



Safety and efficacy of latest generation drug-eluting stents and balloons - Promises and Pitfalls -

원광대학교 순환기내과

오 석 규

PTCA

- **Percutaneous Transluminal Coronary Angioplasty (PTCA)**
 - **Andreas Gruentzig (German radiologist)**
 - **16 September 1977, Zurich, Switzerland**
 - **Presented the results of his first four angioplasty cases at the 1977 AHA meeting**
- **Promise**
 - **Vessel opening and immediate symptomatic relief**
- **Pitfalls**
 - **Abrupt vessel closure**
 - **High restenosis rate : 30-60%**
 - : **Elastic recoil, negative remodeling, neointimal proliferation**

BMS

- **Intracoronary bare-metal stent (BMS)**
 - Developed by Palmaz and Schatz
 - Jacques Puel : first implantation of a stent in human
 - Toulouse, France, in March 1986
- **Promises**
 - To prevent **acute elastic recoil and negative remodeling**
 - Reduced MACE : repeat revascularization, restenosis, and reocclusion
- **Pitfalls**
 - Thrombotic stent occlusion
 - : Dual anti-platelet therapy with aspirin & thienopyridine
 - High restenosis rate (20-40%) : **neointima hyperplasia**

DES

Drug-eluting stent (DES)

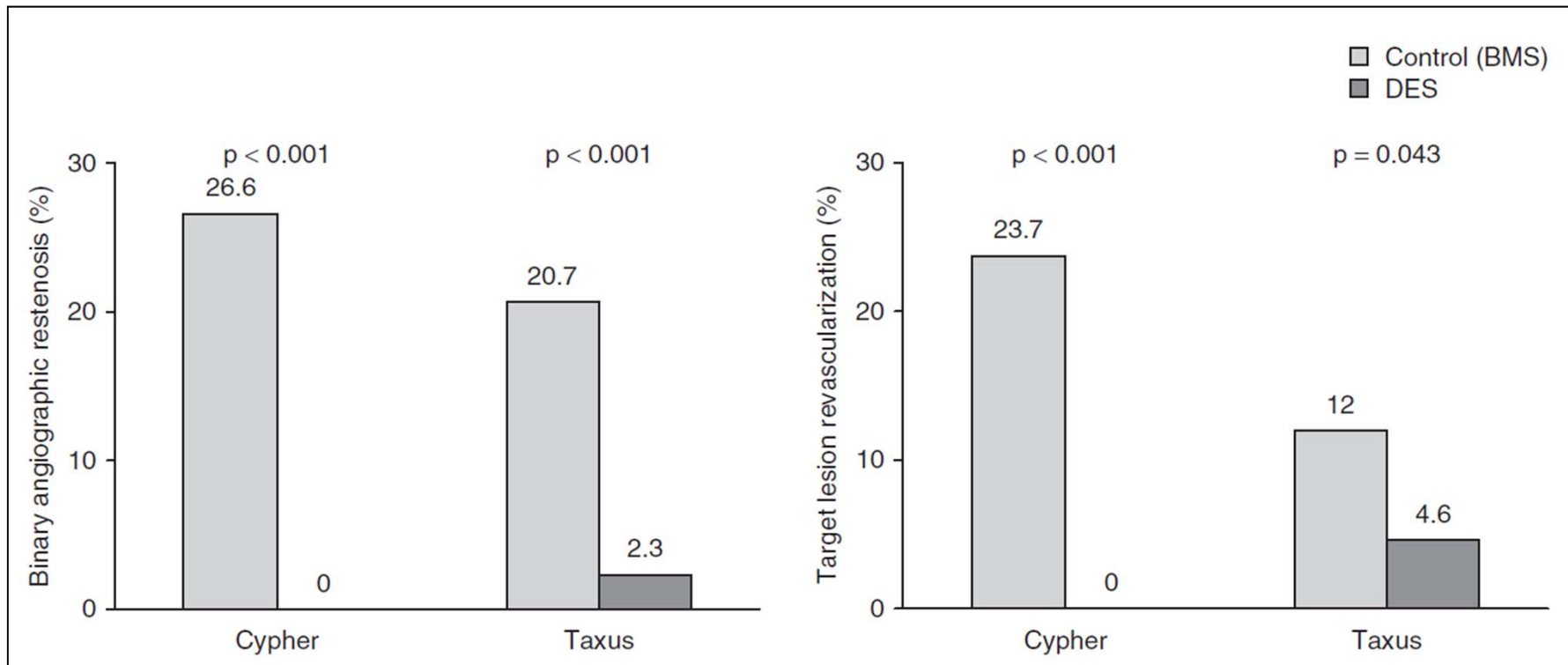
- **DES : most promising method to lower restenosis rate**
- **In April 2003, the US FDA approved the first DES**

1st generation DESs

- **Cypher : Sirolimus-Eluting Stent (SES)**
- **Taxus : Paclitaxel-Eluting Stent (PES)**

Efficacy of 1st generation DES

RAVEL and TAXUS-II



RAVEL : *N Eng J Med* 2002;346:1773-
TAXUS-II : *Circulation* 2003;108:788-

Efficacy of 1st generation DESs

SES trials

- **RAVEL**

N Eng J Med 2002;346:1773-

- **SIRIUS**

N Eng J Med 2003;349:1315-

- **E-SIRIUS**

Lancet 2003;362:1093-

- **C-SIRIUS**

J Am Coll Cardiol 2004;43:1110-

PES trials

- **TAXUS-I**

Circulation 2003;107:38-

- **TAXUS-II**

Circulation 2003;108:788-

- **TAXUS-IV**

N Eng J Med 2004;350:221-

- **TAXUS-V**

JAMA 2005;294:1215-

- **TAXUS-VI**

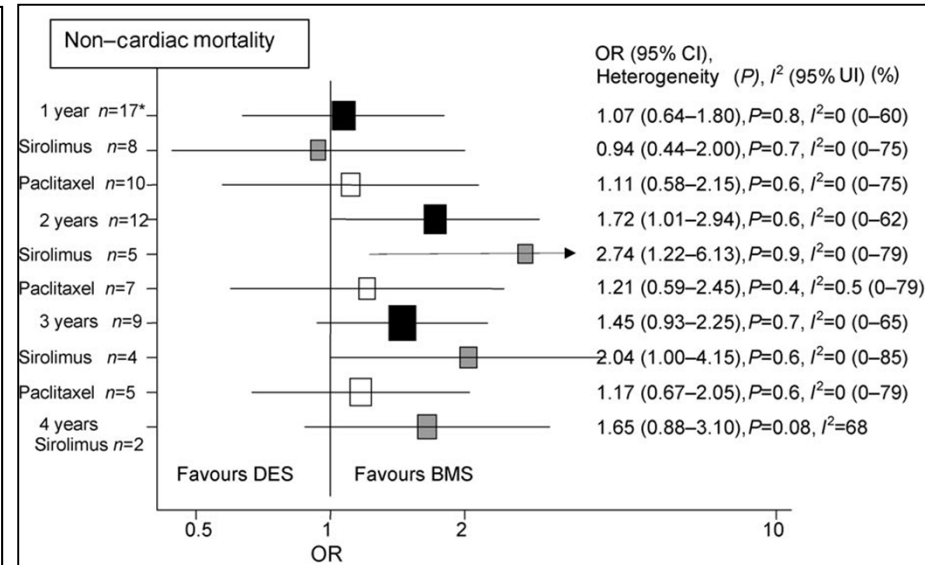
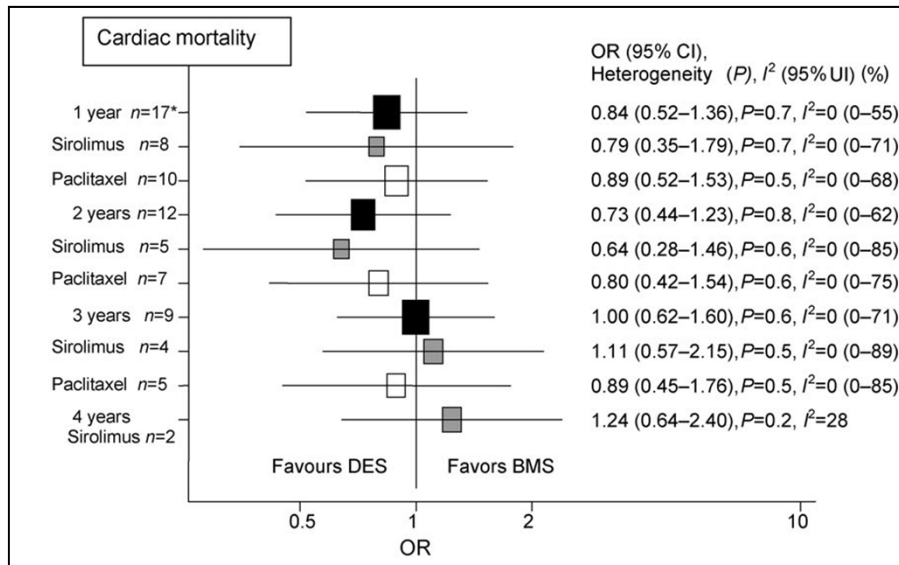
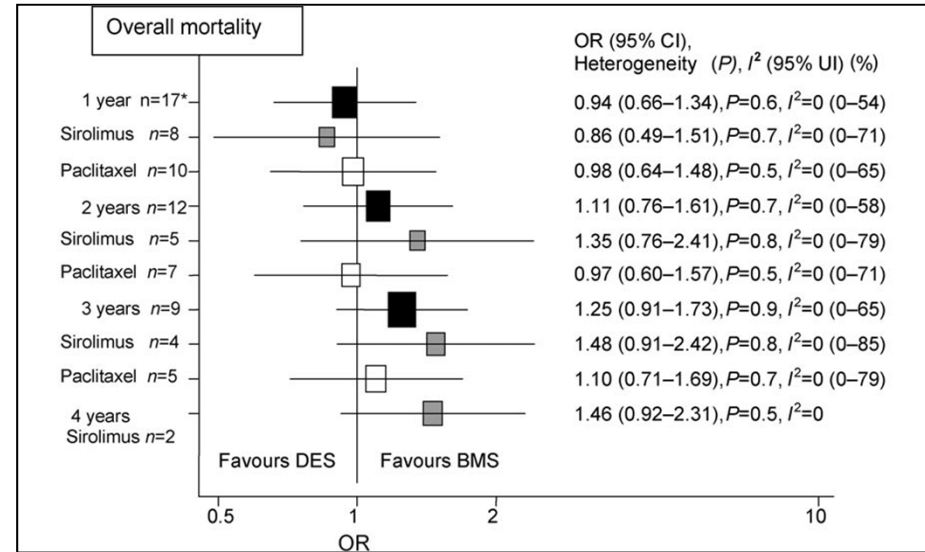
Circulation 2005;112:3306-

Efficacy of DES

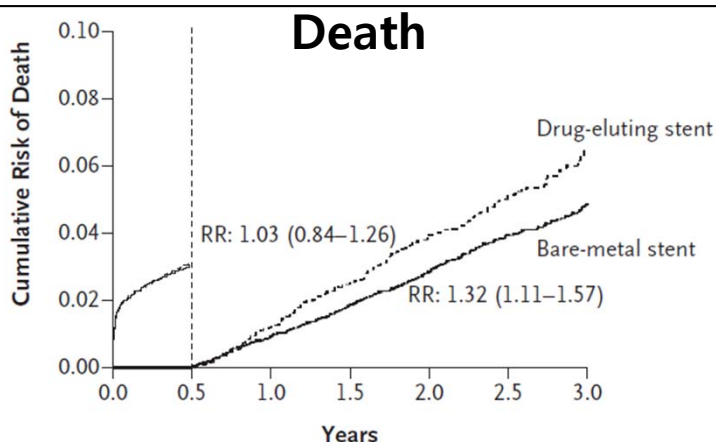
- **The target of DES technology is the minimization of neointimal hyperplasia**
- **Efficacy parameters**
 - **Target lesion revascularization (TLR)**
 - **Angiographic restenosis and late luminal loss**

Mortality of DES vs BMS

- 17 RCT
- >1 year of follow-up
- total 8221 pts

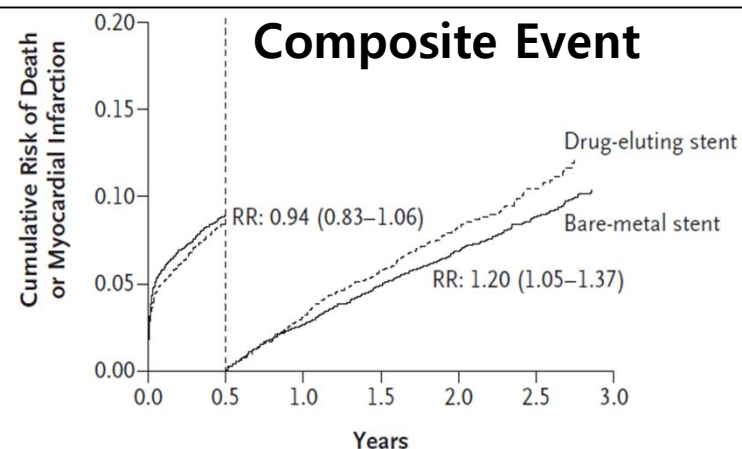


Long-term outcomes with DES *vs* BMS in Sweden : SCAAR study group



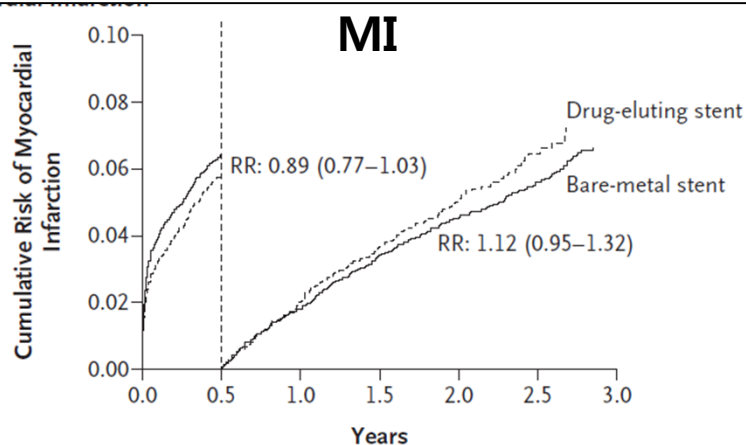
No. at Risk

Bare-metal stent	12,880	12,473	12,354	12,228	9298	5966	3199
Drug-eluting stent	5,770	5,605	5,541	5,471	3434	1777	626



No. at Risk

Bare-metal stent	12,880	12,473	12,146	9158	5810	3104	8
Drug-eluting stent	5,770	5,604	5,426	3378	1704	611	0



No. at Risk

Bare-metal stent	12,880	12,473	12,146	9158	5810	3104	8
Drug-eluting stent	5,770	5,604	5,426	3378	1704	611	0

- The long-term safety of DES needs to be ascertained in large, randomized trials
- Generalized, unselective use of DESs should be avoided

Safety of DES

- **Safety parameters**
 - Overall mortality
 - Myocardial infarction (MI)
 - **Stent thrombosis**
- **Efficacy parameters**

Safety and efficacy of 1st generation DESs

SES trials

- **RAVEL**

N Eng I J Med 2002;346:1773-

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N Eng I J Med 2003;349:1315-

- **E-SIRIUS**

Lancet 2003;362:1093-

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- **TAXUS-V**

JAMA 2005;294:1215-

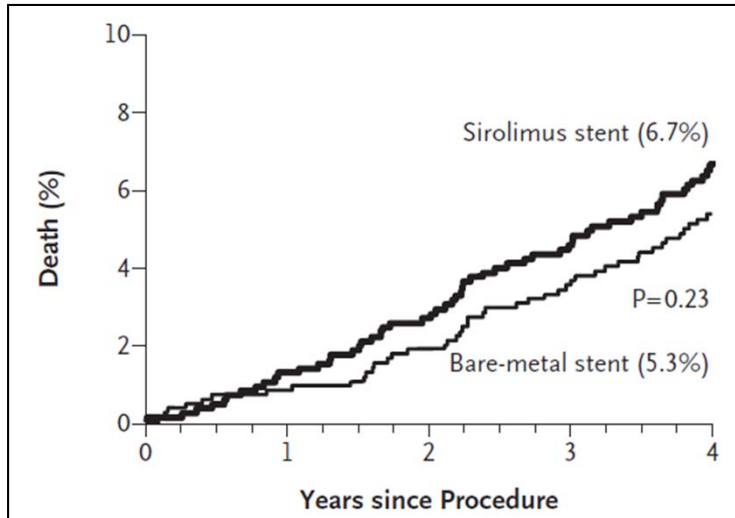
- **TAXUS-VI**

Circulation 2005;112:3306-

N Eng I J Med 2007;356:998-

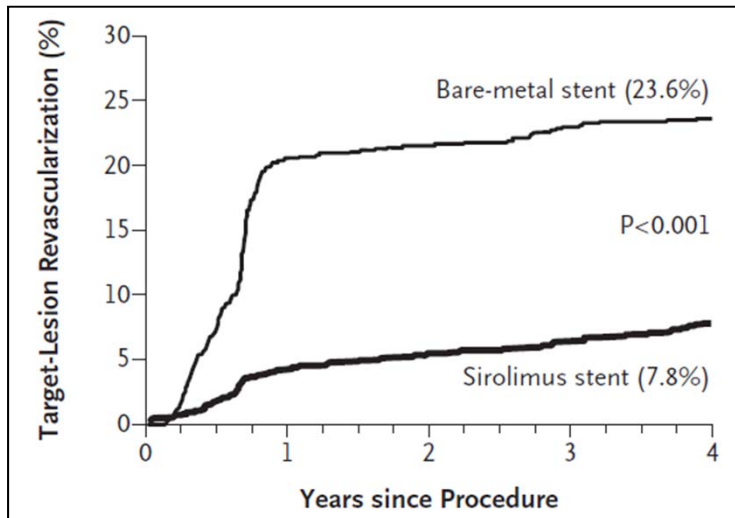
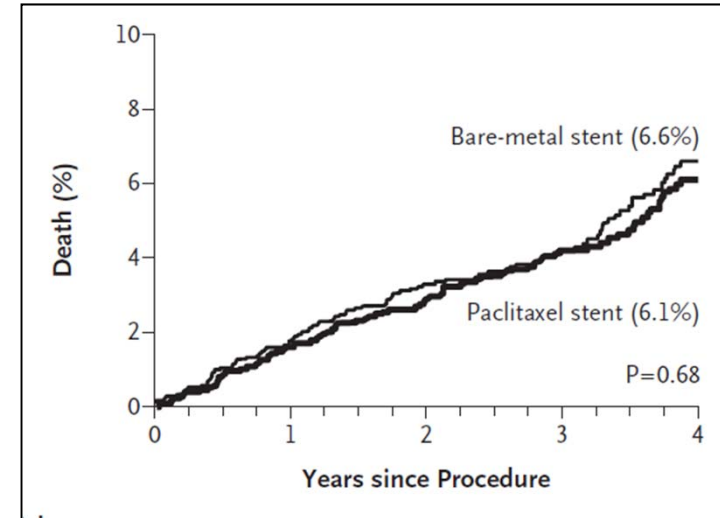
1st generation DESs vs BMS

SES

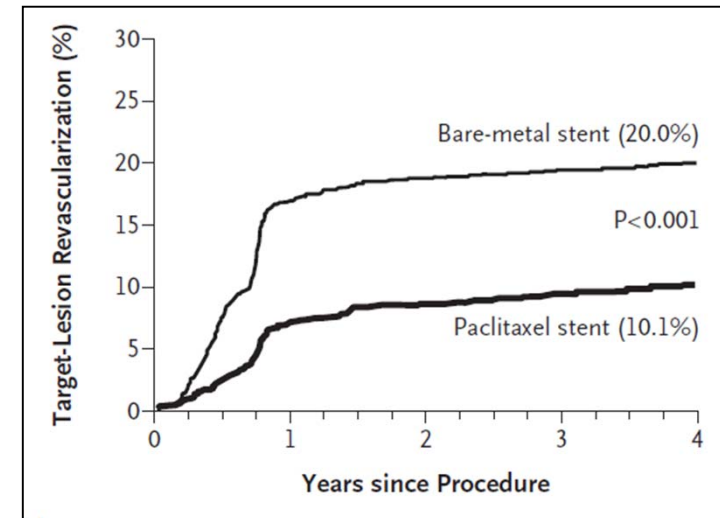


Death

PES

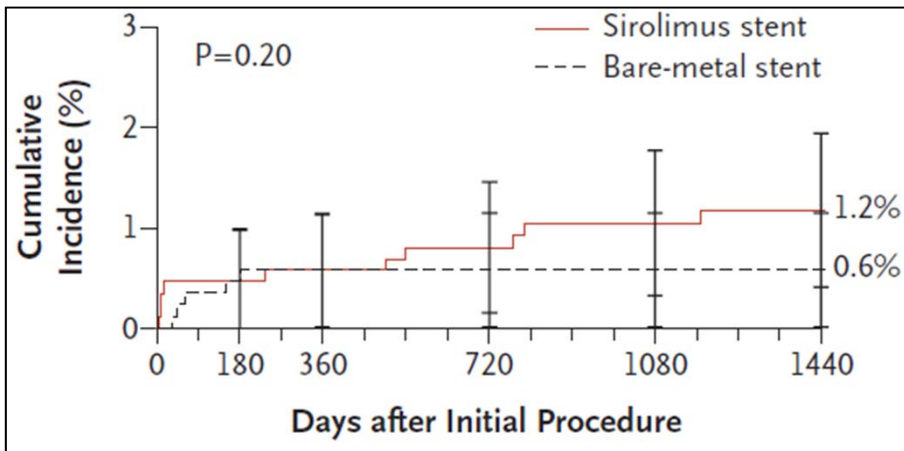


TLR

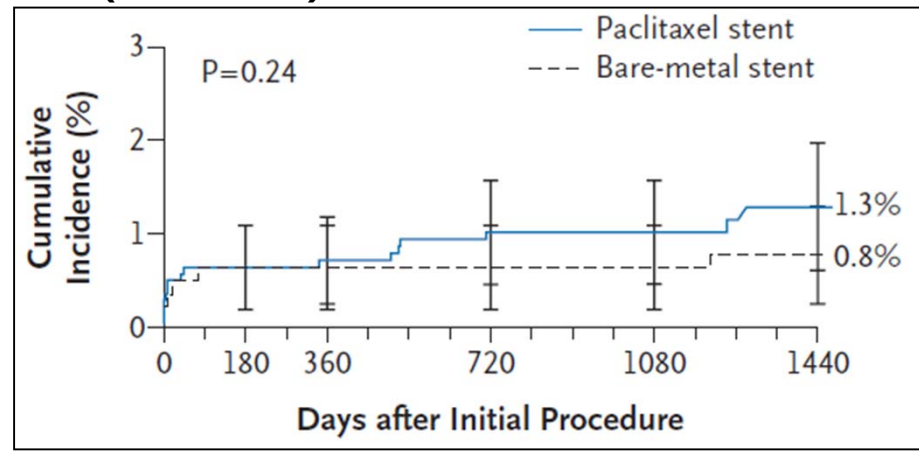


Stent thrombosis of DES vs BMS

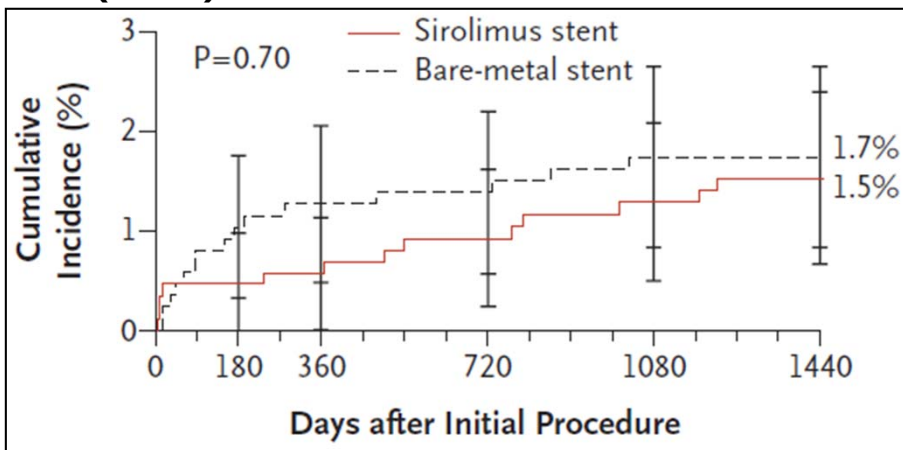
SES(Protocol)



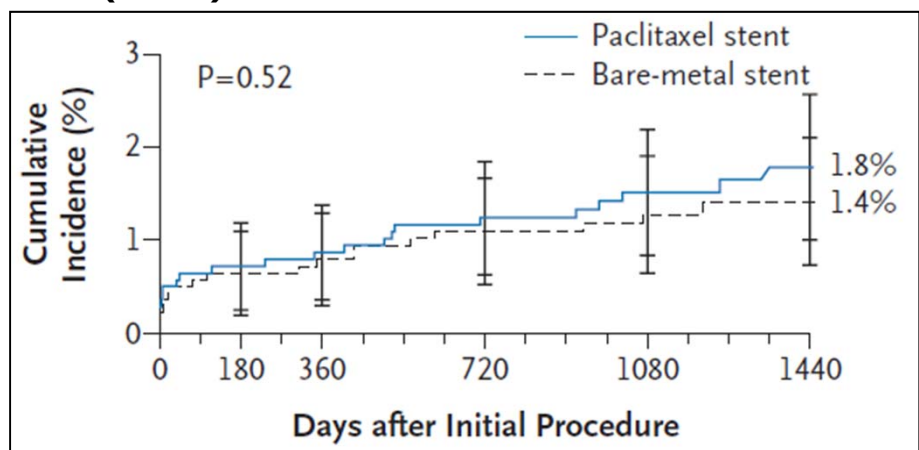
PES(Protocol)



SES(ARC)



PES(ARC)



ARC : definite or probable categories

N Eng J Med 2007;356:1020-

ARC definition of stent thrombosis

Term	Definition
Definite ST	The highest level of certainty Either angiographic or post-mortem evidence of thrombotic stent occlusion
Probable ST	Any unexpected death within 30 days of stent implantation, or any MI in the territories of the implanted stent irrespective of time
Possible ST	Any unexpected death beyond 30 days until the end of follow-up
Early ST	ST occurring in the first 30 days after stent implantation
Late ST	ST occurring between 1 month and 1 yr after stent implantation
Very late ST	ST occurring beyond 1 yr

ARC : Academic Research Consortium

Circulation 2007;115:2344-

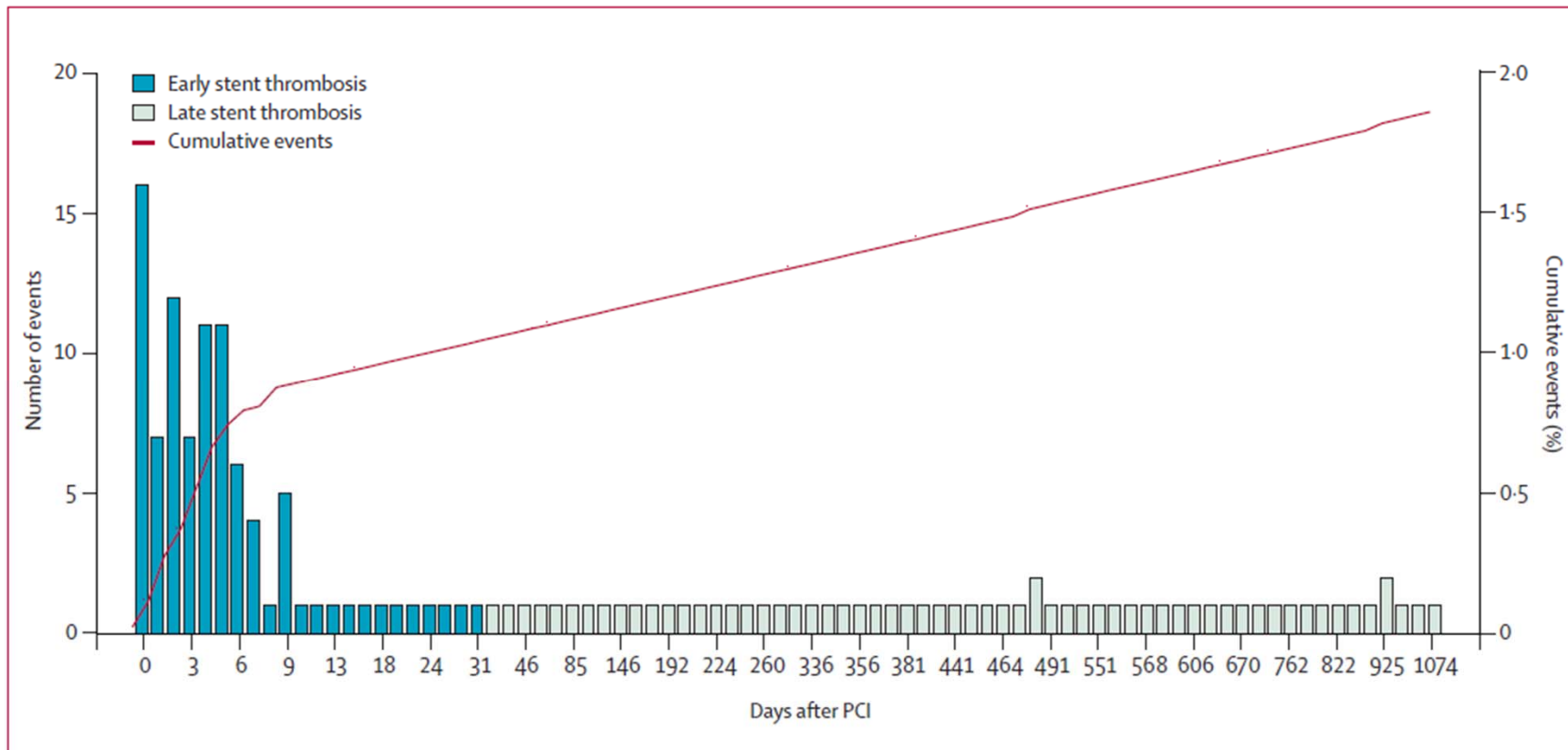
Stent thrombosis of DES vs BMS

	SES	BMS	P-value	PES	BMS	p-value
Stent thrombosis(definite and probable), %						
Early (0-30 d)	0.5	0.3		0.5	0.5	
Late (31-360 d)	0.1	1.0		0.4	0.3	
Very late (>360 d)	0.9	0.4		0.9	0.6	
All	1.5	1.7	0.7	1.8	1.4	0.52
Stent thrombosis (definite, probable, and possible), %						
Early (0-30 d)	0.5	0.3		0.5	0.5	
Late (31-360 d)	0.2	1.3		0.9	0.9	
Very late (> 360 d)	2.9	1.7		1.8	2.1	
All	3.6	3.3	0.8	3.2	3.5	0.84

*N Eng J Med 2007;356:1020-
Ann Intern Med 2008;148:234-*

Stent thrombosis of 1st generation DESs

- RESEARCH (SES, n=3823) & T-SEARCH (PES, n=4323)



Late stent thrombosis rate of DES was **0.4-0.6%** annually

Lancet 2007;369:667-

Very late stent thrombosis of BMS for 10-yr

- Retrospective study, 4503 consecutive pts
- treated with at least 1 BMS and dual antiplatelet therapy

	1 Year		5 Years		10 Years	
	Events, No. at Risk	% (95% CI)	Events, No. at Risk	% (95% CI)	Events, No. at Risk	% (95% CI)
All stent thrombosis	37, 4233	0.8 (0.6–1.1)	57, 3662	1.3 (1.0–1.7)	74, 361	2.0 (1.5–2.5)
On-label patients	12, 2101	0.6 (0.2–0.9)	20, 1851	1.0 (0.5–1.2)	27, 160	1.4 (0.9–2.0)
Off-label patients	25, 2132	1.1 (0.7–1.5)	37, 1811	1.7 (1.2–2.2)	47, 201	2.5 (1.7–3.3)†
Restenosis	421, 3854	9.6 (8.8–10.5)	592, 3184	13.9 (12.8–14.9)	304, 667	18.1 (16.5–19.7)
Stable angina	242, 4018	5.6 (4.9–6.2)	329, 3399	7.7 (8.5–6.9)	358, 329	9.0 (8.0–10.0)
Unstable angina	151, 4111	3.5 (2.9–4.0)	225, 3498	4.3 (4.6–6.0)	258, 346	7.4 (6.3–8.6)
MI	45, 4214	1.0 (1.3–0.7)	76, 3635	1.8 (1.4–2.2)	84, 361	2.1 (1.6–2.6)
Positive stress test	16, 4240	0.4 (0.2–0.5)	27, 3667	0.6 (0.4–0.9)	35, 362	1.4 (0.7–2.2)
Other unstable presentation	8, 4248	0.2 (0.1–0.3)	12, 3684	0.3 (0.1–0.4)	15, 362	0.4 (0.2–0.6)

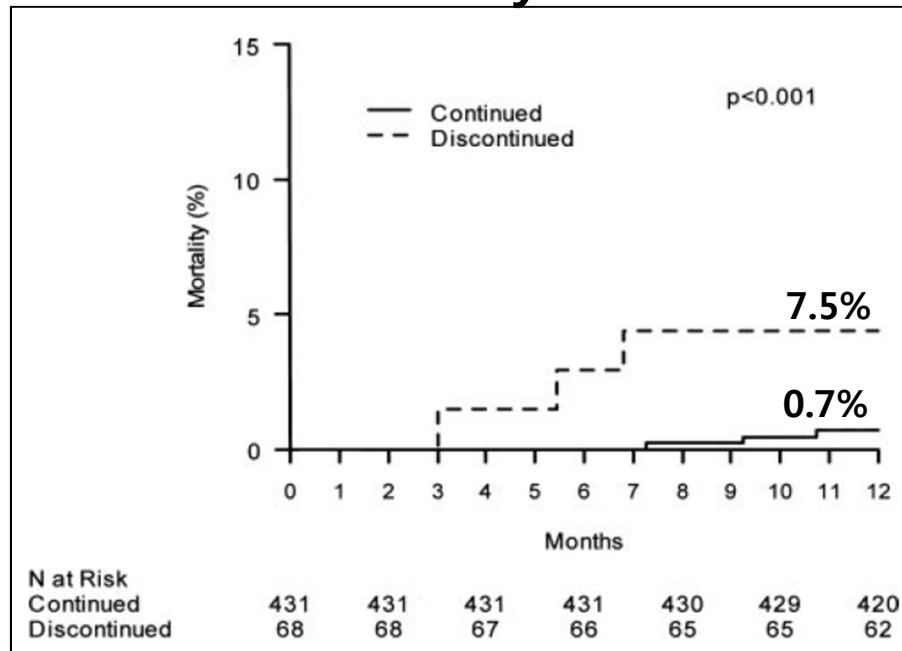
Possible mechanisms of late & very late BMS thrombosis : unclear

- Impaired reendothelialization,
- rupture or ulceration of neoatherosclerotic plaque,

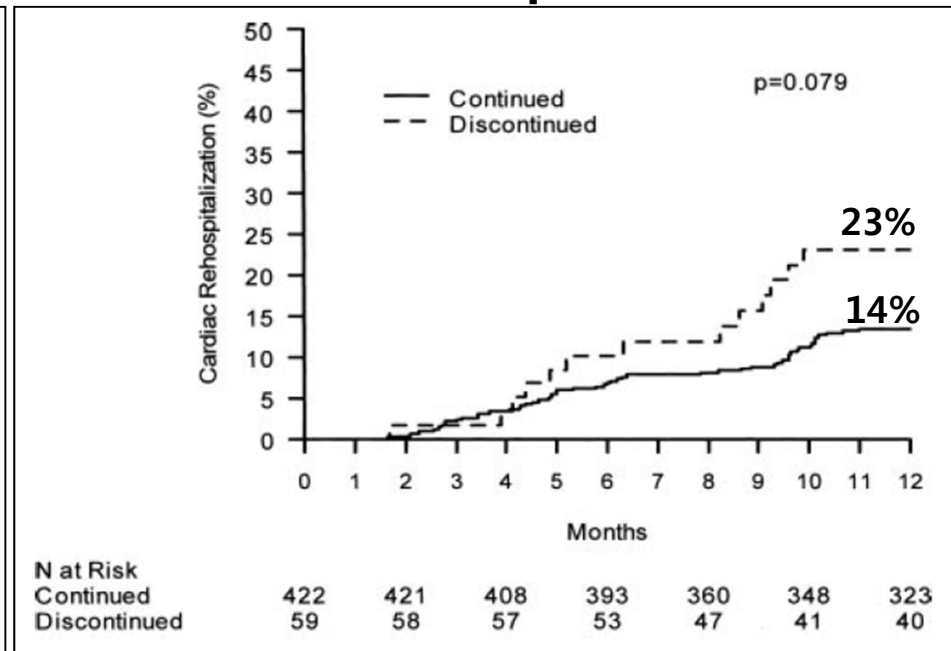
Discontinuation of thienopyridine therapy after DES : PREMIER registry

- Prospective study, 19-center
- 500 DES-treated MI patients
- 68 pts(13.6%) was stopped thienopyridine therapy within 30 days

Mortality



Cardiac rehospitalization



Duration of dual antiplatelet therapy after DES implantation

2005 ACC/AHA/SCAI Guideline

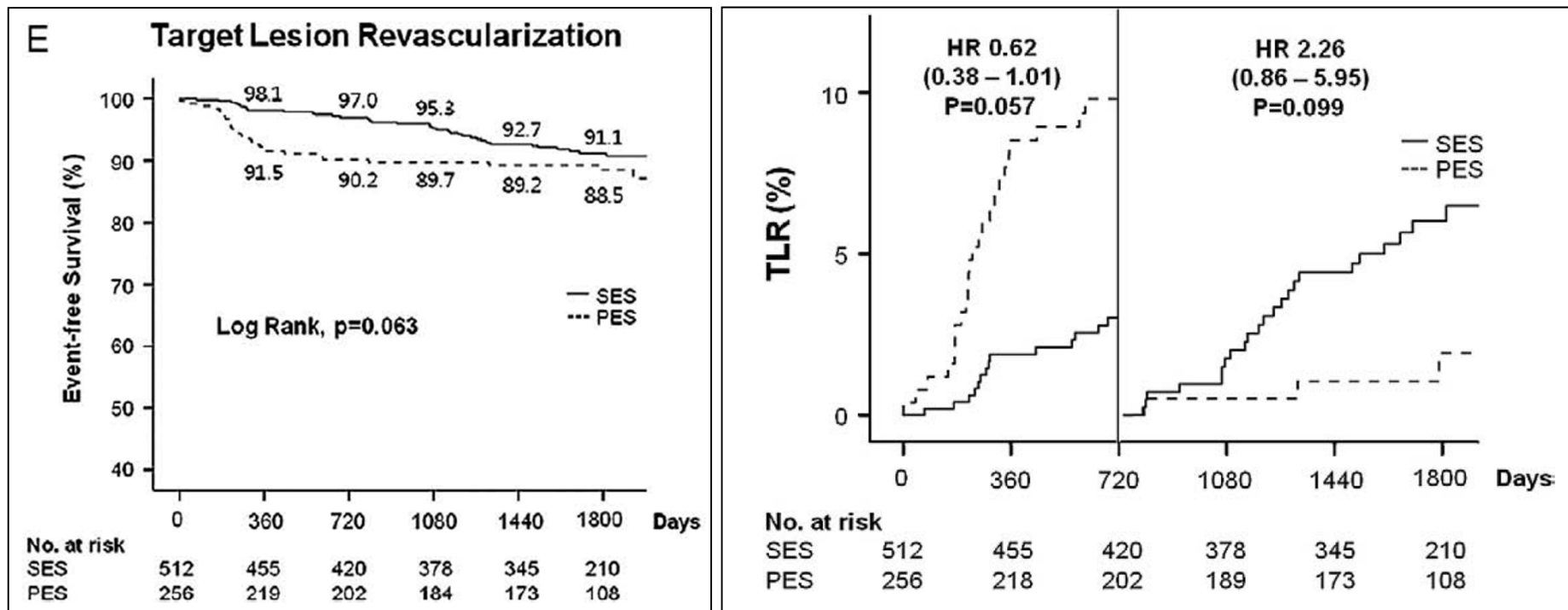
- In pts who have undergone PCI, clopidogrel 75mg daily should be given for **at least 1 month after BMS**(unless the pt is at increased risk of bleeding; then it should be given for a minimum of 2 wks), **3 months after SES**, and **6 months after PES**, and **ideally up to 12 months** in pts who are not at high risk of bleeding

2007 ACC/AHA/SCAI Guideline

- For all post-PCI stented pts receiving a **DES**, clopidogrel 75mg daily **should be given for at least 12 months** if pts are not at high risk of bleeding. For post-PCI pts receiving a **BMS**, clopidogrel should be given for a **minimum of 1 month** and **ideally up to 12 months**

Delayed restenosis : Late catch-up

SES (n=512) vs PES (n=256) for 5 years, Korean clinical registry



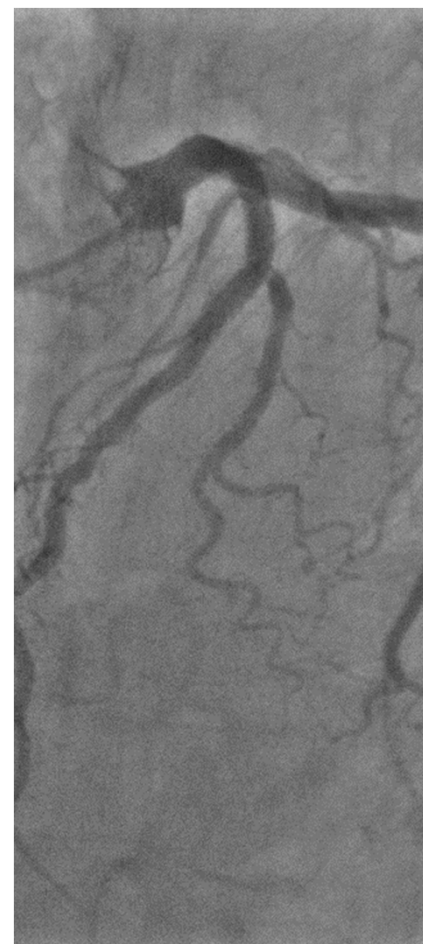
Delayed restenosis : Late catch-up

74-yr, female
STEMI

Cypher
3.5 x 33mm

After 11 months

After 5.5 years



Multifactorial causes of stent thrombosis

Stent factors

- Hypersensitivity to drug coating or polymer
- Incomplete endothelialization
- Stent design

Patients factors

- PCI for ACS/STEMI
- DM
- Rena failure
- Impaired LV function
- Premature cessation of dual antiplatelet therapy
- Aspirin nonresponsiveness
- Clopidogel nonresponsiveness
- Glycoprotein II b/III a inhibitors
- Prior brachytherapy
- Malignancy
- Saphenous vein graft disease

Lesion characteristics

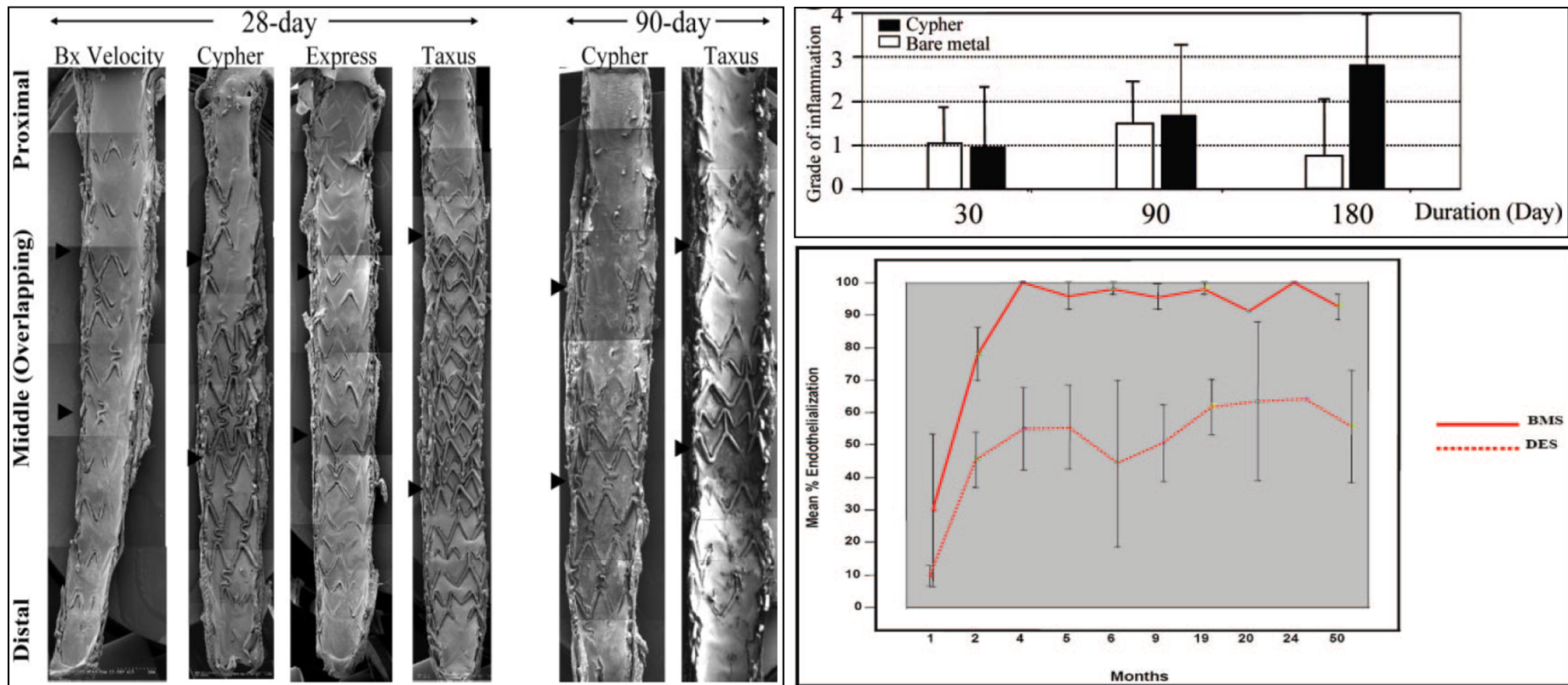
- lesion/stent length
- Vessel/stent diameter
- Complex lesions (bifurcation, CTO)
- Saphenous vein graft target lesion
- Stasis

Procedural factors

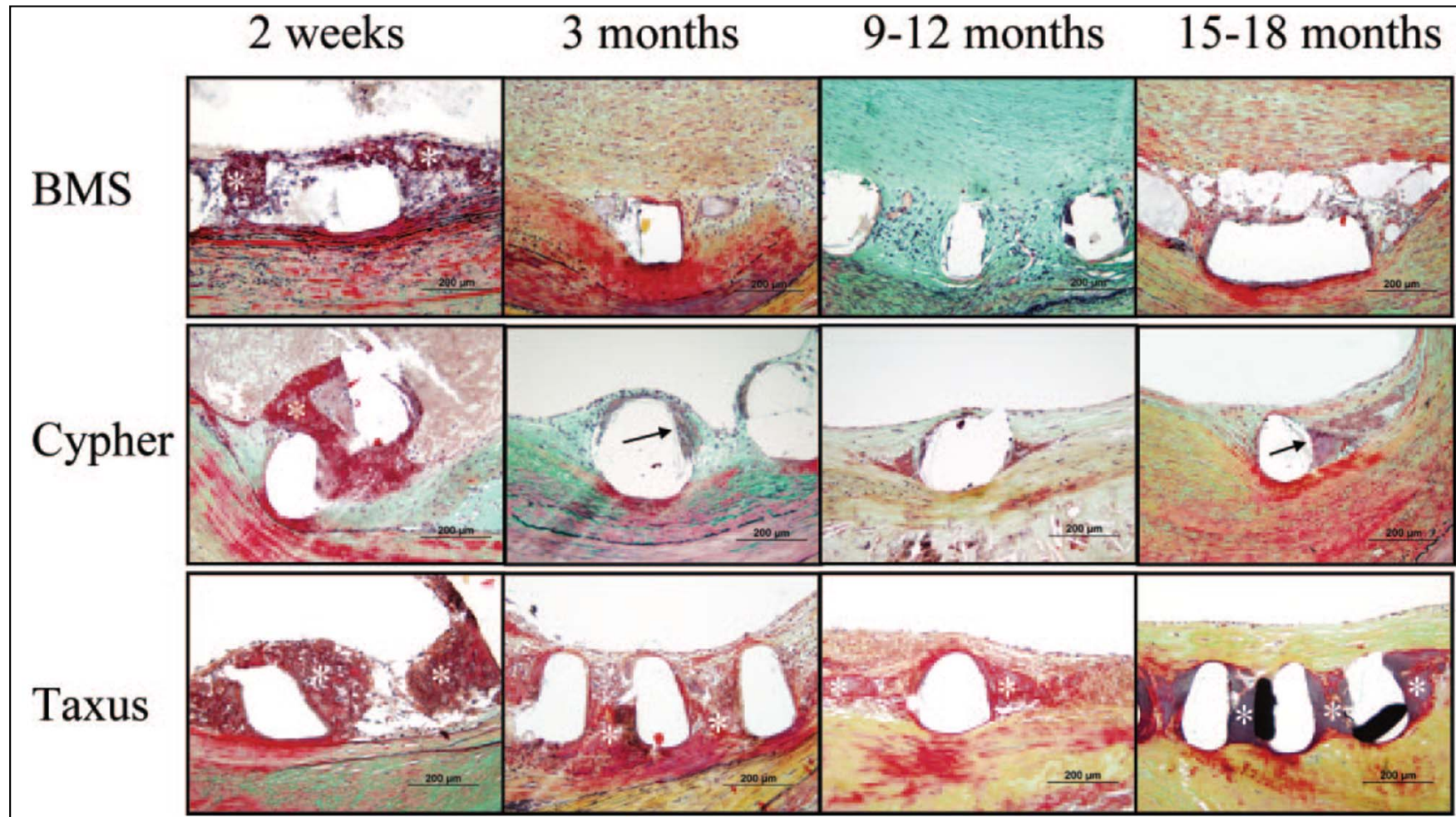
- Inadequate stent expansion/sizing
- Incomplete stent apposition
- Stent deployment in necrotic core
- Residual edge dissection

Vascular response to DES : Importance of delayed healing

Rabbit iliac artery model



Vascular response to DES : Importance of delayed healing



1st generation DES

Promises

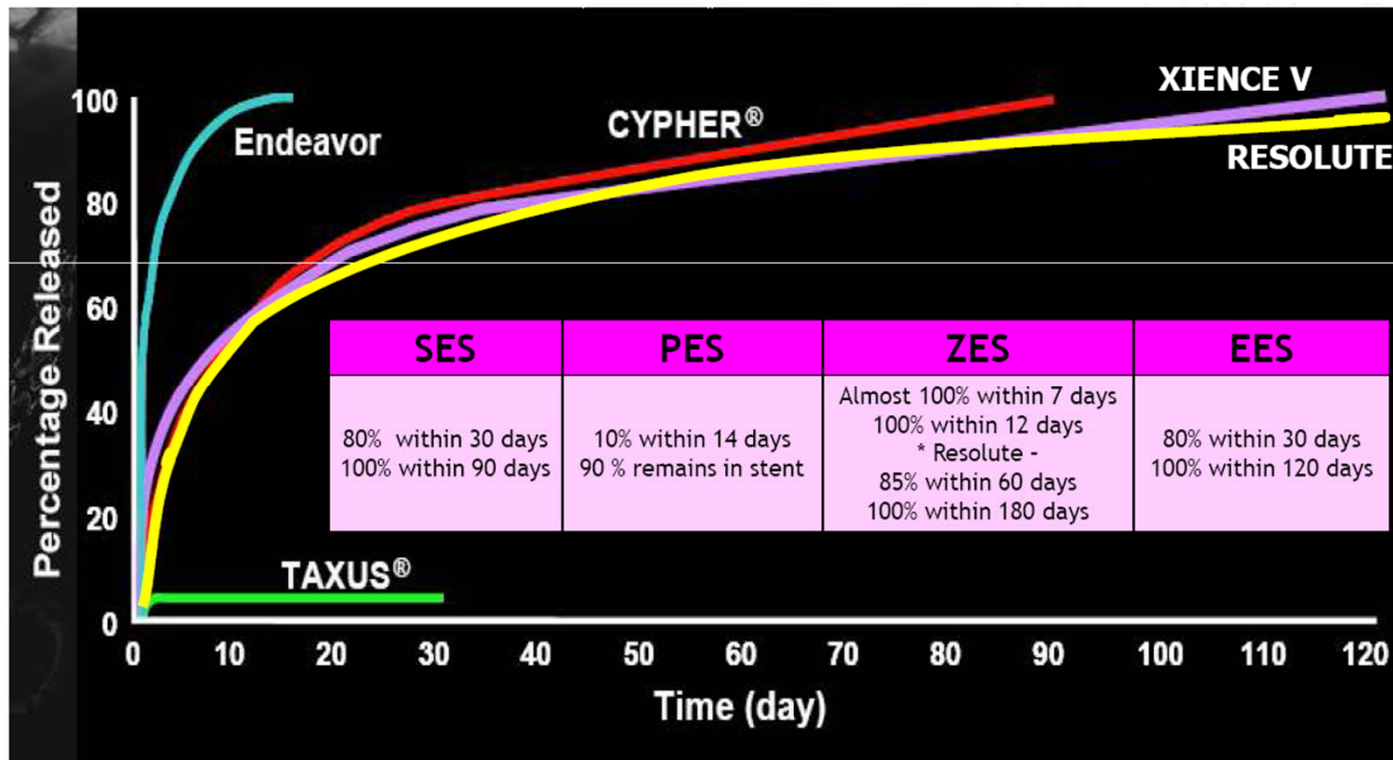
- **Marked reduction of restenosis and TLR**

Pitfalls

- **Remaining of restenosis and TLR**
- **Late or very late stent thrombosis**
- **Delayed restenosis (late catch-up)**

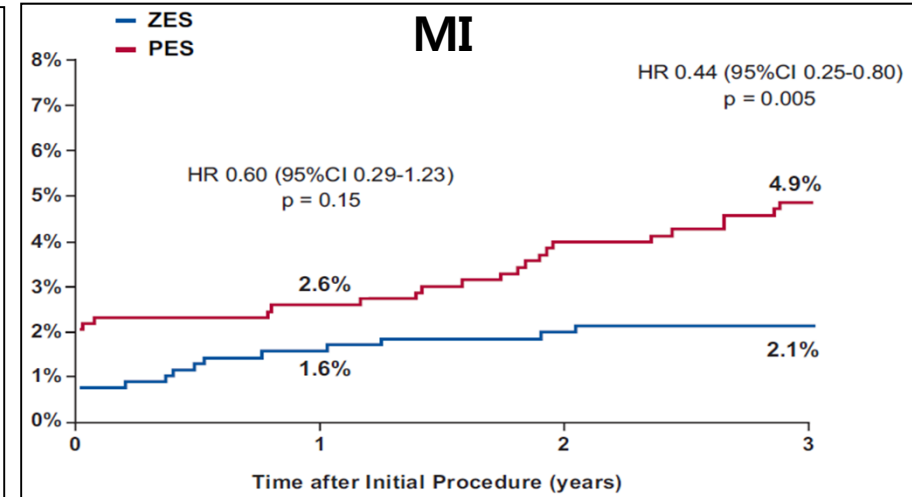
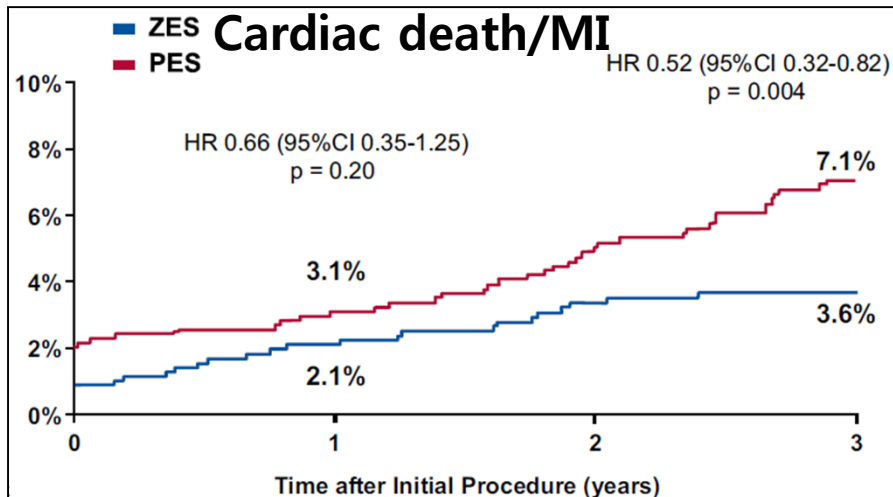
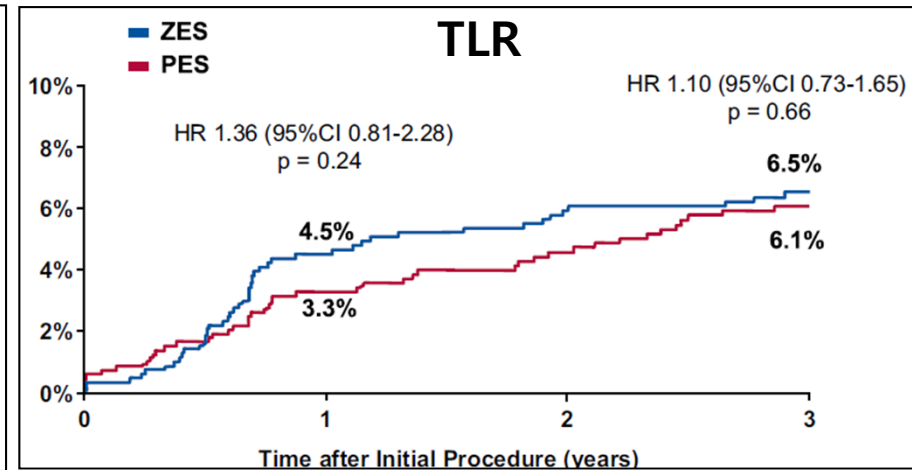
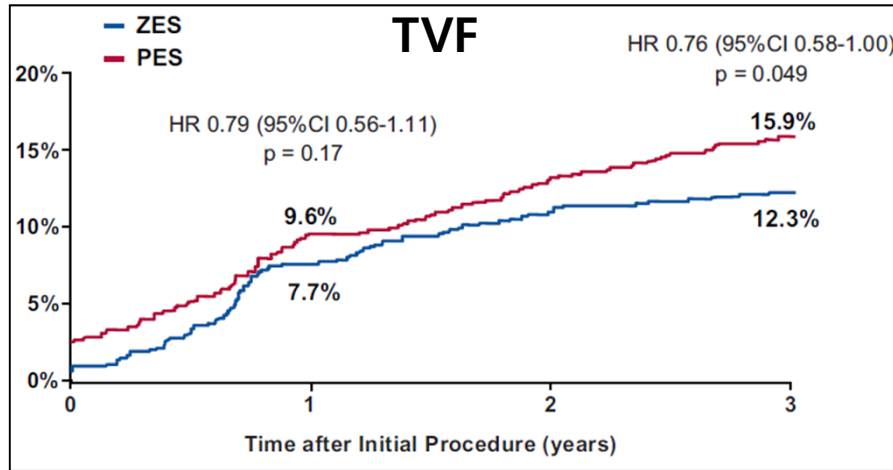
2nd generation DES

- Endeavor : Zotarolimus-Eluting Stent (ZES)
- Xience V : Everolimus-Eluting Stent (EES)
- Endeavor-Resolute : ZES



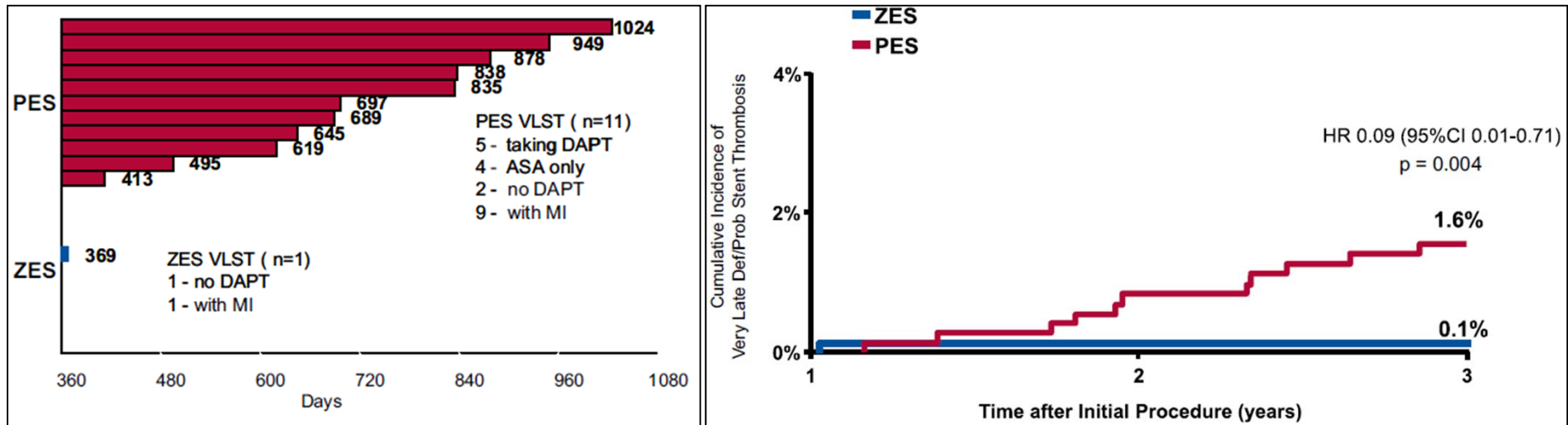
ZES vs PES for 3 yrs : ENDEAVOR IV

ZES (Endeavor stent, n=773) vs PES(n=775)



ZES vs PES for 3 yrs : ENDEAVOR IV

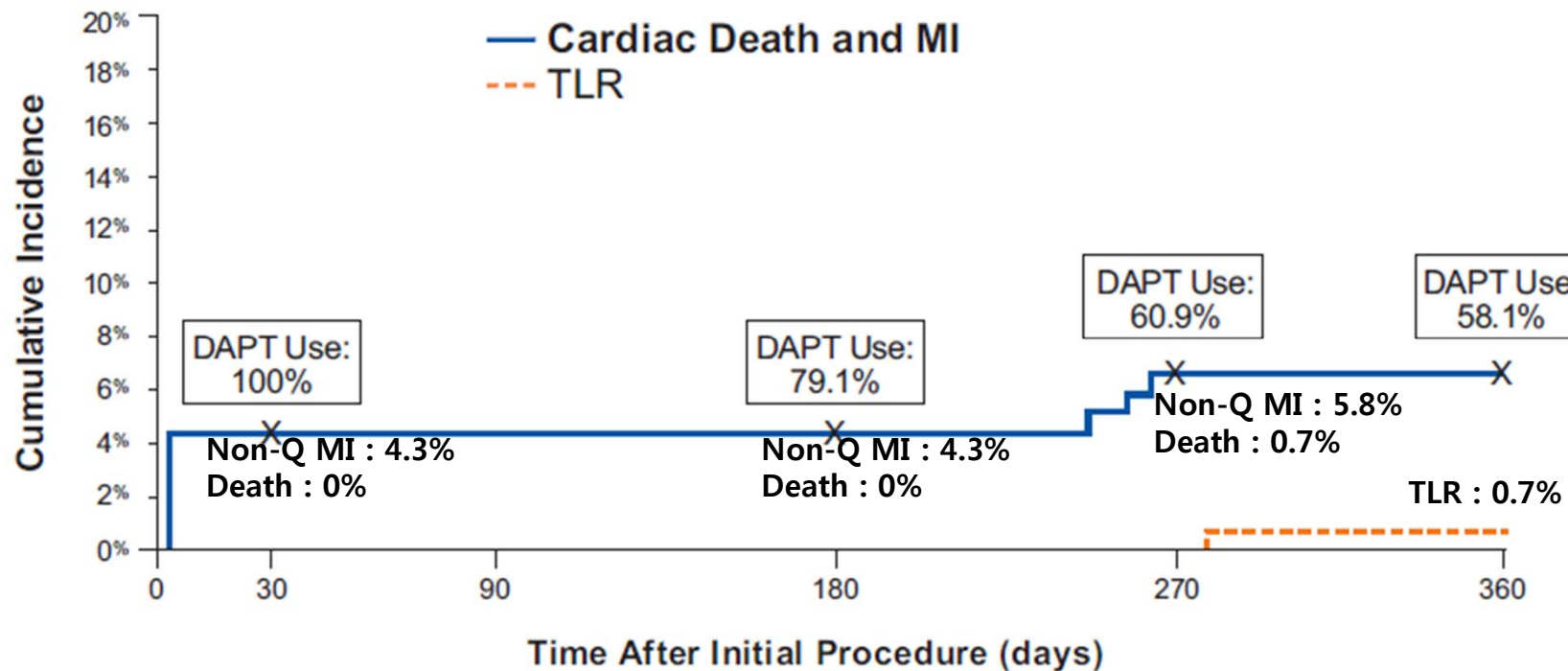
Definite and probable stent thrombosis from 1 to 3 years



ZES (Endeavor stent, n=773) vs PES(n=775)

Endeavor Resolute ZES : RESOLUTE Trial

- Prospective, multicenter, first-in-human trial of Resolute stent
- 139 pts

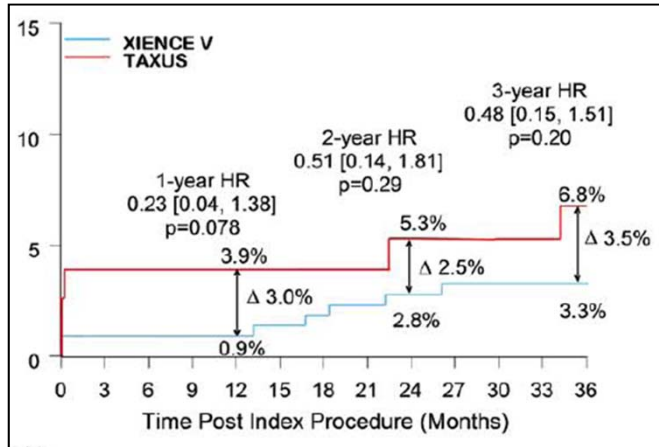


- 9-month, in-stent late lumen loss : 0.22 ± 0.27 mm,
- 9-month, stent thrombosis : 0%

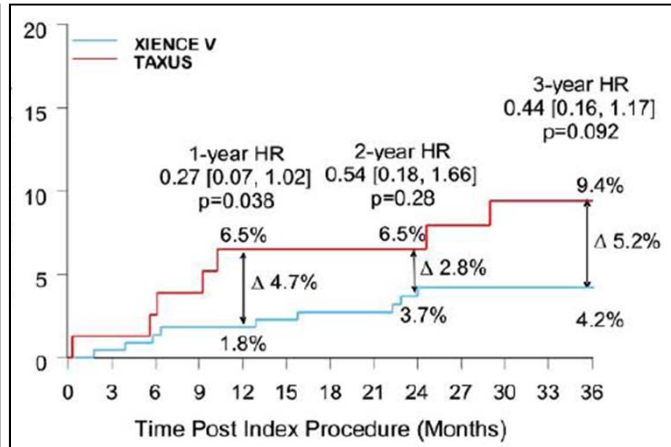
EES vs PES for 3-year

: SPIRIT II

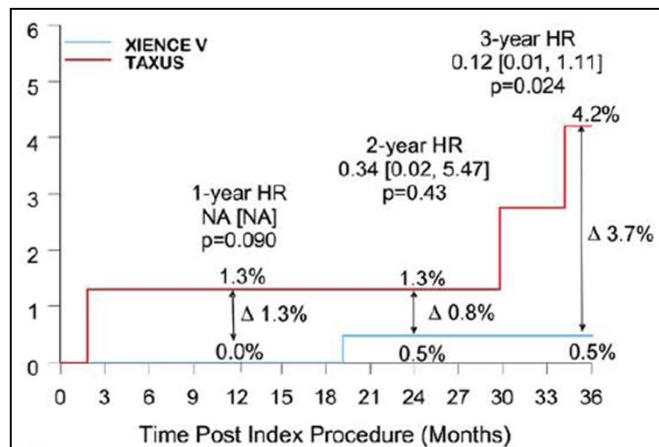
MI



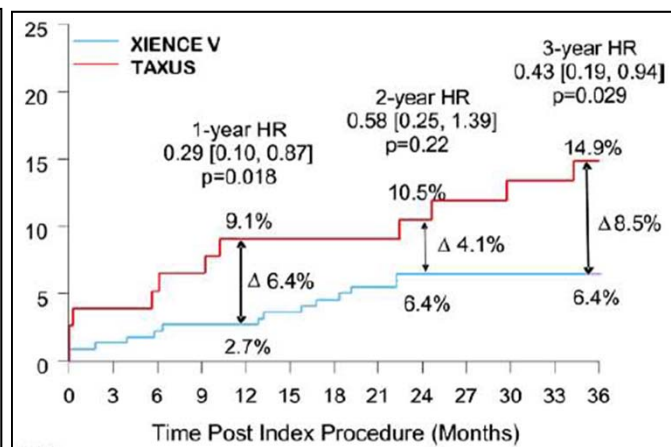
Ischemic TLR



Cardiac Death



Ischemic MACE



Stent thrombosis

EES(n=223) vs
PES(n=77)

Early ST

0% vs 1.3%

Late ST

0% vs 1.3%

Very late ST

1.0% vs 1.5%

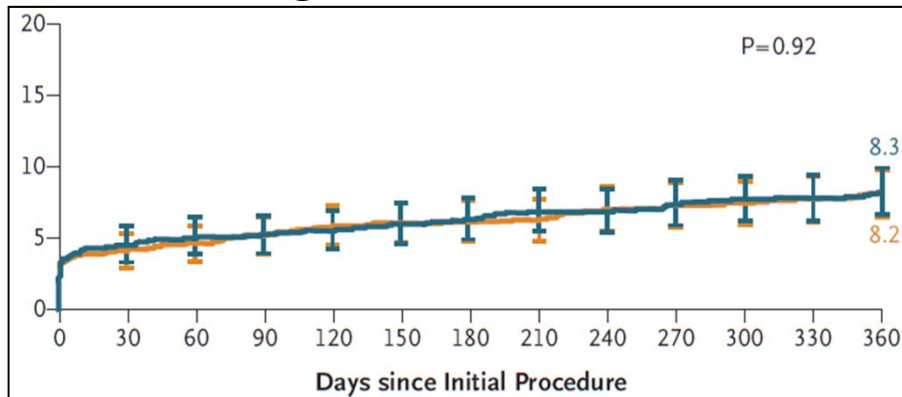
Total ST

1.0% vs 2.9%

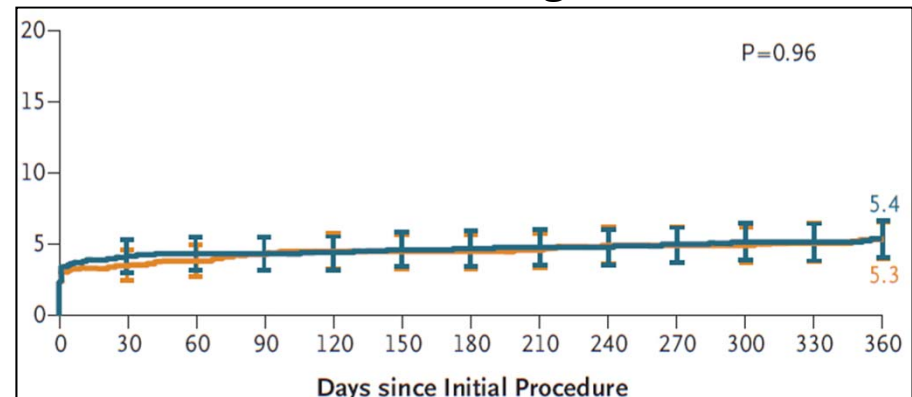
ZES vs EES for 1 year

: Resolute All Comers trial

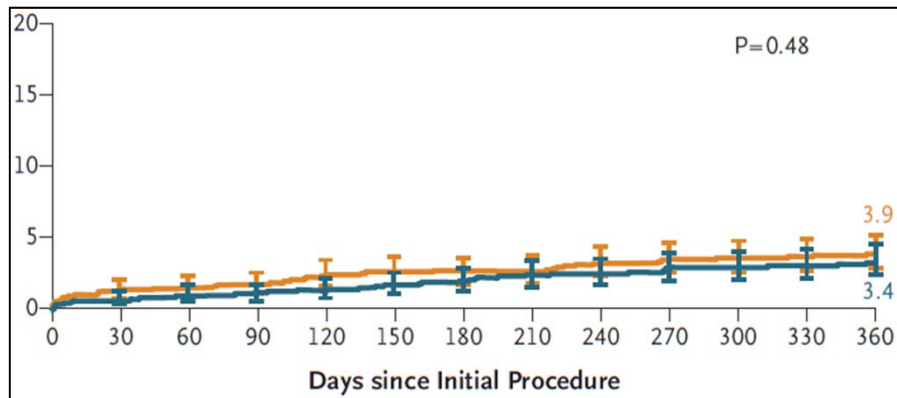
Target lesion failure



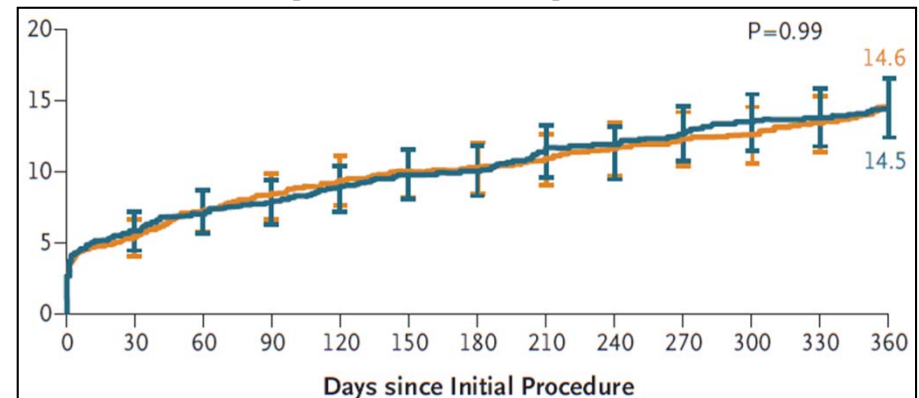
Cardiac death or target-vessel MI



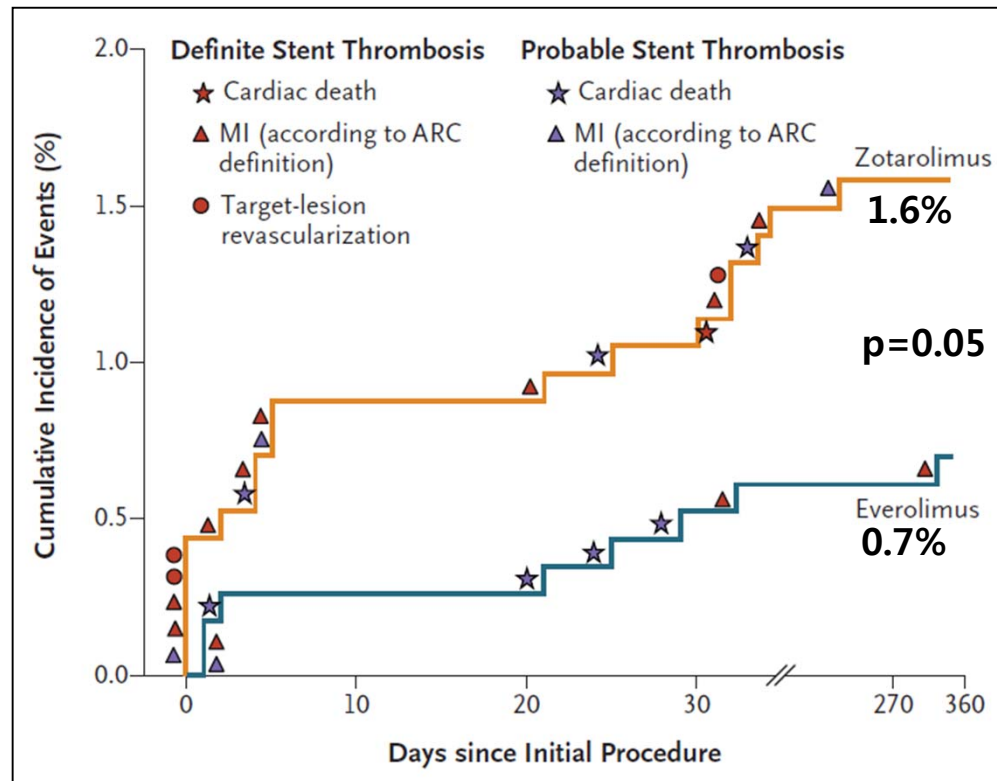
Target lesion revascularization



Composite end point



Stent thrombosis of ZES vs EES for 1 year : Resolute All Comers trial



Definite stent thrombosis (0–360 days)	ZES(n=1119)	EES(n=1126)		
All patients	13 (1.2)	3 (0.3)	0.9 (0.2 to 1.6)	0.01
Acute (0–1 day)	4 (0.4)	1 (0.1)	0.3 (–0.1 to 0.7)	0.22
Subacute (2–30 days)	5 (0.4) †‡§§	0	0.4 (0.1 to 0.8)	0.03
Late (31–360 days)	5 (0.4) †‡	2 (0.2)	0.3 (–0.2 to 0.7)	0.29

2nd generation DES

- **Promises**
 - Reduction of restenosis and TLR
- **Pitfalls**
 - Remaining restenosis and TLR
 - Late and very late stent thrombosis

DES components

- 1. Stent platform**
- 2. Drug-delivery mechanism : polymer**
- 3. Anti-restenotic drug**

1. Stent platform

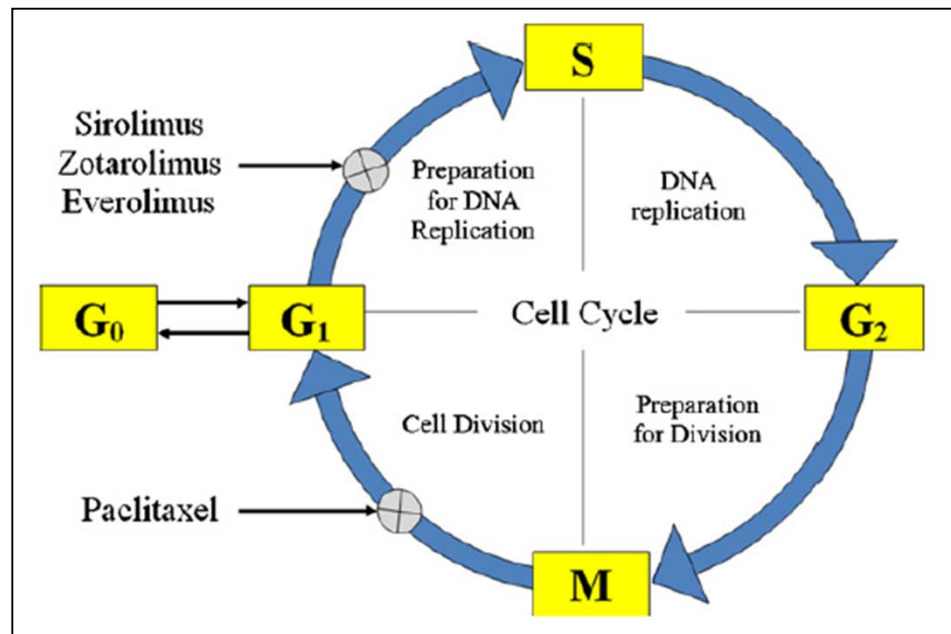
- **Stainless steel**
 - Thick struts(Cypher : 0.140mm, Taxus 0.132 to 0.097mm)
 - Allergic reaction to nickel and molybdenum from stainless steel
- **Cobalt-chromium**
 - Thin struts(0.091mm)
 - Increased radial strength
- **Platinum-chromium**
 - Thinner struts(0.081mm)
 - Increased radial strength and fracture resistance

2. Drug-delivery mechanism : Polymer

- **Permanent synthetic polymer**
 - Polyethylene-co-vinyl acetate (PEVA)
 - Poly-n-butyl methacrylate (PBMA)
 - Styrene-b-isobutylene-b-styrene (SIBS)
- **Biocompatible permanent polymer**
 - Phosphorylcholine (PC)
 - Poly-Vinylidene fluoride-co-hexafluoropropylene (PVDF-HFP)
 - ➔ Polymers mimic the phospholipids on the outer surfaces of RBC resulting in minimal thrombus formation in a stent
- **Bioabsorbable or biodegradable polymer**
 - Polylactic acid (PLA)
 - Polylactic-co-glycolic acid (PLGA)
 - Polyvinyl-pyrrolidone (PVP)
 - ➔ Metabolized to water and CO₂

3. Anti-restenotic drug

- The ideal anti-restenotic drug should exhibit potent anti-proliferative effects but preserve vascular healing
- Immunosuppressive agents
 - Sirolimus
 - Zotarolimus
 - Everolimus
 - Biolimus
- Anti-proliferative agent
 - Paclitaxel



Latest generation DESs

I. Permanent DESs

- Permanent polymer-coated DESs
 - Taxus Element PES and **Promus Element EES**
 - **Endeavor Resolute ZES or Resolute Integrity ZES**
 - **Xience Prime EES**
 - Elixir DESyne Novolimus-Eluting Stent (NES)
- Bioabsorbable polymer-coated DESs
 - Nevo SES
 - Supralimus SES and Infinnium PES
 - **BioMatrix and Nobori biolimus-eluting stents (BES)**
- Polymer-free DESs
 - Yukon SES
 - BioFreedom BES
 - Janus Tacrolimus-Eluting Stent (TES)
 - **Genous Bioengineered R stent** and Combo SES

Latest generation DESs

II. Bioabsorbable DESs

- **Bioabsorbable polymer-coated DESs**
 - BVS EES
 - BTI ideal SES
- **Polymer-free DESs**
 - REVA stent & ReZolve SES
 - AMS stent

1st and 2nd generation DESs

	1 st generation DES			2 nd generation DES		
	Cypher	Taxus Express	Taxus Liberte	Endeavor	Endeavor Resolute	Xience-V
Drug	Sirolimus	Paclitaxel	Paclitaxel	Zotarolimus	Zotarolimus	Everolimus
Stent material	Stainless steel (316L)	Stainless steel (316L)	Stainless steel (316L)	Cobalt chromium	Cobalt chromium	Cobalt chromium
Stent type	Bx-Velocity	Express	Liberte	Driver	Driver	Multi-Link Vision
Strut thickness	0.140 mm	0.132 mm	0.097 mm	0.091 mm	0.091 mm	0.081 mm
Polymer	Permanent : PEVA-PBMA	Permanent : SIBS	Permanent : SIBS	Permanent, biocompatible : PC	Permanent, biocompatible : BioLinx : (C10-C19-PVP)	Permanent, biocompatible : PVDF-HFP

1. Sirolims and paclitaxel
2. Stainless steel
3. Biostable polymer

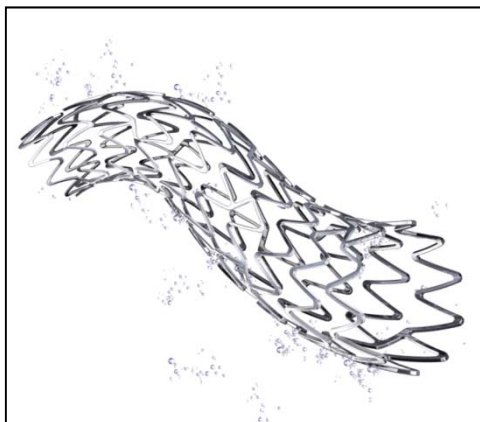


1. Zotarolimus and Everolimus
2. Cobalt chromium
3. Biocompatible polymer

Latest generation DESs

	Permanent polymer			Bioabsorbable polymer	Polymer-free
	Promus Element	Xience Prime	Resolute Integrity	BioMatrix and Nobori	Genous
Drug	Everolimus	Everolimus	Zotarolimus	Biolimus	CD-34 antibody EPC capture
Stent material	Platinum chromium	Cobalt chromium	Cobalt chromium	Stainless steel (316L)	Stainless steel
Polymer	Permanent, biocompatible : PVDF-HFP	Permanent, biocompatible : PVDF-HFP	Permanent, biocompatible : BioLinx (C10-C19-PVP)	Bioabsorbable : PLA	none

Promus Element



Xience Prime



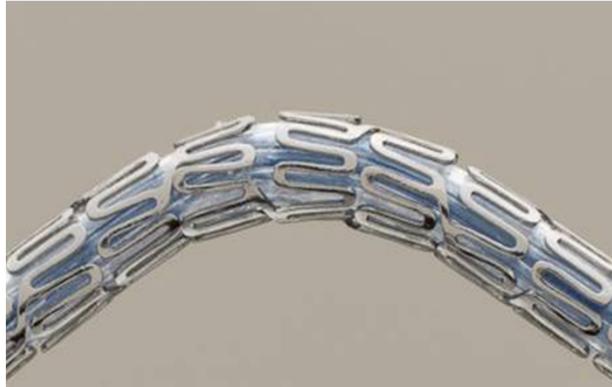
Resolute Integrity



Latest generation DESs

: permanent polymer-coated DESs

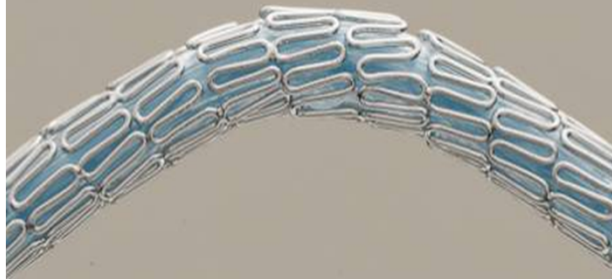
Promus
Element



Xience
Prime



Resolute
Integrity

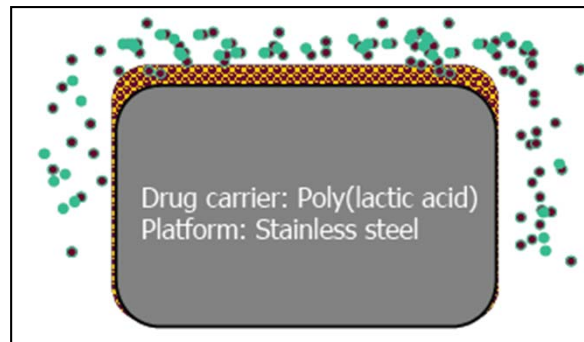


- Superior deliverability
- Excellent flexibility
- Excellent conformability
- Excellent trackability
- Excellent radial strength
- Excellent pushability
- Minimal stent foreshortening
- Excellent side branch access
- Good radiopacity
- Excellent stent crossing profile
- Superior scaffolding

Latest generation DESs

Bioabsorbable polymer : BioMatrix and Nobori BES

- 316L stainless steel S-stent
- Biolimus
- Bioabsorbable polymer : Polylactic acid (PLA)
- Abluminal coating



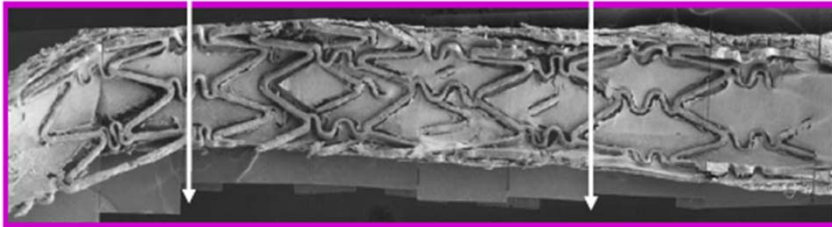
- Two-phase drug release : initial burst release followed by the sustained drug release and polymer degradation
- Both the drug and polymers are fully absorbed within 6-9 months

Latest generation DESs

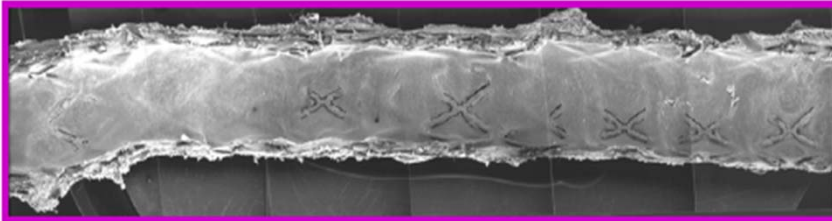
Bioabsorbable polymer : BioMatrix and Nobori BES

Rabbit iliac artery at 28 days

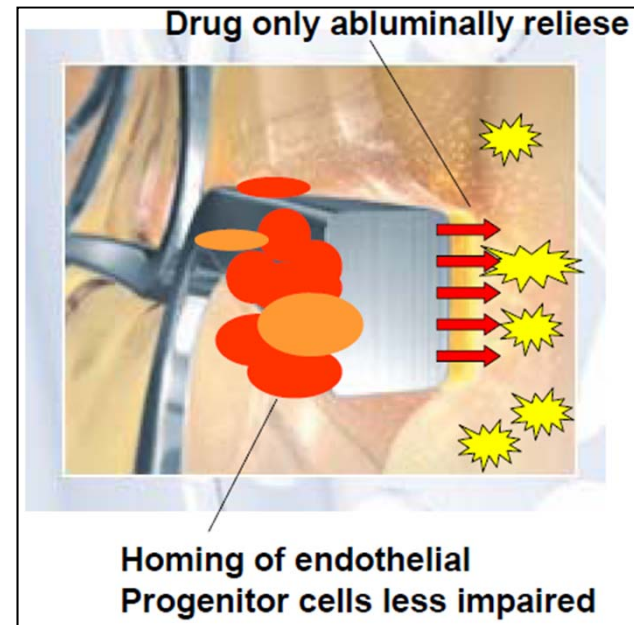
Cypher



Nobori



Not inhibit endothelialization

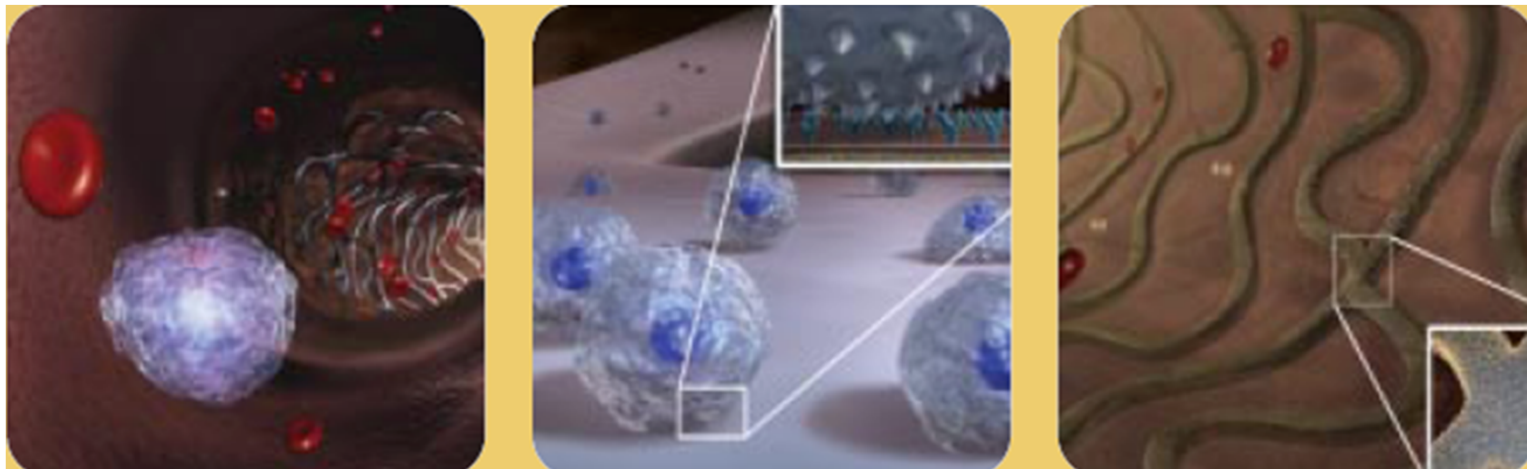


Nobori has all the benefits of current DES, and improved healing characteristics lead to more safety in the current DES era.

Latest generation DESs

Polymer-free DESs : Genous Bioengineered R stent

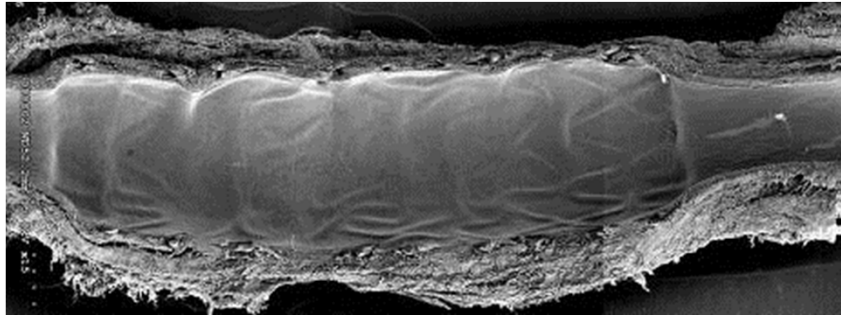
- A novel approach to minimize restenosis and thrombosis
- 316L stainless steel R stent
- Monoclonal, anti-human CD34 antibodies
 - Attract circulating EPCs → promote the establishment of a functional endothelial layer upon the stent surface
- CD34+ marker : non-specific
 - Smooth muscle progenitor cell → neointimal proliferation



Latest generation DESs

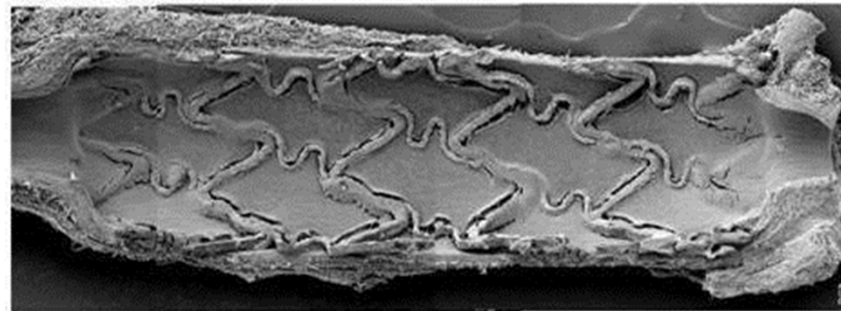
Polymer-free DESs : Genous Bioengineered R stent

Genous Bio-engineered R stent



14 DAY RCA

Cypher Select



14 DAY RCA

Early healing

- Protects against thrombosis
 - Promotes normal endothelial function
 - Reduces inflammation
 - Reduces neointimal proliferation
- **Minimize restenosis and thrombosis**

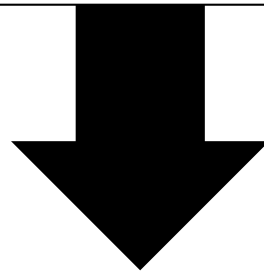
Latest generation DESs

Bioabsorbable DESs

	Bioabsorbable polymer-coated DES		Polymer-free DES	
	BVS EES	BTI ideal SES	REVA stent & ReZolve SES	AMS stent
Stent manufactured	Bioabsorbable polymer (PLLA)	Polylactic anhydride(PA) & salicylic acid	L-tyrosine + iodine (for radiopacity)	Bioabsorbable WE43 magnesium alloy → Biocompatible & bio-corrosive properties → strength similar to stainless steel
Bioabsorbable polymer	Poly-D, L-lactic acid (PDLLA)	Bioabsorbable polymer (salicylic acid)		
Drug	Biolimus	Sirolimus (abluminal coating)	sirolimus	
Drug release	80% within 30-d	100% over 1-m		
Stent & polymer absorption	2 years	6-12 months	3 years	

Promising latest generation DESs

- **Stent platform : Platinum- or Cobalt-chromium**
- **Polymer : Bioabsorbable or abluminal coating**
- **Drug : Zotarolimus, Everolimus, Biolimus, ...**



- **No restenosis and TLR**
- **No stent thrombosis**

감사합니다

