From Clinical Trials to Clinical Practice

How and When Does DES Safety Influence Clinical Decision Making?

David E. Kandzari, MD
Director, Interventional Cardiology Research
Scripps Clinic
La Jolla, California
kandzari.david@scrippshealth.org

Endeavor in Perspective

1. What are the lessons learned about DES in general, and Endeavor specifically, from 2006 to today?

2. What are the most recent Endeavor safety (and efficacy) data?

3. How should our interpretation of Endeavor evidence guide our clinical decision making?

4. What are the present challenges and barriers to PCI? What are the opportunities for iterative improvement or development for ZES?

Endeavor in Perspective

1. What are the lessons learned about DES in general, and Endeavor specifically, from 2006 to today?
2. What are the most recent Endeavor safety and efficacy data?
3. How should our interpretation of Endeavor evidence guide our clinical decision making?
4. What are the present challenges and barriers to PCI? What are the opportunities for iterative improvement or development for ZES?

What Do We Know About DES in 2009?

- Profound, durable reduction in need for repeat revascularization
- From RCTs, no overall differences in D/MI/ST, now entering 6th year of follow-up
- Possibly lower MI and death compared with bare metal stents
- 'Off Label' does not mean 'Unstudied'

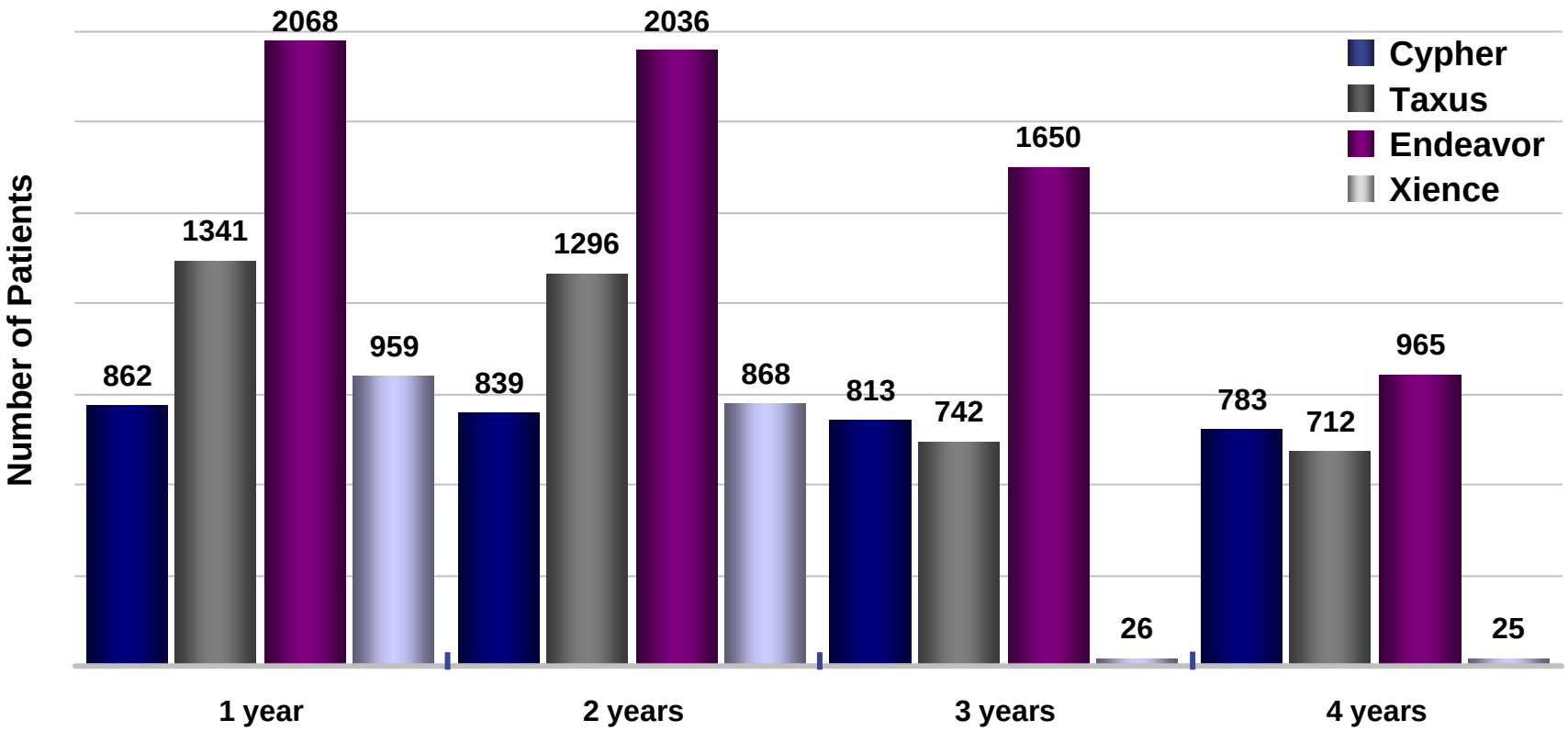
  Majority of data support no difference in off-label safety metrics between DES and BMS

- Emerging differences in efficacy and safety endpoints between DES, no 'class effect'

Lessons Learned From PCI Trials
DES Example

1. Angiographic Endpoints Alone are Insufficient
2. There is not one ‘end all, be all’ trial
3. Avoid indirect, cross trial comparisons—randomized trials represent best opportunity for comparison, but what is standard of comparison?
4. Look for consistency and patterns across trial designs
5. When low frequency and late-occurring events are of interest, there is no substitute for large trials, diverse patient populations and long-term follow-up

Approved DES Key Clinical Trials



Cypher® DES, Taxus DES: Data from trials included in pooled analyses. Kirtane AJ *et al*. TCT. 2007.
Endeavor DES: Mauri TCT 2008
Xience ® DES: SPIRIT FIRST: Windecker S *et al*. EuroPCR. 2008. SPIRIT II: Serruys PW, *et al*. ACC.08.
SPIRIT III: Stone GW, *et al*. EuroPCR. 2008.

Endeavor in Perspective

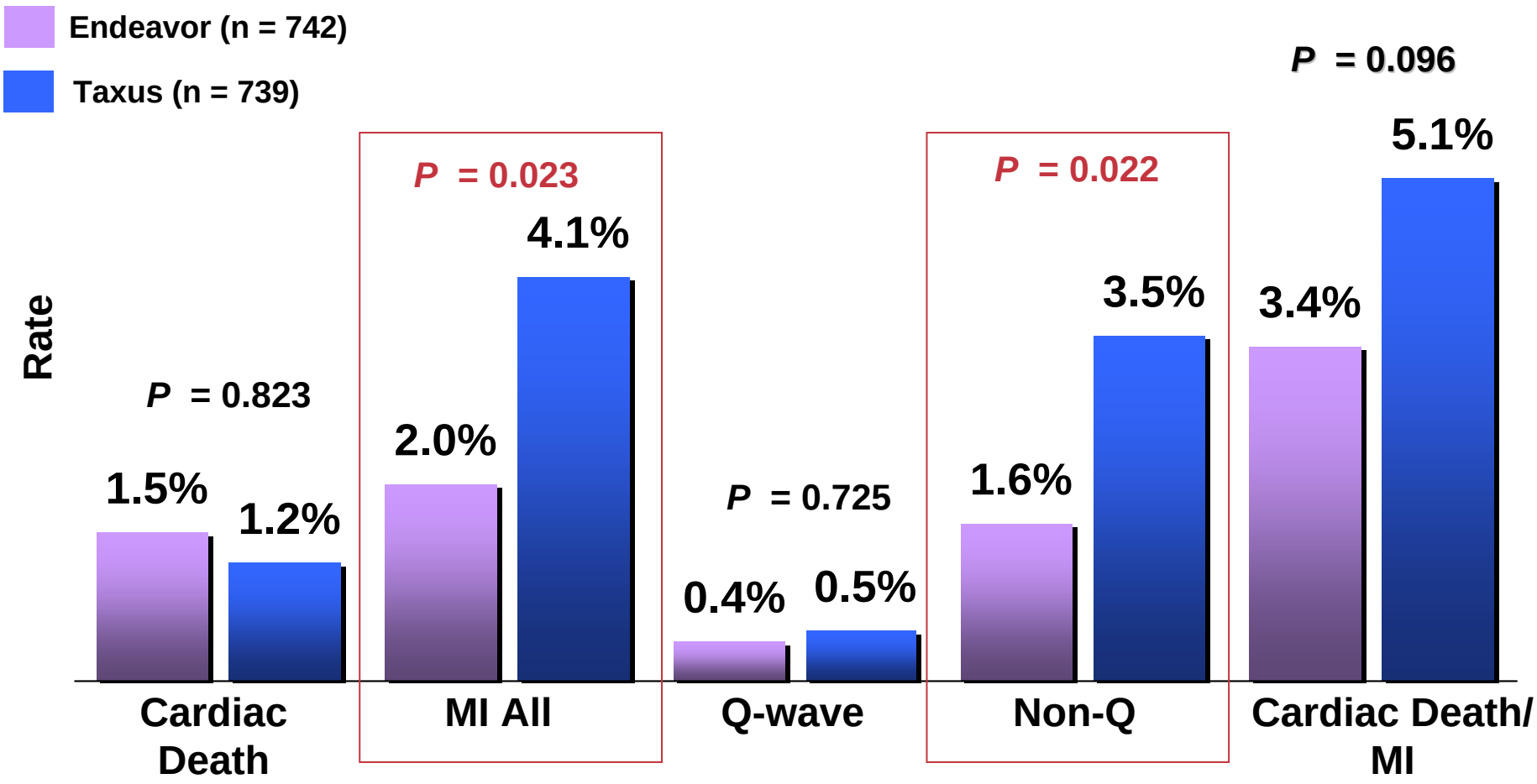
1. What are the lessons learned about DES in general, and Endeavor specifically, from 2006 to today?

2. What are the most recent Endeavor safety (and efficacy) data?

3. How should our interpretation of Endeavor evidence guide our clinical decision making?

4. What are the present challenges and barriers to PCI? What are the opportunities for iterative improvement or development for Endeavor?

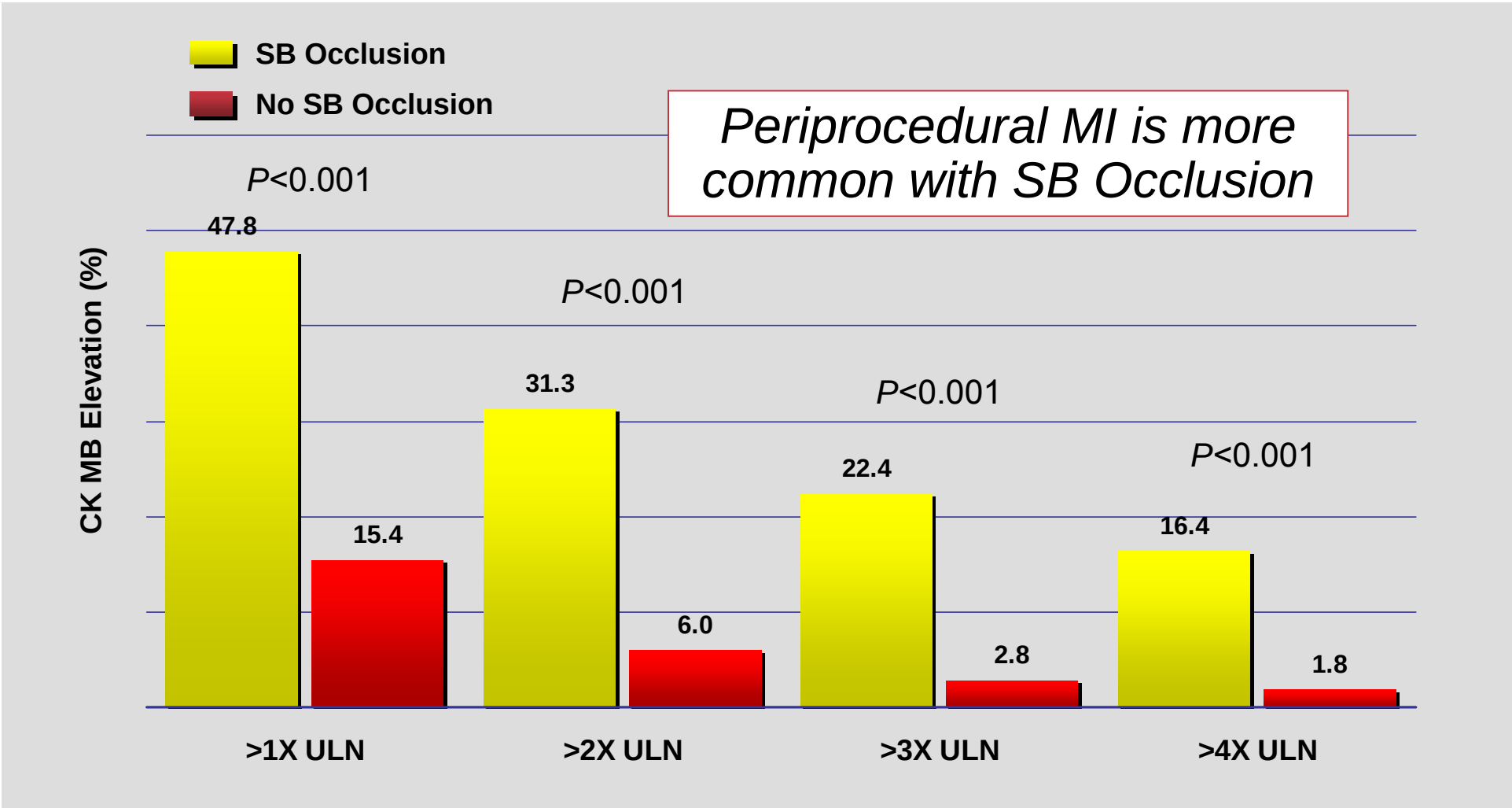
ENDEAVOR IV
Safety Clinical Endpoints at 24 Months



Leon et al. TCT 2008

Frequency and Implications of Sidebranch Occlusion

Periprocedural MI and Relationship with Sidebranch Occlusion



Popma, J. J. et al. Circ Cardiovasc Intervent 2009;2:133-139

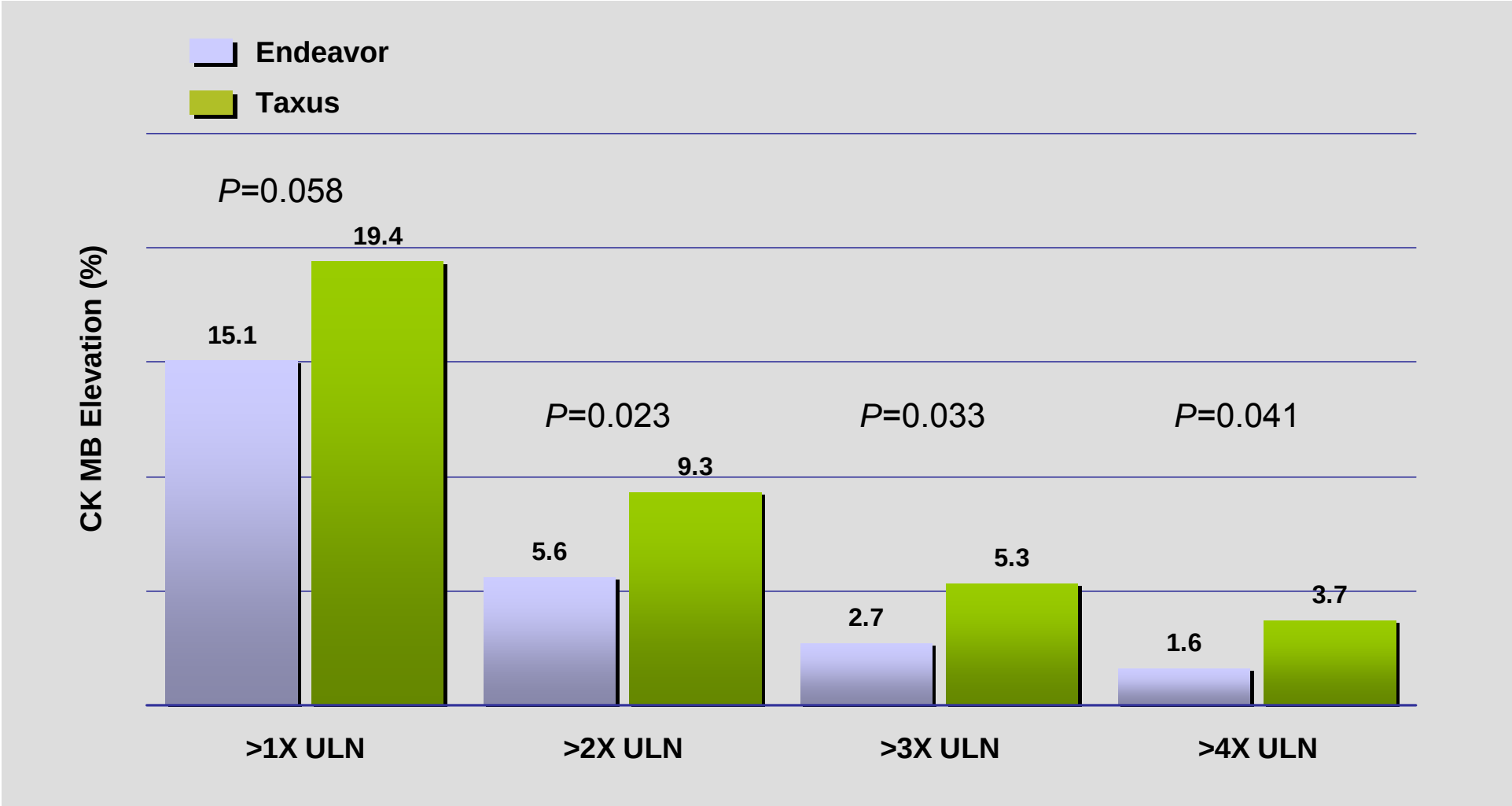
Periprocedural MI and Relationship with Sidebranch Occlusion

- Sidebranch occlusion was significantly less common following first stent implantation with ZES vs PES
  - 2.2% vs 4.0%, *P*=0.032
- Any sidebranch occlusion was significantly less common at end of index procedure with ZES vs PES
  - 2.9% vs 4.8%, *P*=0.042

Popma, J. J. et al. Circ Cardiovasc Intervent 2009;2:133-139

Frequency and Implications of Sidebranch Occlusion

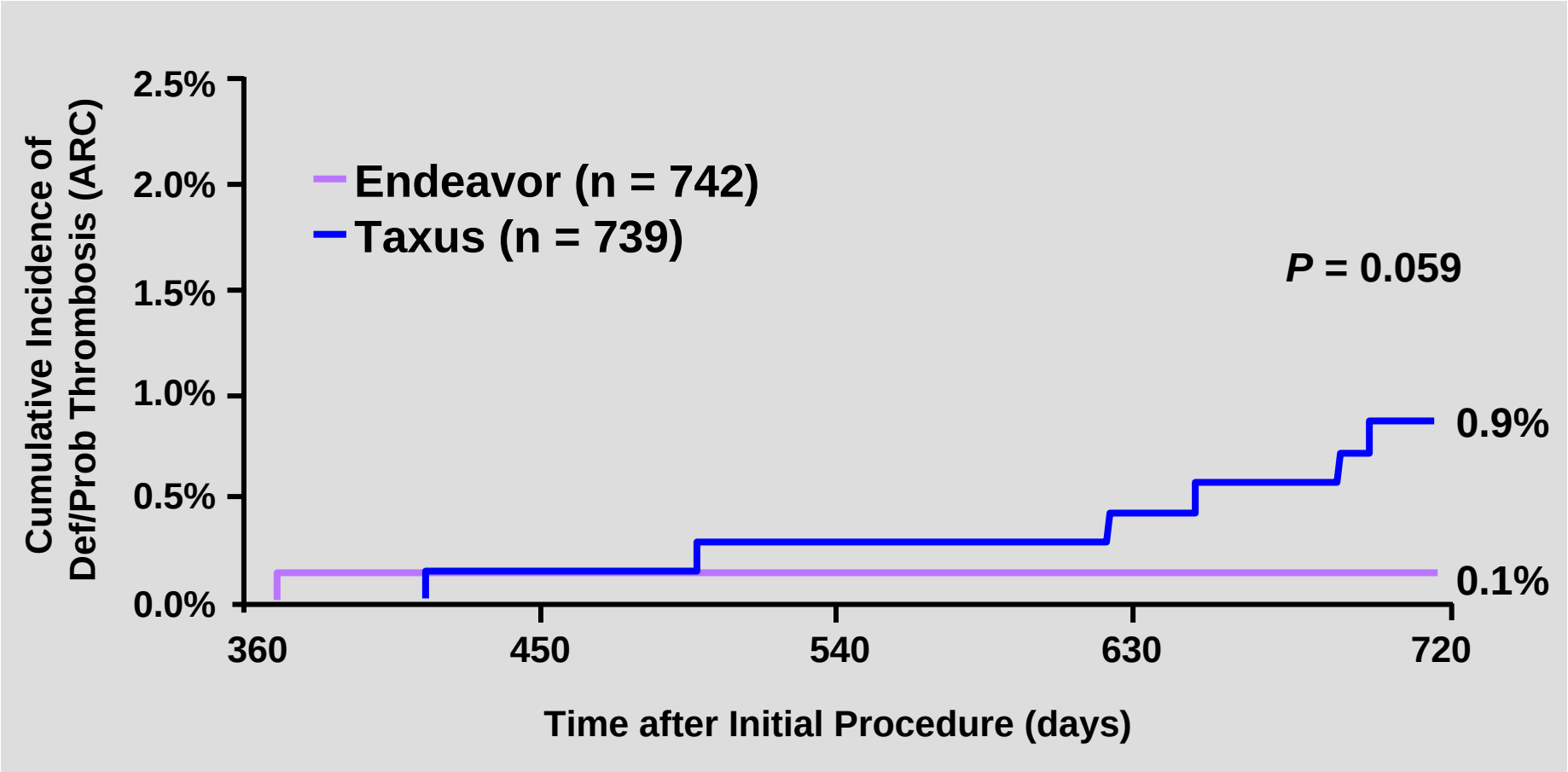
Periprocedural MI and Relationship with Sidebranch Occlusion



Popma, J. J. et al. Circ Cardiovasc Intervent 2009;2:133-139

ENDEAVOR IV

ARC Definite/Probable VLST Δ1-2 years



Clopidogrel adherence at 24 months 71.3% Taxus vs 65.5% Endeavor, *P*= 0.022

Leon et al. TCT 2008

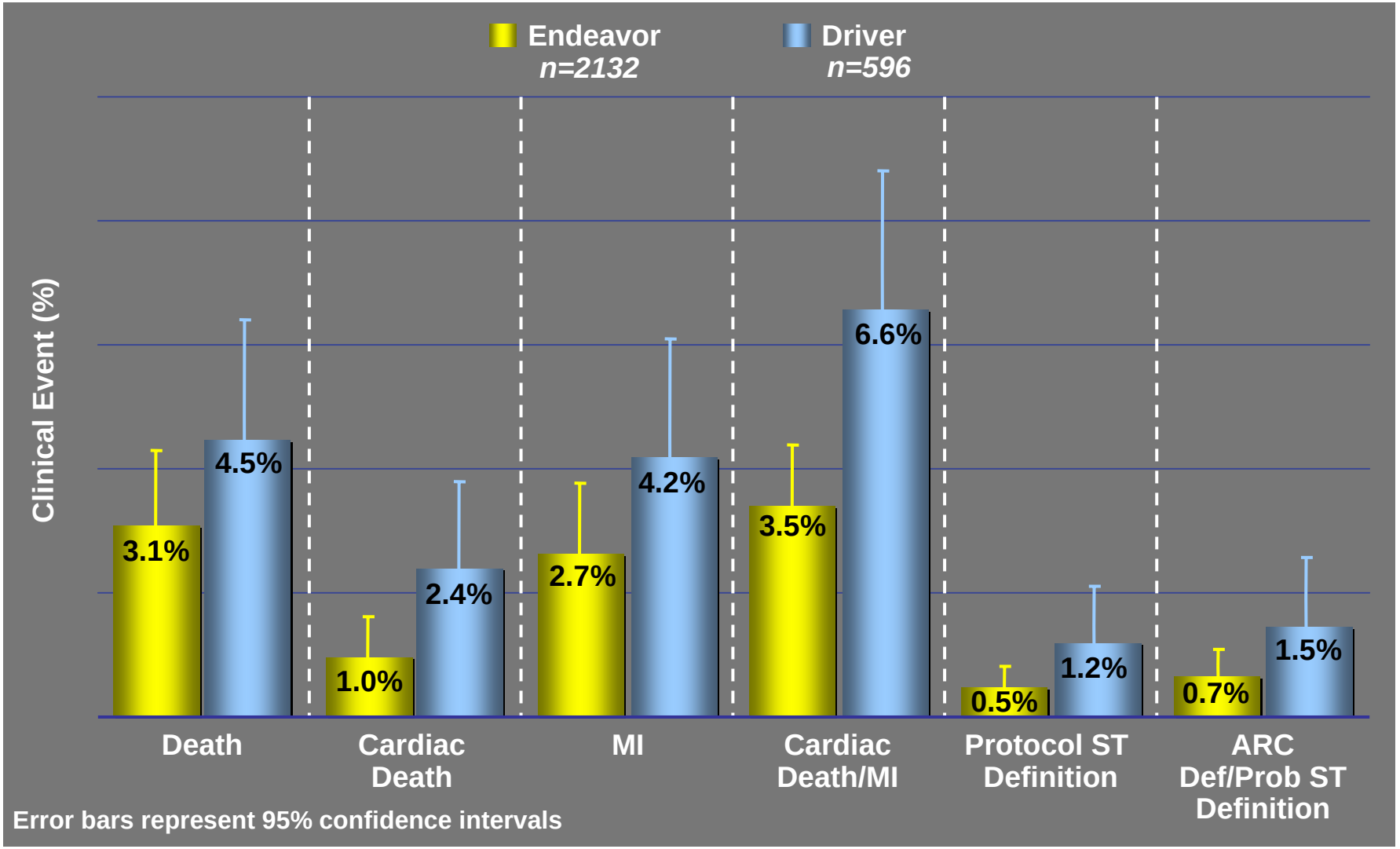
ENDEAVOR IV Stent Thrombosis

Timing of ARC Definite/Probable VLST and DAPT

DES	Definite/ Probable	Time (Days)	Clinical Event	DAPT at event
TAXUS	Definite	413	QMI	ASA Only
TAXUS	Definite	495	NQMI	ASA + Clopidogrel
TAXUS	Definite	619	NQMI	ASA + Clopidogrel
TAXUS	Definite	645	QMI	ASA Only
TAXUS	Definite	689	NQMI	ASA + Clopidogrel
TAXUS	Probable	697	QMI	ASA + Clopidogrel
Endeavor	Definite	369	QMI	None

ENDEAVOR Safety Analysis

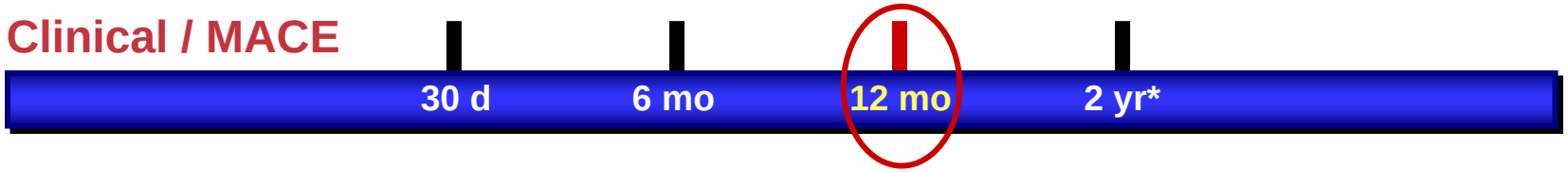
Cumulative Incidence of Safety Endpoints to 1080 Days



E-Five Registry

Single and Multiple Coronary Artery Lesions
Stent Diameters: 2.25-4.0 mm
Stent Length: 8/9-30 mm

N = 8,000 patients
200 sites
Europe, Asia Pacific, Israel,
New Zealand, South America



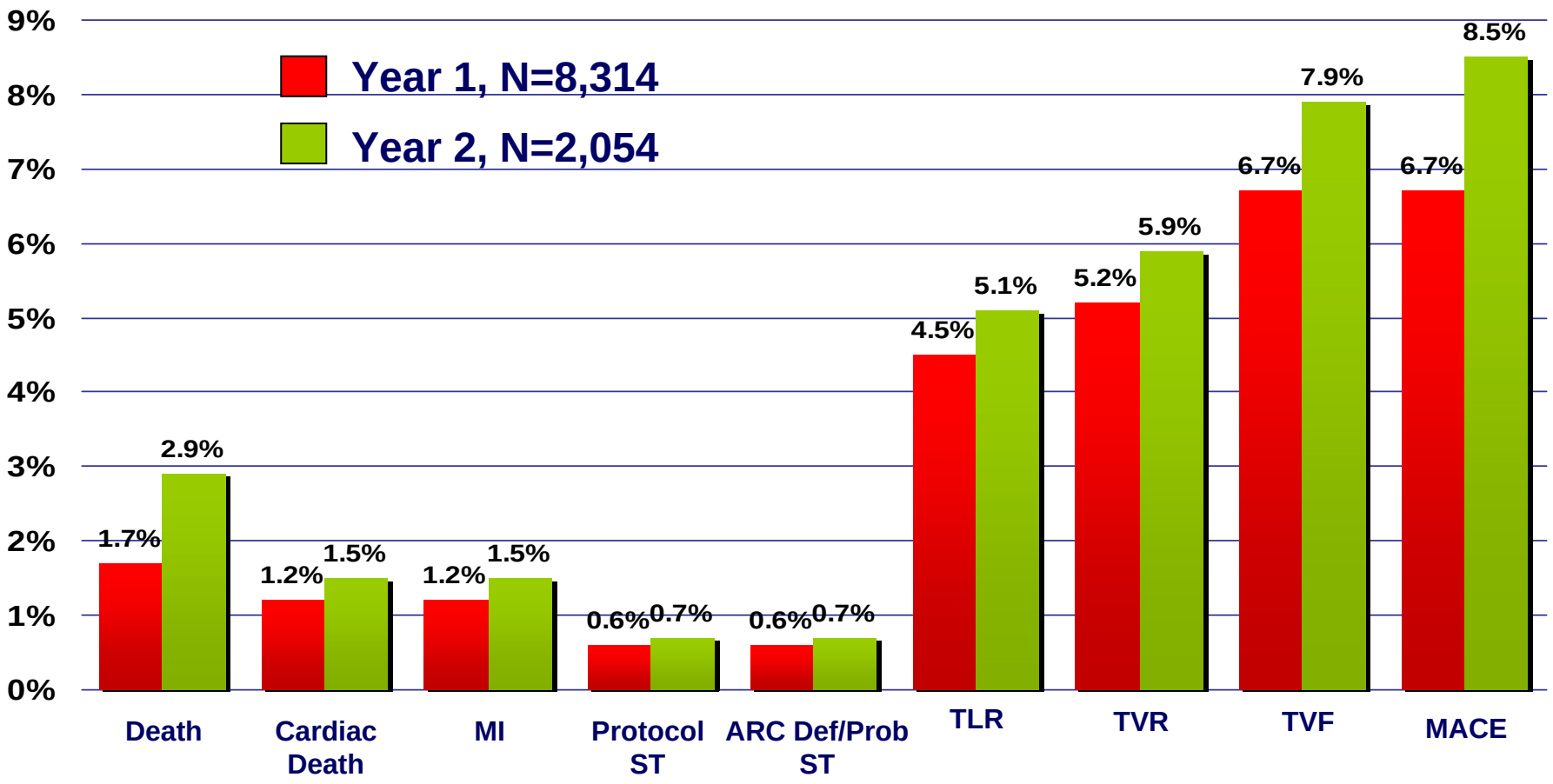
Primary Endpoint: MACE at 12 months

Secondary Endpoints: MACE at 30 days and 6 mo, Stent thrombosis, procedure success rate; device success rate; lesion success rate

Drug Therapy: ASA and Clopidogrel/Ticlid >3 months
Zotarolimus Dose: 10 µg per mm stent length

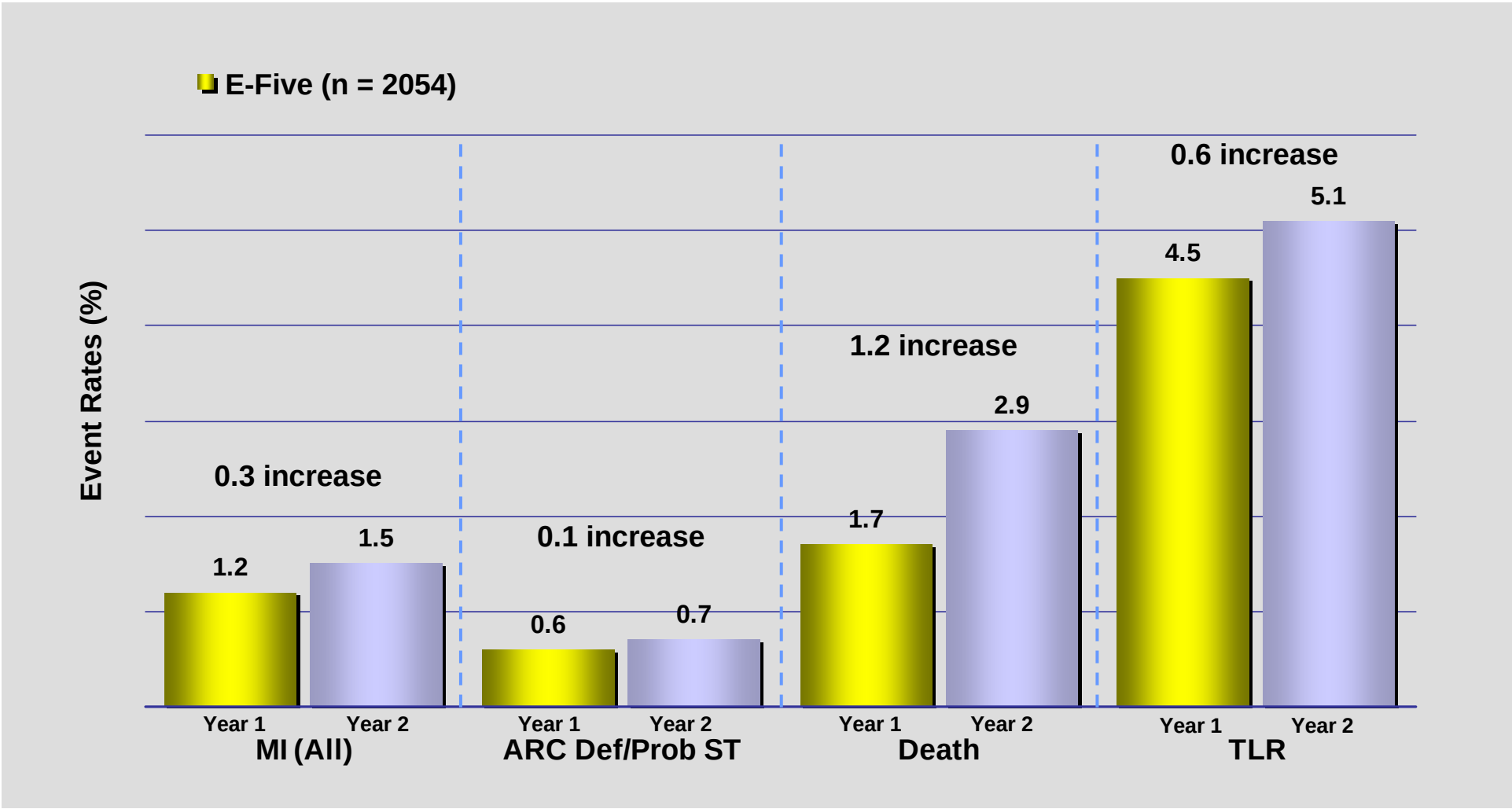
E-Five Registry

Adverse Events at 1 and 2 Years



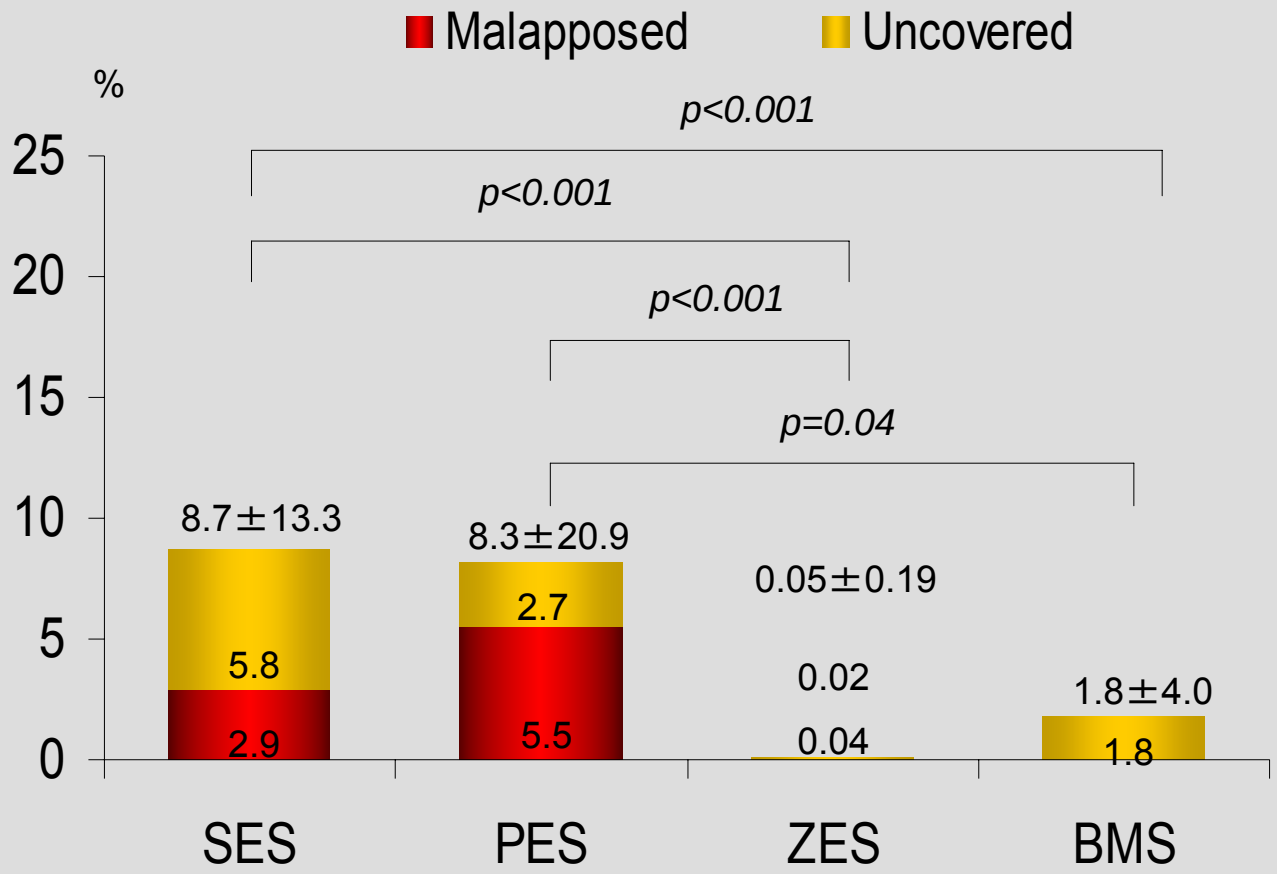
Rothman M. ACC2009

E Five
Prespecified Subgroup Event Rates at 1 vs 2 Years



ODESSA

Overlap Proportion of Uncovered and/or Malapposed Struts by Stent Type



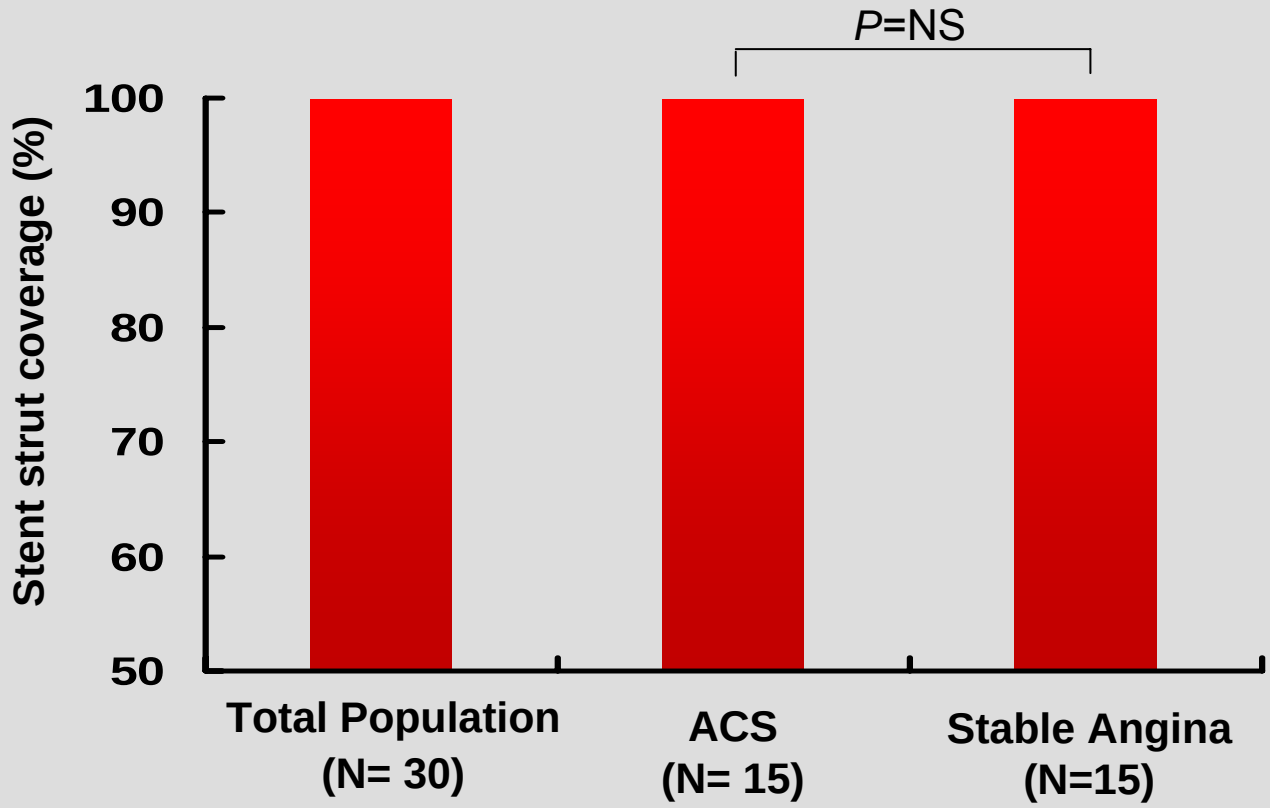
Guagliumi et al. TCT 2008

ENDEAVOR OCT

3 Month OCT Assessment of Strut Coverage in Stable and Unstable Angina

30 patients (20 stents in 15 ACS and 16 stents in 15 SA)

767 mm in stent length including 14017 struts measured every 0.5 mm

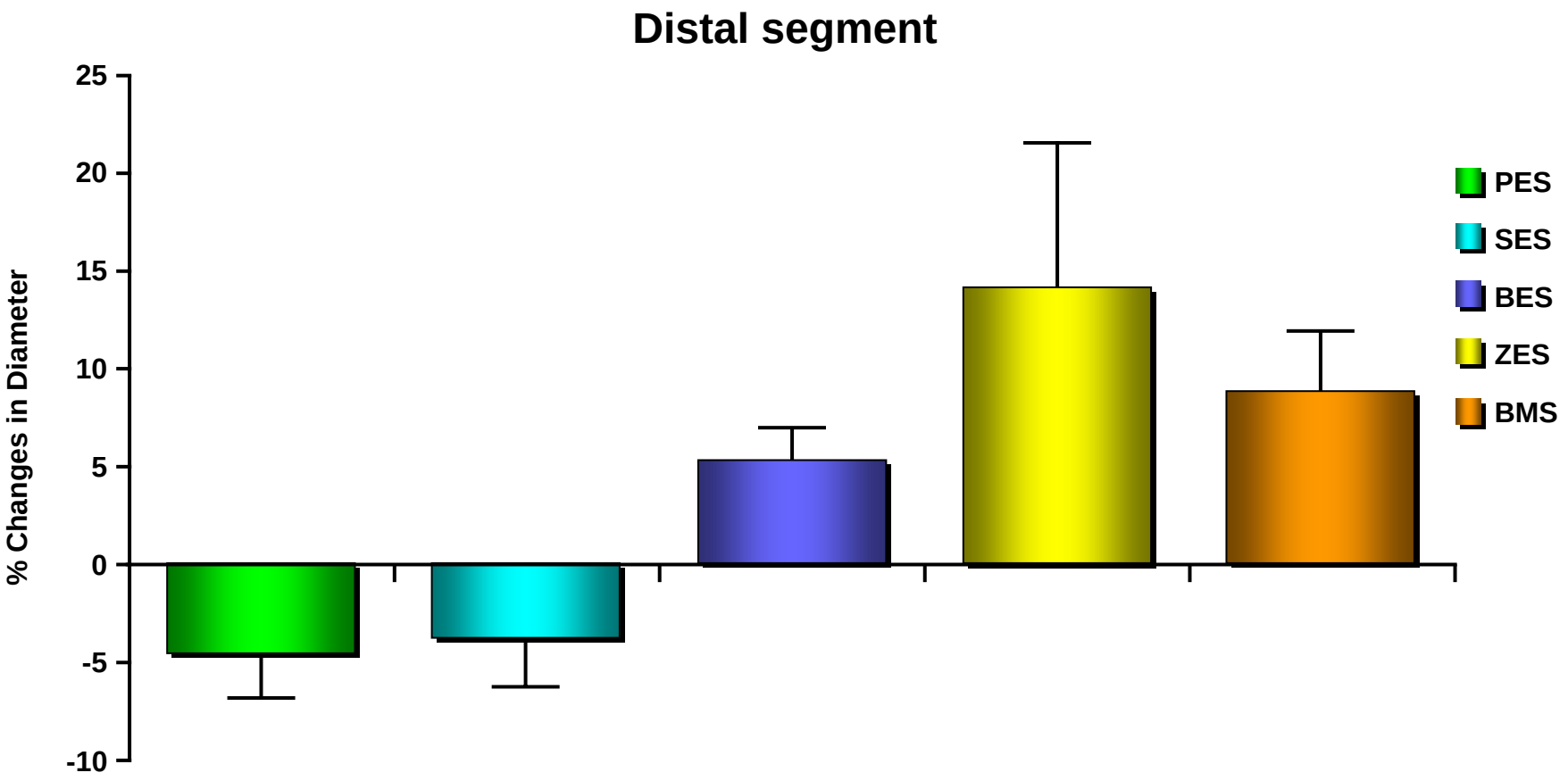


Courtesy, Y. Jang, Yonsei Cardiovascular Center

EC function after DES Implants

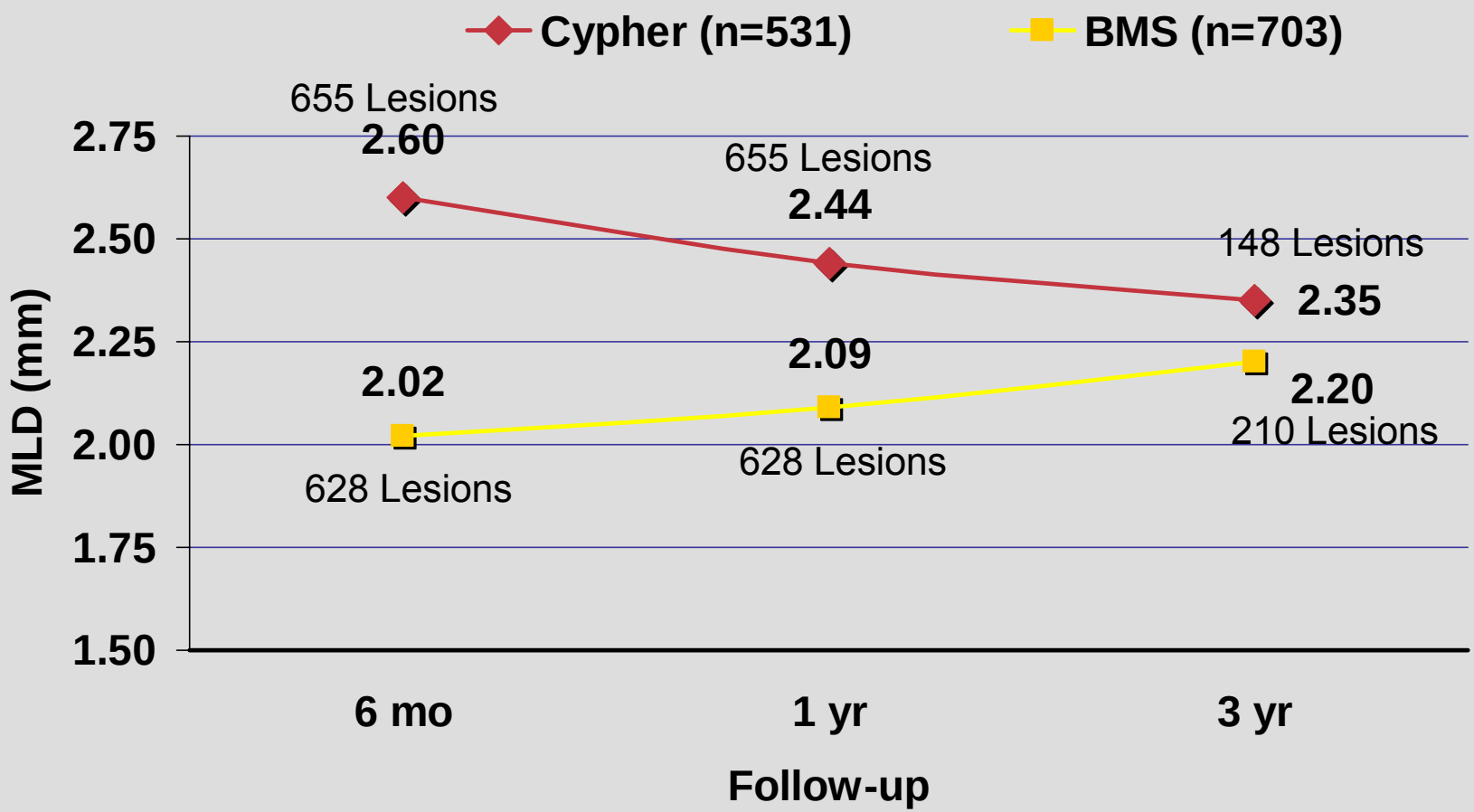
Clinical evaluation of ACH six months post-stenting

Percent changes in mean diameter from baseline (mean±SEM) in all stent groups, at reference distal segment



Hamilos, M. et al. Circ Cardiovasc Intervent. 2008;1:193-200

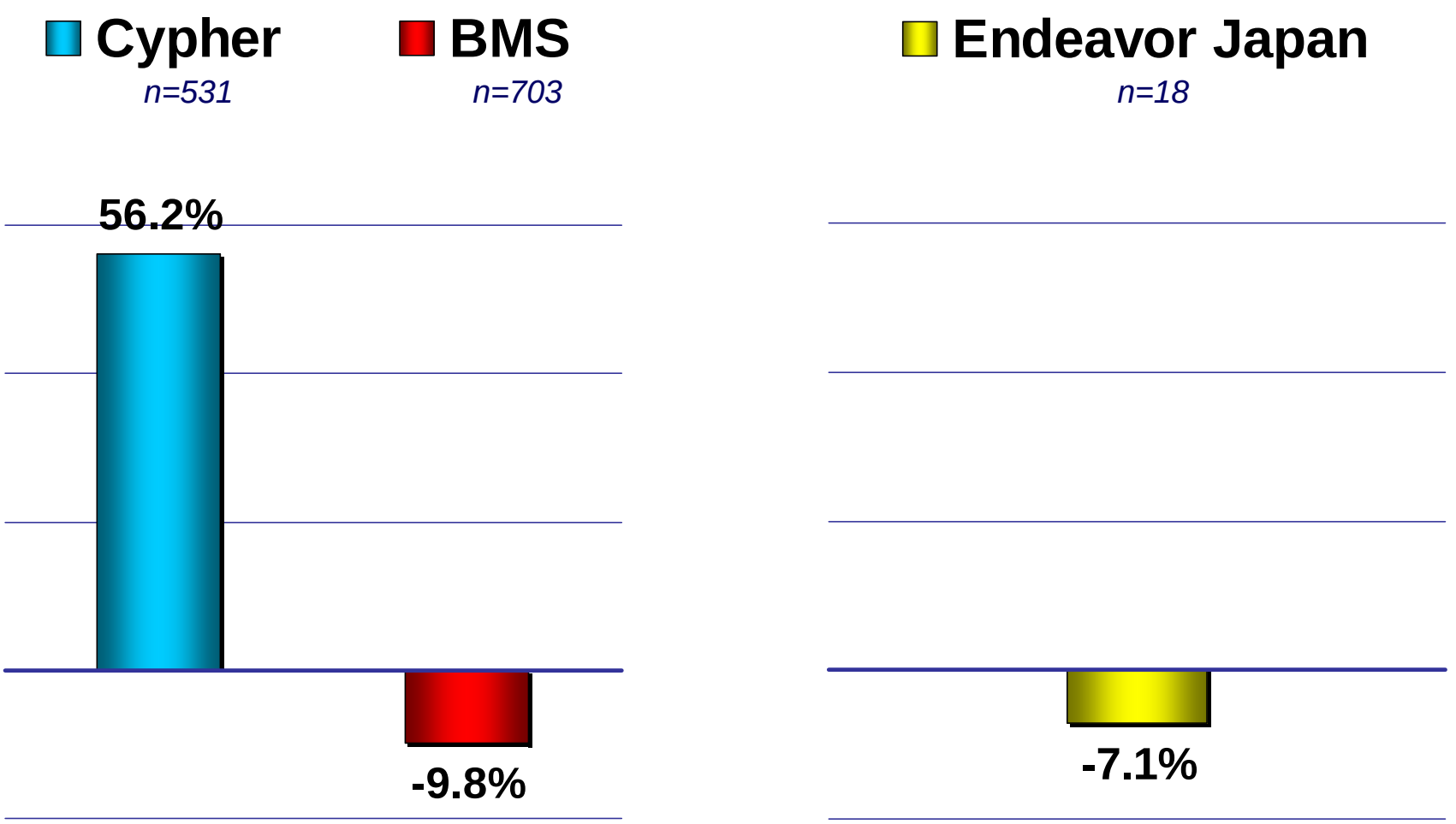
DES Late Loss Progression?
3 Year Angiographic Outcomes



Shiode et. al. Late Progression After Sirolimus-Eluting Stent Implantation: Comparison with Bare Metal Stent Implantation. ACC 2009 Abstract 2501-523/523

Late Loss Regression

Change in Late Lumen Loss between 8 and 24 months

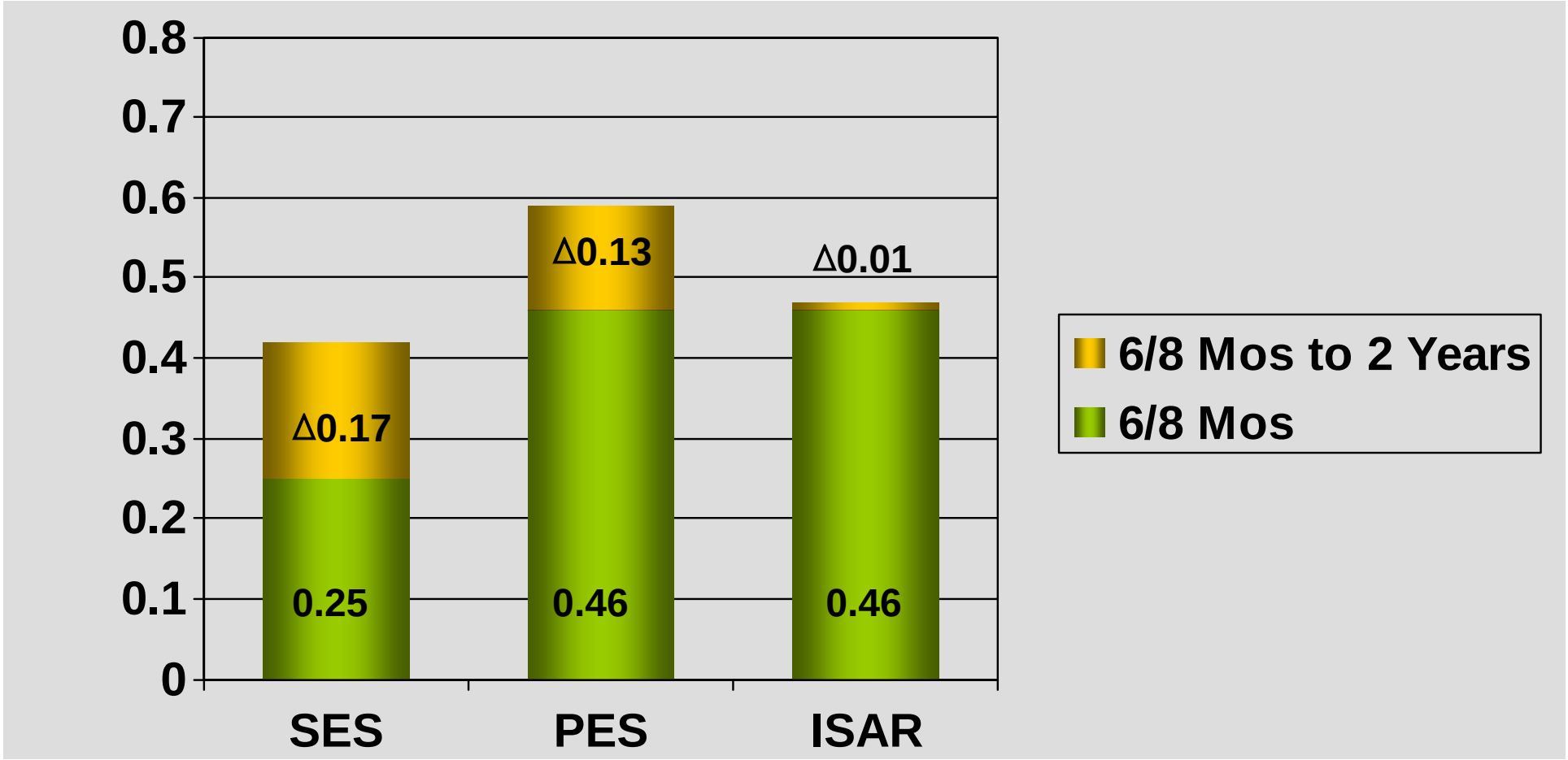


Derived from Shiode et. al. Late Progression After Sirolimus-Eluting Stent Implantation: Comparison with Bare Metal Stent Implantation. ACC 2009 Abstract 2501-523/523

ISAR

Late Term ‘Catch Up’ of Late Lumen Loss and Clinical Restenosis

Angiographic Late Lumen Loss, N=2,030/ 1,331



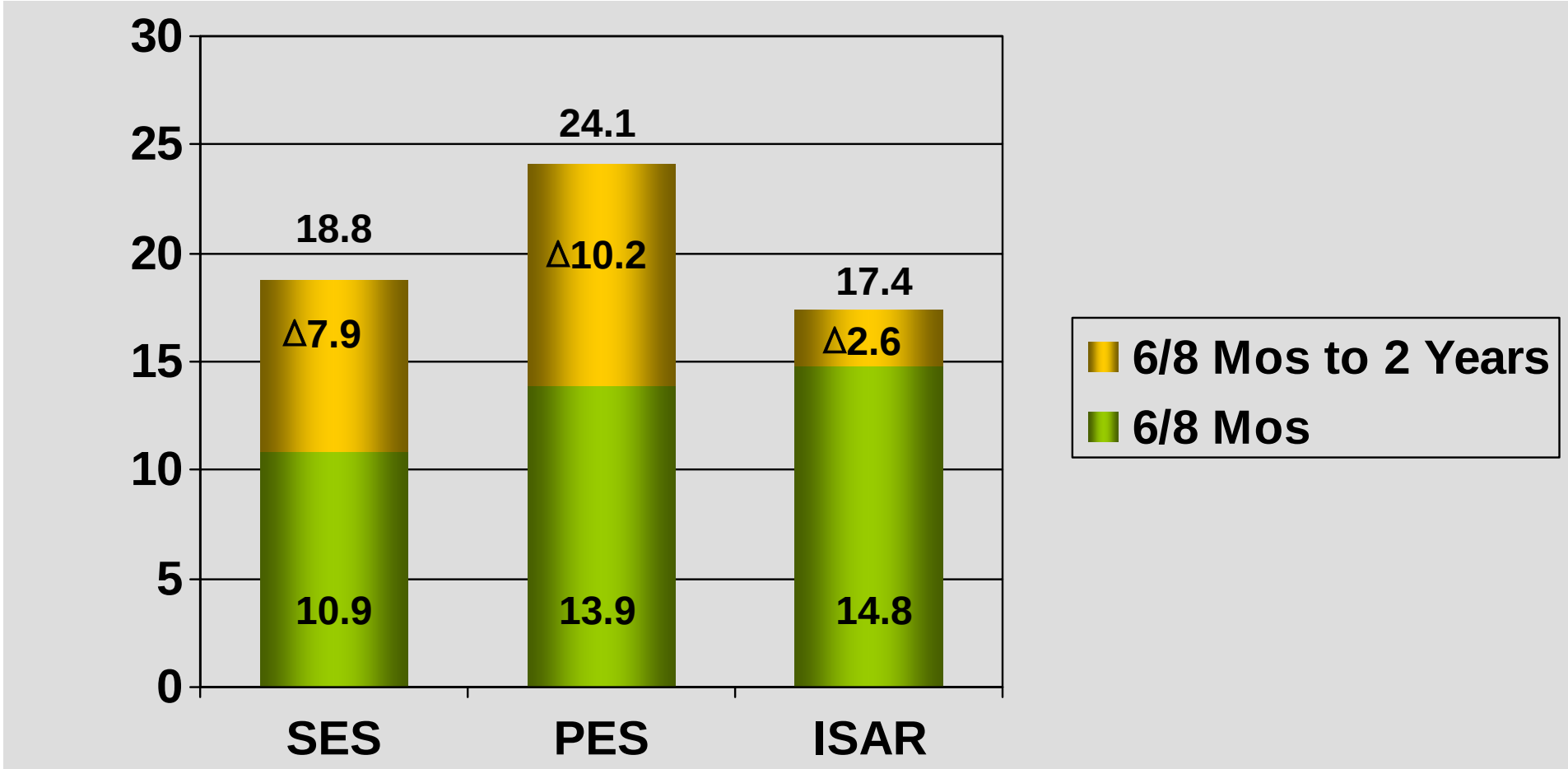
***P*<0.001 for 3-way comparison at 6/8 mos and 2 years**

Byrne RA et al. *J Am Coll Cardiol Cardiovasc Intervent* 2009; 2:291-299.

ISAR

Late Term 'Catch Up' of Late Lumen Loss and Clinical Restenosis

Target Lesion Revascularization, N=2,030/ 1,331



***P*=0.07 for 3-way comparison at 6/8 mos and *P*=0.009 2 years**

Byrne RA et al. *J Am Coll Cardiol Cardiovasc Intervent* 2009; 2:291-299.

Endeavor in Perspective

1. What are the lessons learned about DES in general, and Endeavor specifically, from 2006 to today?

2. What are the most recent Endeavor efficacy data?

3. How should our interpretation of Endeavor evidence guide our clinical decision making?

4. What are the present challenges and barriers to PCI? What are the opportunities for iterative improvement or development for ZES?

Antiplatelet Therapy and DES *2009*

- What is the ‘optimal’ duration of DAPT?
- Is the ‘optimal’ duration same for all DES?
- What are the consequences of brief DAPT interruption?
- Is there a rebound phenomenon with thienopyridine discontinuation?
- Will there be differences between different APT agents in real world practice?
- Is there a role for platelet and/or genomic testing to individualize therapy?

SENS

Outcome of Non-cardiac Surgical Procedure and Brief Interruption of DAPT within 12 Months Following Endeavor Implantation

Purpose

- To examine the safety of Endeavor™ stent (Zotarolimus-eluting stent) associated with non-cardiac surgical procedure and brief interruption of dual anti-platelet agents within 12 months following stent implantation

Method

- A total of 3099 consecutive patients treated with Endeavor™ stent (Zotarolimus-eluting stent; ZES) since January 2006 were retrospectively analyzed in Korean 11 teaching hospitals
- The primary endpoint was the 30-day major adverse cardiac events (MACE) including death, non-fatal myocardial infarction (MI) and target lesion revascularization
- Data collection from retrospective review of medical recordings
  - Consulting record
  - Dental record
  - ER record
  - Endoscopic (Gastro/colono/Broncho-scope) record
  - Phone review
- MI was defined with ≥ 2 of the following 3 criteria
  - Chest pain > 30 mints
  - CK-MB > 2 * upper limit
  - Typical EKG changes
- Major operation: Surgery with high bleeding risk
  - Aorta, Neurosurgery
  - ENT/Abdominopelvic without endoscopy
  - Major tissue detachment

Baseline Characteristics

Characteristics	n (%)
Patients with brief interruption of DAP	194 (6.2)
Age (yrs)/Male	63.5/54.9
Comorbid illness	
Diabetes illness	88 (46.4)
Hypertension	123 (64/1)
Hyperlipidemia	56 (29.1)
Smoking	49 (25.6)
EF (%)	60.1 ± 11.1
ACS at stenting	122 (63.5)
Type of procedure	
Orthopedic/Head and neck	34 (18)
Abdominal	27 (14)
Gynecological/Uro	15 (8)
Vascular	7 (3)
Dental	44 (23)
Ophthalmic	13 (7)
Endoscopy, GI/Broncho	54 (28), 43/11, (23/5)

Cases of MACE

	Early Surgery			Late Surgery
Op Name	**Tracheostomy**	**Wound debridement**	**Aortic-femoral bypass**	**HNR**
Days from stenting to events	28	86	13	334
DAP withdrawal days	7	14	5	3
MACE	Death	Death	MI (LCX)	MI (LCX Os)
Procedural Characteristics				
Stented vessel	LAD	RCA	LAD, LCX	Main to LAD
Stent diameter (mm)	2.75	4.0, 3.5	2.75, 2.5	3.5, 3.3
Stent number	1	2	2	2
Stent length (mm)	24 mm	48 mm	48 mm	35 mm
Technique	Simple	Overlap	Simple	Cross-over
Post-events management			POBA	Medication

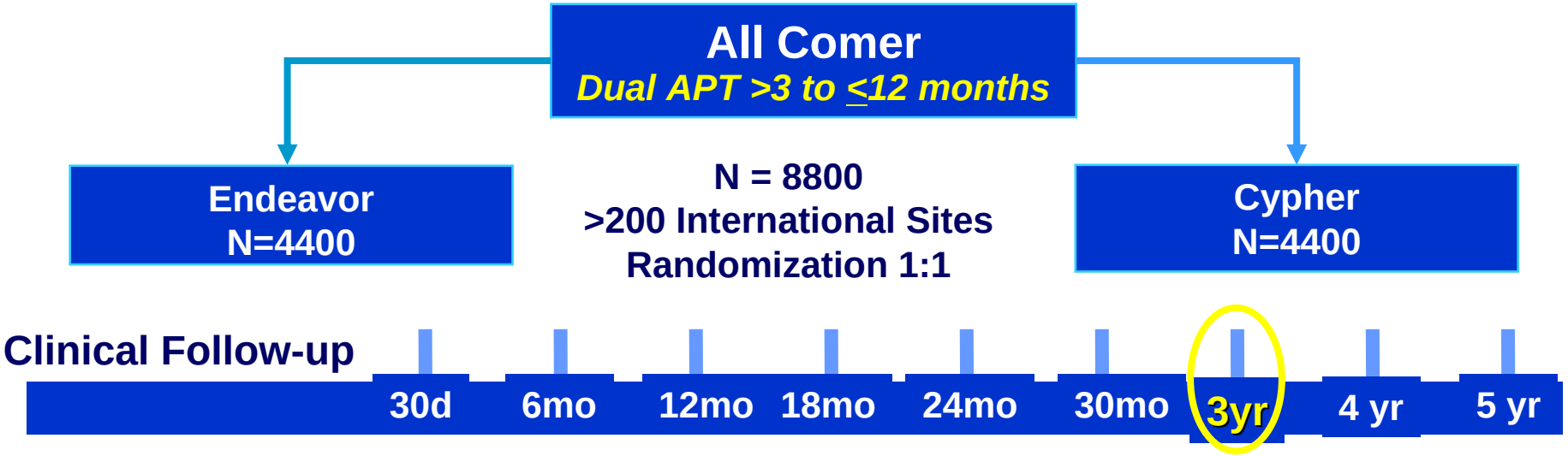
What is the 'Optimal' Trial for the 'Optimal' DAPT Duration?

DAPT durations, inclusion of BMS, landmarking and 'event-free' patients

	Inclusion Group, N	DAPT Duration	DES Type	1° Endpoint	2° Endpoint(s)
DAPT	20,645 12-month event free	12 vs 30 months	All DES	1. D/MI/Stroke at 33 mos 2. Def/prob ST at 33 mos	GUSTO Bleeding
ISAR-SAFE	6,000 6-month event free	6 vs 12 months	All DES	D/MI/Stroke/TIMI major bleed at 15 mos	Individual component endpoints
REAL-LATE	2,000 12-month event free	12 vs 24 months	All DES	2-yr Cardiac D/MI	ARC ST, Bleeding
ZEST-LATE	2,000 12-month event free	12 vs 24 months	SES, PES, ZES	2-yr D/MI	ARC ST, Bleeding
OPTIMIZE	3,120 non-STEMI	3 vs. 12 months	Endeavor ZES	1-yr D/MI/Stroke/TIMI major bleed	ARC ST
SEASIDE	900 non-ACS	6 months	Endeavor ZES	1-yr D/MI/Stroke	GUSTO Bleeding

PROTECT

International RCT Designed to Estimate VLST (>1 year)



Primary Endpoint: ARC Definite or Probable Stent Thrombosis at 3 years

Principal Secondary Endpoints: Death/Non-Fatal MI, Cardiac death/Non-Fatal MI

Additional Endpoints: MACCE, TLR, TVR, Procedural Success

Clinical Follow up and Dual Antiplatelet Monitoring:

At 30 days, and every 6 months until 3 years, than each year until 5 years

Endeavor in Perspective
Summary

- As attention to late-term outcomes is increasingly more common, Endeavor results are distinguished by safety and highlight potentially unique durability in efficacy
  - Late-term (2-4 years) efficacy at least as comparable with alternative DES
  - Consistency in TLR results in subgroup analyses and real-world clinical practice
  - Biocompatibility supported by mechanistic studies
  - Unparalleled safety across clinical trial designs and indications
- Trials should not simply focus on device approval or product labeling but also inform current clinical practice
  - ENDEAVOR V, Investigator Initiated Studies: DAPT duration, 'real world' efficacy and safety
  - PROTECT: DAPT durations, late and very late ST