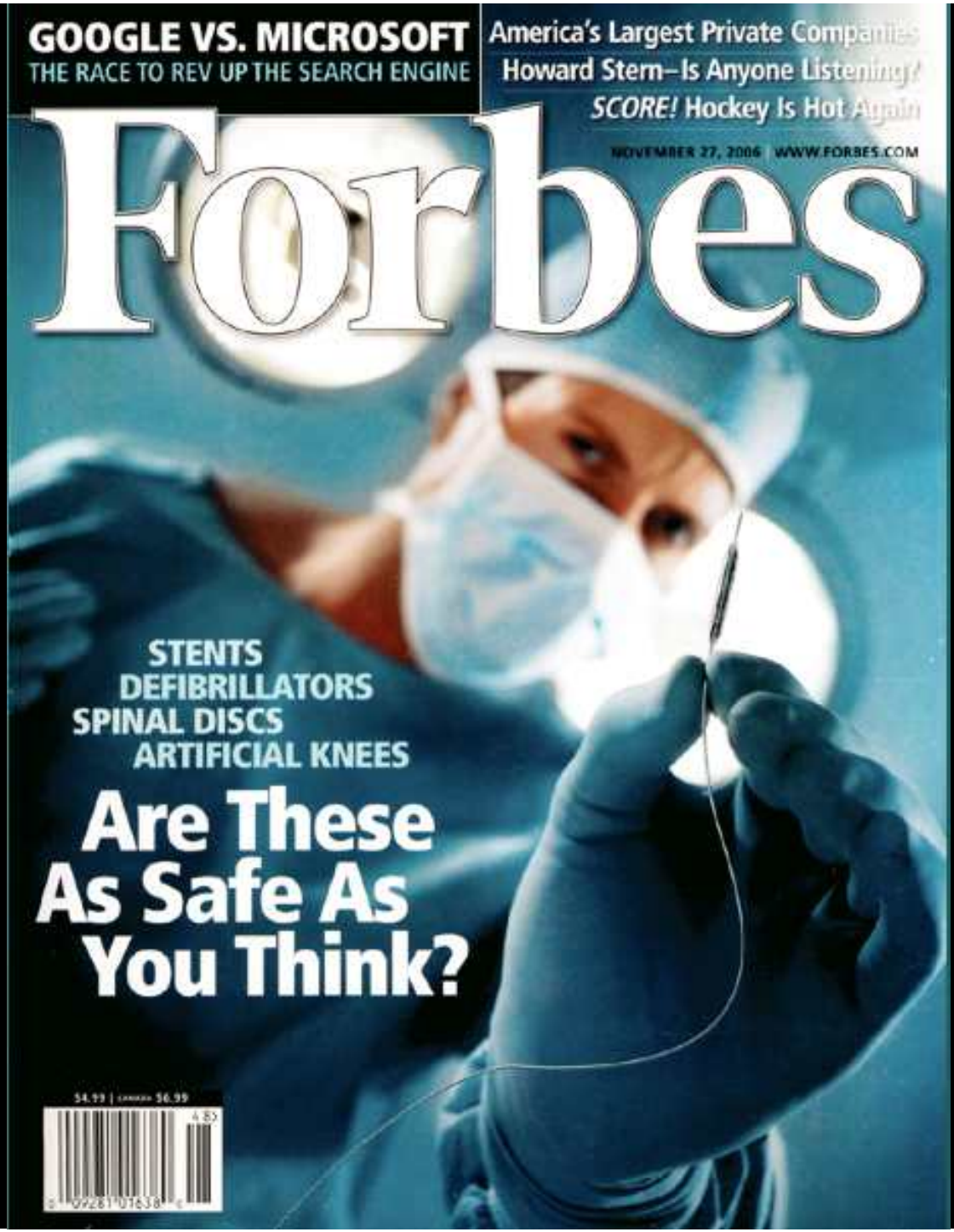
Stent Safety: Fear Not

Paul S.Teirstein, MD

Chief of Cardiology
Director of Interventional Cardiology
Scripps Clinic

Disclosures:

Cordis, Boston, Medtronic:	**Research Grants**
	Consultant
	Speakers Bureau
Shepherd Scienti	**Equity**


GOOGLE VS. MICROSOFT
THE RACE TO REV UP THE SEARCH ENGINE
America's Largest Private Companies
Howard Stern–Is Anyone Listening?
SCORE! Hockey Is Hot Again
NOVEMBER 27, 2006 WWW.FORBES.COM
Forbes
STENTS
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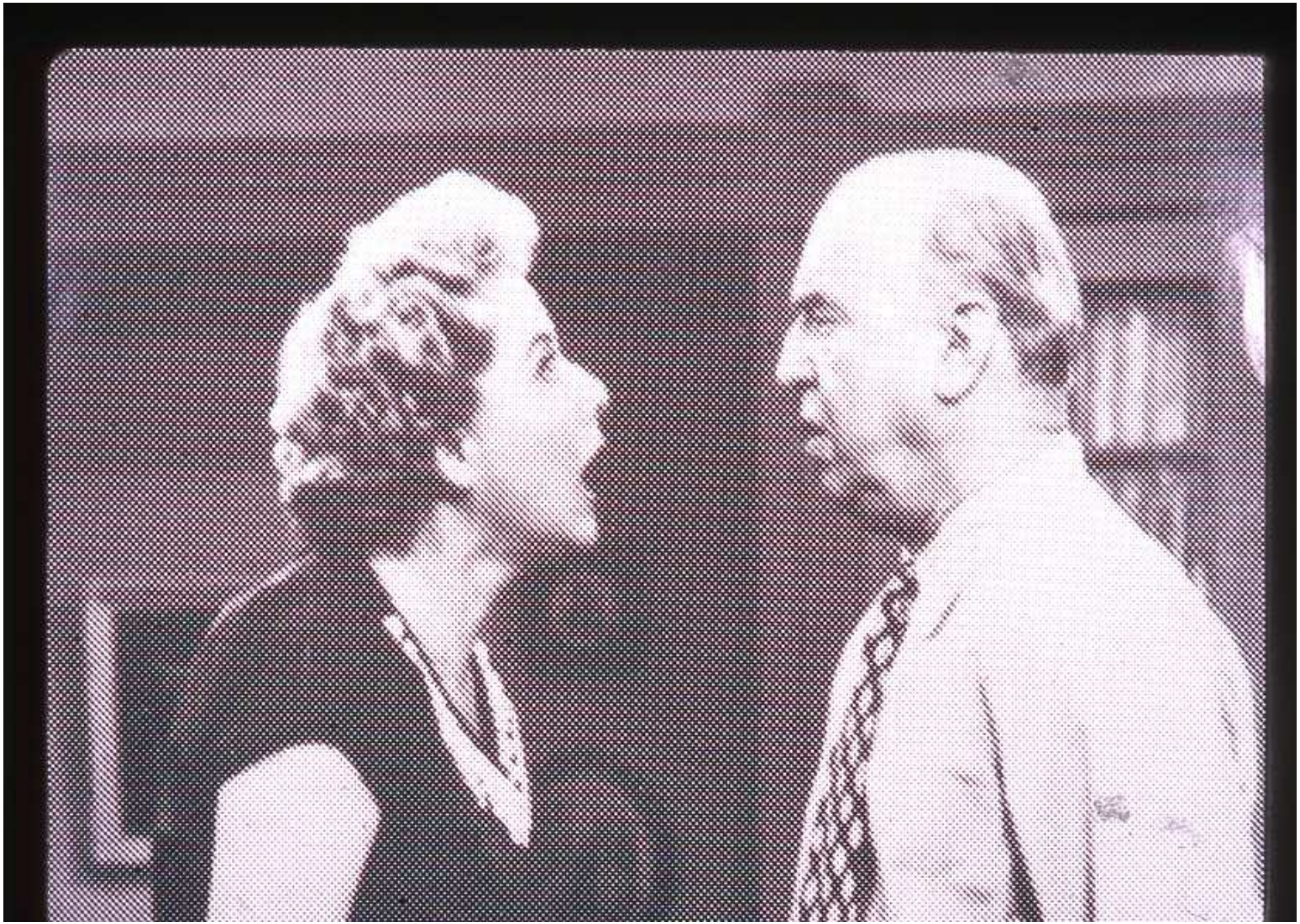
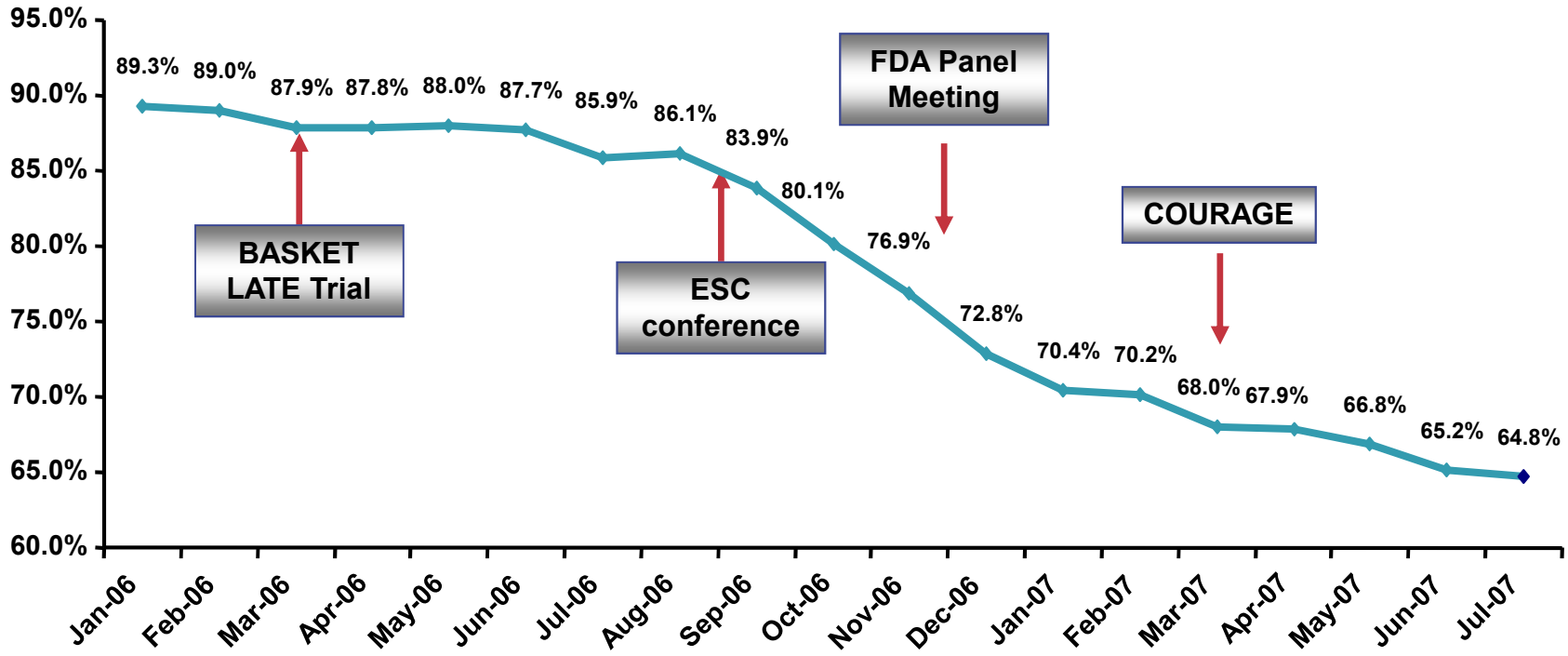


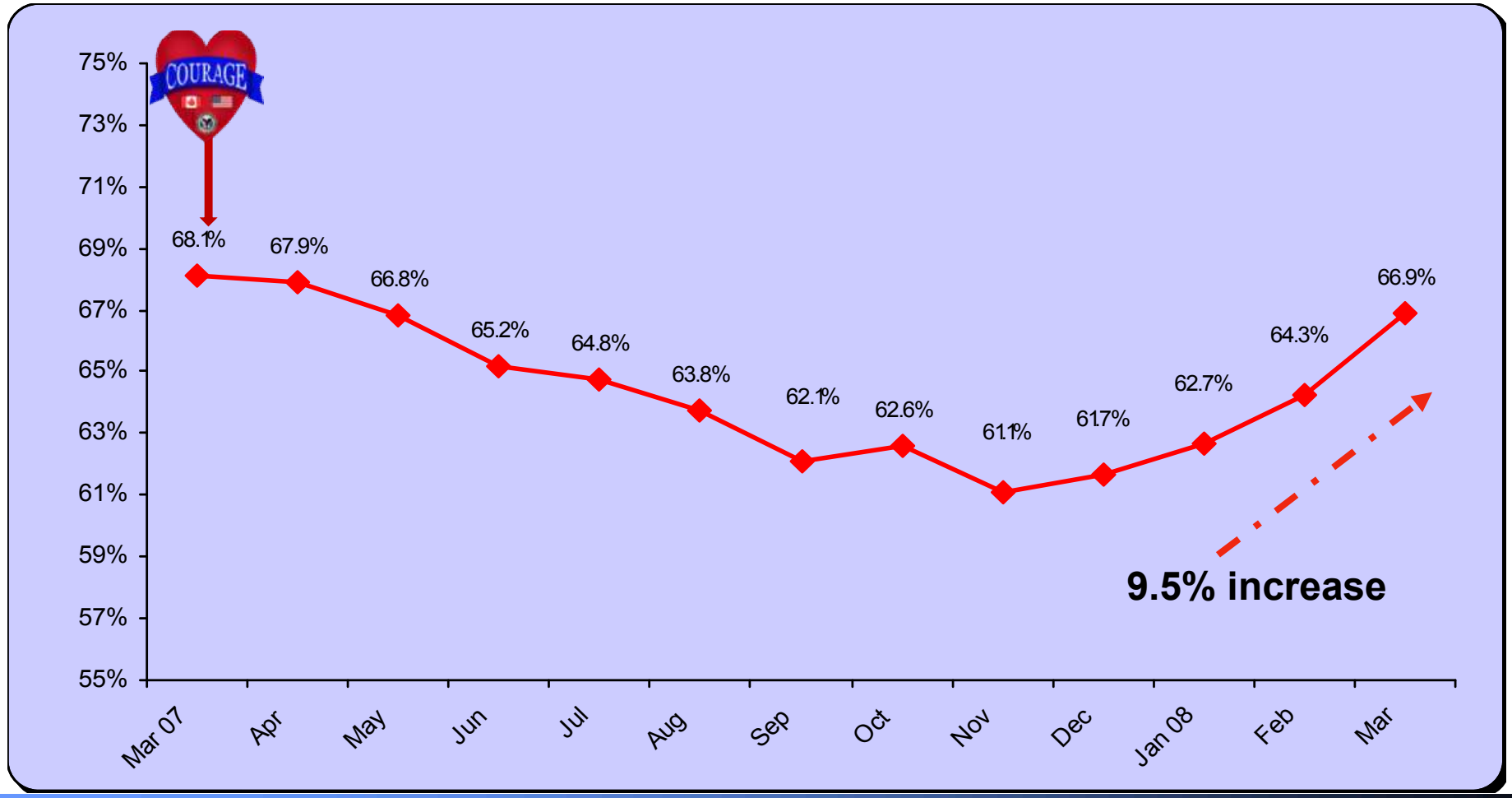
Renu Vermani gives informed consent to a DES patient

Influence of Clinical Trials Results *and* Perception: DES Penetration in the US



Source: Millennium Research Group

DES Penetration in the US



Source: Millennium Research Group

SCAAR-
Swedish Coronary Angiography and Angioplasty Registry

SCAAR UCR SWEDEN 2006

DES pts = 13,738

Bare metal pts = 6,033

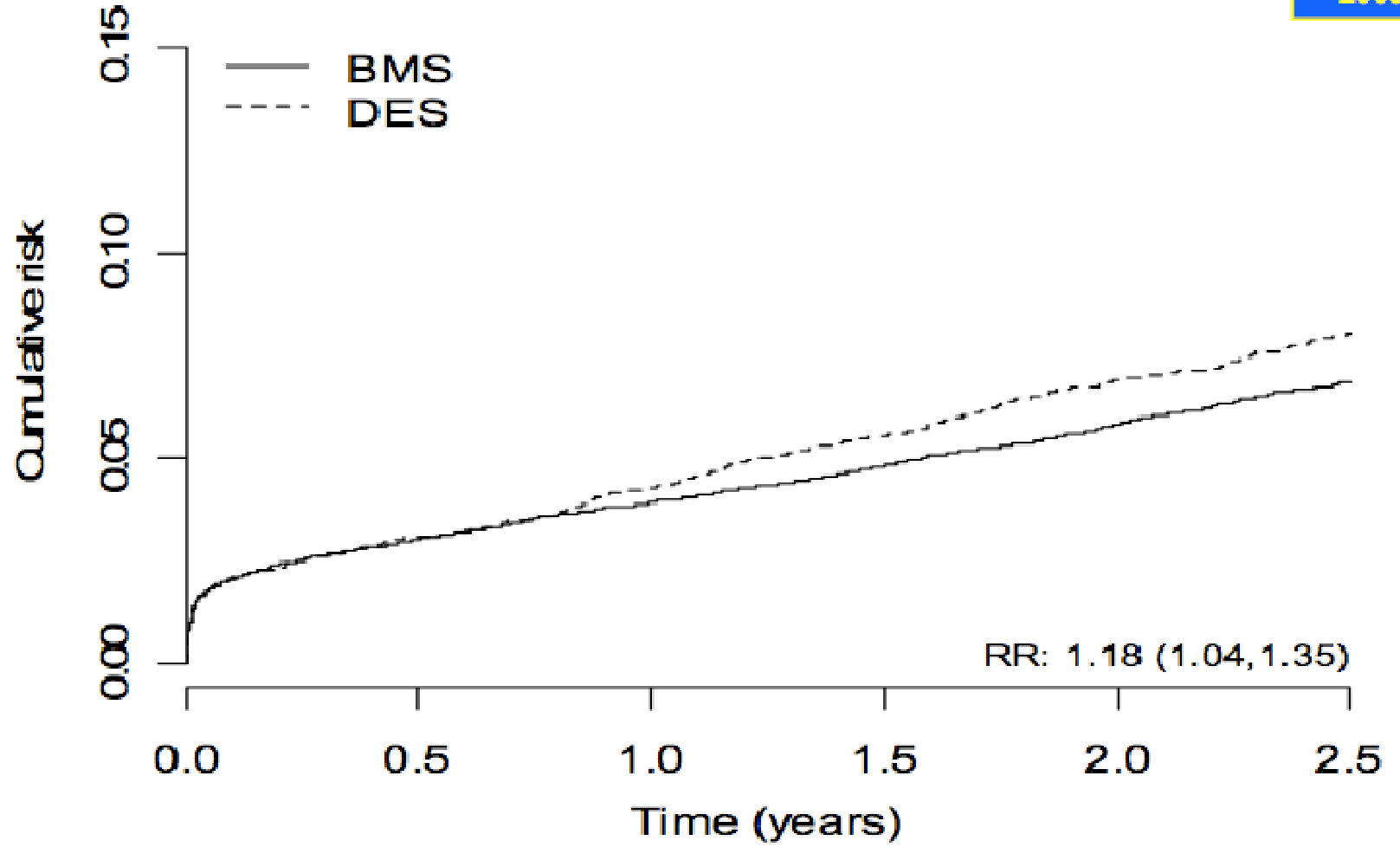
Long-term outcome of DES vs BMS implanted in Sweden 2003 – 2004

RESULTS

Lagerqvist et al, NEJM 2007

Death (Adjusted)

SCAAR
UCR
SWEDEN
2006



BMS	12880	12473	12354	12213	9298	5960
DES	5770	5604	5541	5468	3434	1776

Lagerqvist et al, NEJM 2007

Stent Thrombosis

SCAAR-
Swedish Coronary Angiography and Angioplasty Registry

SCAAR UCR SWEDEN 2006

DES pts = 13,738

What a difference a year makes!

of DES vs BMS

implanted in Sweden

2003 – 2004

RESULTS

Lagerqvist et al, NEJM 2007

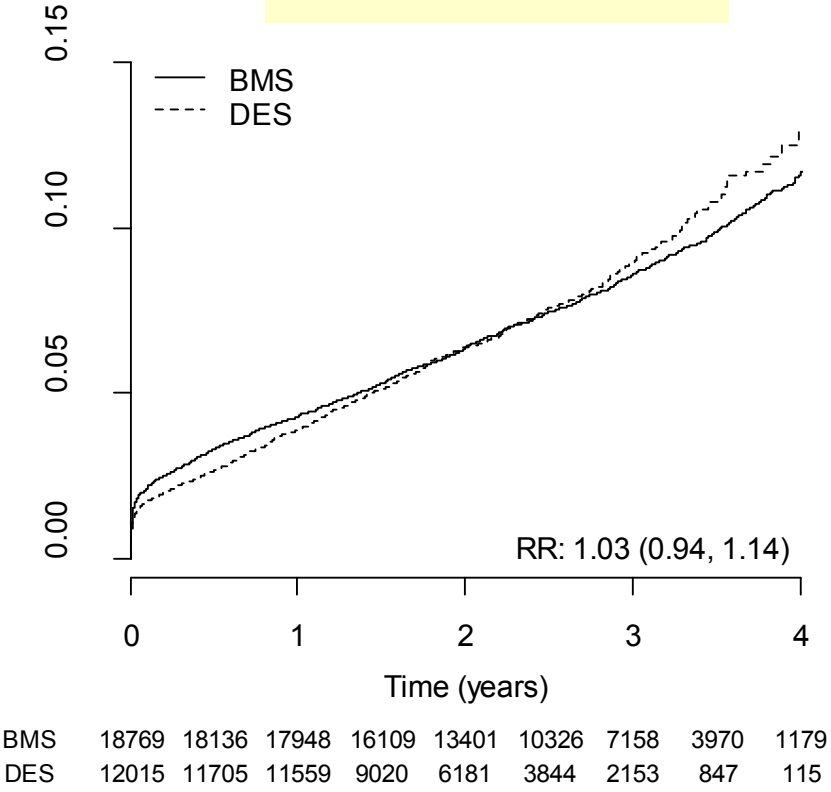
SCAAR
UCR
SWEDEN
2007

2003 – 2005 data: One more year of patients and follow-up. Mortality is no longer higher for DES

Adjusted Death

Total cohort

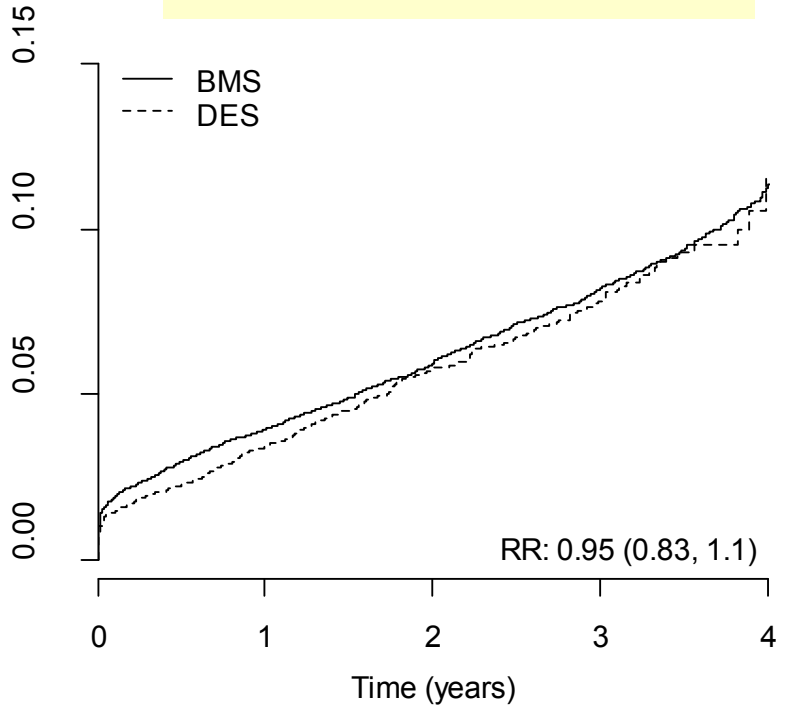
N=35 262



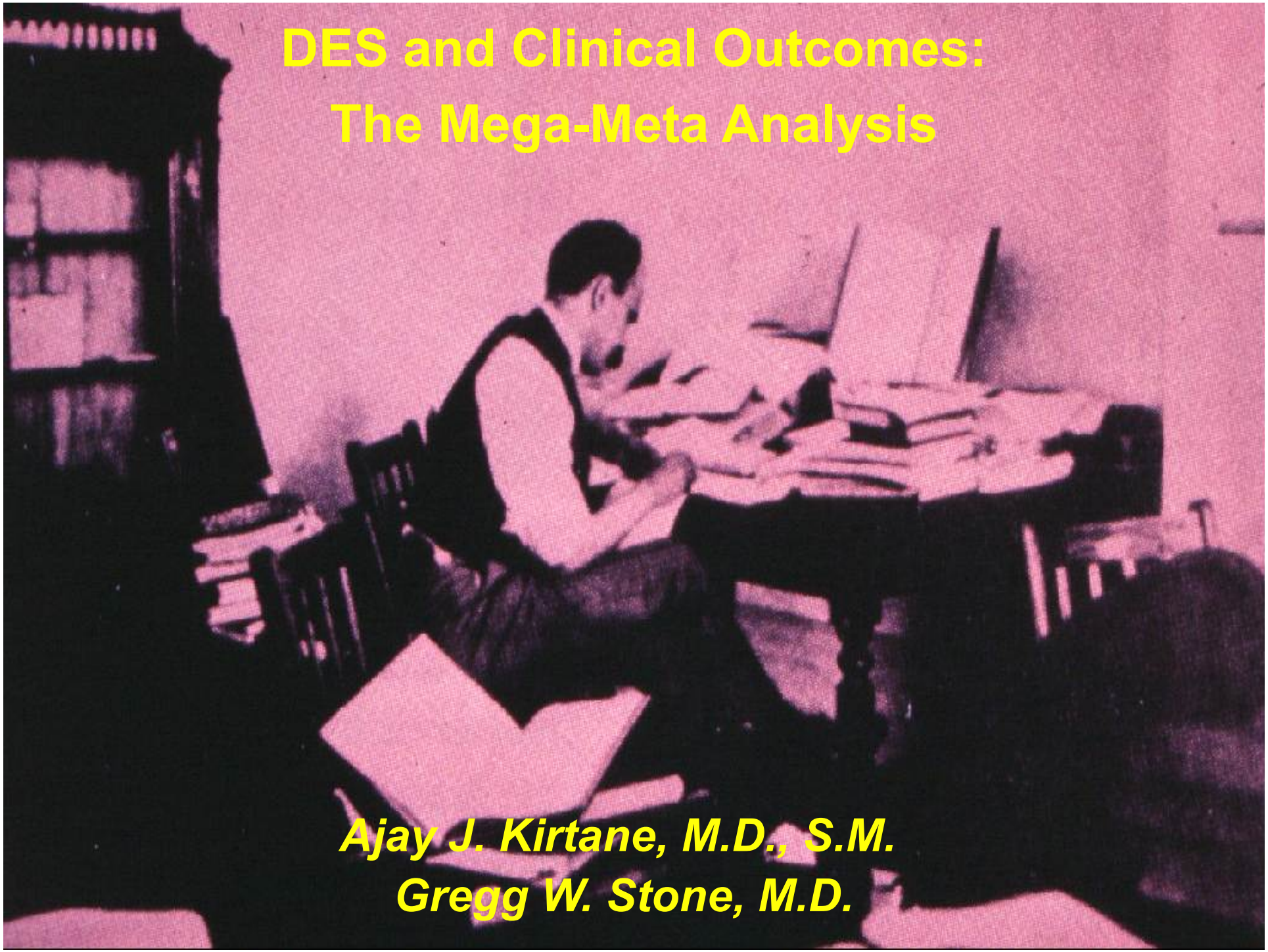
BMS	18769	18136	17948	16109	13401	10326	7158	3970	1179
DES	12015	11705	11559	9020	6181	3844	2153	847	115

One stent cohort

N=18 937

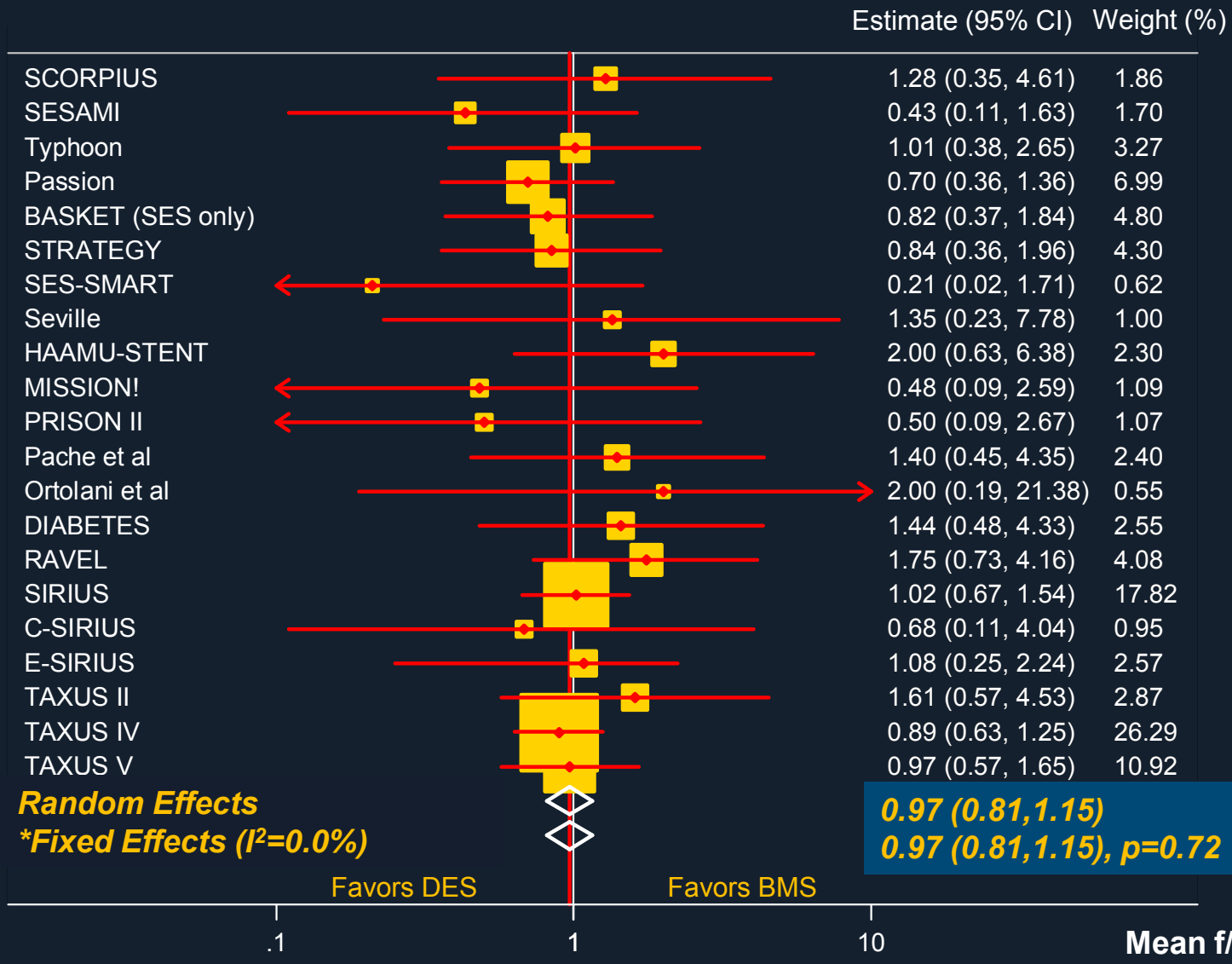


BMS	12556	12185	12061	10837	9001	6920	4824	2697	783
DES	6381	6237	6161	4844	3280	2038	1140	462	58


DES and Clinical Outcomes:
The Mega-Meta Analysis
Ajay J. Kirtane, M.D., S.M.
Gregg W. Stone, M.D.

All-Cause Mortality: All RCTs

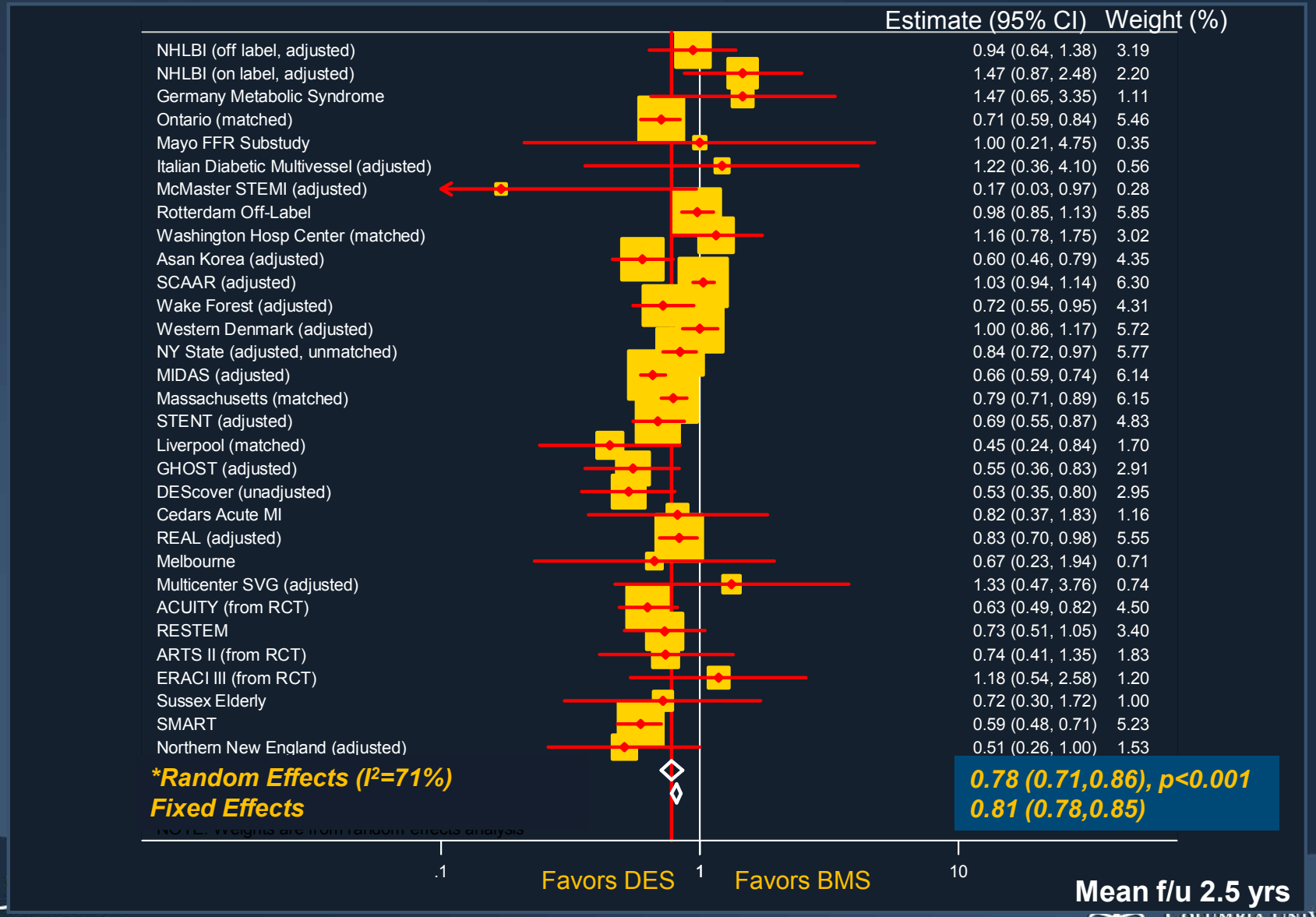
8,867 patients, 21 trials



Mean f/u 2.9 yrs

All-Cause Mortality: All Registries

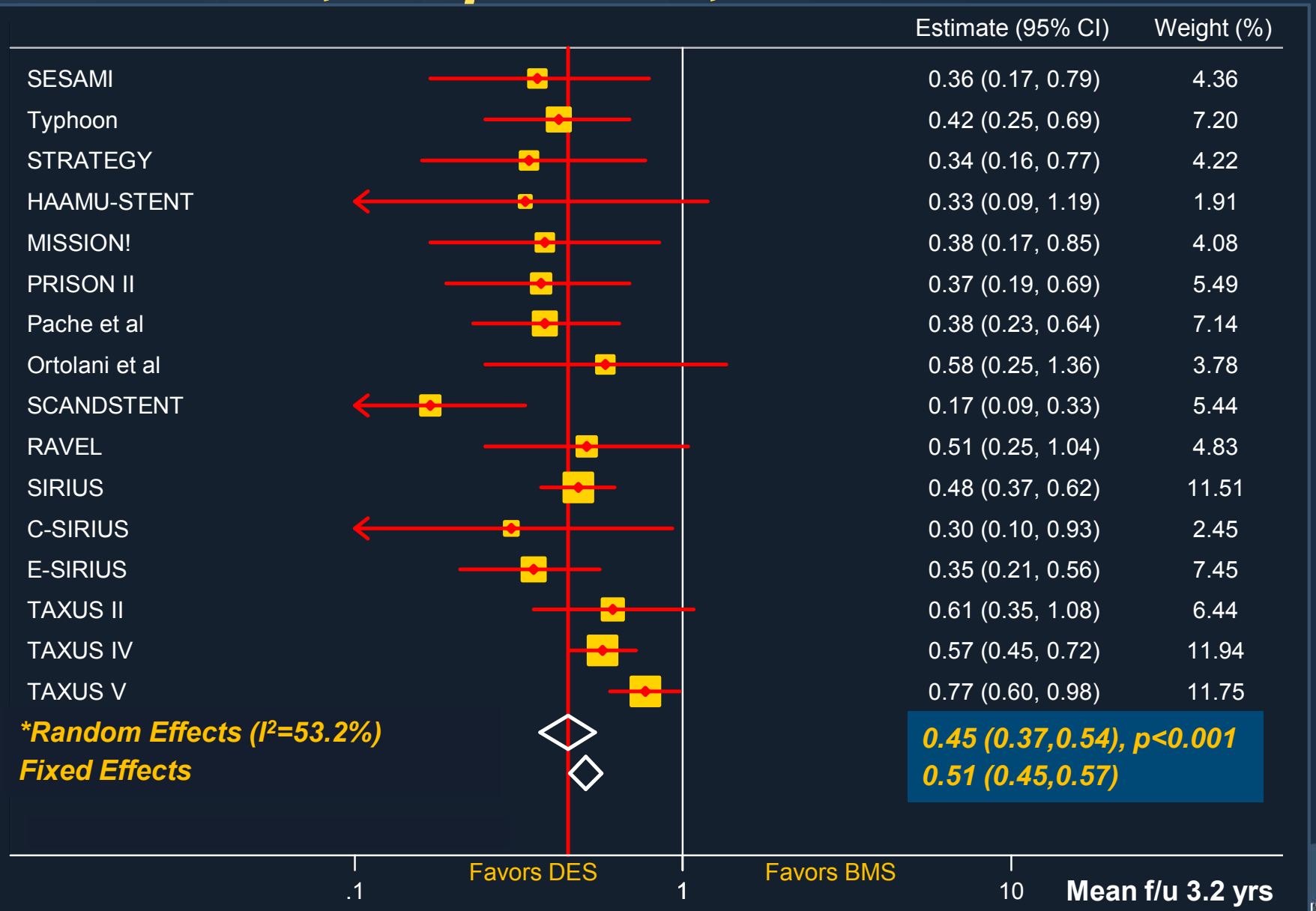
169,595 patients, 31 registries



Mean f/u 2.5 yrs

TVR: All RCTs

7,291 patients, 16 trials



Ajay J. Kirtane and Gregg W. Stone, 2008

Is there a DES safety problem?

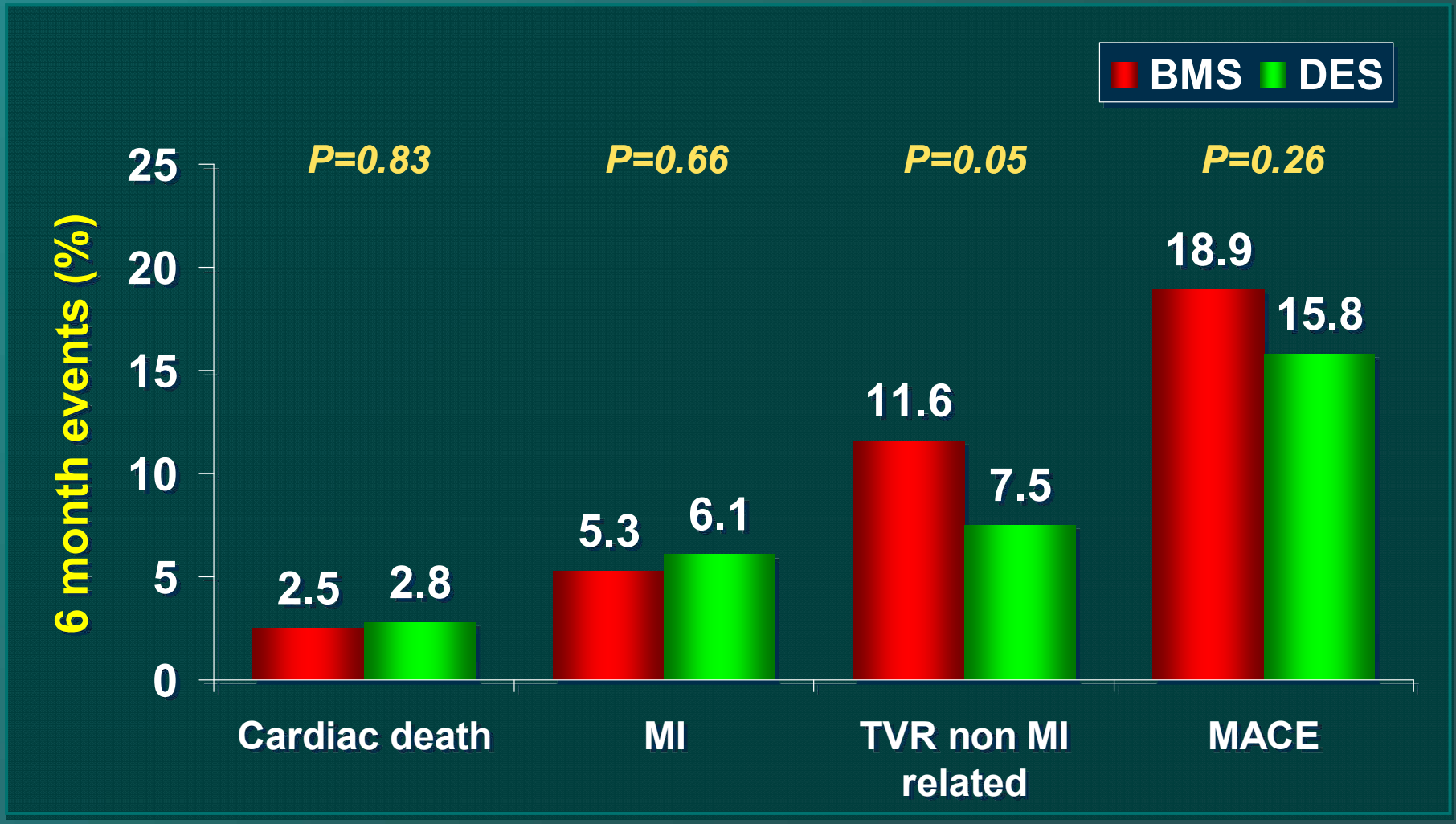
- **Probabably *NOT!***
- ***There may even be a safety advantage for some DES patient subgroups***
- **TVR benefit makes DES the right choice for most patients**

Do DES patients need prolonged dual antiplatelet therapy?

- Evils of dual antiplatelet therapy
  - Bleeding
  - Bruising
  - Cost
  - Need for unplanned surgery
  - Endless, daily, phone calls and questions from physicians and patients

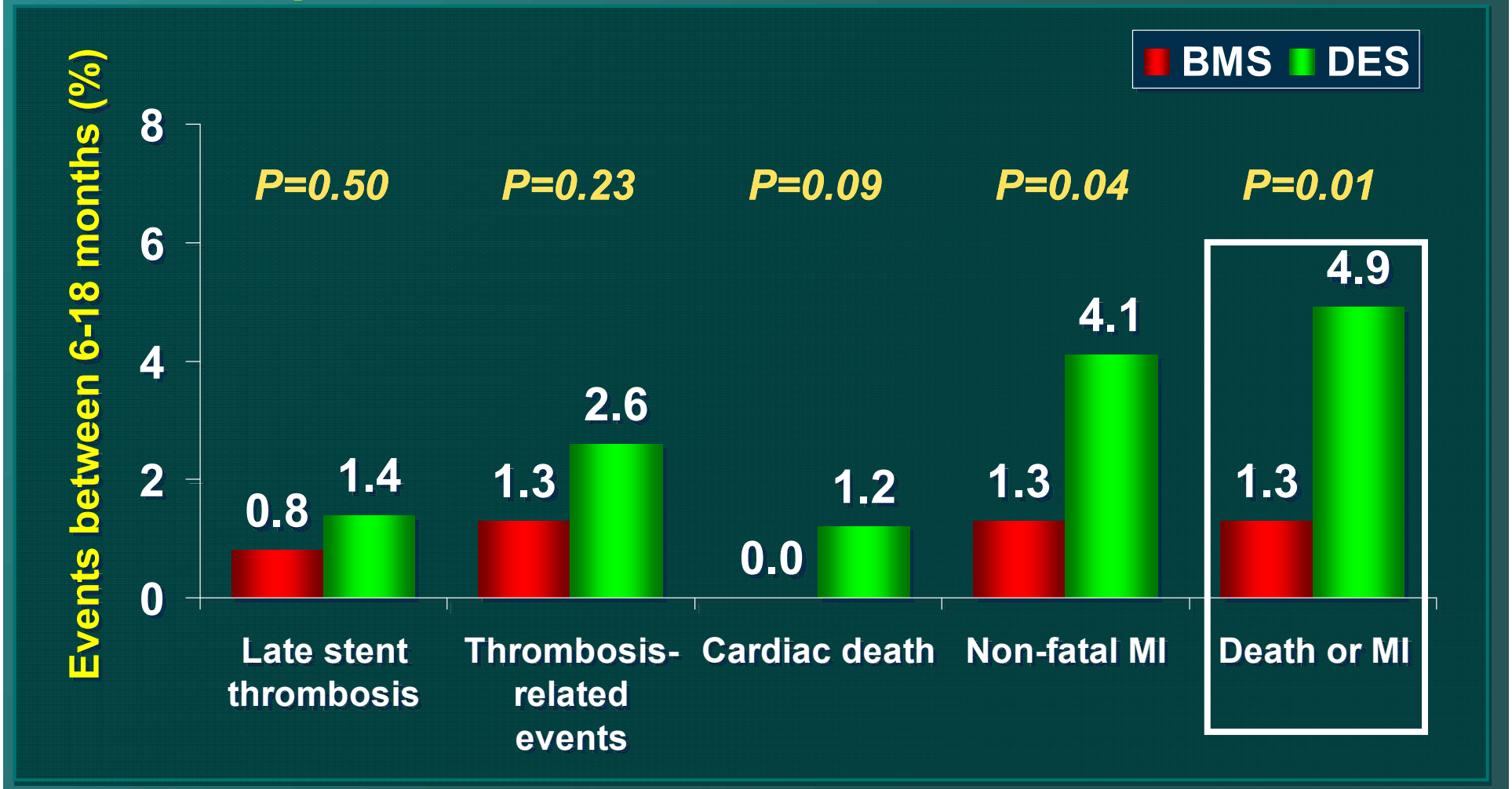
BASKET Trial: 18 Month MACE

N=836 (All pts with 18 month FU)

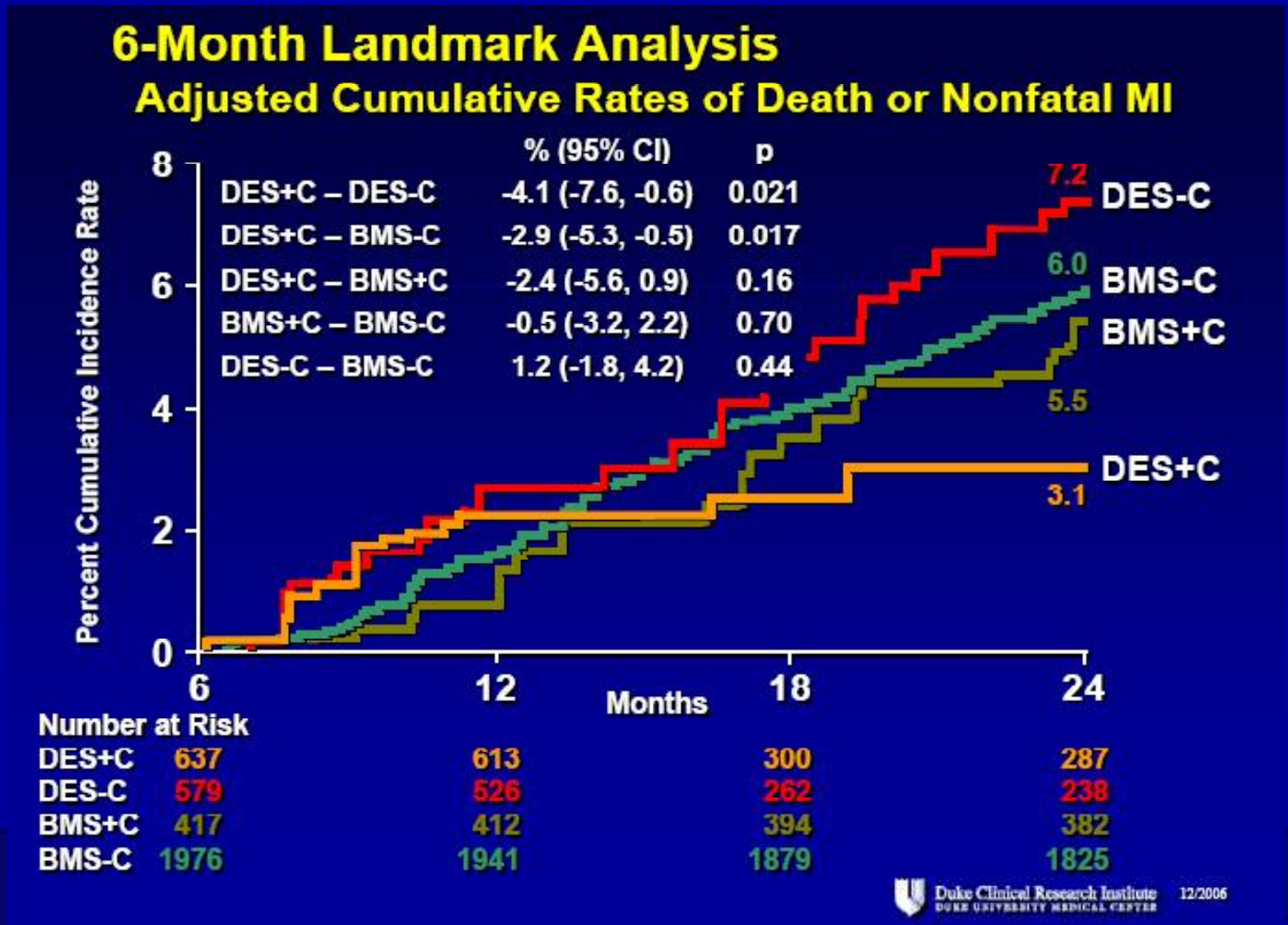


BASKET LATE Trial: 6-18 Mo MACE

N=743 (pts with early events excluded)



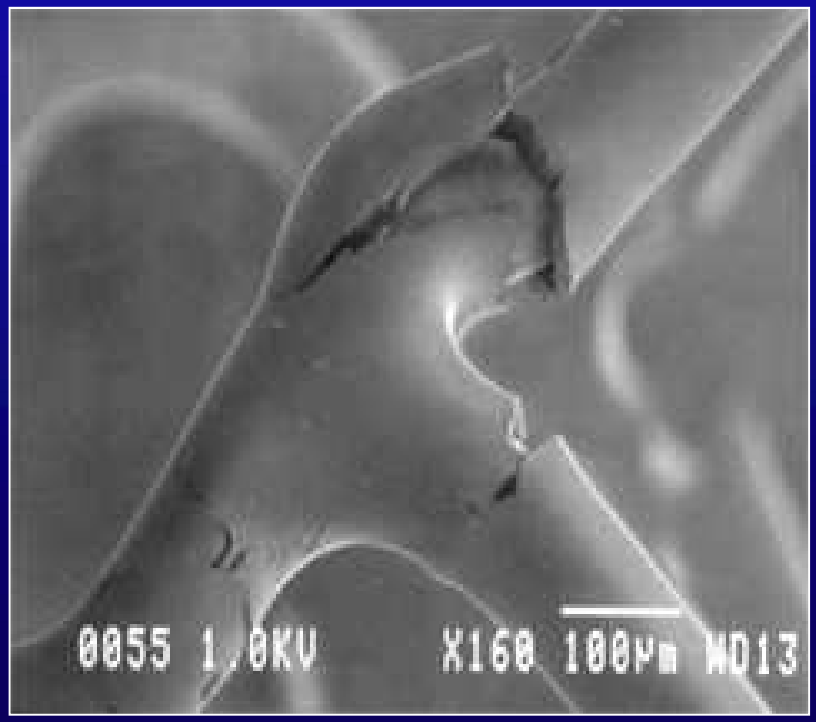
Antiplatelet Therapy and DES

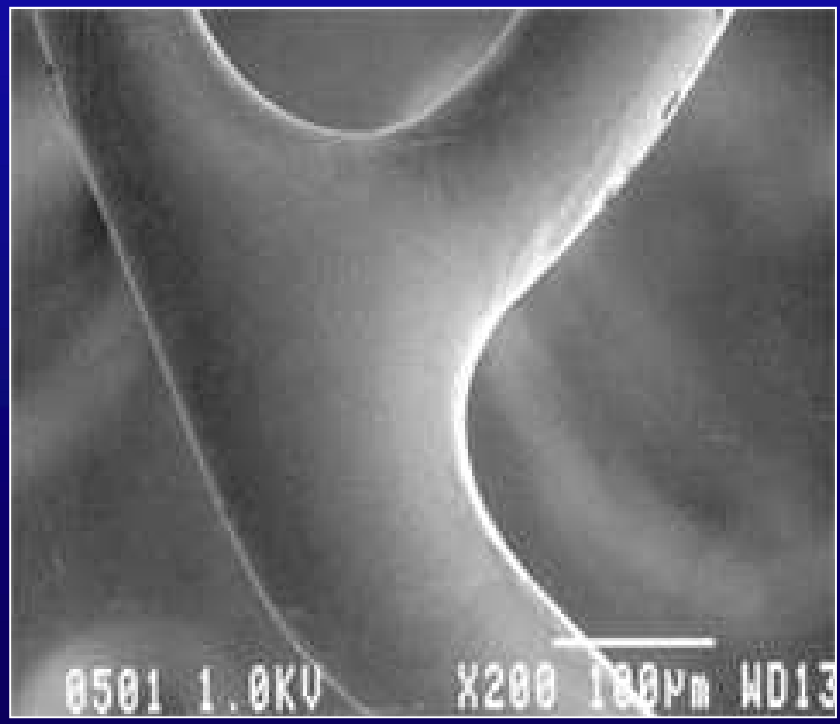


Kandzari.GreatWall_2007

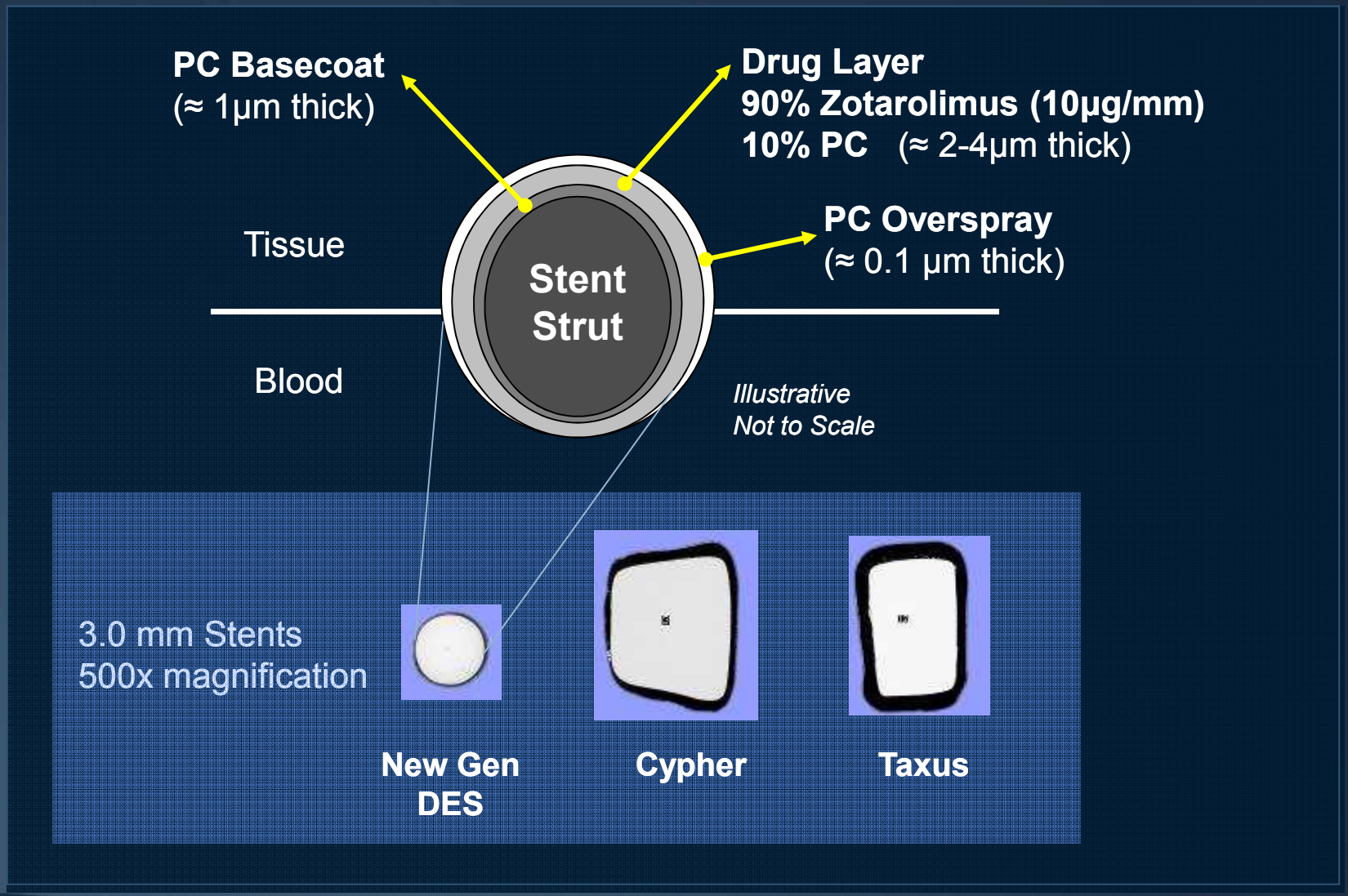
Eisenstein et al. JAMA 2007

Will new stent technology improve stent safety and reduce the need for long term antiplatelet therapy?

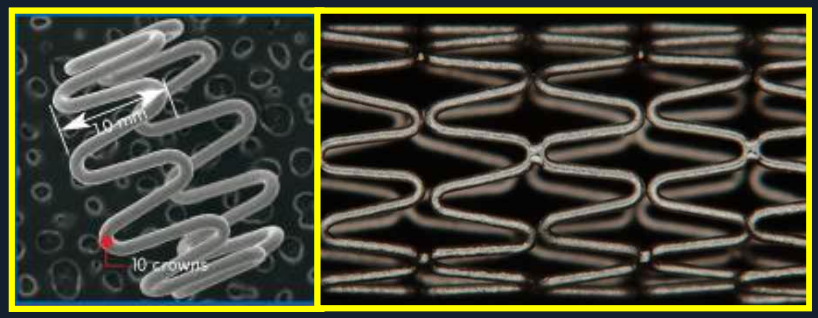




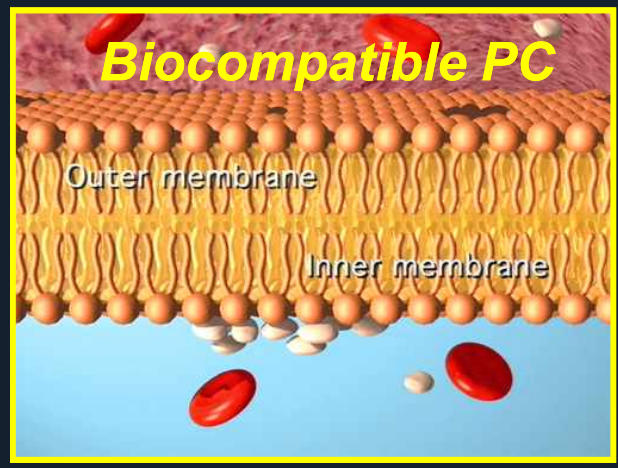
Polymer and Drug Matrix

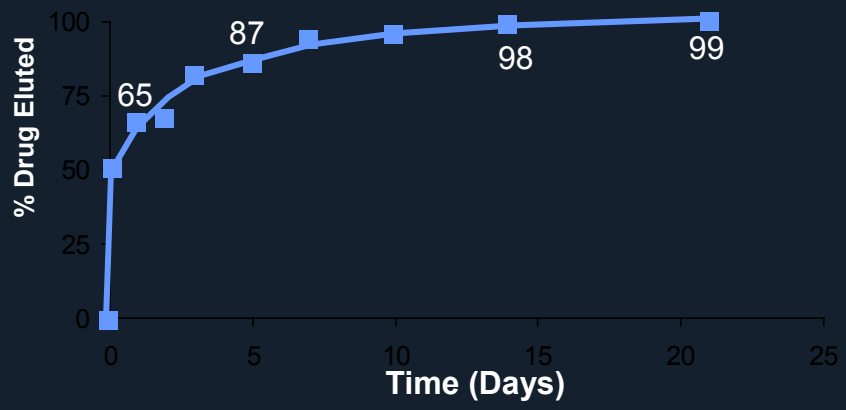


ENDEAVOR Safety Considerations
Design Features

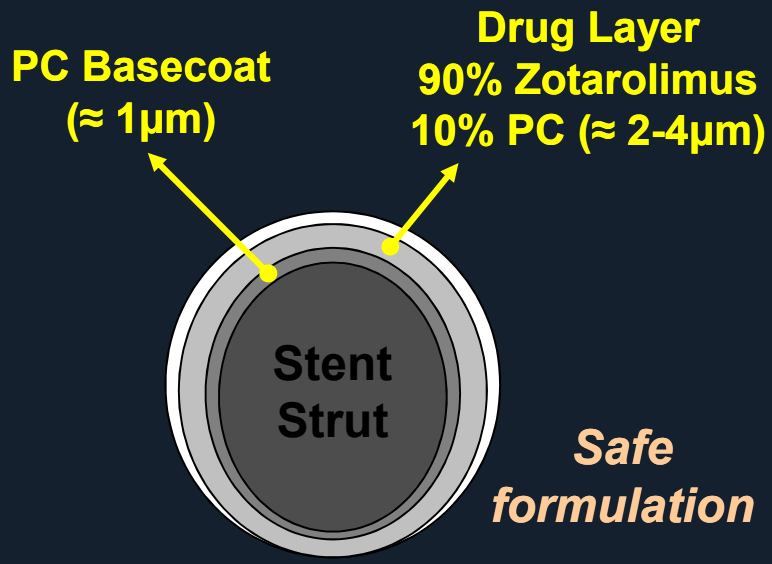


Stent design = reduced injury (rounded thin struts)



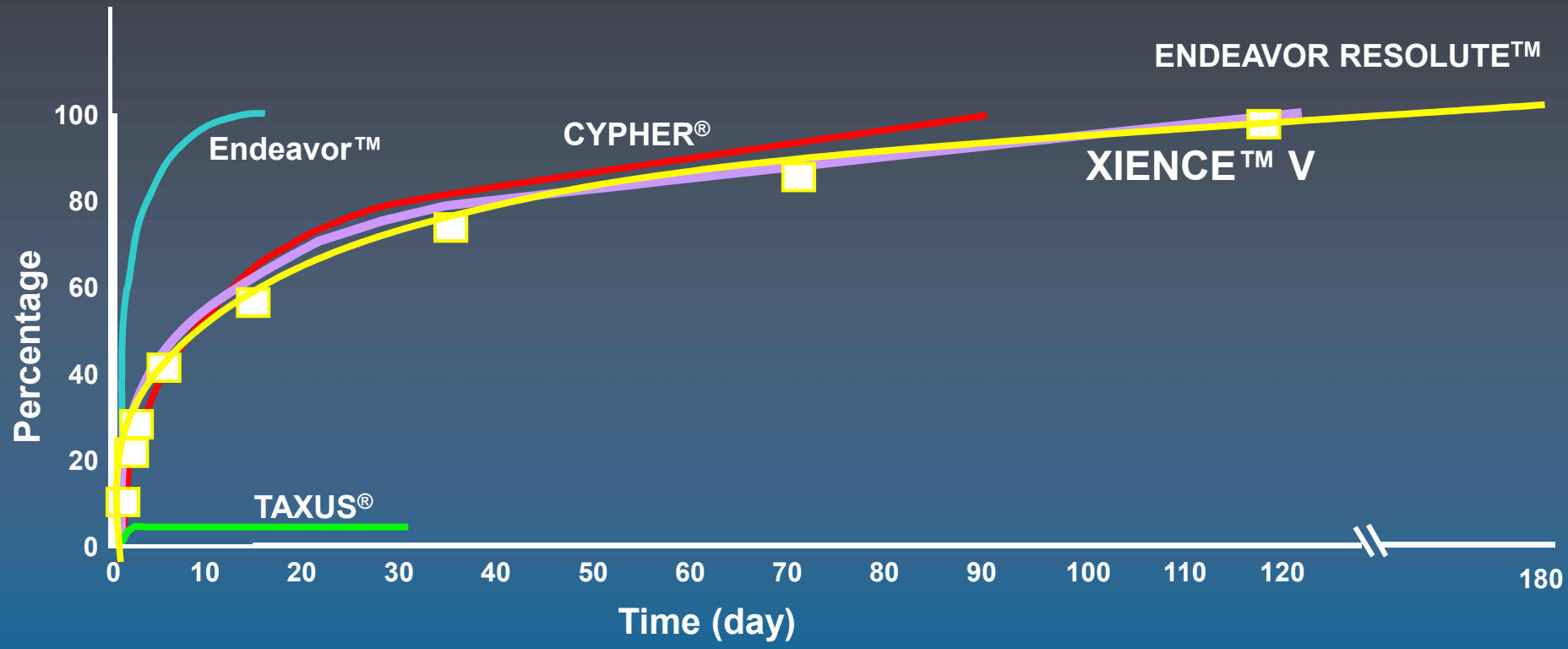


Rapid drug elution



Safe formulation

DES Release Profiles (in vivo)

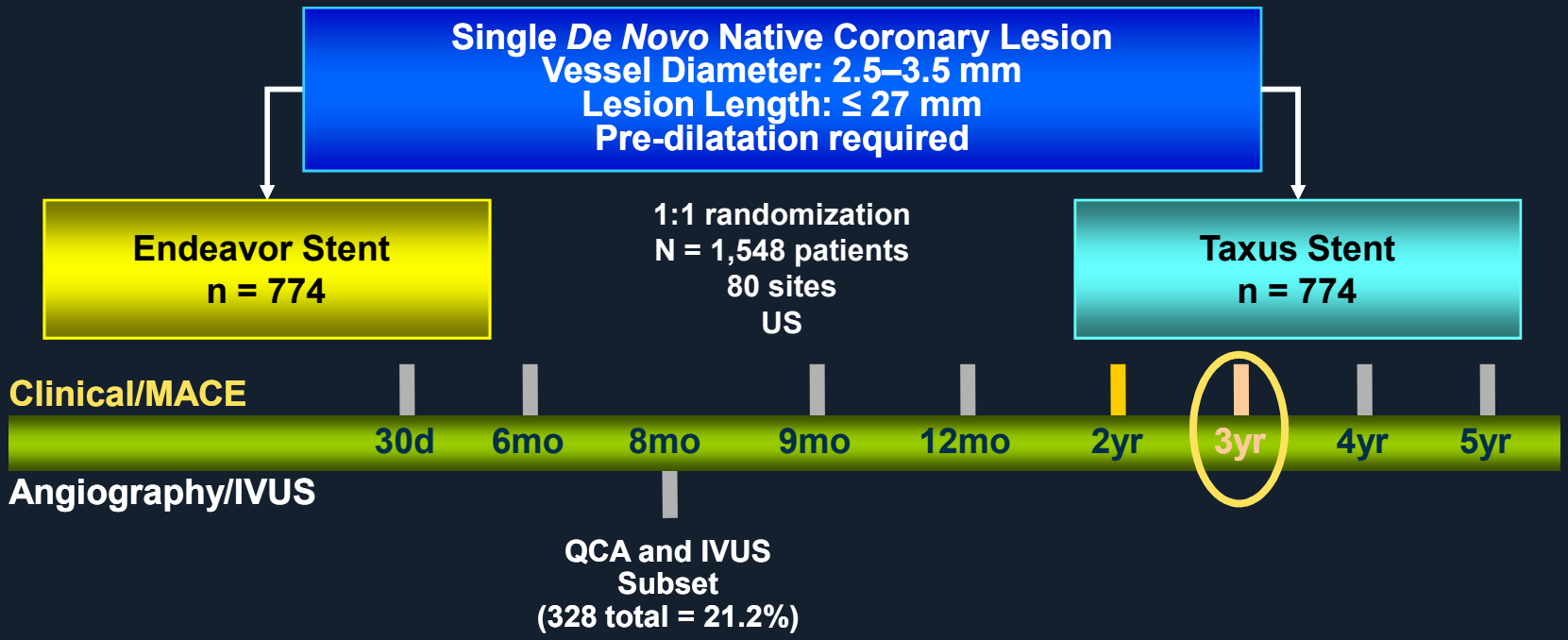


Source: Medtronic Vascular Data Presentation, TCTMD; TAXUS IV SR Presentation, TCTMD; Cypher Presentation, TCTMD; Data on file at Abbott Vascular.

ENDEAVOR IV – 3yr FU

Clinical Trial Design

PIs: Martin B. Leon and David E. Kandzari



Primary Endpoint: TVF at 9 months

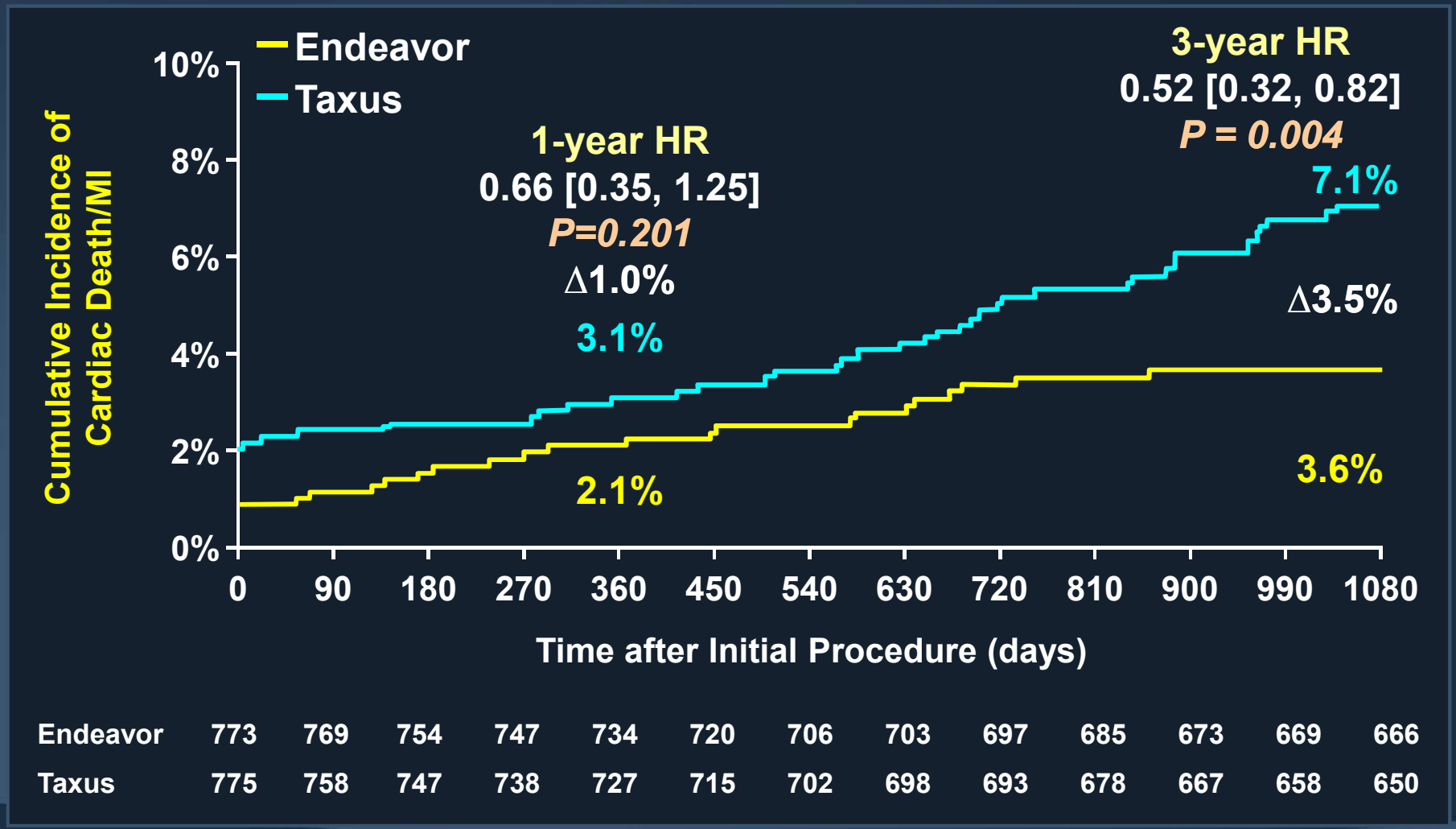
Secondary Endpoints: In-segment % DS at 8 months; TLR and TVR at 9 months

Drug Therapy: ASA and Clopidogrel/Ticlid ≥6 months

Zotarolimus Dose: 10 μg per mm stent length

ENDEAVOR IV – 3yr FU

CD/MI to 36 months



Endeavor	773	769	754	747	734	720	706	703	697	685	673	669	666
Taxus	775	758	747	738	727	715	702	698	693	678	667	658	650

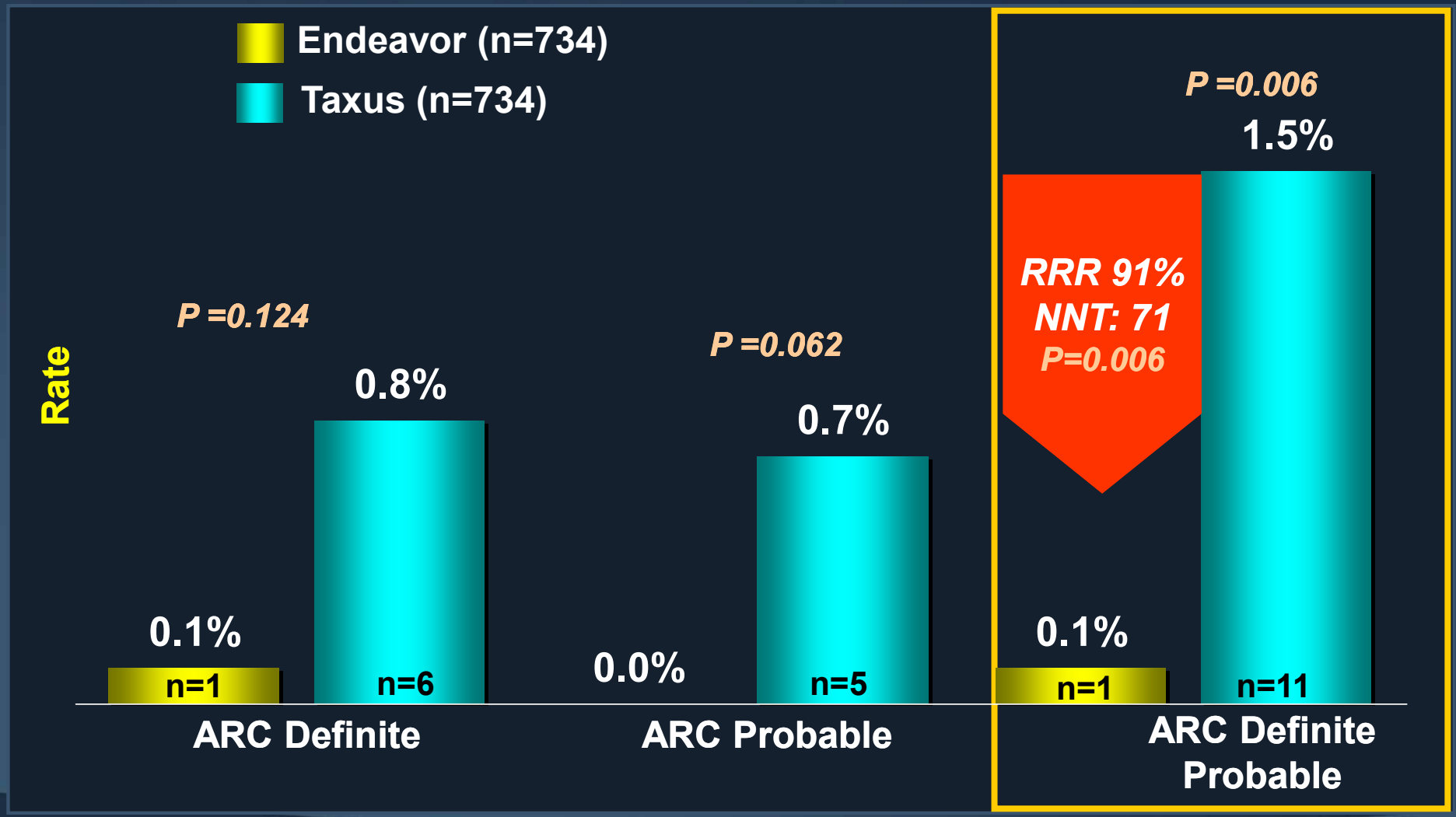
CARDIOVASCULAR RESEARCH FOUNDATION

Values are the KM estimates
P values were calculated by Log Rank Test

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian
The University Hospital of Columbia and Cornell

ENDEAVOR IV – 3yr FU

ARC VLAST 12-36 mos



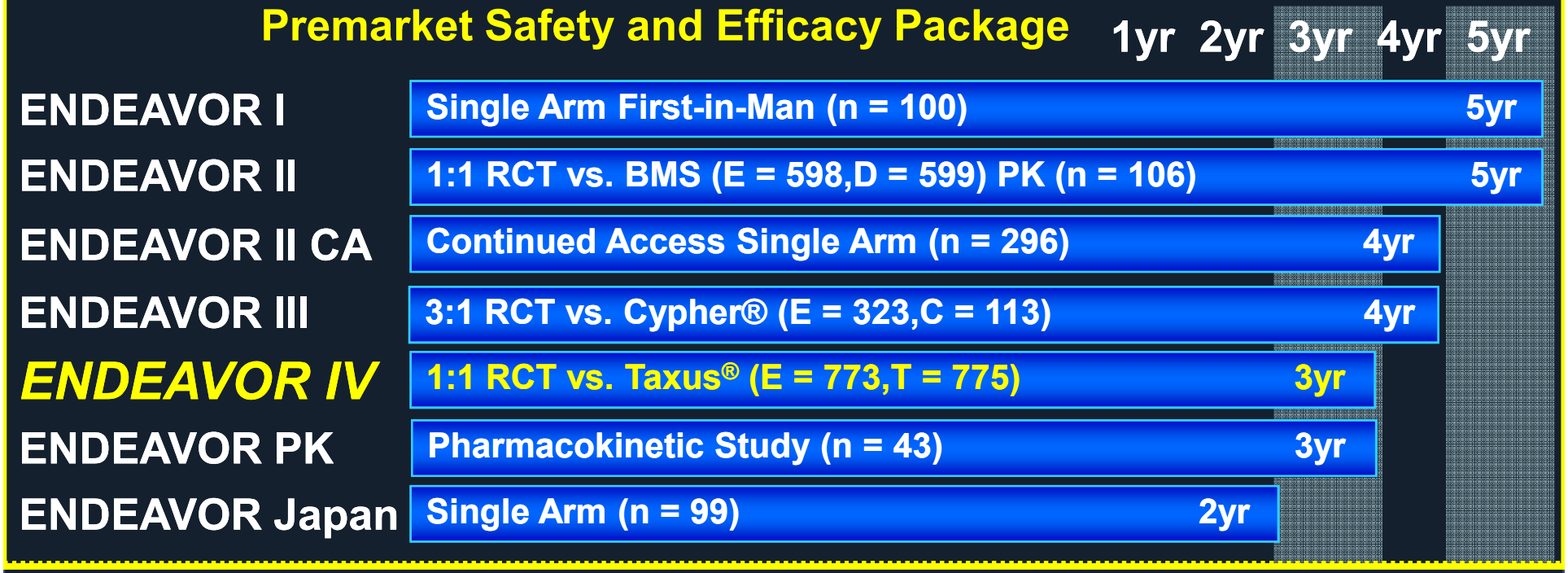
Values are the event rates
P values were calculated by Fisher Exact Test

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Endeavor Clinical Program
Pooled Safety and Efficacy Analyses

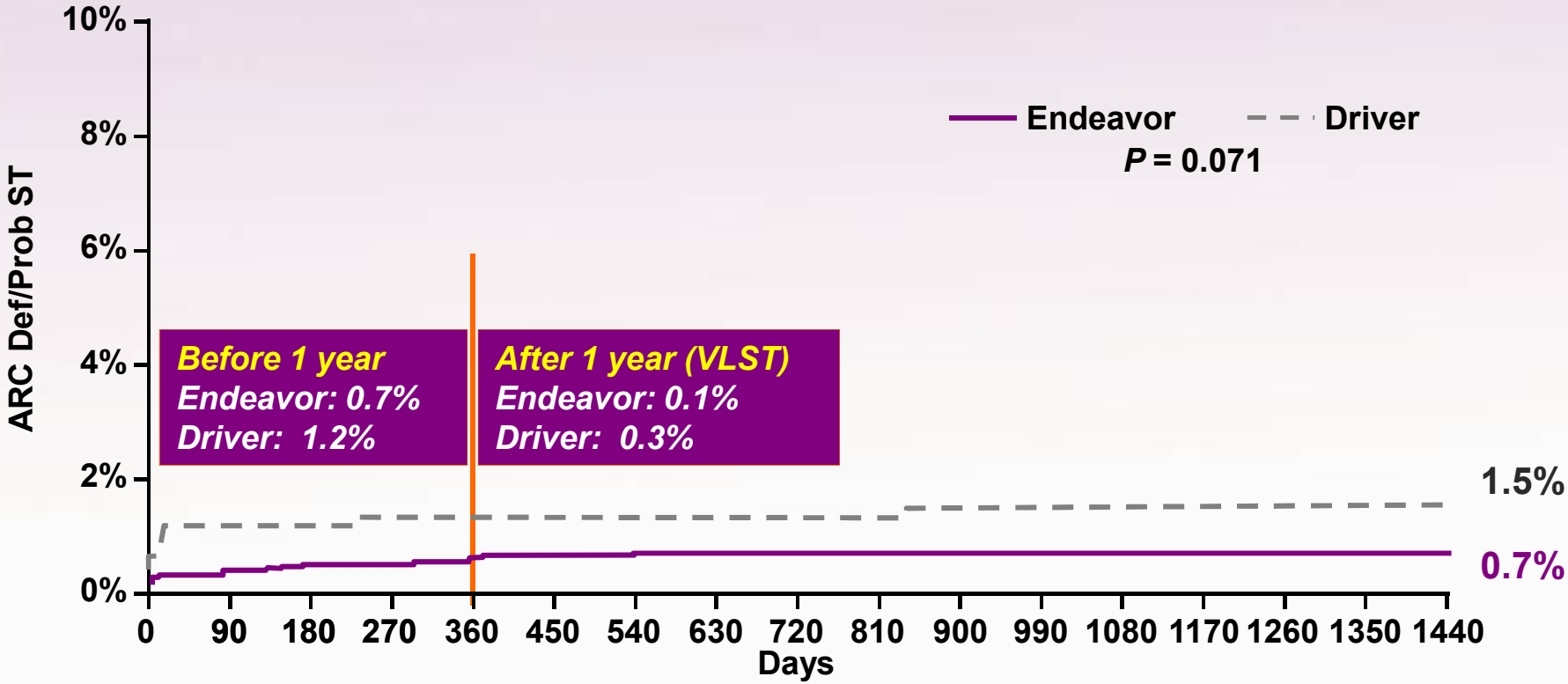
Premarket Safety and Efficacy Package



Included in Pooled Safety and Efficacy Analyses (N=2132)

Pooled Endeavor: Long-term safety

ARC Definite/Probable ST to 4 years



Days	0	30	270	360	720	1080	1440
Endeavor	*2132*	*2131*	*2114*	*2068*	*2036*	*1650*	*1087*
% CI	0.0%	0.3%	0.5%	0.6%	0.7%	0.7%	0.7%
Driver	*596*	*595*	*587*	*576*	*570*	*559*	*543*
% CI	0.2%	1.2%	1.3 %	1.3%	1.3%	1.5%	1.5%

ENDEAVOR Pooled Safety: Mauri, TCT 2008.
E I (5 yr), E II (4 yr), E IICA (4 yr), E III (3 yr), E IV (2 yr) & E PK (1 yr).
p-values are unadjusted for multiple comparisons. Pooled Kaplan-Meier analysis.

SPIRIT IV Study Algorithm

3690 pts enrolled at 66 U.S. sites

RVD ≥2.5 mm - ≤3.75 mm; Lesion length ≤28 mm

Max. 3 lesions with a maximum of 2 per epicardial vessel

Pre-rand: ASA ≥300 mg, clopidogrel ≥300 mg load unless on chronic Rx

Randomized 2:1 XIENCE V®:TAXUS® Express²

Stratified by diabetes and presence of complex lesions

Pre-dilatation mandatory

Everolimus-eluting

XIENCE V

Paclitaxel-eluting

TAXUS

Aspirin ≥80 mg QD for 5 years; clopidogrel 75mg QD for at least 12 mos (if not at high risk for bleeding)

Clinical f/u only: 1, 6, 9 months and yearly for 1-5 years

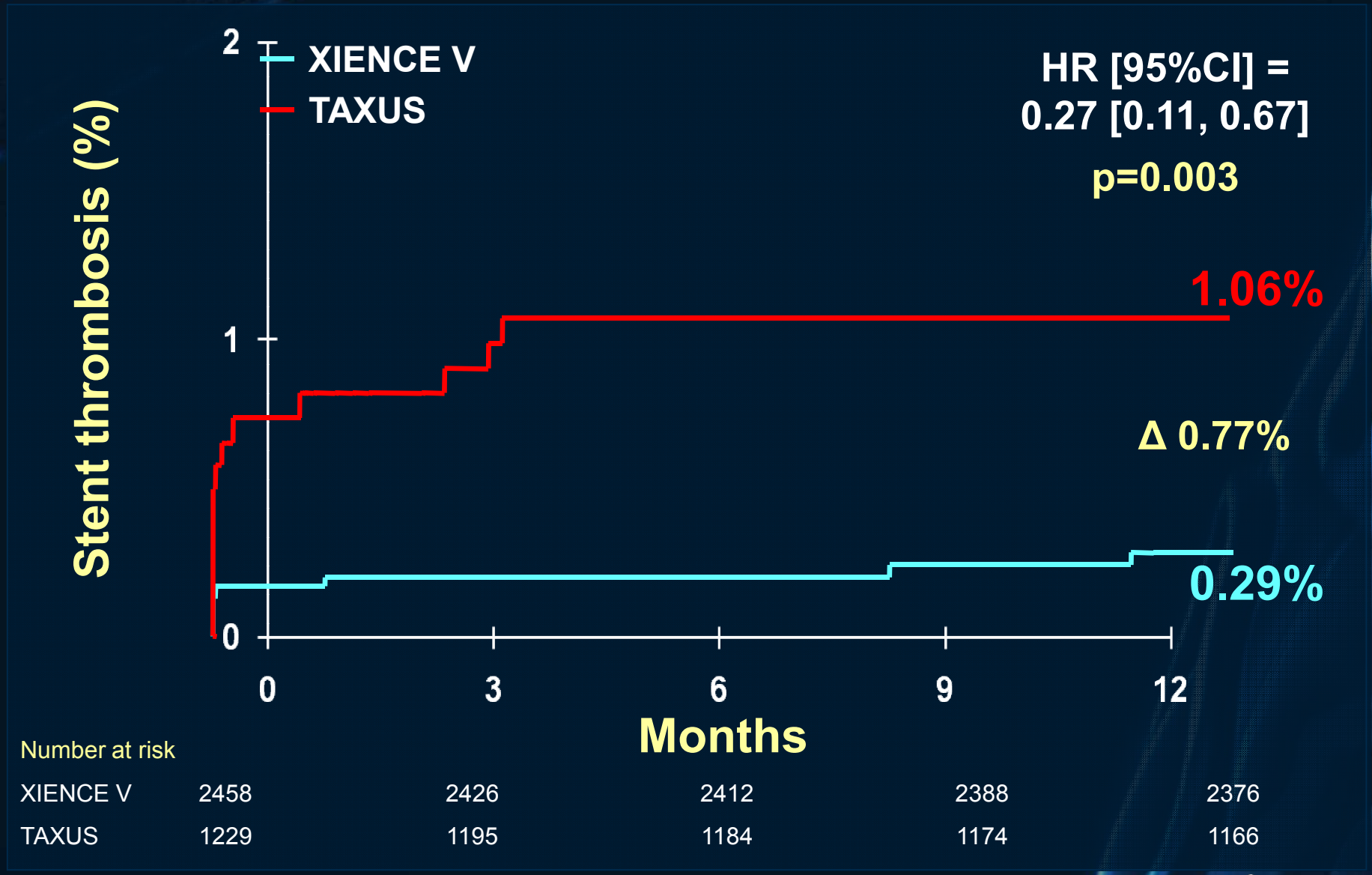
Death and MI at 1 Year

Spirit IV

	XIENCE V 2458 pts	TAXUS 1195 pts	P value
Death, all	1.0%	1.3%	0.61
- Cardiac	0.4%	0.4%	1.00
- Non cardiac	0.6%	0.8%	0.52
MI, all	1.9%	3.1%	0.02
- Q-wave	0.1%	0.4%	0.13
- Non Q-wave	1.7%	2.8%	0.05
All death or MI	2.8%	4.1%	0.05
Cardiac death or MI	2.2%	3.3%	0.07

MI = Target Vessel MI + Non-Target Vessel MI
Categorical data, 365 ± 28 days

Stent Thrombosis (ARC Def or Prob)

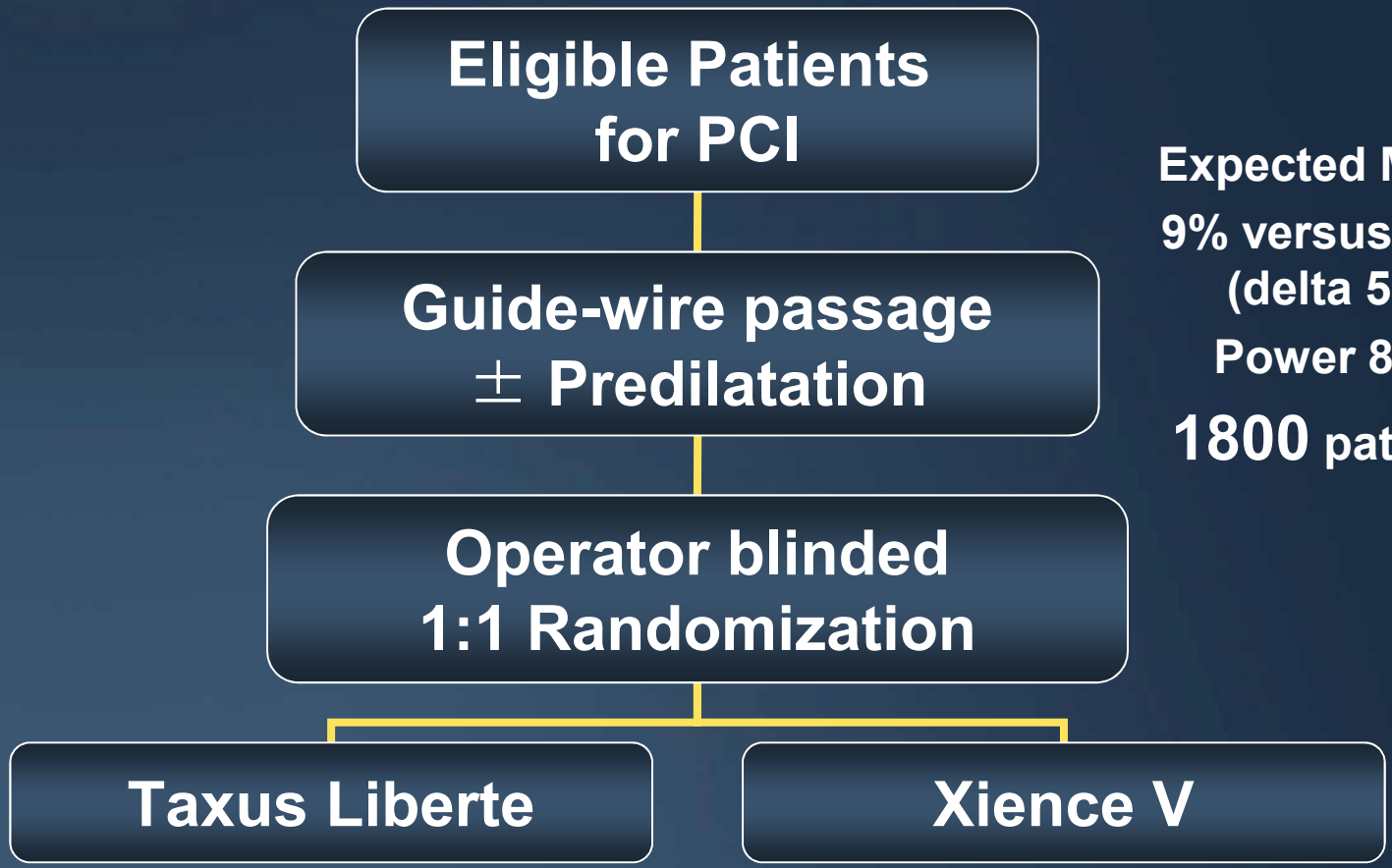


Number at risk

XIENCE V	2458	2426	2412	2388	2376
TAXUS	1229	1195	1184	1174	1166

Spirit IV

COMPARE - Study Outline



Expected MACE

9% versus 14 % (delta 5%)

Power 85%

1800 patients

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

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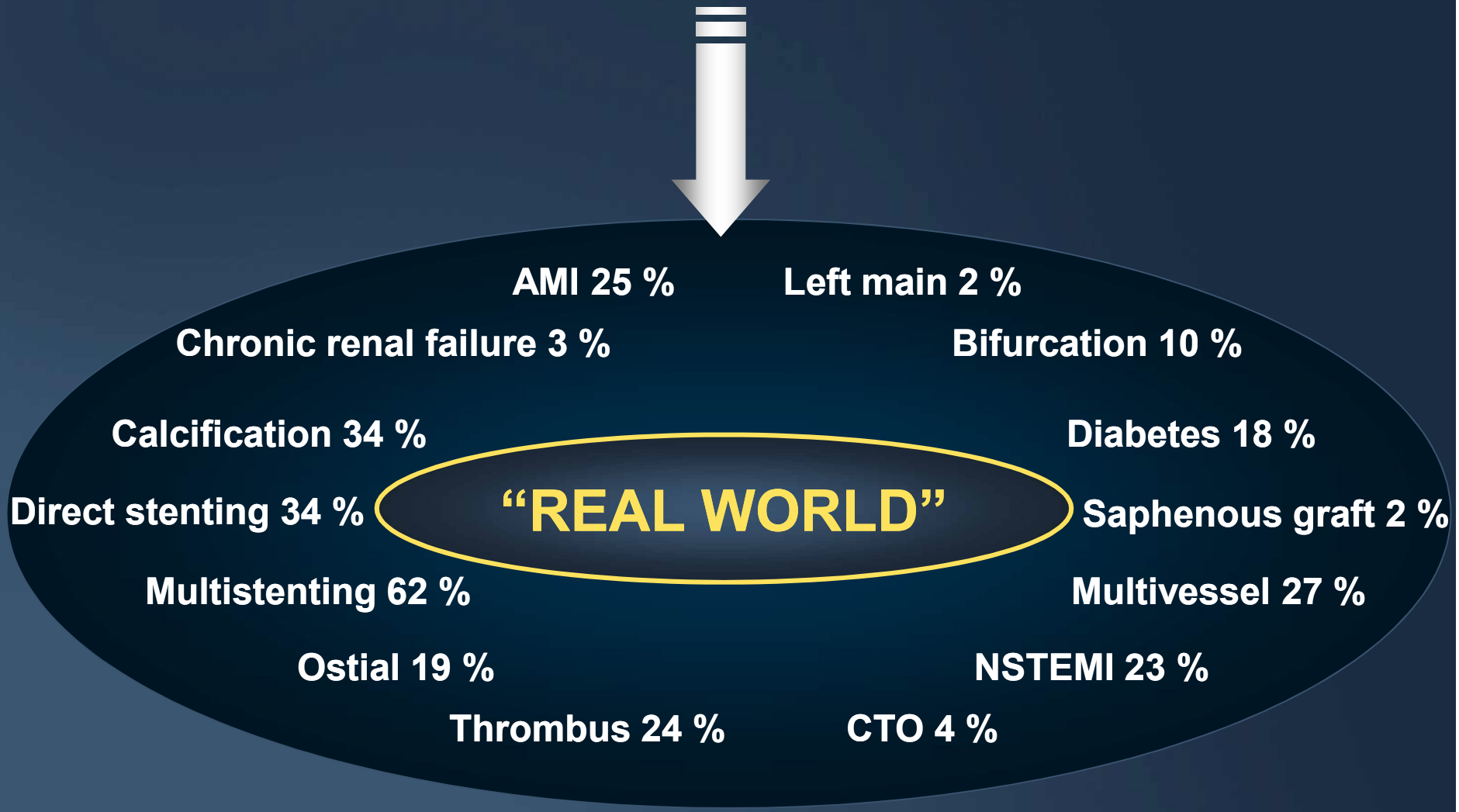
NewYork-Presbyterian
The University Hospital of Columbia and Cornell

COMPARE Trial



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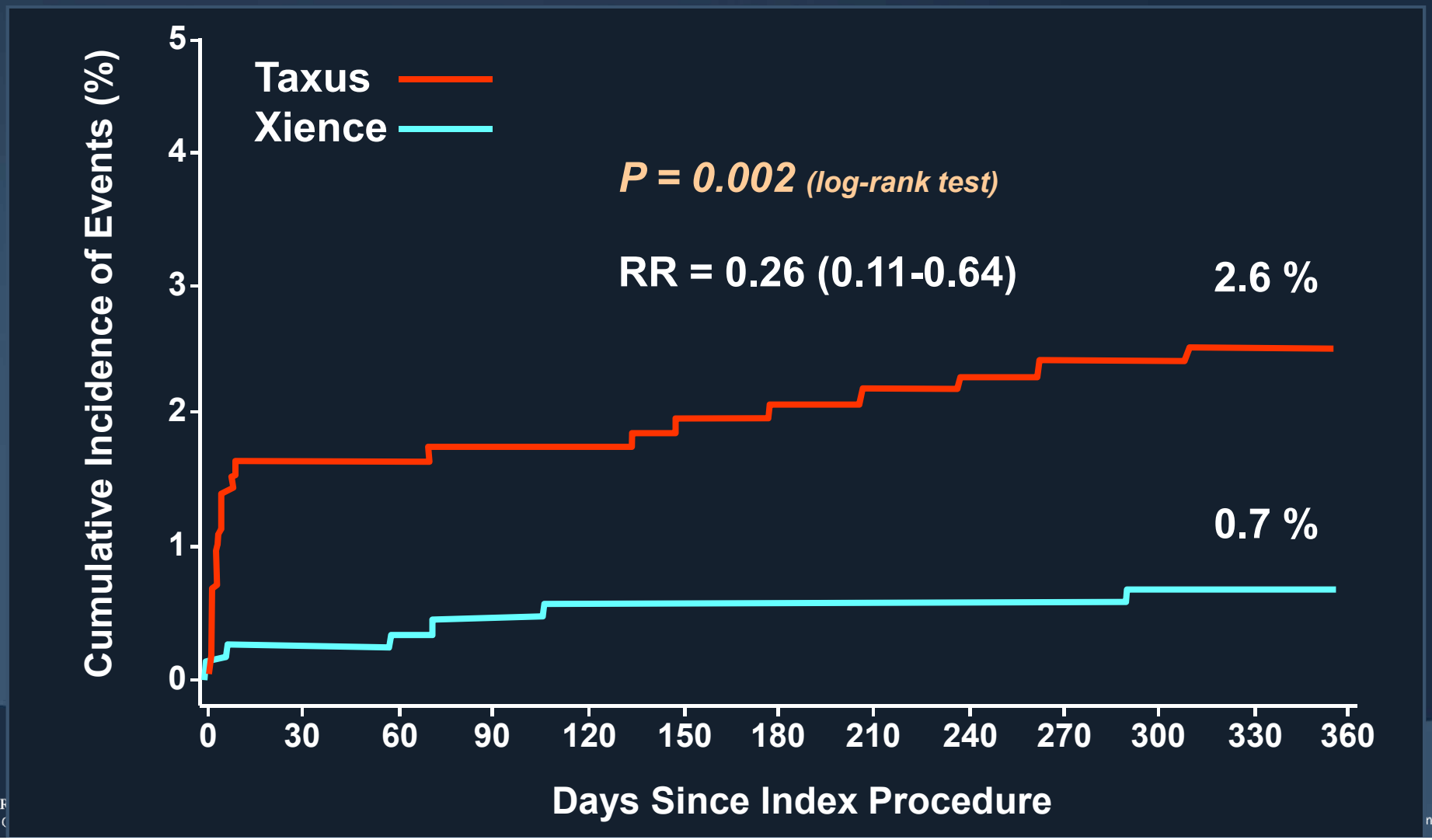
COMPARE – 2ry Endpoint Result

Early and Late Stent Thrombosis

(definite & probable according ARC)

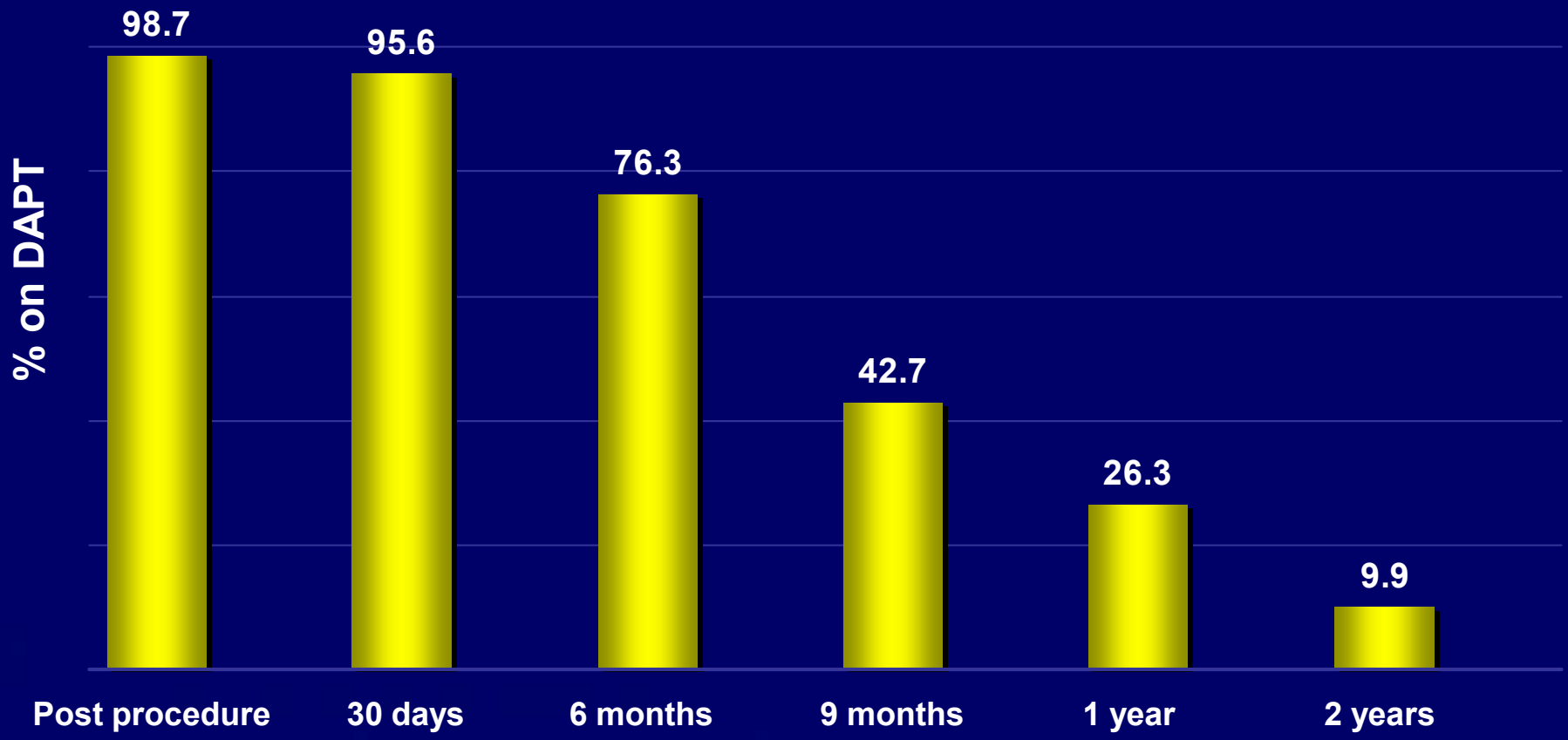


Are we creating Plavix Addicts?

Endeavor Clinical Program

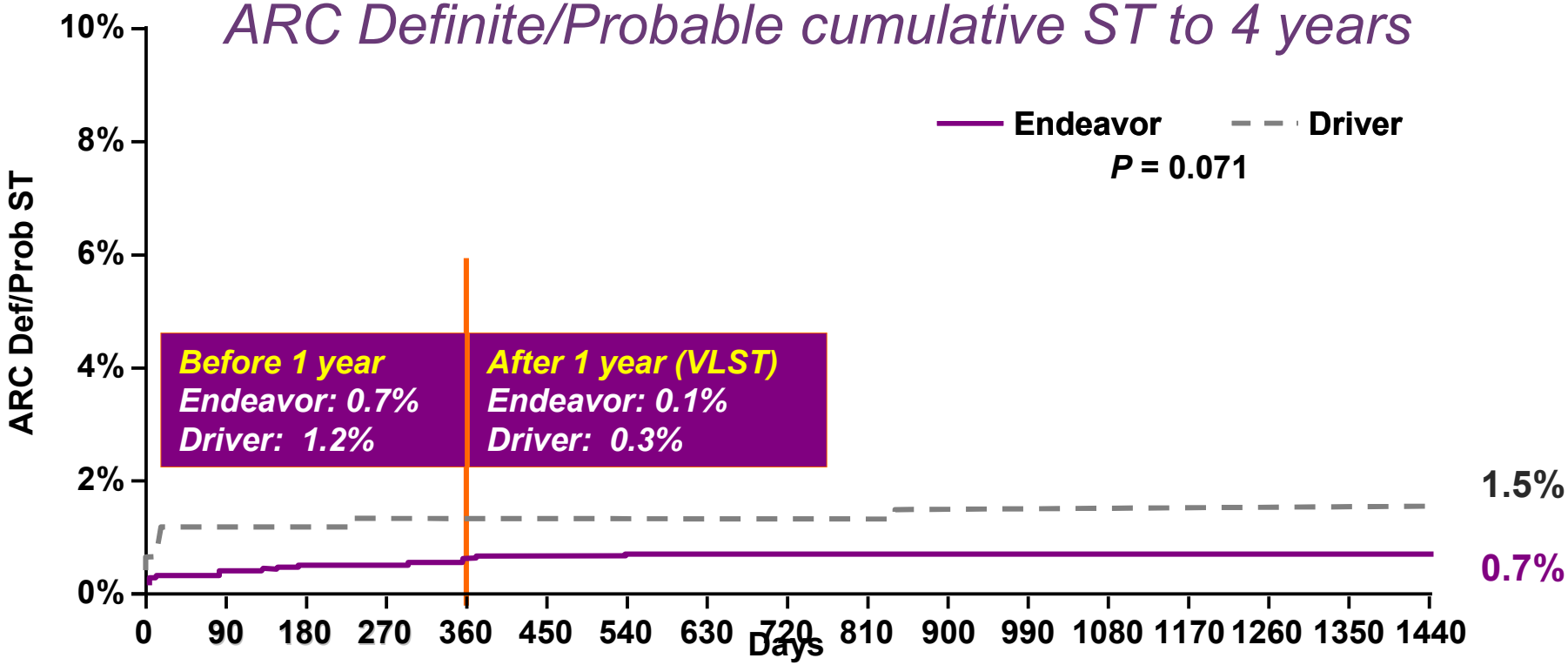
Dual Antiplatelet Therapy Usage

(average)



Data on file Medtronic Inc.UC200802485a

Pooled Endeavor: Reassuring long-term safety



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% CI	0.2%	1.2%	1.3 %	1.3%	1.3%	1.5%	1.5%

SEASIDE

N = 900 patients treated with Endeavor stents

Thienopyridine x 6 months:

- Single *de novo* atherosclerotic lesion with diameter stenosis 50% to 100% (includes total coronary occlusions
- Lesion length ≤40 mm
- Reference vessel diameter ≥2.25 mm to 4.0 mm
- Lesion not involving side-branch intended to be stented
- Ostial or non-ostial location
- In-stent restenosis not treated with prior brachytherapy
- 1 or 2 vessels per patient (up to two lesions per vessel with each lesion meeting anatomic criteria above)
- Saphenous vein or arterial bypass graft

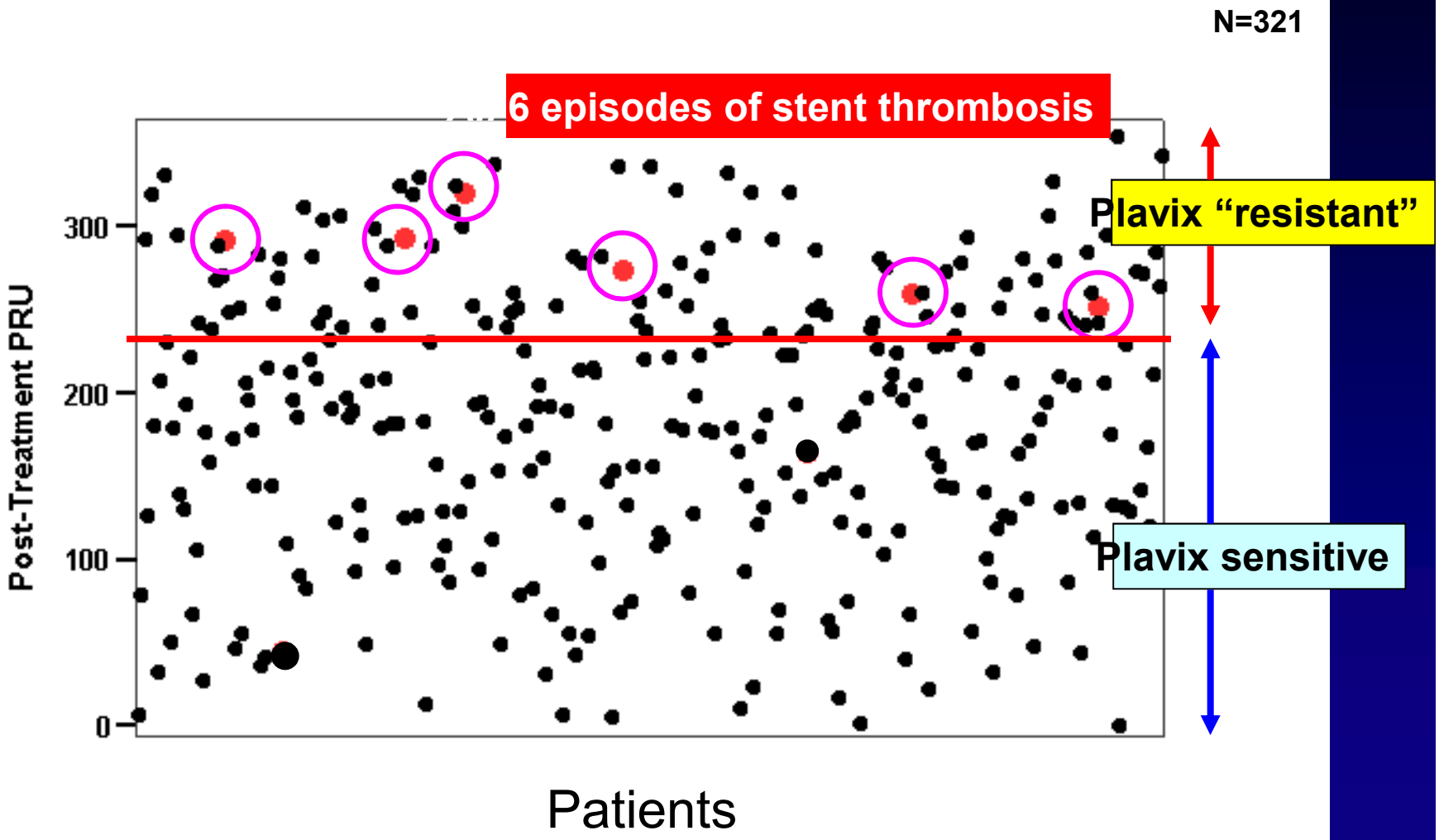
Bedside Monitoring of Platelet Reactivity: Accumetrics VerifyNow Assay for Plavix responsiveness

Insert assay device

Add blood sample

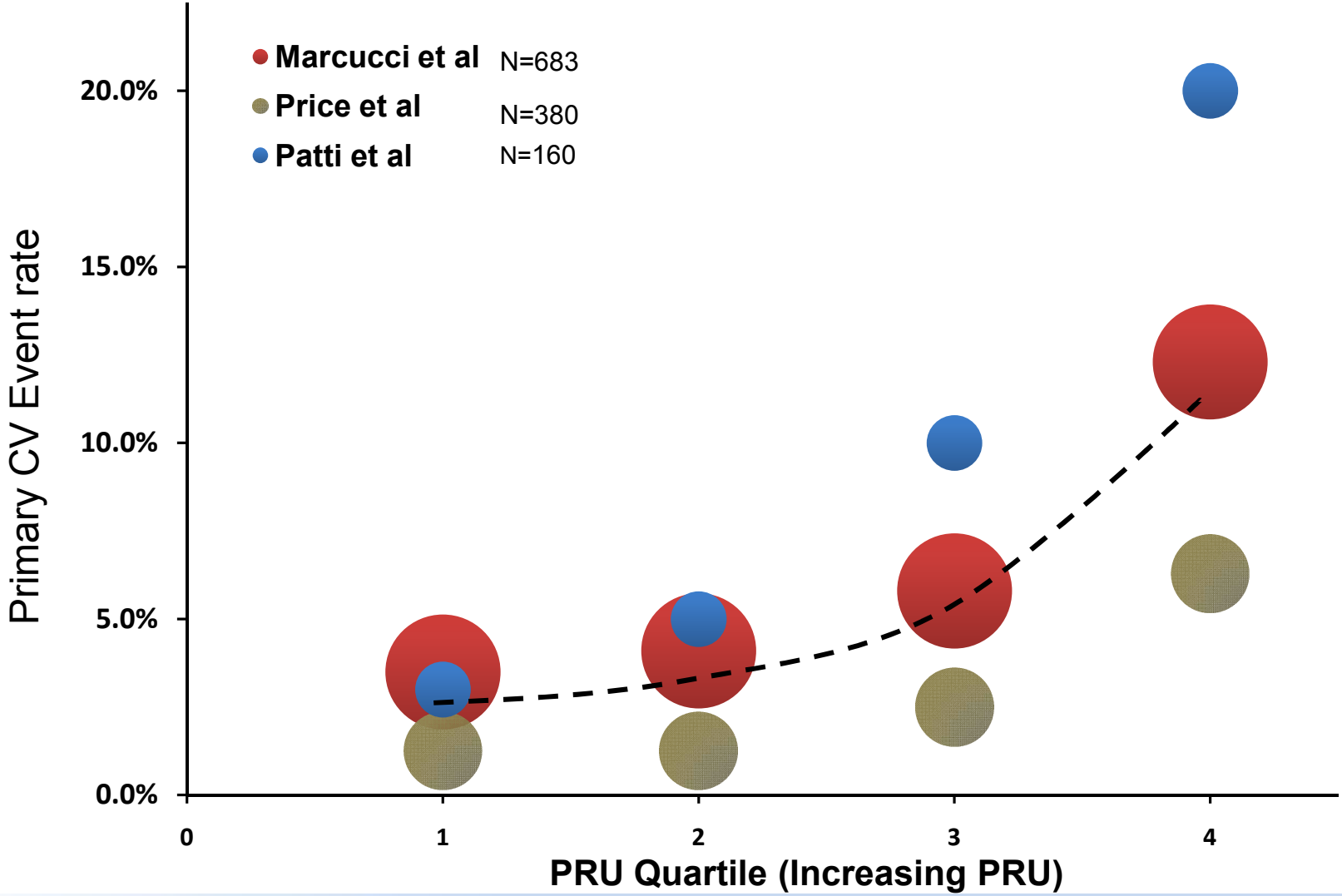
Read result in minutes

Stent Thrombosis after DES Implantation at 6 Month Follow-up



Increasing Risk With Greater Residual Reactivity After Clopidogrel According to VerifyNow P2Y12 Assay

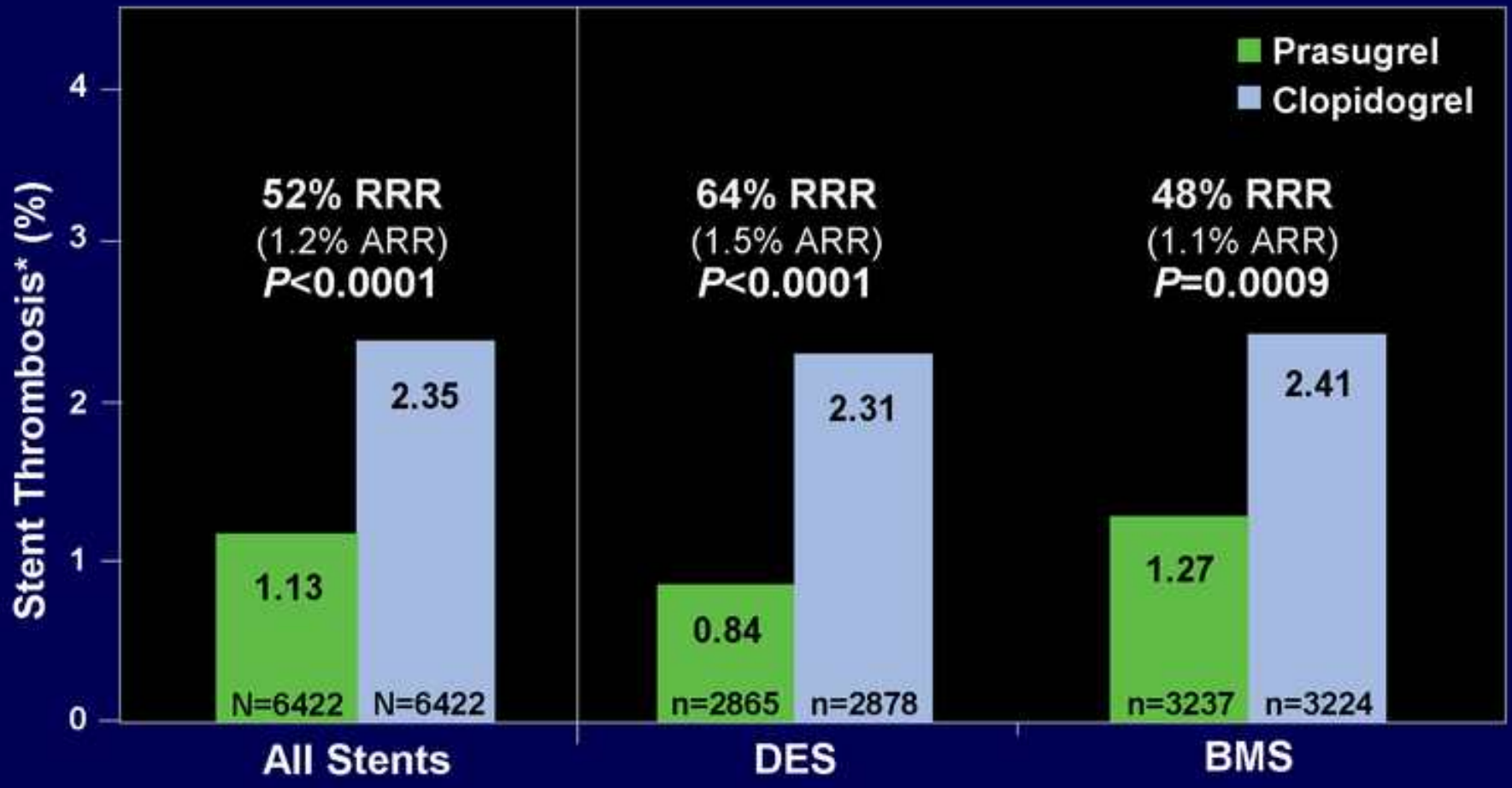
Event Rates In Prospective PCI Studies Stratified By PRU Quartile



Adapted from Price MJ, *Circulation*. 2009;119(19):2625-2632

Stent Thrombosis Rates at End of Study

Tritron Study



Based on Kaplan-Meier estimates.

*Stent thrombosis defined as Academic Research Consortium definite or probable.

Wiviott et al. *Lancet.* 2008;371(9621):1353-1363.

Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

GRAVITAS

Successful PCI with DES (with 600mg clopidogrel load) without major complication or GPIIb/IIIa use

VerifyNow P2Y12 Assay 12-24 hours post-PCI

PRU ≥ 230?

Yes → **Non-Responder**

R ACS

A N = 1100 — ***"Tailored Therapy"*** clopidogrel 600-mg*, then clopidogrel 150-mg/day

B N = 1100 — **"Standard Therapy"** placebo loading dose, then clopidogrel 75mg +placebo/day

No → **Responder** → Random Selection

C N = 583 — **"Standard Therapy"** placebo loading dose clopidogrel 75mg +placebo/day

Clinical Follow-up And Platelet Function Assessment at 30 days, 6M

Primary Endpoint: 6 month CV Death, Non-Fatal MI, ARC definite/prob ST

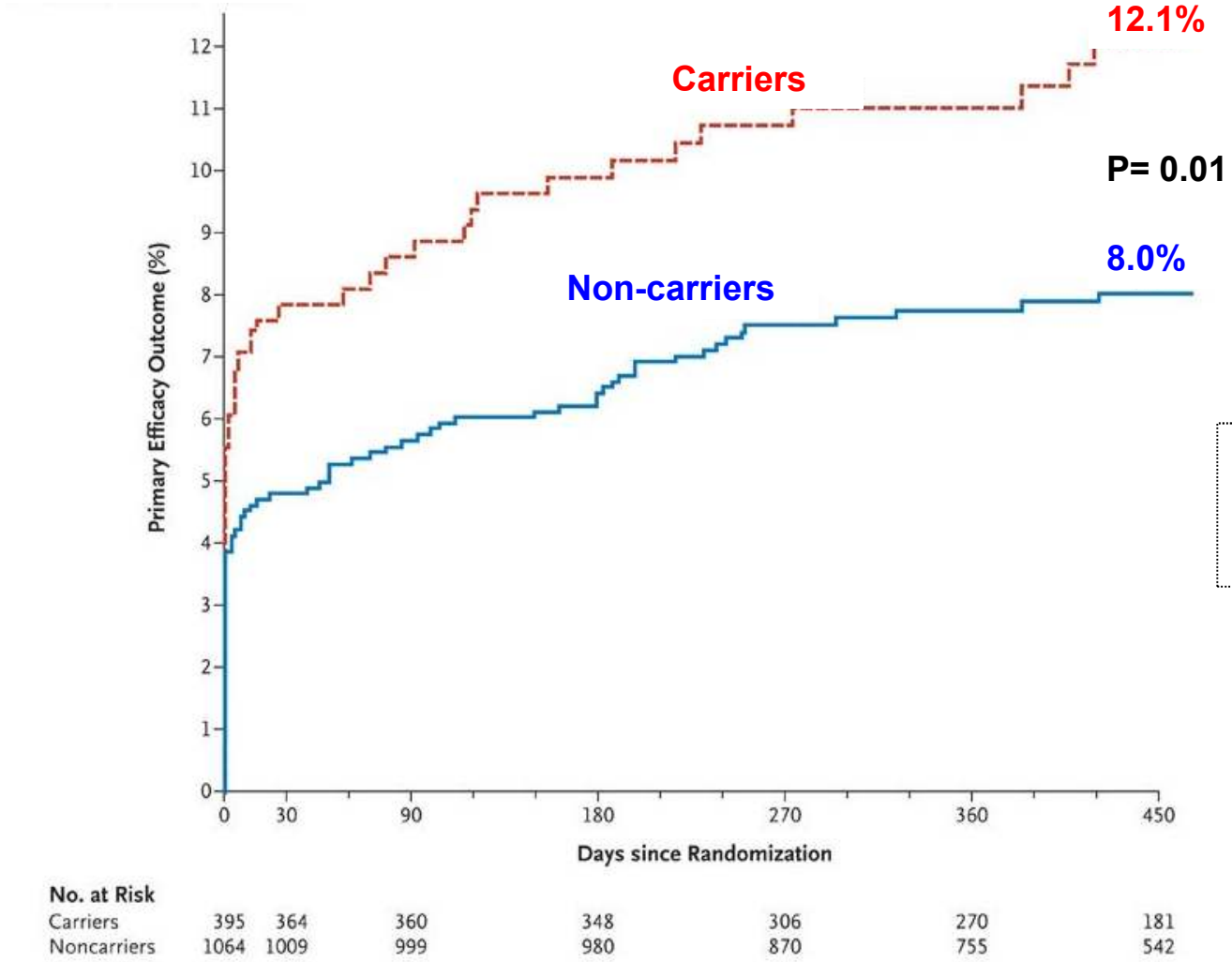
Safety Endpoint: GUSTO Moderate or Severe Bleeding

*total first day dose

Price MJ et al, Am Heart J 2009

Clopidogrel, Genotype, and Clinical Outcomes in ACS

TRITON Results According to Carriage of Reduced Fxn CYP2C19 Allele in ACS Patients Receiving Clopidogrel



Reduced function allele present in 30% of population

Mega JL et al, NEJM 2009;360:354-62

FEAR NOT

- Stent Thrombosis scare was never justified
- New DES technology has significantly improved safety
  - Stent Thrombosis rates are lower
  - Duration of dual anti-platelet requirement may shorter
- Personalized medicine - titrating anti-platelet therapy to individual's genotype and platelet reactivity has likely further improved stent safety