Late Clinical Outcome After DES

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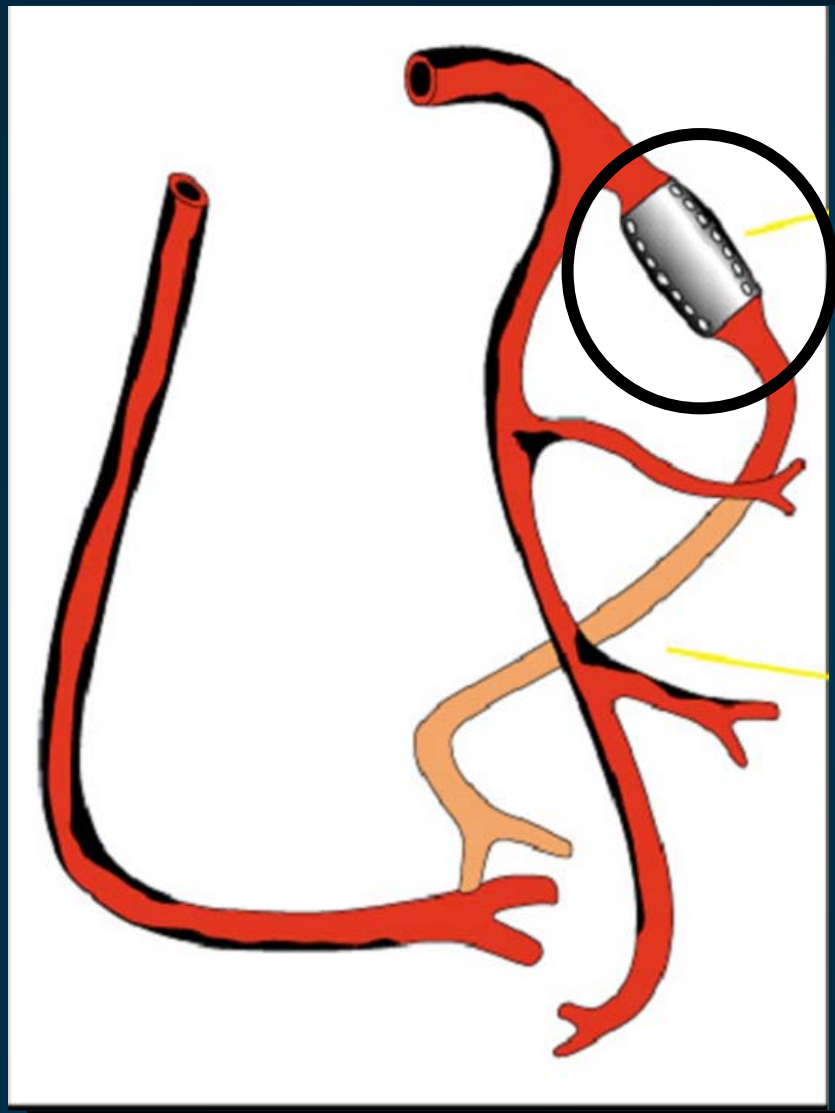
Conflict of Interest Statement

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

Physician Name	**Company/Relationship**
Jeffrey J. Popma, MD	Research Grants: Cordis, Boston Scientific, Medtronic, Abbott-Guidant, Biosensors, Radiant, eV3 Medical Advisory Board: Cordis, Boston Scientific, Medtronic Speaker's Bureau: Sanofi, BMS, Boston Scientific Pfizer

The Goals of Ischemia Management In Patients With Ischemic Coronary Disease



- Provide a sustained and durable results of ischemia- generating, flow-limiting obstructions (angina)
  - e.g., drug eluting stents
- Prevent the occurrence of new plaque rupture due to underlying atherosclerosis (death, MI)
  - e.g., aspirin, clopidogrel, lipid lowering therapy, ? PCI
  - ? Vulnerable plaque

We expect the 40 Year old undergoing DES to be around from the next 50 years . . . .

Beyond Restenosis

Five-Year Clinical Outcomes From Second-Generation Coronary Stent Trials

Donald E. Cutlip, MD; Amit G. Chhabra, MBBS, MPH; Donald S. Baim, MD; Manish S. Chauhan, MD; Sachin Marulkar, MBBS, MPH; Joseph Massaro, PhD; Ameet Bakhai, MD; David J. Cohen, MD, MSc; Richard E. Kuntz, MD, MSc; Kalon K.L. Ho, MD, MSc

Background—In the first year after coronary stent implantation, clinical failures are driven mainly by procedural complications and restenosis, but the subsequent relative contributions of restenosis and disease progression to late failures are less clear.

Methods and Results—We observed 1228 patients for 5 years after the implantation of stents as part of pivotal second-generation coronary stent trials. Clinical events of death, myocardial infarction, repeat revascularization, and repeat hospitalization for acute coronary syndrome or congestive heart failure were attributed to the index stented (target) lesion or other distinct sites (either in the target or other coronary vessels) and further classified as procedural, restenosis, or nonrestenosis. During the first year the hazard rate was 18.3% for target-lesion events and 12.4% for events unrelated to the target lesion. After the first year the average annual hazard rate was 1.7% for target-lesion events and 6.3% for nontarget-lesion events. By the fifth year, restenosis events occurred in 20.3% of patients, whereas 30-day procedural complications or later nonrestenosis events occurred in 37.9%, including 11.4% who also experienced a restenosis event, for a combined cumulative event rate of 46.4%. Diabetes mellitus and multivessel disease were independently associated with increased risk for both restenosis and nonrestenosis events.

Conclusion—In a low-risk clinical trial population, the clinical outcome beyond 1 year after stenting is determined by a high rate of events related to disease progression in segments other than the stented lesion, which itself remains relatively stable. (***Circulation***. **2004;110:1226-1230.**)

Cutlip 2004;110:1226-1230

Is This Considered A Success?

TABLE 2. Clinical Event Hazard Rates

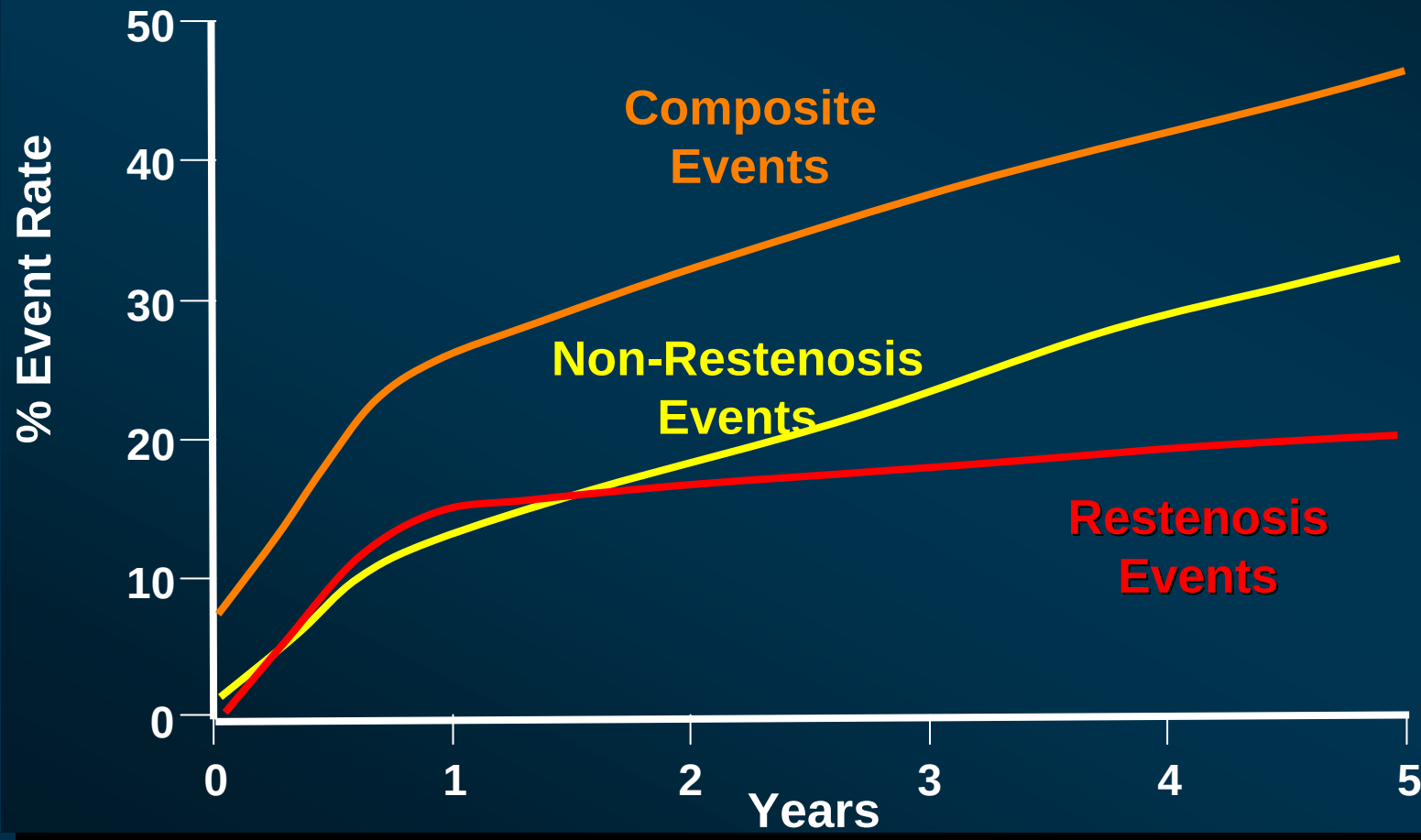
	Year 1		Years 2–5			
End Point	Failures	HR	Failures	HR	Average Annualized HR	Cumulative Failures, n (%)
Composite	321	26.1	221	25.3	7.2	542 (46.4)
All-cause death	11	0.9	78	6.9	1.9	89 (8.2)
Cardiac death	9	0.7	44	3.9	1.0	53 (5.0)
MI or ACS	104	8.5	76	7.4	2.0	180 (15.9)
TLR	146	12.0	57	5.7	1.5	203 (17.5)
TVR (excluding TLR)	40	3.2	47	4.5	1.2	87 (7.6)
Total TVR	185	15.1	86	8.9	2.4	270 (23.4)
Non-TVR	109	8.9	133	12.8	3.5	242 (21.7)
CHF	2	0.2	17	1.5	0.4	19 (1.5)

HR indicates hazard rate, which is the probability of event within a given interval if survived before interval free of event. Cumulative event rates were determined using survival analysis estimates at 5 years.

Cutlip 2004;110:1226-1230

5-Year Clinical Outcome in 1228 Low-Risk Patients Treated with BMS

Composite Events: Any death, MI, repeat revasc, ACS or CHF admit.



After year 1 average annual hazard rate for target-lesion events was 1.7% and 6.3% for non-target lesion events.

Cutlip DE. Circulation 2004;110:1226-30

Late Clinical Events After DES

- Target Lesion Related Events
  - Stent Thrombosis
  - Late Ischemia-Driven TLR
- Non Target Lesion Related Events
  - Some ARC Probable Stent Thromboses
  - Remote non TLR – TVR
  - Non TVR Revascularization
  - Death and Spontaneous MI

SIRIUS - Study Design

n = 1058 patients

***De Novo* Coronary Lesions**

Diameter: 2.5-3.5 mm
Length: 15-30 mm

Control
Bx VELOCITY™
n = 525

Sirolimus-eluting Bx
VELOCITY™
n = 533

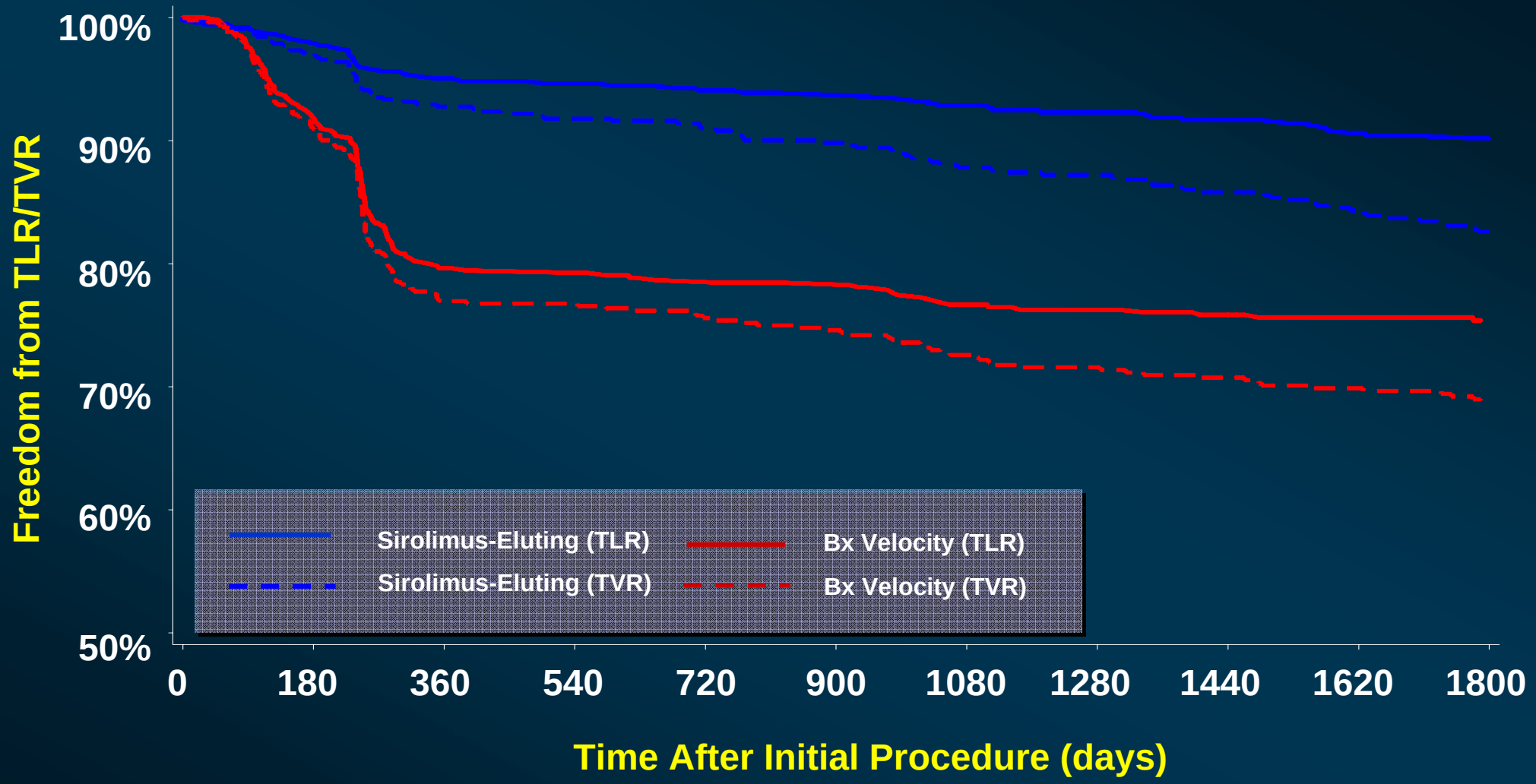
Primary Endpoint: target vessel failure (TVF) = cardiac death, MI or TVR (FU at 9 mos)

Angiographic Substudy: first 850 pts (FU at 8 mos)

IVUS Substudy: 250 pts at selected sites (FU at 8 mos)

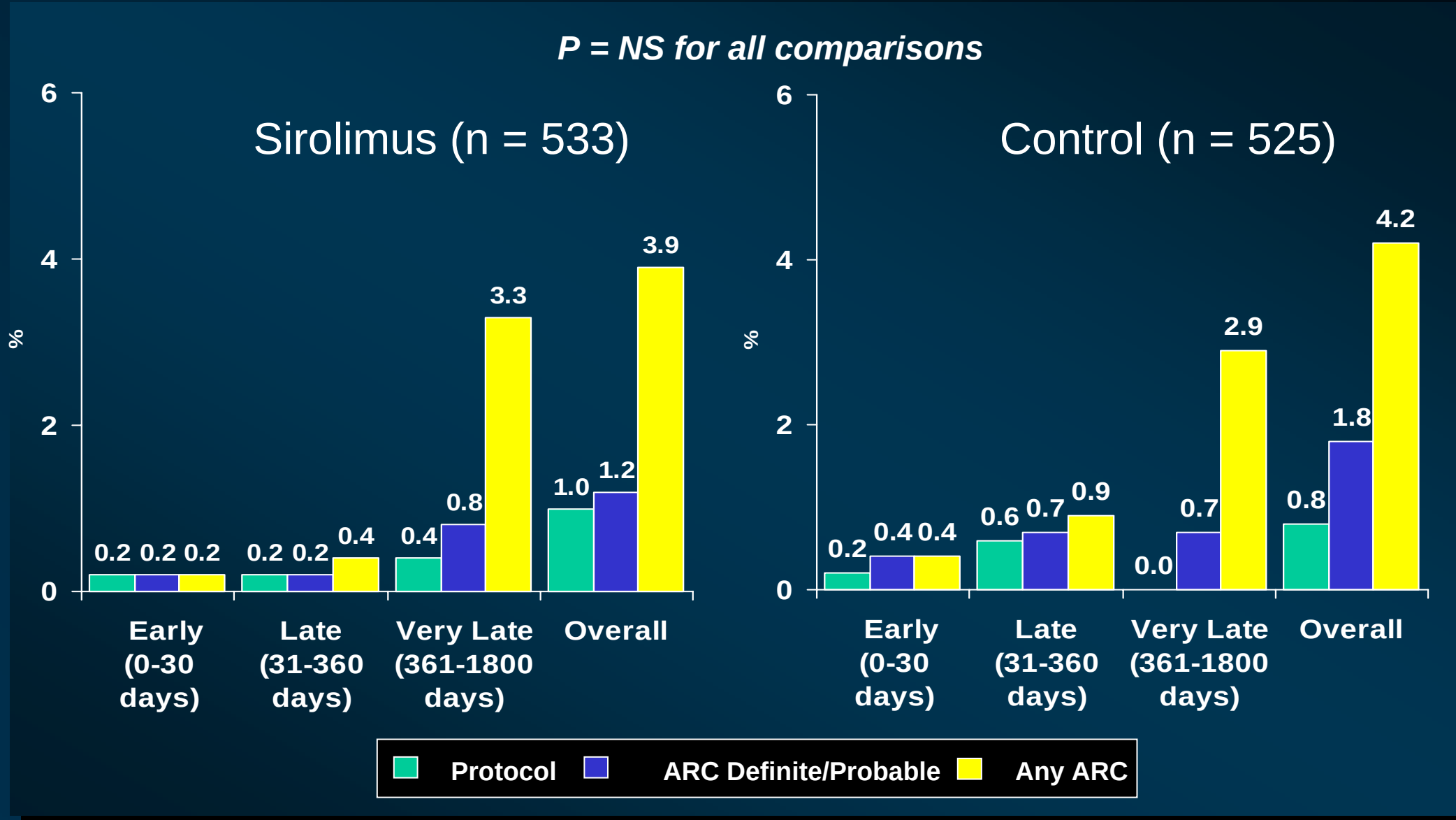
Leon M.B. et al, ACC 2007

5 Year SIRIUS – Free from TLR-TVR



Leon M.B. et al, ACC 2007

SIRIUS – Stent Thrombosis @ 5 Yrs

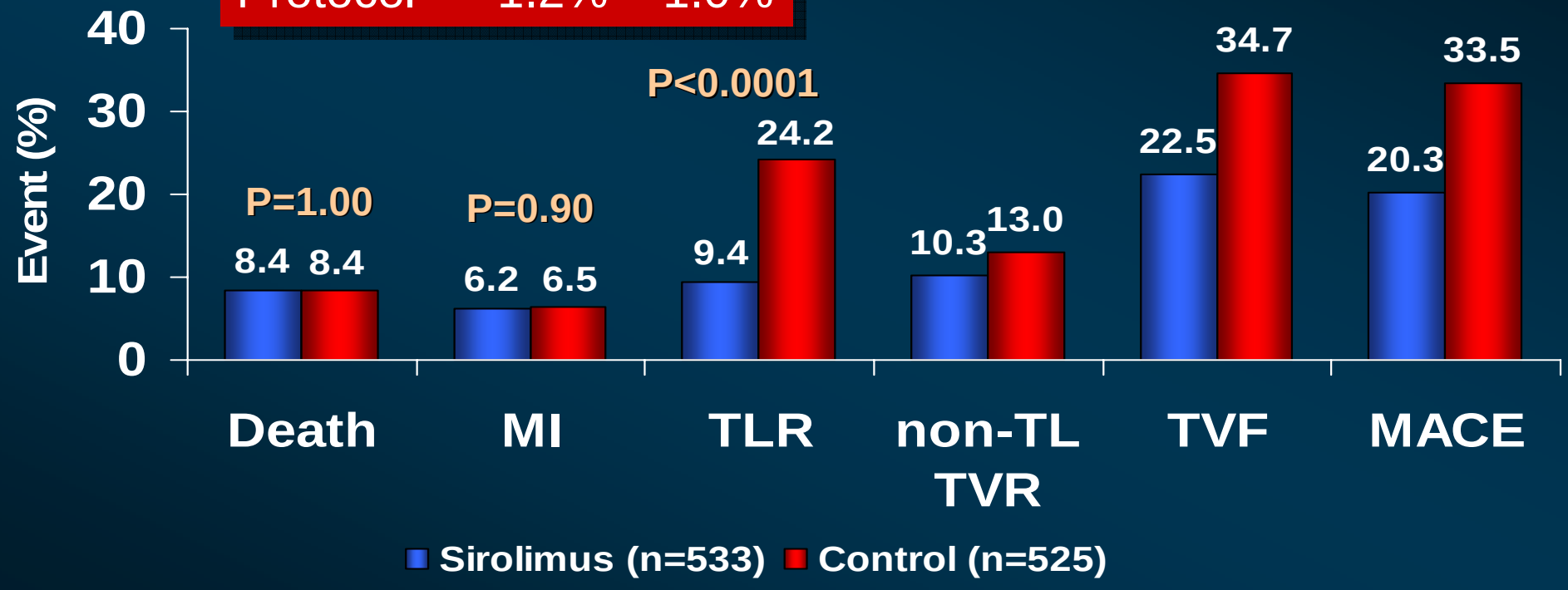


Leon M.B. et al, ACC 2007

SIRIUS – Clinical Events @ 5 yrs

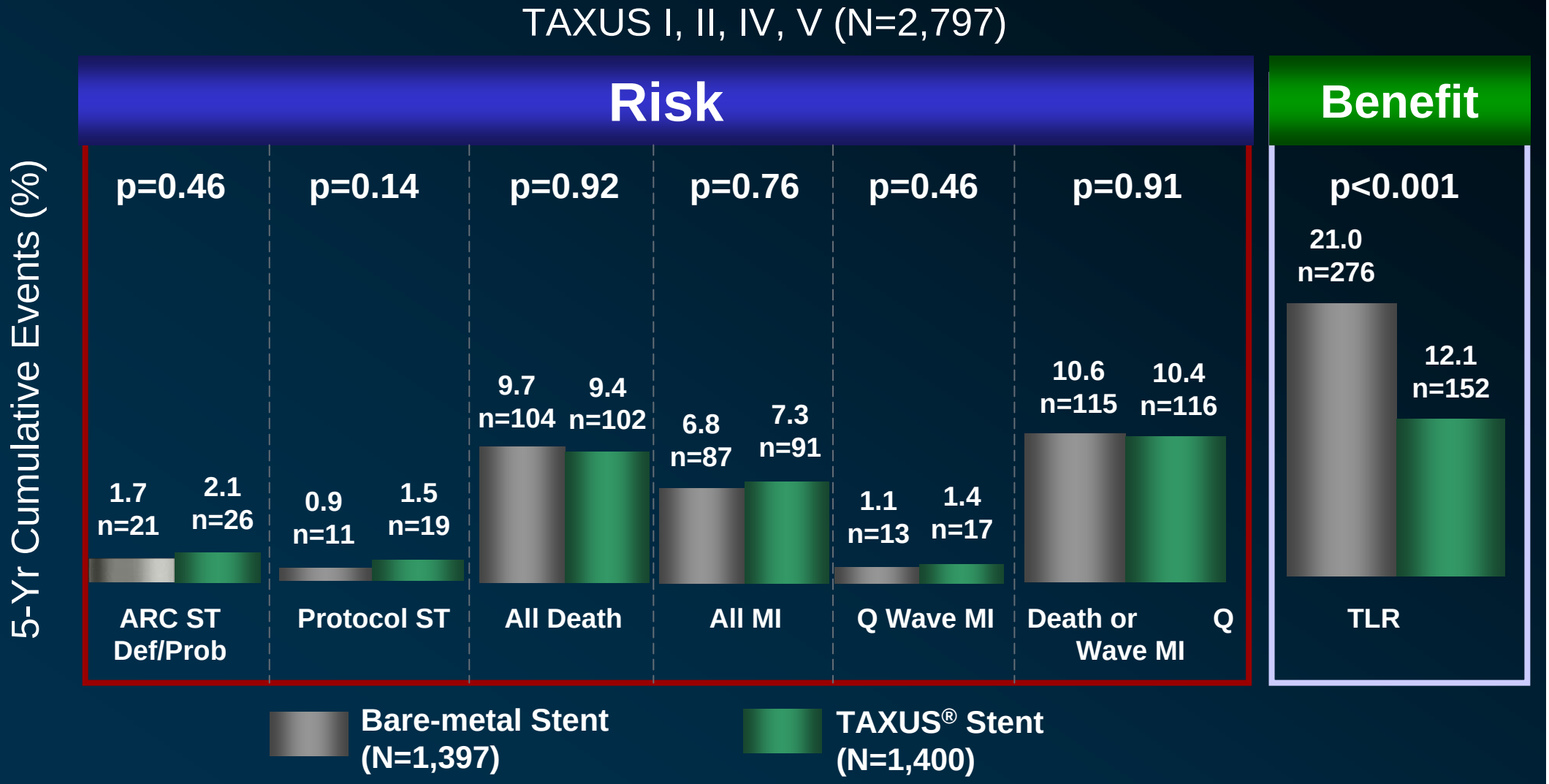
Major Adverse Cardiac Events

Total Adjudicated ST	BMS	DES
Def-Prob	1.8%	1.2%
Protocol	1.2%	1.0%



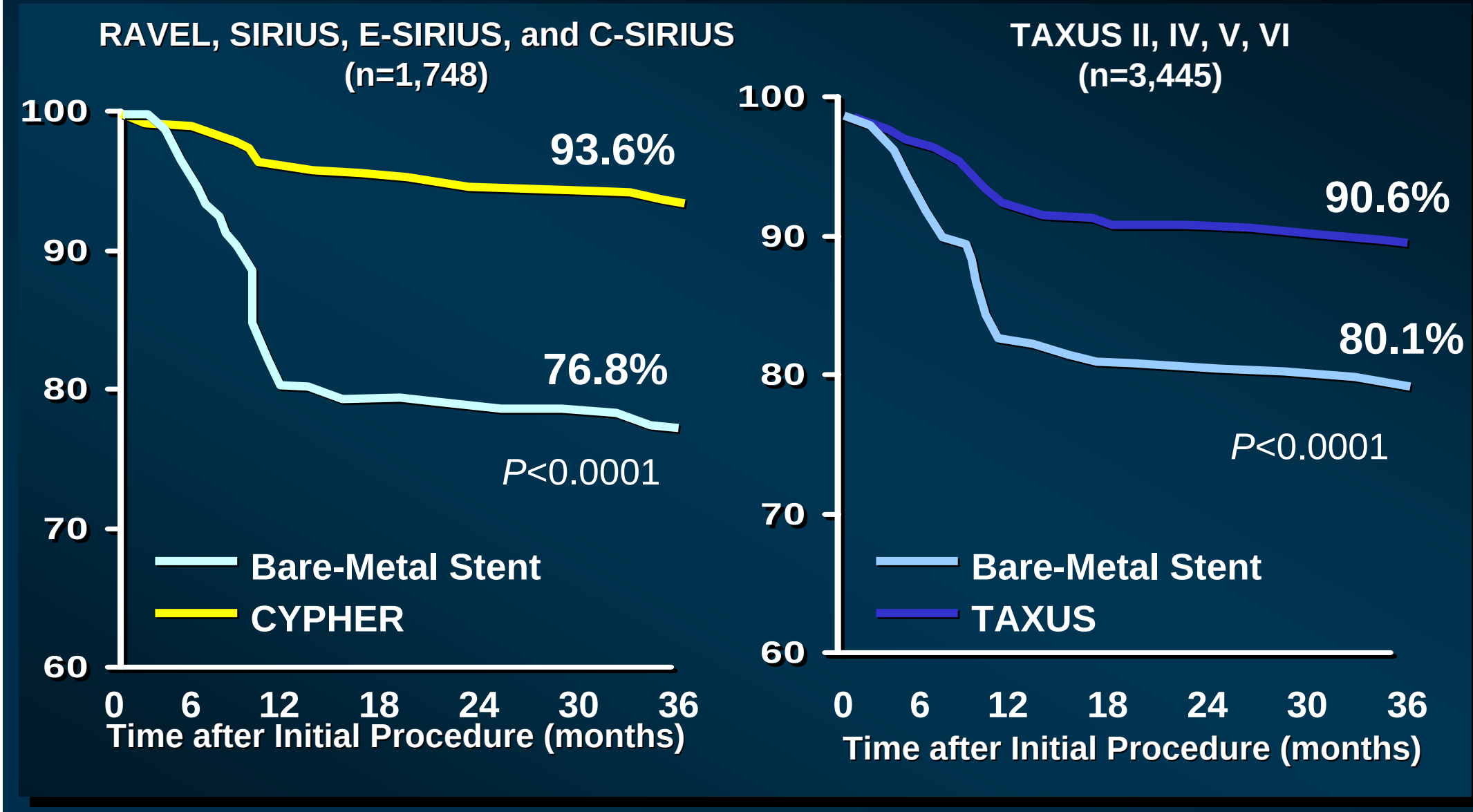
Leon M.B. et al, ACC 2007

TAXUS® Stent Patient Level Meta-analysis
5-year Results – SR only



Presented by Stephen G. Ellis MD, TCT 2007. TAXUS Stent 5-year meta-analysis includes TAXUS I (5 yr), II (5 yr), IV (5 yr), V (3 yr) (N=2,797).

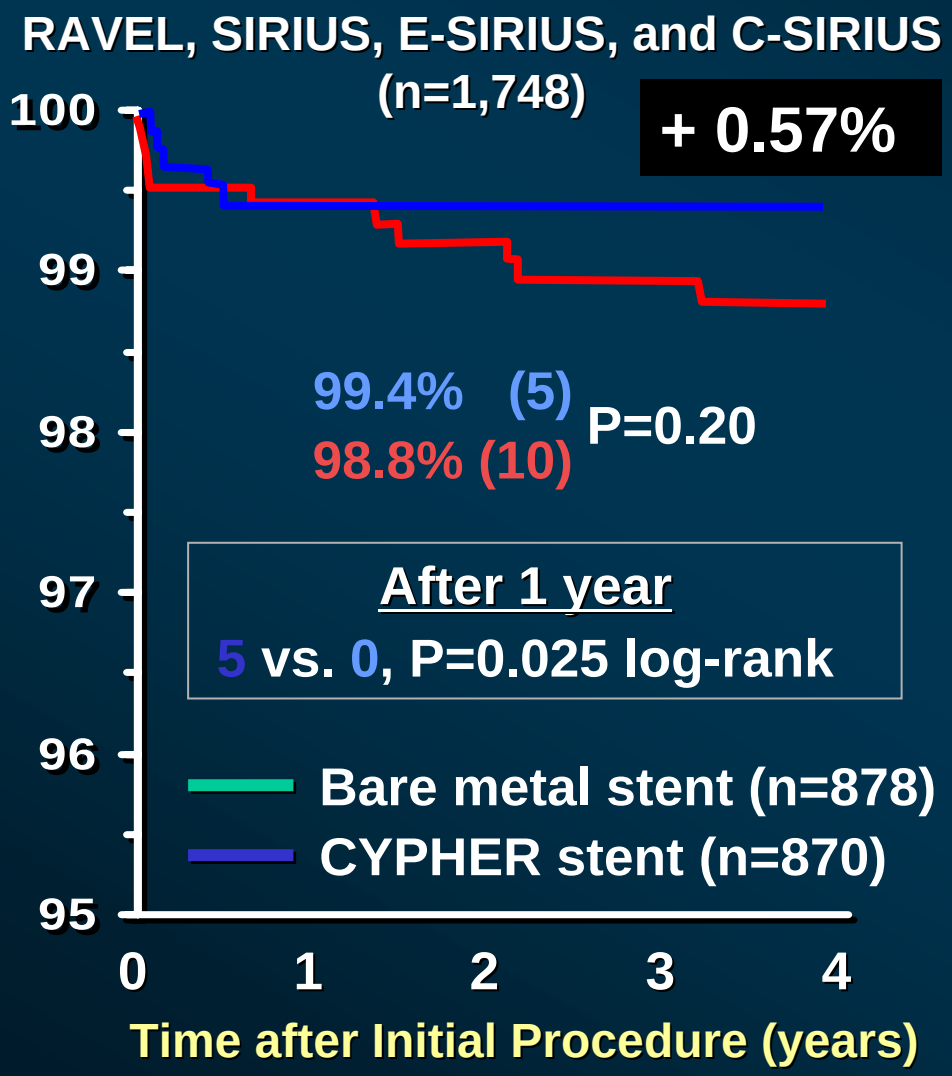
In the Beginning – Efficacy Was The Only Concern

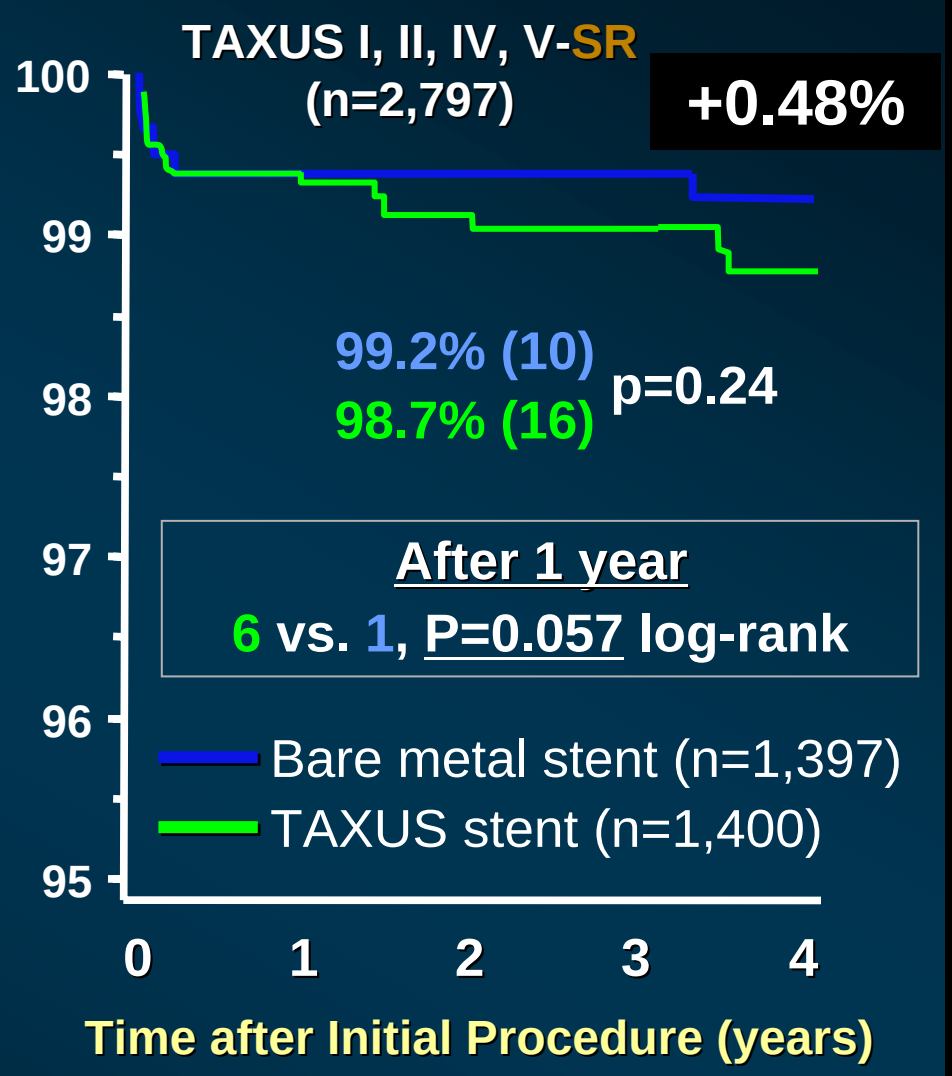


Schampaert et al. Circulation 2005;112;II-650; Stone et al. Circulation 2005;112;II-651

TCT:2006: Independent CRF patient-level meta-analysis

Freedom From (Protocol) Stent Thrombosis





Stone GW NEJM 2006

Offsetting Impact of Thrombosis and Restenosis on the Occurrence of Death and Myocardial Infarction After Paclitaxel-Eluting and Bare Metal Stent Implantation

Gregg W. Stone, MD; Stephen G. Ellis, MD; Antonio Colombo, MD; Keith D. Dawkins, MD; Eberhard Grube, MD; Donald E. Cutlip, MD; Mark Friedman, MD; Donald S. Baim, MD; Joerg Koglin, MD

Background—Drug-eluting stents compared with bare metal stents (BMS) may increase late stent thrombosis (ST), although an accompanying increase in the rates of death and myocardial infarction (MI) has not been observed. We hypothesized that the prevention of restenosis-related adverse events by drug-eluting stents might offset some or all of the excess risk from ST.

Methods and Results—We analyzed a pooled patient-level database from 4 prospective, double-blind trials in which 3445 patients were randomized to paclitaxel-eluting stents or BMS. The occurrence of death or MI within 7 days of ST or target lesion revascularization was assessed. With a median follow-up of 3.2 years, ST occurred in 34 patients (1.0%), 31 (91.1%) of whom sustained death or MI within 7 days. Target lesion revascularization was performed in 425 patients (12.3%), 15 (3.5%) of whom died or had MI within 7 days. ST occurred in 14 BMS and 20 paclitaxel-eluting stent

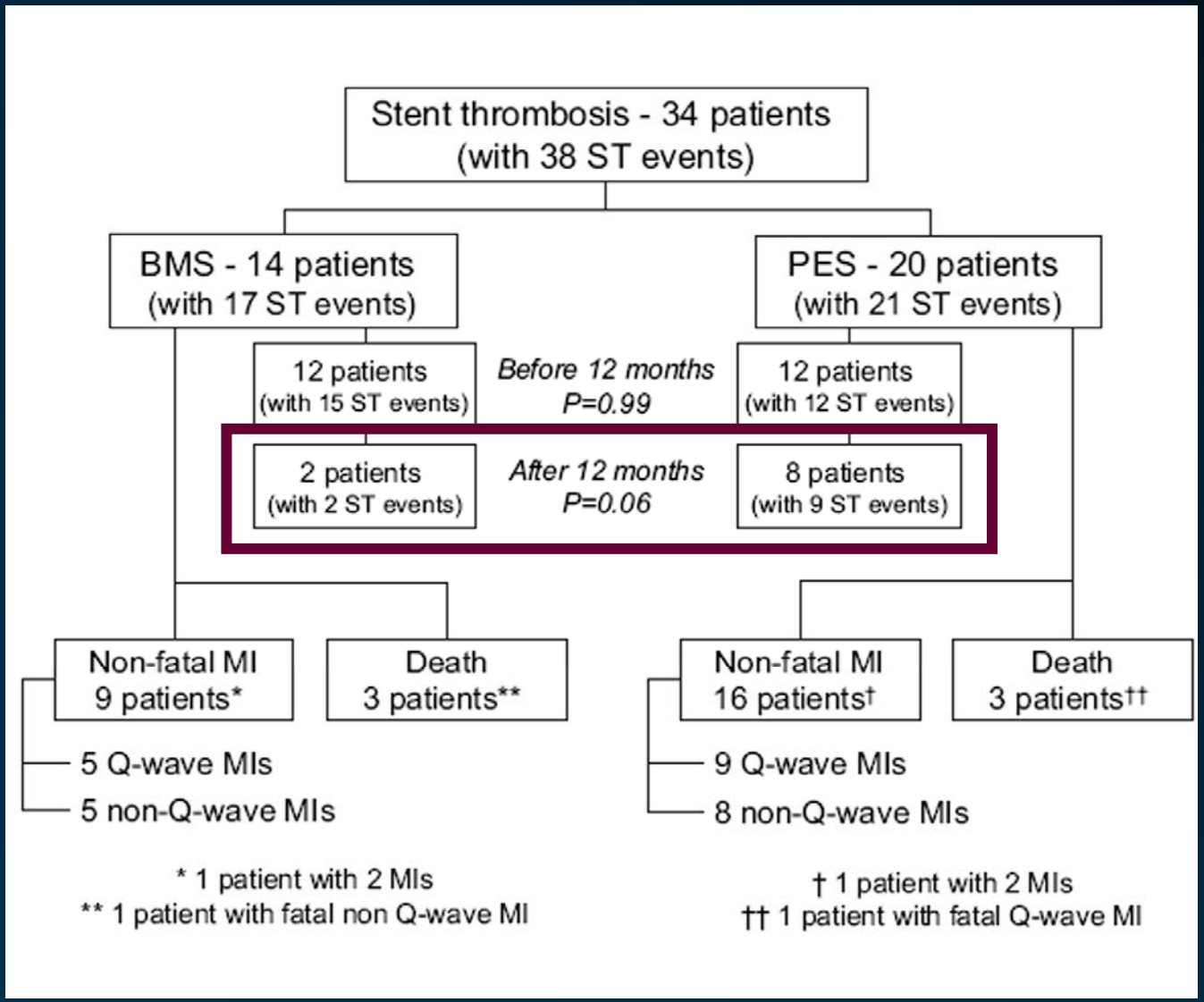
7 days of either ST or target lesion revascularization.

Conclusions—ST, although infrequent, results in a high incident rate of death and MI, whereas the more frequent occurrence of target lesion revascularization is associated with a finite but lower rate of death and MI. The marked reduction in restenosis with drug-eluting stents compared with BMS may counterbalance the potential excess risk from late ST with drug-eluting stents. (***Circulation***. **2007;115:2842-2847.**)

Key Words: mortality ■ myocardial infarction ■ restenosis ■ stent ■ thrombosis

Stone GW Circulation 2007;115:2842

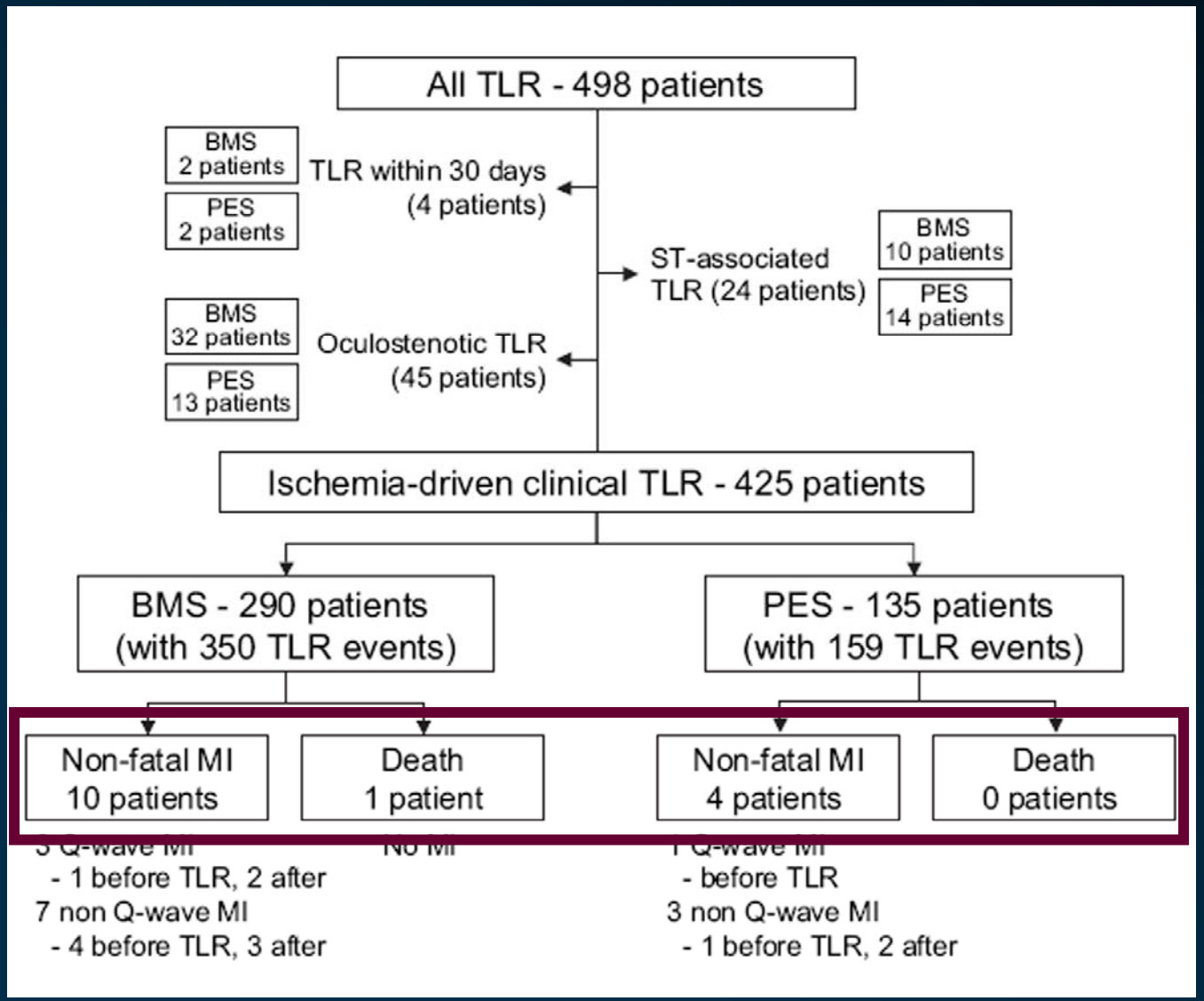
TAXUS Meta-analysis (N=3,445)



Stent Thrombosis Remains a Morbid and Potentially Fatal Event

Stone GW Circulation 2007;115:2842

TAXUS Meta-analysis (N=3,445)



TLR is Not Benign and Also Associated with Higher Rates of Death-MI

Stone GW Circulation 2007;115:2842

TAXUS Meta-analysis (N=3,445)

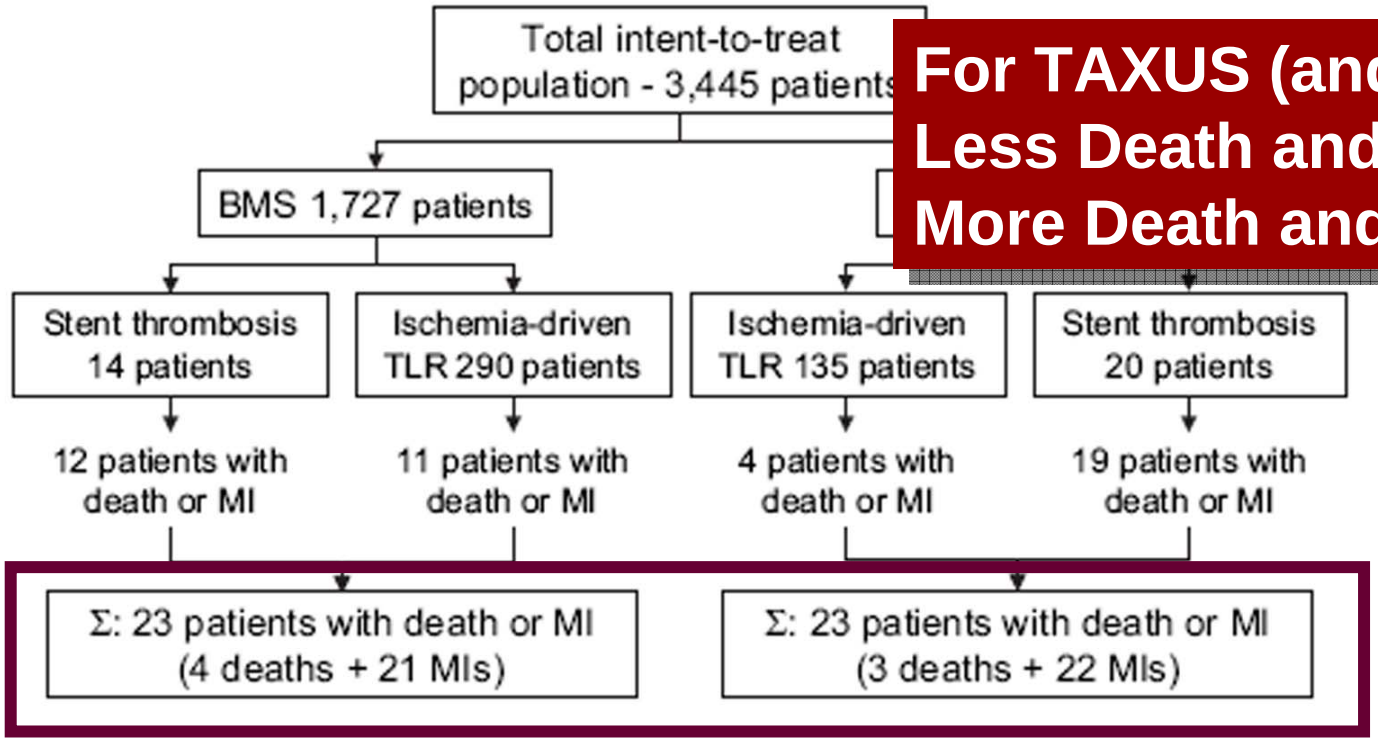


Figure 3. The greater rate of death or nonfatal MI resulting from an excess of ST in the PES group was counterbalanced by an increase in the rate of death or nonfatal MI caused by the more frequent occurrence of ischemia-driven TLR in the BMS group. As a result, death or nonfatal MI within 1 week of occurrence of either ST or ischemia-driven TLR occurred in 23 patients in both stent groups.

For TAXUS (and CYPHER)
Less Death and MI due to less TLR
More Death and MI due to VLST

Similar Rates of Late Death and MI at 3.2 yrs

Stone GW Circulation 2007;115:2842

Late Clinical Events After DES

- This is a fair balance of risk – benefit, but
  - What about extension into “real world” patients?
  - What if a DES reduced restenosis without the “cost” of late death and MI – would outcomes be improved?

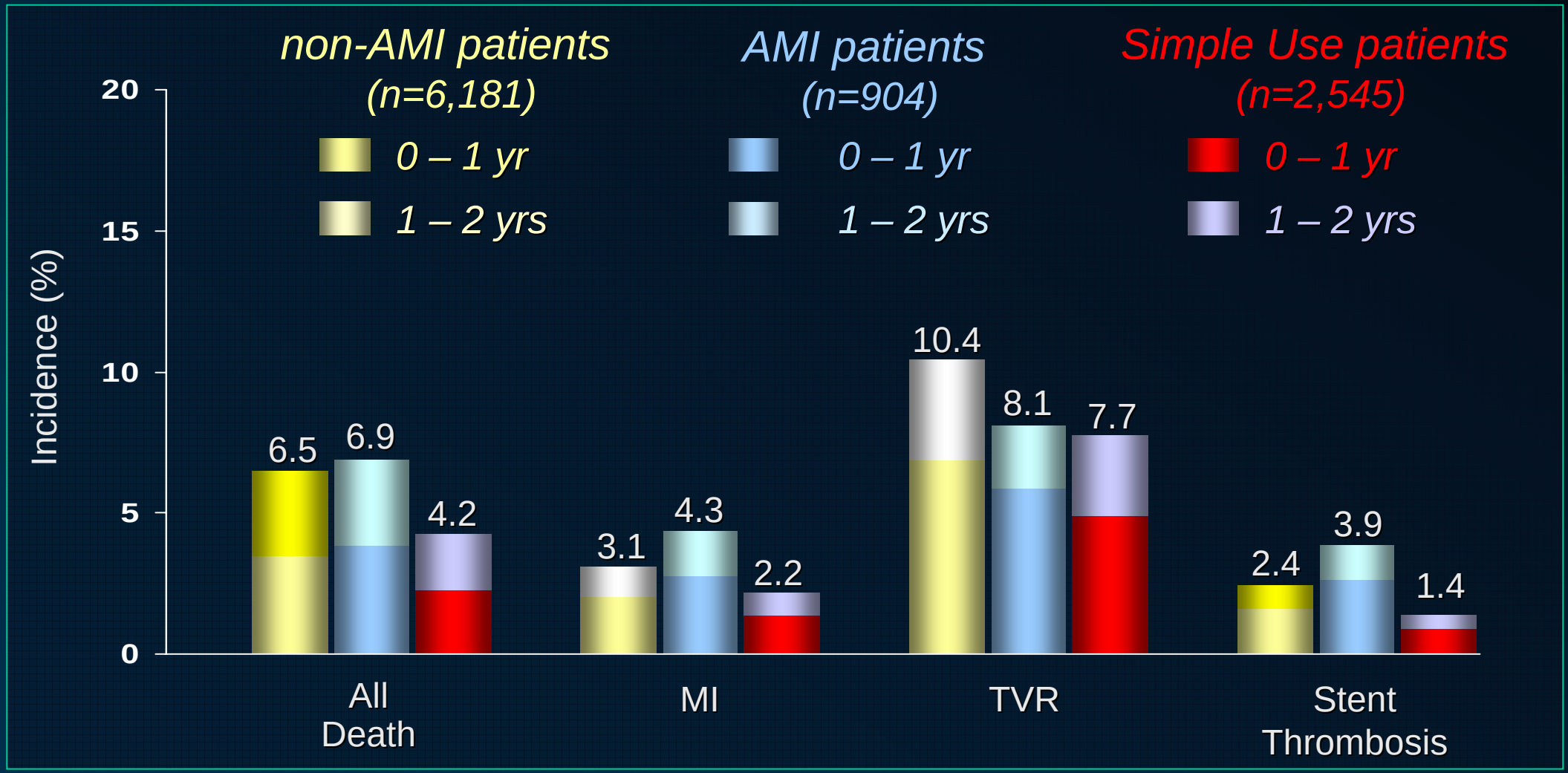
Meta-analysis DES vs. BMS
Findings from 180,749 patients

- In 22 RCTs involving 9,470 patients randomized to DES or BMS and followed for ≥1 year, DES resulted in:
  - A non-significant 3% reduction in mortality - ***HR 0.97 (0.81,1.15)***
  - A non-significant 6% reduction in MI - ***HR 0.94 (0.79,1.13)***
  - A significant 55% reduction in TVR – ***HR 0.45 (0.37,0.54)***

- In 30 Registries with 171,279 patients treated with either DES or BMS and followed for ≥1 year, DES resulted in:
  - A significant 20% reduction in mortality - ***HR 0.80 (0.72,0.88)***
  - A significant 11% reduction in MI – ***HR 0.89 (0.80-0.98)***
  - A significant 47% reduction in TVR – ***HR 0.53 (0.47-0.61)***

Presented by Gregg W. Stone MD and Ajay Kirtane MD, ACC 2008

ARRIVE 1+2: Cardiac Events at 1- 2 Years



Presented by J Lasala MD, ACC 2008. The safety and effectiveness of the TAXUS® Express ® Stent have not been established in patients with a recent acute myocardial infarction where there is evidence of thrombus or poor flow.

Multivariate Predictors of ARC ST in ARRIVE
Strongest year 1 predictor = Limited clopidogrel use

N=7492 patients	*0–1 year (n=128 ST)*	*1–2 years (n=56 ST)*	*0–2 year (n=184 ST)*
Predictor	*Hazard Ratio (P value)*		
Thienopyridine ≤6 Mon	3.95 (<0.0001)	NS	3.01 (<0.0001)
Multiple Stents	1.94 (0.0006)	2.37 (0.0016)	1.86 (0.0002)
Lesion Length >28 mm	1.77 (0.0113)	NS	1.60 (0.0130)
Calcification (Mod./Severe)	1.58 (0.0200)	NS	NS
Failed Brachytherapy	NS	9.42 (0.0019)	NS
Smoking at Baseline	2.61 (<0.0001)	1.79 (0.0404)	2.23 (<0.0001)
Congestive Heart Failure	2.23 (0.0017)	NS	2.06 (0.0010)
Diabetes-Insulin	2.02 (0.0022)	NS	1.66 (0.0115)
Renal Disease	NS	3.86 (0.0098)	NS
Prior Myocardial Infarction	NS	2.51 (0.0007)	1.61 (0.0014)
Expanded- vs. Simple-use	NS	NS	1.57 (0.0258)

→ *Factors differ in year 2; thienopyridines no longer predictive*

Definite & probable stent thrombosis (ST) is per Cutlip, et al. *Circulation* 2007;115:2344; NS=not significant

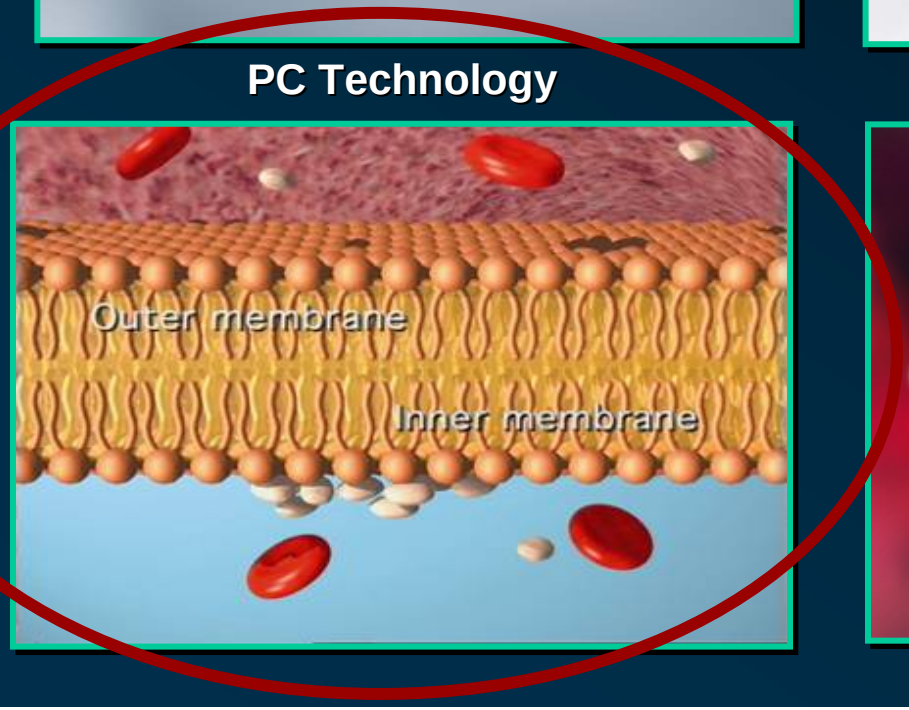
John Lasala MD, ACC 2008. Simple-use excludes, and the safety and effectiveness of the TAXUS® Stent have not been established in patients with one or more of the following: acute MI, bifurcation lesion, cardiogenic shock, chronic total occlusion, congestive heart failure, failed brachytherapy, graft stenting, in-stent restenosis, large vessel (RVD>3.75), left main disease/stenting, long lesion (>28mm), moderate/severe calcification, multivessel stenting, ostial lesion, renal dysfunction, severe tortuosity, small vessel (RVD<2.5mm); expanded-use cases are not simple-use.

The Endeavor DES System

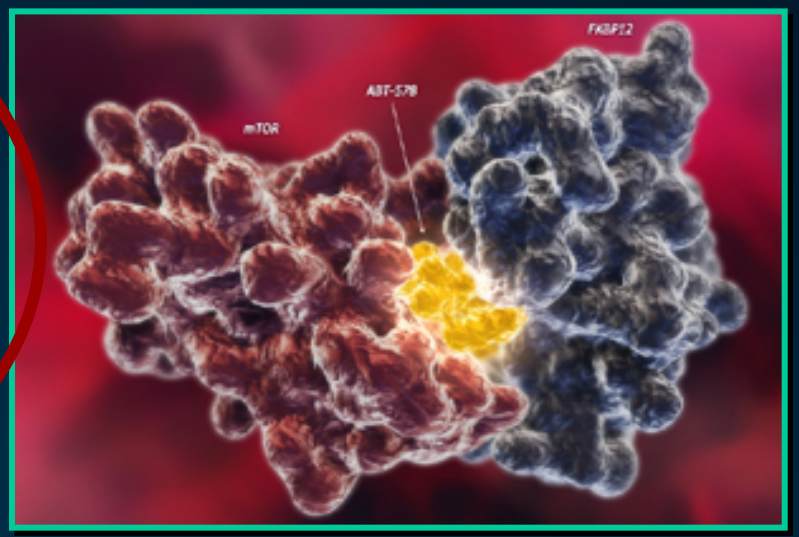
Driver® Cobalt Alloy Stent

Stent Delivery System

PC Technology

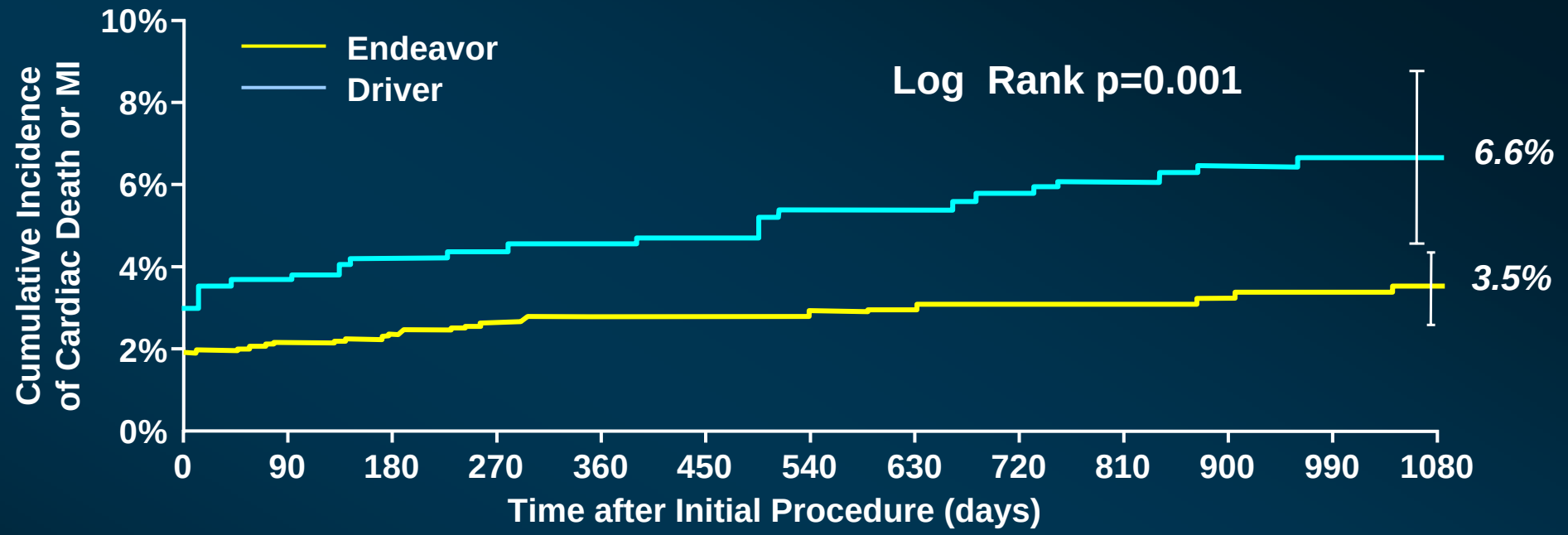


Drug: Zotarolimus



Endeavor Versus Driver

Cumulative Incidence of Cardiac Death and MI to 1080 Days



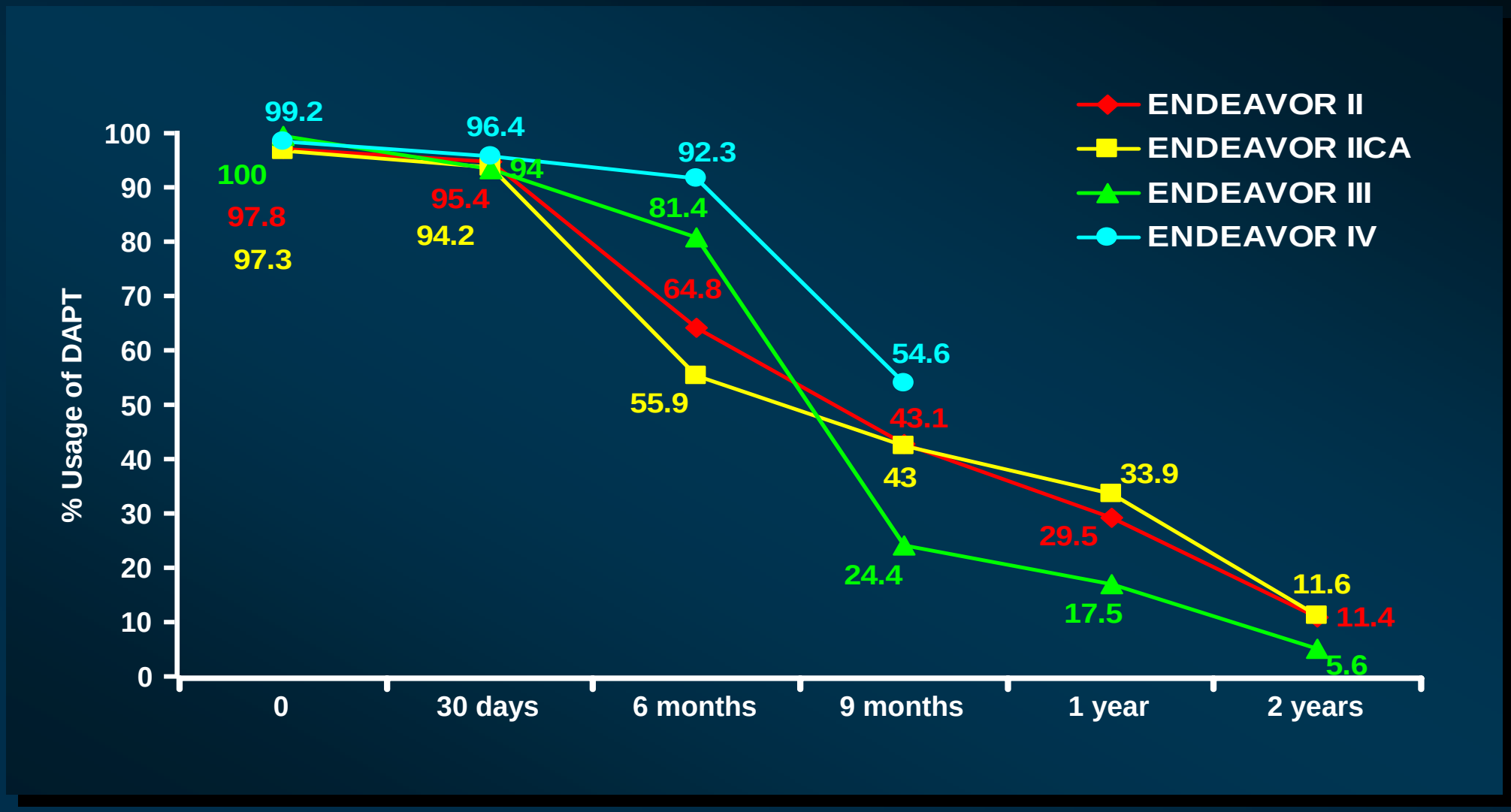
Cardiac Death or MI	0	30	270	360	720	1080
Endeavor	2132	2083	2052	2029	1222	1184
# Events	**30**	**12**	**14**	**4**	**3**	**5**
% CI	**1.4%**	**2.0%**	**2.6%**	**2.8%**	**3.1%**	**3.5%**
Driver	596	573	566	560	545	528
# Events	**15**	**6**	**5**	**1**	**7**	**5**
% CI	**2.5%**	**3.5%**	**4.4%**	**4.5%**	**5.8%**	**6.6%**

ENDEAVOR RCT Summary

	ENDEAVOR II	ENDEAVOR III	ENDEAVOR IV
Control	Driver BMS	Cypher	Taxus
N	E = 598 D = 599	E = 323 C = 113	E = 774 T = 775
Primary Endpoint	TVF (cardiac death, MI, TVR) at 9 months	In-segment late lumen loss by QCA at 8 months	TVF at 9 months
QCA, IVUS Subset	QCA = 600 (44.7%); IVUS = 300	QCA, IVUS = All	QCA, IVUS = 328 (21.2%)
DAPT	≥ 3 months	≥ 3 months	≥ 6 months[1]
Inclusion criteria	Single De Novo Native Coronary Artery Lesions Pre-dilatation required		
	Diameters: 2.25–3.5 mm Lesion Length: 14–27 mm	Stent Diameters: 2.5–3.5 mm Lesion Length: 14–27 mm	
Key Exclusion Criteria	Left ventricular ejection fraction <30%. Acute MI within 72 hours. Creatinine >2.0 mg/dl. Left main, ostial lesion, or bifurcation lesion		

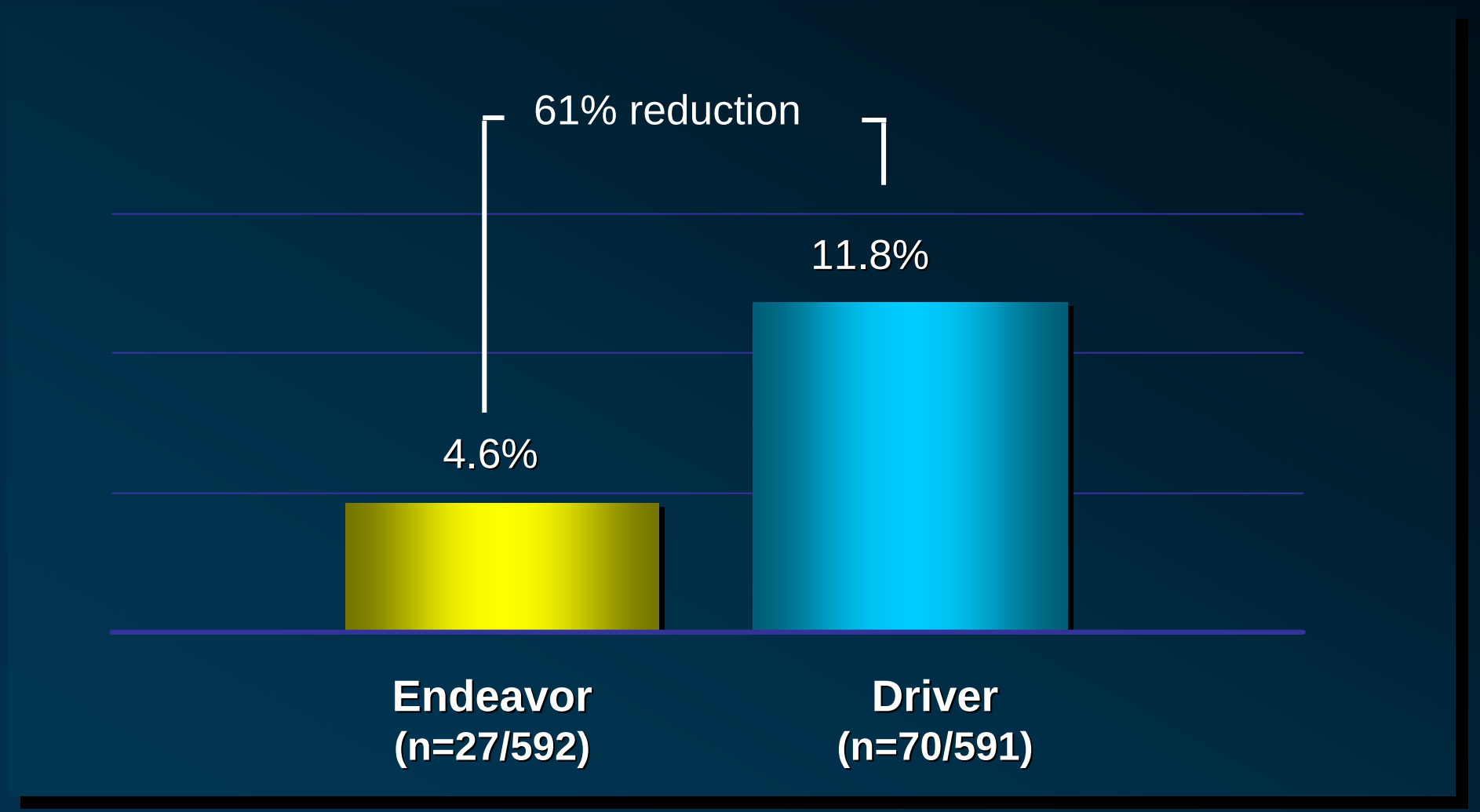
[1] ≥6 month DAPT regimen in EIV due to 1:1 randomization vs. Taxus.

Dual Antiplatelet Therapy Usage
ENDEAVOR Clinical Program

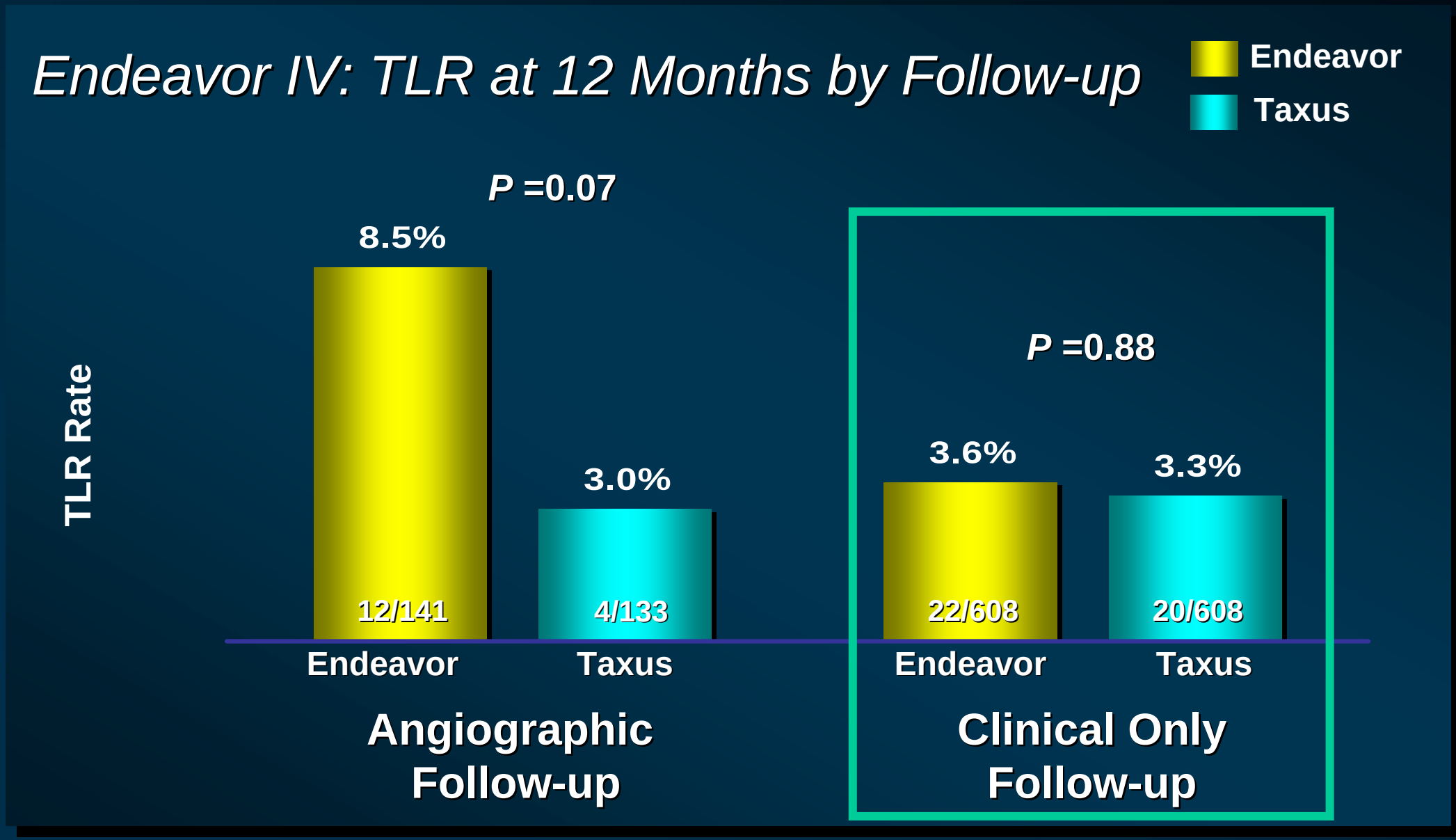


ENDEAVOR II

9-Month Target Lesion Revascularization



What Can be Said about TLR Rates?



ENDEAVOR Clinical Program

Patient Demographics

	EI n = 100	EII n = 598	EII CA n = 296	EIII n = 323	EIV n = 773	EPK n = 43	E2 Driver N = 599
Diabetes (%)	16.0	18.2	25.8	29.7	31.2	41.9	22.2
RVD (mm)	2.96	2.73	2.63	2.75	2.73	2.54	2.76
Lesion Length (mm)	10.94	14.04	16.49	14.96	13.41	15.02	14.38
Recommended Clopidogrel Duration	3m	3m	3m	3m	6m	3m	3m
Clinical F/U							
12m (%)	99	98.7	98.6	99.1	96.9	100	98.3
2y (%)	99	98.2	98.2	96.9			97.8
3y (%)							96.7

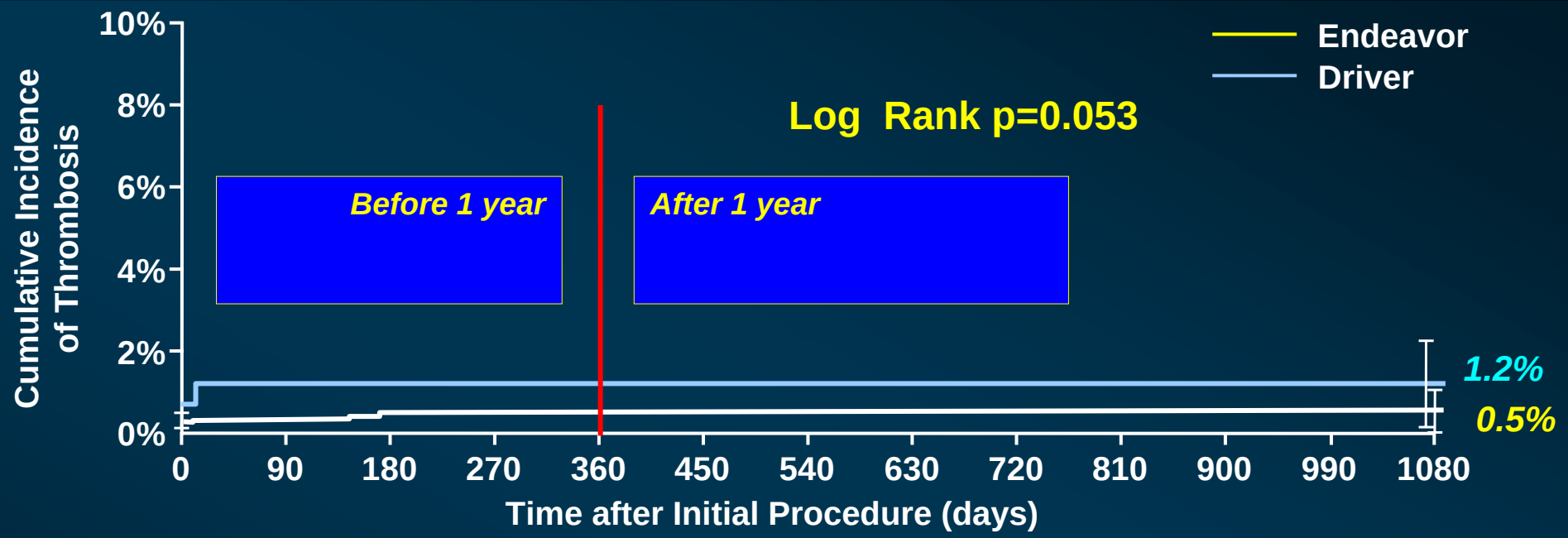
2050 patients followed to 12 months

1287 patients followed to 2 years

1217 patients followed to 3 years

Endeavor Safety Analysis

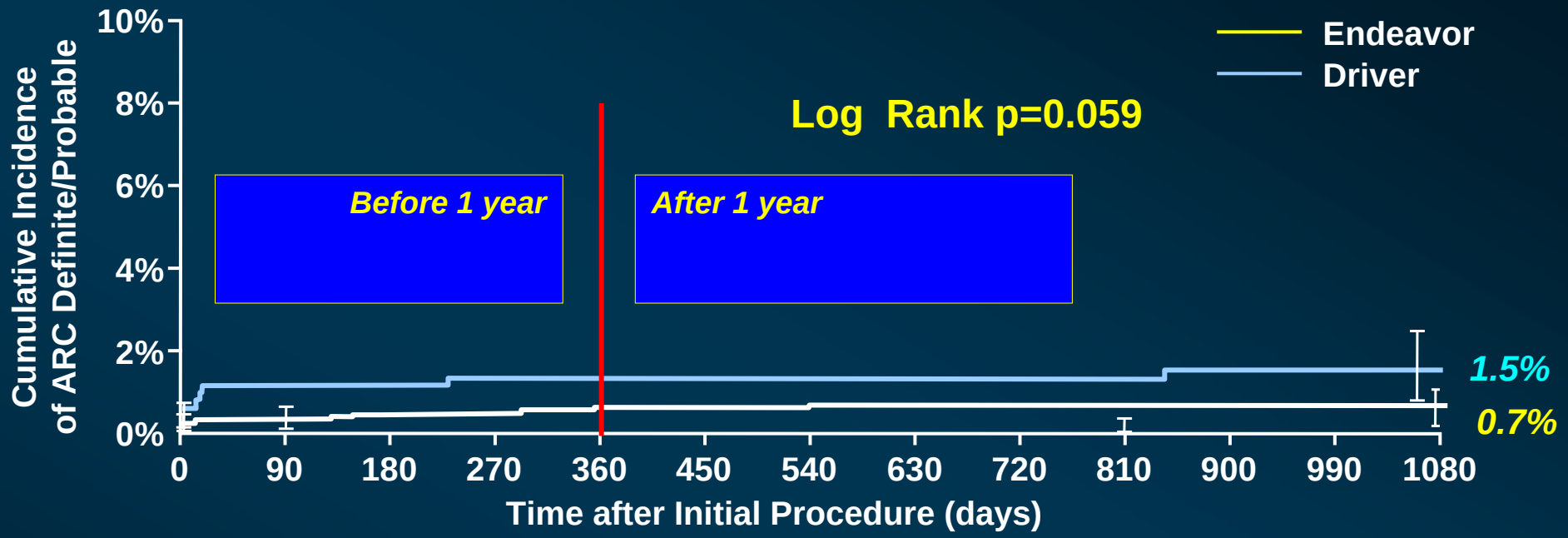
Cumulative Incidence of Stent Thrombosis (Protocol) to 1080 Days



Days	0	30	270	360	720	1080
Endeavor	2132	2117	2086	2065	1252	1214
# Events	**1**	**6**	**3**	**0**	**0**	**0**
% CI	**0.0%**	**0.3%**	**0.5%**	**0.5%**	**0.5%**	**0.5%**
Driver	596	587	581	576	561	544
# Events	**1**	**6**	**0**	**0**	**0**	**0**
% CI	**0.2%**	**1.2%**	**1.2%**	**1.2%**	**1.2%**	**1.2%**

Endeavor Safety Analysis

Cumulative Incidence of ST (ARC Definite /Probable) to 1080 Days



Def/Prob Thrombosis	0	30	270	360	720	1080
Endeavor	2132	2117	2085	2049	1251	1214
# Events	**1**	**6**	**4**	**2**	**1**	**0**
% CI	**0.0%**	**0.3%**	**0.5%**	**0.6%**	**0.7%**	**0.7%**
Driver	596	585	581	575	560	542
# Events	**1**	**6**	**1**	**0**	**0**	**1**
% CI	**0.2%**	**1.2%**	**1.3%**	**1.3%**	**1.3%**	**1.5%**

TAXUS Meta-analysis (N=3,445)

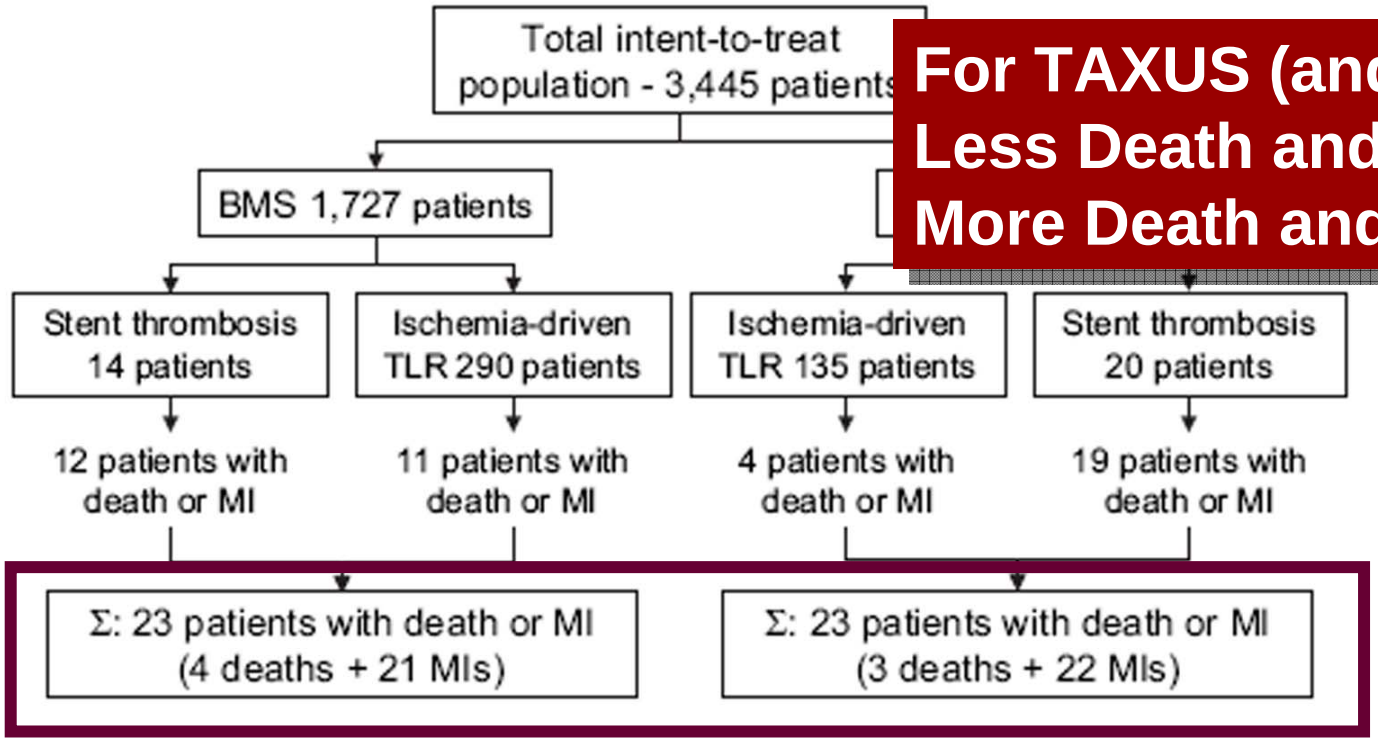


Figure 3. The greater rate of death or non... an excess of ST in the PES group was co... increase in the rate of death or nonfatal M... frequent occurrence of ischemia-driven TL... As a result, death or nonfatal MI within 1 y... either ST or ischemia-driven TLR occurred in 23 patients in both stent groups.

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Less Death and MI due to less TLR
More Death and MI due to VLST

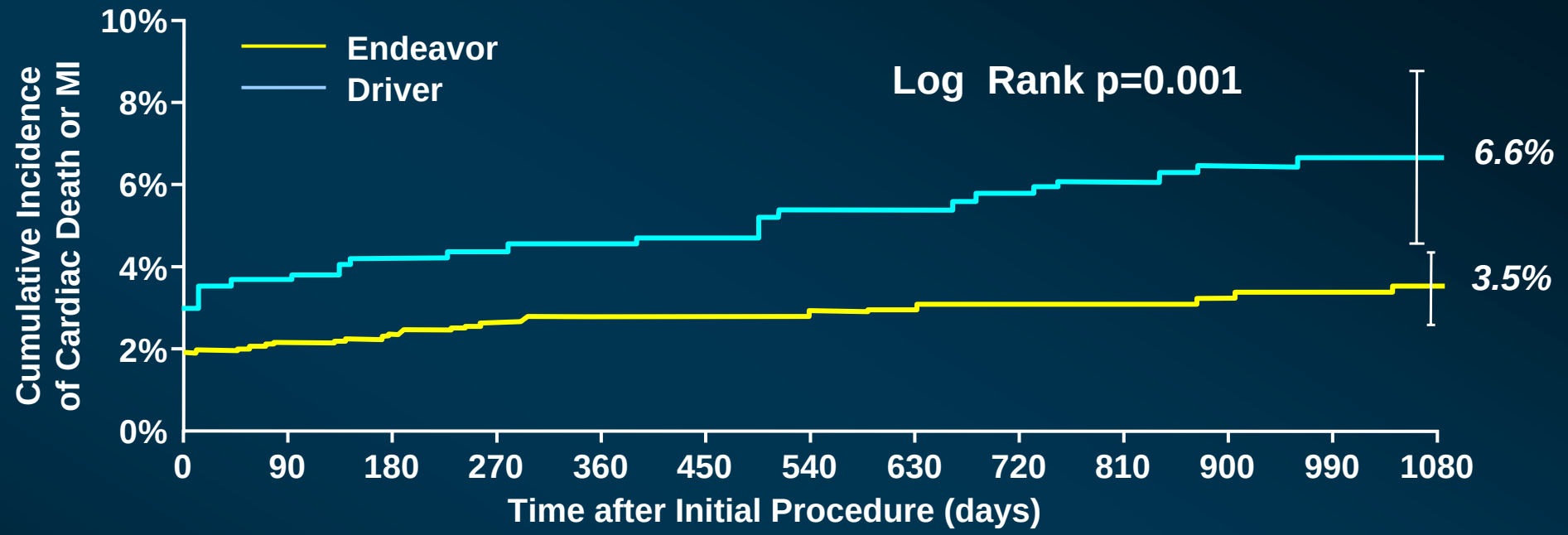
Similar Rates of Late Death and MI at 3.2 yrs

For Endeavor
Less Death and MI due to less TLR
~~**More Death and MI due to VLST**~~

Stone GW Circulation 2007;115:2842

Endeavor Versus Driver

Cumulative Incidence of Cardiac Death and MI to 1080 Days



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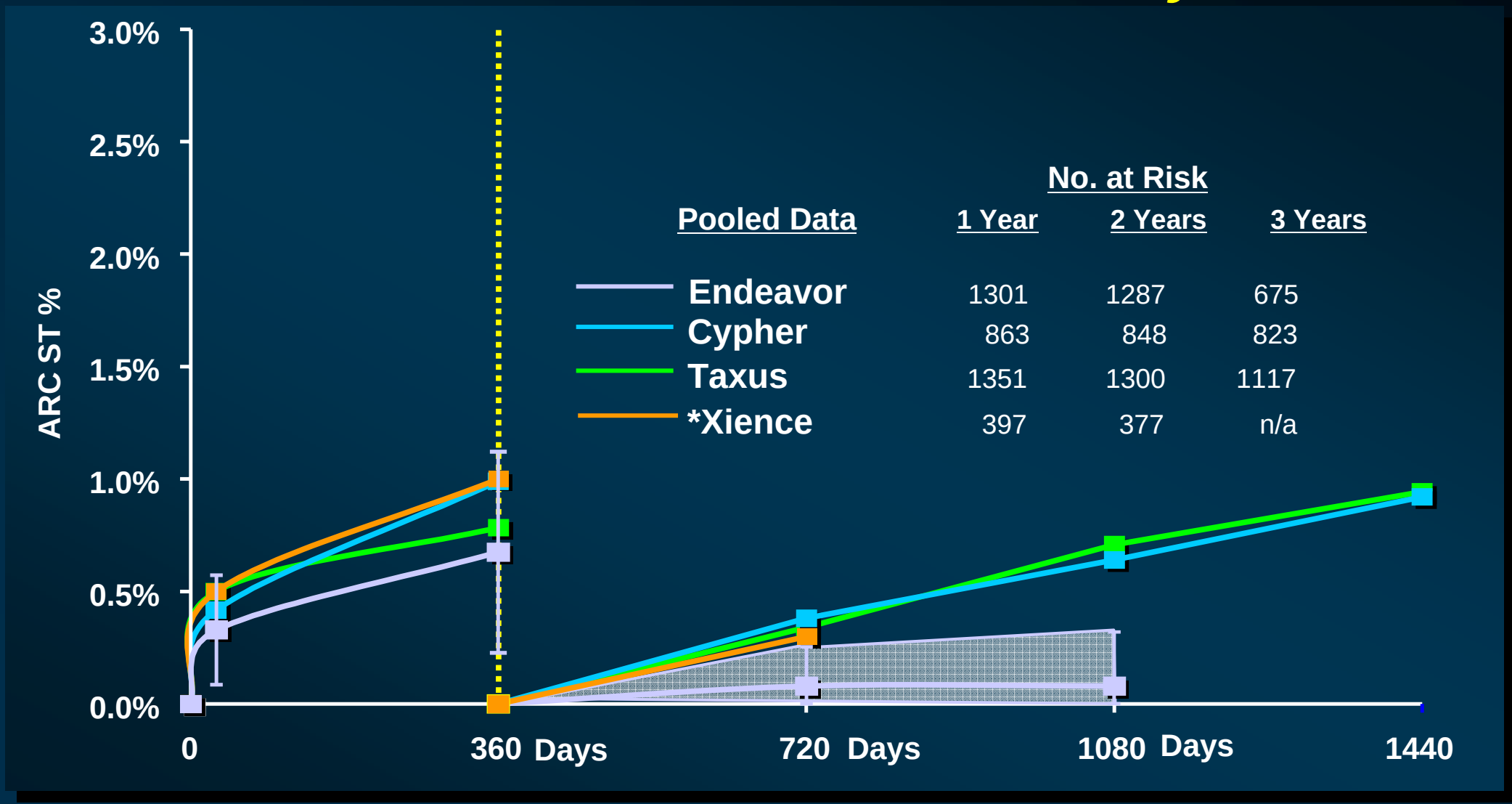
Endeavor	2132	2083	2052	2029	1222	1184
# Events	**30**	**12**	**14**	**4**	**3**	**5**
% CI	**1.4%**	**2.0%**	**2.6%**	**2.8%**	**3.1%**	**3.5%**
Driver	596	573	566	560	545	528
# Events	**15**	**6**	**5**	**1**	**7**	**5**
% CI	**2.5%**	**3.5%**	**4.4%**	**4.5%**	**5.8%**	**6.6%**

DES In Perspective

ARC Definite and Probable to 3 years



Mauri et al. N Engl J Med 2007;356:1020-9; Endeavor: Mauri et al. TCT. 2007; Xience: FDA Panel Meeting Nov. 29, 2007; *Represents “SPIRIT II and III 2-year Complete Analysis” from Panel

Changing Long-Term Outcomes

- Watch for “late” restenosis
- Non TLR natural progression events may impact on our interpretation of safety, i.e., probable VLST and TVR → MACE
- DES reduce restenosis – but the answer in changing the net balance in death+MI is dependent on eliminating VLST and reducing the requirements for DAP
- Aggressive secondary prevention is essential