INSTITUT CARDIOVASCULAIRE PARIS SUD

Metallic DES: Is there a room for further progress? Yes!

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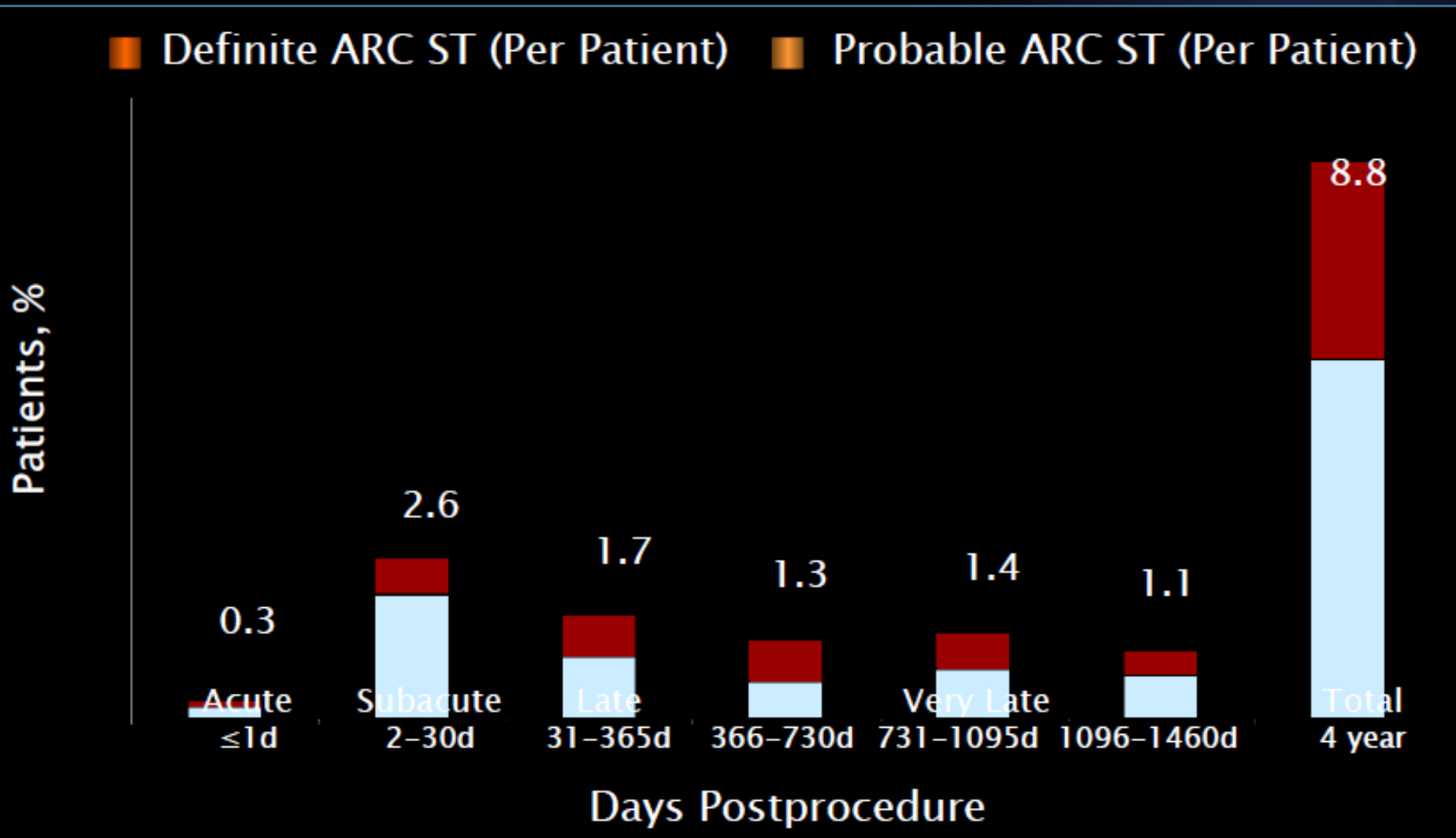
ICPS Massy , France

- In the last five years , I received research grants or speaker fees or I am/was consultant for: Abbott Vascular, Asahi, Astra Zeneca, AVI, Boston Scientific, Biotronik, Colibri, Cook, Cordis, Daichi-Sankyo, Eli-Lilly, Iroko, Medtronic, Terumo. I am currently minor shareholder & general director of CERC

My wish list

- More efficient DES in complex CAD including diabetic patient

ARC ST



Definite plus probable per ARC definitions (Cutlip, et al. *Circulation* 2007;115:2344). 1PCI patient had an ST 1d and 6d post-procedure; therefore, counted in the ≤1d and 2–30d intervals but only once in the total.

Neth Heart J. 2010 Sep;18(9):451-3.

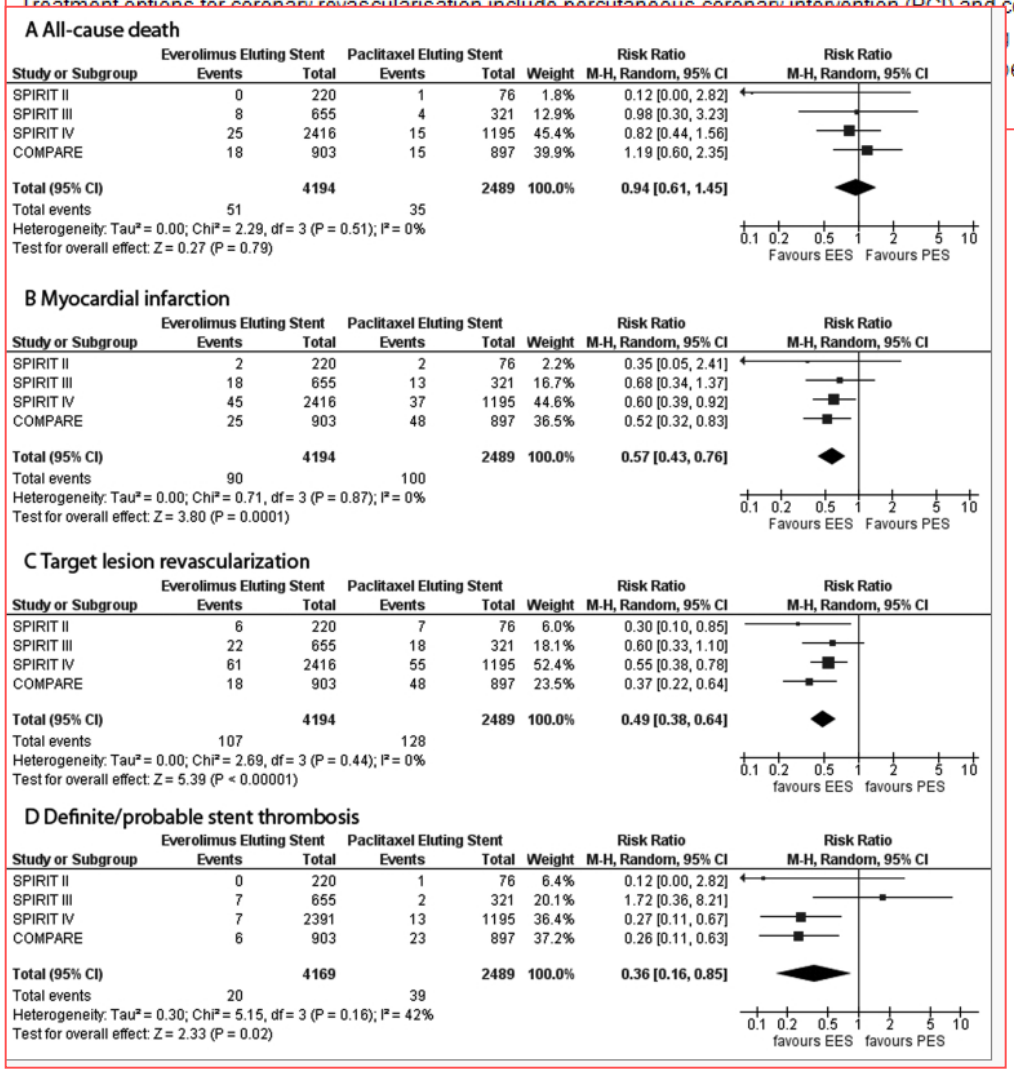
Would SYNTAX have been a positive trial if XIENCE V had been used instead of TAXUS?: A meta-analysis of a first-generation vs. a second-generation drug-eluting stent system.

Claessen BE, Stone GW, Smits PC, Kedhi E, Kikkert WJ, Piek JJ, Henriques JP.

Department of Cardiology, Academic Medical Center, Amsterdam, the Netherlands.

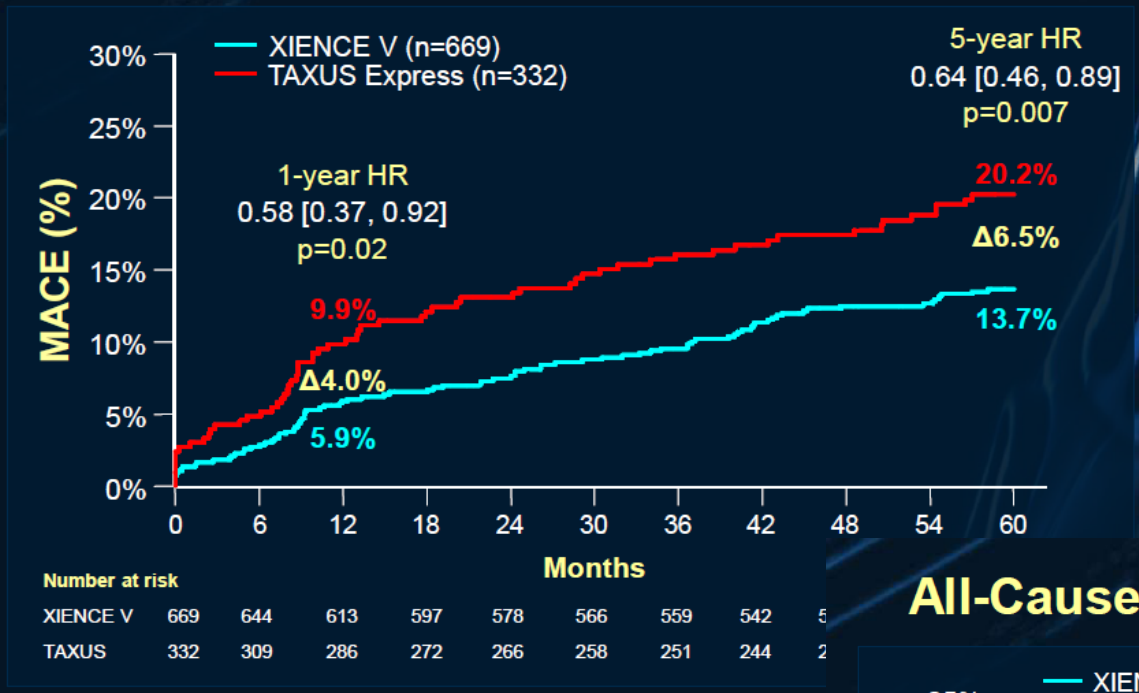
Abstract

Treatment options for coronary revascularisation include percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). In the 'synergy between PCI with TAXUS and ... stents and arterial grafts, respectively) were compared in the treatment of complex ...eat intervention rate. We hypothesised that the use of a superior drug-eluting stent



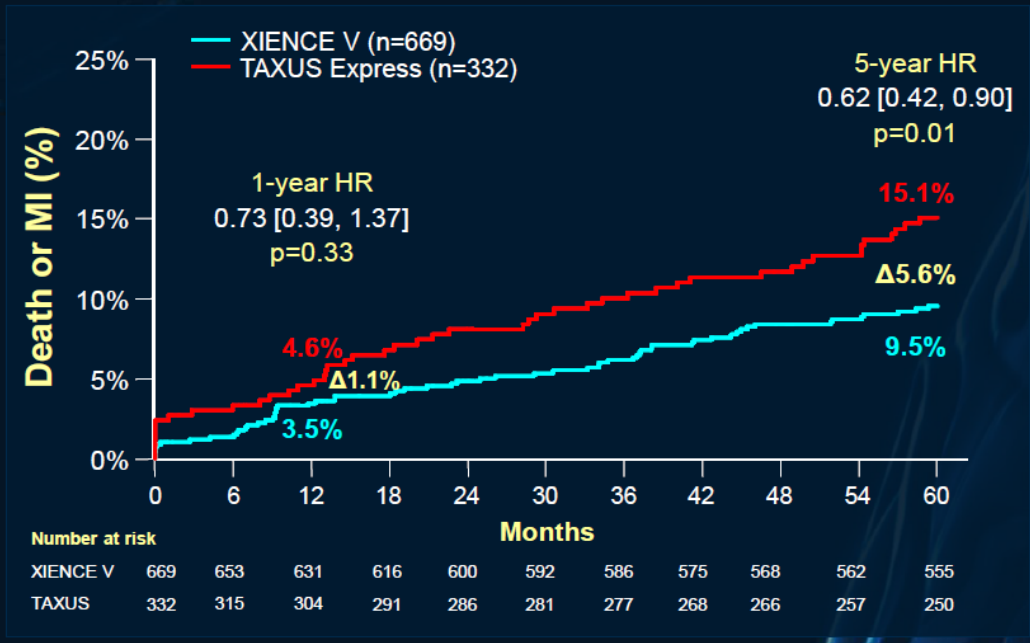
Use modern DES !!

Major Adverse Cardiac Events Through 5 Years



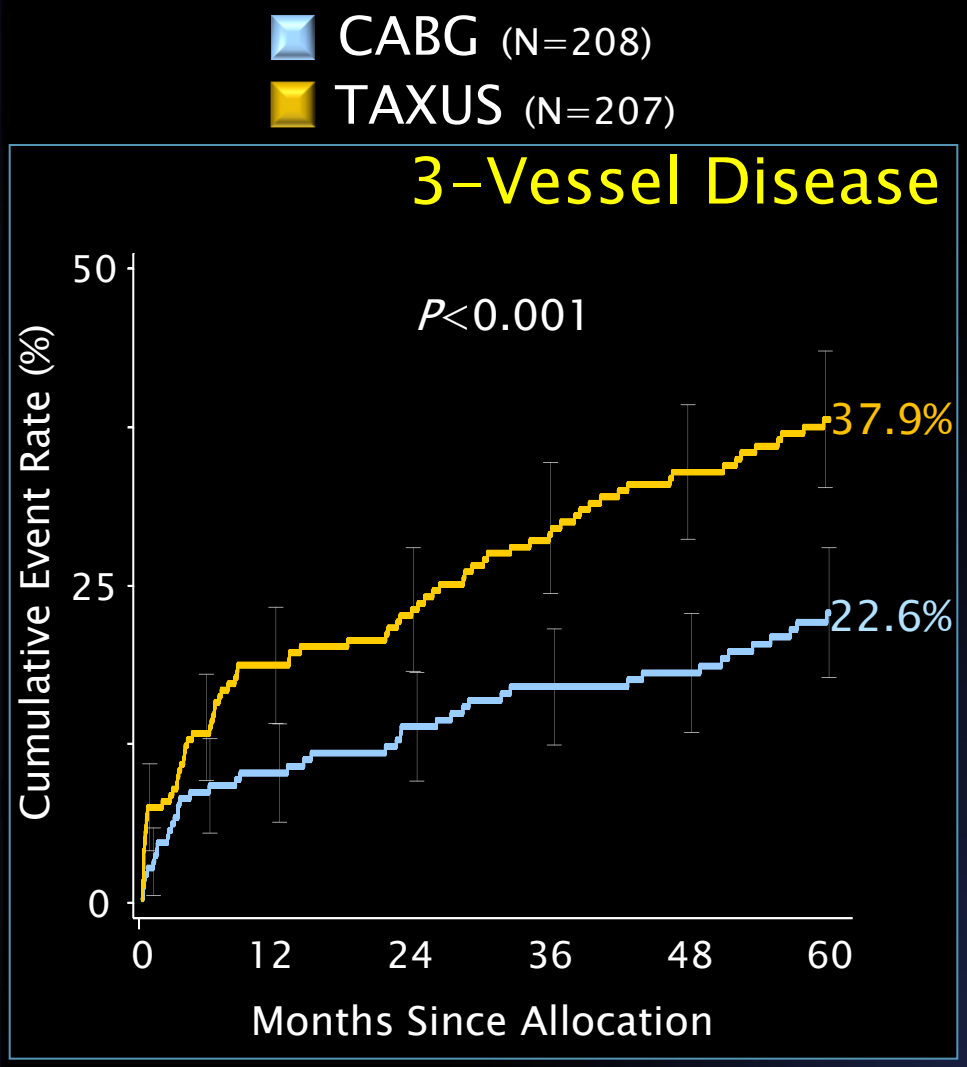
MACE = cardiac death, MI, or ischemic-driven TLR

All-Cause Death or MI Through 5 Years



MACCE to 5 Years by SYNTAX Score Tercile

3VD Subset Intermediate Scores 23–32



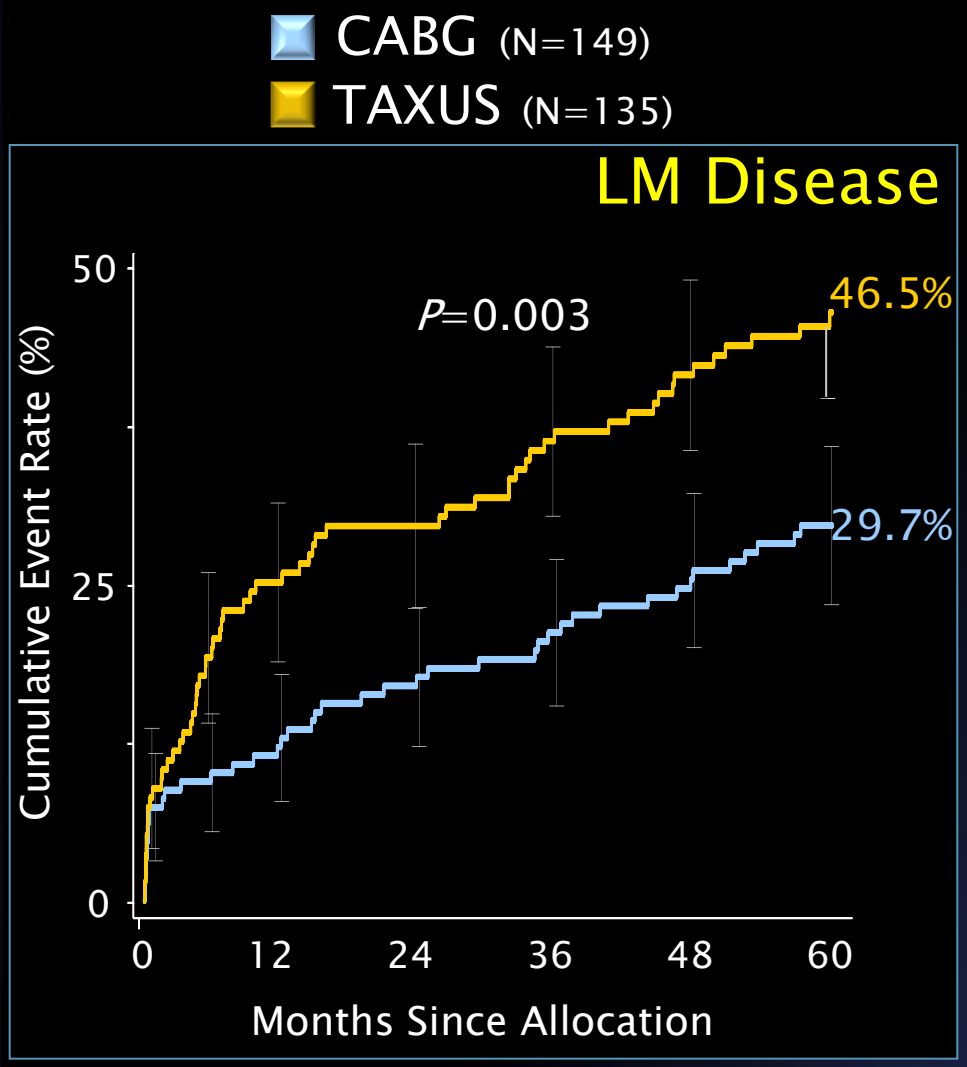
	CABG	PCI	*P* value
Death	9.6%	16.3%	0.047
CVA	3.6%	2.5%	0.53
MI	3.1%	13.8%	<0.001
Death, CVA or MI	14.7%	23.2%	0.04
Revasc.	11.0%	25.1%	<0.001

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value

Site-reported Data; ITT population

MACCE to 5 Years by SYNTAX Score Tercile

LM Subset High Scores ≥33



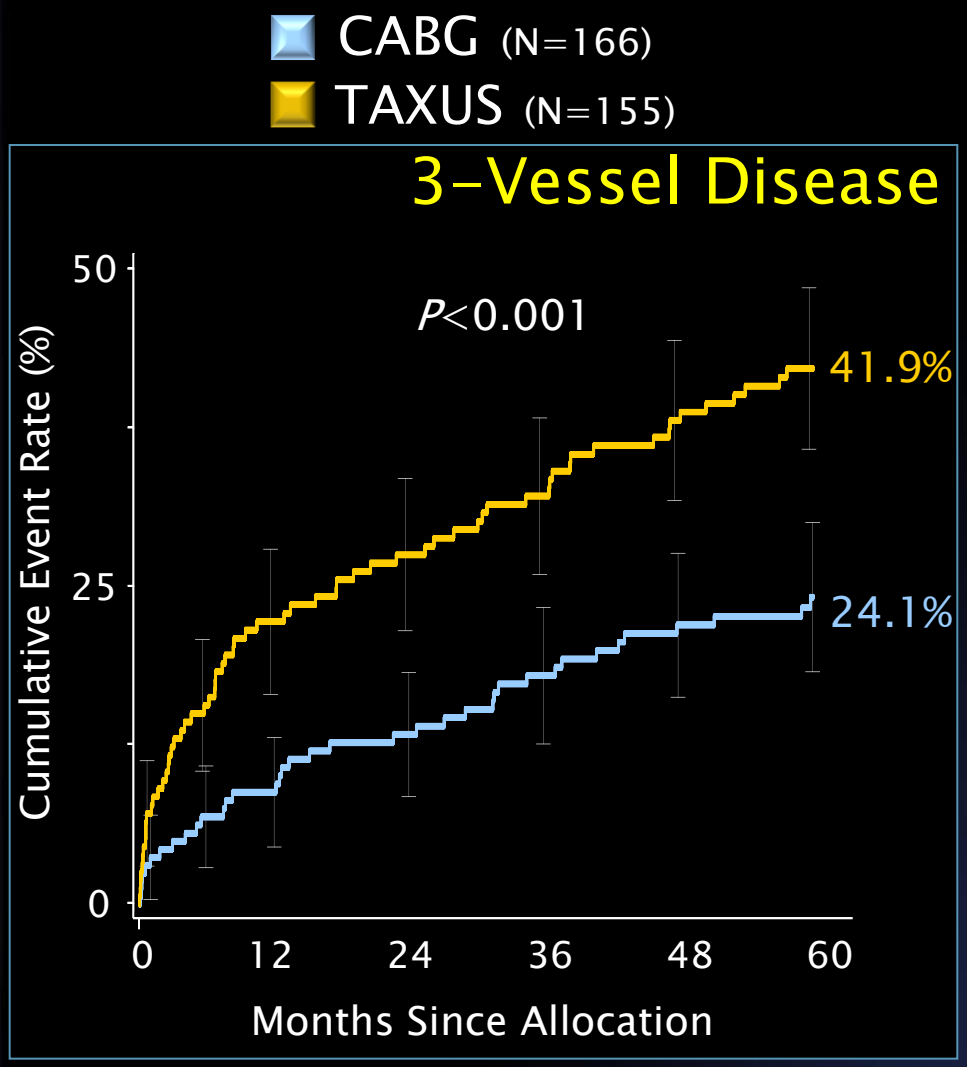
	CABG	PCI	*P* value
Death	14.1%	20.9%	0.11
CVA	4.9%	1.6%	0.13
MI	6.1%	11.7%	0.13
Death, CVA or MI	22.1%	26.1%	0.40
Revasc.	11.6%	34.1%	<0.001

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value

Site-reported Data; ITT population

MACCE to 5 Years by SYNTAX Score Tercile

3VD Subset High Scores ≥33



	CABG	PCI	*P* value
Death	8.8%	17.8%	0.02
CVA	2.6%	5.1%	0.31
MI	1.9%	8.7%	0.008
Death, CVA or MI	12.5%	26.2%	0.002
Revasc.	12.6%	28.2%	<0.001

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value

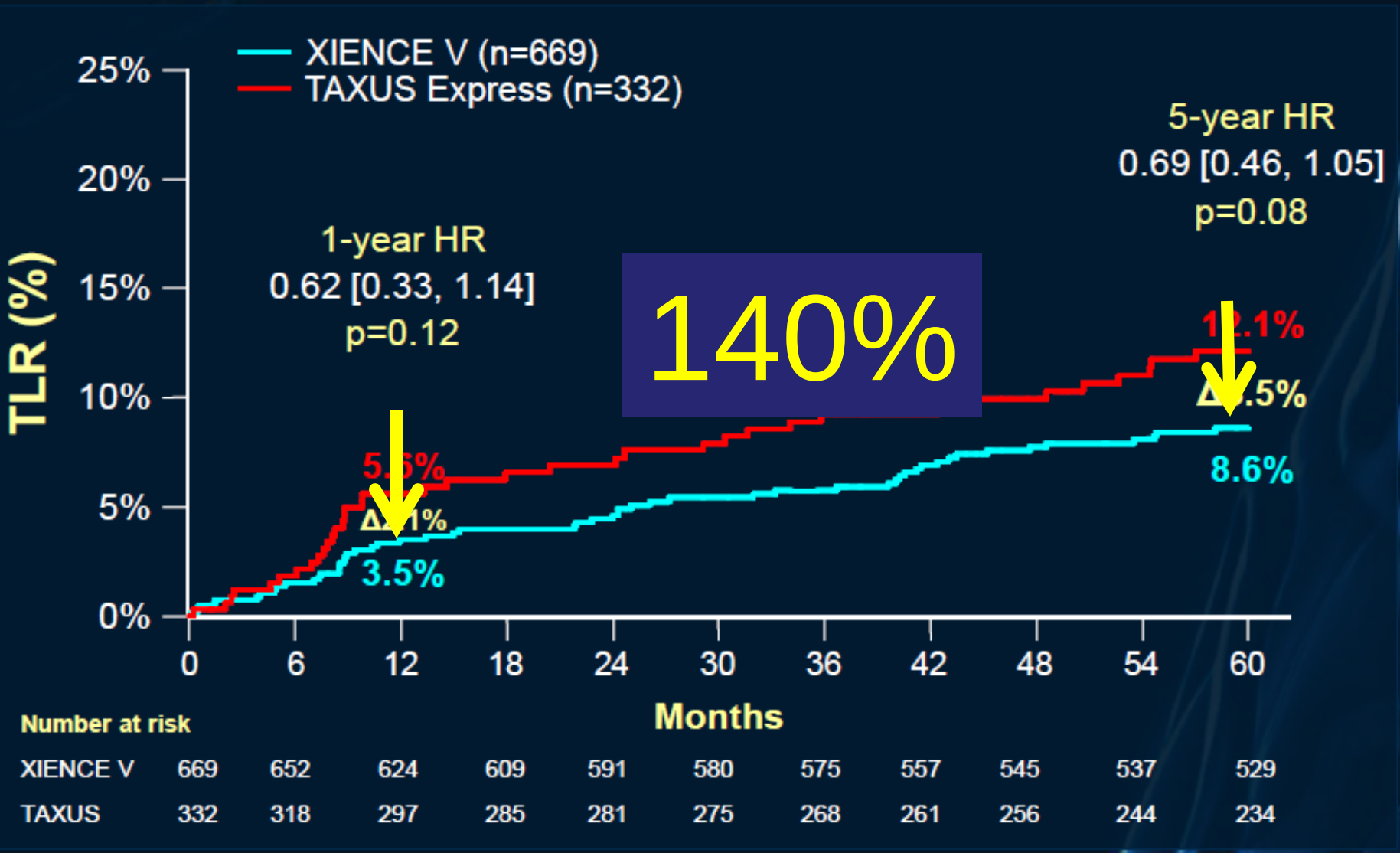
Site-reported Data; ITT population

My wish list

- More efficient DES in complex CAD including diabetic patient

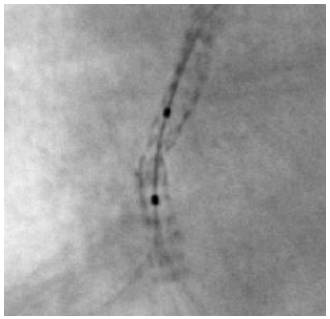
- DES with less late catch-up

Ischemia-driven TLR Through 5 Years



Spirit III

- Conformability ?
- Fracture ?
- Drug resistance ?
- Polymer compatibility ?



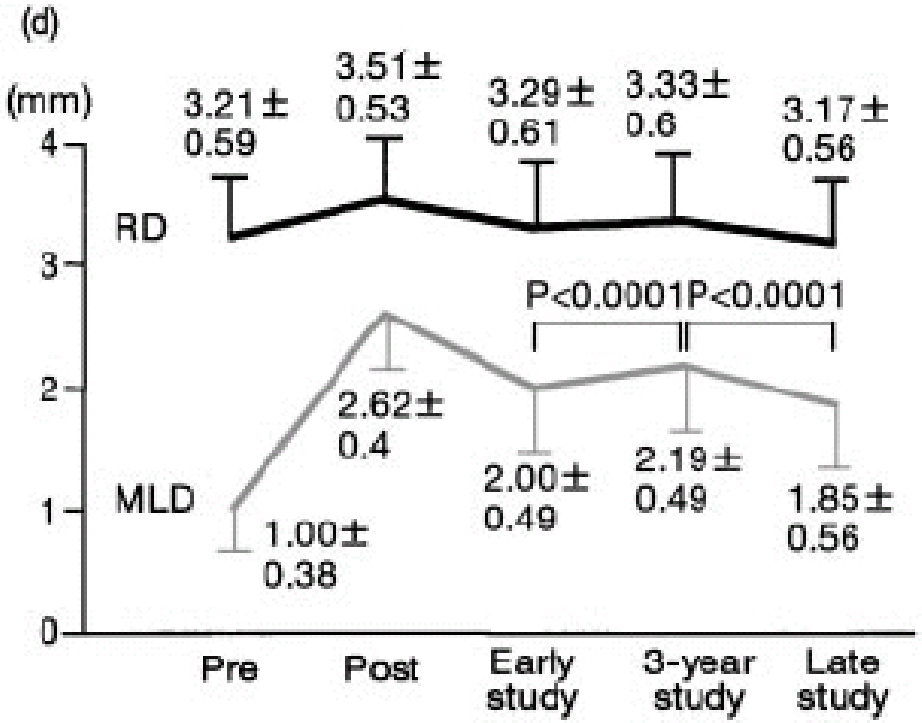
Biological effect: Brenner hypothesis

- Vessel 3 mm lesion <15 mm
- 1 million of SMC
- Doubling time : 1.7 m.
- 5 millions=severe restenosis
- Delay 4 m. + for BMS

- Proliferation inhibition in 99,9% of SMC
- 1 000 SMC
- 5 000 SMC @ 4 m.
- 5 millions @ 23 m. + for DES

Brenner et al. *Int J Radiat Oncol Biol* Phy 1996; 36: 805-810

Very late restenosis exists for BMS: 173 patients/179 lesions @ 6.6 years



VERY late restenosis : 28%

VERY late TLR : 11%

Kimura et al. Circulation 2002

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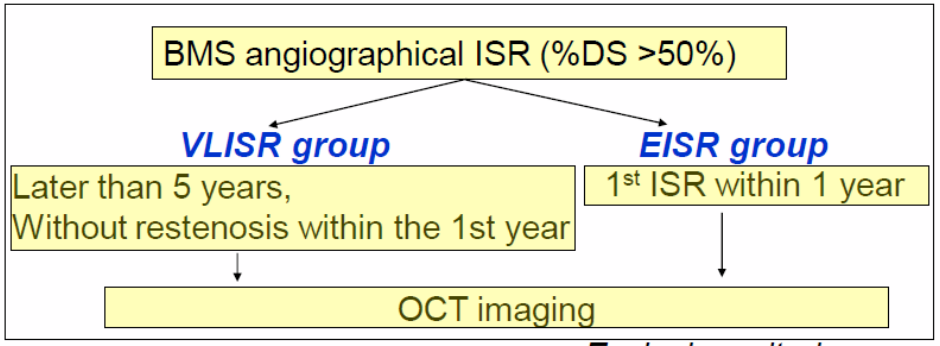
Study design



Inclusion criteria

1)with E-ISR or VL-ISR of a BMS in angiography
2)underwent OCT according to clinical and angiographic characteristics

Exclusion criteria

1) left main coronary artery disease
2) totally occluded lesion
3) bifurcation stenting lesion
4) bypass graft lesion
5) hybrid stenting lesion with DES
6) cardiogenic shock
7) left ventricular ejection fraction < 30%
8) serum creatinine > 2mg/dl
9) ST elevation myocardial infarction

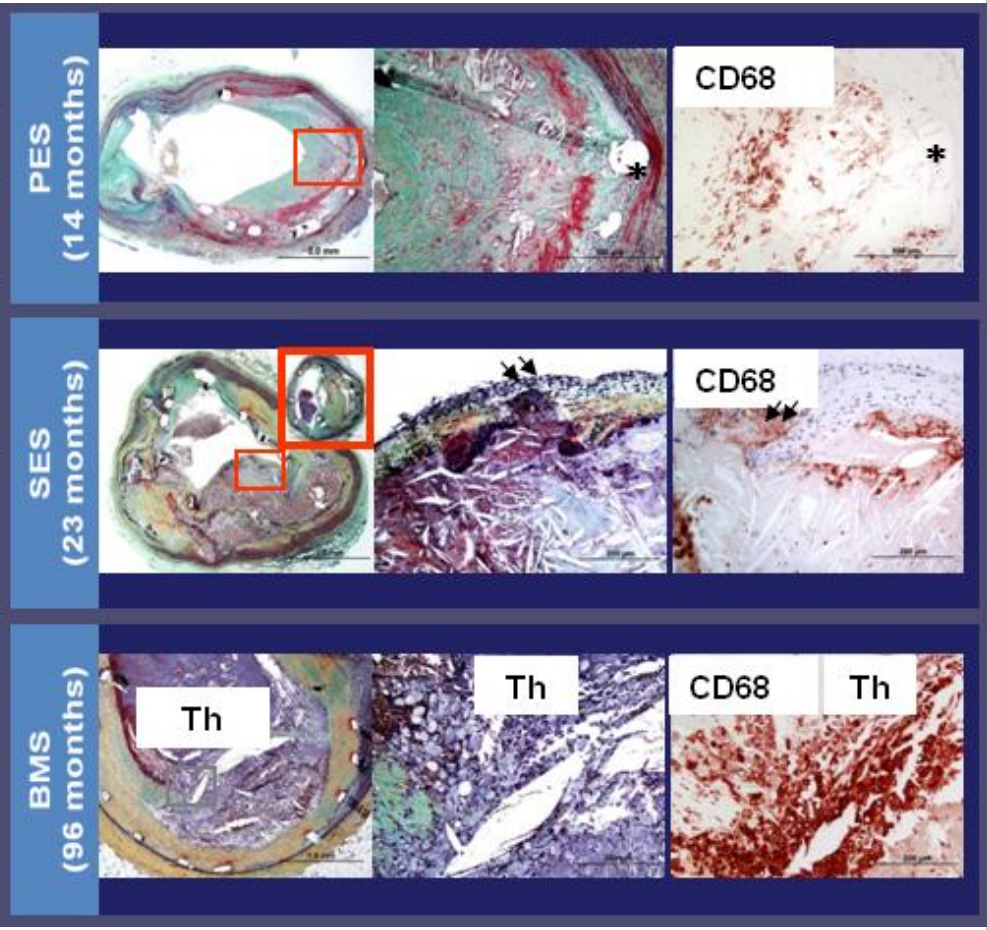
OCT analysis at MLA site

		VL-ISR n=43	E-ISR n=39	*p*
Quantitative analysis				
Minimum lumen area, mm^2		**1.9±1.1**	**2.2±0.9**	**0.17**
Stent area, mm^2		**9.1±2.2**	**10.1±2.9**	**0.11**
Neointimal hyperplasia area,mm^2		**7.2±2.2**	**7.9±2.4**	**0.23**
Percent neointimal hyperplasia area, %		**79.0±10.0**	**77.6±7.1**	**0.46**
Qualitative analysis				
Homogeneous intima, %		**4 (9.3%)**	**32 (82.1%)**	**<0.0001**
Heterogeneous intima, %		**39 (90.7%)**	**7 (17.9%)**	**<0.0001**
Microvessels	peri-stent, %	**11(25.6%)**	**5 (12.8%)**	**0.17**
	Intraintima , %	**7 (16.3%)**	**0 (0%)**	**0.01**
Disrupted intima with visible cavity, %		**6 (13.9%)**	**0 (0%)**	**0.03**
Intraluminal material, %		**7 (16.2%)**	**0 (0%)**	**0.01**
	With shadowing	**6 (14.0%)**	**0 (0%)**	**0.03**
	Without shadowing	**1 (2.3%)**	**0 (0%)**	**>0.99**

Toyohashi Heart Centre

Late atheroma for DES

Thin-cap Fibroatheroma (TCFA)	Plaque Rupture (PR)
58 M BMS (NIR) 61 months LAD prox Non-cardiac death	43 M BMS (Mini-Crown) 84 months LAD prox Stent related death (thrombosis)
63 M BMS (Multi-Link) 98 months RCA mid Non-stent related cardiac death	87 F BMS (AVE) 61 months RCA prox Stent related death (thrombosis)
73 M BMS (Bx Velocity) 50 months RI prox Non-cardiac death	47 M BMS (GR II) 96 months RCA prox Stent related death (thrombosis)
40 F DES (SES) 17 months RCA prox Stent related thrombosis secondary to hypersensitivity	43 M BMS (ML ZETA) 61 months RCA prox-dist Stent related death (thrombosis)
67 M DES (SES) 13 months RCA prox Non-stent related cardiac death	59 M DES (SES) 23 months RCA dist Stent related death (thrombosis)



My wish list

- More efficient DES in complex CAD including diabetic patient
- DES with less late catch-up
- No need for prolonged DAPT

ESC guidelines 2010

(b) Recommended duration of dual antiplatelet therapy

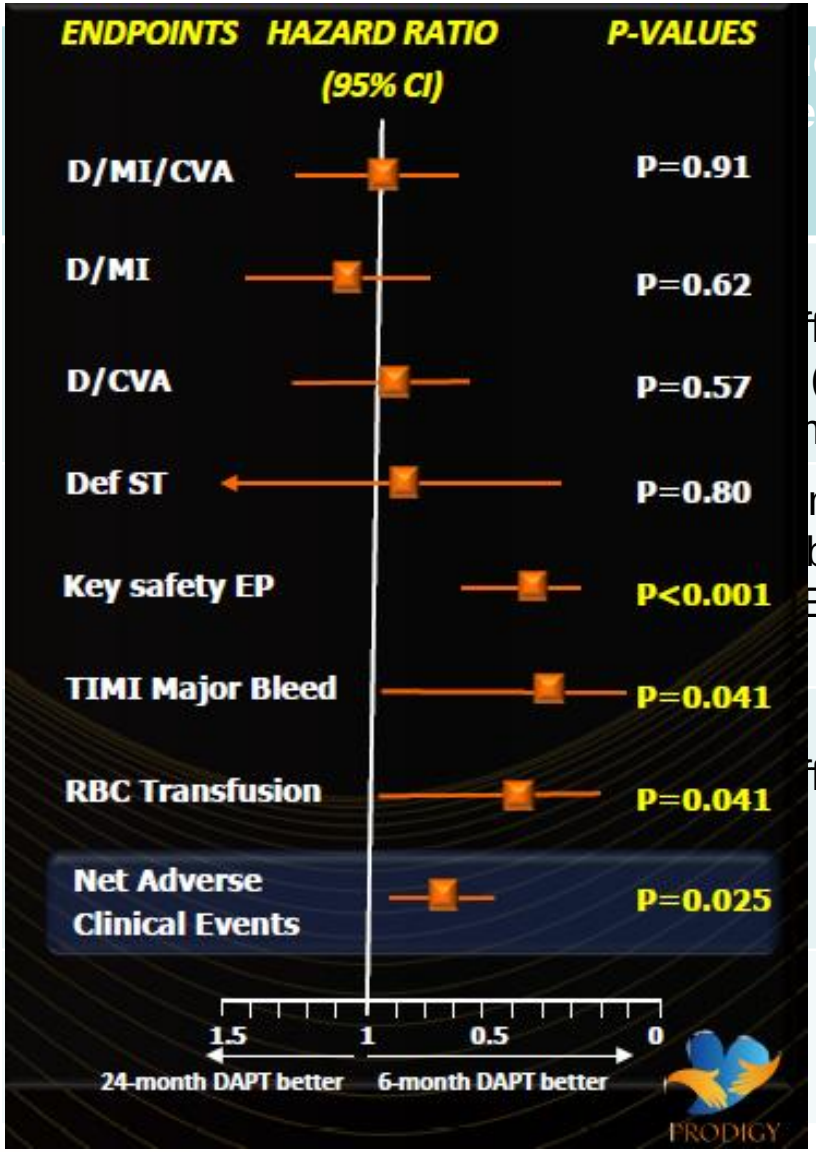
After percutaneous coronary intervention

- 1 month after BMS implantation in stable angina;[55,60,94]
- 6–12 months after DES implantation in all patients;[60,94]
- 1 year in all patients after ACS, irrespective of revascularization strategy.

Eur Heart J 2010; 31: 2501-2555

Selected trials of DAPT duration

Trial	Candidates for prolonged DAPT	eeding vents	Status
Park et al	Yes	No ference (TIMI major)	Published (NEJM 2010)
PRODIGY	Yes	months better BARC)	Published (Circ 2012)
RESET	Yes	No ference	Presented (ACC 2012)
DAPT	Yes	NYK	Ongoing



* death, MI, CVA
** death, MI , ST

Non DES candidate whatever risk of restenosis ??

Table 35 **Relative clinical contraindications to the use of drug-eluting stents**

• Clinical history difficult to obtain, especially in the setting of acute severe clinical conditions (STEMI or cardiogenic shock).
• Expected poor compliance with DAPT, including patients with multiple comorbidities and polypharmacy.
• Non-elective surgery required in the short term that would require interruption of DAPT.
• Increased risk of bleeding.
• Known allergy to ASA or clopidogrel/prasugrel/ticagrelor.
• Absolute indication for long-term anticoagulation.

ASA = acetylsalicylic acid; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; STEMI = ST-segment elevation myocardial infarction.

2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention

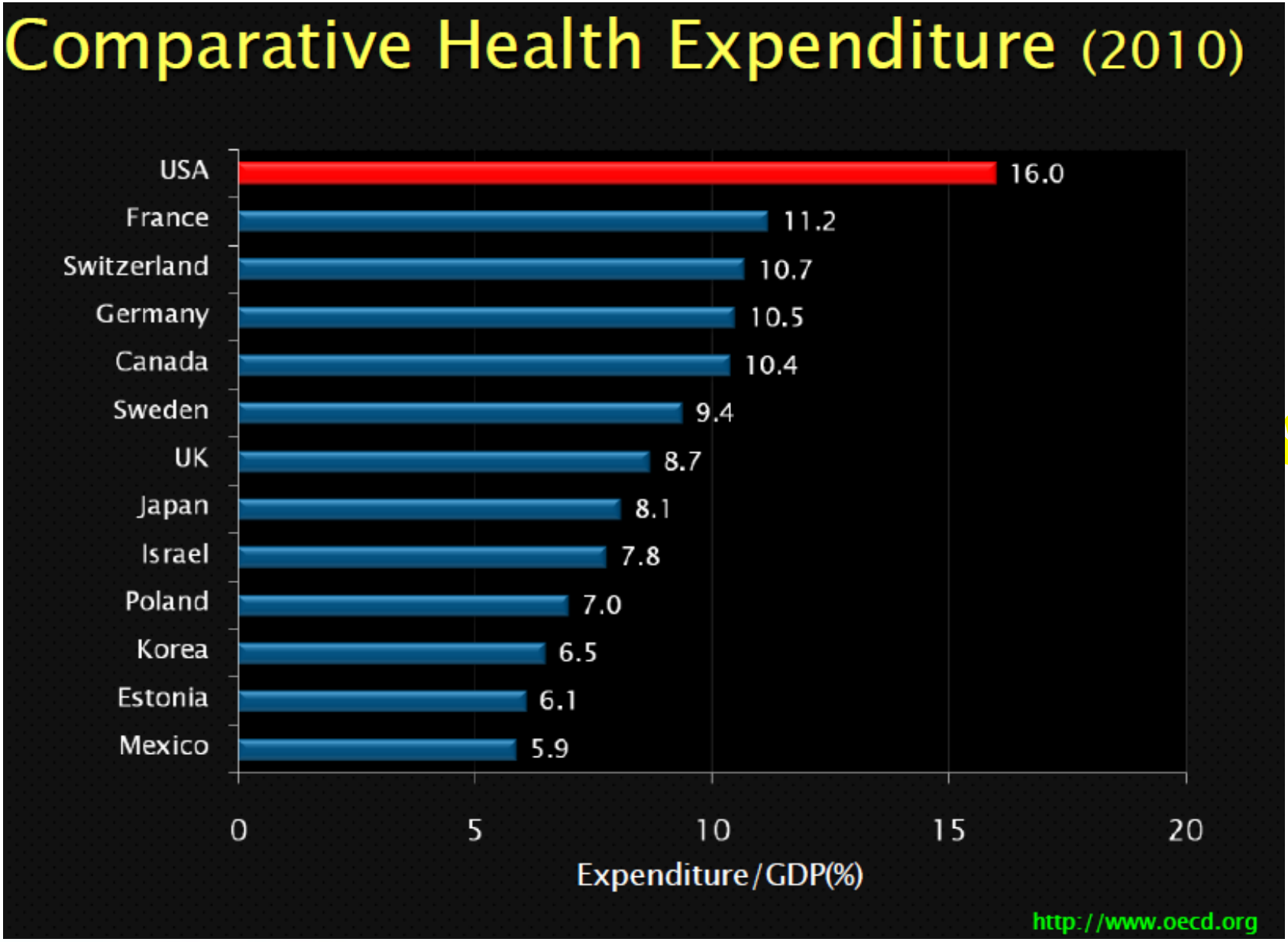
A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions

DES Generally Preferred Over BMS (Efficacy Considerations)	BMS Preferred Over DES (Safety Considerations)
• Left main disease • Small vessels • In-stent restenosis • Bifurcations • Diabetes • Long lesions • Multiple lesions • Saphenous vein grafts	• Unable to tolerate or comply with DAPT • Anticipated surgery requiring discontinuation of DAPT within 12 mo • High risk of bleeding

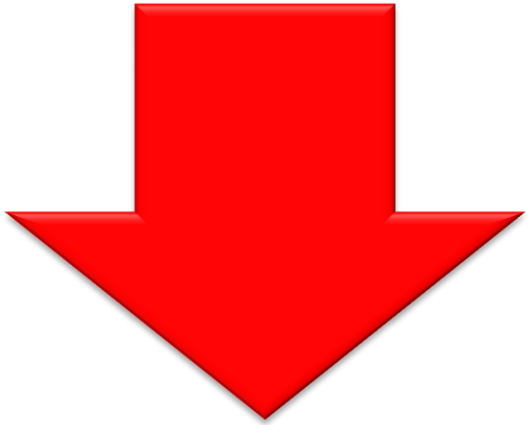
My wish list

- More efficient DES in complex CAD including diabetic patient
- DES with less late catch-up
- No need for prolonged DAPT
- Less costly DES

Comparative Health Expenditure (2010)



A turning point for stent manufacturers?



Flat market

New indications?

Market expansion ??

Development cost

Clinical program

Regulatory burden

Low cost competition

Shareholder pressure

Superiority validation? A challenge

Trial Requirements for New DES
Superiority RCT (*vs.* SPIRIT IV – 12 months)

Event	PROMUS (n=2416) (%)	NEW DES RCT 50% Reduction[#]	NEW DES RCT 30% Reduction[#]
Death (all)	25 (1.0)	10,000	31,000
Death (cardiac)	10 (0.1)	102,000	310,000
AMI (all)	45 (1.9)	5,300	16,000
Stent Thrombosis*	7 (0.3)	34,000	104,000
TLR	61 (2.5)	4,010	12,000
TVR	94 (3.9)	2,544	7,700
TLF[†]	101 (4.2)	2,358	7,120
MACE	102 (4.2)	2,358	7,120

[#]Total sample size is based on equal allocation of New DES and PROMUS with 80% power and 2-sided alpha of 5%
*Stent Thrombosis = ARC Definite/Probable
[†]Primary Endpoint (TLF = Cardiac Death, Target Vessel MI, or ischemia driven TLR)

N Engl J Med 2010;362:1663-74
BSC: Internal Data

Should we believe in the miracle?

Is my dream becoming real?

- Reduced/absorbable polymer or no polymer
  - No efficacy compromise ?
- Low dose drug combination
  - No safety compromise ?
- Fully absorbable DES

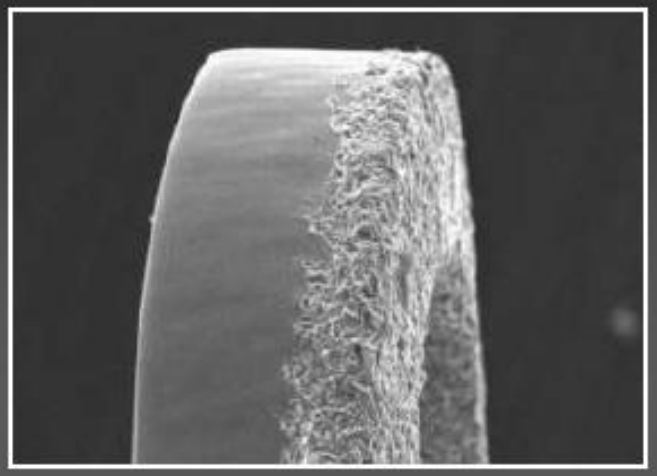
BioFreedom Drug Coated Stent (DCS)

Hypothesis: Polymer-free drug release via porous-eluting stents may reduce late events caused by polymer stent coatings

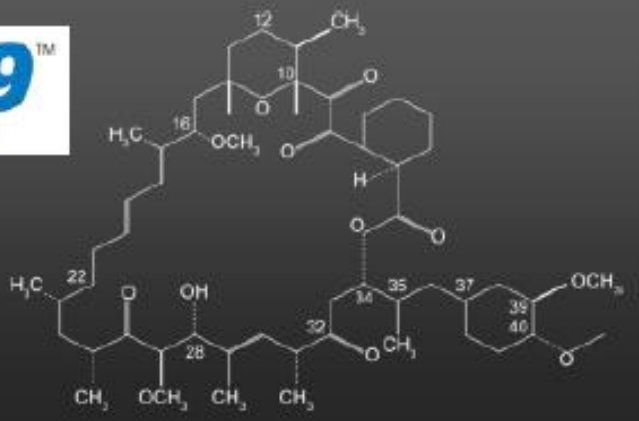
Potential advantage

- Avoid long-term late adverse effects that might be attributable to the polymer
- Improved surface integrity since there is no polymer to be sheared or pealed away from the stent struts
- Possible shorter need of dual antiplatelet therapy

Selectively micro-structured surface holds drug in abluminal surface structures



BA9™



European Cardiovascular Research Center

LEADERS FREE TRIAL

- Age ≥ 75 years old
- Adjunctive oral anticoagulation treatment planned to continue after PCI
- Baseline Hb <11 g/dl (or anemia requiring TF during the prior 4 weeks)
- Any prior intra-cerebral bleed at any time
- Any stroke during the past year
- Hospital admission for bleeding during the prior 12 months
- Non-skin cancer diagnosed or treated ≤ 3 years
- Planned daily NSAID (other than aspirin) or steroids for ≥ 30 days after PCI
- Planned major surgery (within 1 year)
- Expected non-compliance to prolonged DAPT for other non-financial reasons

- There is room for improvement
- There are some technical solutions (even for late catch-up??)
- Validation of benefit is only possible in high risk groups of patients
- And absorbable DES are on their way…