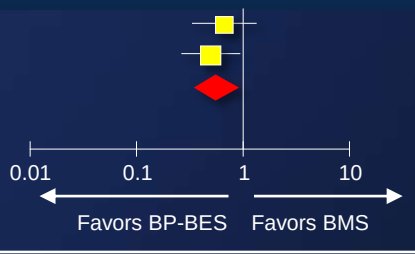
- **Bayesian random effects model**
  - Bayesian extension of the hierarchical random-effects model proposed by Lumley for networks of multi-arm trials
  - Markov chain Monte Carlo samplers in WinBUGS
    - Running 3 chains with different starting values
    - A burn-in phase of 20,000 iterations were followed by 50,000 updates
  - Noninformative prior distributions
  - Odds ratios (OR) with 95% credible intervals (CrIs)
  - Results for which the CrIs of the ORs did not include 1 were considered significant

- **Sensitivity analysis**
  - (1) Excluding studies with any potential risk of bias
  - (2) Excluding studies with exclusive enrollment of diabetic patients
  - (3) Excluding studies with exclusive enrollment of STEMI
  - (4) Excluding studies with mandatory angiographic follow-up

Consistency Between Direct And Indirect Estimates of Stent Thrombosis

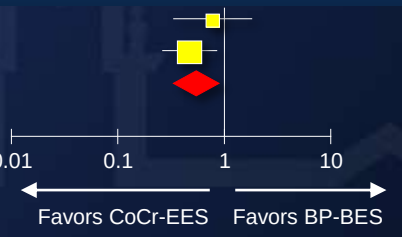
BP-BES Versus BMS

	Log (OR)	SE	Weight	OR with 95% CI Random Effects Model
Direct estimate	-0.405	0.350	45.6%	0.67 [0.34, 1.32]
Indirect estimate	-0.696	0.320	54.4%	0.50 [0.27, 0.93]
Total			**100.0%**	**0.57 [0.36, 0.90]**
Heterogeneity P=0.54; I^2=0%				
Test for overall effect: Z = 2.38 (P = 0.02)				



CoCr-EES Versus BP-BES

	Log (OR)	SE	Weight	OR with 95% CI Random Effects Model
Direct estimate	-0.237	0.429	32.6%	0.79 [0.34, 1.83]
Indirect estimate	-0.735	0.298	67.4%	0.48 [0.27, 0.86]
Total			**100.0%**	**0.74 [0.29, 1.92]**
Heterogeneity P=0.34; I^2=0%				
Test for overall effect: Z = 2.34 (P = 0.02)				

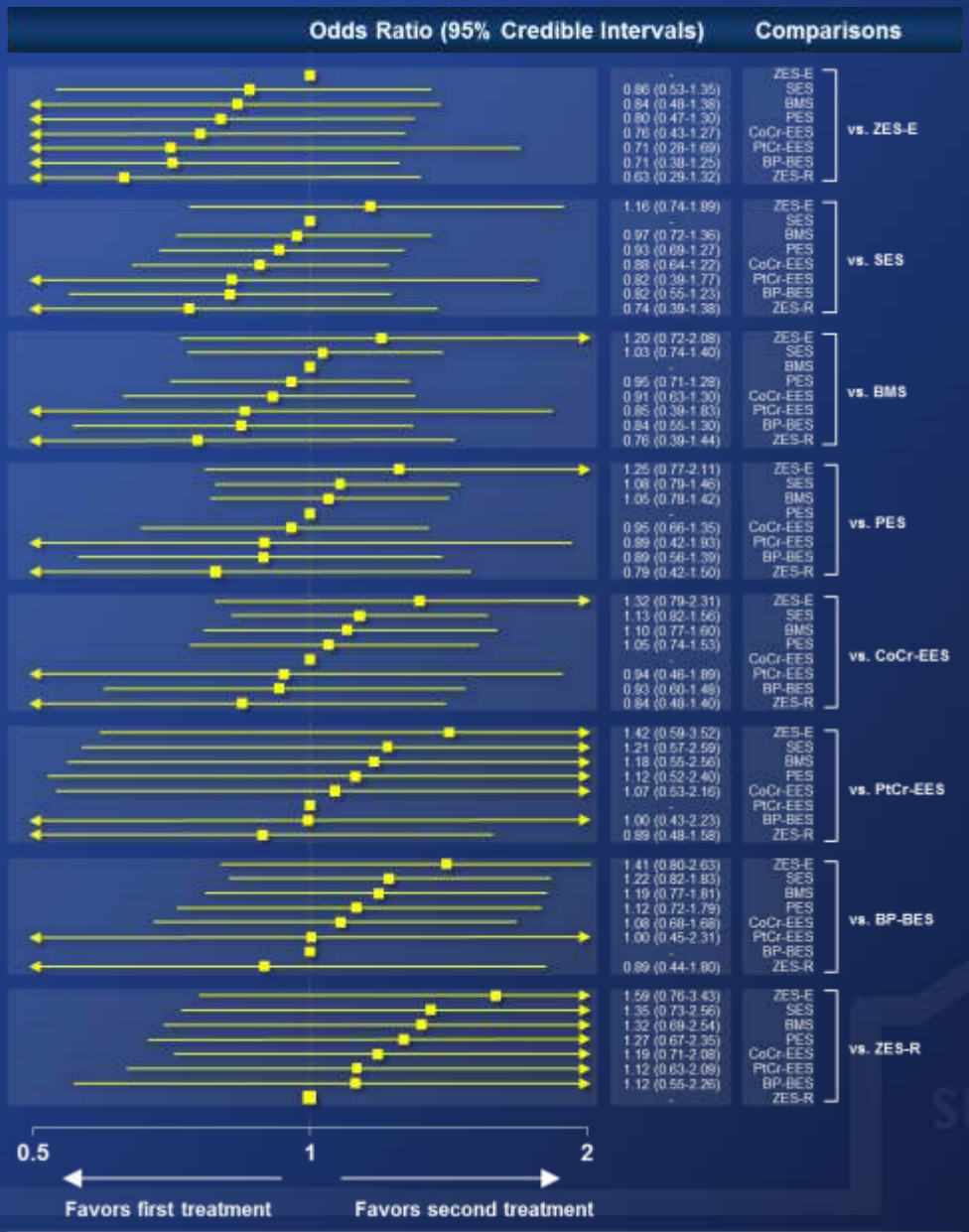


Kang SH, Park KW,, Kim HS. Euro Heart J 2014

SNU-Hospital (Seoul National University)

Cardiac Death in 1 Year

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

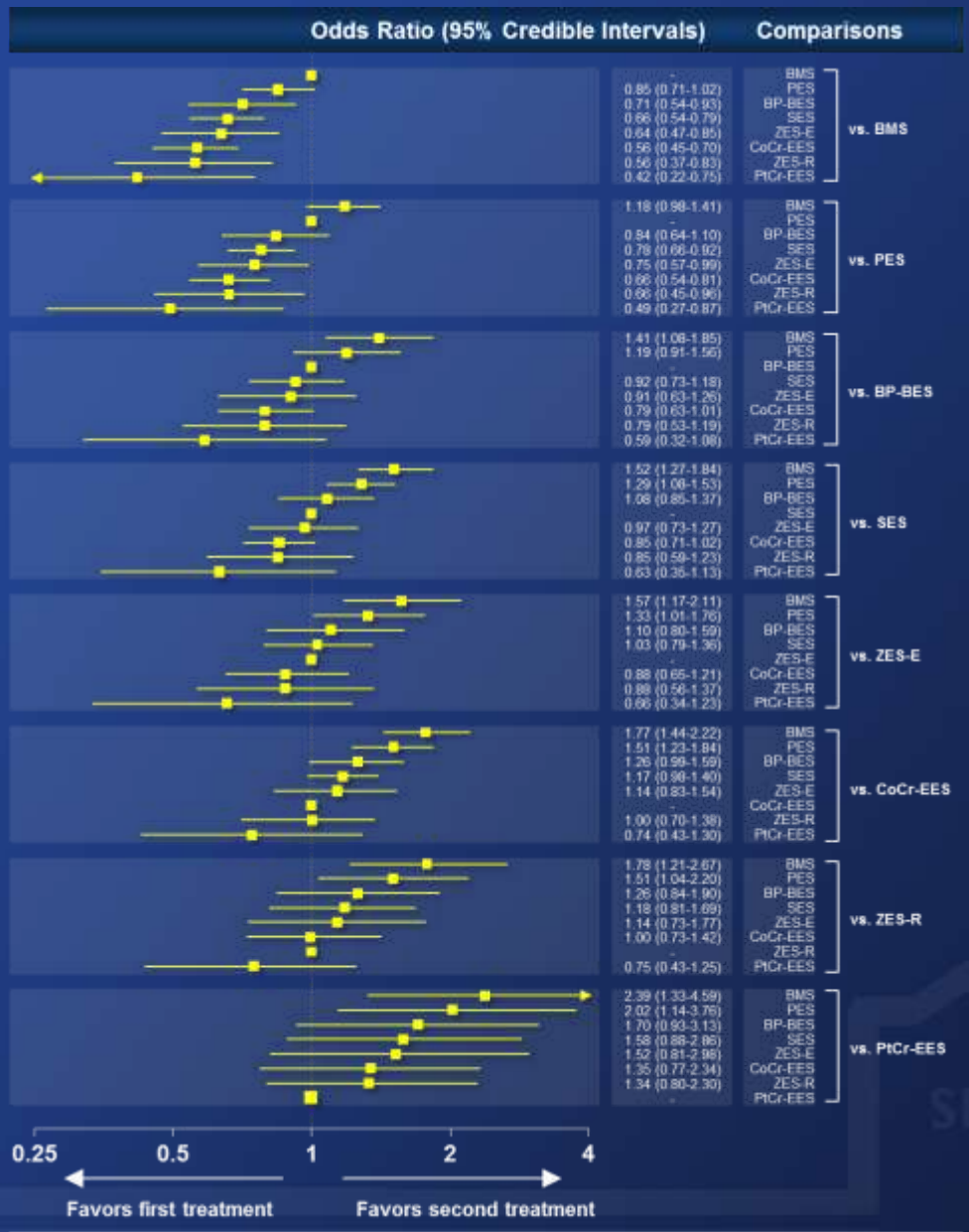


- No significant difference between any comparisons

SNU-Hospital (Seoul National University)

MI Within 1 Year

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

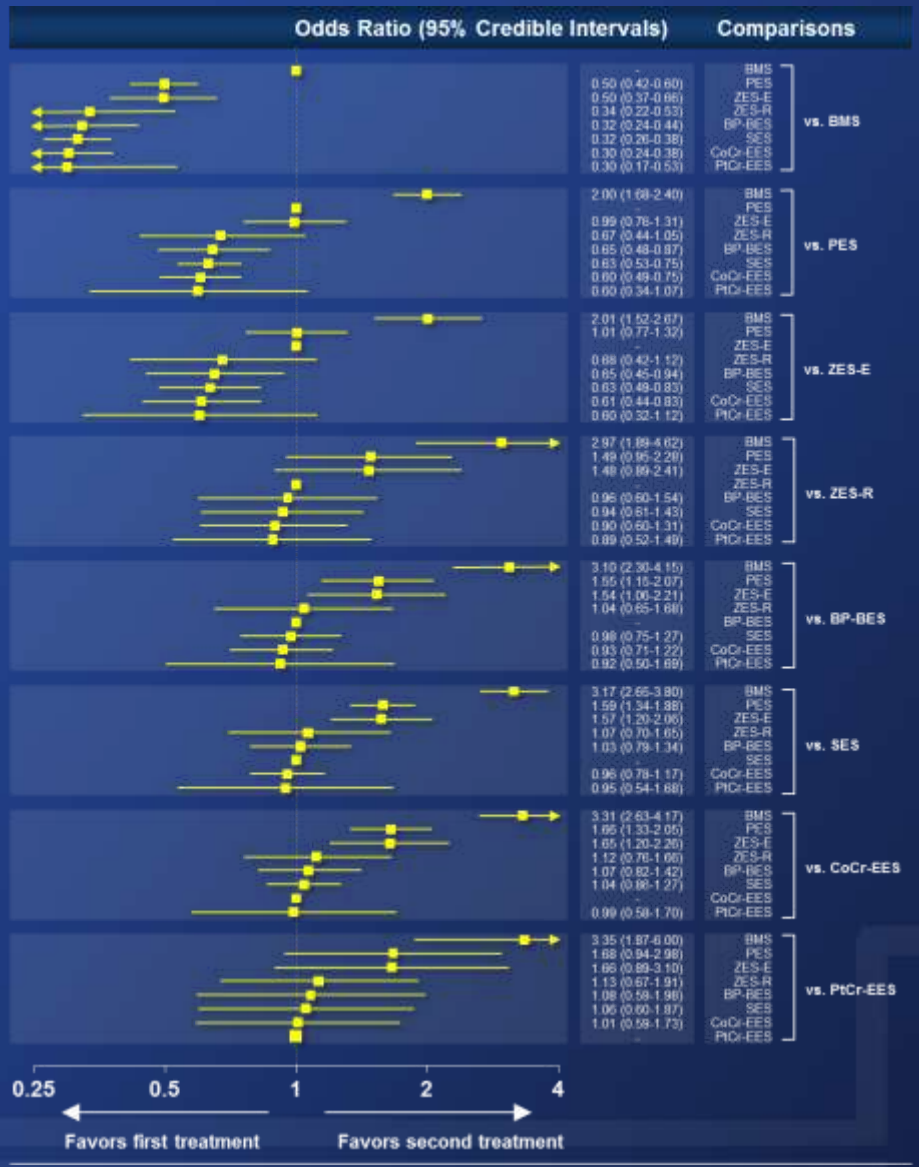


- PtCr-EES, ZES-R, CoCr-EES, ZES-E, SES, and BP-BES superior to BMS
- PtCr-EES, ZES-R, CoCr-EES, ZES-E, and SES superior to PES
- CoCr-EES tended to be superior to BP-BES and SES

TVR Within 1 Year

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

BMS << (PES ≒ ZES-E) < (ZES-R ≒ BP-BES ≒ SES ≒ CoCr-EES ≒ PtCr-EES)

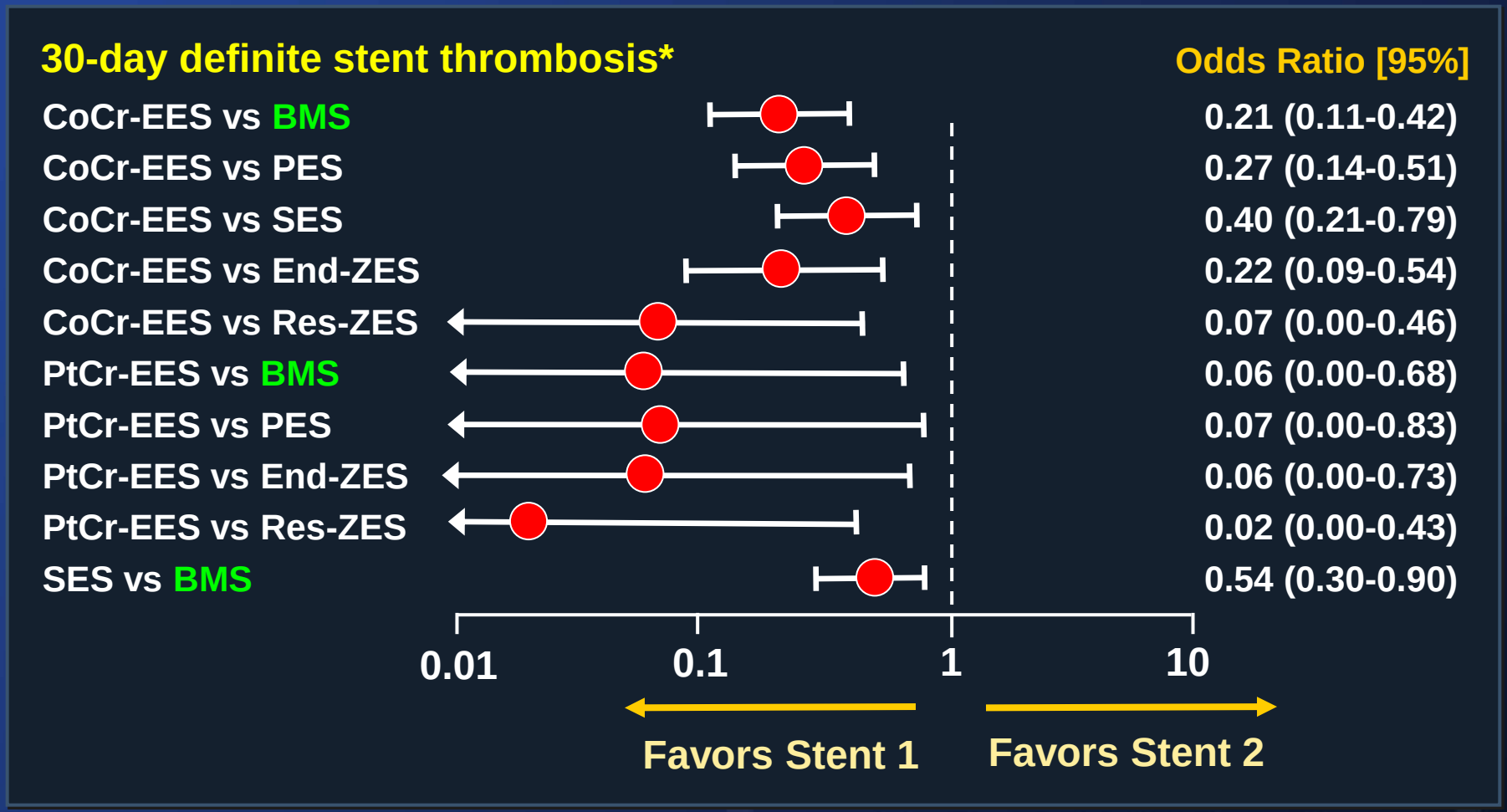


- All DES superior to BMS
- CoCr-EES, SES, and BP-BES superior to PES
- CoCr-EES, SES, and BP-BES superior to ZES-E

Stent Thrombosis Network Meta-analysis

Primary EP: ARC Definite ST (FU through 2 years)

49 RCTs, 50,844 pts



Palmerini T et al. *Lancet* 2012

Myocardial Infarction

Control	Treatment	Treatment	Control	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
Sirolimus (Ref)						
	Paclitaxel			1.26	1.11	1.43
	Everolimus			0.77	0.64	0.95
	Zotarolimus			0.84	0.66	1.08
	Zotarolimus-R			0.84	0.57	1.22
Paclitaxel (Ref)						
	Everolimus			0.61	0.51	0.75
	Zotarolimus			0.66	0.52	0.86
	Zotarolimus-R			0.67	0.45	0.96
Everolimus (Ref)						
	Zotarolimus			1.09	0.81	1.49
	Zotarolimus-R			1.09	0.76	1.51
Zotarolimus (Ref)						
	Zotarolimus-R			1.01	0.65	1.51

0.10 1.00 10.00

RR (95% CrI)

larization

				io	95%	CrI
				.89	0.79	1.09
				.89	0.78	1.07
				.81	0.64	1.01
				.94	0.73	1.24
				.71	0.31	1.09
				.00	0.87	1.15
				.87	0.71	1.07
				.05	0.83	1.27
				.76	0.38	1.22
				.87	0.71	1.08
				.05	0.82	1.29
	Zotarolimus-R			0.77	0.37	1.23
Everolimus (Ref)						
	Zotarolimus			1.22	0.88	1.54
	Zotarolimus-R			0.87	0.45	1.32
Zotarolimus (Ref)						
	Zotarolimus-R			0.74	0.33	1.23

0.10 1.00 10.00

RR (95% CrI)

rization

tate Ratio	95%	CrI
0.32	0.27	0.38
0.48	0.41	0.58
0.28	0.22	0.38
0.56	0.43	0.72
0.39	0.23	0.66
1.50	1.30	1.76
0.88	0.69	1.15
1.73	1.35	2.23
1.20	0.74	2.04
0.59	0.45	0.76
1.14	0.88	1.49
0.80	0.49	1.33
1.96	1.39	2.75
1.36	0.90	2.11
0.70	0.41	1.22

Ratio	95%	CrI
0.39	0.34	0.45
0.61	0.53	0.69
0.39	0.31	0.48
0.61	0.48	0.77
0.44	0.27	0.68
1.54	1.36	1.75
0.98	0.79	1.20
1.55	1.25	1.94
1.11	0.70	1.74
0.63	0.52	0.78
1.01	0.80	1.27
0.72	0.45	1.12
1.58	1.20	2.11
1.13	0.76	1.68
0.72	0.43	1.17

Everolimus (Ref)
Zotarolimus
Zotarolimus-R
Zotarolimus (Ref)
Zotarolimus-R

1.00 10.00

RR (95% CrI)

0.10 1.00 10.00

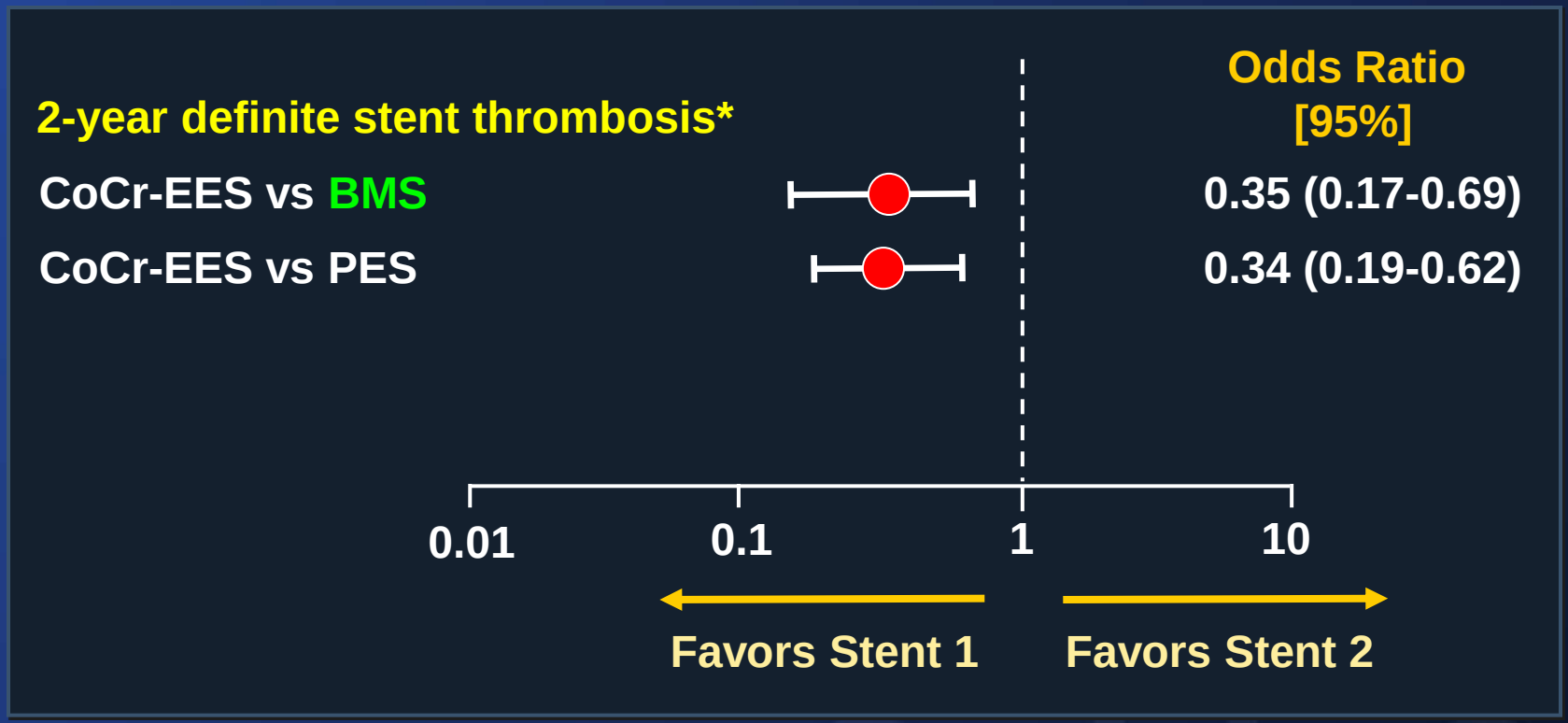
RR (95% CrI)

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

Stent Thrombosis Network Meta-analysis

Primary EP: ARC Definite ST (FU through 2 years)

49 RCTs, 50,844 pts



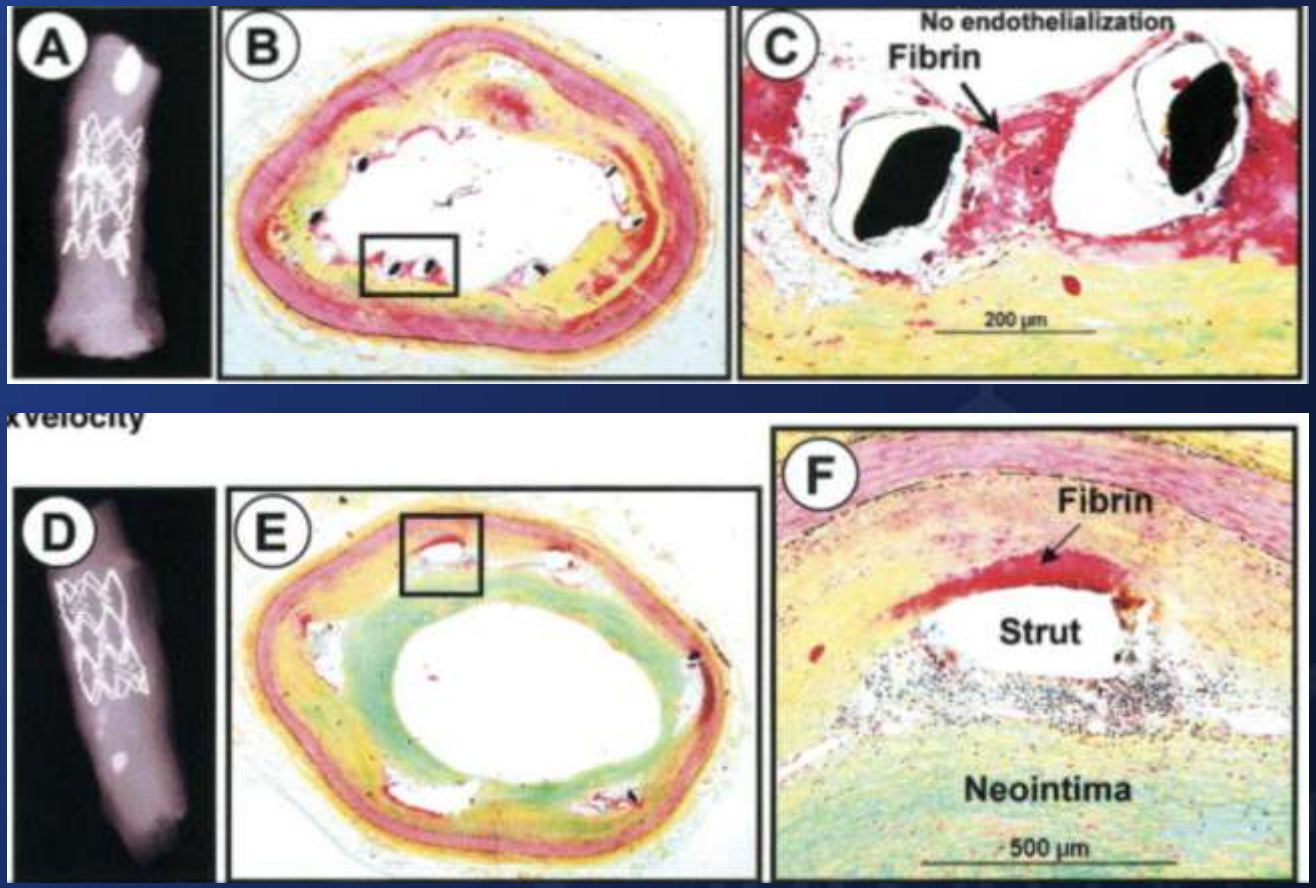
Palmerini T et al. *Lancet* 2012

DES and Late Stent Thrombosis

- DES ➔ repeat revascularization ↓
- DES ➔ delayed vessel wall healing
  ➔ abnormal vascular response ➔ potential for stent thrombosis
- Polymer in DES ➔ Thrombogenic nidus

DES

BMS



Joner et at. JACC 2006

Development of Newer Generation DES

	Drug	Stent	Strut Thickness	Polymer	Polymer Thickness
SES	Sirolimus	Stainless steel	140 μm	PEVA/PBMA	13.7 μm
PES	Paclitaxel	Stainless steel	97 μm	SIBS	17.8 μm
ZES-E	Zotarolimus	Cobalt Nickel	91 μm	Biolinx	4.8 μm
CoCr-EES	Everolimus	Cobalt Chromium	81 μm	PVDF	7.8 μm
PtCr-EES	Everolimus	Platinum Chromium	81 μm	Fluorinated copolymer	8 μm
ZES-R	Zotarolimus	Cobalt Chromium	89 μm	Biolinx	6 μm
BP-BES	Biolimus A9	Stainless Steal	120 μm	PLA	10 μm