REDUCTION DE LA DUREE DE LA DOUBLE ANTI AGREGATION PLAQUETTAIRE APRES IMPLANTATION DE STENTS ACTIFS

LA PREUVE PAR L'IMAGE

Didier Carrié

CHU TOULOUSE RANGUEIL

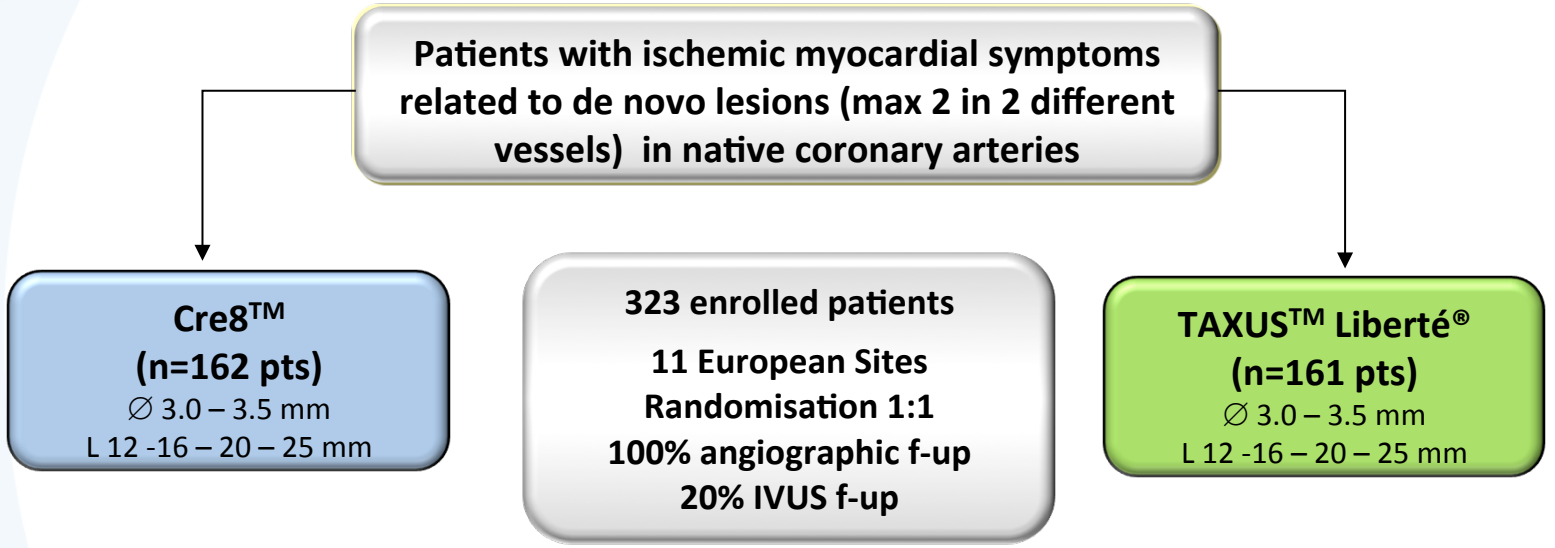
SYMPOSIUM CID

6 Juin 2012

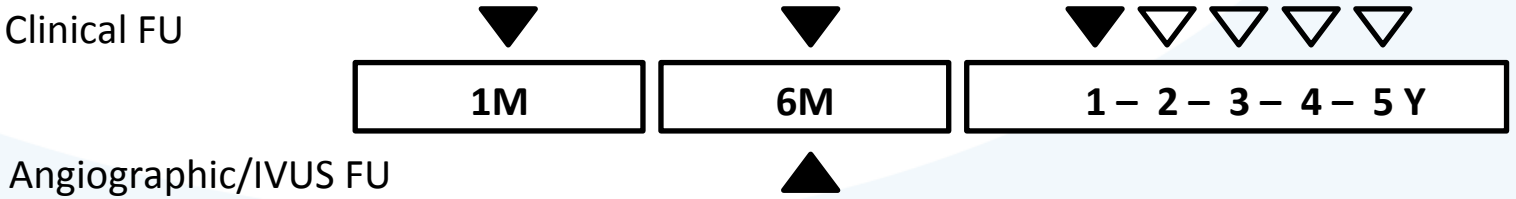
APPAC Biarritz

Aucun Conflit d’intérêt

NEXT Study Overview



Primary Endpoint: In-stent LLL at 6 months



NEXT Study Management

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Angiographic Core Lab

BioClinica Leiden, The Netherlands

IVUS Core Lab

BioClinica Leiden, The Netherlands

Sponsor

CID S.p.A.

Baseline Clinical Characteristics

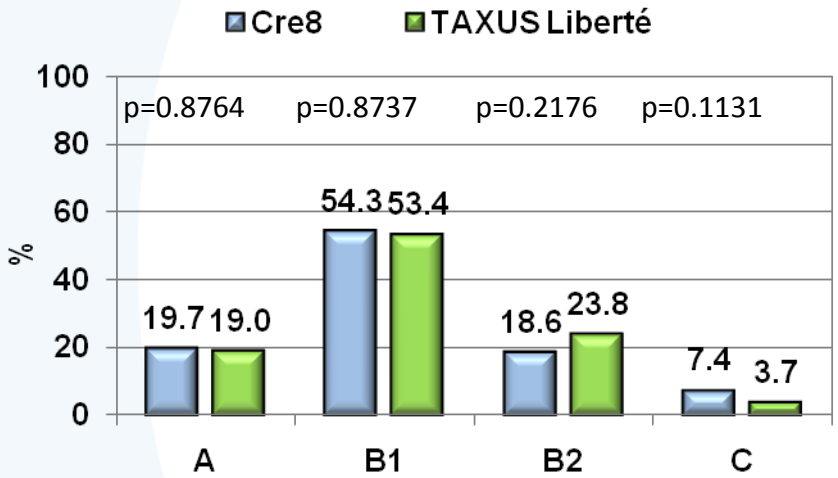
	Cre8 (162 pts)	TAXUS Liberté (161 pts)	p value
Male	76.5% (124/162)	67.7% (109/161)	0.0832
Mean Age (yrs)	64.90±10.20	64.39±10.45	0.6576
Silent ischemia	19.1% (31/162)	14.3 % (23/161)	0.2428
Stable angina	48.8% (79/162)	55.9% (90/161)	0.1992
Unstable angina	17.3% (28/162)	14.9% (24/161)	0.5611
ACS > 72 h	14.8% (24/162)	14.9% (24/161)	0.9815
Prior MI	8.6% (14/162)	9.3% (15/161)	0.8320
Prior PCI	16.0% (26/162)	14.3% (23/161)	0.6586
Prior CABG	3.1% (5/162)	4.3% (7/161)	0.5490

Patients' Risk Factors

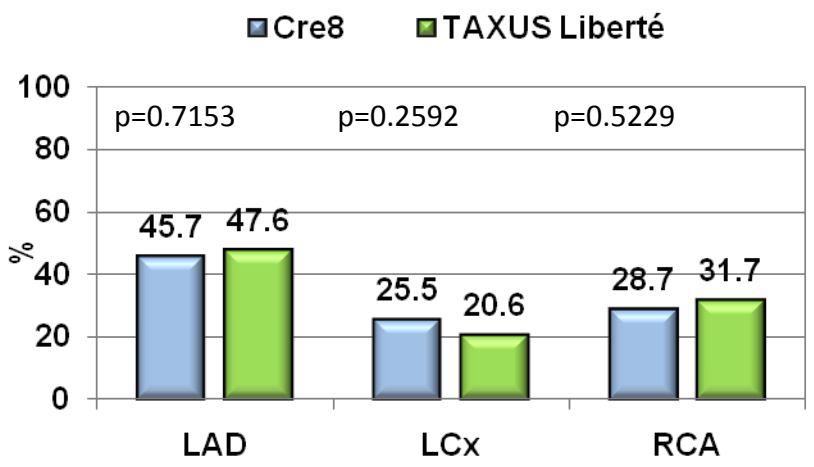
	Cre8 (162 pts)	TAXUS Liberté (161 pts)	p value
Smoker	55.6% (90/162)	54.7% (88/161)	0.8712
Current	24.1% (39/162)	24.8% (40/161)	0.8720
Ex-smoker	31.5% (51/162)	29.8% (48/161)	0.7451
Diabetes	29.6% (48/162)	24.2% (39/161)	0.2735
ID Diabetes	6.2% (10/162)	6.8% (11/161)	0.8101
Non-ID Diabetes	23.5% (38/162)	17.4% (28/161)	0.1765
Hypertension	64.2% (104/162)	64.6% (104/161)	0.9403
Hyperlypidemia	63.0% (102/162)	60.9% (98/161)	0.6985
CAD Family History	29.0% (47/162)	25.5% (41/161)	0.4741

Target Lesion Characteristics

Lesion classification ACC/AHA



Vessel location

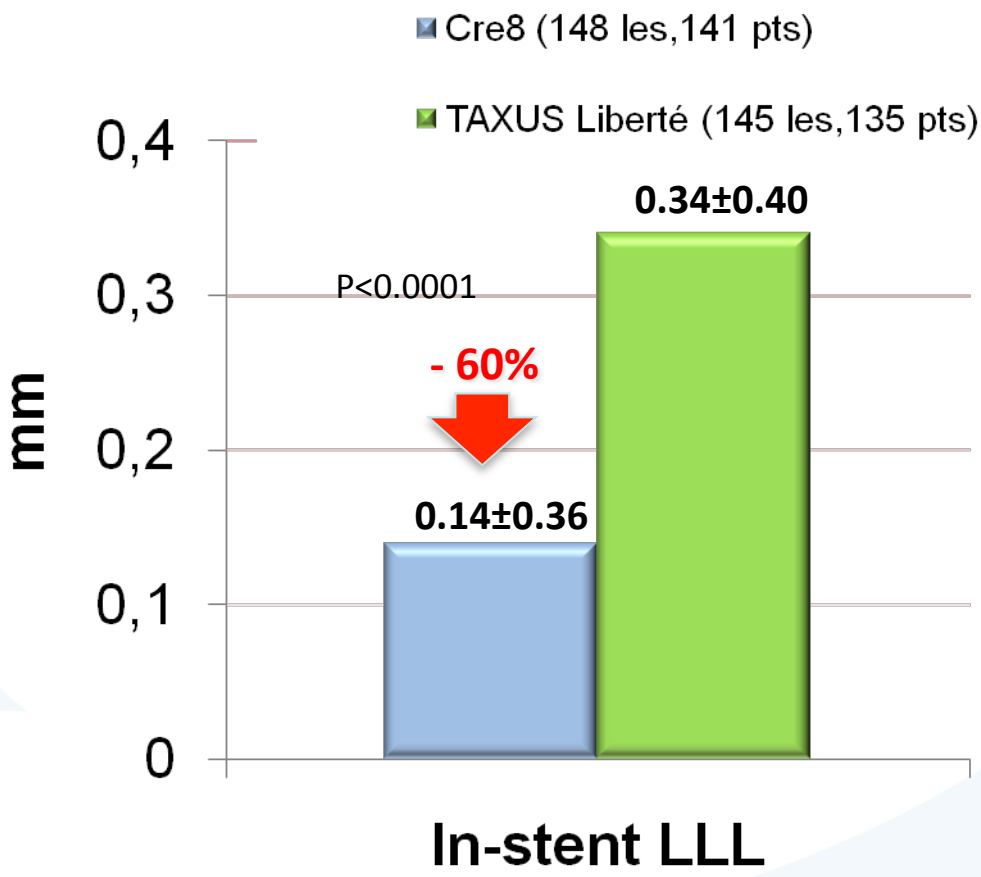


	Cre8 (162 pts)	TAXUS Liberté (161 pts)	p value
Device success*	98.9% (186/188)	100% (189/189)	0.1551
Procedural success#	96.3% (156/162)	99.4% (160/161)	0.1209

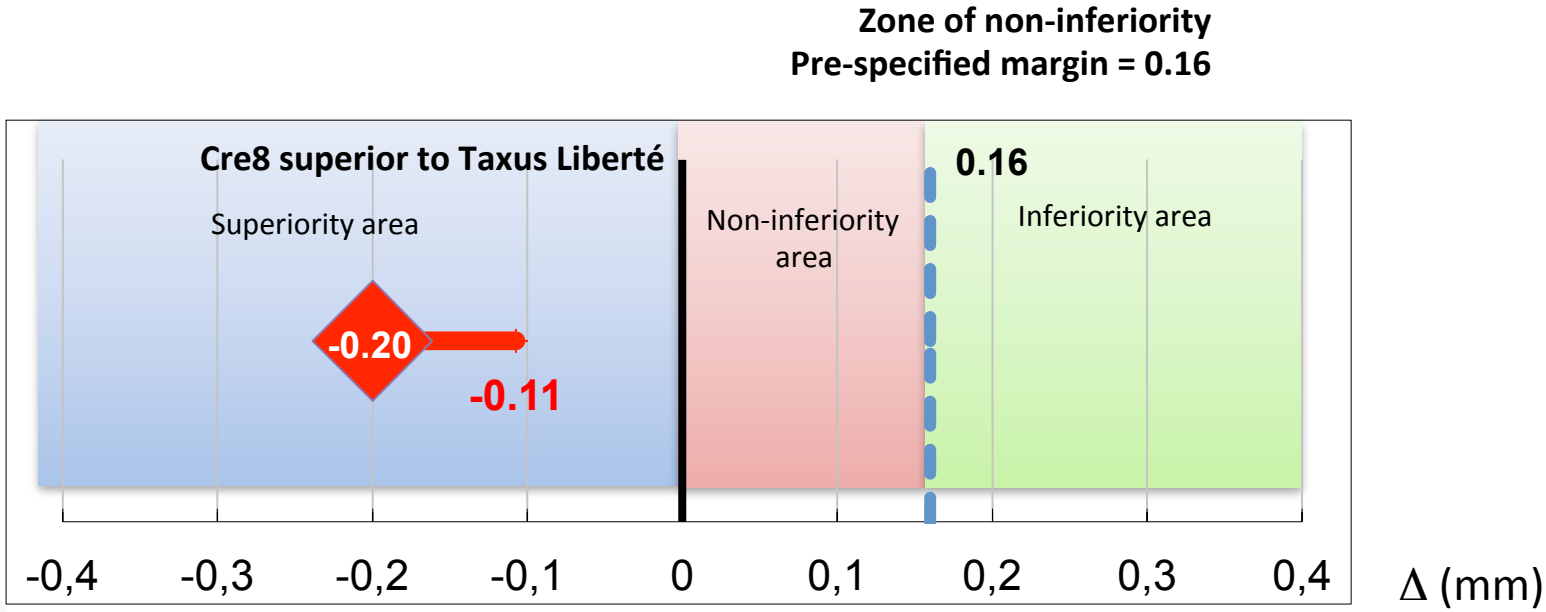
*Defined as successful stent implantation with final stenosis < 30% using the assigned device only. Calculated on number of lesions.

Defined as device success without the occurrence of cardiac death, MI or TLR during the hospital stay, to a maximum of first 7 days post procedure. Calculated on number of patients.

Primary Endpoint:
6-month in-stent Late Lumen Loss



Primary Endpoint Analysis:
6-month in-stent Late Lumen Loss



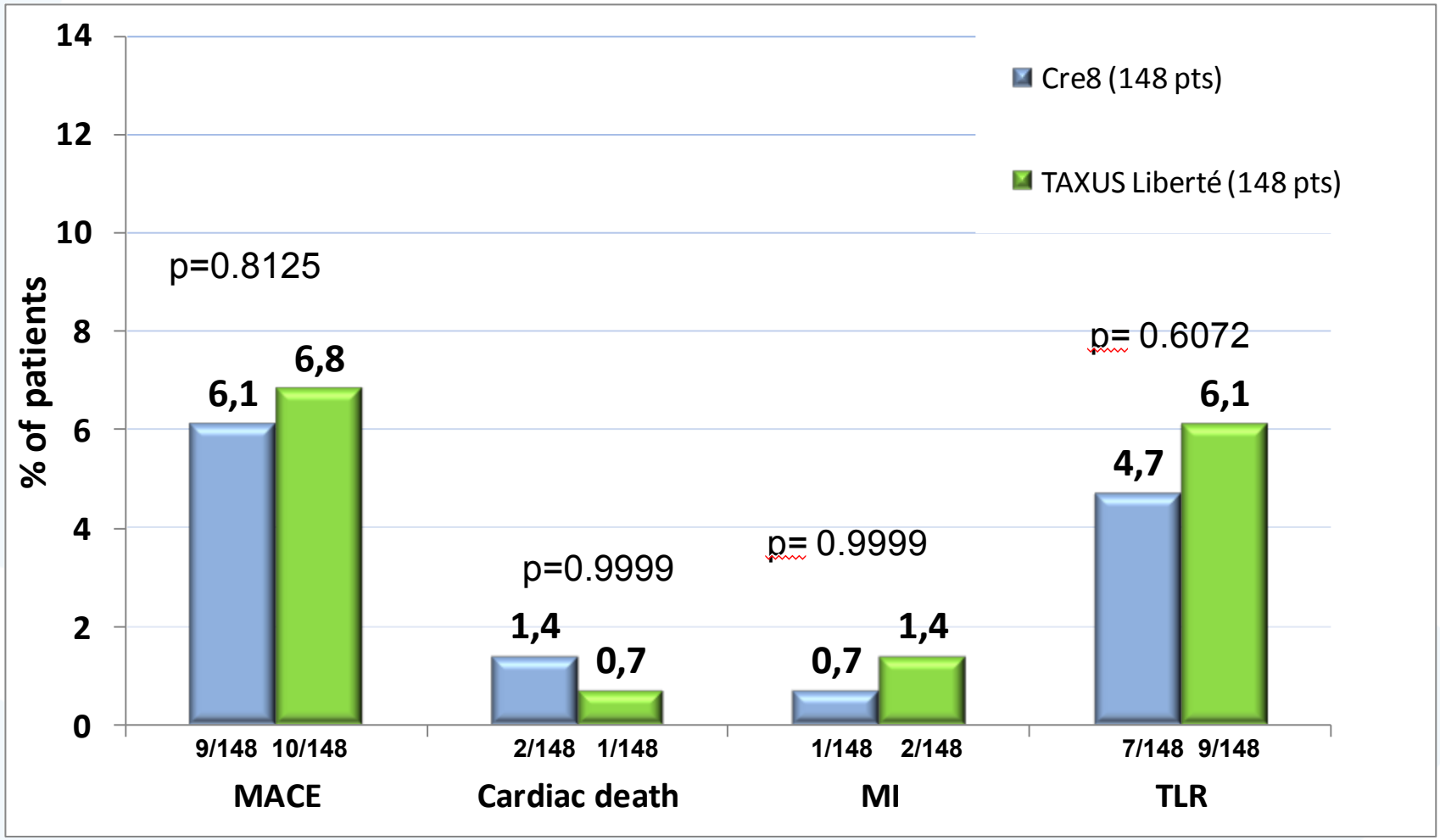
Δ (mm)= Cre8 LLL – TAXUS Liberté LLL
-0.20 = 0.14 - 0.34

Upper 1-sided 97.5% confidence interval
-0.11

Superiority p-value < 0.0001	Non-Inferiority p-value < 0.0001

12-month Cumulative Major Adverse Cardiac Event (MACE)

(Cardiac death, all MI, all TLR)



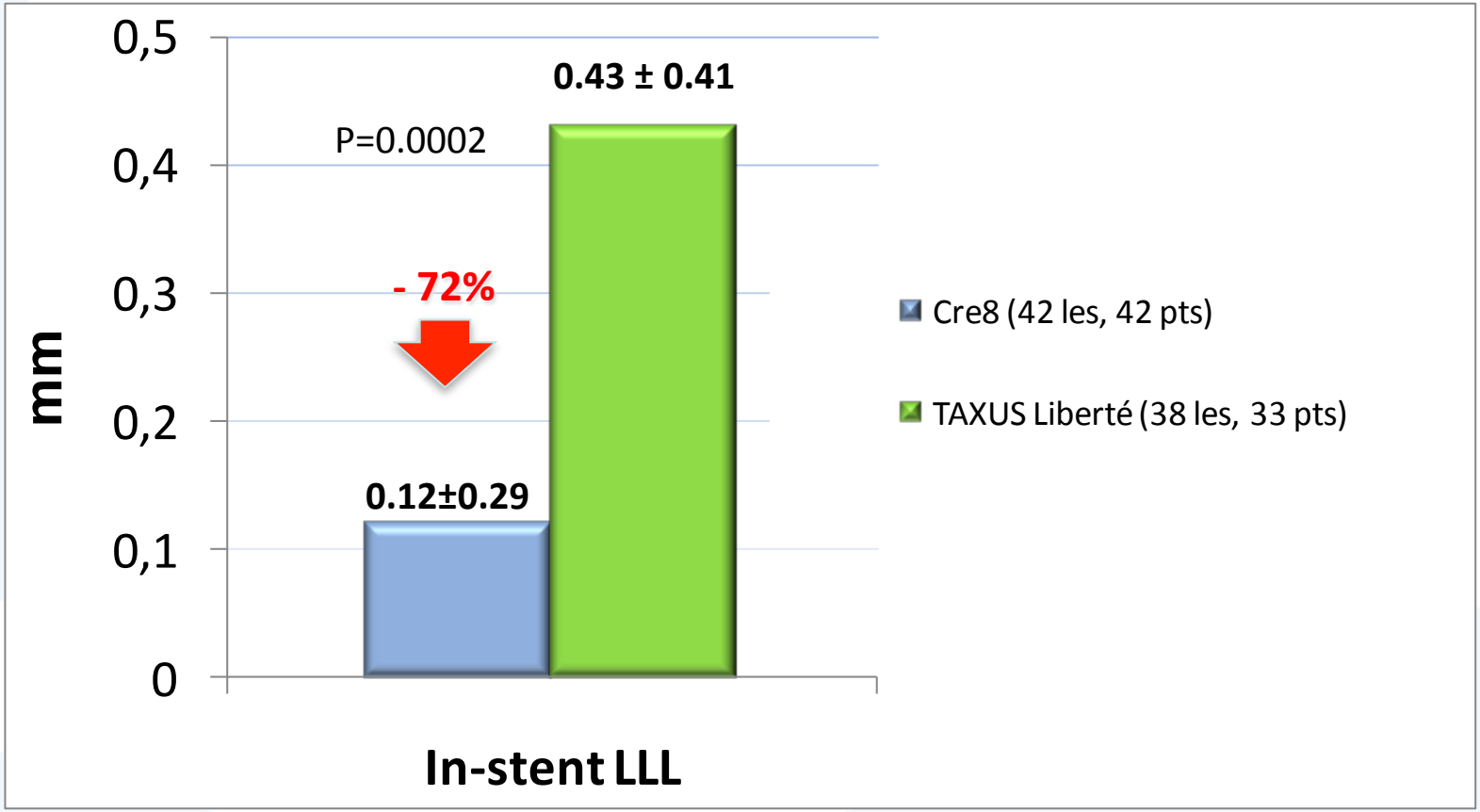
ARC Stent Thrombosis

	Cre8 (158 pts)	TAXUS Liberté (157 pts)	p value
Definite Stent Thrombosis			
Acute Thrombosis (0-1 day)	0%	0%	-
Sub-acute Thrombosis (2-30 days)	0%	0.6% (1/157)*	0.4984
Late Thrombosis (31-365 days)	0.6% (1/158)§	0%	1.0000
Probable Stent Thrombosis			
All (0-365 days)	0%	0%	-
TOTAL (Definite + Probable)	**0.6% (1/158)§**	**0.6% (1/157)***	**1.0000**

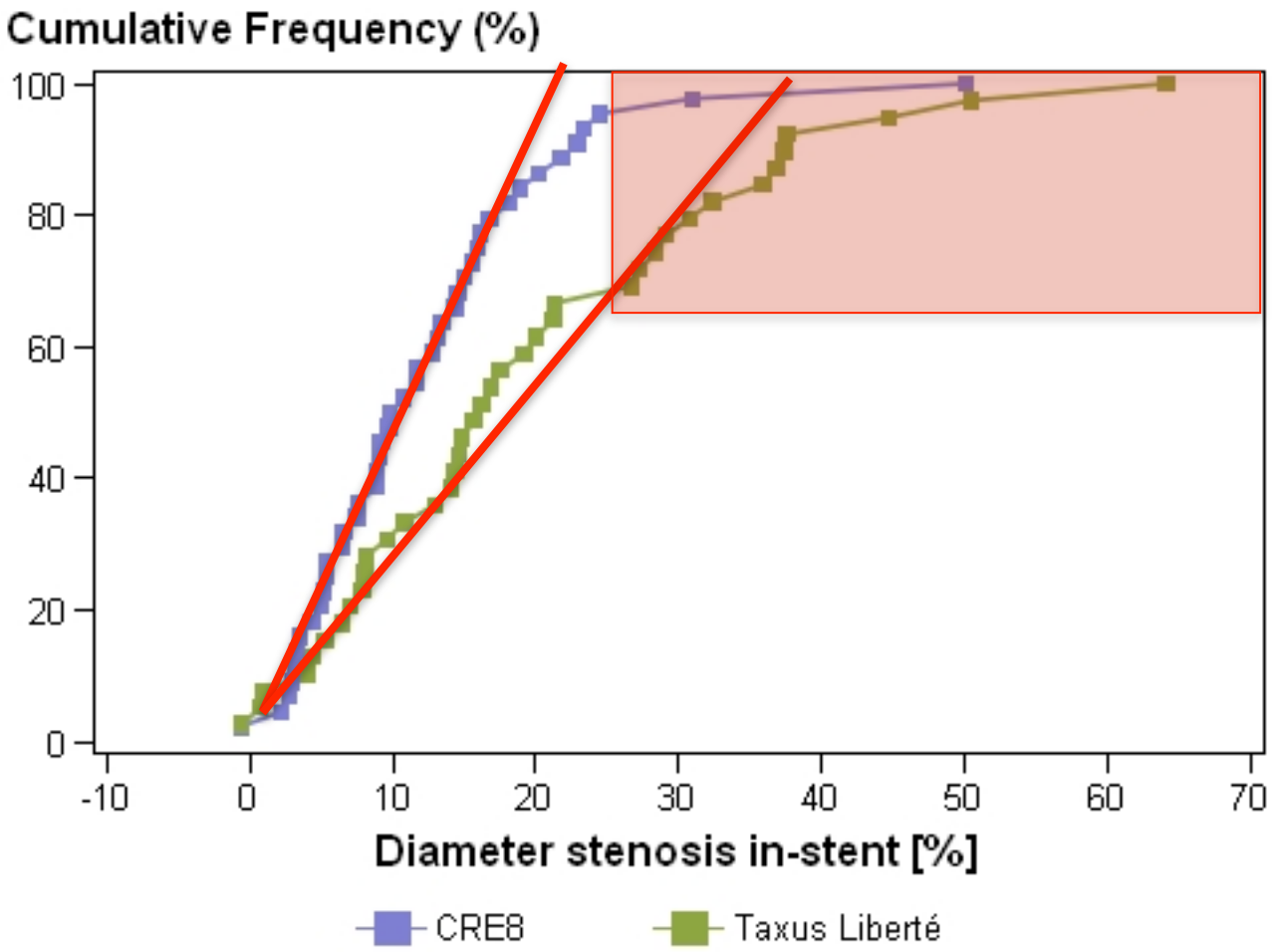
*Definite sub-acute thrombosis: 48 hours after the procedure the patient came back to hospital with MI. Angio control showed a stent thrombosis. Blood exams revealed clopidogrel not responsiveness. The patient was submitted to medical treatment.

§Definite late thrombosis: 11 months after the procedure the patient came back to hospital with MI. Angio control showed a stent thrombosis. The patient ,not responder to thienopyridine due to genetic mutation, had also stopped ASA treatment.

Diabetic Subgroup:
6-month Late Lumen Loss

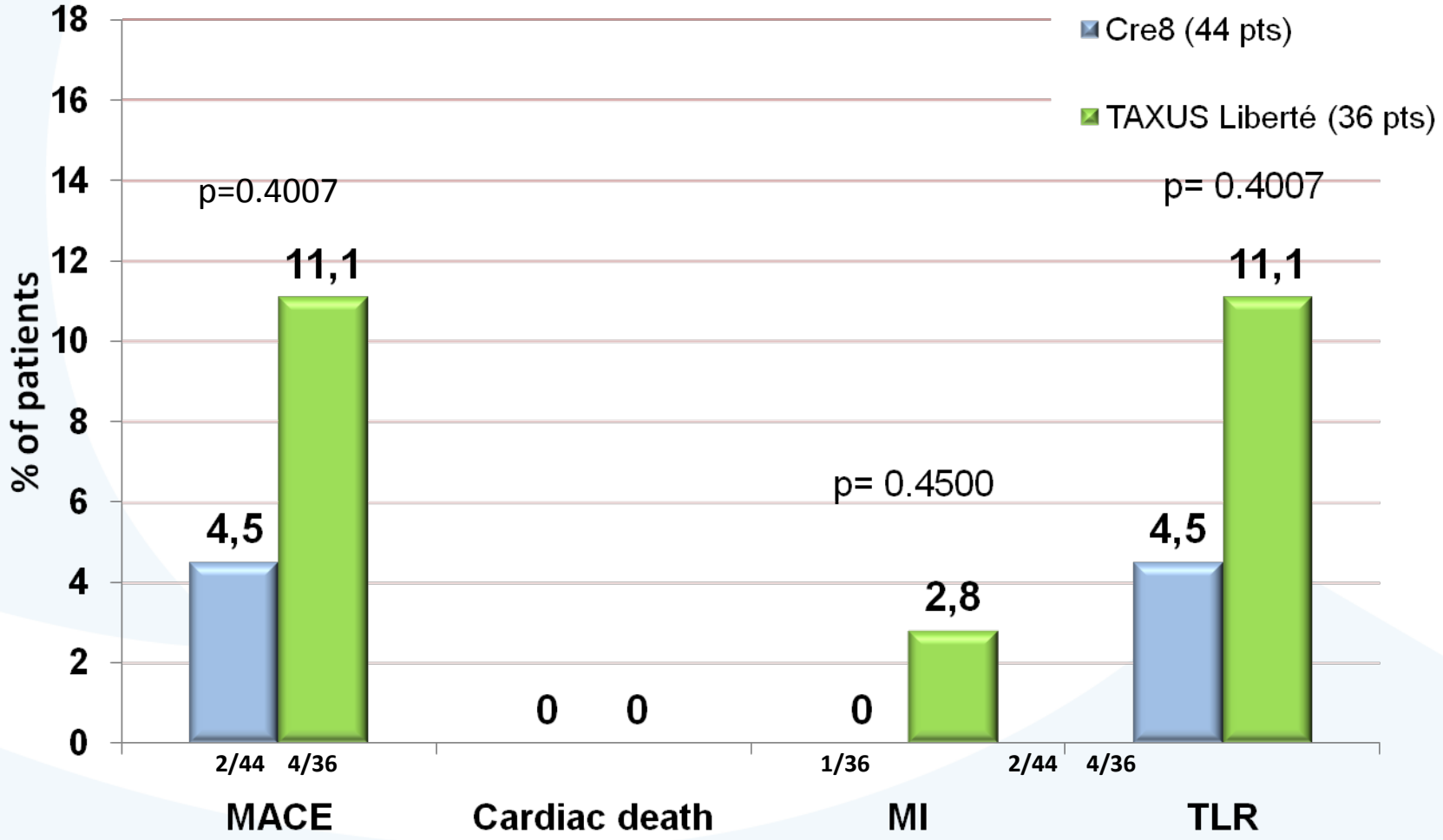


Diabetic Subgroup



Diabetic subgroup

12-month Cumulative Major Adverse Cardiac Event (MACE)
(Cardiac death, all MI, all TLR)



Cre8 clinical plan

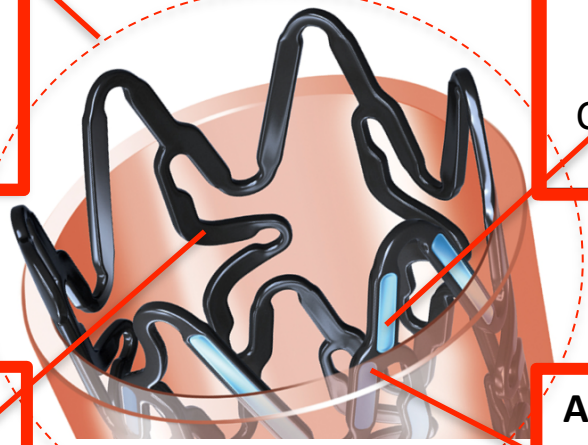
Cre8™: Distinctive Features

Polymer-Free platform

Avoids all the well known drawbacks due to the presence of a polymer interface with blood flow or vessel wall

Abluminal Reservoir Technology (ART)

Controlled and directed elution to the vessel wall



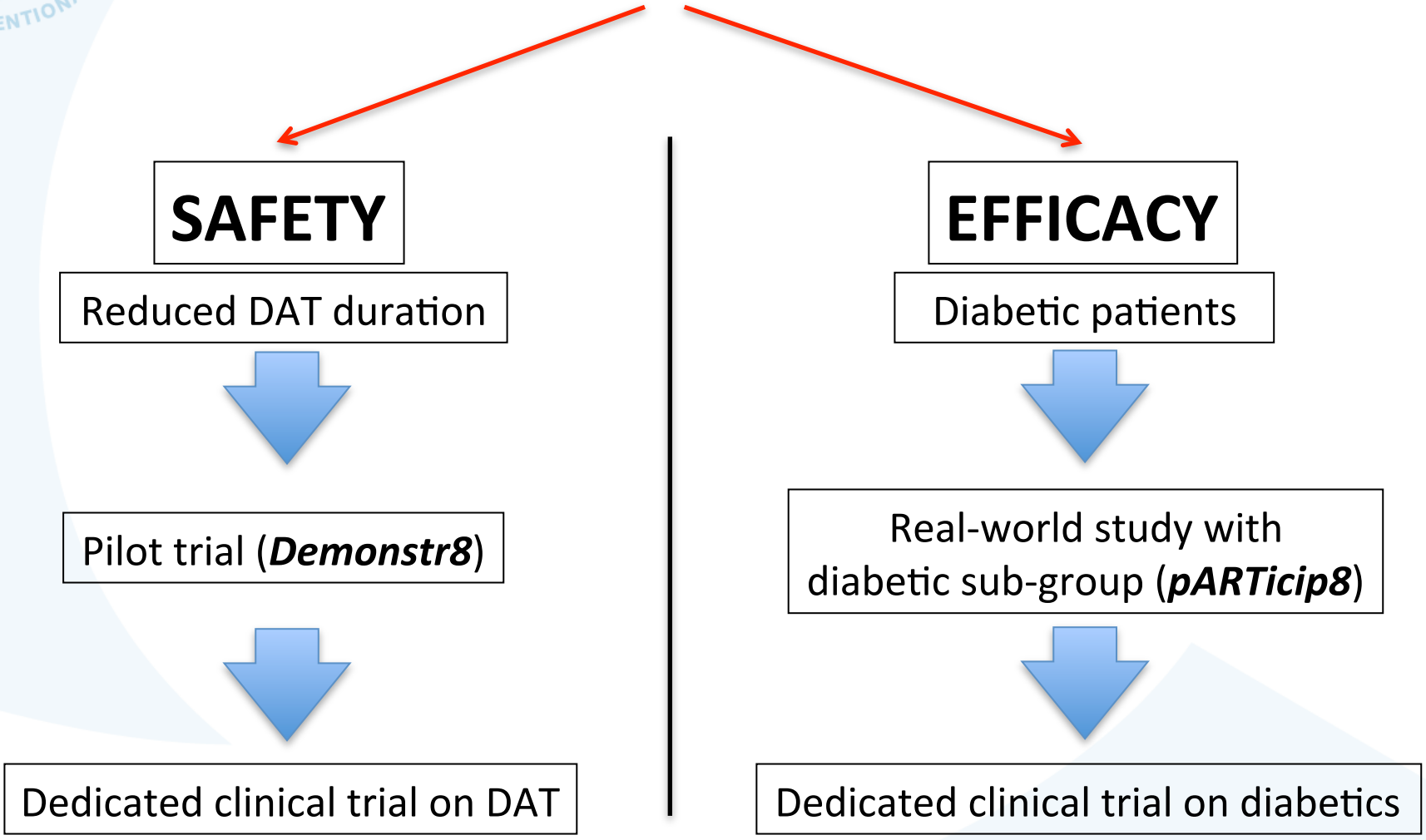
Bio Inducer Surface (BIS) = 2nd generation pure carbon coating

Optimal haemo-compatibility vs. lumen blood flow

Amphilimus Formulation = Sirolimus + organic acid

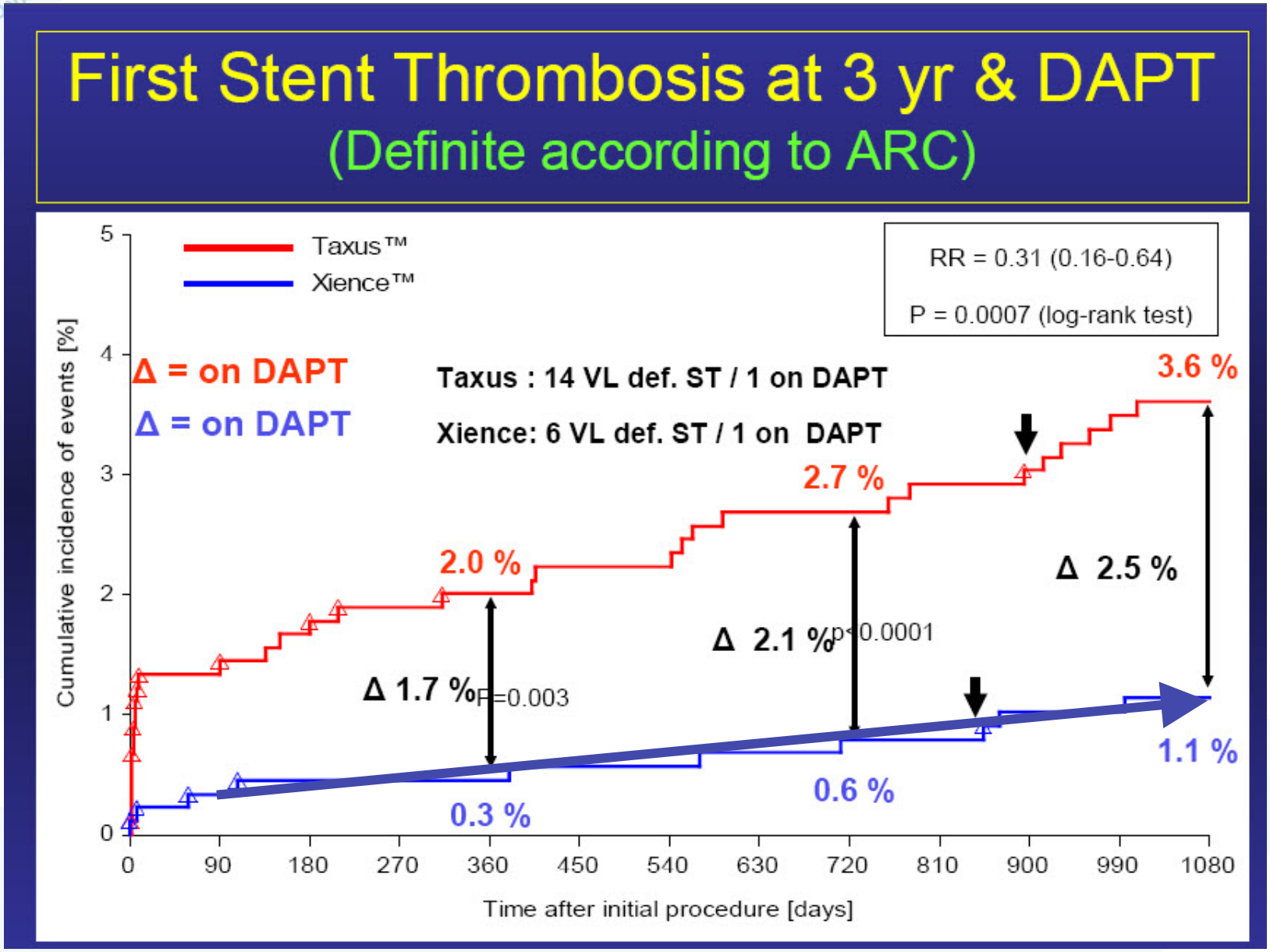
Enhanced drug bioavailability, permeability and maximized product overall safety and efficacy

Cre8™ Clinical plan

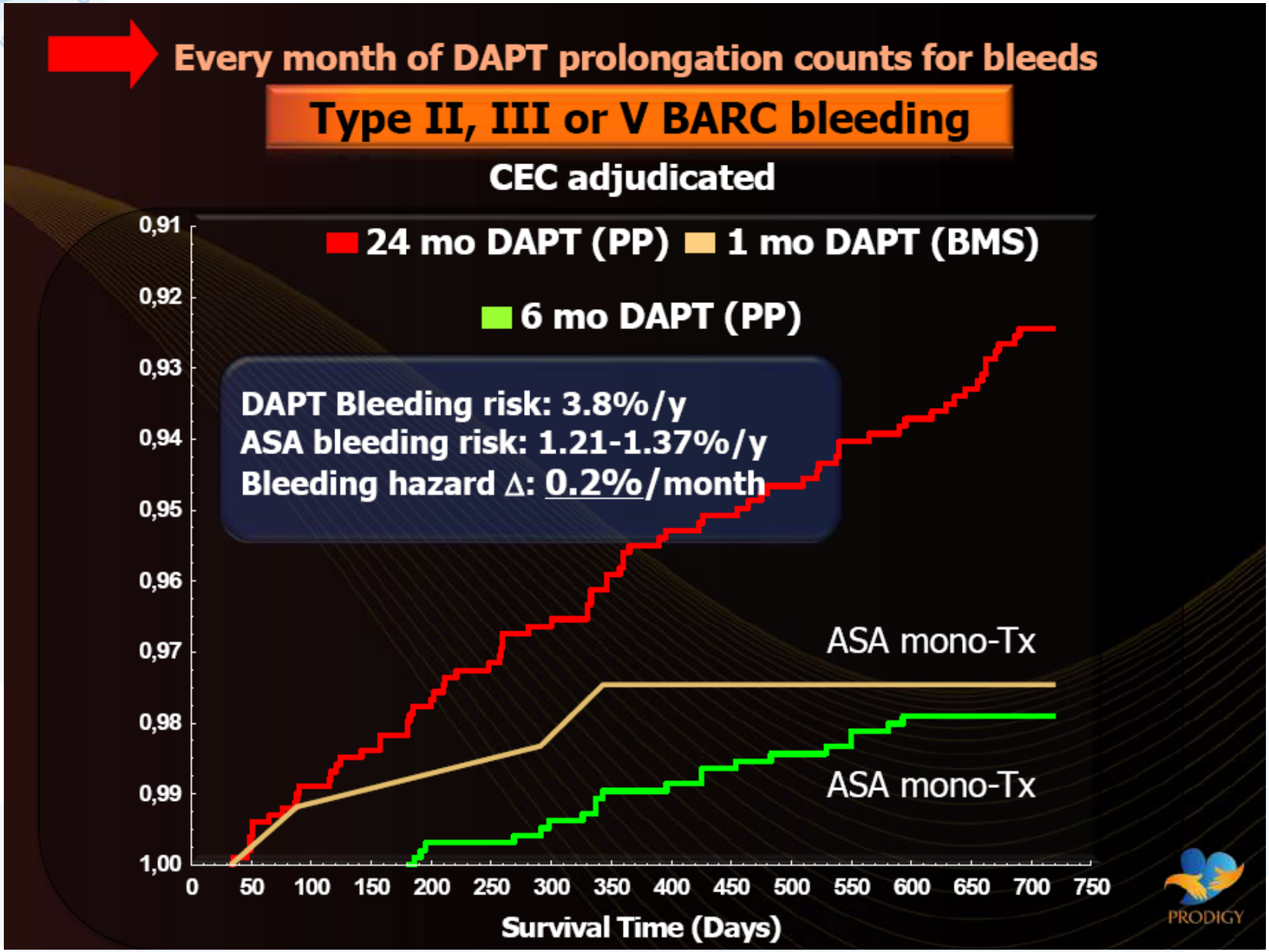


Cre8 and Safety

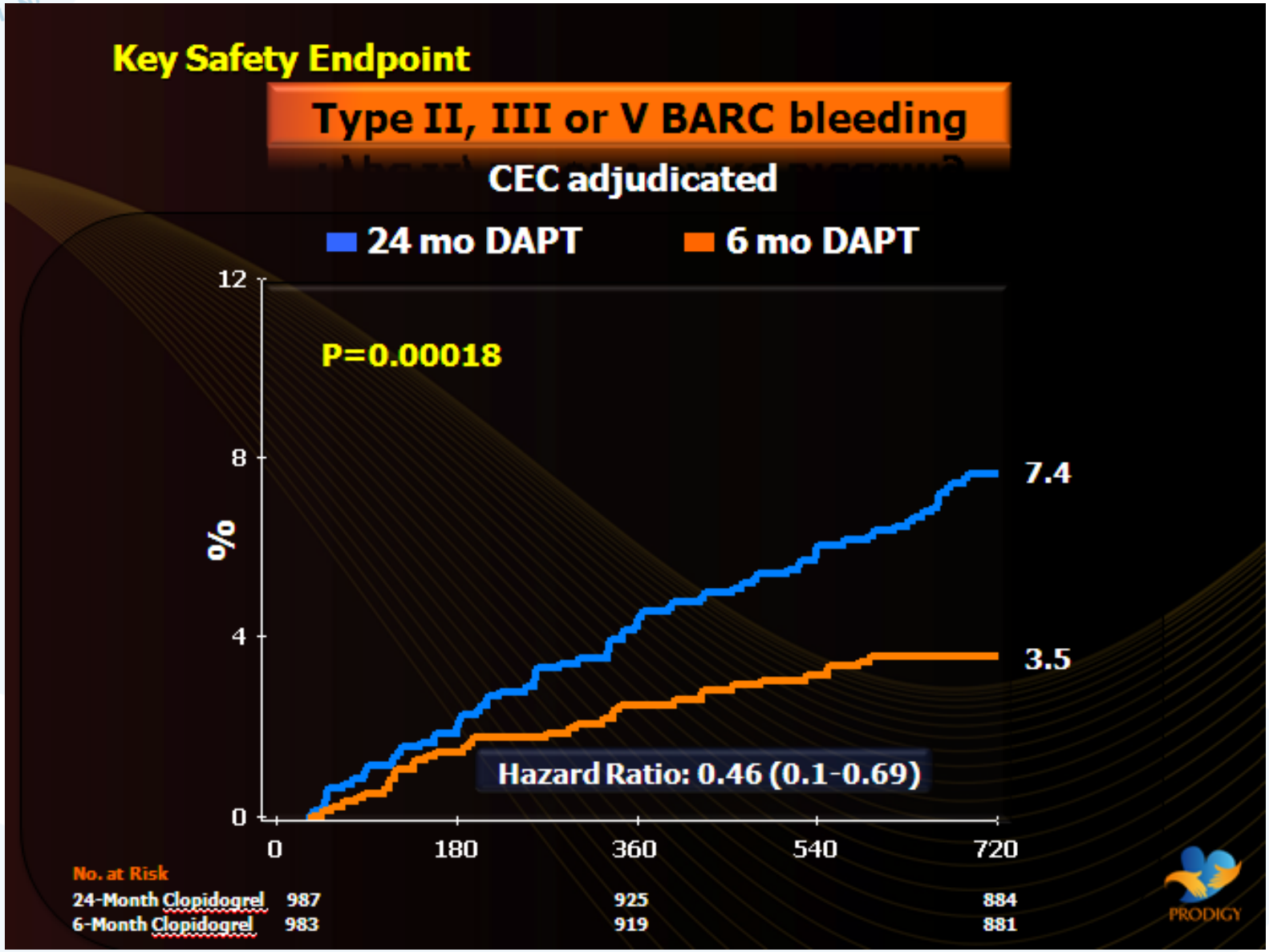
2nd gen DES has lower ST rates vs 1st gen, but still show ST increase every year



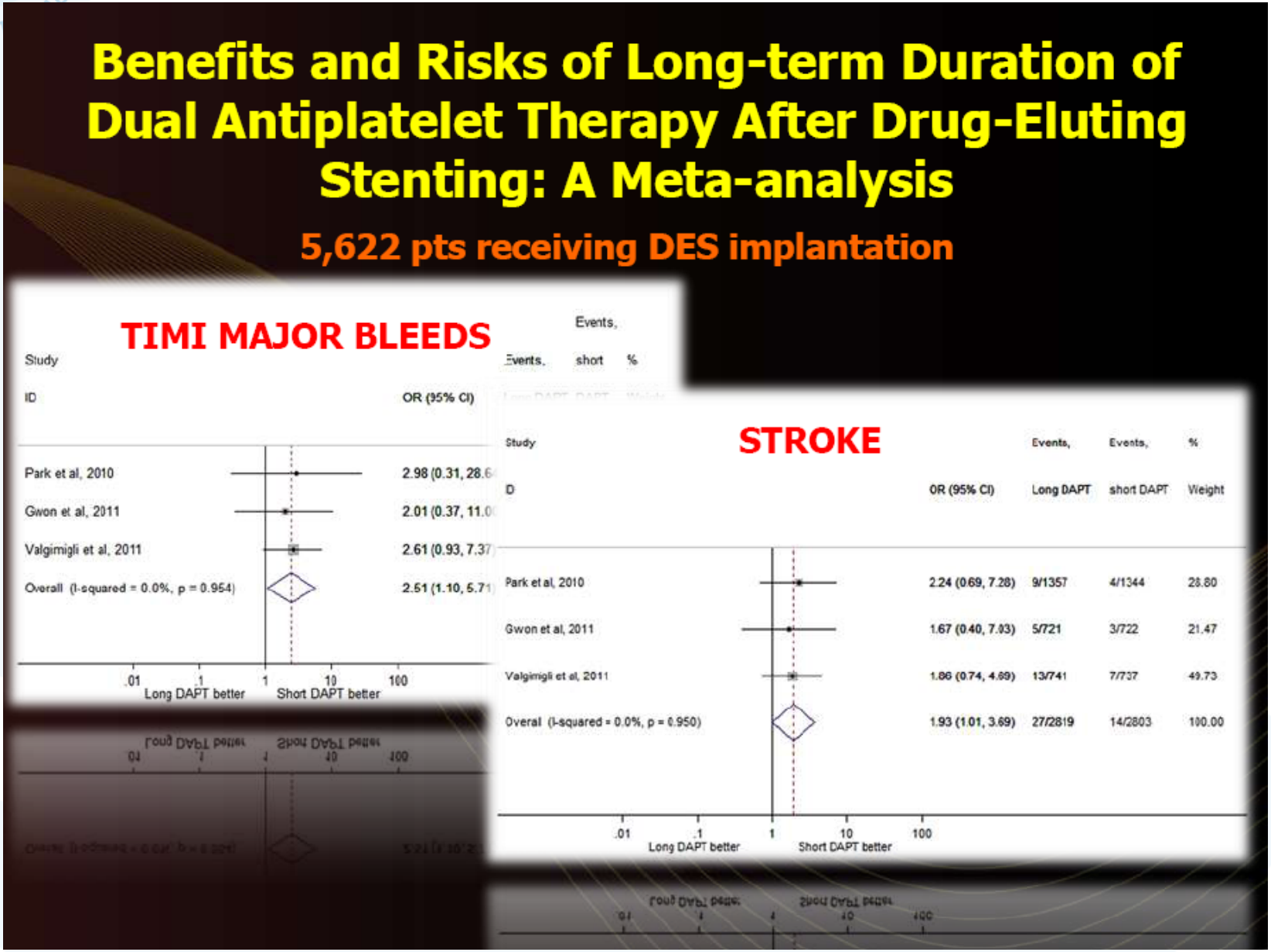
Mono-TX implies less bleeding vs DAPT
(0,2%/month bleeding hazard)



Long-term DAPT causes higher bleeding events



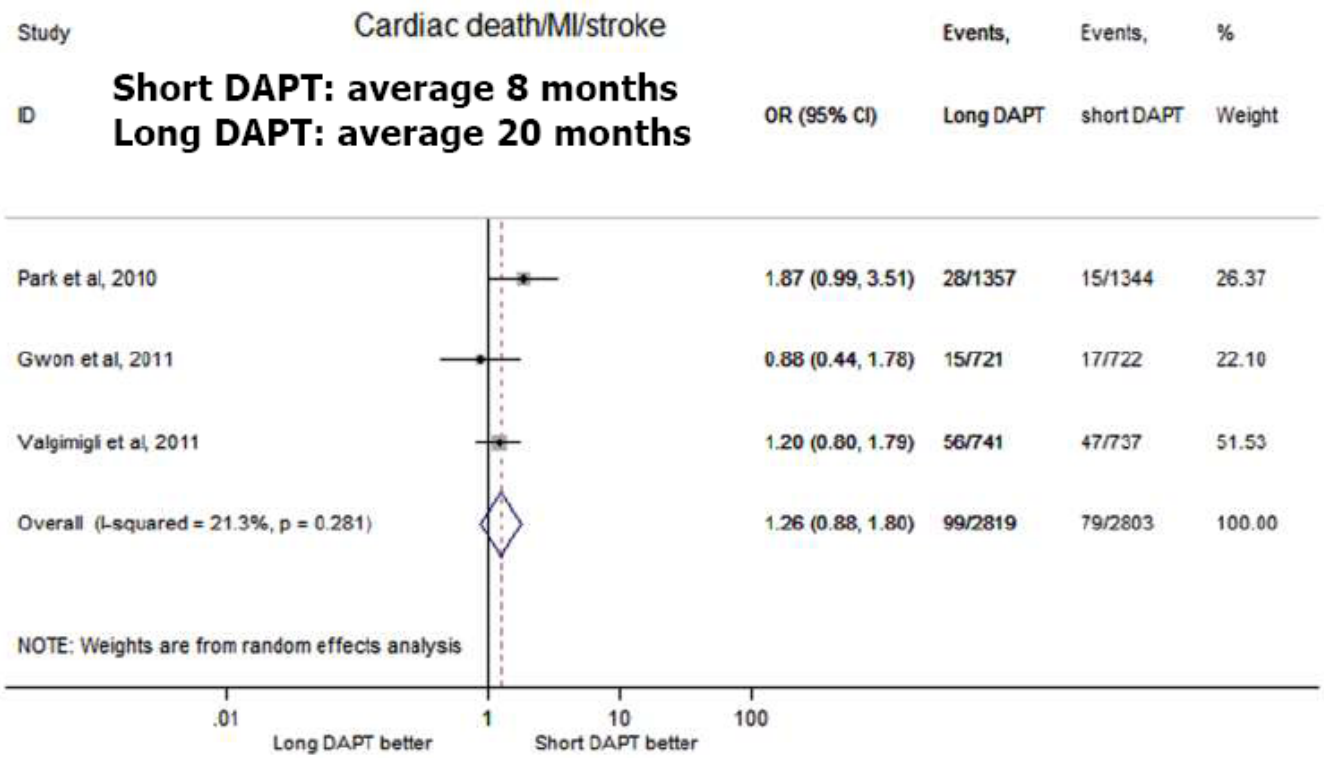
Short DAPT results in lower Major Bleeding and Stroke evaluated alone!



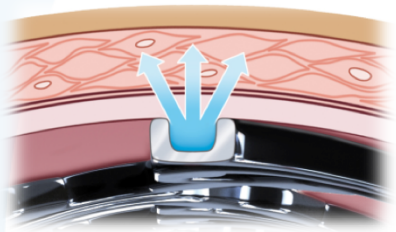
Short DAPT results in lower composite value of cardiac death/ MI/ Stroke

Benefits and Risks of Long-term Duration of Dual Antiplatelet Therapy After Drug-Eluting Stenting: A Meta-analysis

5,622 pts receiving DES implantation



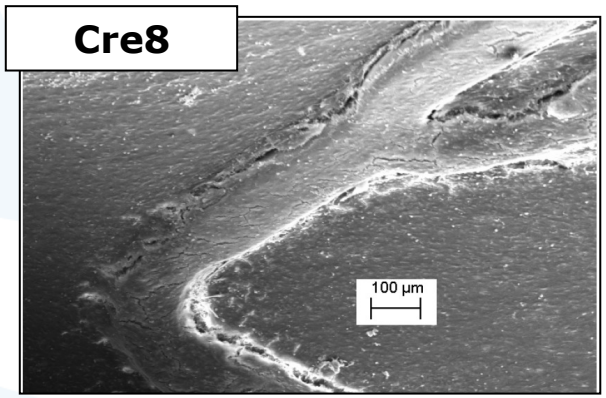
Cre8™ distinctive features for improved safety



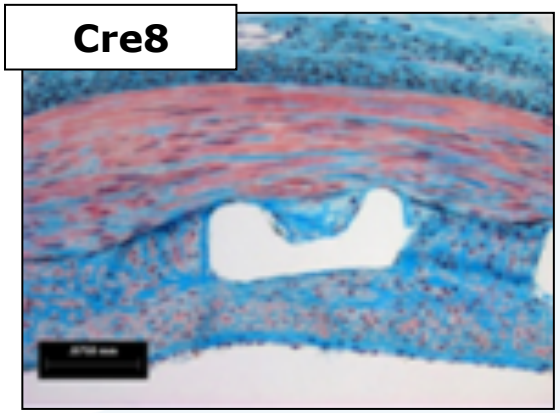
Polymer-free abluminal eluting DES
+
Bio Inducer Surface (BIS)

- **Pre-clinical results**

Endothelization @ 7days*

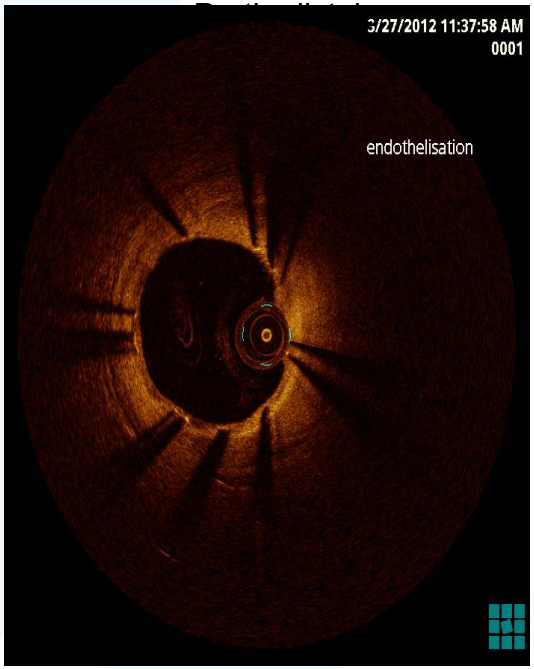


Histological results @ 90days*

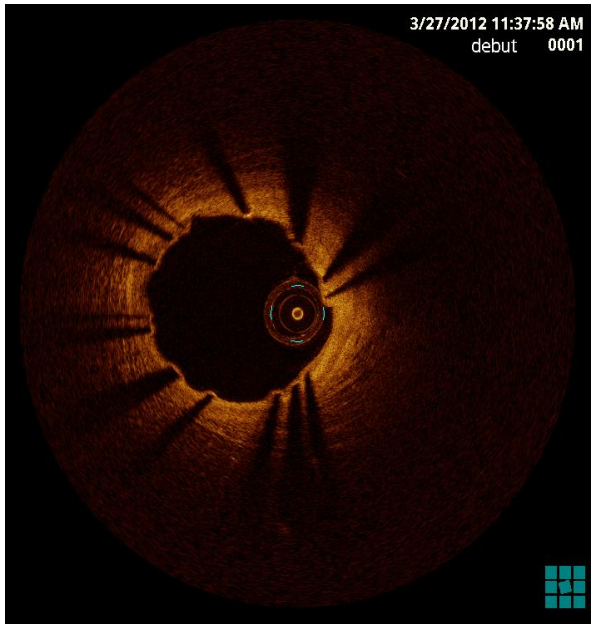


* Published on Eurointervention, November 2011

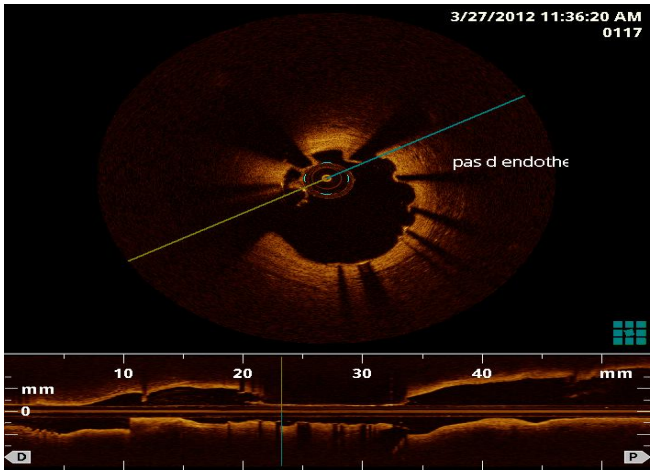
Contrôle OCT IVA à 7 semaines
CRE8 stent



Partie distale



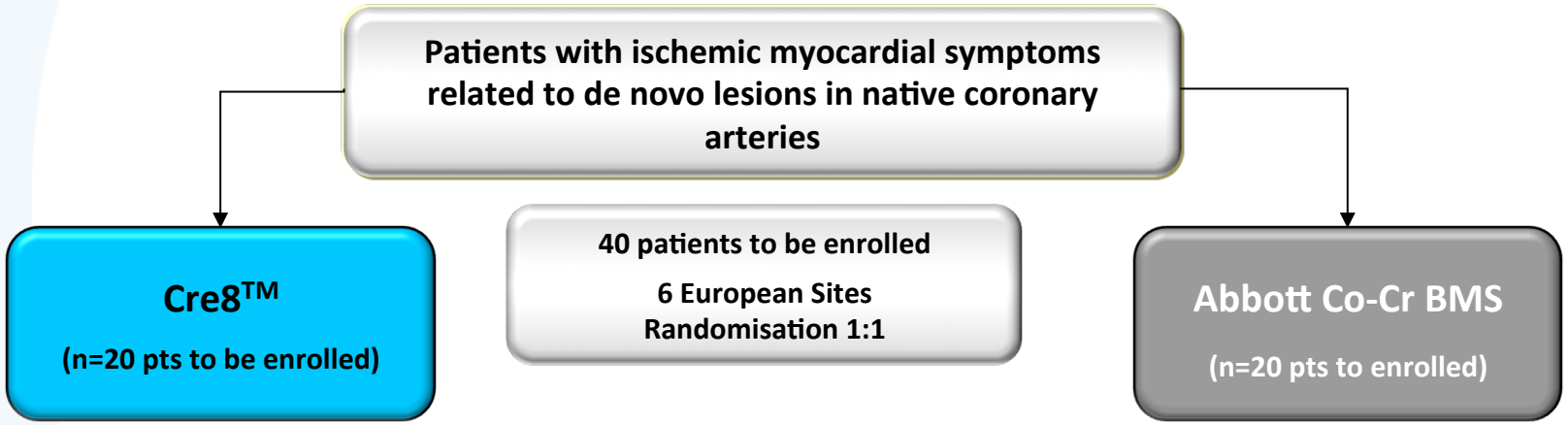
Partie moyenne



Partie proximale

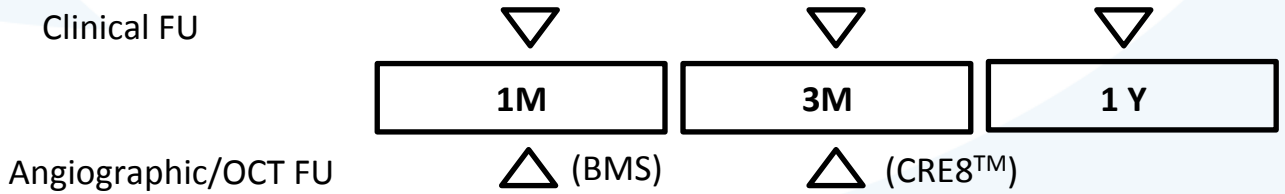
Demonstr8 Clinical Trial

- Randomized comparison between a DES and a BMS to assess neointimal coverage by OCT evaluation



OBJECTIVE: demonstrate non-inferiority in terms of neointimal coverage, assessed by OCT, at 3 months (for Cre8 DES) vs. 1 month for Abbott Co-Cr BMS.

PRIMARY ENDPOINT: rate of cross-sections with RUTTS score of ≤0.3, determined by OCT, at 1 or 3 months, according to the randomization group

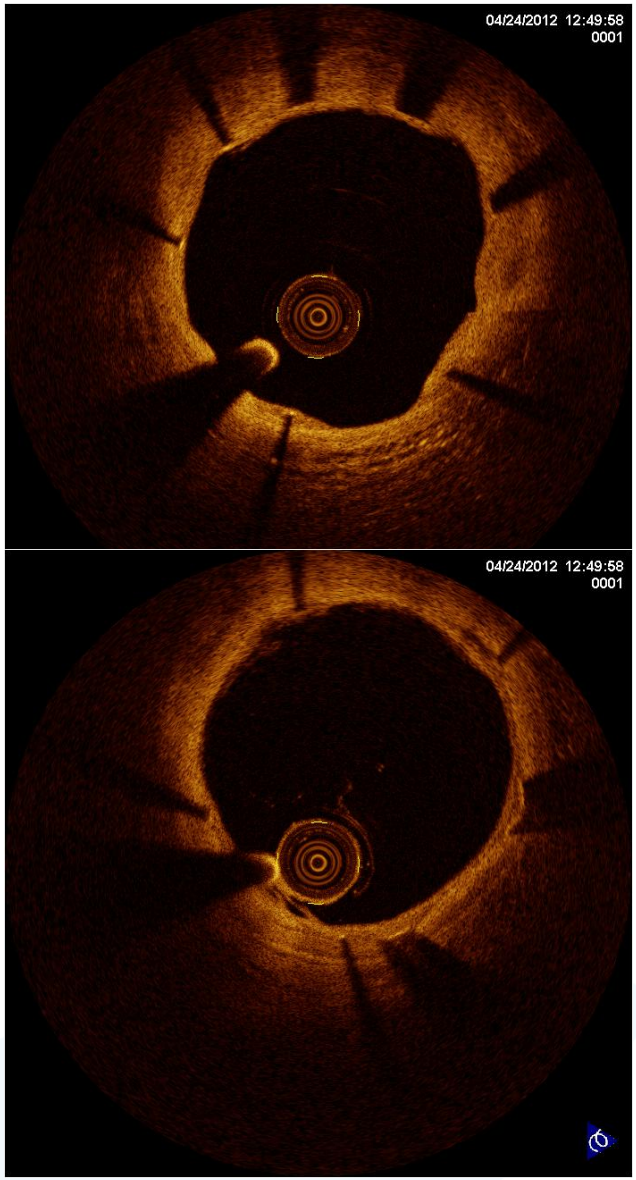


Demonstr8 Clinical Trial

Center N 01, Pt N 02

- **Cre8 positioned in the RCA**
- **FD-OCT assessment at 90 days**

Stent strut coverage in all the 415 analysed struts: 100%

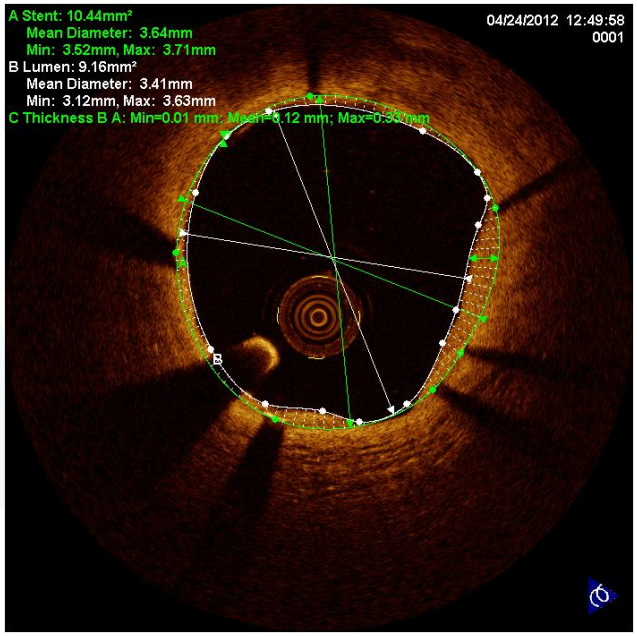


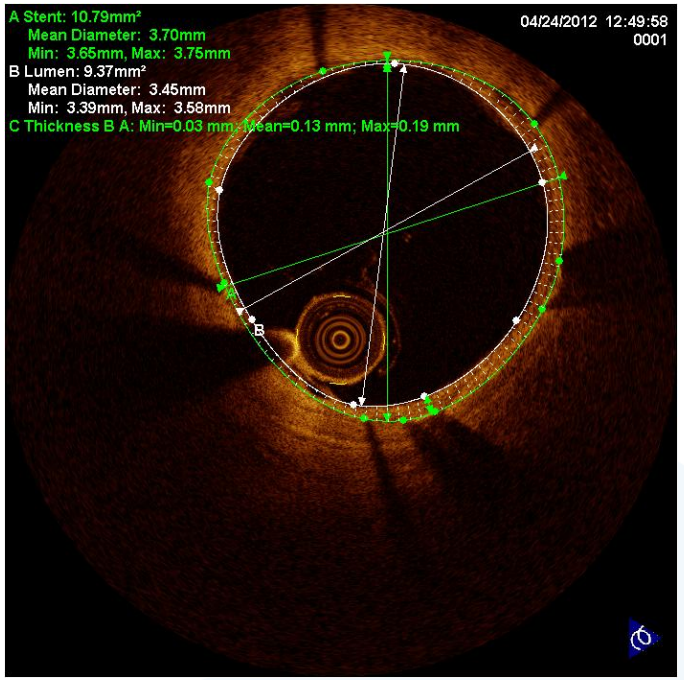
Courtesy of Prof. Francesco Prati and Demonstr8 trial investigators

Demonstr8 Clinical Trial

Center N 01, Pt N 02.

- **Complete stent coverage at 3 months with a regular thin layer of neointima**
- **Mean percentage Neointima = 7%**





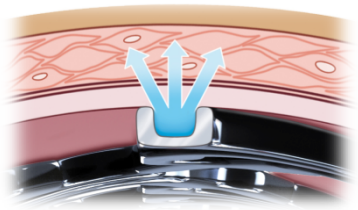
Courtesy of Prof. Francesco Prati and Demonstr8 trial investigators

Cre8 and Efficacy

Cre8™ distinctive features for improved efficacy

1) Polymer-free with controlled abluminal elution

ARTERIAL WALL
Drug elution is precisely controlled

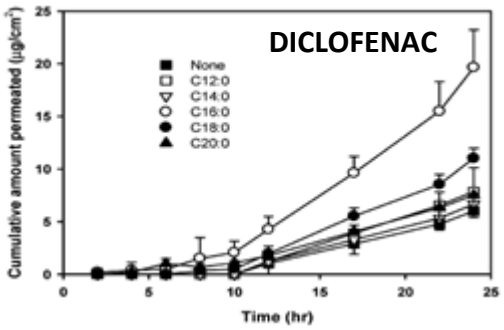


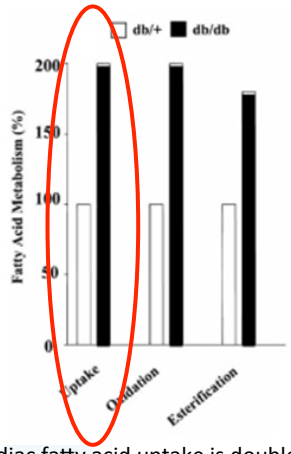
BLOOD FLOW
Lack of any polymer
Lack of any drug

NO Polymer = **reduced inflammatory trigger**

2) Cre8 employs a permeation enhancer (organic acid) in its formulation

Fatty acids are used to improve transdermal and skin delivery of many different drugs.

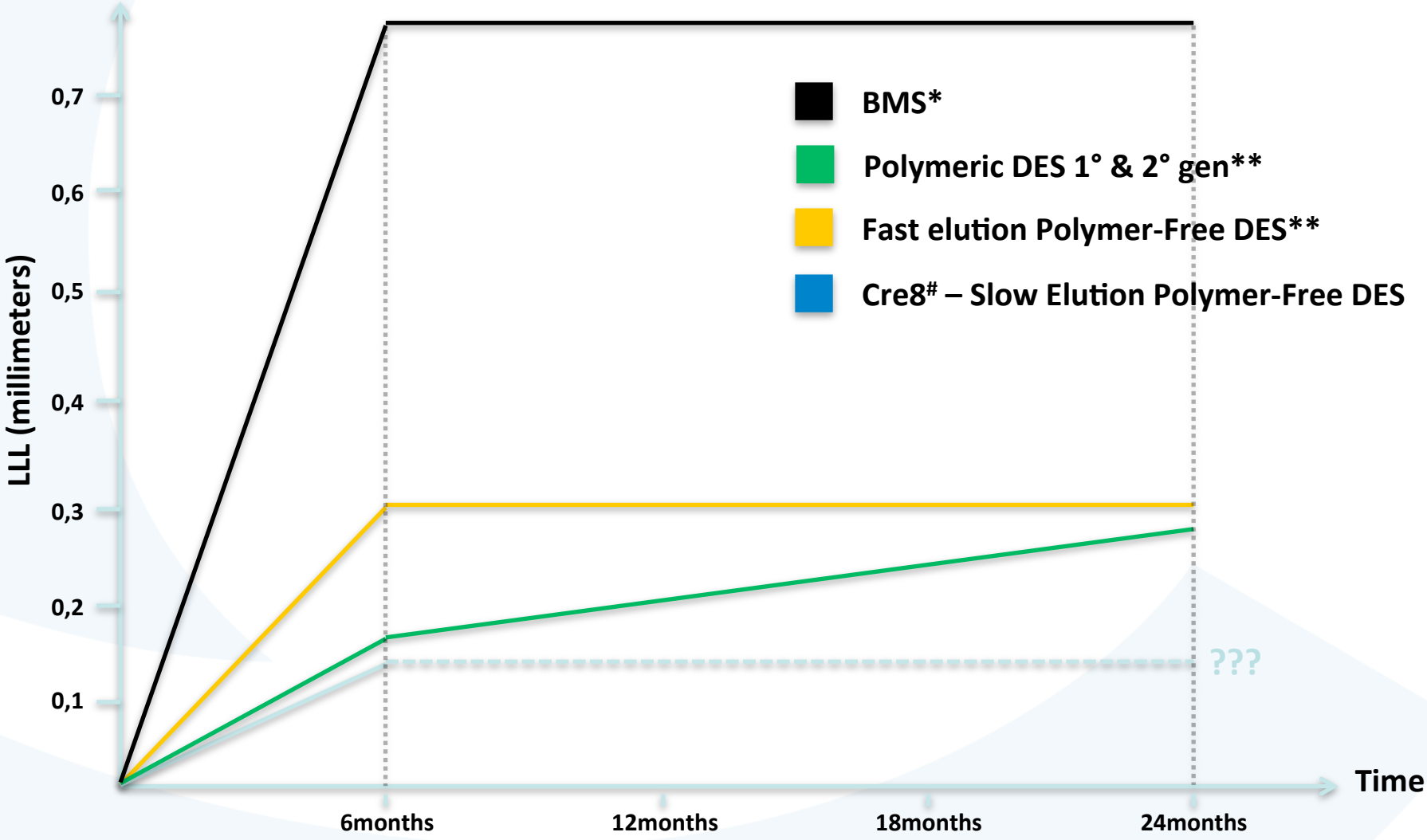




Cardiac fatty acid uptake is double in diabetic mice model.

Drug + Permeation enhancer = **Increased drug concentration**

Stent type/technology and LLL evolution



*Kimura et al, N Engl J Med 1996
*Kimura et al, Circulation 2002

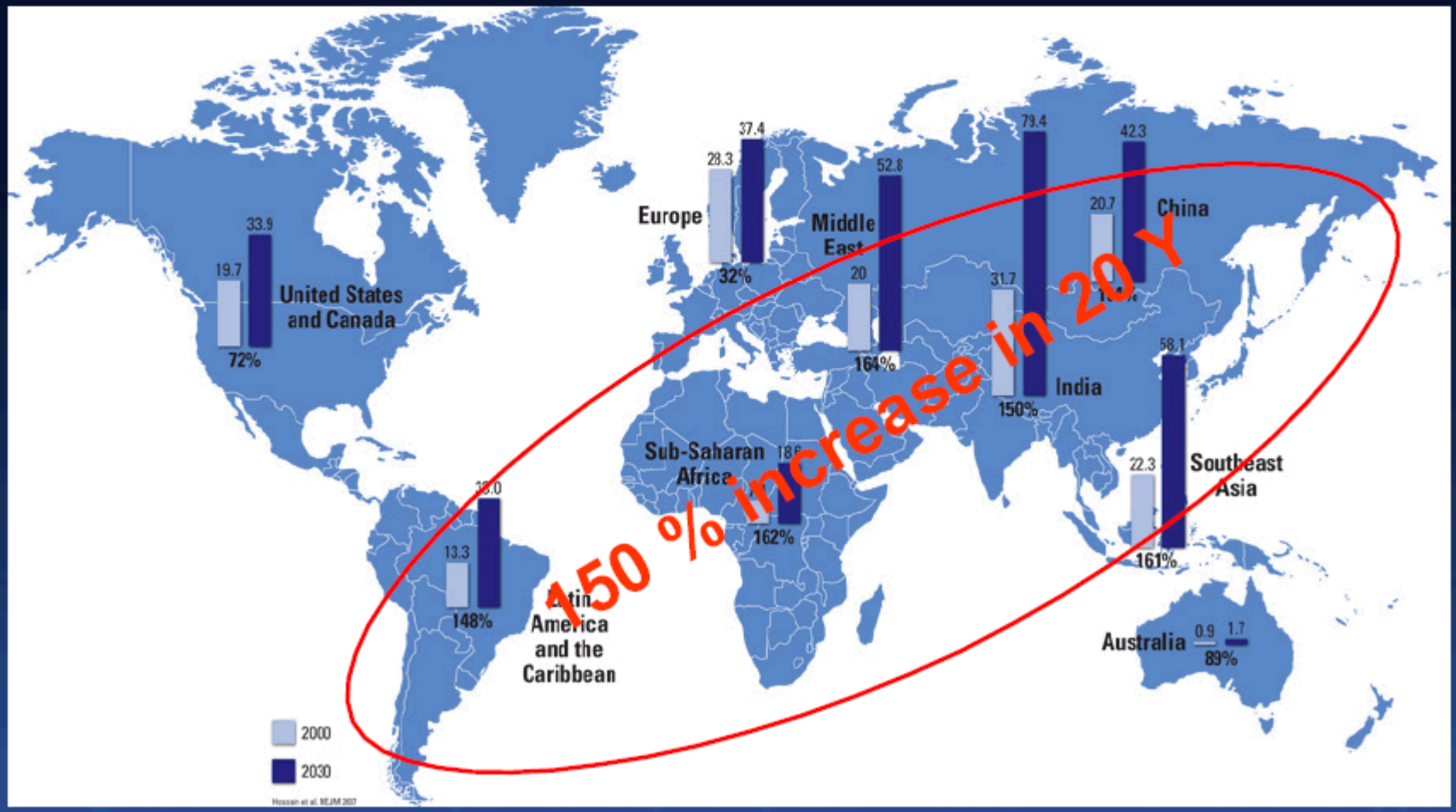
**Byrne et al, JACC 2011
**Byrne et al, Heart 2009

#NEXT study, JACC 2012

New Challenges in diabetic patients

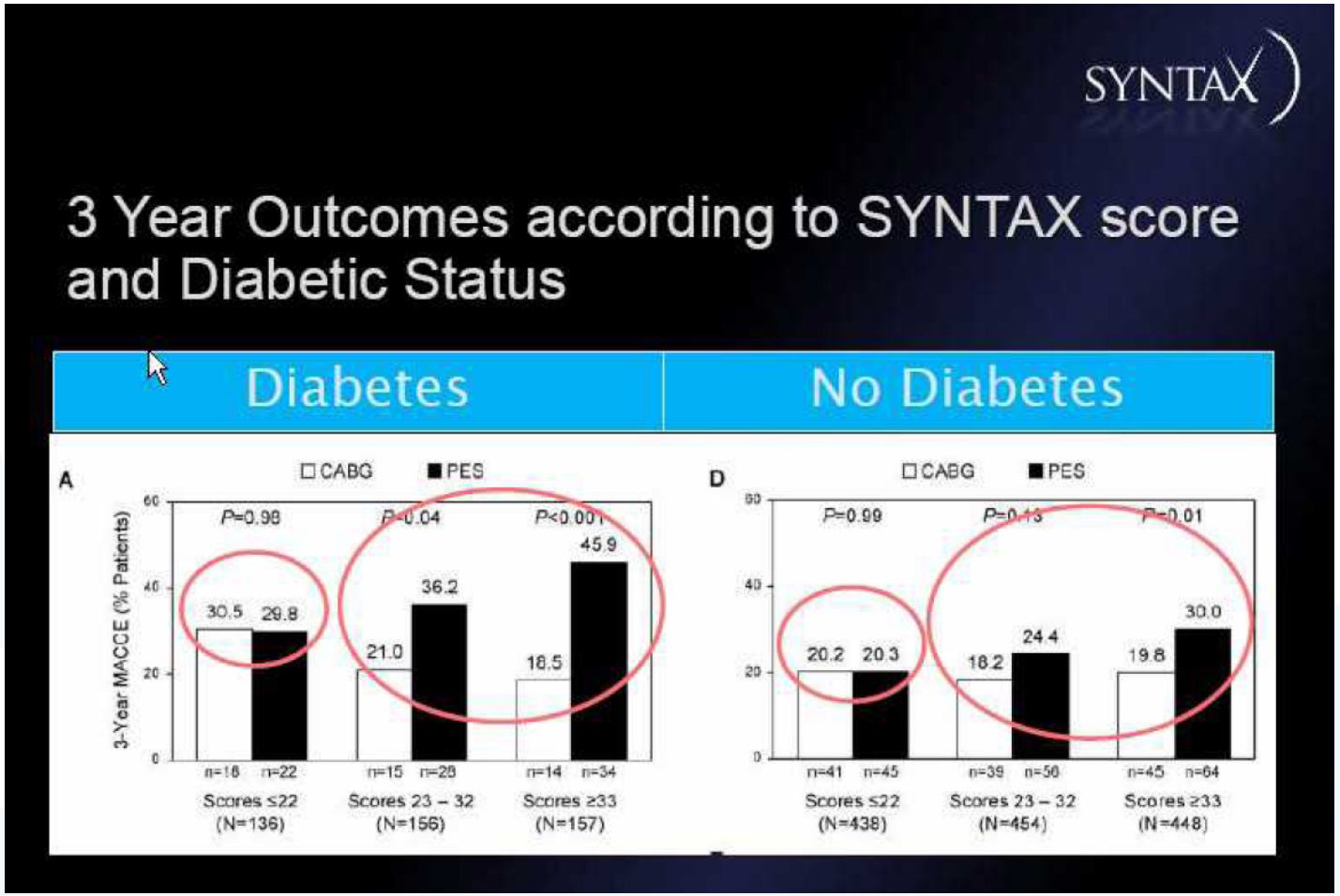
- Improve 2nd gen DES efficacy
- Maintain efficacy at long term

Diabetes incidence

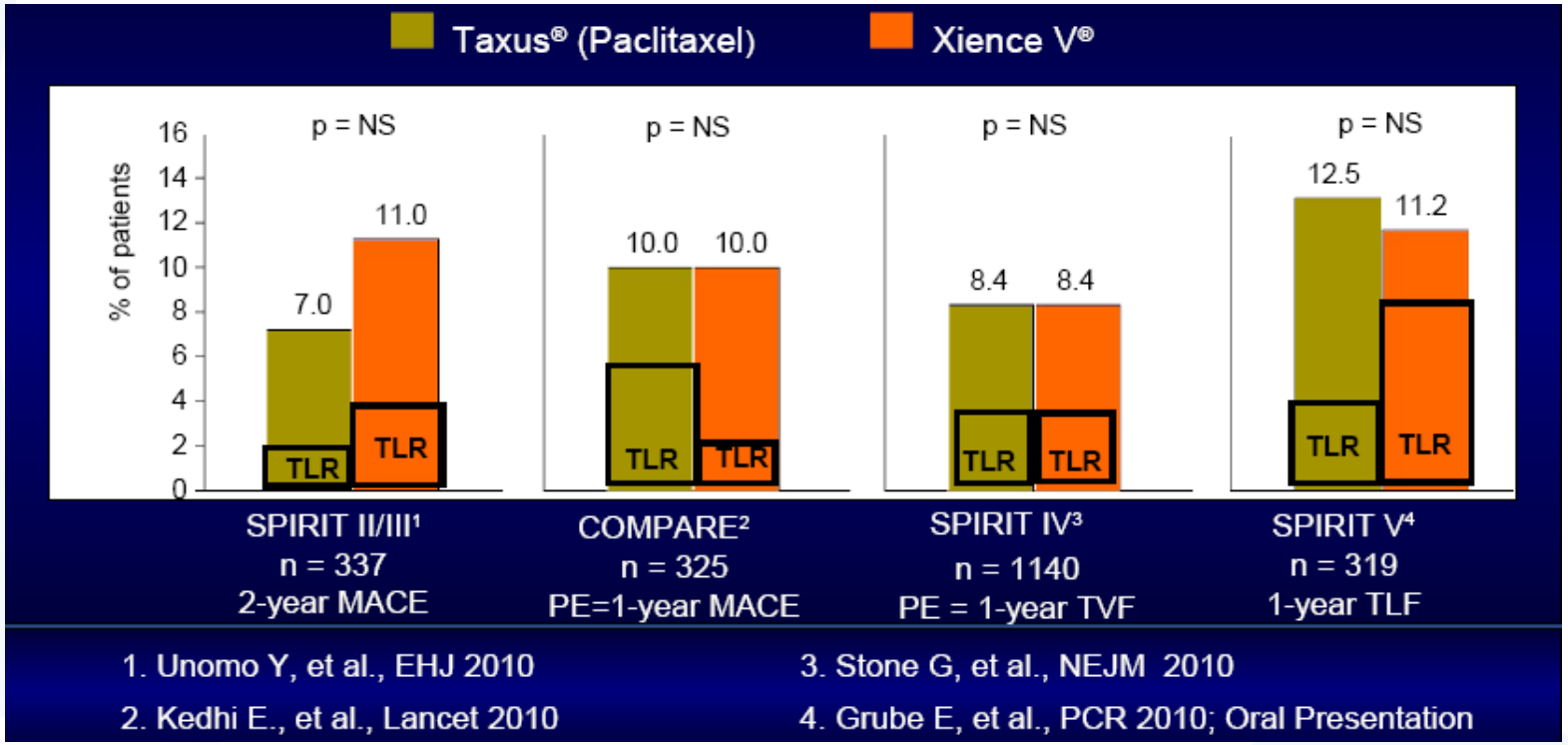


CABG better than PCI (Taxus, 1st gen DES) in diabetic patients

(driven by TLR reduction)

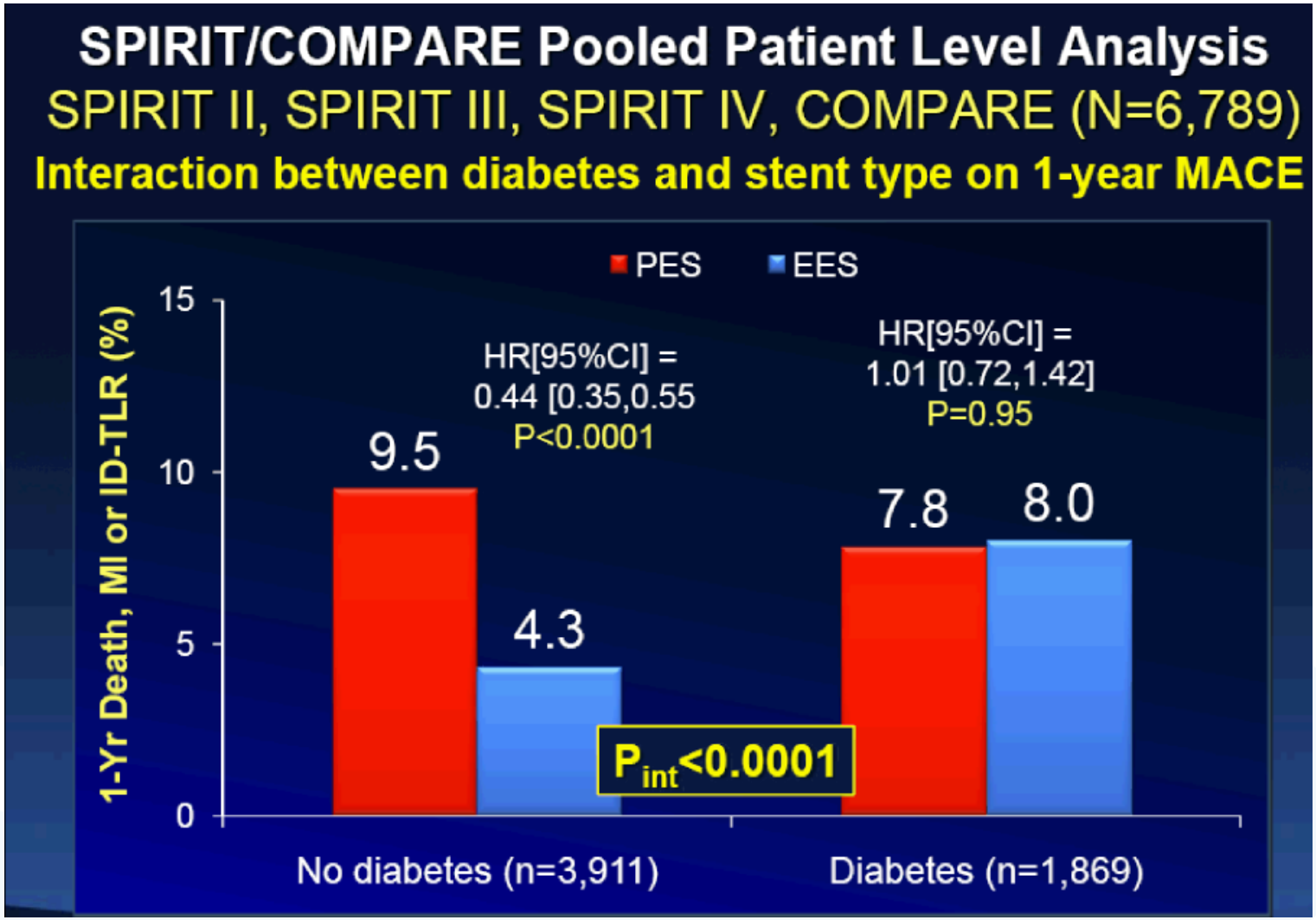


Xience (2nd gen DES) clinical efficacy equals Taxus in diabetic patients



2nd gen. everolimus-eluting stents have not shown to improve the results of the 1st gen. DES in diabetic patients

Xience (2nd gen DES) clinical efficacy equals Taxus in diabetic patients



Conclusions

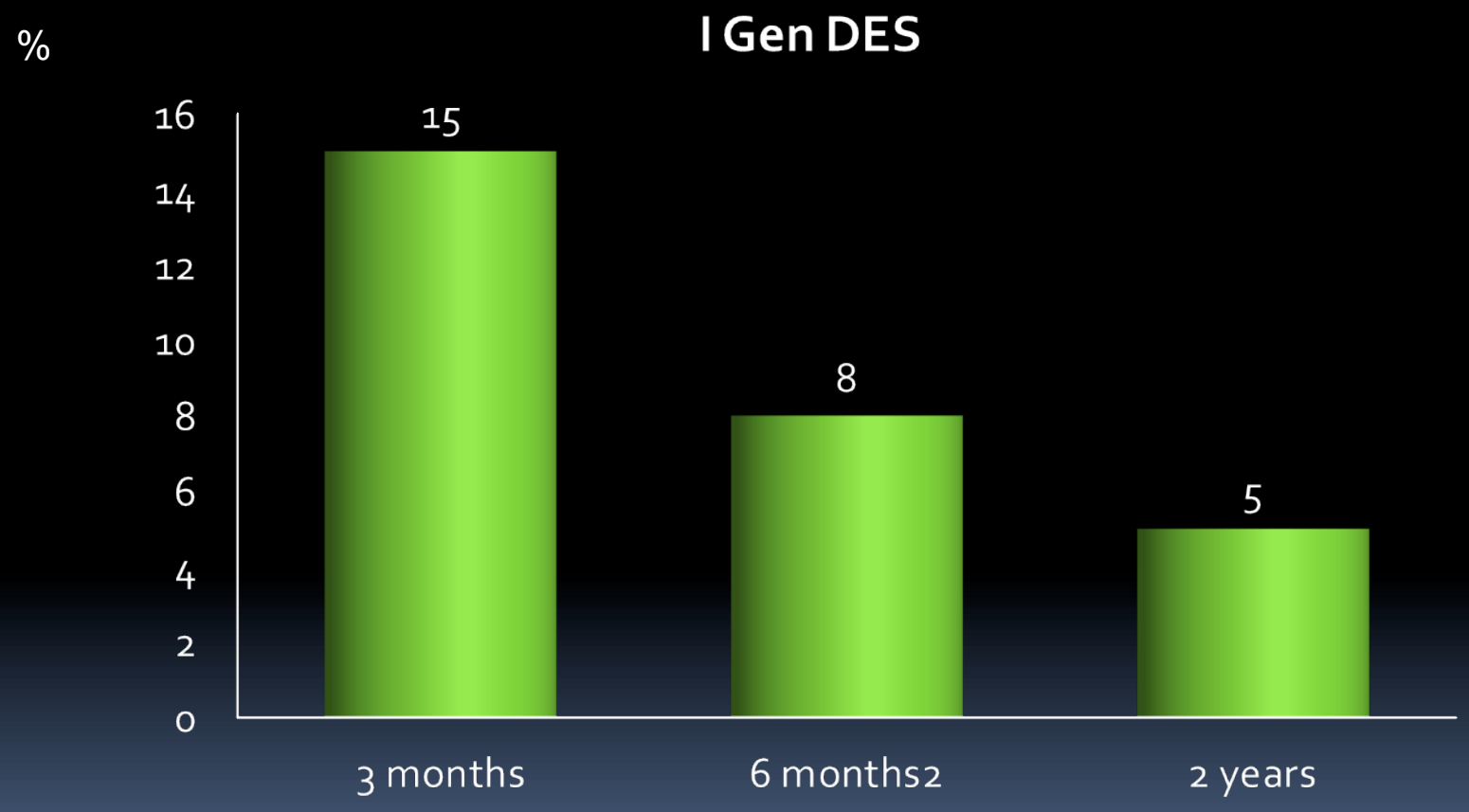
The NEXT randomized study has shown:

- Cre8 6-month in-stent LLL superiority over TAXUS Liberté (0.14 ± 0.36 vs. 0.34 ± 0.40 mm; $p<0.0001$).
- Low incidence of cumulative cardiac death, MI and TLR at 1 year, resulting in an overall CRE8 MACE rate of 6.5% consistent with patients complexity.
- Unchanged angiographic and clinical performances between overall and diabetic populations in the CRE8 arm.

The CID Clinical Plan is aimed to:

- Validate Cre8 allowance in shortening DAPT duration when needed
- Confirm Cre8 excellent efficacy in patients at high-risk of restenosis (diabetics)

Uncoverage rate for DES at OCT



Takano
AM J Card. 2007

Matsumoto
Eur H J 2007

Takano
JACC 2008