Revisiting Standards of Comparison in DES Trials

SORT OUT IV, EXCELLENT, BASKET PROVE, ISAR TEST 4

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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
Consulting Fees/Honoraria	Abbott Vascular, Cordis Corporation, Medtronic CardioVascular, Micell Technologies, Terumo Medical
Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

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Lessons Learned from Comparative DES Trials

1. Class effect of existing DES is an oversimplification evidenced by comparative trials

2. Not all randomized trials are alike, and not all ‘all comers’ trials include everyone

3. How a stent fares in clinical practice may not always be represented through clinical trials

4. Despite their intuitive appeal, the threshold for novel and ‘advanced generation’ stent designs to demonstrate superiority over selected existing DES is formidable

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LESSON 1
3 Year Outcomes, N=1,342 Matched Comparison of EES vs SES

End point	Everolimus (%)	Sirolimus (%)	HR (95% CI)	*P* value
Death, MI, TVR*	14.9	18.0	0.83 (0.68–1.0)	0.056
MI	3.3	5.0	0.62 (0.42–0.92)	0.017
TVR	7.0	9.6	0.76 (0.57–0.99)	0.039
Definite stent thrombosis	0.5	1.6	—	0.010
Definite or probable stent thrombosis	2.5	4.0	—	0.041

*Primary end point

Windecker et al. ESC 2010

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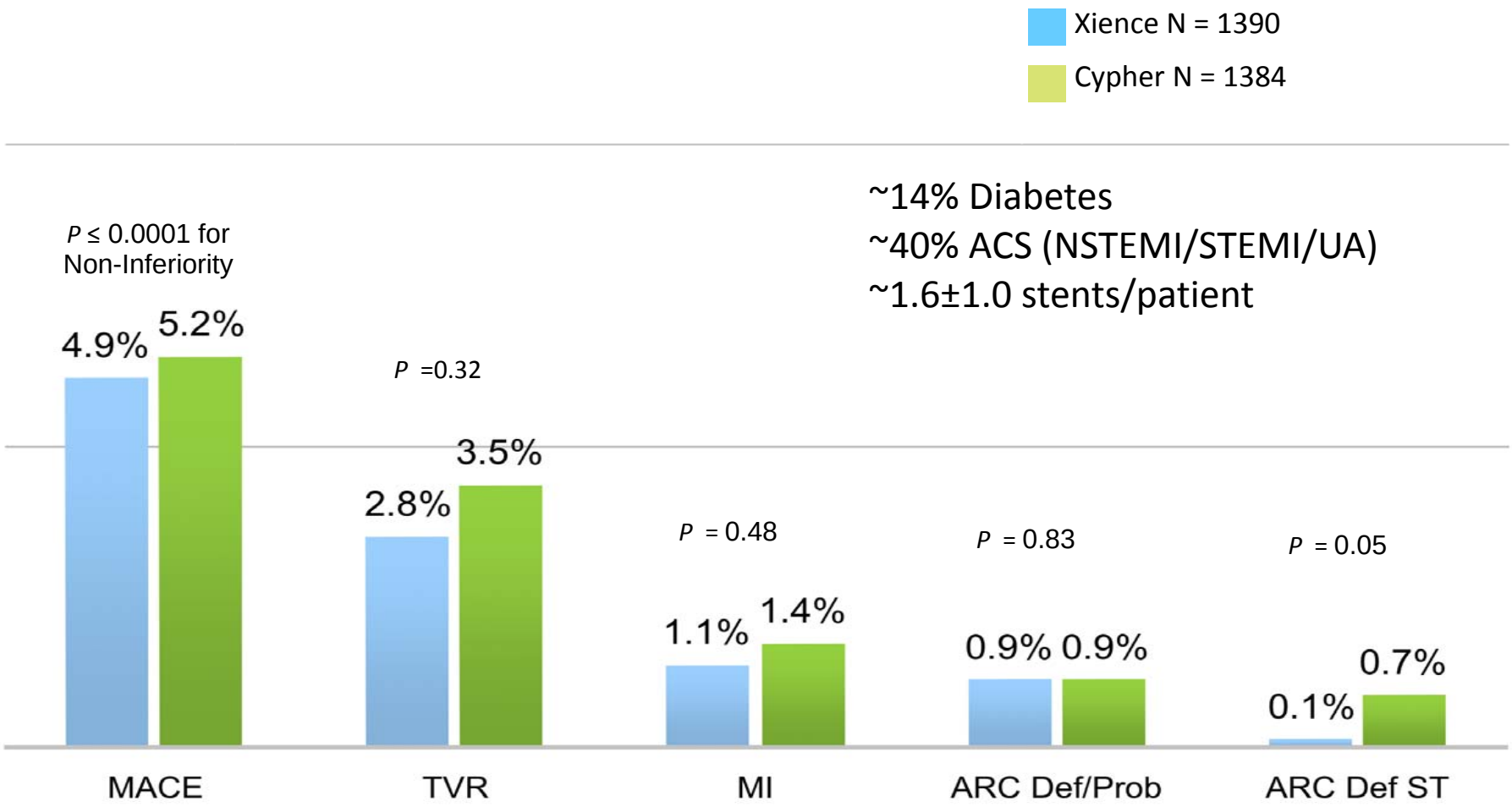
SORT OUT IV

Event Rates at 9 Months



Okkels Jensen et al. TCT 2010

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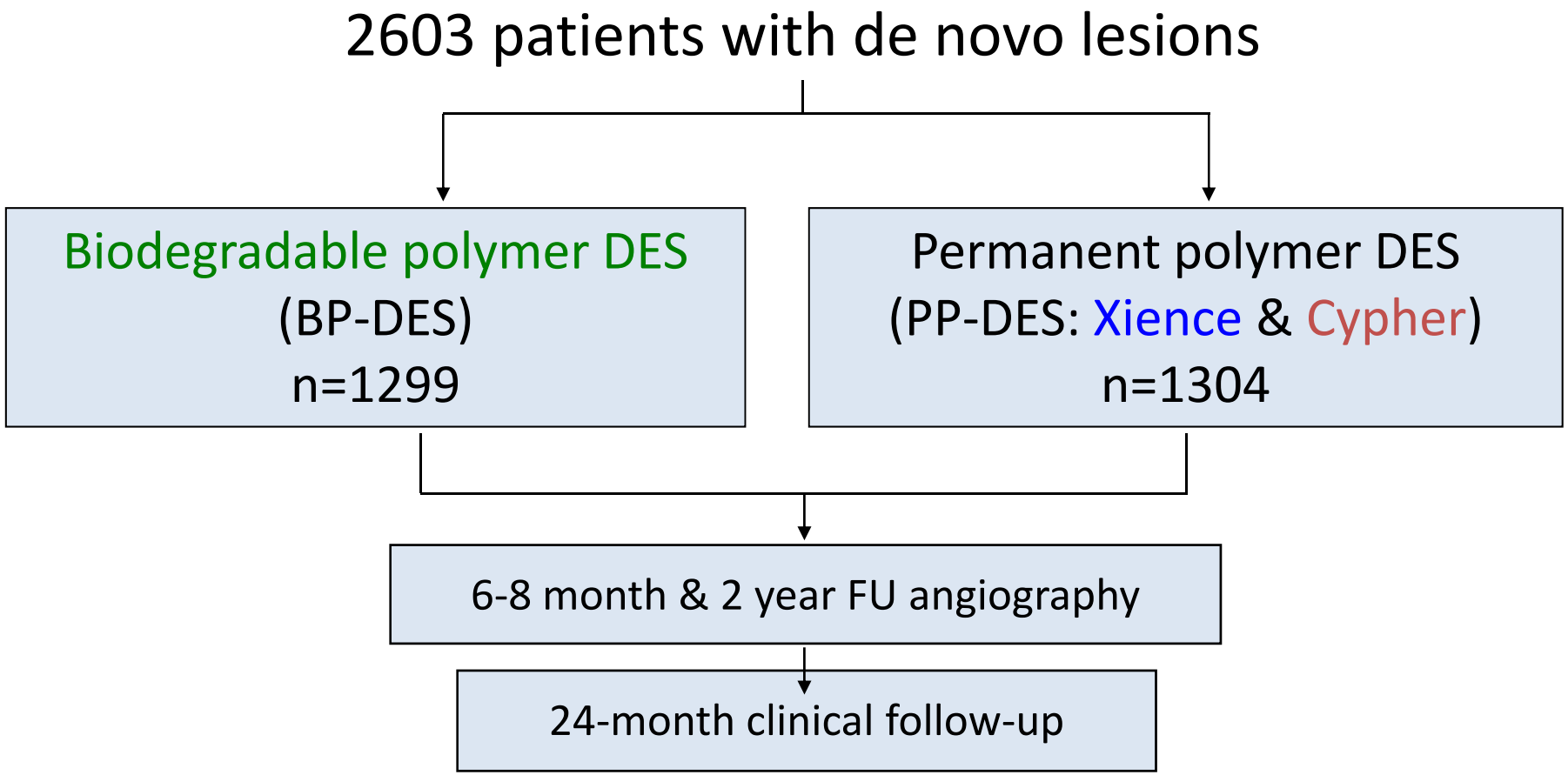
ISAR-TEST 4 Study Algorithm

Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents - 4



Byrne et al. Eur Heart J 2009

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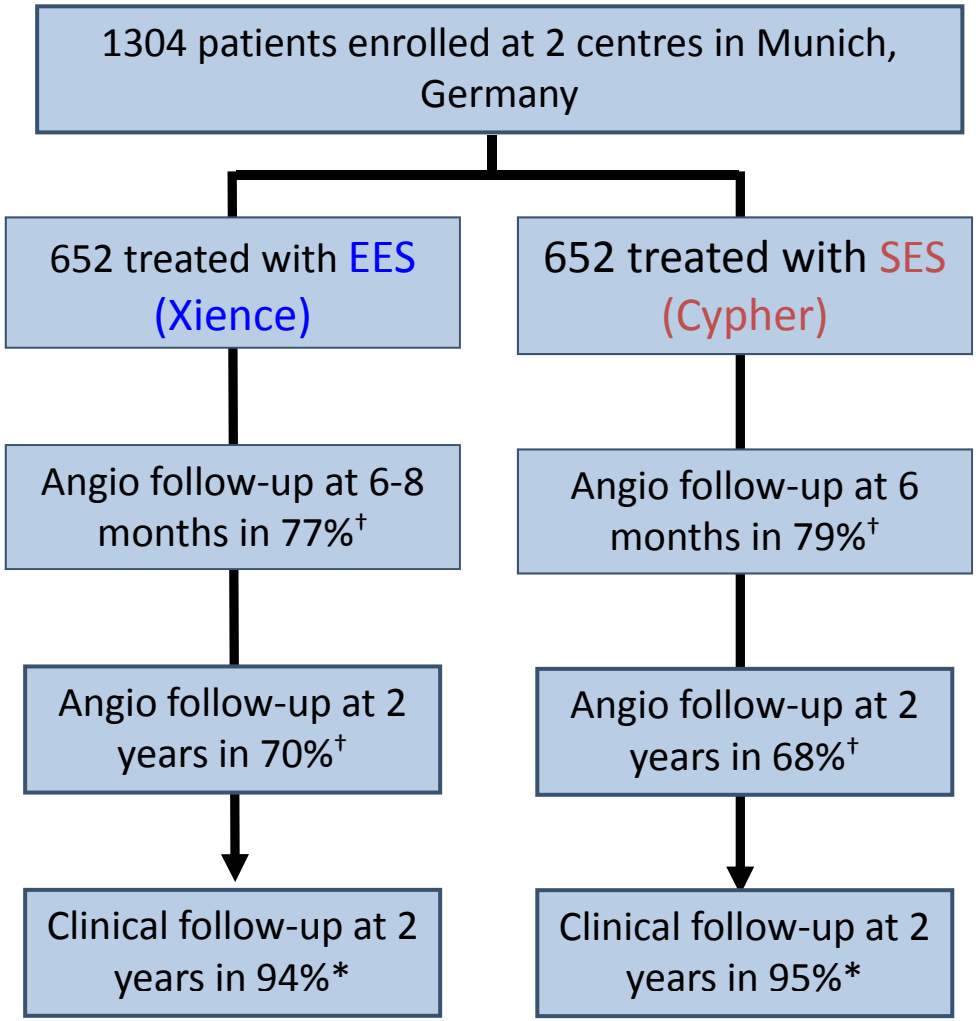
ISAR-TEST 4 EES vs. SES

Design

- DESIGN: Investigator-initiated, industry-independent, randomized, two-center clinical trial
- INCLUSION:
  Patients with de novo coronary artery stenosis ≥ 50% AND symptoms or objective evidence of ischaemia
- EXCLUSION CRITERIA: Left main stem disease
  Cardiogenic shock

~29% Diabetes
~41% ACS (NSTEMI/STEMI/UA)
~87% Multivessel Disease

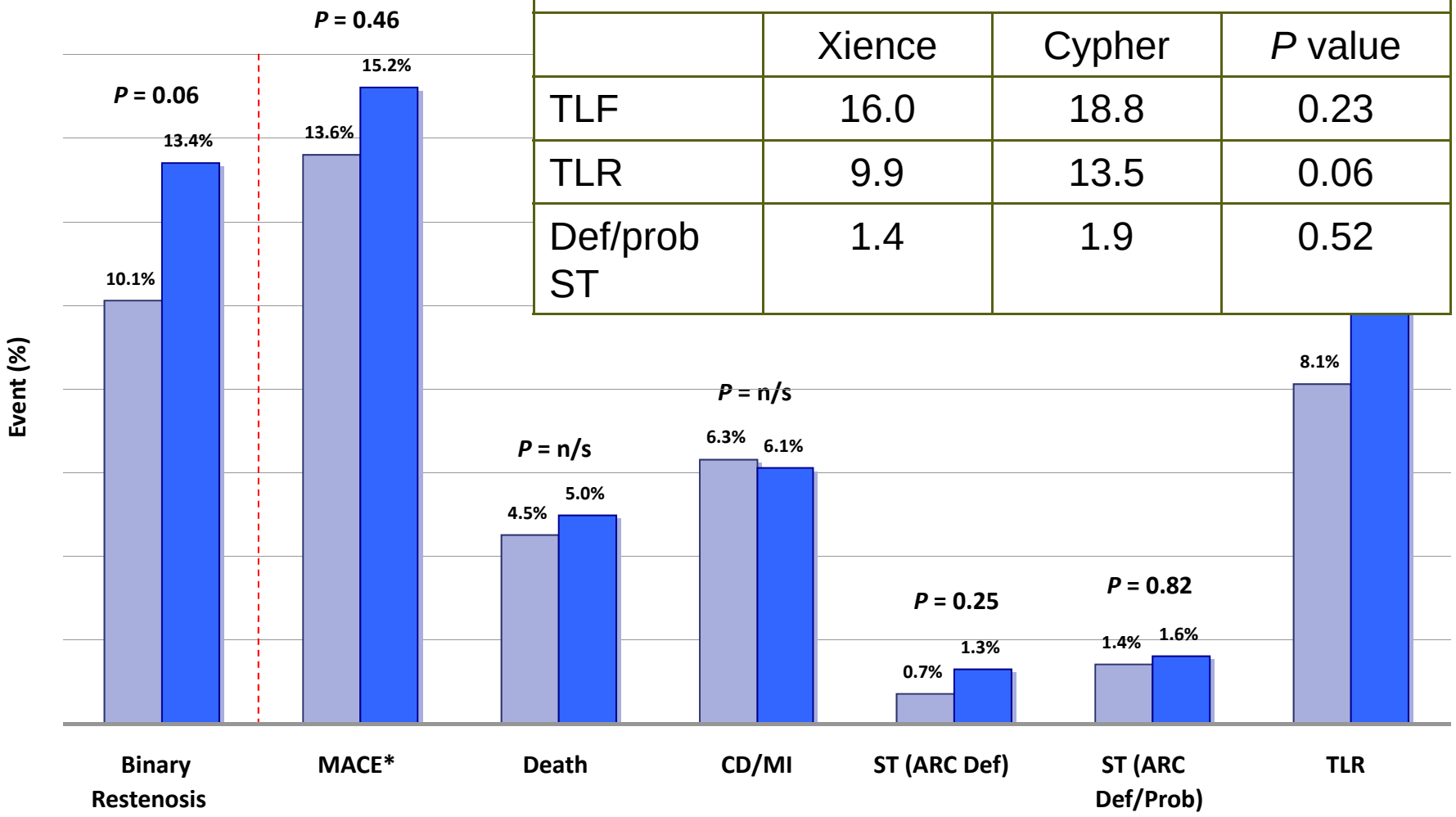


† of eligible
* of incomplete, median FU = 12 [3-16] mos

ISAR-TEST-4

1- and 2-Year Outcomes: Cypher SES vs Xience EES

2 Years			
	Xience	Cypher	*P* value
TLF	16.0	18.8	0.23
TLR	9.9	13.5	0.06
Def/prob ST	1.4	1.9	0.52



*MACE = CD, MI, TLR

Byrne, Mehilli et al. ACC 2010; EHJ 2010; Byrne et al. TCT 2010

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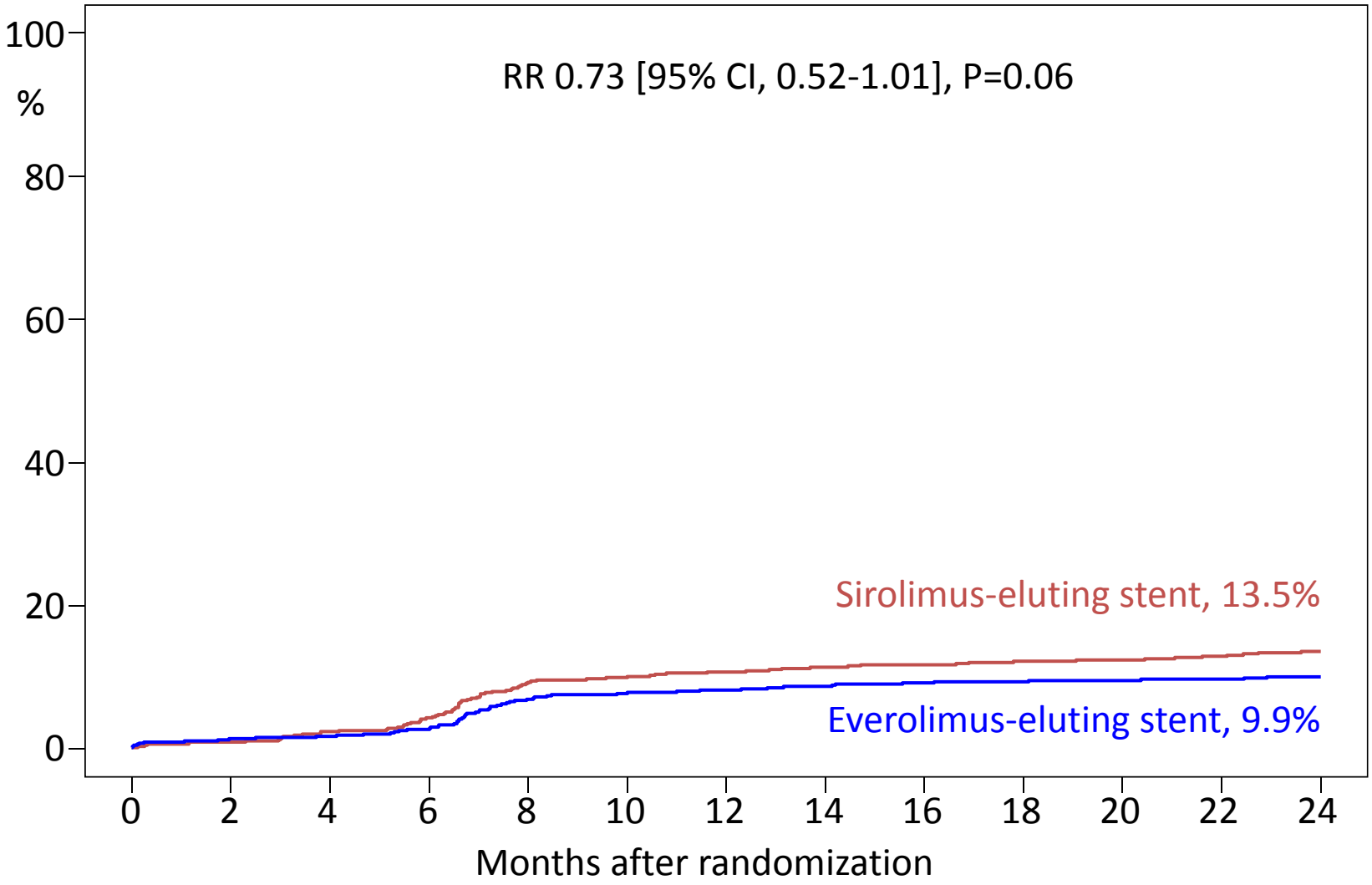
ISAR TEST 4
2-Year Target Lesion Revascularization



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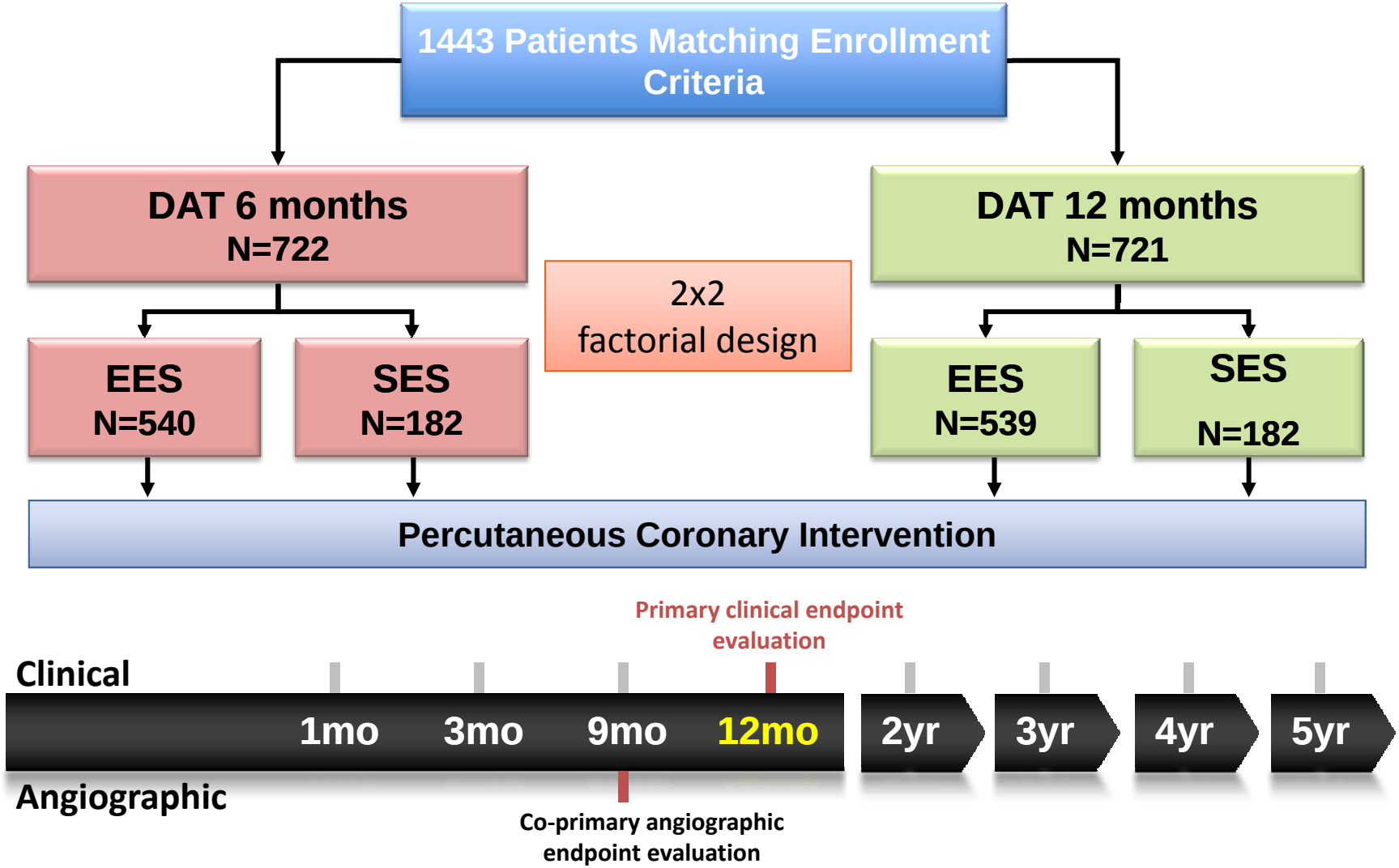
EXCELLENT

Prospective, open label, two-arm, randomized multi-center trial



Am Heart J 2009 May;157:811-817.e1

www.clinicaltrials. gov (NCT00698607).

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EXCELLENT
Patient Eligibility

Inclusion Criteria

- > 50% stenosis by visual estimation
- Evidence of myocardial ischemia
  - ✓ Stable angina
  - ✓ Unstable angina
  - ✓ Recent infarction, silent ischemia
  - ✓ + functional study or reversible changes in the ECG c/w ischemia
- Target lesion must be located in a native coronary artery
- 2.25mm ≤ RVD ≤ 4.25mm
- Lesion length: no limitation
- Multiple stenting: no limitation

General Exclusion Criteria

- GI or GU bleeding ≤3 months, major surgery ≤ 2 months
- Hb<10 g/dL, PLT<100K
- Elective surgical procedure planned ≤ 12 months
- LVEF < 25%, or in shock
- MI ≤ 72 hours
- Creatinine level ≥ 3.0mg/dL or dependence on dialysis
- Severe hepatic dysfunction (AST, ALT ≥ x3 UNL)
- Patients who have received any stent implantation in the target vessel prior to enrollment

Angiographic Exclusion Criteria

- Patients with significant LM stenosis
- BMS or DES ISR
- CTO
- True bifurcation lesions requiring two stents

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EXCELLENT
9 Month Angiographic and 1-Year Clinical Outcomes

	Sirolimus, N=266	Everolimus N=935	*P* Value
Angiographic Outcomes			
In-Stent Late Loss, mm	0.15±0.33	0.19±0.33	$0.005_{\text{Noninferiority}}$
In-Segment Late Loss, mm	0.05±0.34	0.10±0.36	$0.017_{\text{Noninferiority}}$
Clinical Outcomes, %			
TLF	3.0	3.7	0.58
Cardiac Death/MI	1.9	1.5	0.55
TLR	1.6	2.4	0.42
Def/prob ST	0.8	0.4	0.27

Kim et al. TCT 2010

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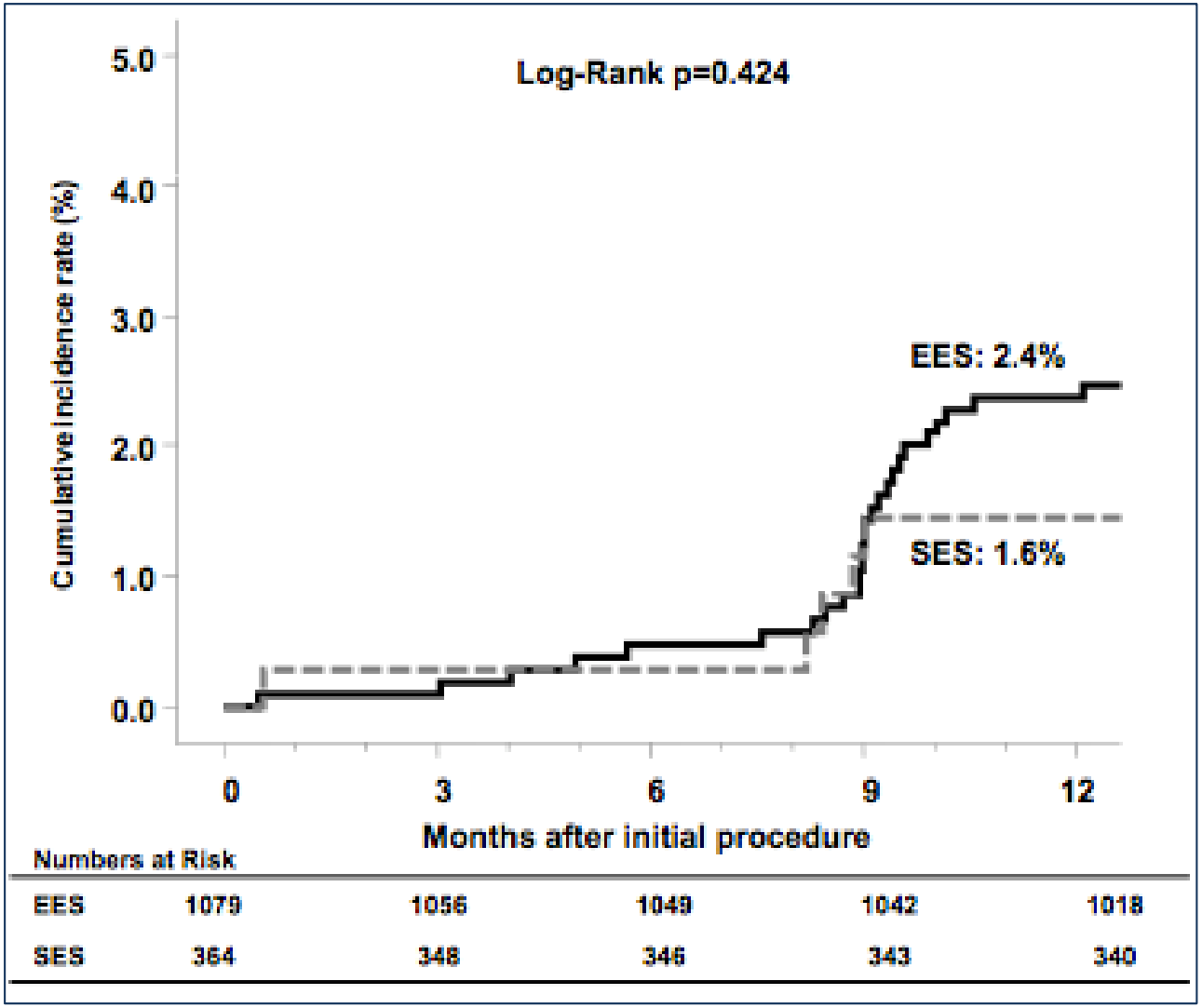
EXCELLENT
1 Year Target Lesion Revascularization



Numbers at Risk					
EES	1079	1056	1049	1042	1018
SES	364	348	346	343	340

Kim et al. TCT 2010

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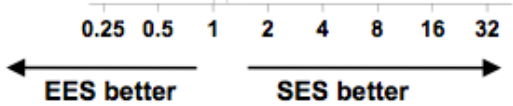
EXCELLENT
Subgroup Analysis

Subgroups	Pt No.	TLF (%) EES	TLF (%) SES	RR (95% CI)	Int P
Diabetes mellitus					0.34
Yes	544	5.8	3.4		
No	884	2.5	2.8		
Long lesions (Lesion length ≥ 20mm)					0.82
Yes	576	4.9	4.7		
No	785	2.5	2.1		
Multivessel stenting					0.63
Yes	392	5.8	6.0		
No	1036	2.9	2.2		
Sex					0.22
Male	925	3.2	3.5		
Female	503	4.9	2.2		
Acute myocardical infraction					0.36
Acute MI	139	7.9	2.7		
Non Acute MI	1289	3.3	3.1		
Renal Dysfunction					0.59
CCr ≤ 60	243	5.2	2.9		
CCr > 60	1183	3.5	3.1		
Reference vessel diameter					0.88
≥2.75mm	864	3.6	3.2		
< 2.75mm	539	3.7	3.0		
Overall	1428	3.8	3.1		-



Kim et al. TCT 2010

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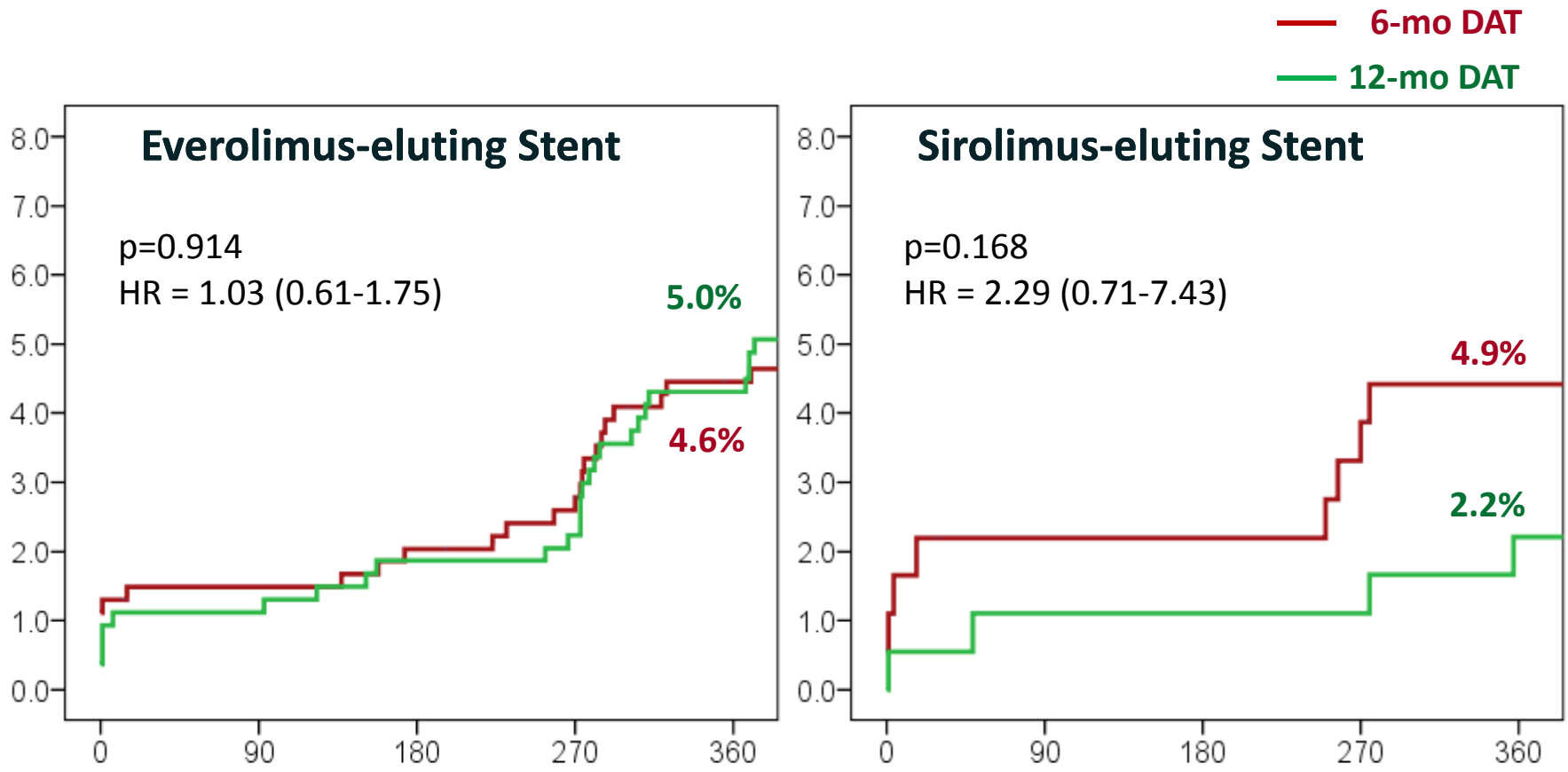
EXCELLENT
1-Year TVF According to Stent Type and DAPT Duration



Patient Number at Risks

6-mo	540	531	528	524	511
12-mo	539	531	524	521	505

Patient Number at Risks

6-mo	182	176	176	174	171
12-mo	182	179	179	178	176

Gwon et al. ACC 2011

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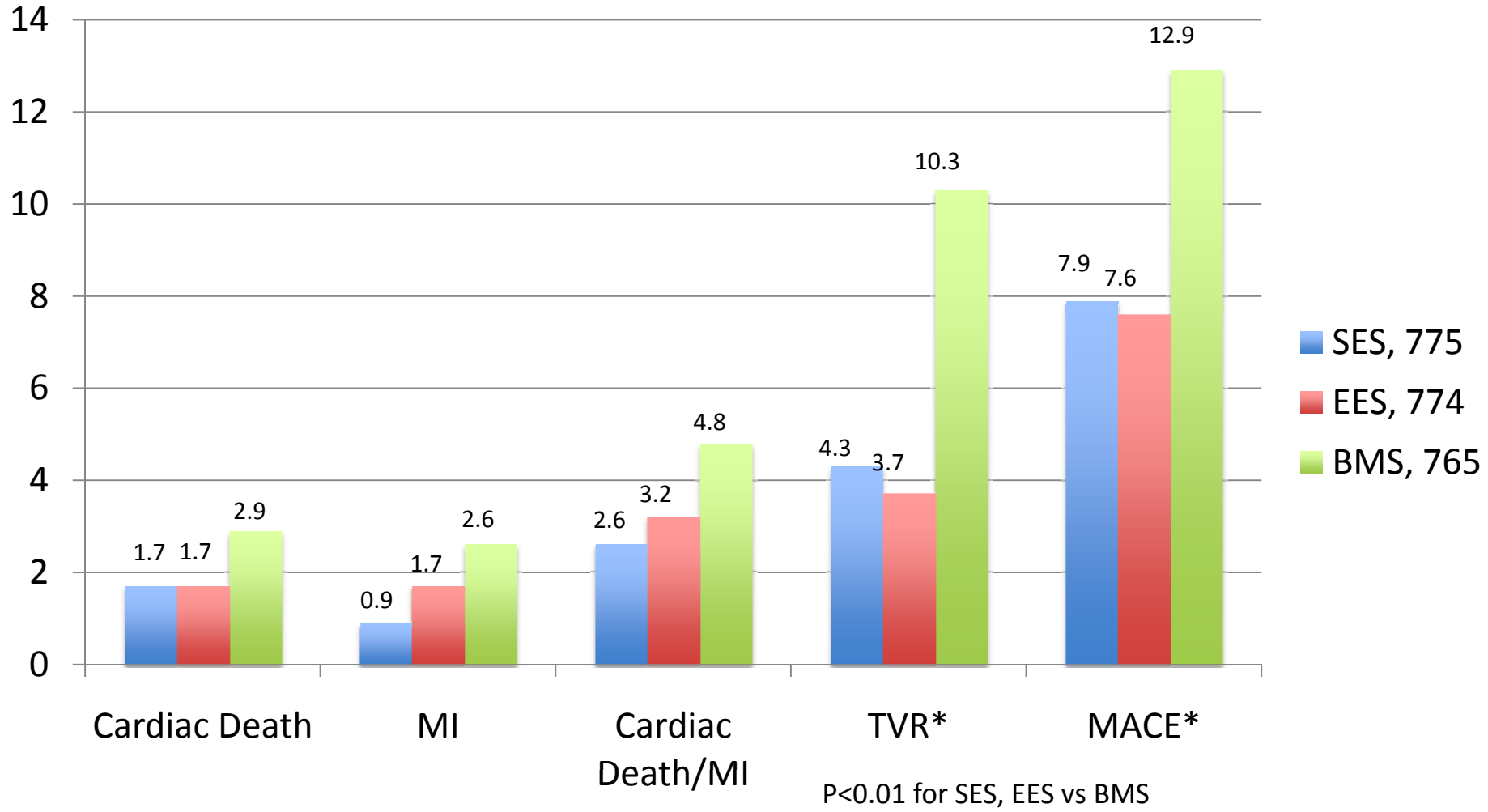
BASKET PROVE
2-Year Outcomes for Vessel Caliber ≥3.0



P<0.01 for SES, EES vs BMS

Kaiser et al. NEJM 2010

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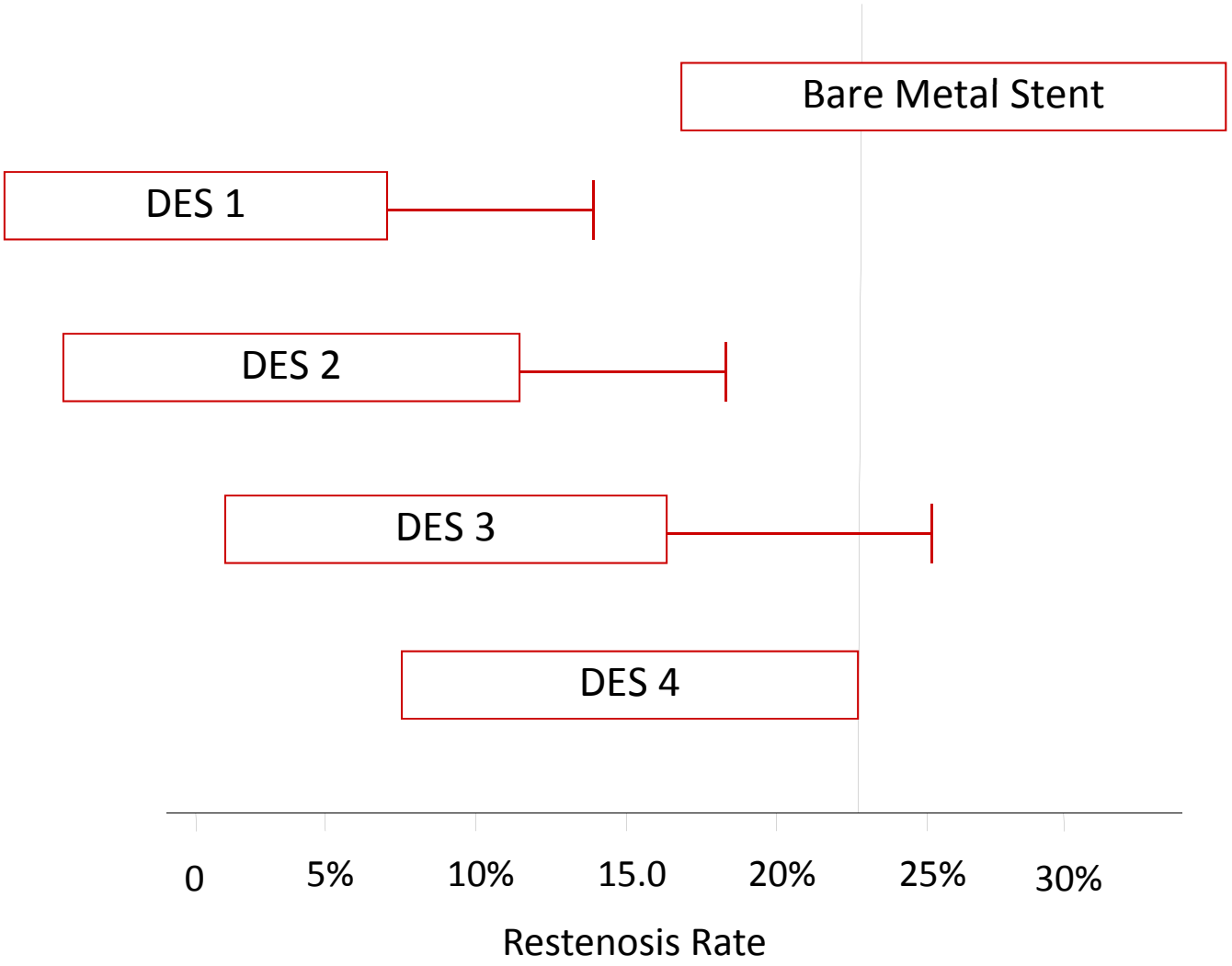

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Revisiting Standards of Comparison in DES Trials

- While recent comparative study has highlighted safety and efficacy differences with new DES compared with PES, no well designed trial to date has demonstrated superiority to SES
- As newer DES are introduced, adoption will be driven more by intuition than scientific evidence as the opportunity to refine outcomes is increasingly difficult
  - 'Next generation' in *most* instances will represent iterative modifications to existing platforms rather than 'game changing' technology
- Rather than focus on device approval through non-inferiority, an opportunity exists for new technologies to inform existing practice with new DES

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