DES (R)Evolution

Selected Key Clinical Trials in Interventional Cardiology

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Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below

Affiliation/Financial Relationship	Company
Grant/Research Support	Abbott Vascular, Cordis Corporation, Medtronic CardioVascular
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Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

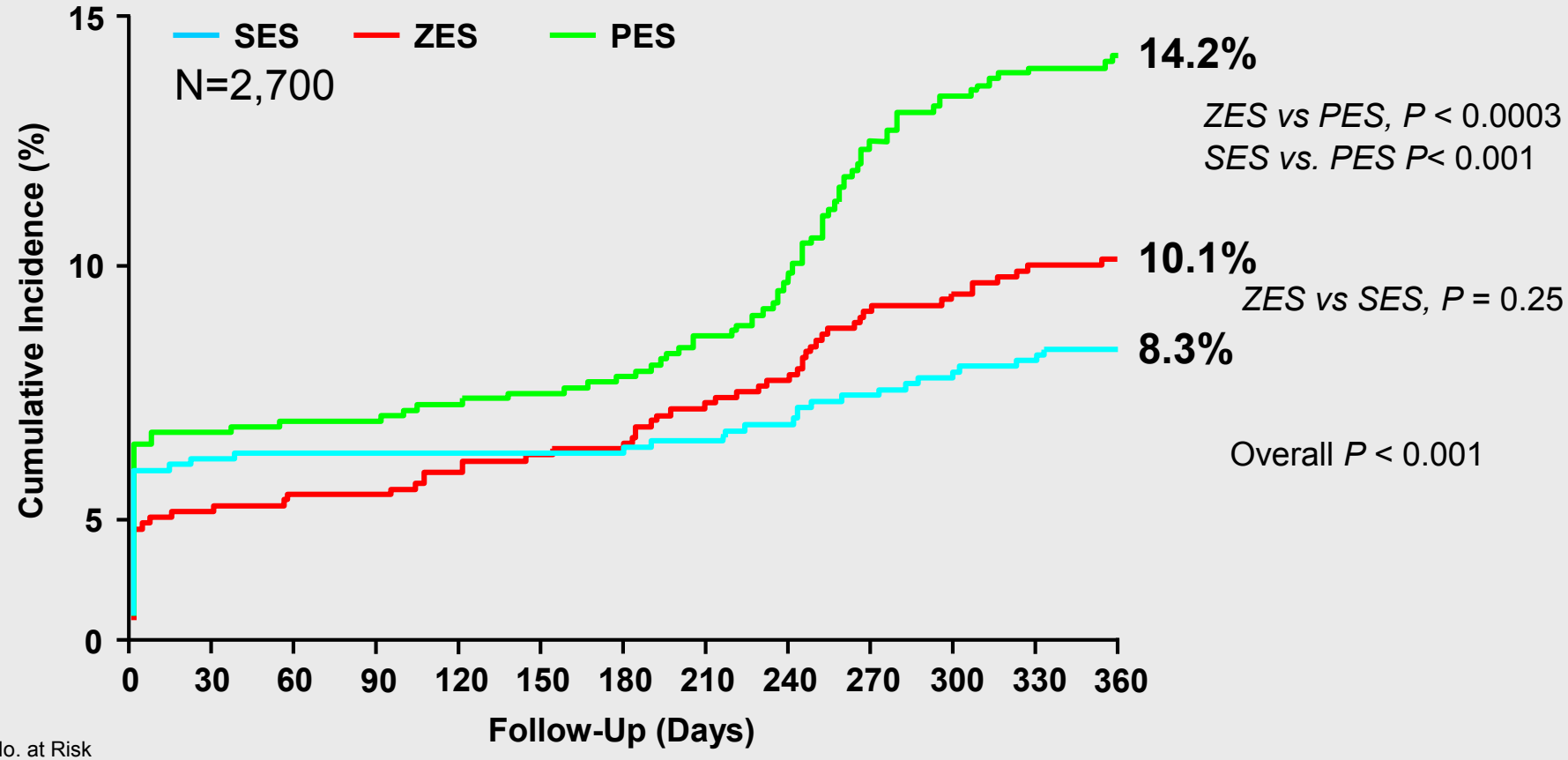
Key Clinical Trials 2010

- Comparative DES Trials
  - ZEST
  - SPIRIT IV
  - COMPARE
- Management of DES In-stent Restenosis
  - ISAR DESIRE 2
- Complex Coronary Disease: Bifurcation Dilemmas
  - Nordic/Baltic Bifurcation Study III
- Novel Non-polymeric DES and Drug Eluting Balloons
  - ISAR TEST 4
  - PEPCAD III

What Do We Know About DES in 2010?

- Profound, durable reduction in need for repeat revascularization
- From RCTs, no overall differences in D/MI/ST, now entering 7th year of follow-up
- ‘Off Label’ does not mean ‘Unstudied’
- Possibly lower MI and death compared with bare metal stents
- The story of safety and efficacy with DES does not stop at the primary endpoint
- Emerging differences in efficacy and safety endpoints between DES, no ‘class effect’

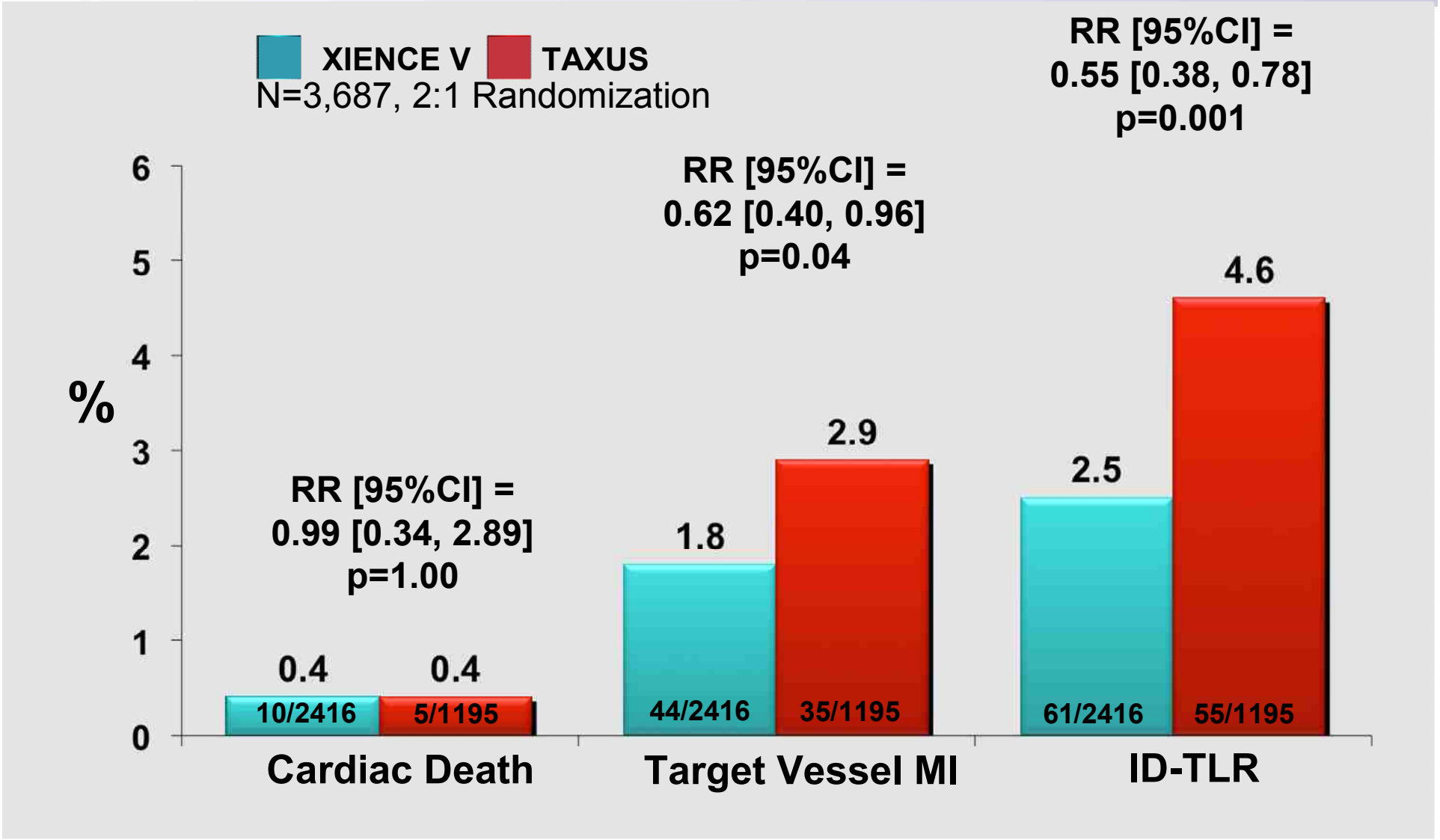
ZEST Primary End Point at 12 months
Death, MI, Ischemia-Driven TVR



No. at Risk					
ZES	883	827	816	790	782
SES	878	816	813	802	792
PES	884	821	808	763	745

ZEST: Park et al. ACC 2009

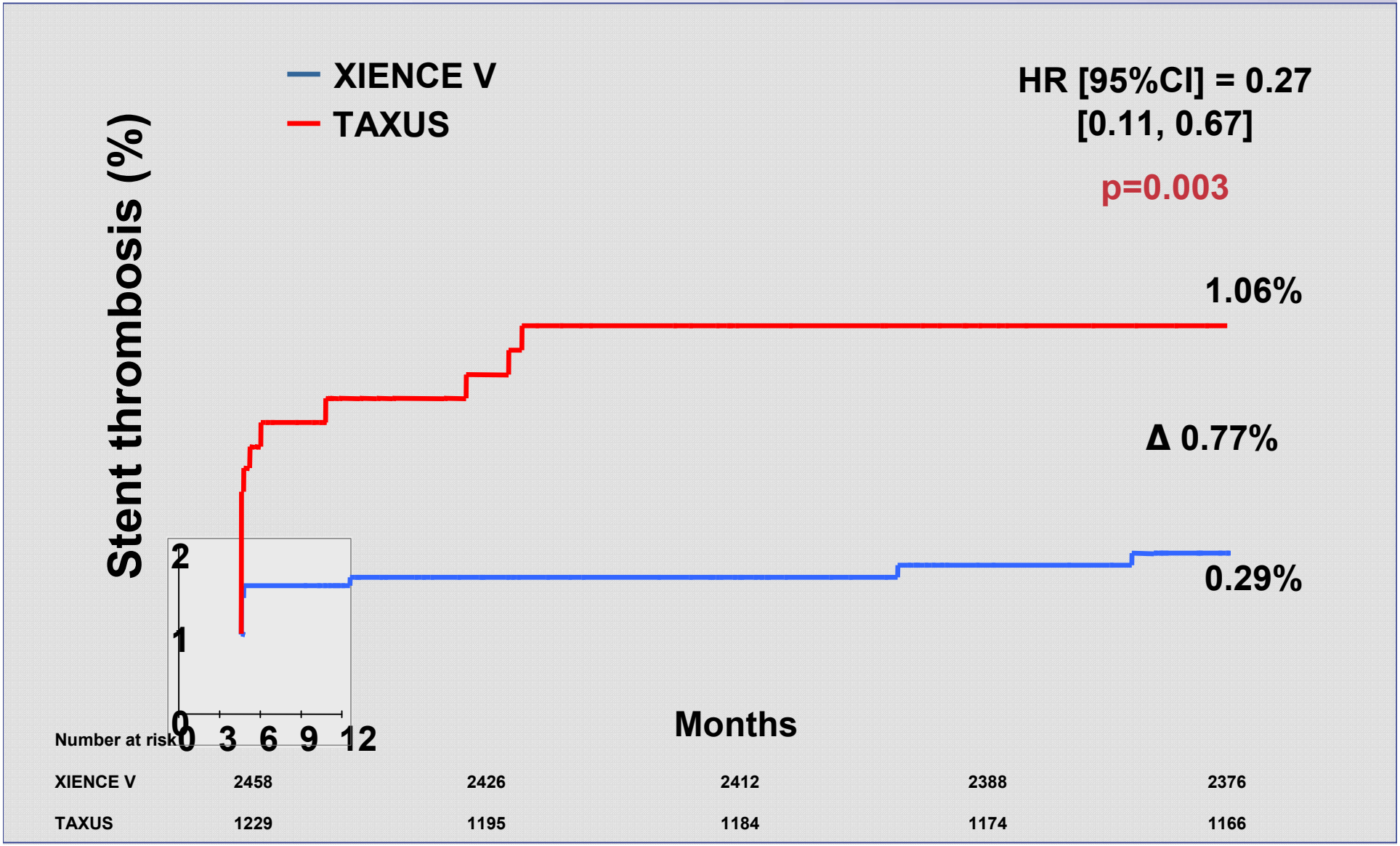
SPIRIT IV:
TLF Components Through 1 Year



TLF = cardiac death, target vessel MI, or ischemia-driven TLR
1 Year = 365 ± 28 days

Stone et al. TCT 2009

SPIRIT IV
Stent Thrombosis (ARC Def or Prob)



Stone et al. TCT 2009

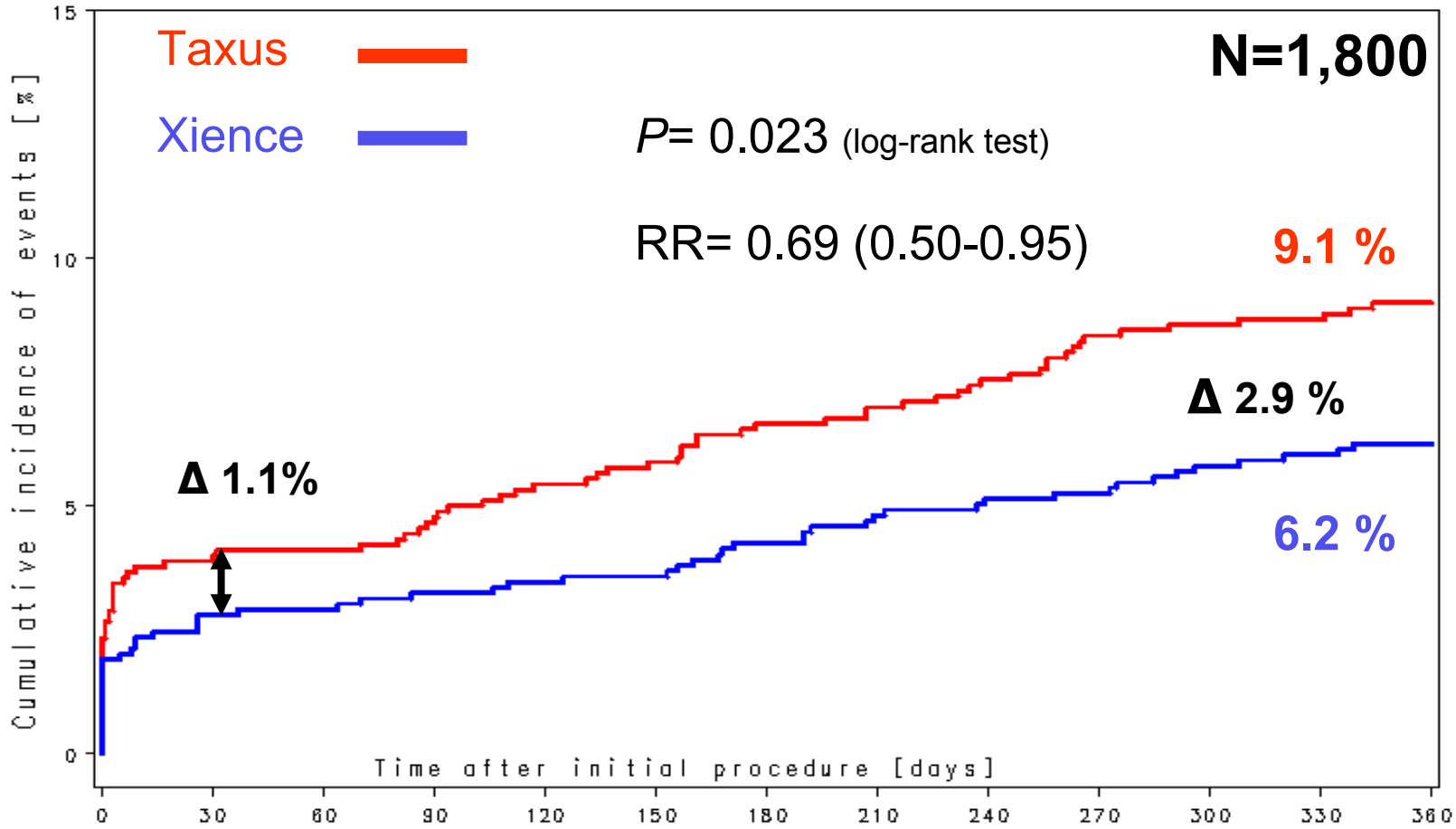
Pooled Analysis of SPIRIT III/IV Trials

1 Year Outcomes, N=4,689

	EES N=3,127	PES N=1,562	RR (95% CI)	*P* value
TLF	4.4	7.4	0.60 [0.47, 0.76]	<0.0001
MACE	4.6	7.6	0.60 [0.48, 0.77]	<0.0001
Death	1.1	1.3	0.86 [0.49, 1.50]	0.66
Cardiac Death	0.5	0.5	0.92 [0.39, 2.18]	0.83
MI	2.1	3.3	0.62 [0.43, 0.90]	0.01
TV MI	1.9	3.0	0.62 [0.42, 0.91]	0.02
TLR	2.7	4.8	0.56 [0.41, 0.76]	0.0003
Def/Prob ST	0.4	1.0	0.43 [0.20, 0.89]	0.03

Values expressed as percent and relative risk. Source: Abbott Vascular 2010

COMPARE Primary Endpoint Result
All death, Non-fatal MI and TVR

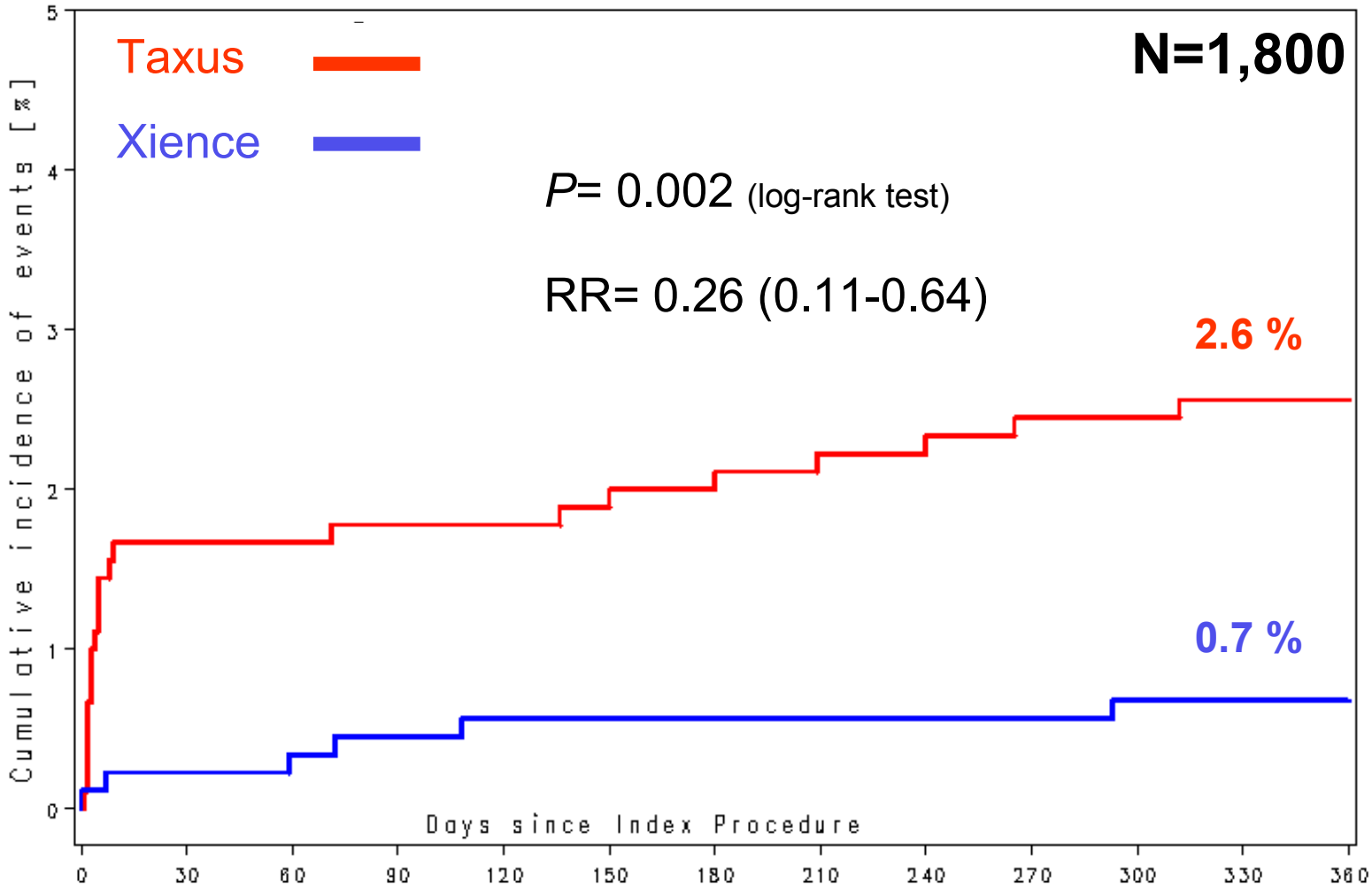


Patients at Risk

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

Smits et al. TCT2009; Kedhi et al. Lancet 2010

COMPARE
Definite/Probable Stent Thrombosis



Smits et al. TCT2009; Kedhi et al. Lancet 2010

Key Clinical Trials 2010
Comparative DES Trials: Perspective

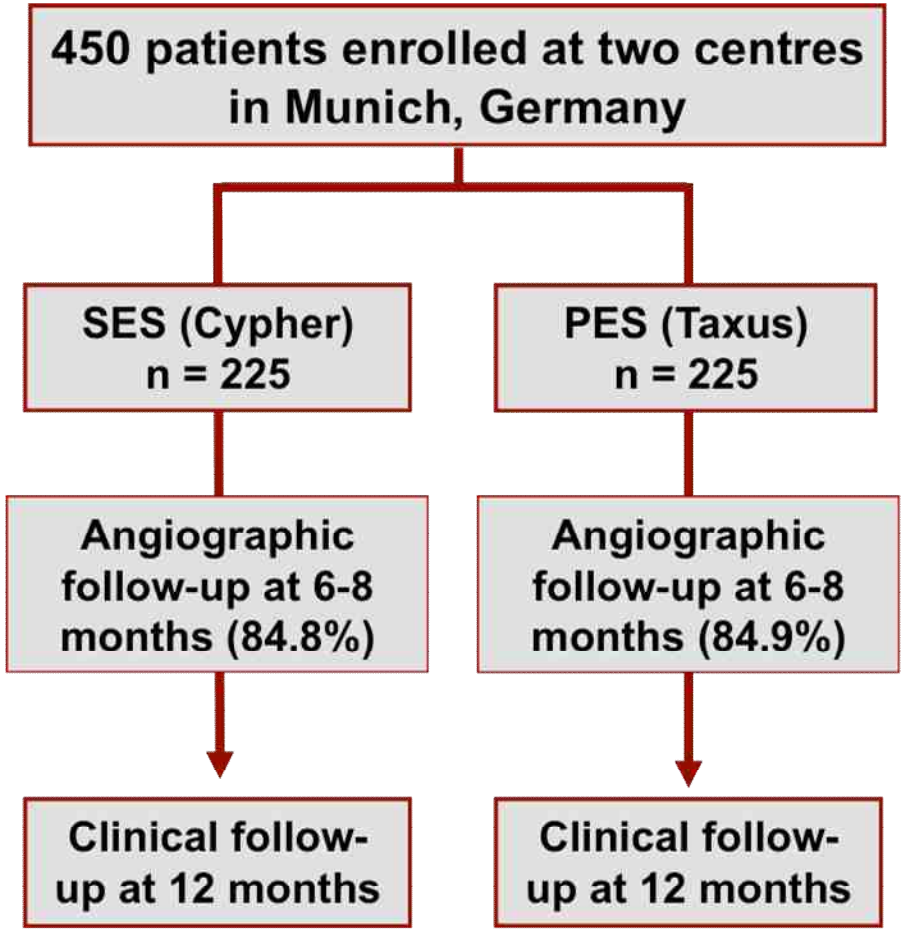
- Recent trials highlight emerging *efficacy and safety* differences between available DES
- Not all randomized trials are alike
  - Differences in endpoint definition and ascertainment may preclude generalizability of results
- 'Noninferiority Creep'
  - Successive non-inferiority trials may lead to result no better than predicate
- Our 'future' for advancing outcomes likely relates more to forthcoming trials focused on clinical strategy rather than novel device technologies

ISAR DESIRE 2

Randomized Comparison of SES vs PES for SES ISR

Design

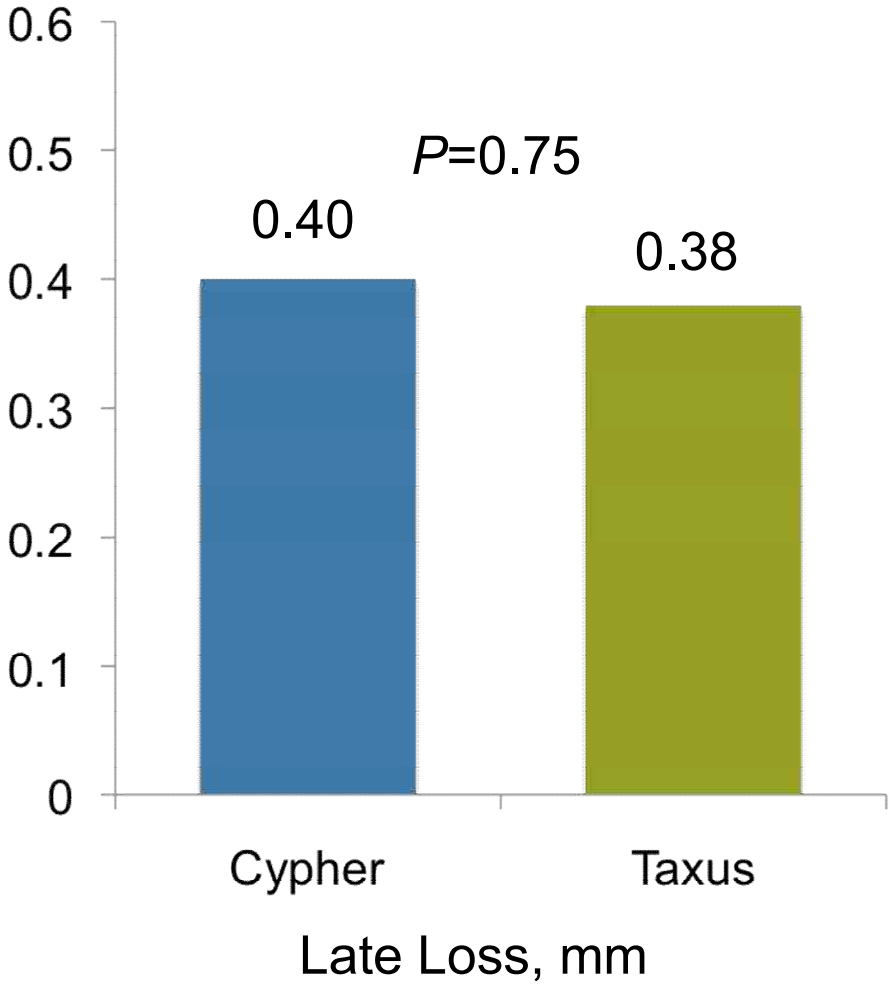
- **DESIGN: Randomized, open-label, active-control trial**
- **INCLUSION CRITERIA:**
  1. **In-SES restenosis > 50%**
  2. **Symptoms/signs of ischemia**
- **EXCLUSION CRITERIA:**
  1. **Cardiogenic shock**
  2. **Lesion in LMCA or graft**
  3. **Acute myocardial infarction**
- **PRIMARY ENDPOINT:**
  In-stent late loss

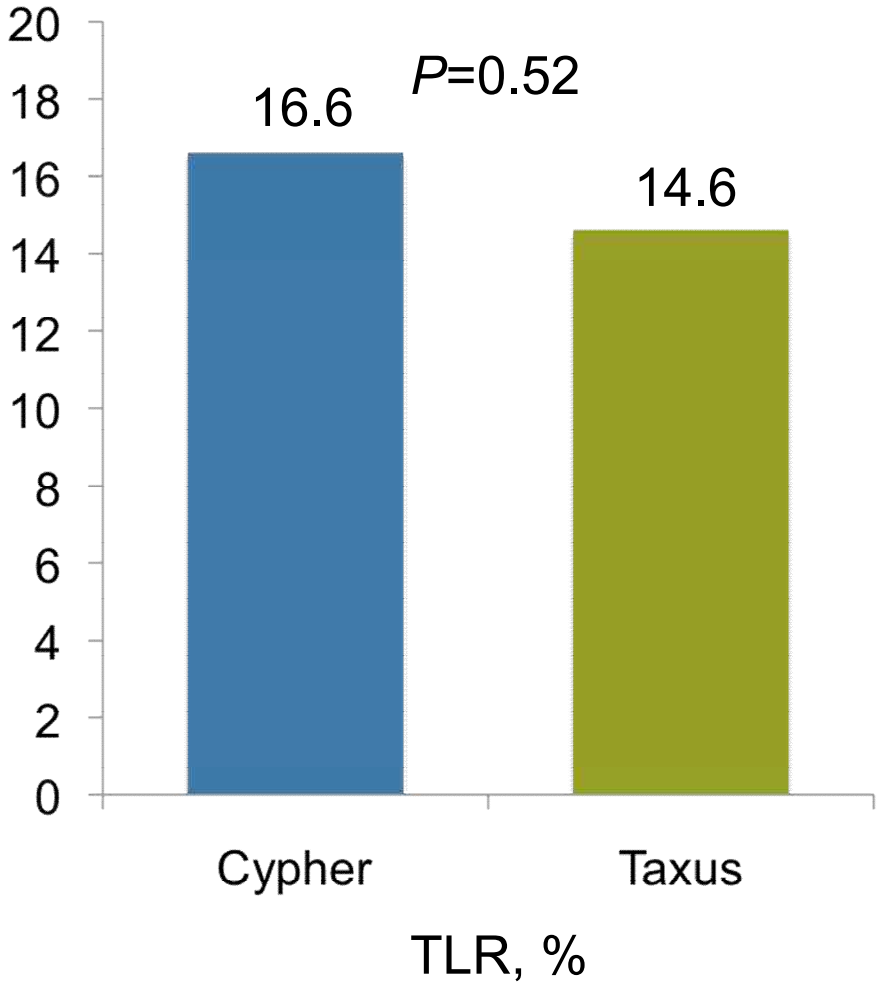


18% ACS; 62% ISAR stent, 38% Cypher

Mehillia et al. TCT 2009; JACC 2010

ISAR DESIRE 2
Randomized Comparison of SES vs PES for SES ISR





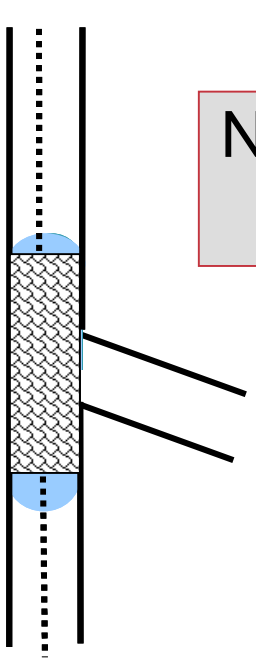
Mehillia et al. TCT 2009; JACC 2010

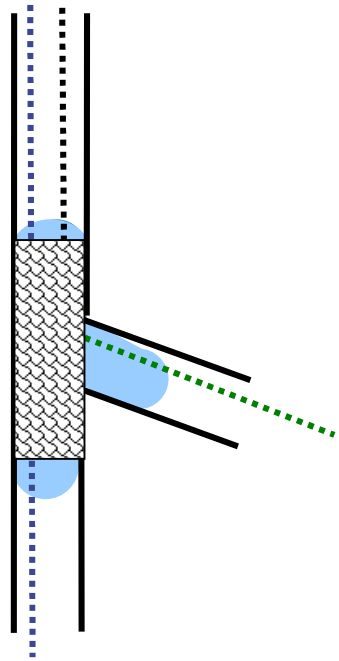
Nordic Baltic Bifurcation Study III

477 Bifurcation Disease Pts

No Kissing Balloon
N=239

Kissing Balloon
N=238

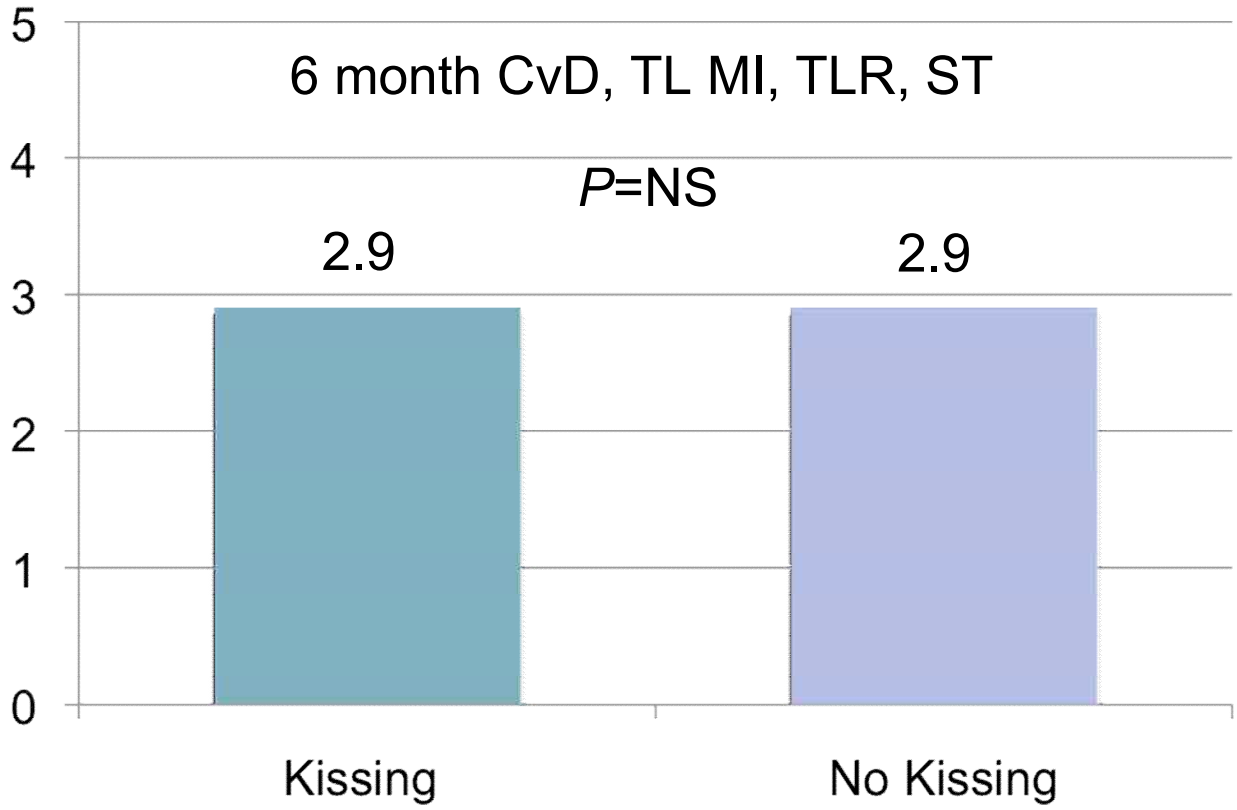




Primary Endpoint (6 months): Cardiac Death, Target lesion related MI*, TLR, Stent Thrombosis
*MI unrelated to index procedure

Niemela et al. TCT 2009

Nordic Baltic Bifurcation Study III



	No Kissing	Kissing	*P* value
Procedure time (min)	47 ± 22	61 ± 28	0.0001
Fluoro time (min)	11 ± 10	16 ± 12	0.0001
Contrast (ml)	200 ± 92	235 ± 97	0.0001

Niemela et al. TCT 2009

Key Clinical Trials 2010
DES in Complex Lesions: Perspective

- Modest sized trials in treatment of complex disease provide insight to treatment strategies but are not definitive
- DES In-stent Restenosis
  - Role of alternative DES (*eg*, non-polymeric, EES) and DEB in ISR evolving
- Bifurcation Disease
  - Theme of less intervention consistent with 1 vs 2 stent strategies, FFR data
  - 'High-risk' bifurcation disease (*eg,* UPLM) remains a dilemma
  - Evolution of bifurcation data presents increasing challenge to development of bifurcated stent technologies

ISAR-TEST-4

Intracoronary **S**tenting and **A**ngiographic **R**esults:
Test **E**fficacy of 3 Limus-Eluting **ST**ents - 4

2603 patients with *de novo* lesions

600 mg Clopidogrel at least 2 hours before index PCI + 500 mg ASA

Biodegradable polymer DES *(BP-DES)* n=1299	Permanent polymer DES *(PP-DES: Cypher & Xience)* n=1304

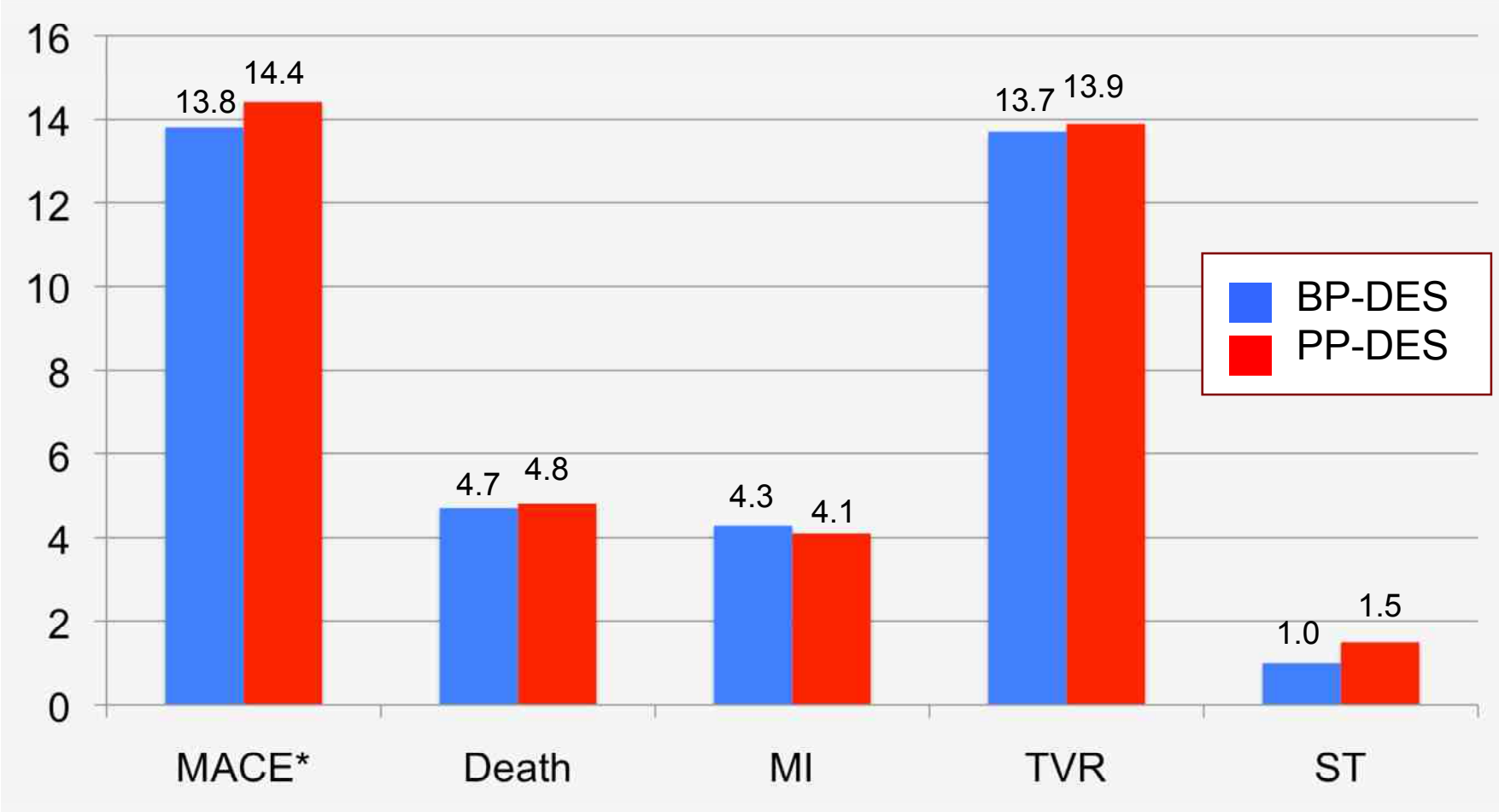
6 to 8-month repeat angiogram (78%)

12-month clinical follow-up (97%)

Clopidogrel	2x75 mg/day	until discharge
	75 mg	at least 6 months after index PCI
Aspirin	200 mg/d	indefinitely

Mehilli et al. ESC 2009; Eur Heart J 2009

ISAR-TEST-4
1-Year Outcomes

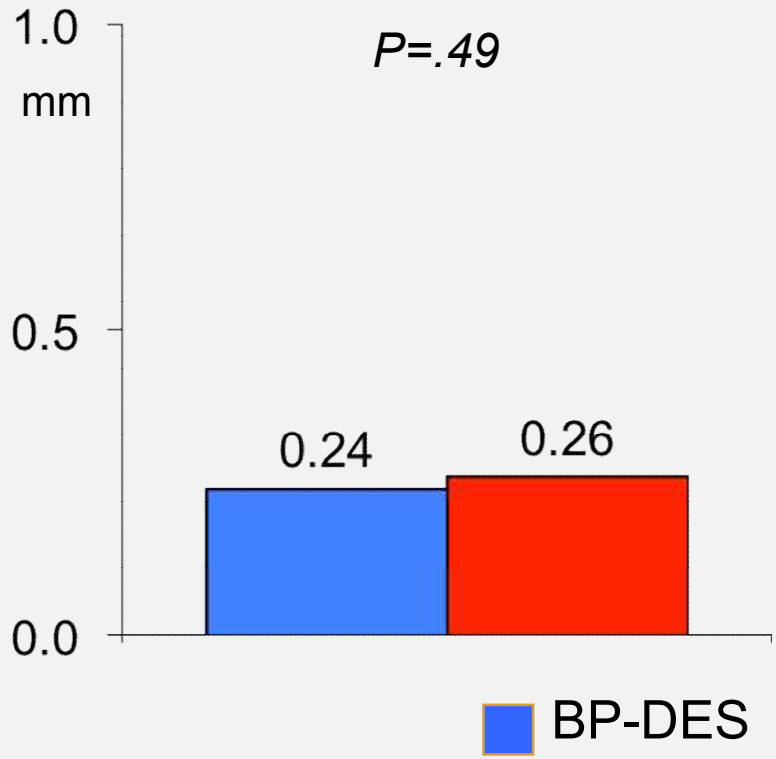


**Primary Endpoint, $P_{noninferiority}$=0.005; P=NS for all other comparisons*

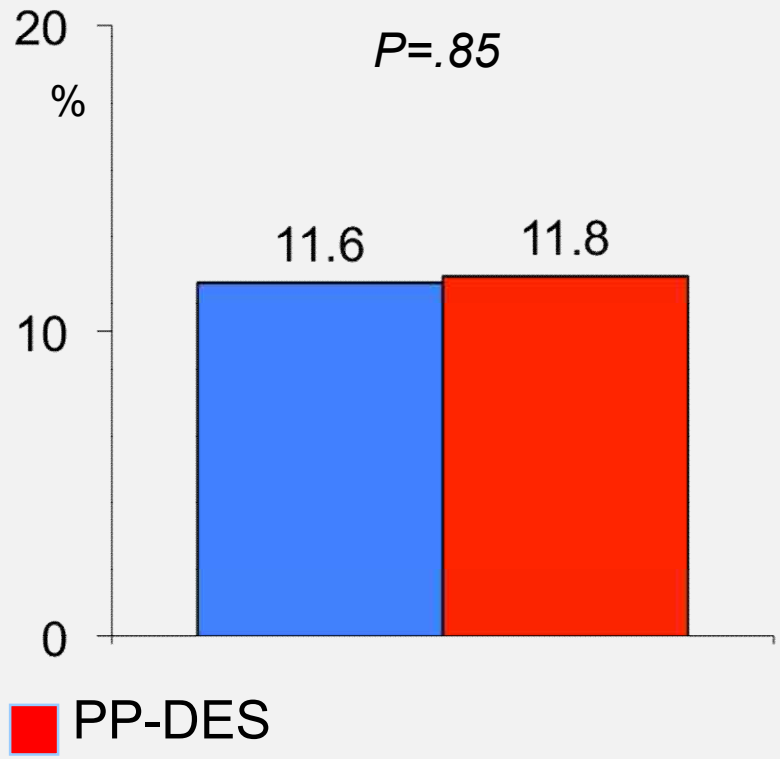
Mehilli et al. ESC 2009; Eur Heart J 2009

ISAR-TEST-4
Secondary Angiographic Outcomes

In-stent late lumen loss



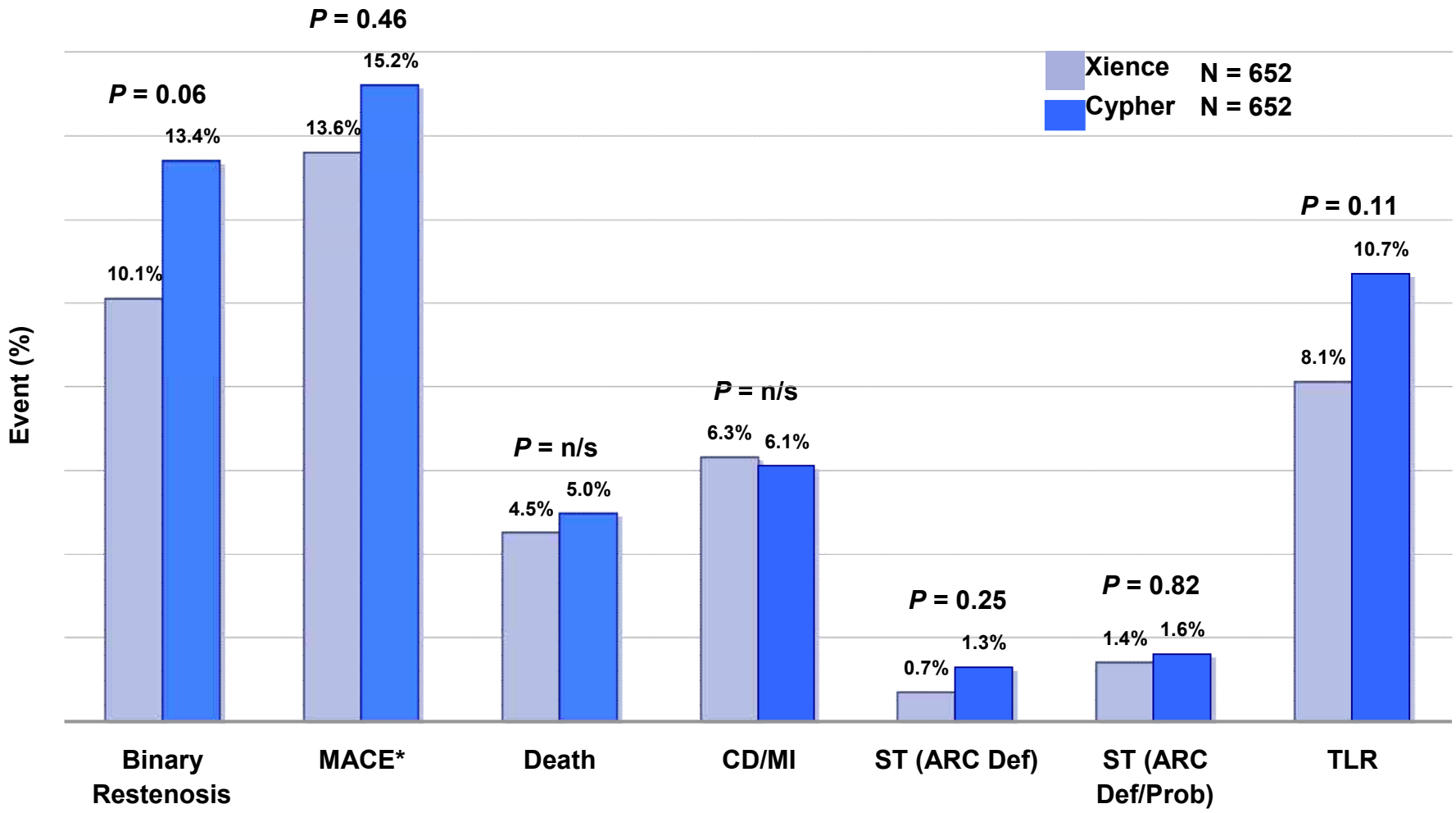
In-segment binary restenosis



Mehilli et al. ESC 2009; Eur Heart J 2009

ISAR-TEST-4

1-Year Outcomes: Cypher SES vs Xience EES



*MACE = CD, MI, TLR

Byrne, Mehilli et al. ACC 2010

PEPCAD III
Paclitaxel DEB plus BMS versus Cypher SES

	DEB+BMS Coroflex DEBlue N=269	DES Cypher N=273	*P* value
Binary Restenosis			
In-stent	10.0 %	2.9 %	<0.01
In-segment	13.8 %	4.9 %	<0.001
MLD 9 months			
In-stent	2.17 ± 0.63	2.46 ± 0.49	< 0.0001
In-segment	1.95 ± 0.62	2.05 ± 0.50	0.07
Late Lumen Loss			
In-stent*	**0.41 ± 0.51 mm**	**0.16 ± 0.39 mm**	**<0.001**
In-segment	**0.20 ± 0.52 mm**	**0.11 ± 0.40 mm**	**0.06**

*Primary endpoint

Hamm CW, et al. AHA 2009

PEPCAD III
Paclitaxel DEB plus BMS versus Cypher SES

	DEB+BMS Coroflex DEBlue® N = 310	DES Cypher® N = 324	*P* value
Death (9 months) Cardiac death	1.0 % 0.7 %	0.3 % 0.0 %	0.29
MI (9 months) STEMI NSTEMI	4.6 % 3.0 % 2.0 %	0.3 % 0.3 % 0.3 %	<0.001
TVR	13.8 %	6.9 %	<0.01
TLR	10.5 %	4.7 %	<0.01
Stent Thrombosis (ARC) Definite Probable	2.0 % 1.3 % 0.6 %	0.3 % 0.3 % 0.0 %	< 0.05

Hamm CW, et al. AHA 2009

Key Clinical Trials 2010

Novel Drug-Eluting Stents and Balloons: Perspective

- Opportunities for iterative development with novel drug-eluting platforms exist
  - Improved vessel healing and reduced ST
  - Decreased obligatory DAPT requirements
- With escalating regulatory standards and cost, 'next generation' in *most* instances will represent iterative modifications to existing platforms rather than 'game changing' technology
- As newer DES are introduced, clinical adoption will be driven more by intuition than scientific evidence as the opportunity to refine outcomes is increasingly difficult

  Must a 'new, but similar' DES demonstrate similar head-to-head outcomes or is inference good enough?

  Are preclinical (endothelialization) and mechanistic (OCT, vasomotion) data sufficient to support a new DES with limited human experience?