COMPARE Trial

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MAASSTAD ZIEKENHUIS

Disclosures

Research Foundation of the Cardiology Department has received unrestricted research grants from:

- Abbott Vascular
- Boston Scientific

COMPARE TRIAL

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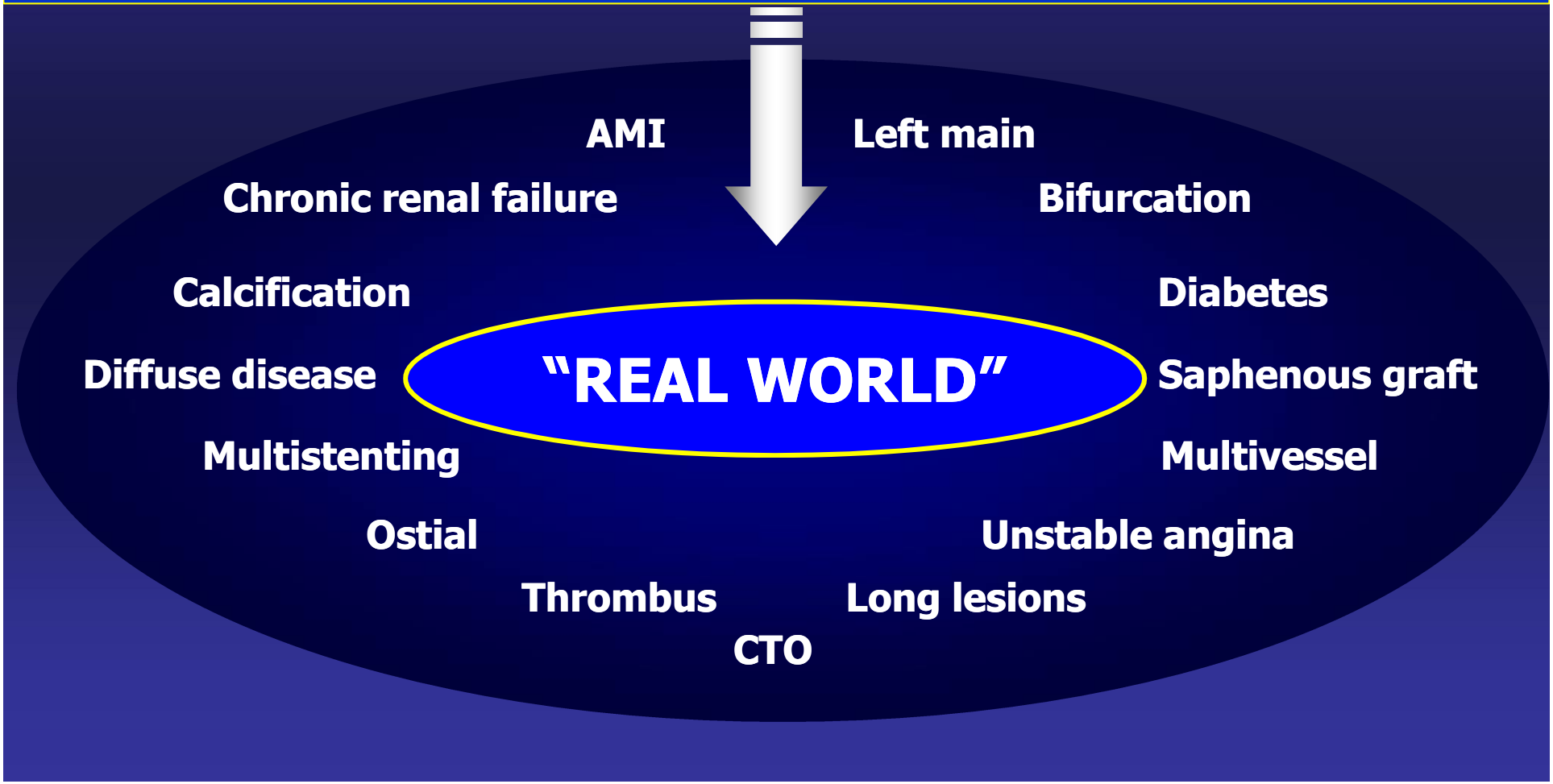
The **COMPARE trial** is
a ***physician initiated***
single center
prospective randomized trial
comparing the
Taxus Liberté *versus* **Xience V** stent
in an all-comer / real world situation

Lancet 15 jan 2010; 375:201-209

Randomized Controlled Trials
Pitfalls



COMPARE Trial
Purpose of the study

To study the outcome of drug eluting stents in a study design that reflects everyday clinical practice

The study is patient oriented and uses only symptom driven clinical end-points

Taxus Liberté

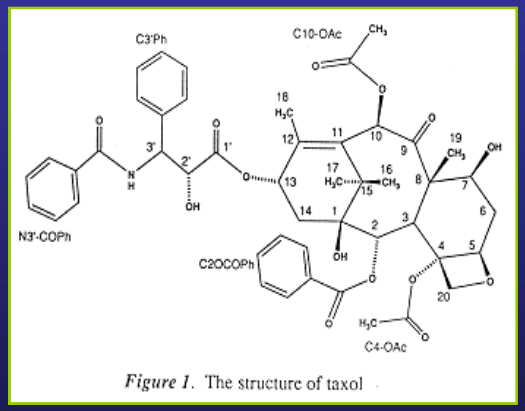
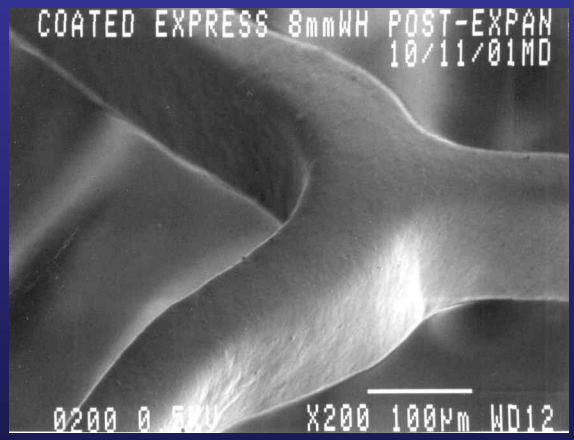


Figure 1. The structure of taxol

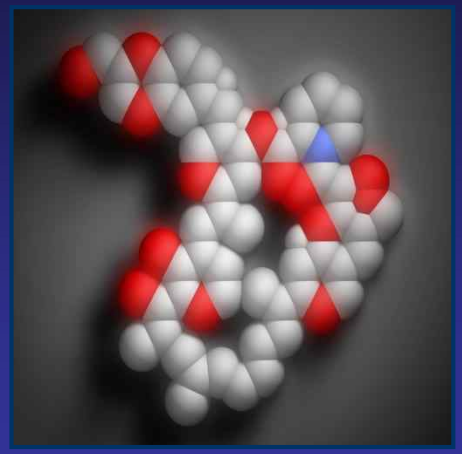
Paclitaxel



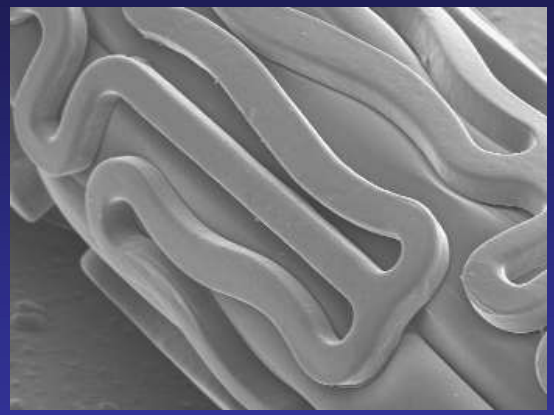
Hydro-carbon

Liberté™

Xience V



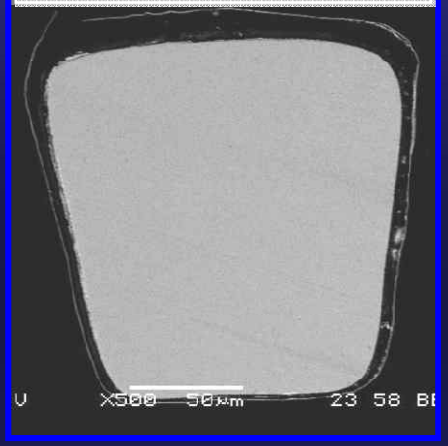
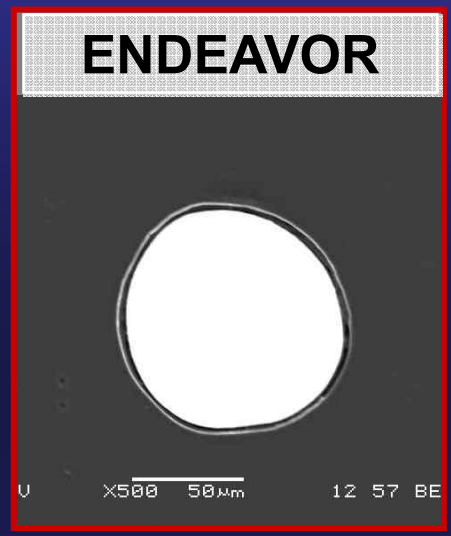
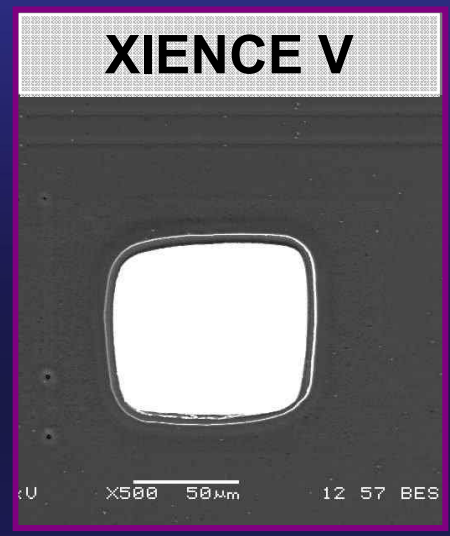
Everolimus



Fluoropolymer

Vision™

Strut and Polymer Thickness

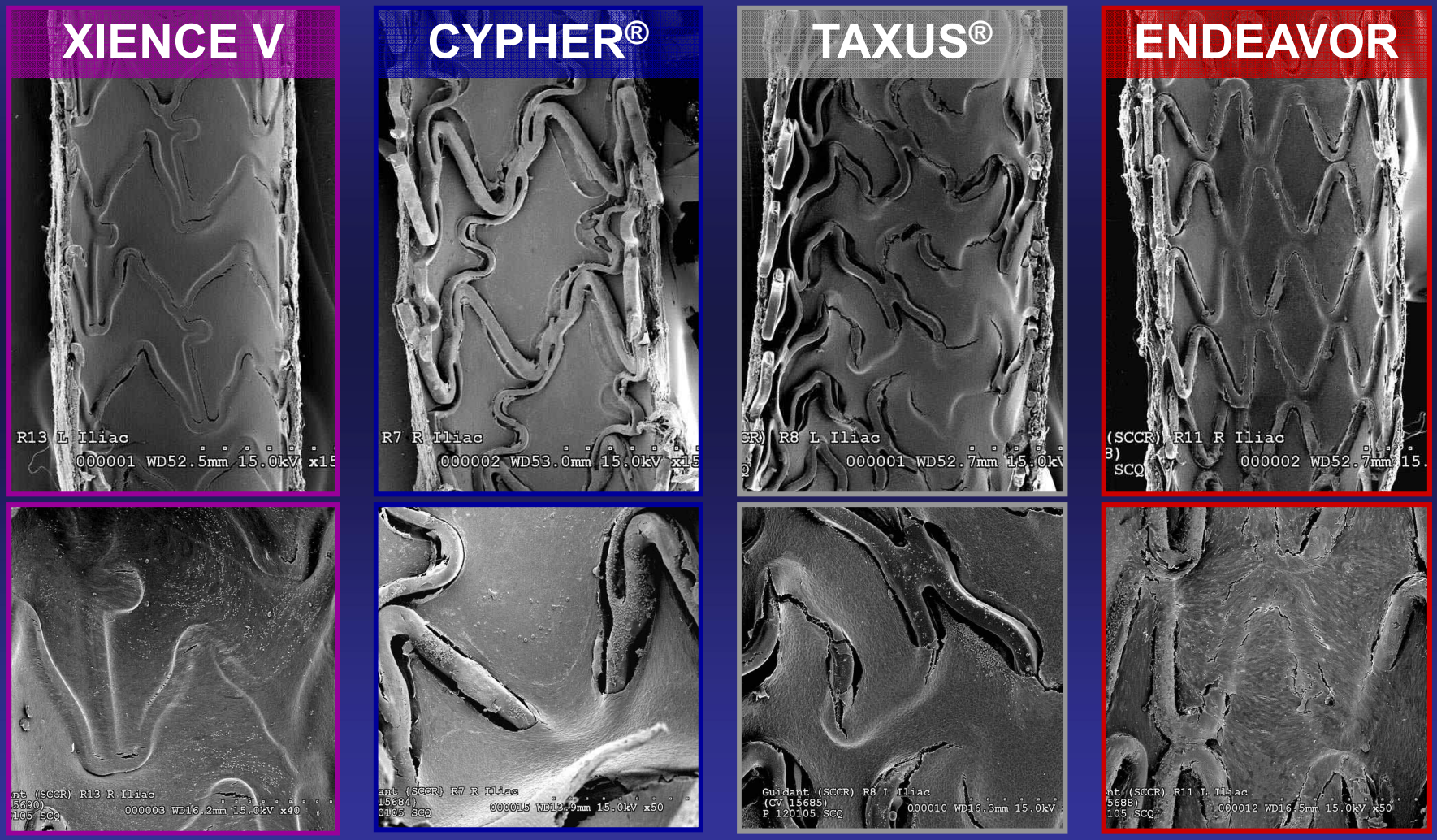
CYPHER®	TAXUS® Liberté	ENDEAVOR	XIENCE V
			
Strut Thickness:	Strut Thickness:	Strut Thickness:	Strut Thickness:
140 µm	97 µm	91 µm	81 µm
Polymer Thickness:	Polymer Thickness:	Polymer Thickness:	Polymer Thickness:
13.7 µm	17.8 µm	4.8 µm	7.8 µm

3.0 mm diameter stents, 500x magnification

Data on file at Abbott Vascular.

Rapid Re-endothelialization

14-Day Rabbit Iliac Study

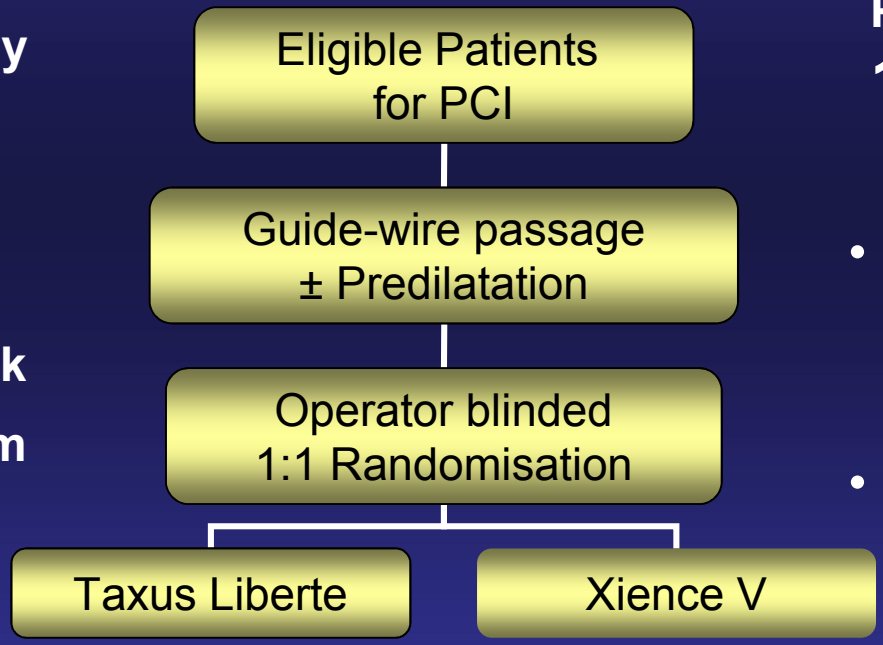


Joner M et al. JACC 2008:52:333-342

Study Outline

- **Inclusion criteria**
- **All patients <86 y**
- **Life expect of > 5 y**

- **Exclusion criteria**
- **No DPT for 12 m**
- **Cardiogenic shock**
- **Surgery within 1 m**
- **Pt on other trial**
- **No pt consent**



Expected MACE
9% vs 14 % (delta 5%)
Power 85%
1800 patients

- **Patients were monitored for 12 m**
- **Only 3 pt (0.16%) were lost for FU.**

Clinical events were adjudicated by an independent CEC
Target vessel revascularizations were analysed by an independent QCA core lab.

Endpoints

- Primary endpoint

  all death, non fatal MI and TVR at 12 months

- Secondary endpoints
- cardiac death, non fatal MI and ischemia driven TLR at 12 months.
- all death, non fatal MI, TVR at 3 and 5 y
- stent thrombosis (ARC) at 1, 3 and 5 y

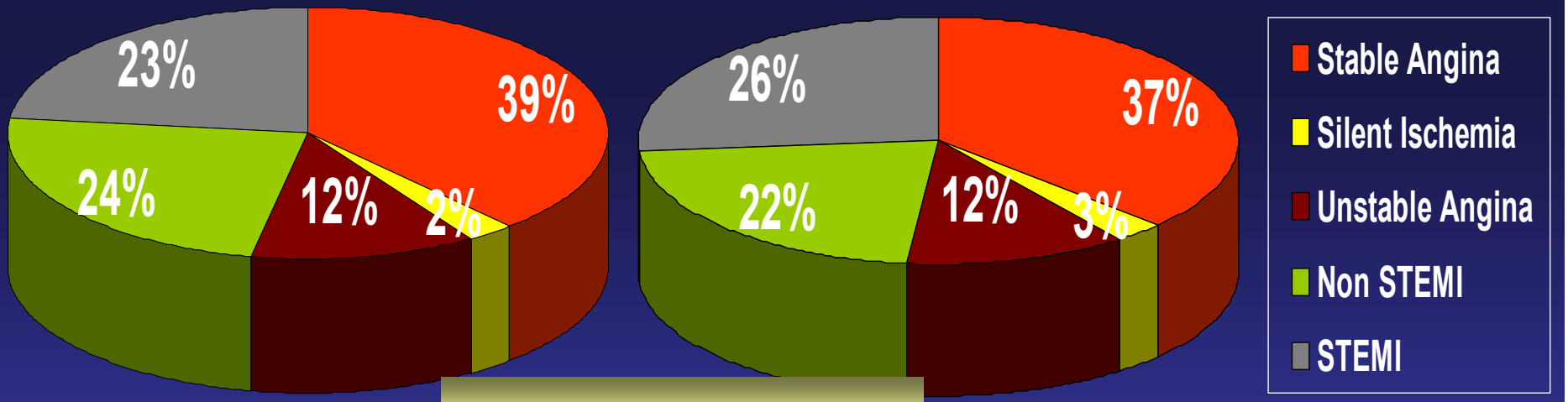
Baseline Characteristics
Clinical presentation

	Taxus **903 pts**	**Xience** **897 pts**	p
Male	72 %	69 %	0.11
• Previous AMI	17.6 %	15.2 %	0.37
• Previous PCI	13.6 %	13.0%	0.57
• Previous CABG	5.9 %	6.7 %	0.47
• Previous CVA	6.4 %	4.2 %	0.07
• Peripheral artery disease	3.5 %	5.7 %	0.07
Diabetes	19 %	17.1 %	0.33
Smoking (active)	29 %	32.9 %	0.23
Hypercholesterolemia	49.9 %	53.2 %	0.24
Hypertension	49.5 %	46.5%	0.29
Family History	44.6 %	44.5 %	0.61

Clinical Presentation

Taxus

Xience



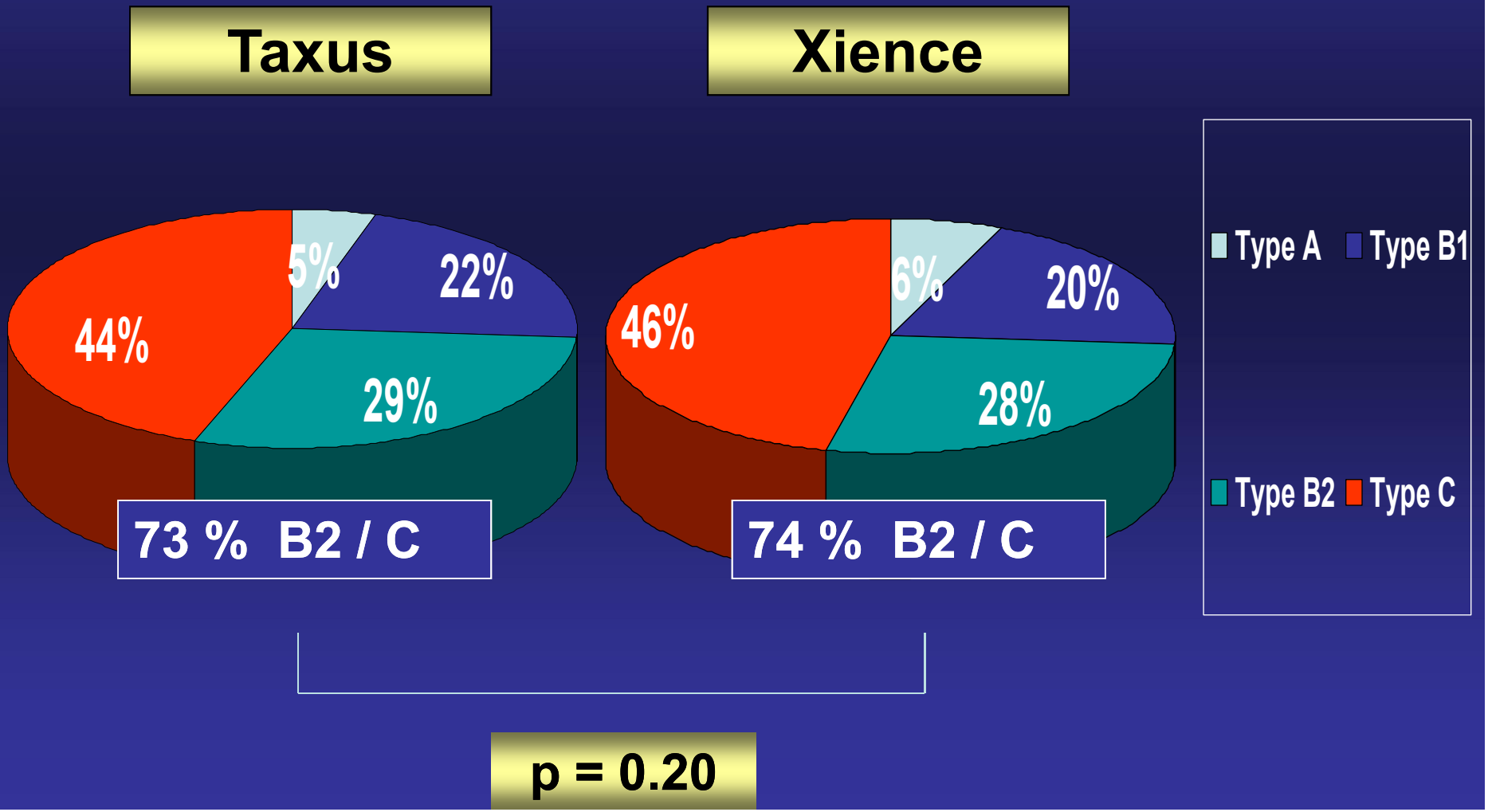
± 60% ACS

p = ns

Baseline Angiographic Characteristics

	Taxus	Xience	p
Lesions	**1294**	**1286**	ns
• LM	1.6 %	1.6 %	0.46
• LAD	37.4 %	39.9 %	0.46
• RCX	25.7 %	23.2 %	0.46
• RCA	33.3 %	32.9 %	0.46
• Grafts	1.9 %	2.1 %	0.55
Lesion per patient	1.46	1.45	0.92
Stent length per lesion	34.0	34.0	0.97
Stent per lesion	1.57	1.67	**0.07**
GP 2b3a blockers	32 %	32 %	0.64

Lesion Characteristics



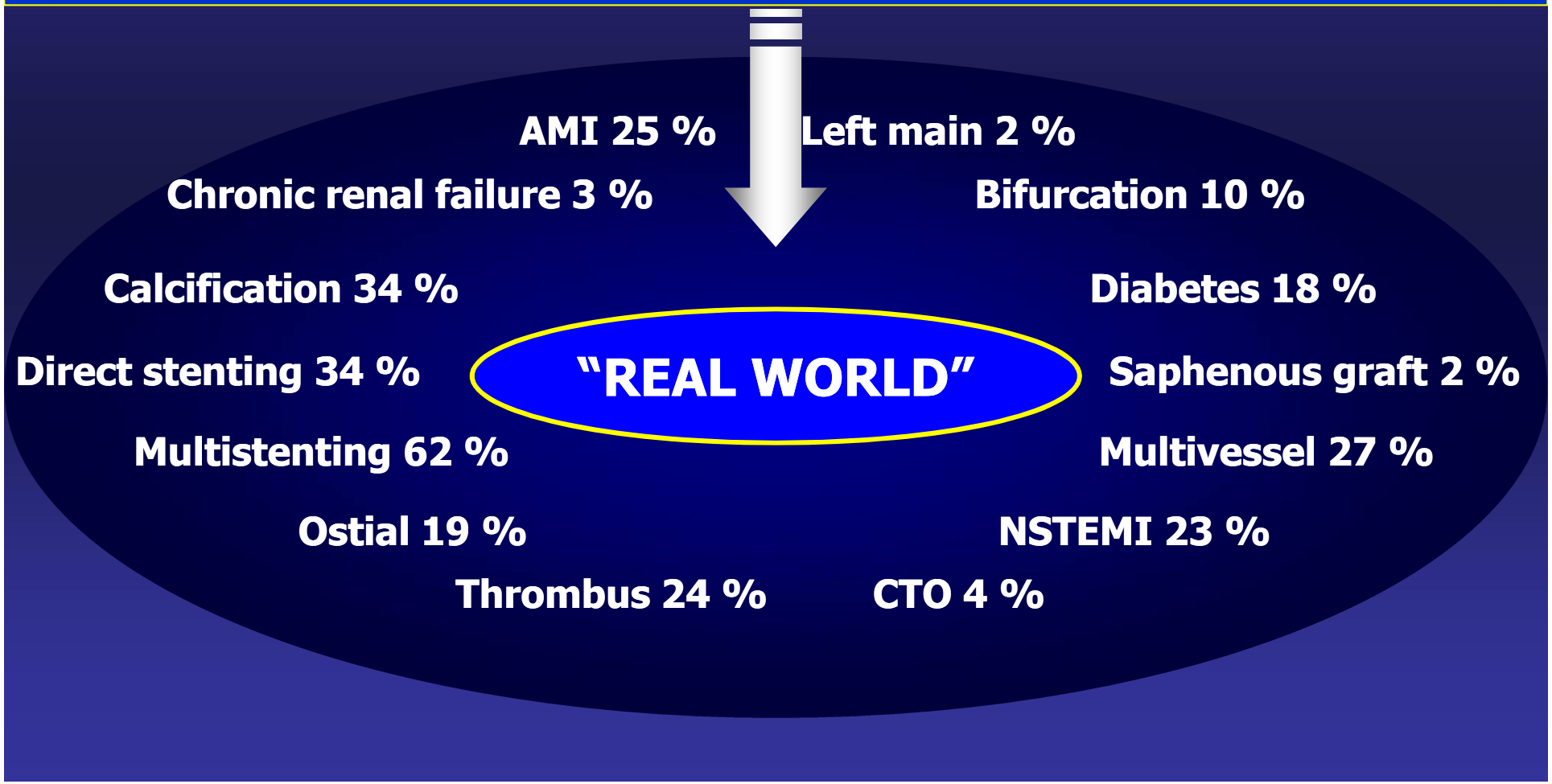
Angiographic data RCT > 1000 pts

	Lesion Length	Vessel size	Type B2	Type C
SIRIUS	14.4	2.78	33 %	26 %
TAXUS IV	13.6	2.75	NA	NA
TAXUS V	17.3	2.68	40 %	37 %
REALITY	17.1	2.40	60 %	26 %
SIRTAX	12.2	2.82	23 %	13 %
SPIRIT III	14.7	2.76	NA	NA
All comer RCT				
LEADERS	12.6	2.60	NA	NA
COMPARE	22.1	2.62	28 %	45 %

Procedure data RCT > 1000 pts

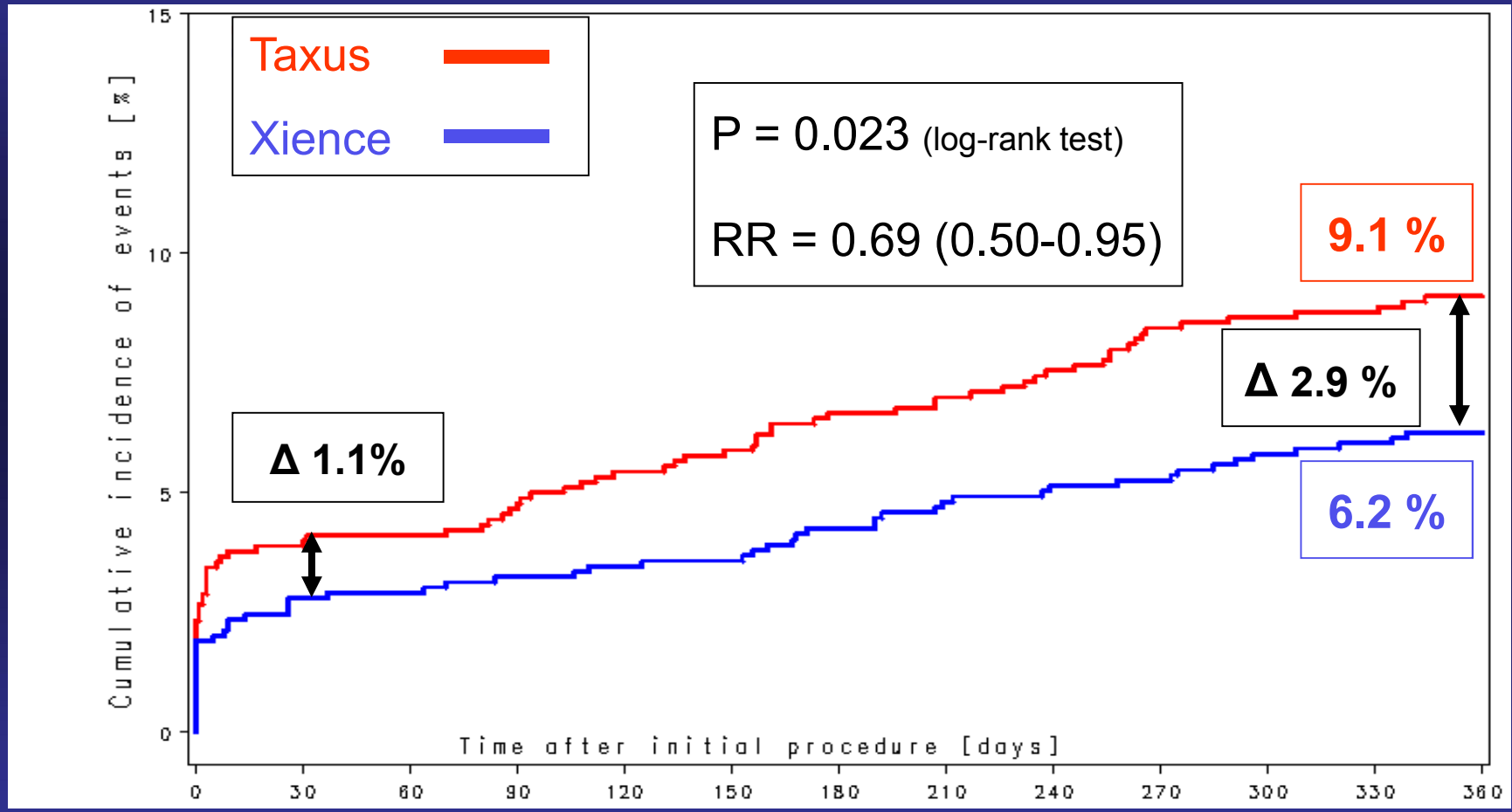
	Lesions Patient	Per lesion: Stent Length	Per lesion: Number stents	Per patient: Stent Length	Per patient: Number stents
SIRIUS	1.0	21.5	1.4	21.5	1.4
TAXUS IV	1.0	21.8	1.1	21.8	1.1
TAXUS V	1.0	28.5	1.4	28.5	1.4
REALITY	1.4	23.1	1.4	31.9	1.9
SIRTAX	1.4	18.9	1.2	26.1	1.6
SPIRIT III	1.2	22.3	1.2	25.6	1.3
All comer RCT					
LEADERS	1.4	24.7	1.3	35.7	1.9
COMPARE	1.4	34.0	1.6	48.4	2.3

COMPARE TRIAL



Primary Endpoint Result

MACE (all death, non-fatal MI and TVR)

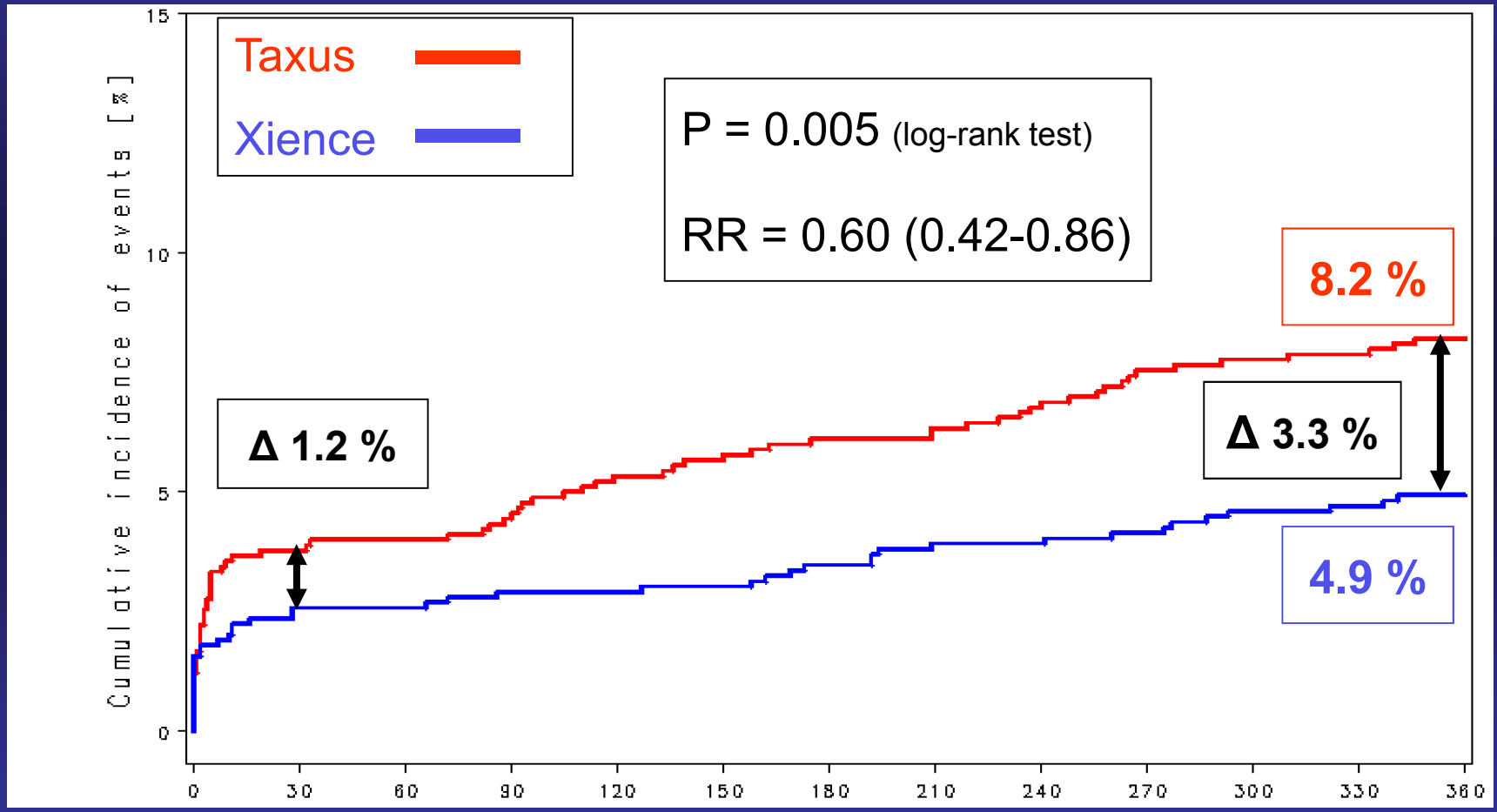


 # Patients at Risk

Taxus	903	868	865	860	853	849	842	838	833	825	823	822	819
Xience	897	872	870	867	865	864	858	854	851	849	844	842	840

Secondary Endpoint Result

MACE (cardiac death, non-fatal MI and TLR)

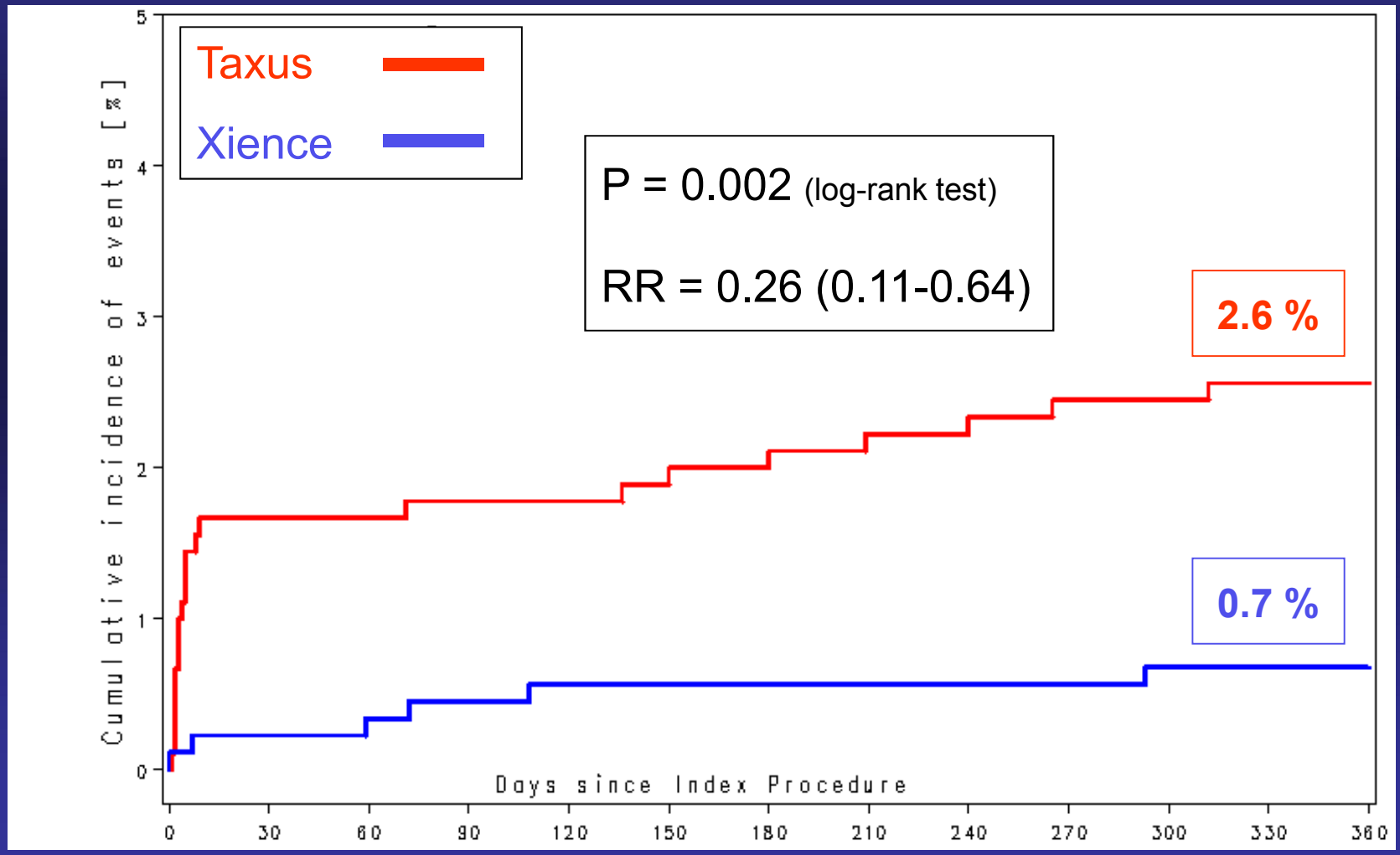


 # Patients At Risk:

Taxus	**903**	**869**	**866**	**861**	**854**	**849**	**844**	**841**	**835**	**828**	**826**	**825**	**822**
Xience	**897**	**873**	**872**	**869**	**869**	**867**	**862**	**857**	**855**	**853**	**848**	**847**	**845**

Secondary Endpoint Result

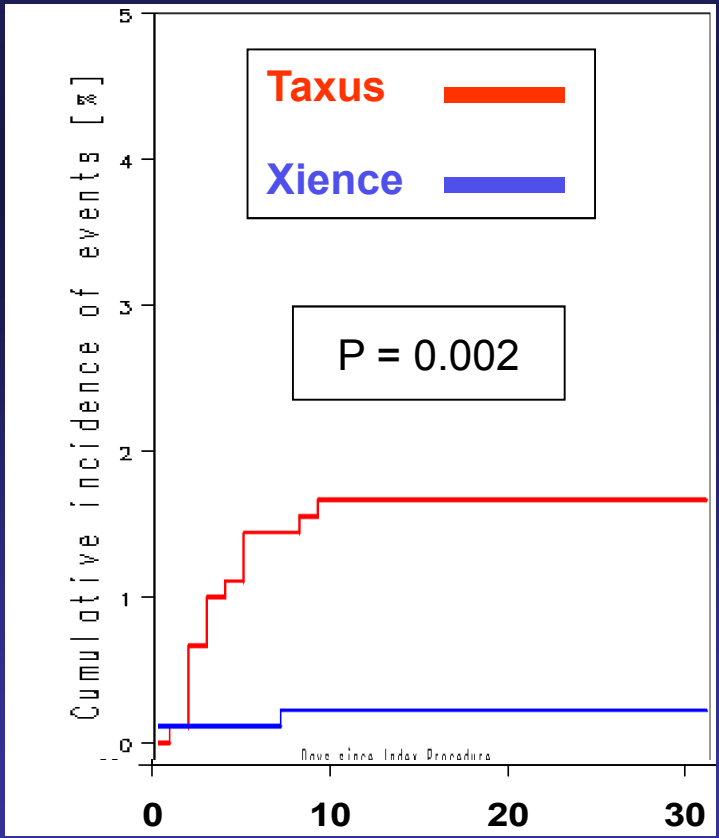
Stent Thrombosis
(Definite & probable according to ARC)



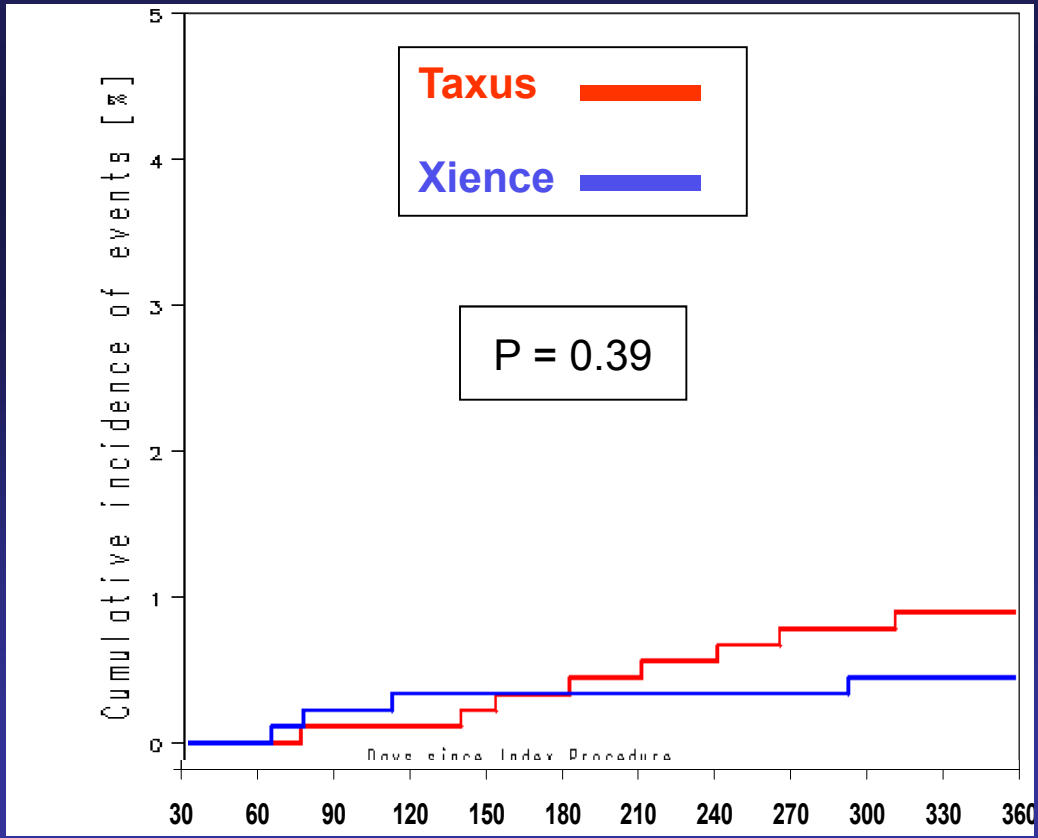
Secondary Endpoint Result

Early and Late Stent Thrombosis (definite & probable according ARC)

Early ST

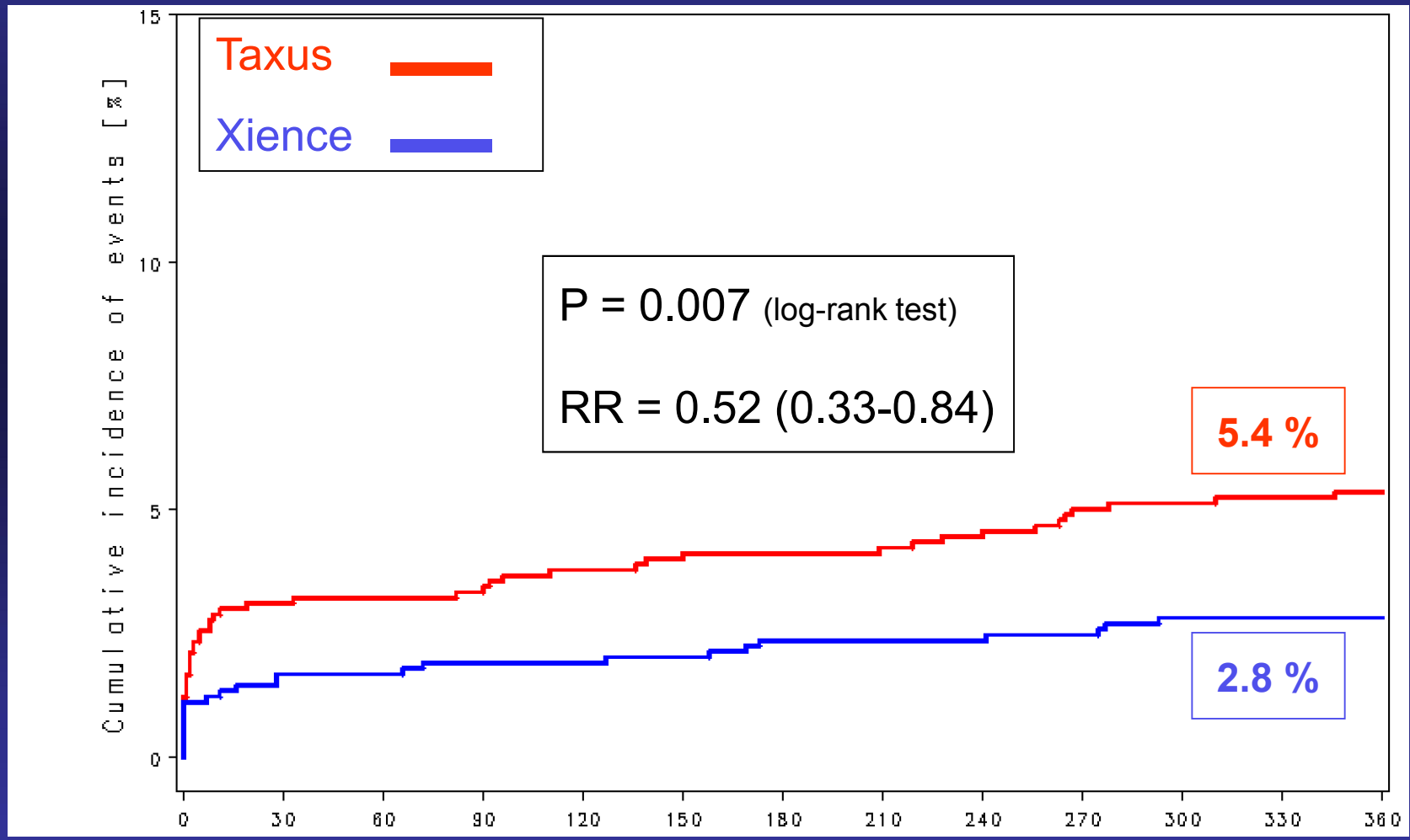


Late ST



Endpoint Analysis

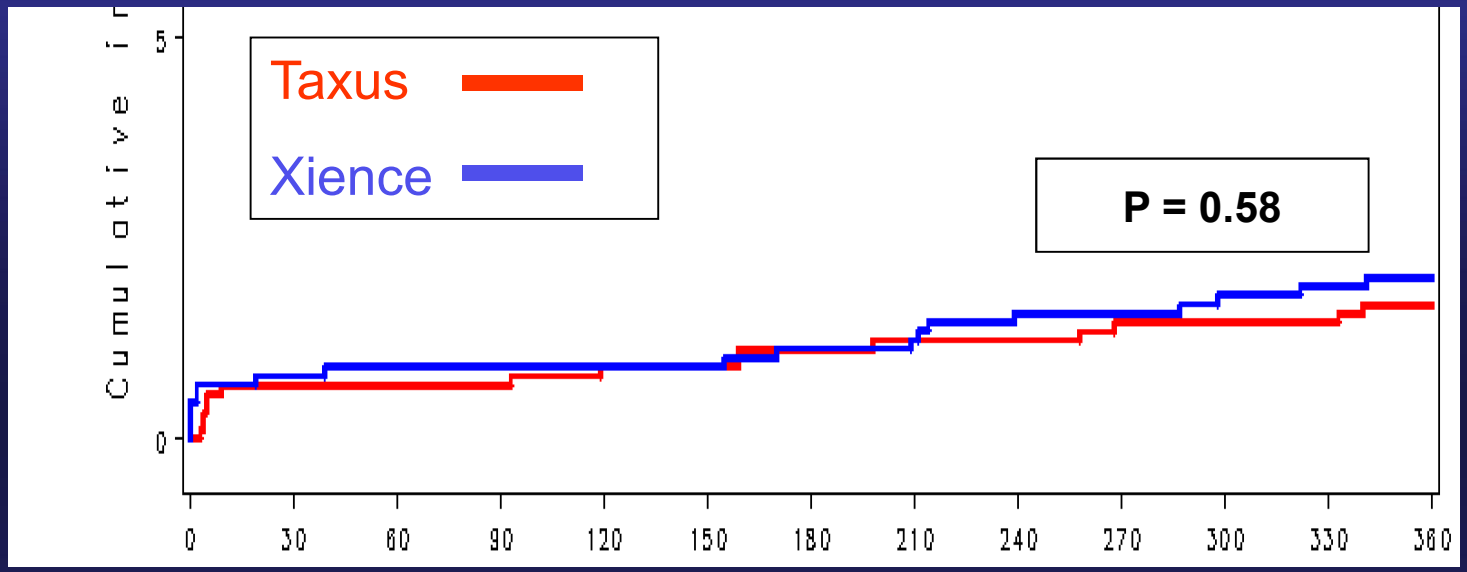
Non Fatal MI



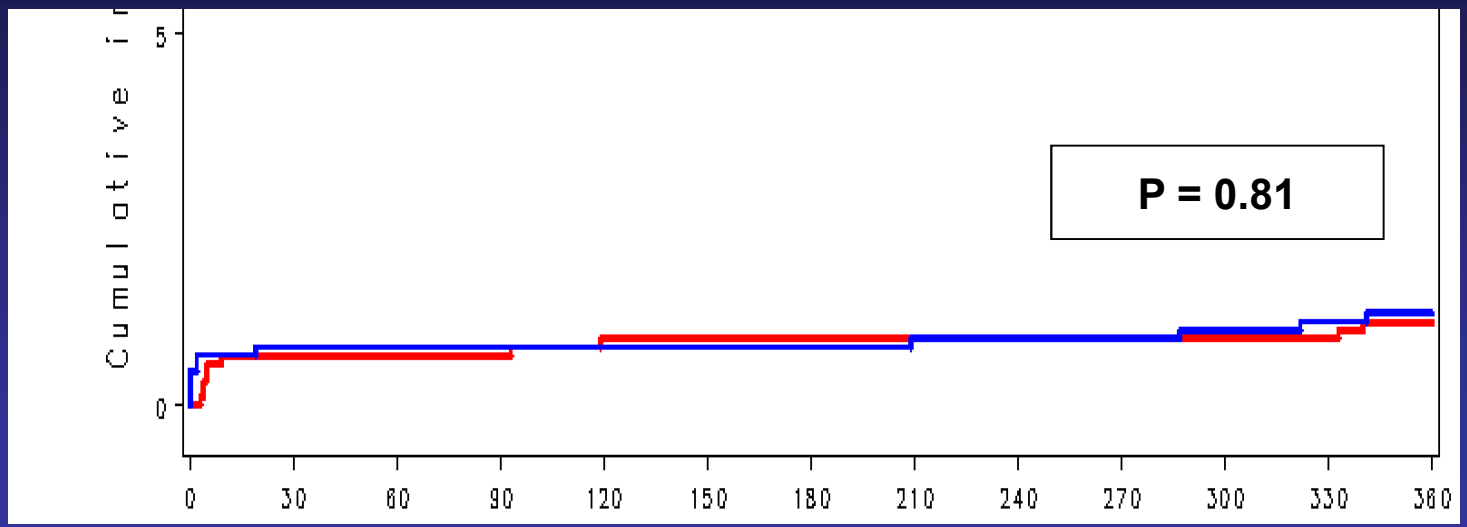
Endpoint Analysis

All Death & Cardiac Death

All Death



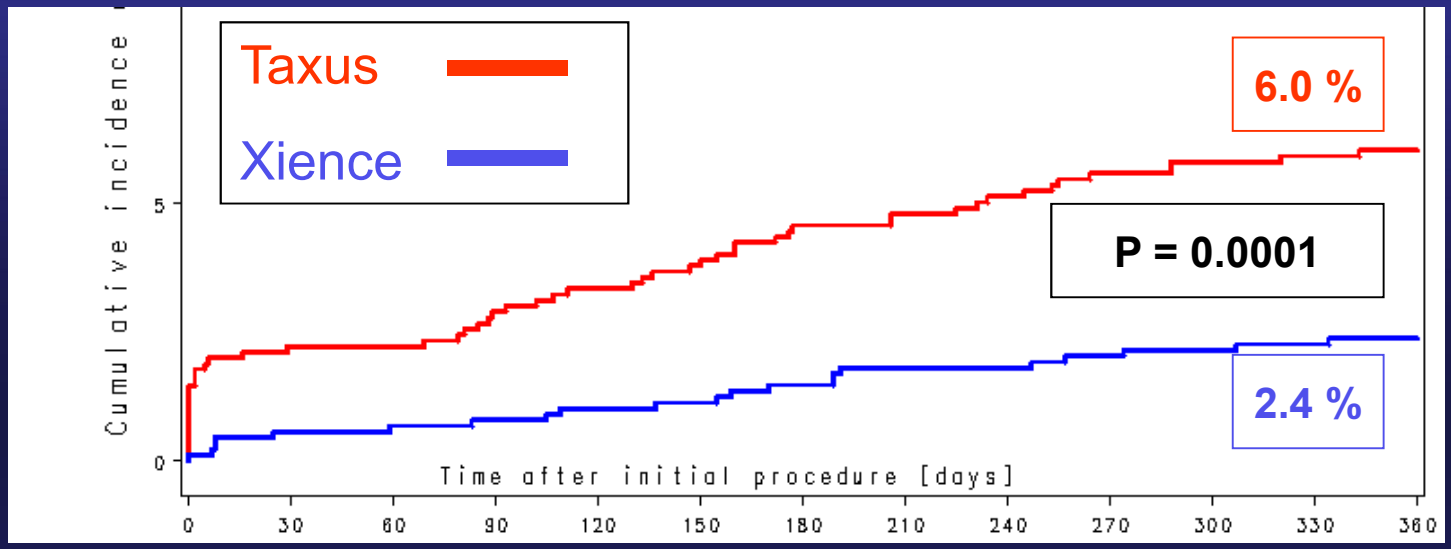
Cardiac Death



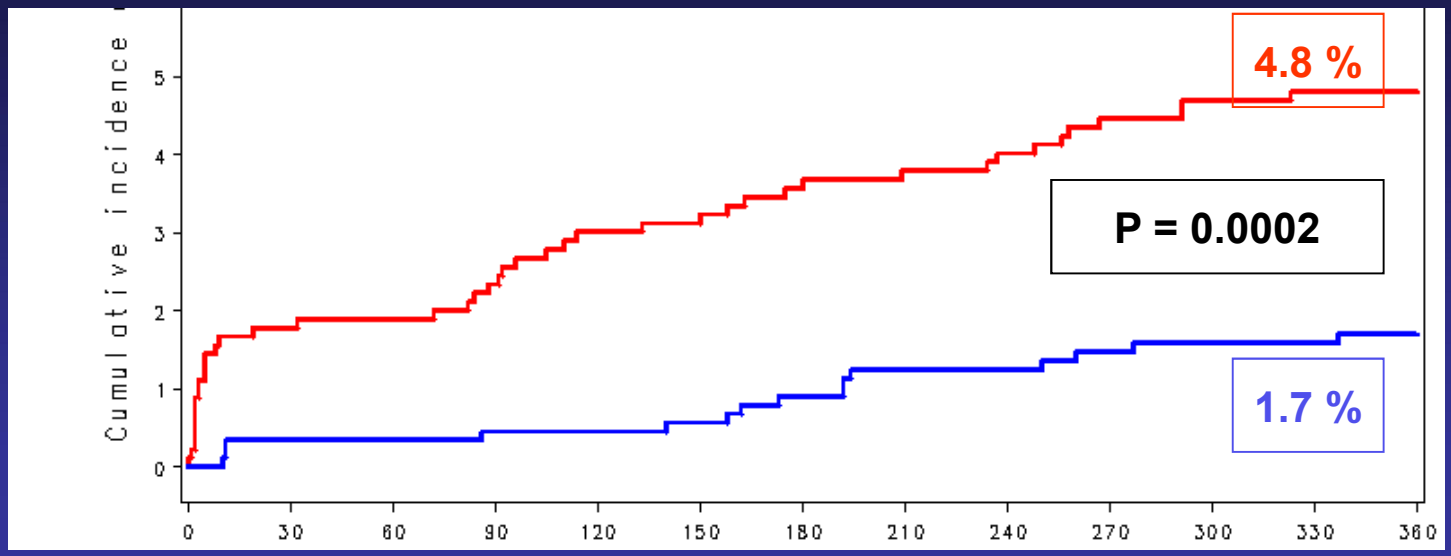
Endpoint Analysis

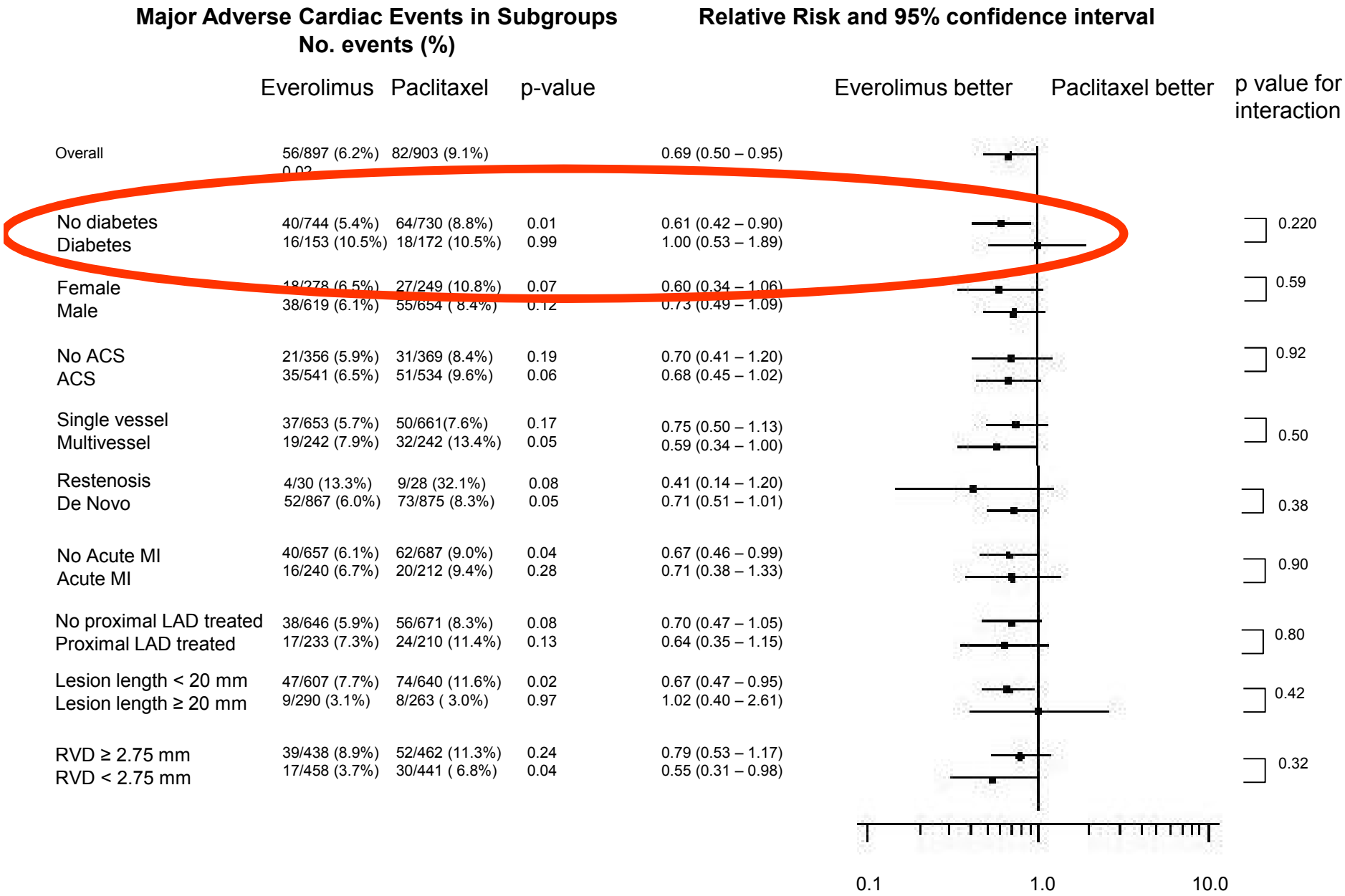
TVR & Ischemic driven TLR

TVR

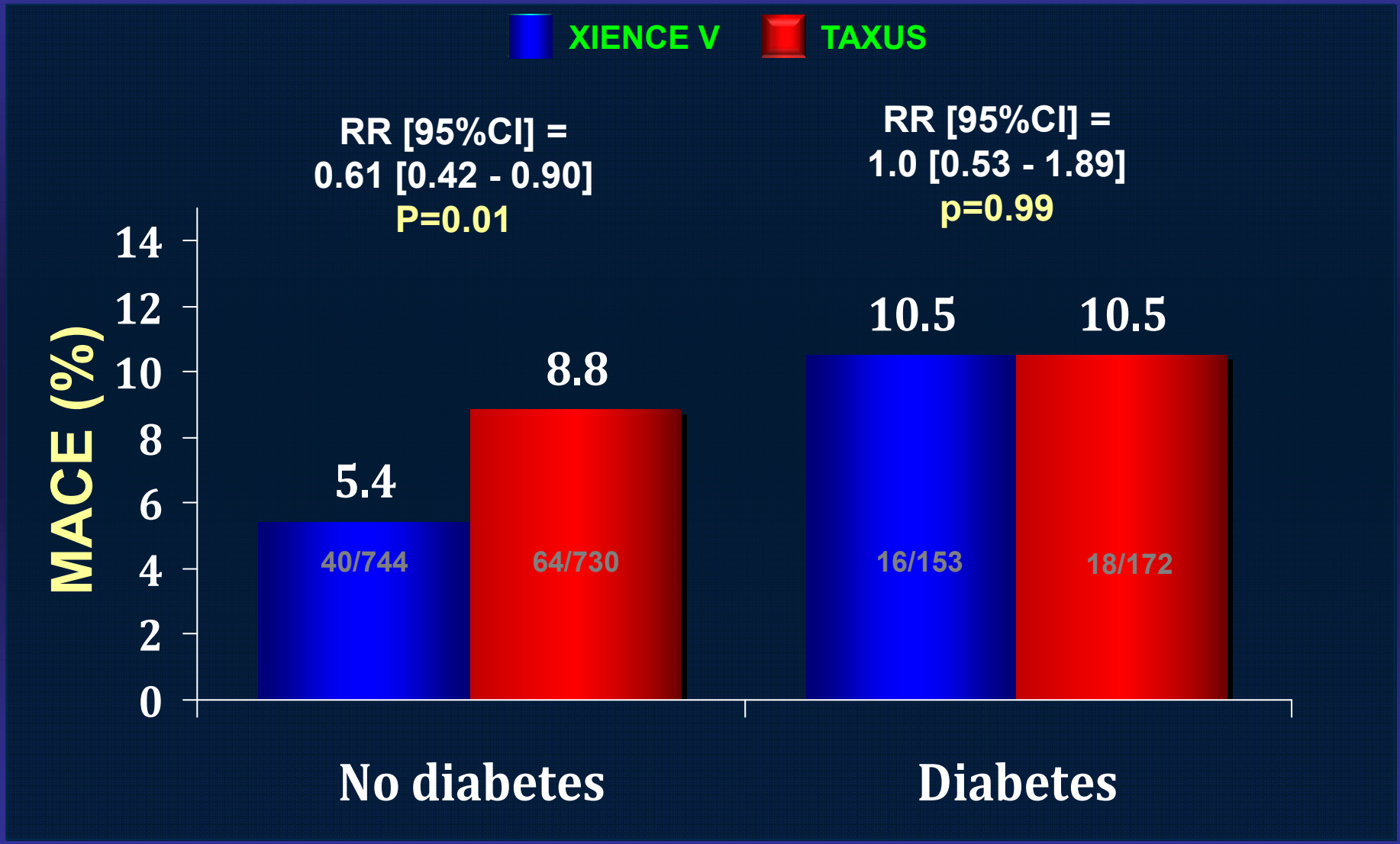


TLR




Major Adverse Cardiac Events in Subgroups
No. events (%)
Relative Risk and 95% confidence interval
Everolimus
Paclitaxel
p-value
Everolimus better
Paclitaxel better
p value for interaction
Overall
56/897 (6.2%)
82/903 (9.1%)
0.69 (0.50 – 0.95)
0.02
No diabetes
40/744 (5.4%)
64/730 (8.8%)
0.01
0.61 (0.42 – 0.90)
0.220
Diabetes
16/153 (10.5%)
18/172 (10.5%)
0.99
1.00 (0.53 – 1.89)
Female
18/278 (6.5%)
27/249 (10.8%)
0.07
0.60 (0.34 – 1.06)
0.59
Male
38/619 (6.1%)
55/654 (8.4%)
0.12
0.73 (0.49 – 1.09)
No ACS
21/356 (5.9%)
31/369 (8.4%)
0.19
0.70 (0.41 – 1.20)
0.92
ACS
35/541 (6.5%)
51/534 (9.6%)
0.06
0.68 (0.45 – 1.02)
Single vessel
37/653 (5.7%)
50/661(7.6%)
0.17
0.75 (0.50 – 1.13)
0.50
Multivessel
19/242 (7.9%)
32/242 (13.4%)
0.05
0.59 (0.34 – 1.00)
Restenosis
4/30 (13.3%)
9/28 (32.1%)
0.08
0.41 (0.14 – 1.20)
0.38
De Novo
52/867 (6.0%)
73/875 (8.3%)
0.05
0.71 (0.51 – 1.01)
No Acute MI
40/657 (6.1%)
62/687 (9.0%)
0.04
0.67 (0.46 – 0.99)
0.90
Acute MI
16/240 (6.7%)
20/212 (9.4%)
0.28
0.71 (0.38 – 1.33)
No proximal LAD treated
38/646 (5.9%)
56/671 (8.3%)
0.08
0.70 (0.47 – 1.05)
0.80
Proximal LAD treated
17/233 (7.3%)
24/210 (11.4%)
0.13
0.64 (0.35 – 1.15)
Lesion length < 20 mm
47/607 (7.7%)
74/640 (11.6%)
0.02
0.67 (0.47 – 0.95)
0.42
Lesion length ≥ 20 mm
9/290 (3.1%)
8/263 (3.0%)
0.97
1.02 (0.40 – 2.61)
RVD ≥ 2.75 mm
39/438 (8.9%)
52/462 (11.3%)
0.24
0.79 (0.53 – 1.17)
0.32
RVD < 2.75 mm
17/458 (3.7%)
30/441 (6.8%)
0.04
0.55 (0.31 – 0.98)
0.1
1.0
10.0

Impact of Diabetes on MACE



MACE : all death, non-fatal MI and TVR

$P_{interaction} = 0.22$

COMPARE TRIAL : DM Patients
Clinical events through 1 year

	TAXUS 172 pts	XIENCE V 155 pts	P value
Death, all	5 (2.9 %)	10 (6.4 %)	0.185
- Cardiac death	4 (2.3 %)	6 (3.9 %)	0.526
MI, all	5 (2.9 %)	3 (1.9 %)	0.726
TVR	11 (6.4%)	4 (2.6%)	0.118
- CABG	3 (1.7 %)	0 (0.0 %)	0.250
- re-PCI	8 (4.7 %)	4 (2.6 %)	0.387
TLR	10 (5.8 %)	3 (1.9 %)	0.092
ST (def & prob)	3 (1.7 %)	3 (1.9 %)	1.0

Conclusions COMPARE trial

- In an *all-comer* population, reflecting real world, implantation of the Everolimus eluting Xience V stent significantly reduced major adverse cardiac events compared to the Paclitaxel eluting Taxus Liberté stent

Conclusions COMPARE trial

- Superiority of the Everolimus eluting Xience V stent was obtained in safety **and** efficacy, mainly due to less early stent thrombosis and less target lesion revascularization

Messages from COMPARE

- For the first time changed concept of the Class effect for DES
- Shifted the attention from late stent thrombosis to early stent thrombosis
- Opens new perspectives in complex patient population

Shifting attention from

Late to Early stent thrombosis

Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study

Joost Daemen, Peter Wenaweser, Keiichi Tsuchida, Linda Abrecht, Sophia Vaina, Cyrill Morger, Neville Kukreja, Peter Juni, Georgios Sianos, Gerrit Hellige, Ron T van Domburg, Otto M Hess, Eric Boersma, Bernhard Meier, Stephan Windecker, Patrick W Serruys

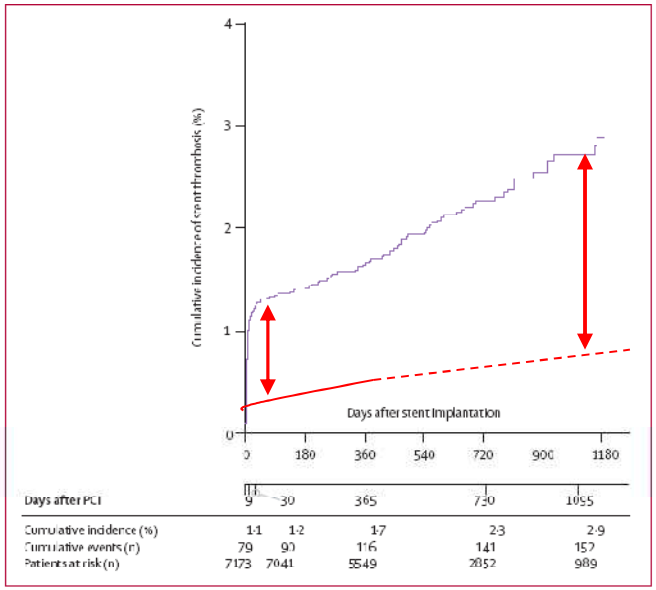
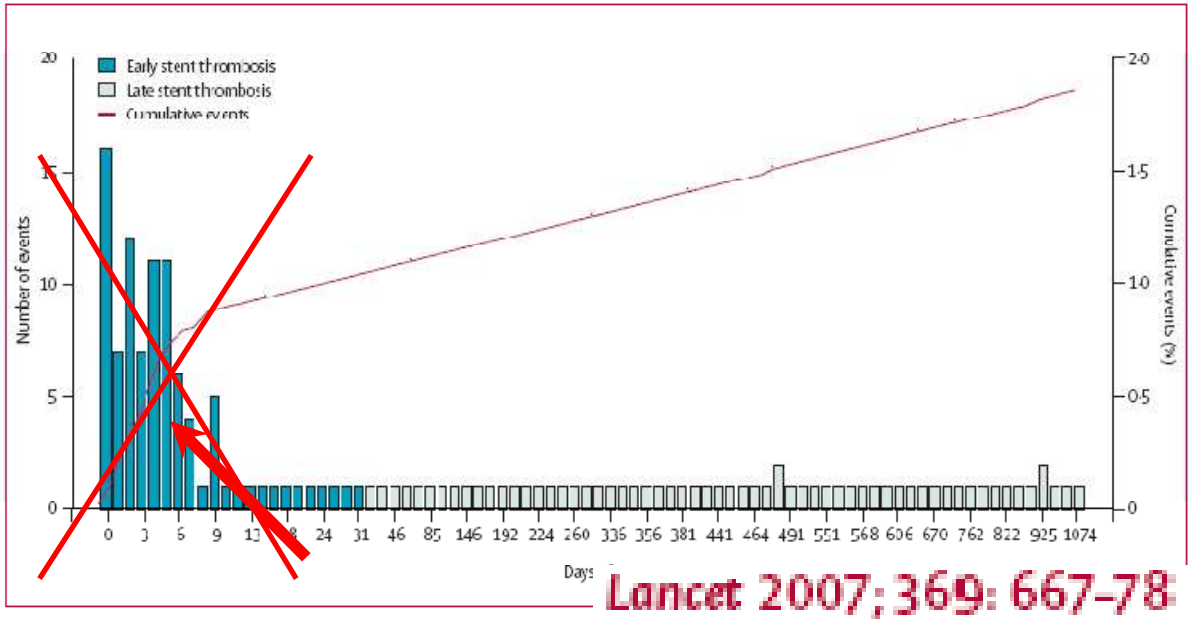


Figure 3: Kaplan-Meier survival curve showing cumulative incidence of stent thrombosis in patients with SES or PES



Lancet 2007; 369: 667–78

Device related factors that influence early stent thrombosis

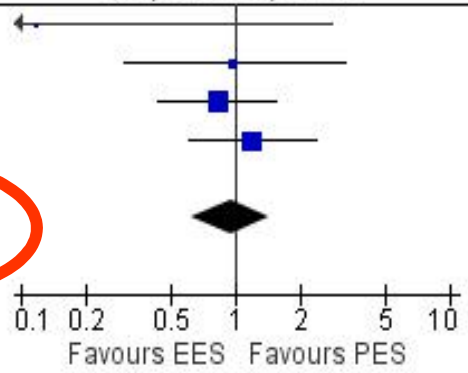
- Mechanical properties
  - Balloon compliance & Stent struts thickness
    - Better apposition
- Polymers
  - Biocompatibility
  - Polymer resistance to mechanical stress
- Drugs
  - Debated role, probably not of importance on early stent thrombosis

New perspectives in complex patients
Meta-analysis

A All-cause death

Study or Subgroup	Everolimus Eluting Stent Events	Total	Paclitaxel Eluting Stent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPIRIT II	0	220	1	76	1.8%	0.12 [0.00, 2.82]
SPIRIT III	8	655	4	321	12.9%	0.98 [0.30, 3.23]
SPIRIT IV	25	2416	15	1195	45.4%	0.82 [0.44, 1.56]
COMPARE	18	[illegible]	15	897	39.9%	1.19 [0.60, 2.35]
Total (95% CI)		**4194**		**2489**	**100.0%**	**0.94 [0.61, 1.45]**
Total events	51		35			

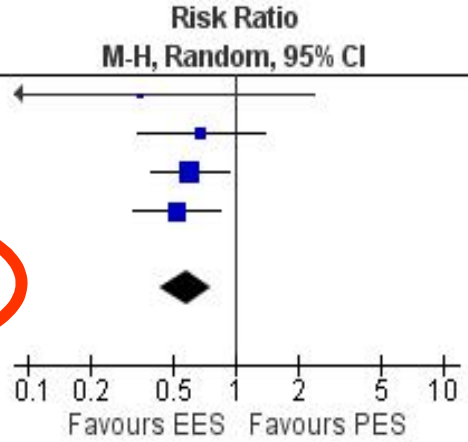
Heterogeneity: Tau² = 0.00; Chi² = 2.29, df = 3 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.79)



B Myocardial infarction

Study or Subgroup	Everolimus Eluting Stent Events	Total	Paclitaxel Eluting Stent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPIRIT II	2	220	2	76	2.2%	0.35 [0.05, 2.41]
SPIRIT III	18	655	13	321	16.7%	0.68 [0.34, 1.37]
SPIRIT IV	45	2416	37	1195	44.6%	0.60 [0.39, 0.92]
COMPARE	25	[illegible]	48	897	36.5%	[illegible] 0.83]
Total (95% CI)		**4194**		**2489**	**100.0%**	**0.57 [0.43, 0.76]**
Total events	90		100			

Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 3 (P = 0.87); I² = 0%
Test for overall effect: Z = 3.80 (P = 0.0001)



Courtesy : Dr. Claessen, AMC

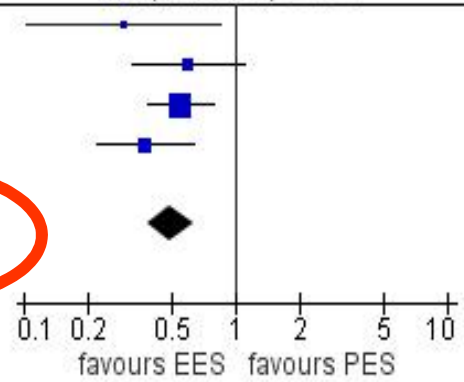
Meta-analysis

C Target lesion revascularization

Study or Subgroup	Everolimus Eluting Stent Events	Total	Paclitaxel Eluting Stent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPIRIT II	6	220	7	76	6.0%	0.30 [0.10, 0.85]
SPIRIT III	22	655	18	321	18.1%	0.60 [0.33, 1.10]
SPIRIT IV	61	2416	55	1195	52.4%	0.55 [0.38, 0.78]
COMPARE	18	[illegible]	48	897	23.5%	0.37 [0.22, 0.64]
Total (95% CI)		**4194**		**2489**	**100.0%**	**0.49 [0.38, 0.64]**
Total events	107		128			

Heterogeneity: Tau² = 0.00; Chi² = 2.69, df = 3 (P = 0.44); I² = 0%

Test for overall effect: Z = 5.39 (P < 0.00001)

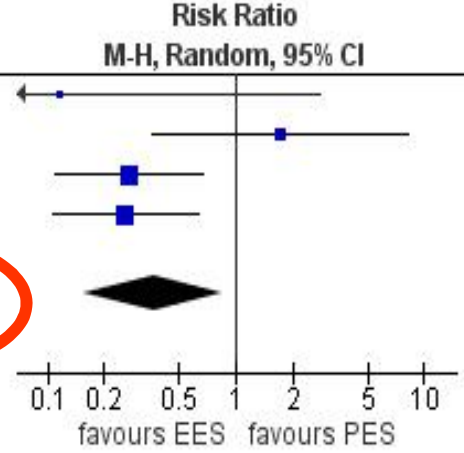


D Definite/probable stent thrombosis

Study or Subgroup	Everolimus Eluting Stent Events	Total	Paclitaxel Eluting Stent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
SPIRIT II	0	220	1	76	6.4%	0.12 [0.00, 2.82]
SPIRIT III	7	655	2	321	20.1%	1.72 [0.36, 8.21]
SPIRIT IV	7	2391	13	1195	36.4%	0.27 [0.11, 0.67]
COMPARE	6	[illegible]	23	897	37.2%	0.26 [0.11, 0.63]
Total (95% CI)		**4169**		**2489**	**100.0%**	**0.36 [0.16, 0.85]**
Total events	20		39			

Heterogeneity: Tau² = 0.30; Chi² = 5.15, df = 3 (P = 0.16); I² = 42%

Test for overall effect: Z = 2.33 (P = 0.02)



Courtesy : Dr. Claessen, AMC

What if Xience-V was used in SYNTAX ?

- In Syntax trial, overall PCI was inferior to CABG at 1 year, entirely due to repeat revascularization.
- In order to reach non-inferiority between PCI and CABG in the SYNTAX trial, a reduction of **20** events per 891 patients in the PCI group is needed

What if Xience-V was used in SYNTAX ?

- Based on the meta-analysis, the use of Xience-V in stead of Taxus in SYNTAX Trial might have lead to a total reduction of approximately **81** events in the PCI group
- Indicating that the overall SYNTAX trial outcome could have been equivalent for PCI and CABG

What have we learned from COMPARE

- In all-comer situation the everolimus eluting Xience-V stent is superior in safety and efficacy outcome compared to the paclitaxel eluting Taxus Liberte stent
- Further evidence/analysis for DM patients is needed
- Potentially with Xience-V improved PCI options for the complex multivessel diseased patient, compared to CABG