Drug-Eluting Balloon Leaving Nothing Behind:

Attractive Treatment with "Procedure Optimization"

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ISR in the Contemporary DES Era

- **The development of DES created a milestone** in the field of PCI, by markedly **reducing the rates of ISR**
- **However, ISR occurs even in the newer generation DES era** with considerable incidence **ranging from 3% to 20%** of patients
- **ISR is still a major concern of interventionists**, because

1. More than **half of ISR patients present with acute coronary syndrome**
2. ISR, compared to *de novo* lesion, **increases rates of future MACE**
   - even after successful treatment of ISR

*** ISR, in-stent restenosis**
*** DES, drug-eluting stents**
*** MACE, major adverse cardiovascular events**

B Scheller et al. JACC Intervention 2012
F Alfonso et al. JACC 2014
JM Lee, J Park, HS Kim et al. JACC Intervention 2015

How to Treat ISR? Still in Controversy

Repeat revascularization

Recommendations	Class[a]	LoE[b]	Ref[c]
Restenosis			
Repeat PCI is recommended, if technically feasible.	I	C	
DES are recommended for the treatment of in-stent restenosis (within BMS or DES).	I	A	501,502,508 511,524
Drug-coated balloons are recommended for the treatment of in-stent restenosis (within BMS or DES).	I	A	507– 511,524
IVUS and/or OCT should be considered to detect stent-related mechanical problems.	IIa	C	

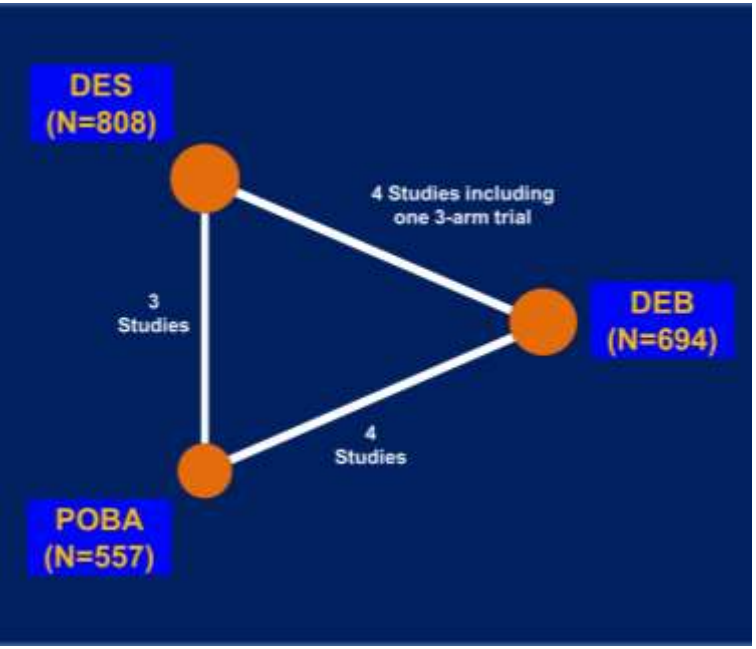
- **2014 ESC/EACTS guideline provide an equivalent recommendation**
  - **DES or DEB** for the treatment of ISR (class I, LoE A)

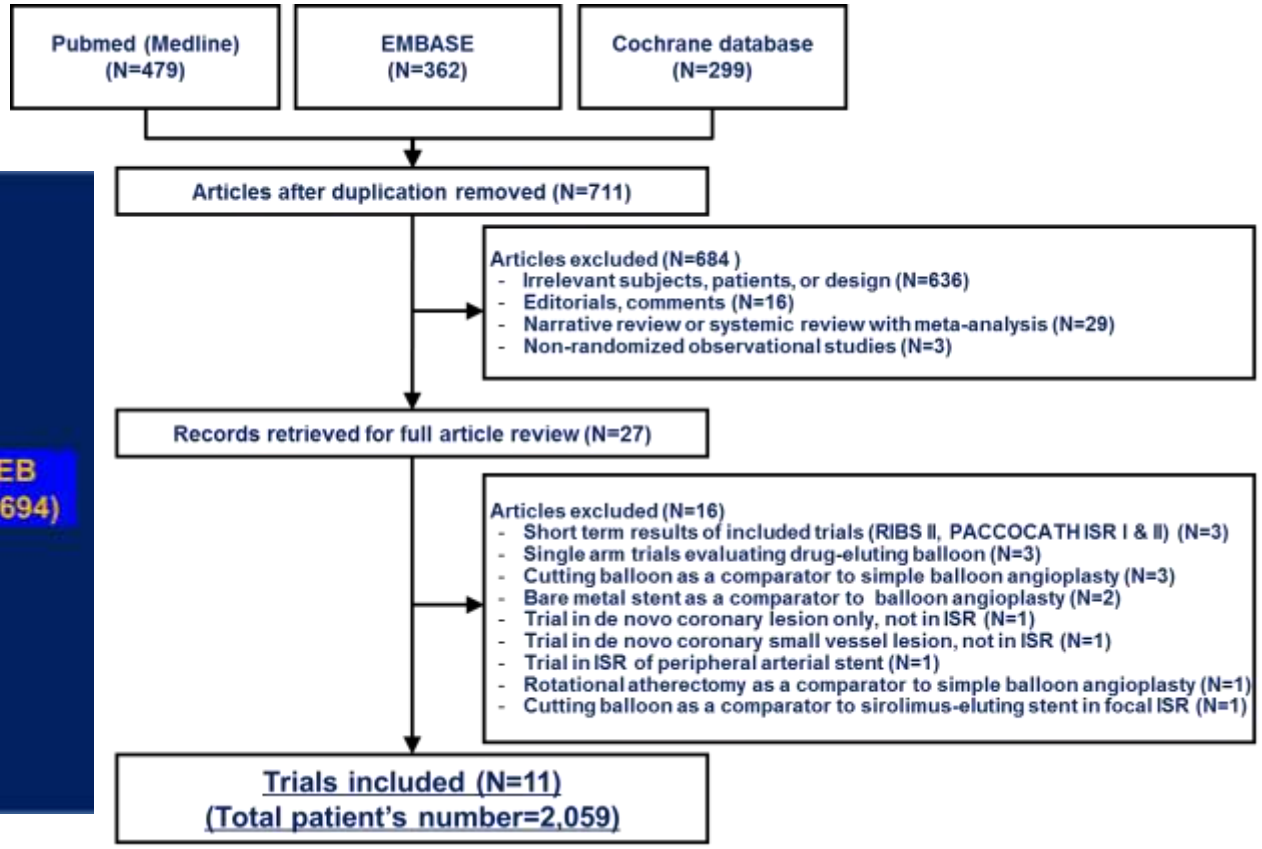
- **All references supporting this recommendation are based on trials comparing DEB with "old-fashioned" 1st generation DES**
  - Limits the applicability to the contemporary PCI practice

- **Optimal treatment strategy for ISR is still under debate.**

S Windecker et al. EHJ 2014, Guideline for Myocardial Revascularization

A Bayesian Network Meta-Analysis Compared the Efficacy and Safety of DEB, DES, and POBA





Lee JM, Park J,, Kim HS. J Am Coll Cardiol interv, 2015

Included Trials - Characteristics

Trial (Year)	Treatment and Patients number (Total patients number 1,862)			BMS or DES ISR	Type of Device		DAPT protocol	CAG F/U	Clinical F/U
	DEB (N=672)	DES (N=694)	POBA (N=496)		DEB	DES			
ISAR-DESIRE (2005)	N/A	200	100	BMS ISR	N/A	Cypher, Taxus	6M	6M	1Y
RIBS-II (2008)	N/A	76	74	BMS ISR	N/A	Cypher	9M	9M	4Y
PEPCAD-II (2009)	66	65	N/A	BMS ISR	Sequent Please	Taxus Liberte	3M in DEB, 6M in DES	6M	1Y
Habara et al. (2011)	25	N/A	25	DES ISR	Sequent Please	N/A	3M (recommended) → 6M (all patient)	6M	6M
ISAR-DESIRE 3 (2012)	137	131	134	DES ISR	Sequent Please	Taxus Liberte	6M	6-8M	1Y
PEPCAD-DES (2012)	72	N/A	38	DES ISR	Sequent Please	N/A	6M	6M	6M
PACCOCATH-ISR I&II Pooled Analysis (2012)	54	N/A	54	96% BMS ISR 4% DES ISR	PACCOCATH	N/A	1M	6M	5Y
CRISTAL (2012)	N/A	136	61	58% BMS ISR 42% DES ISR	Sequent Please	Cypher Select	3M	6M	6M
Habara et al. (2013)	136	N/A	71	58% BMS ISR 42% DES ISR	Sequent Please	N/A	3M	6M	6M
PEPCAD China ISR (2014)	109	106	N/A	DES ISR	Sequent Please	Taxus Liberte	12M	9M	1Y
RIBS V (2014)	95	94	N/A	BMS ISR	Sequent Please	Xience Prime	3M for DEB, 1Y for DES	6-9M	1Y

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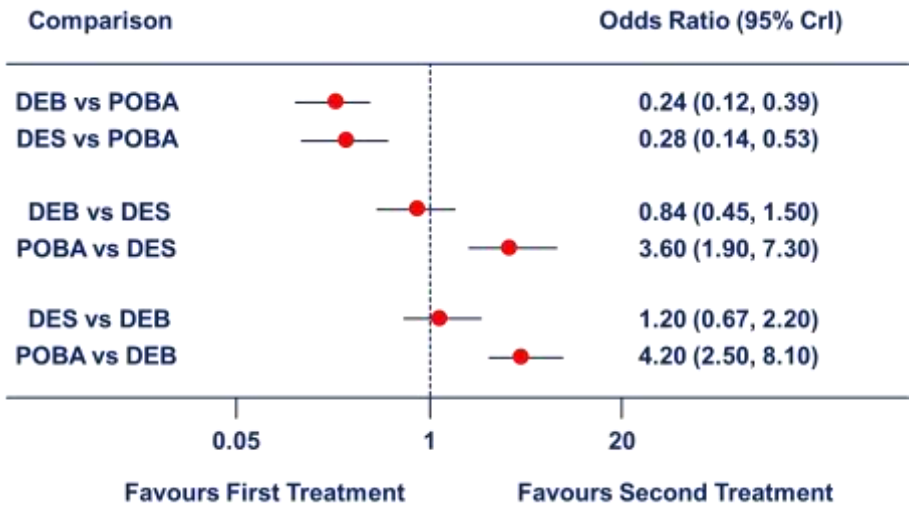
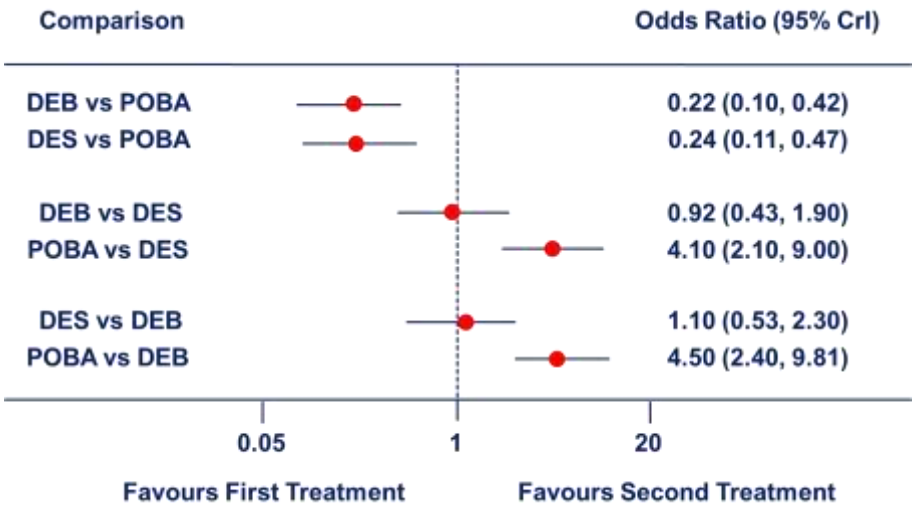
Efficacy and Safety Endpoints

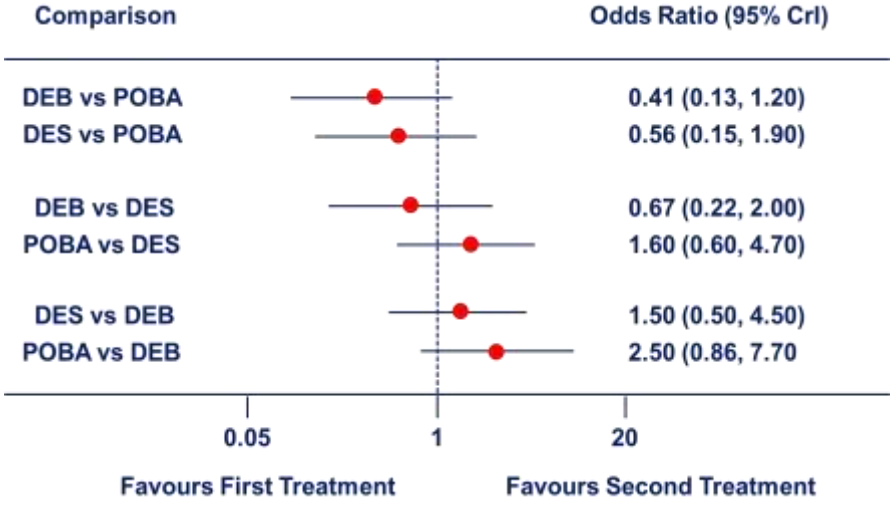
MACE



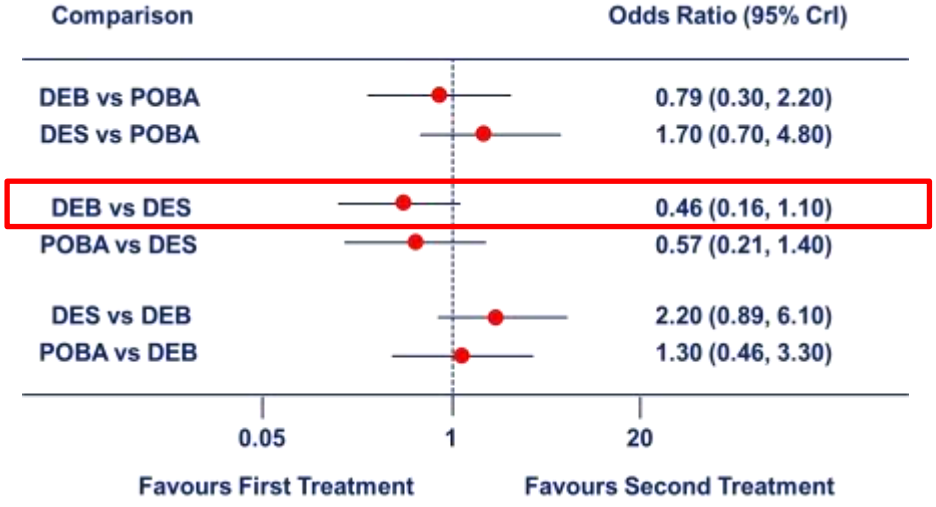
Target Lesion Revascularization



All-Cause Mortality



Myocardial Infarction (Any)



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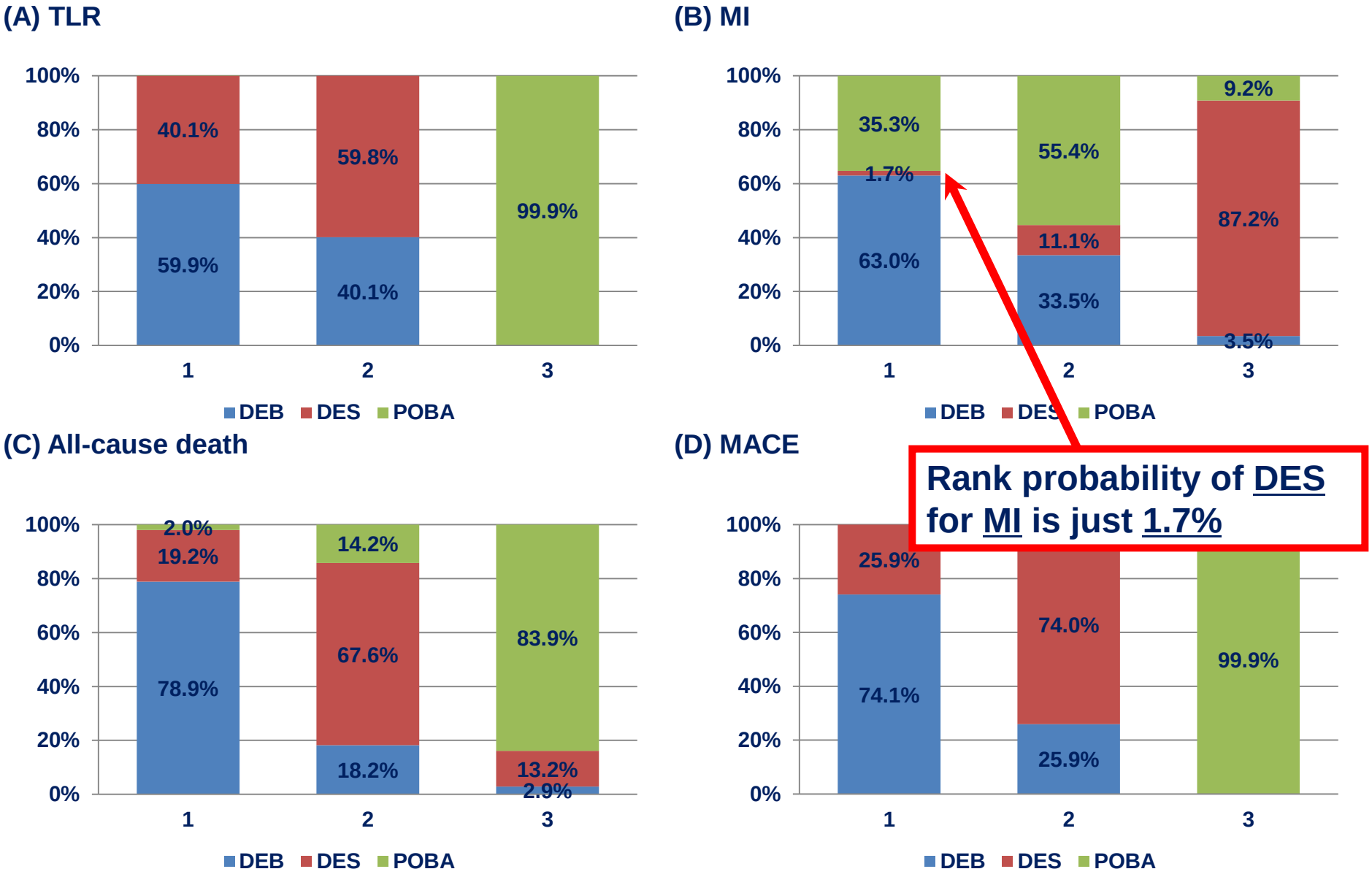
Rank Probability for Clinical Outcomes

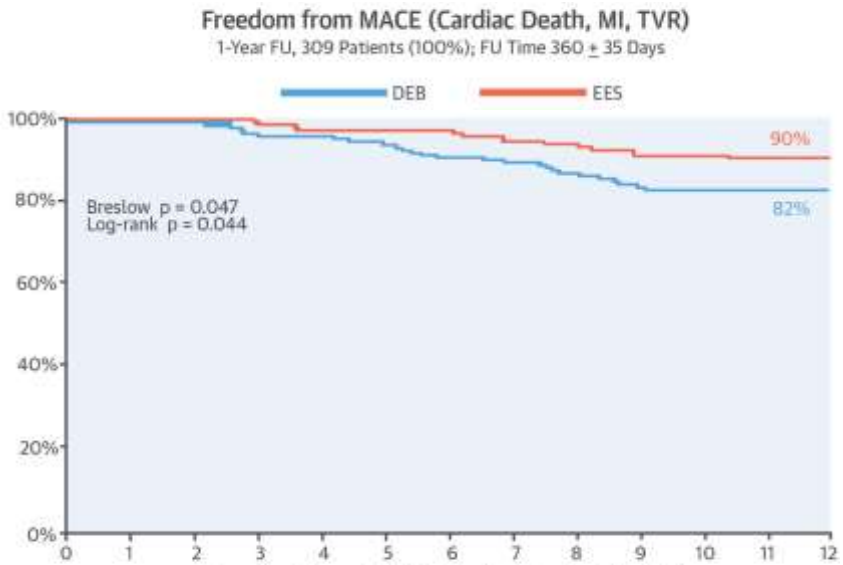


Lee JM, Park J,, Kim HS. J Am Coll Cardiol interv, 2015

Summary of Network Meta-analysis Findings

- Our results showed superior efficacy of DEB and DES, compared with POBA, and similar efficacy between DEB and DES.
- However, in terms of safety, DES showed lowest rank probability for the risk of MI.
- DEB showed marginal benefit in the risk of MI, compared with 1st generation DES.

The Most Recent RIBS-IV RCT
DEB vs. Xience for DES-ISR



Xience showed superior clinical and angiographic efficacy

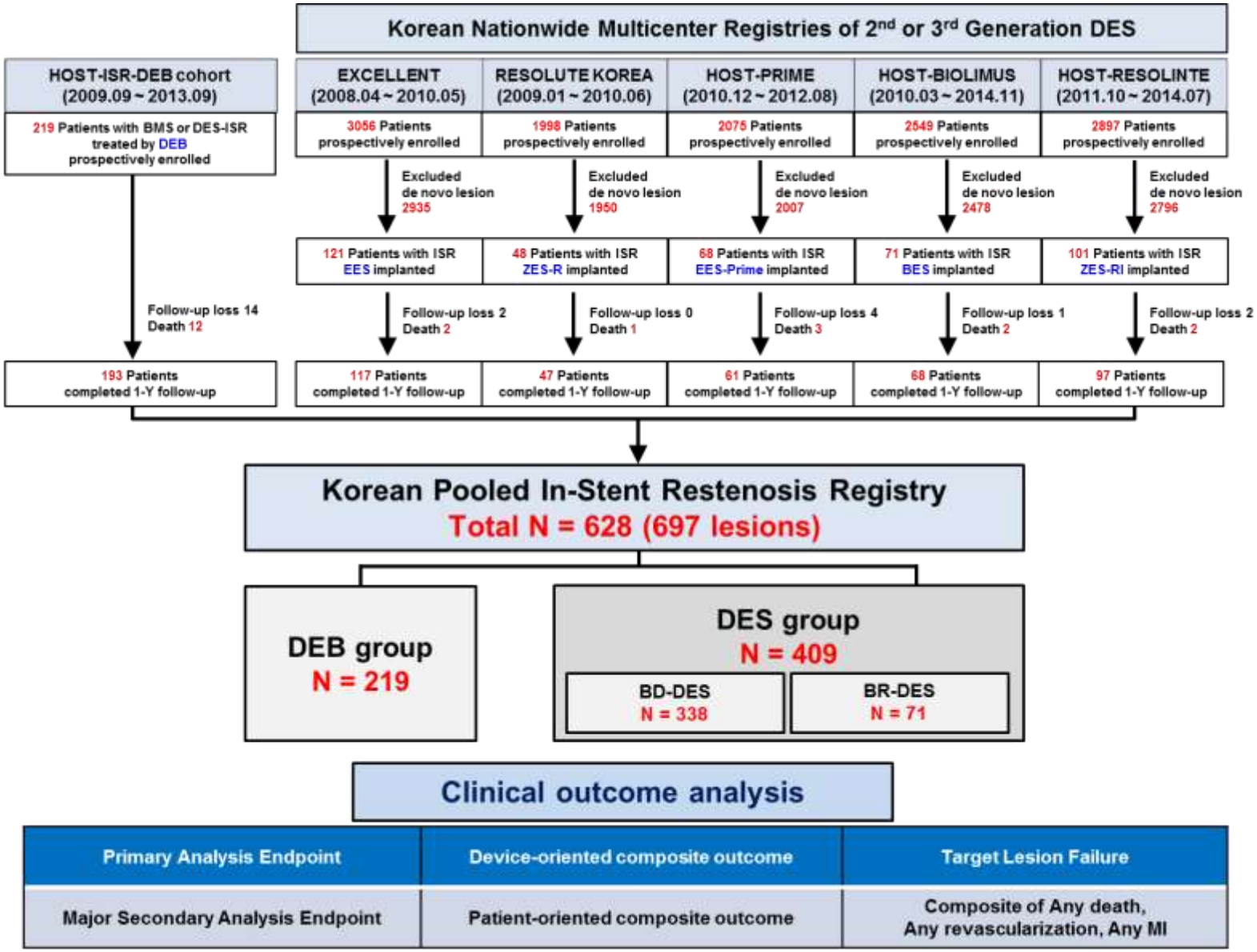
But, clinical safety was still equivalent between DEB and EES

1) **In patients with high clinical and lesion character ?**
   e.g. ACS presentation, small vessel, long lesion, total occlusion
2) **In other types of DES as Treatment option ?**
   e.g. ZES, bioresorbable polymer-coated DES
3) **There have been scarce evidence for DES-ISR, except RIBS-IV.**

Therefore, further studies with more generalizability are needed.

F. Alfonso et al. JACC 2015

DEB vs. Newer generation DES



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Baseline Clinical Characteristics

Characteristics (per patient)	**DEB (N = 219)**	**DES (N = 409)**	***P***	**Standardized Differences**	
				Before IPW	**After IPW**
Age, years	66.2 ± 9.9	65.3 ± 10.1	0.272	9.8958	6.1703
Men	140 (63.9%)	288 (70.4%)	**0.096**	**14.2807**	**-8.0810**

Patients had CKD in 28.3%, and LV dysfunction in 15.1%
Presented with ACS 55.1%, with AMI 16.9%

Represent unselected patients including high-risk clinical profiles

Prior congestive heart failure	22 (10.0%)	16 (3.9%)	**0.002**	**25.6742**	**0.0369**
LV dysfunction (EF <50%)	38 (17.4%)	57 (13.9%)	0.741	-2.8795	6.6088
Present with ACS	102 (46.6%)	244 (59.7%)	**0.001**	**-26.3819**	**-0.6797**
Present with AMI	24 (11.0%)	82 (20.0%)	**0.004**	**-26.8141**	**-12.7701**
Multi-vessel disease	168 (76.7%)	243 (59.4%)	**< 0.001**	**38.1949**	**-12.0571**

Baseline Angiographic Characteristics

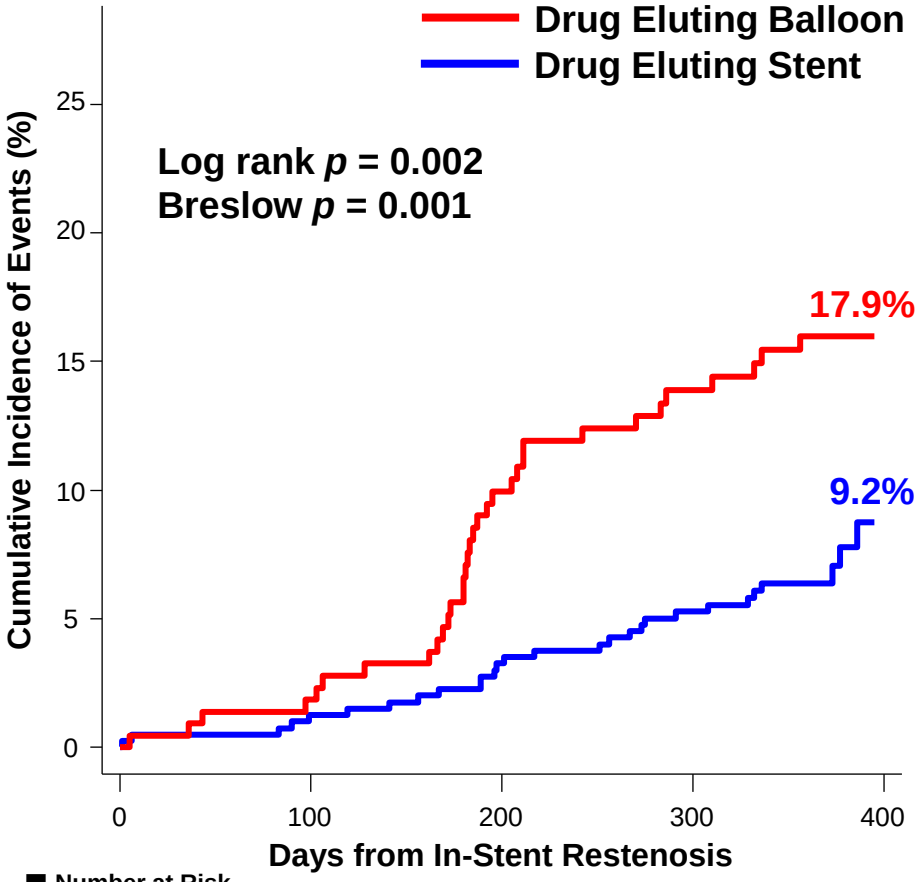
Characteristics (per lesion)	DEB (N = 265)	DES (N = 432)	*P*	Standardized Differences	
				Before IPW	After IPW
ISR in left main artery	16 (6.0%)	30 (6.9%)	0.196	-3.6754	-3.0770
BMS	17 (6.4%)	69 (16.0%)			
DES	248 (93.6%)	363 (84.0%)			
Type of inserted stent			N/A	-	-
Biodurable polymer DES	-	359 (83.1%)			
Bioresorbable polymer DES	-	73 (16.9%)			

Left main ISR in 6.6% of total lesions
Small vessels in 17.2%, Long lesions in 28.0%, DES-ISR 87.7%

Included complex lesions with high risk of adverse outcomes, reflecting the real-world contemporary practice

Target Lesion Failure
Patient-Oriented Composite Outcome

(A) Target Lesion Failure†

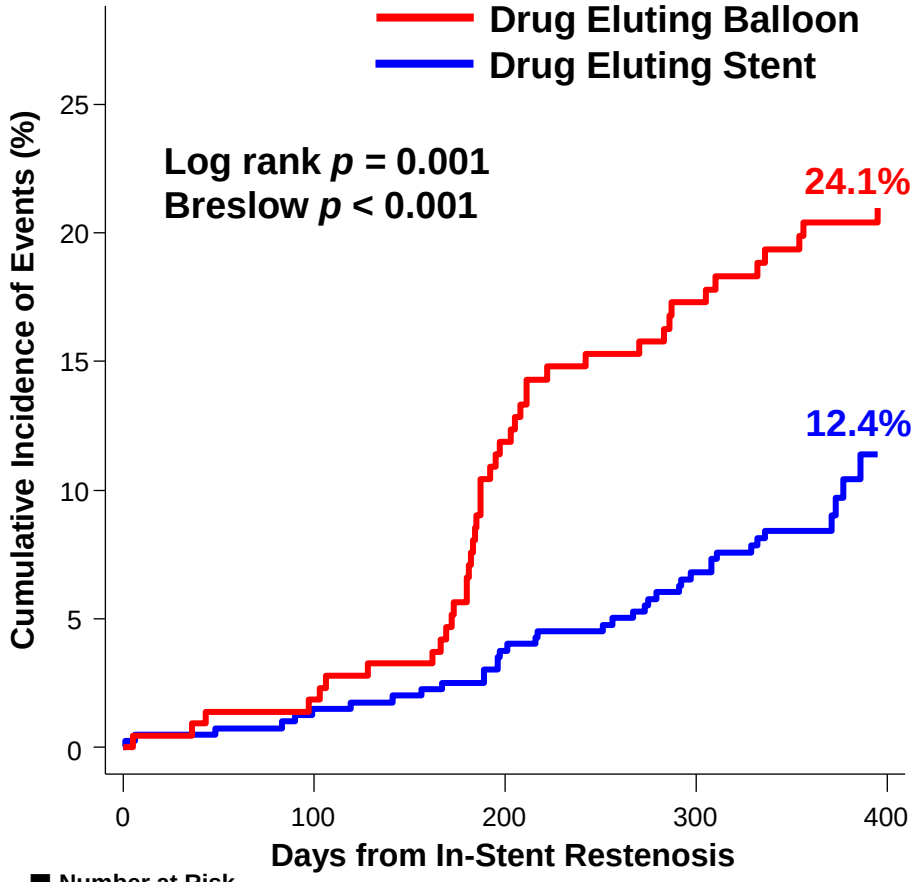


■ Number at Risk

DEB	219	211	187	168	164
DES	409	394	386	372	365

† Composite of cardiac death, target-vessel MI, and clinically-driven target lesion revascularization

(B) Patient-Oriented Composite Outcomes‡



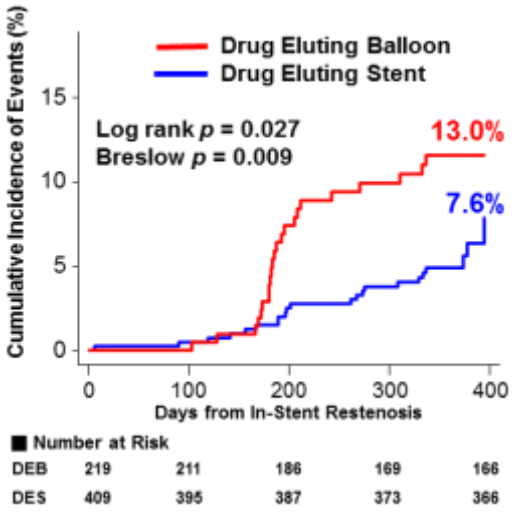
■ Number at Risk

DEB	219	211	183	161	154
DES	409	392	383	365	355

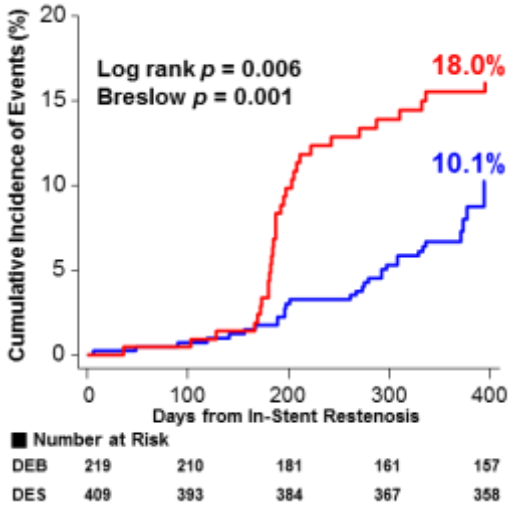
‡ Composite of all-cause death, all-cause MI, and any repeat revascularization

Individual Outcomes: Efficacy

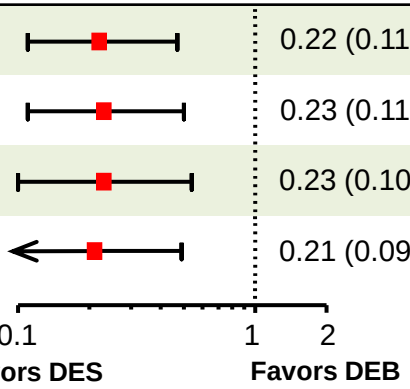
Target Lesion Revascularization



Any Revascularization



	DEB (N = 219)	DES (N = 409)	IPW adjusted HR (95% CI) of DES insertion	*P* value
Target lesion failure	17.9% (33)	9.2% (30)	0.22 (0.11 - 0.47)	**< 0.001**
Any revascularization	18.0% (32)	10.1% (31)	0.23 (0.11 - 0.50)	**< 0.001**
Clinically-driven TVR	14.0% (25)	8.8% (27)	0.23 (0.10 - 0.54)	**< 0.001**
Clinically-driven TLR	13.0% (23)	7.6% (23)	0.21 (0.09 - 0.49)	**< 0.001**



Superior efficacy of newer generation DES over DEB
Mainly driven by the lower rates of TLR in DES group

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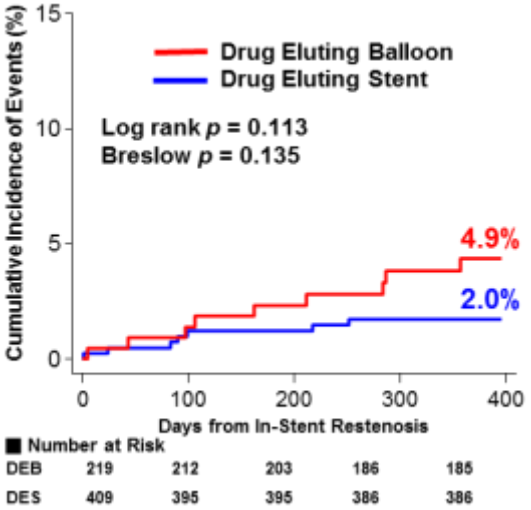
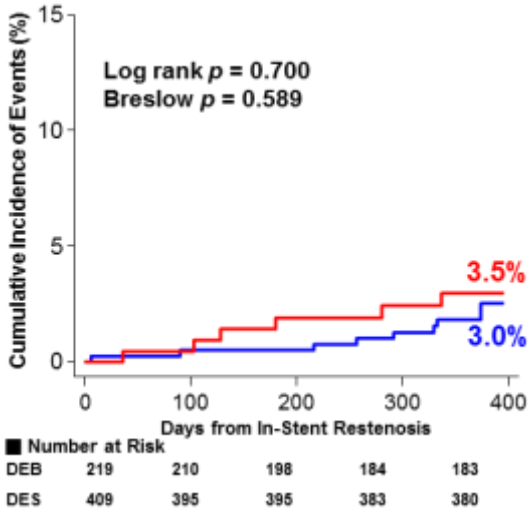
Individual Outcomes: Safety

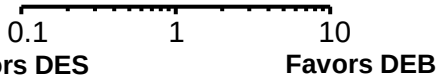
Cardiac Death



Any Myocardial Infarction



	DEB (N = 219)	DES (N = 409)	IPW adjusted HR (95% CI) of DES insertion	*P* value
All-cause mortality	7.4% (12)	3.0% (10)	0.50 (0.18 - 1.39)	0.182
Cardiac death	4.9% (9)	2.0% (8)	0.49 (0.16 - 1.49)	0.209
Any MI	3.5% (6)	3.0% (9)	1.89 (0.59 - 6.03)	0.286
Target-vessel MI	3.0% (5)	2.5% (7)	1.95 (0.53 - 7.13)	0.313
Definite/probable ST	1.0% (2)	2.3% (6)	3.33 (0.55 - 20.4)	0.192



Comparable clinical safety between DES and DEB groups
But,
DES showed numerically 2.5 folds higher rates of definite or probable ST

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How to Optimize DEB treatment?

Angiographically Diagnosed In-Stent Restenosis
Treated by Paclitaxel-coated DEB (2009.9 ~ 2014.8)
323 Lesions (269 Patients)

→ **14 Lesions (13 Patients) Were Excluded d/t BMS ISR**

309 Lesions (256 Patients) of DES ISR
Median Follow-Up Duration of 761.0 Days
8.2% Lost to Follow-Up (21 Patients)

- **Angiographic follow-up at 6-month visit**
  - Not routinely mandated but depended on physician's discretion
- **Quantitative coronary analysis (QCA) of index DEB procedures**
  - Baseline and final images **+ Images after lesion preparation (POBA)**

* BMS, bare-metal stents

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How to Optimize DEB treatment?

Independent Factors Predicting TLF after DEB

Results of multivariable Cox regression with stepwise selection

	Hazard Ratio (95% CI)	*P*
Procedure-related factors		
Residual %DS after lesion preparation (per 1%↑)	**1.021**	1.014 – 1.028
DEB-to-stent ratio (per 0.1↑)	**0.778**	0.608 – 0.994
Total inflation time of DEB (per 1 second↑)	**0.993**	0.990 – 0.996
Patient-related factors		
Peripheral vascular disease	2.274	1.574 – 3.285
Diabetes mellitus	1.687	1.290 – 2.206
Prior history of myocardial infarction	1.226	1.052 – 1.429
Hypertension	1.184	1.012 – 1.385
Lesion-related factors		
Complex (type B2 or C) lesion	1.737	1.198 – 2.517
Long lesion (≥ 28 mm)	1.272	1.045 – 1.549

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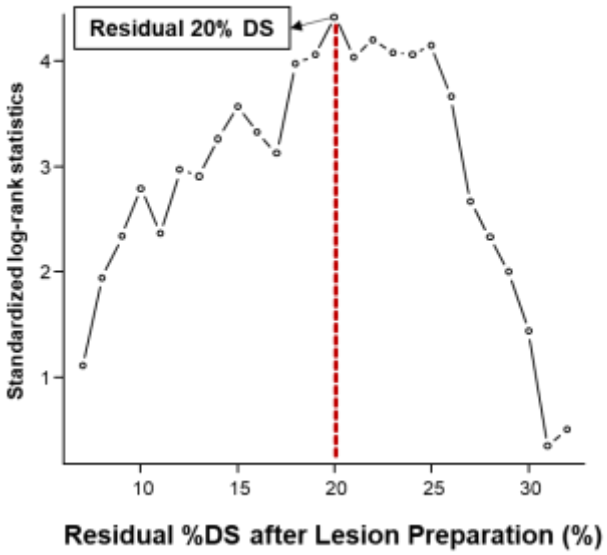
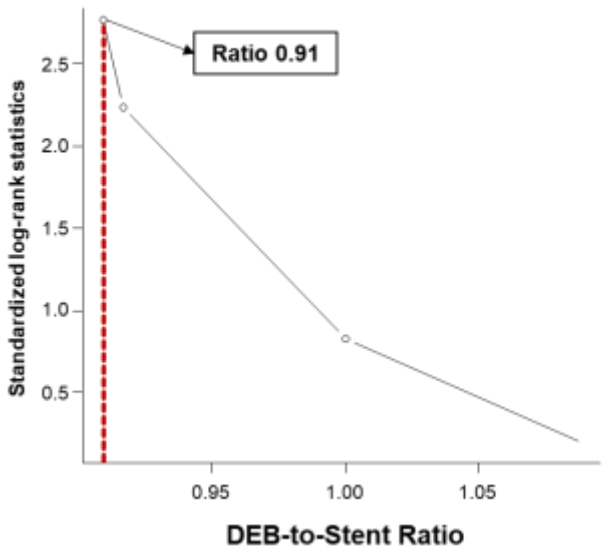
Optimal Cut-Off Values for Individual Procedure-related Factors

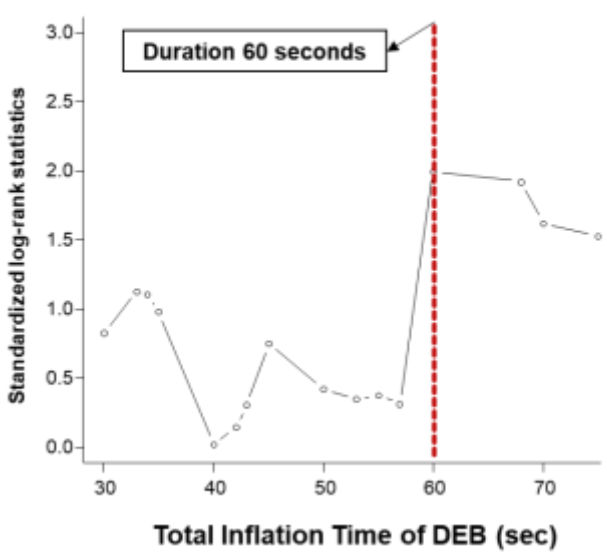
A. Residual %DS after Lesion Preparation



B. DEB-to-Stent Ratio



C. Total Inflation Time of DEB



Optimal residual %DS after lesion preparation : 20%

Optimal DEB-to-stent ratio : 0.91

Optimal total inflation time of DEB : 60 sec

Were the best cut-off values to discriminate the occurrence of TLF

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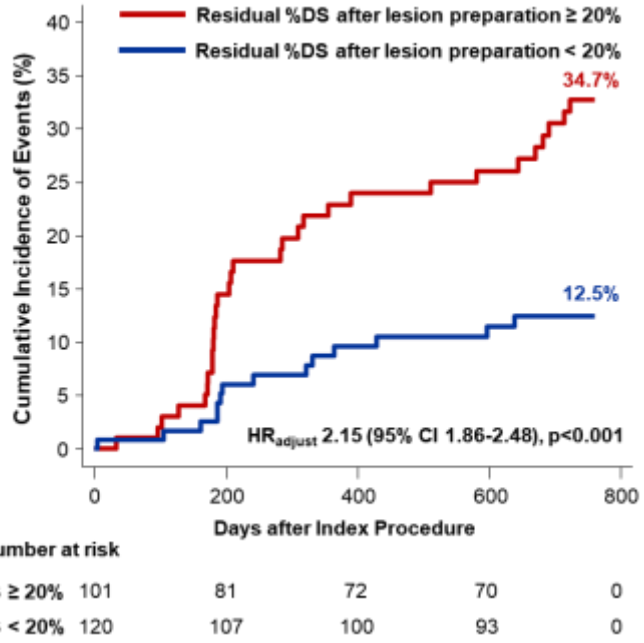
Composite and Individual Clinical Outcomes by Residual %DS after Lesion Preparation

Target Lesion Failure at 2-yr



	Residual %DS after lesion preparation		Multivariable-adjusted Hazard ratio (95% CI)	*P* value
	≥ 20% (N = 101)	< 20% (N = 120)		
Target lesion failure	34.7% (31)	12.5% (14)	**2.15 (1.86-2.48)**	**< 0.001**
Target vessel MI	6.4% (5)	0.0% (0)	12.5 (0.53-293.7)	**N/A**
Clinically-driven TVR	31.4% (27)	12.9% (14)	**2.44 (1.84-3.22)**	**< 0.001**
Clinically-driven TLR	30.4% (26)	10.2% (11)	**2.62 (2.04-3.38)**	**< 0.001**

Hazard ratios were calculated with residual %DS < 20% as a reference group
*** %DS, percent diameter stenosis; TVR/TLR, target vessel/lesion revascularization**

Superior efficacy outcomes in group with residual %DS < 20% than with residual %DS ≥ 20%, Mainly driven by the lower rates of TLR

Infers importance of proper lesion preparation until residual %DS < 20%

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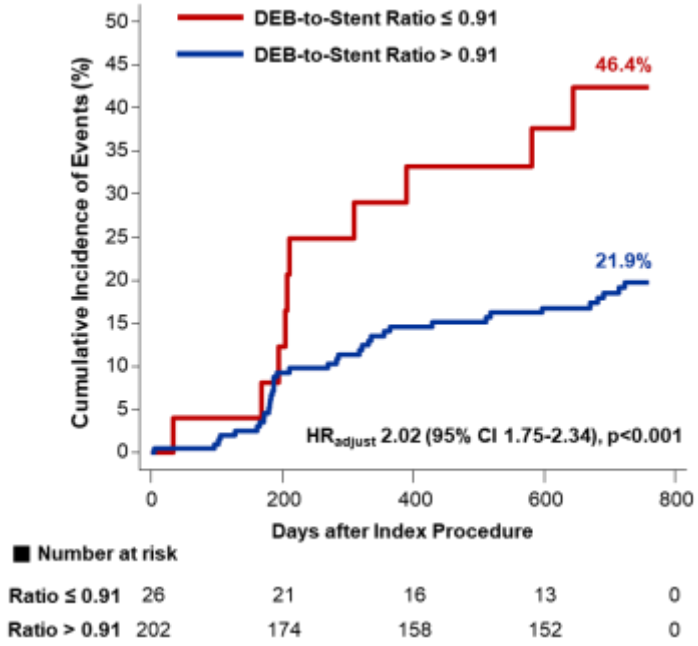
Composite and Individual Clinical Outcomes by DEB-to-Stent Ratio

Target Lesion Failure at 2-yr



	DEB-to-stent ratio		Multivariable-adjusted Hazard ratio (95% CI)	*P* value
	≤ 0.91 (N = 26)	> 0.91 (N = 202)		
Target lesion failure	46.4% (10)	21.9% (38)	**2.02 (1.75-2.34)**	**< 0.001**
Target vessel MI	4.0% (1)	3.2% (5)	1.52 (0.18-12.8)	**0.703**
Clinically-driven TVR	46.4% (10)	19.4% (32)	**2.33 (1.95-2.78)**	**< 0.001**
Clinically-driven TLR	42.2% (9)	18.3% (30)	**2.12 (1.76-2.55)**	**< 0.001**

Hazard ratios were calculated with DEB-to-stent ratio > 0.91 as a reference group
*** TVR/TLR, target vessel/lesion revascularization**

Superior efficacy outcomes in group with DEB-to-stent ratio > 0.91 than with ratio ≤ 0.91, Mainly driven by the lower rates of TLR

Infers importance of sufficient dilation of DEB with DEB-to-stent ratio > 0.91

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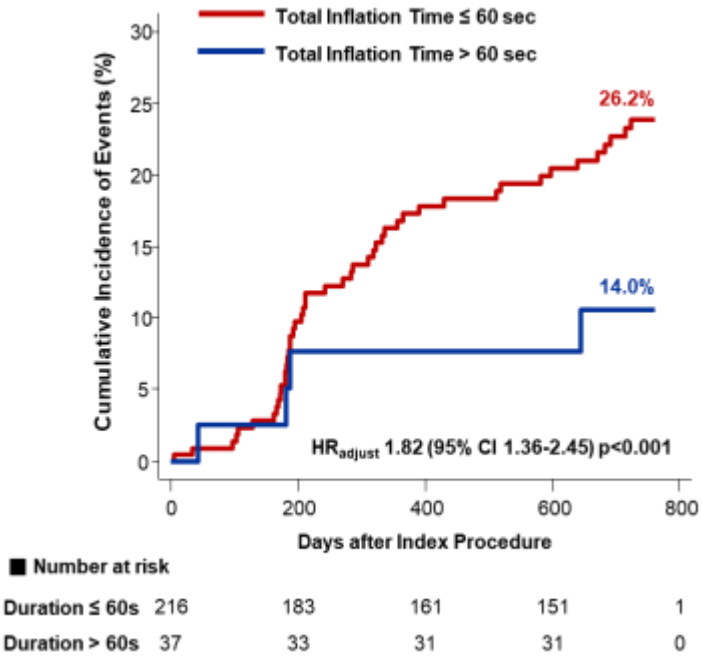
Composite and Individual Clinical Outcomes by Total Inflation Time of DEB

Target Lesion Failure at 2-yr



	Total inflation time of DEB		Multivariable-adjusted Hazard ratio (95% CI)	*P* value
	≤ 60 sec (N = 216)	> 60 sec (N = 37)		
Target lesion failure	26.2% (48)	14.0% (4)	**1.82 (1.36-2.45)**	**< 0.001**
Target vessel MI	3.5% (6)	0.0% (0)	1.11 (0.05-26.5)	**0.948**
Clinically-driven TVR	23.5% (41)	17.4% (5)	**1.83 (1.37-2.45)**	**< 0.001**
Clinically-driven TLR	22.5% (39)	11.5% (3)	**2.33 (1.87-2.90)**	**< 0.001**

Hazard ratios were calculated with inflation time ≤ 60 sec as a reference group
*** TVR/TLR, target vessel/lesion revascularization**

Superior efficacy outcomes in group with total inflation time > 60s than with inflation time ≤ 60s, mainly driven by the lower rates of TLR

Infers importance of prolonged inflation of DEB until total inflation time > 60 seconds

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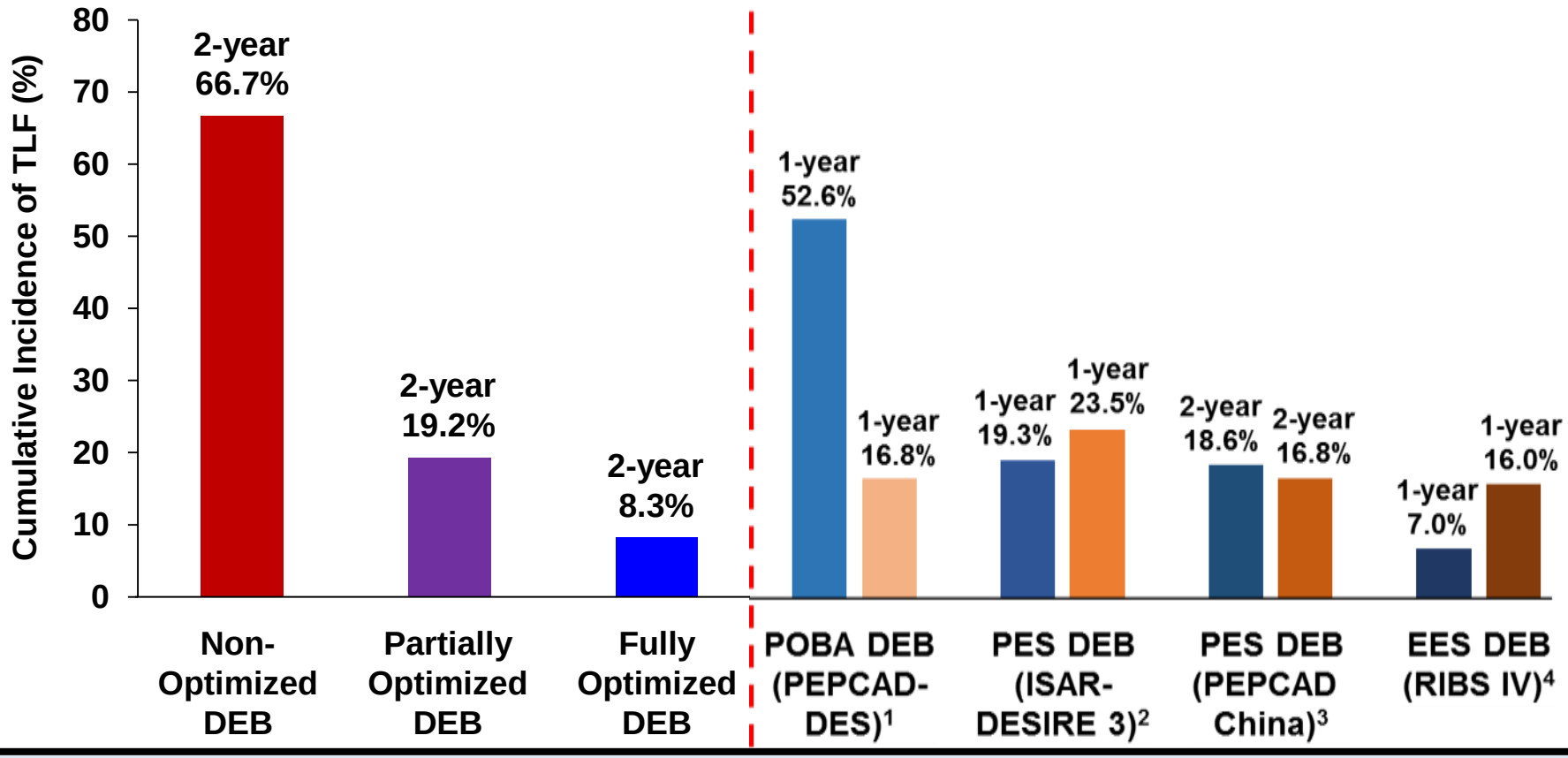
Incidence of Target Lesion Failure by Combined Procedure-related Factors



2-year TLF rate in fully-optimized DEB group was 8.3%, Similar to or even better than 1st or 2nd generation DES groups in previous ISR trials

1. Alfonso et al. JACC 2015

"Four Major Procedural factors" to Enhance Clinical Outcomes after DEB treatment

1) **Perfect lesion preparation before DEB treatment: Residual %DS < 20%**
   - Makes the lesion easy to be coated with drug

2) **Balloon-to-stent ratio : beyond at least 0.9**
   - Increases the contact area to maximize drug delivery
   - Also warrants the optimal lesion preparation

3) **Total Inflation Time of DEB : beyond at least 60 seconds**
   - Increases the time and chance for drug to be delivered
   - Needs the **ischemic preconditioning before DEB treatment**

4) **Rapid delivery of DEB device : delivery time < 30 seconds**
   - Minimizes the amount of drug lost during delivery
   - May need additional supporting devices

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Summary and Conclusions

- Given the prognostic importance of ISR, optimal treatment strategy should be carefully selected.
- Newer generation DES showed superior clinical efficacy compared with DEB, especially in terms of repeat revascularization
- However, DES and DEB showed equivalent clinical safety, with marginal benefit of DEB for the risk of ST
- In order to maximize DEB results, procedural factors especially perfect lesion preparation, total inflation time, and DEB-to-stent ratio are important