Endeavor-Combining Safety with Efficacy

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RESTENOSIS

- Primary limiting factor in long term vessel patency
- Time course variable
  - In ~ 30% of patients within 9 months after procedure
    - Median at 3 months
    - Reported to occur up to 7 years after procedure with a rate of 1 – 2% per year = as for progression of disease
- Poor understanding of cause
  - Predictors only explain 20 – 30% of restenosis
- Accounts for significant
  - Morbidity
  - Health care expenditures


Deliverability
Efficacy
Safety

DES - OPTIMAL SAFETY – EFFICACY BALANCE

Incomplete vascular healing
+
Endothelial dysfunction

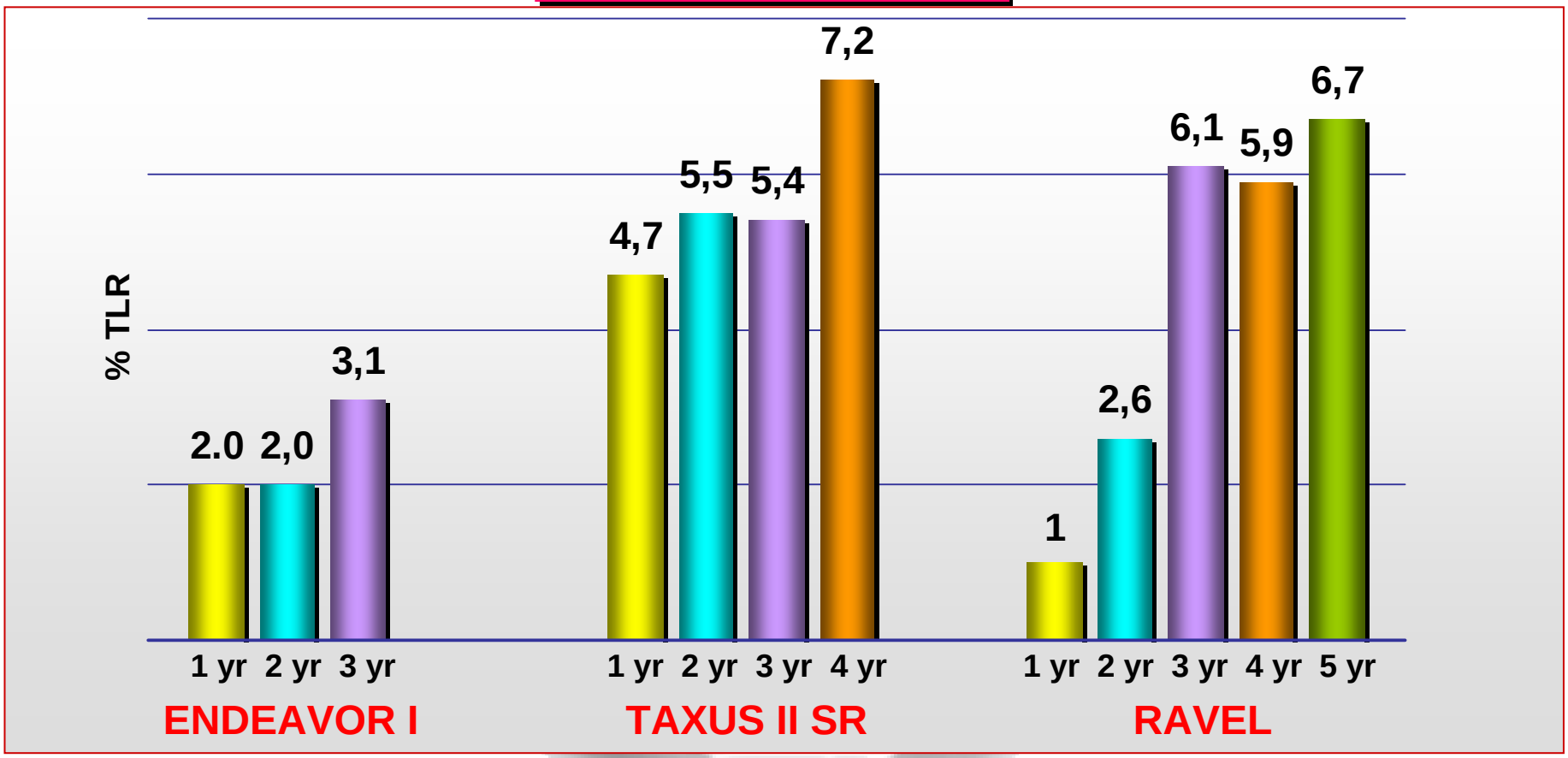
Hypothesis – link has not been established so far

Overall results of DES implantation

N. Kipshidze and M. Leon, J Am Coll Cardiol 2005, 47(9): 1911-1913

Early Trials

TLR Rates



Randomized Study TAXUS II, Colombo et al, *Circulation* 2003;108:788-794.
2 Year Clinical Results of TAXUS II, TCT.
4 Year Clinical Results TAXUS II WCC.
3 Year Results of RAVEL Trial, *Circulation* DOI:10.11661/01.CIR.0000156334.24955.B2.
RAVEL 4 Year Results, Sousa, PCR.
RAVEL 5 Year Results, Morice, WCC.

Clinical results are not suitable for comparison

ENDEAVOR II

Randomized, Double-Blind Trial Design

Single De Novo Native Coronary Artery Lesions
Stent Diameters: 2.25-3.5 mm
Stent Lengths: 18-30 mm (8/9 mm bailout)
Lesion Length: 14-27 mm
Pre-dilatation required

Endeavor Stent
Active Arm
n = 600

N = 1,200 patients
72 sites
Europe, Asia Pacific, Israel, New Zealand and Australia

Driver Stent
Control Arm
n = 600

Clinical/MACE

30d | 6mo | 8mo | 9mo | 12mo | 2yr | 3yr | 4yr | 5yr

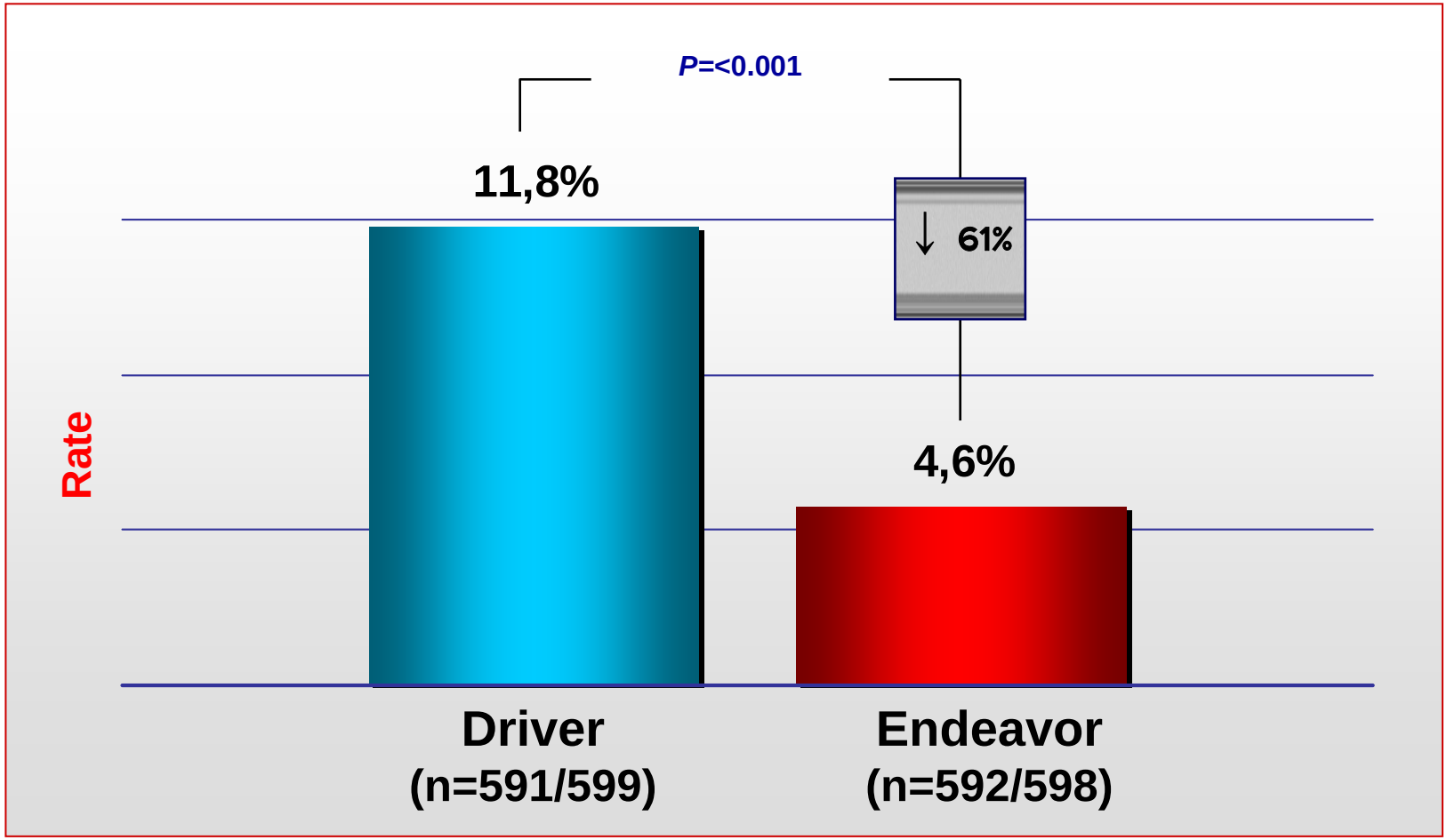
Angiography/IVUS

Angio N = first 600
IVUS N = first 300
IVUS for overlapping stents

Primary Endpoint: TVF (cardiac death, MI, TVR) at 9 months
Dual antiplatelet therapy for 3 months. 10 μg Zotarolimus per mm stent length

ENDEAVOR II

TLR at 9 Months

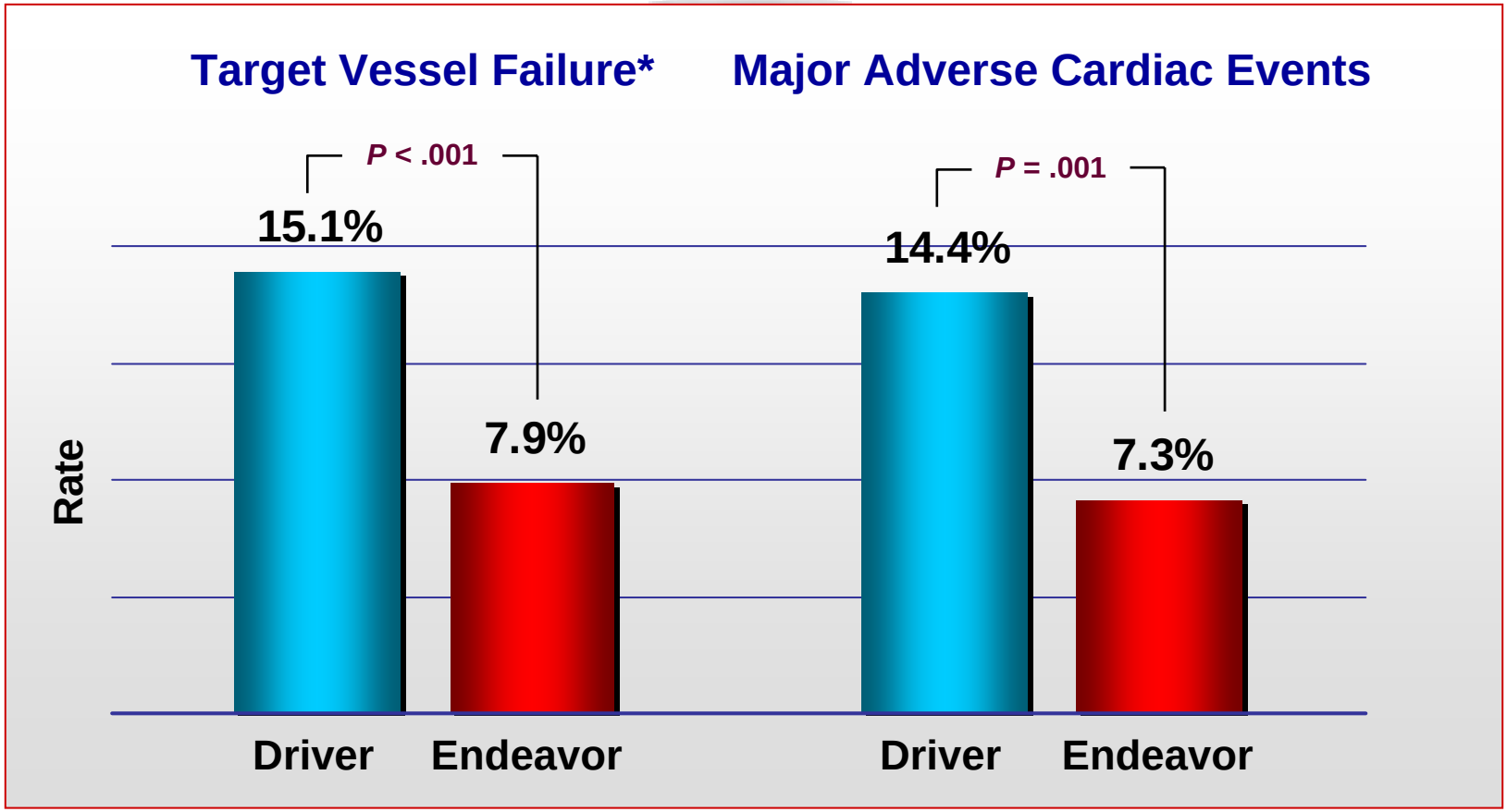


Fajadet et al. *Circulation*. 2006;114:98-806.

ENDEAVOR II

Clinical Outcomes

Primary Endpoint at 9 Month Follow-up



*Target Vessel Failure is a composite of target vessel revascularization, Q- or non Q-wave MI, or cardiac death.

Fajadet et al. *Circulation*. 2006;114:98-806.

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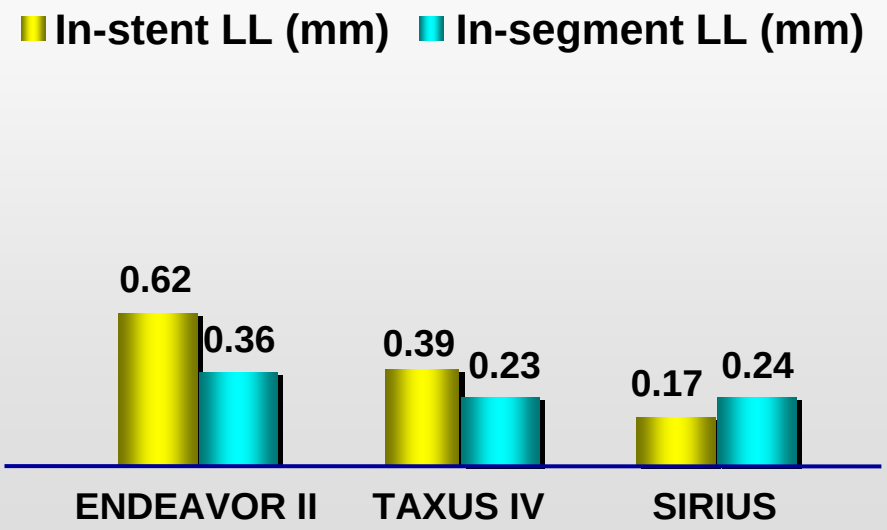
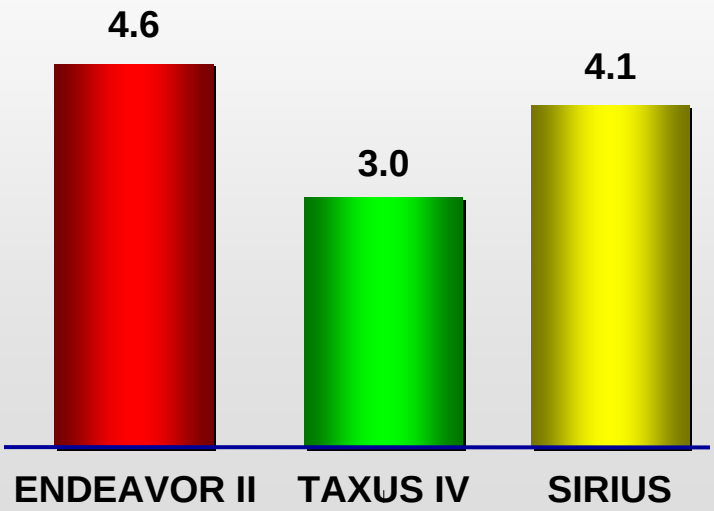
Pivotal Trials: Late loss vs. TLR

Late loss (mm)



TLR at 9 months (%)

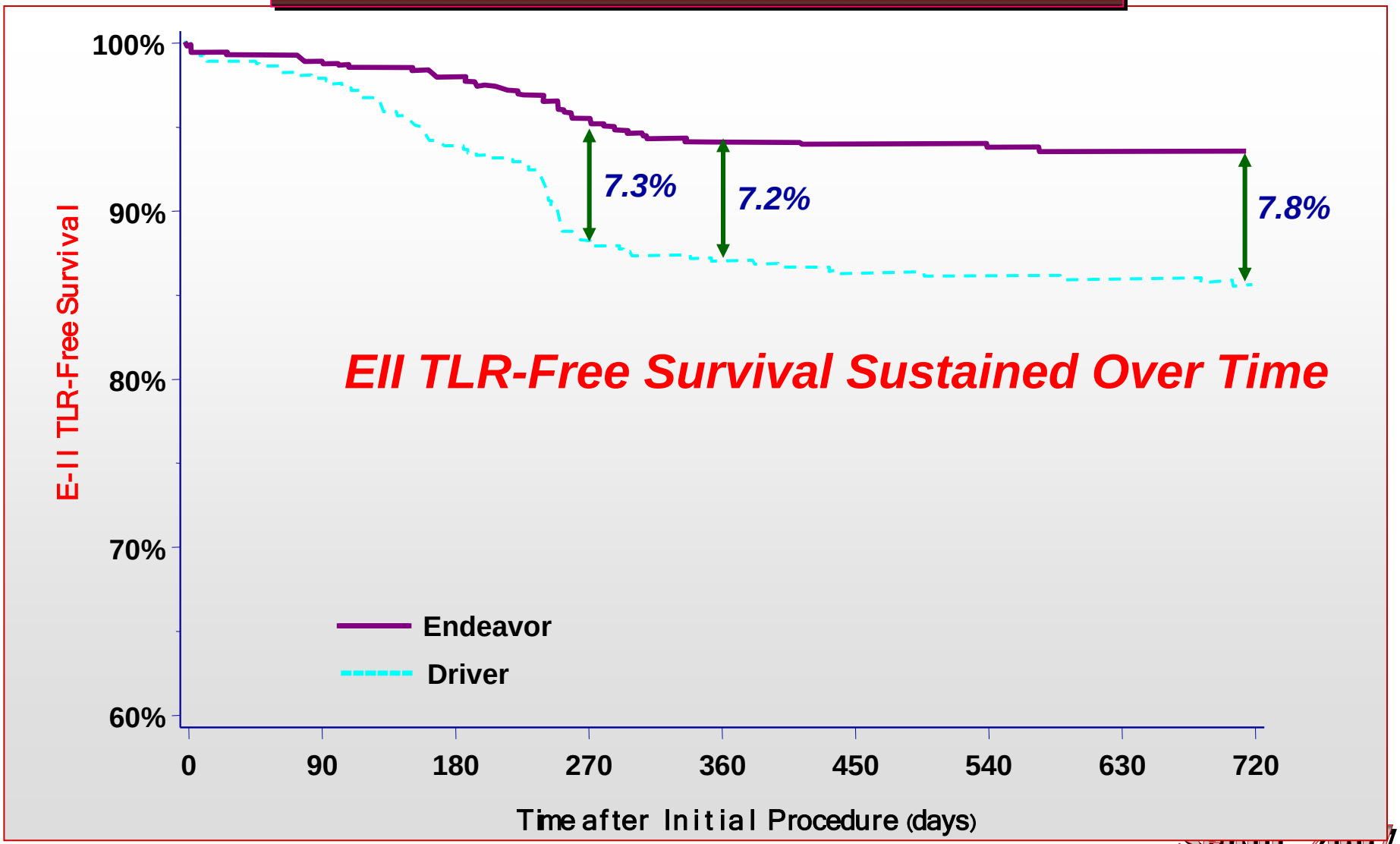


*12 month analysis
Data from different clinical trials are not suitable for comparison.

SIRIUS. Moses et al. *NEJM*. 2003;349:1315-1323.
TAXUS IV. Stone et al. *NEJM*. 2004;350:221-231.
SIRIUS diabetes subset. *Circulation*. 2004;109:2273-2278.
TAXUS IV diabetes subset. *J Am Coll Cardiol*. 2005;45:1172-1179.
Fajadet et al. Circulation. 2006;114:98-806.

ENDEAVOR II

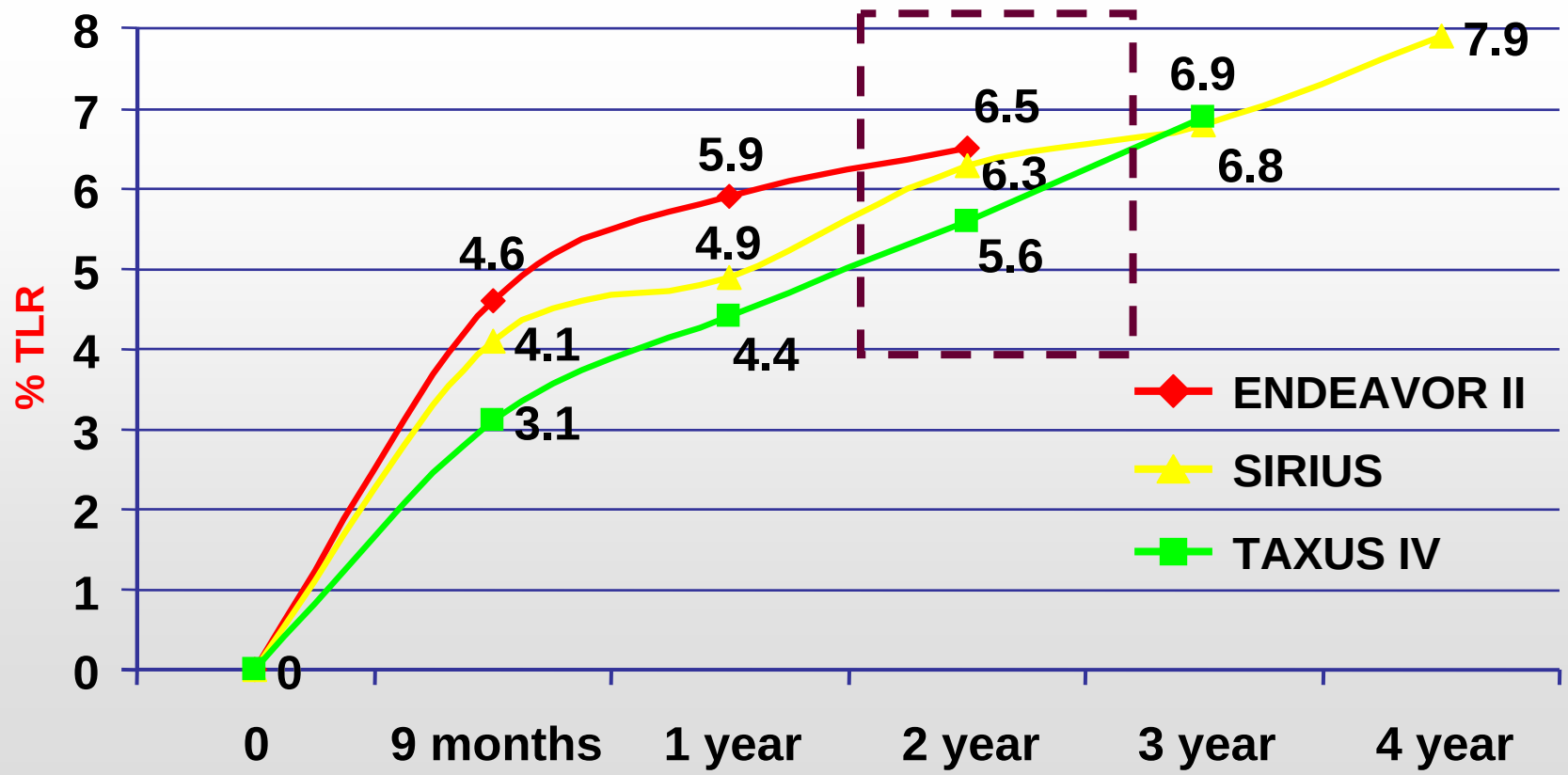
Event Free Survival at 2 Years



Fajadet et al. *Circulation*. 2006;114:98-806.

Efficacy Measures

TLR Rates



1 year Outcomes in the Sirius Trial, Holmes et al, Circulation 2004
1 Year Clinical Results of TAXUS IV, Stone et al, Circulation 2004
2 year Outcomes in the Sirius Trial, Leon, ACC 2004
2 Year Clinical Results of TAXUS IV, Stone, TCT 2004

3 year Outcomes in the Sirius Trial, Leon, TCT 2005
3 Year Clinical Results of TAXUS IV, Stone, ACC 2005
4 year Outcomes in the Sirius Trial, Leon, TCT 2006
Fajadet et al. Circulation. 2006; 114:98-806

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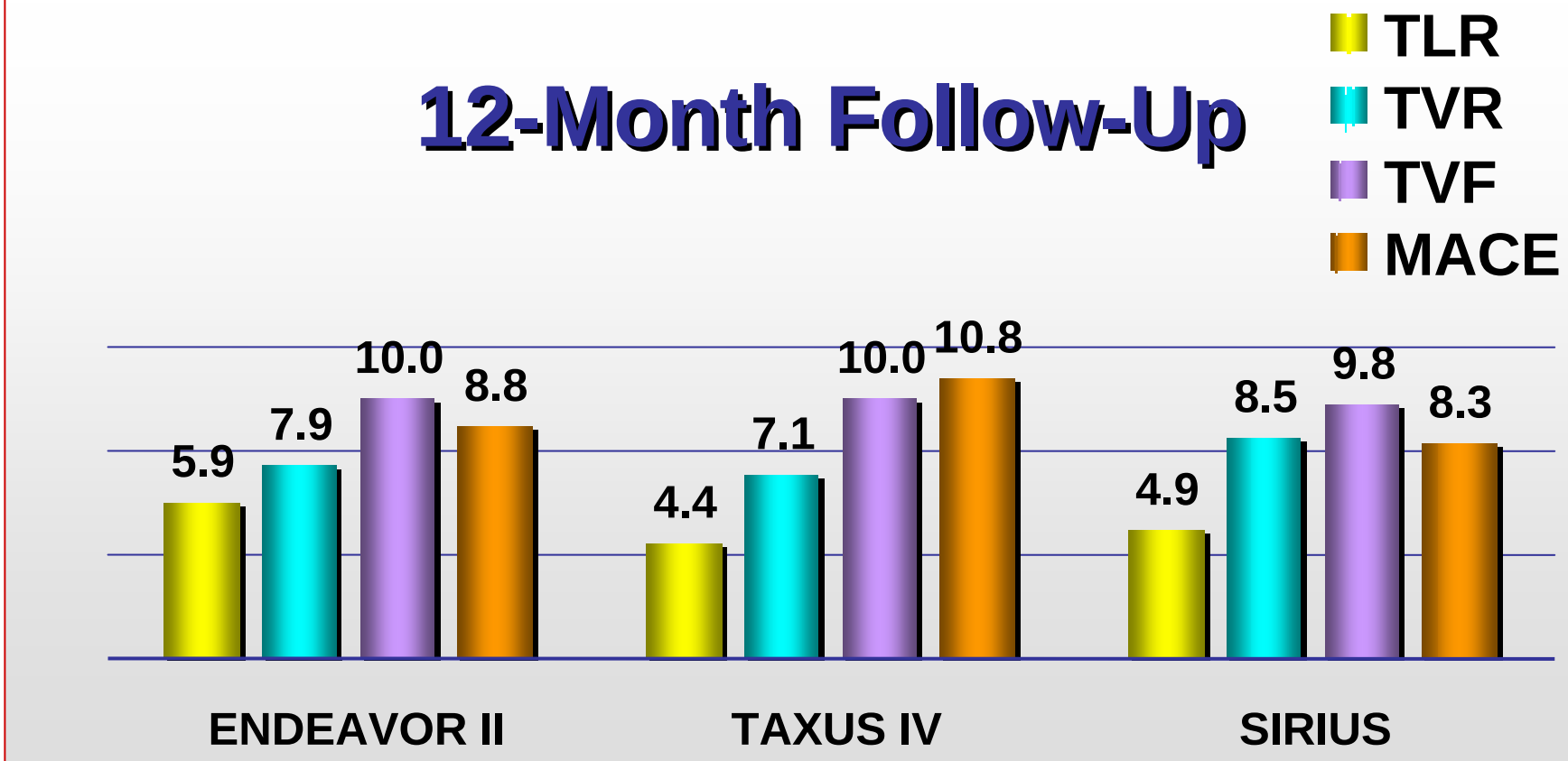
Clinical results are not suitable for comparison

Clinical Events (%)

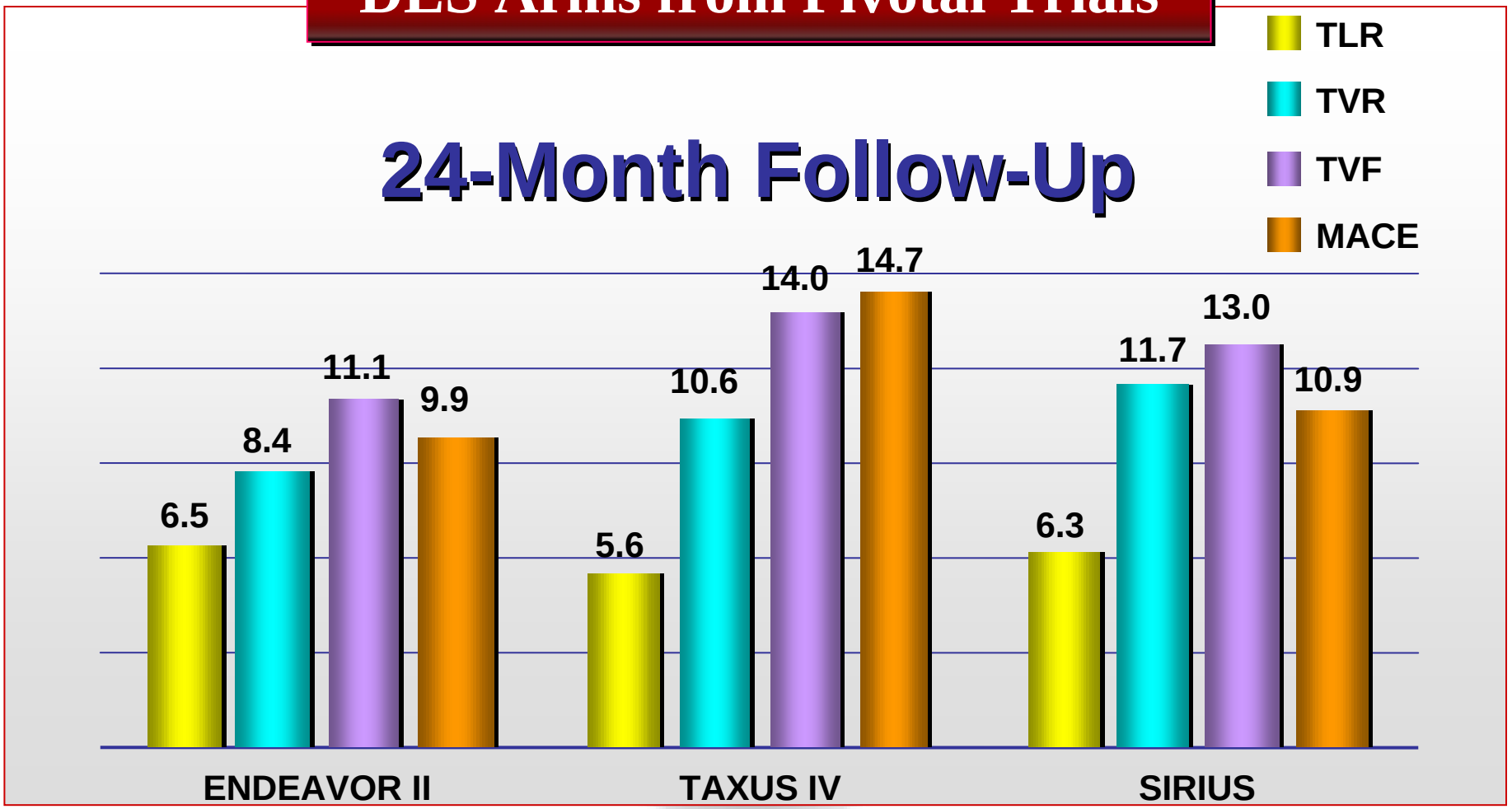
DES Arms from Pivotal Trials



SIRIUS. Holmes et al. *Circulation*. 2004;109:634-640.
TAXUS IV. Stone et al. *Circulation*. 2004;109:1942-1947.
Fajadet et al. Circulation. 2006; 114:98-806

Clinical Events (%)

DES Arms from Pivotal Trials



SIRIUS. Holmes et al. *Circulation.* 2004;109:634-640.
TAXUS IV. Stone et al. *Circulation*. 2004;109:1942-1947.
Sirius Study 2 year Results Kereiakes. TCTMD.
TAXUS IV 2 Year Results. Stone TCTMD.
Fajadet et al. Circulation. 2006;114:98-806.

ENDEAVOR III

Multicenter Randomized Trial

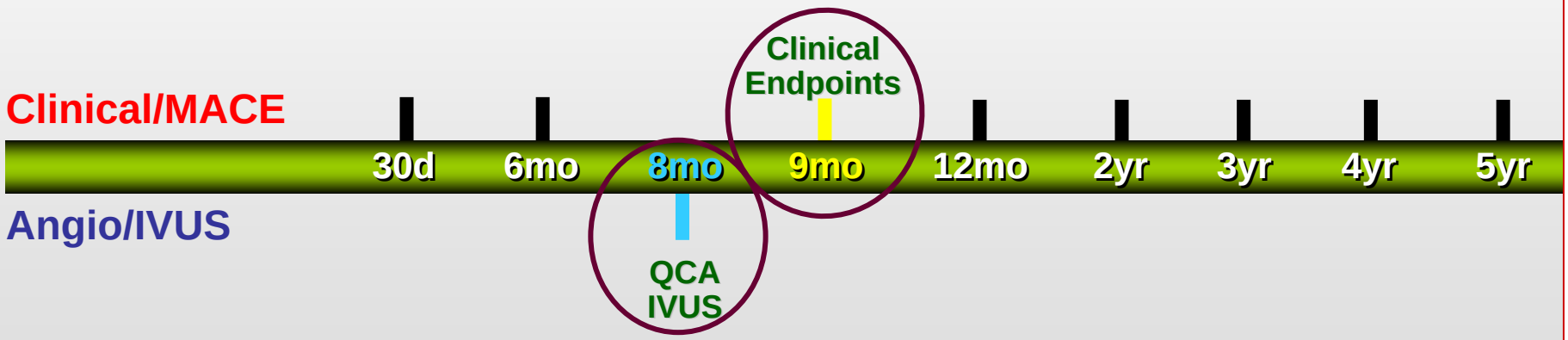
3:1 Randomization
Single Blind - Single Vessel - No Staging

Single De Novo Native Coronary Lesion
Vessel Diameter: 2.5-3.5 mm
Lesion Length: 14-27 mm
Stent Lengths: 18-30 mm (8/9) mm bailout
Pre-dilatation required

Endeavor Stent
n = 327

Control Cypher Stent
n = 109

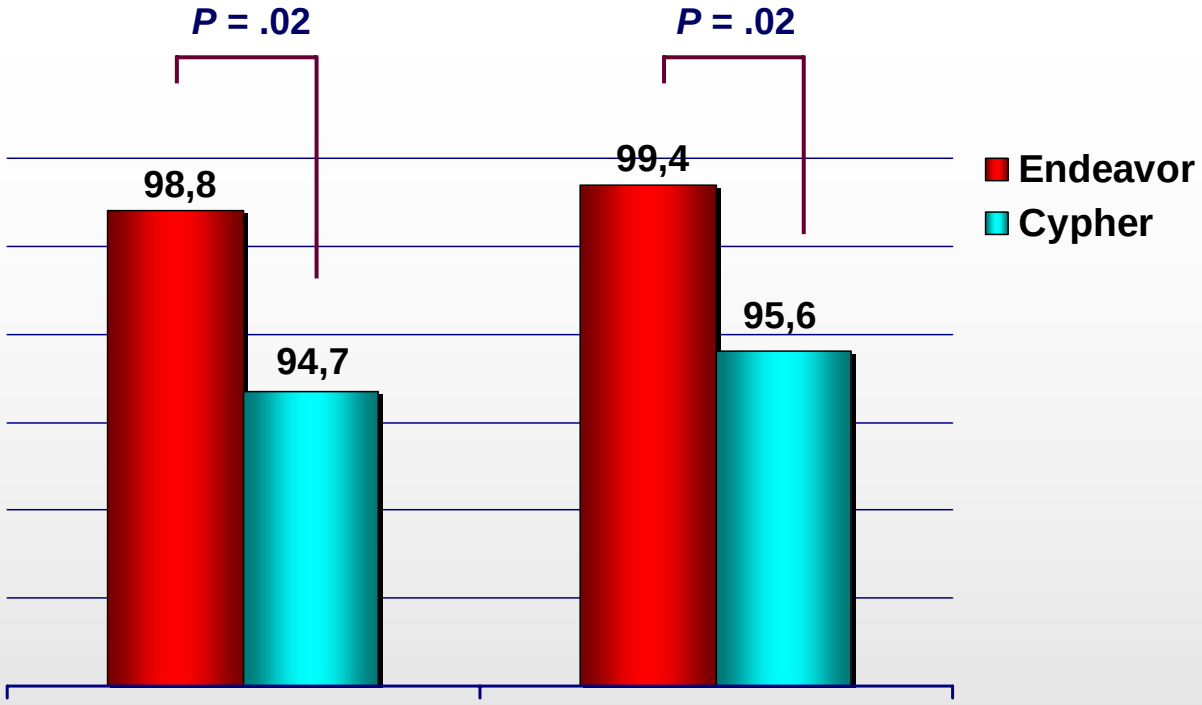
N = 436 patients
30 sites
United States



Primary Endpoint: In-segment late lumen loss by QCA at 8 months
Secondary Endpoints: TLR, TVR, TVF at 9 months & ABR at 8 months
Antiplatelet therapy for ³3 months 10 μg Zotarolimus per mm stent length

ENDEAVOR III

Confirms Endeavor Deliverability



	Endeavor n = 323	Cypher n = 113	*P*-value
In-hospital events			
Q-Wave MI	0	0	–
Non Q-Wave MI	0.6 (2)	3.5 (4)	0.04

Kandzari et al. JACC Vol. 48, No. 12, 2006.

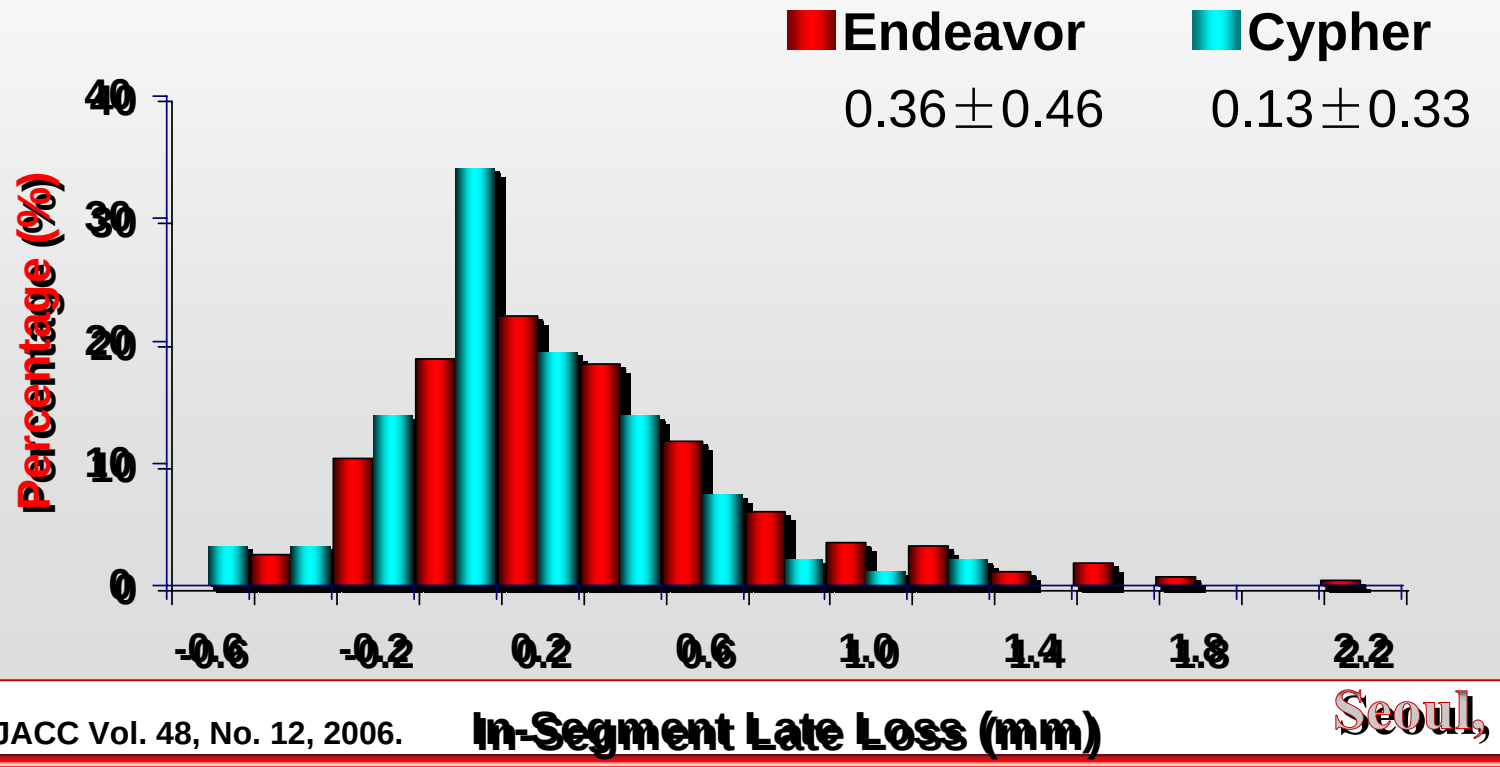
ENDEAVOR III

Primary Endpoint at 8 Months

- **Non-Inferiority Margin of Difference: 0.20 mm**

-90% Power, 5% α-one sided

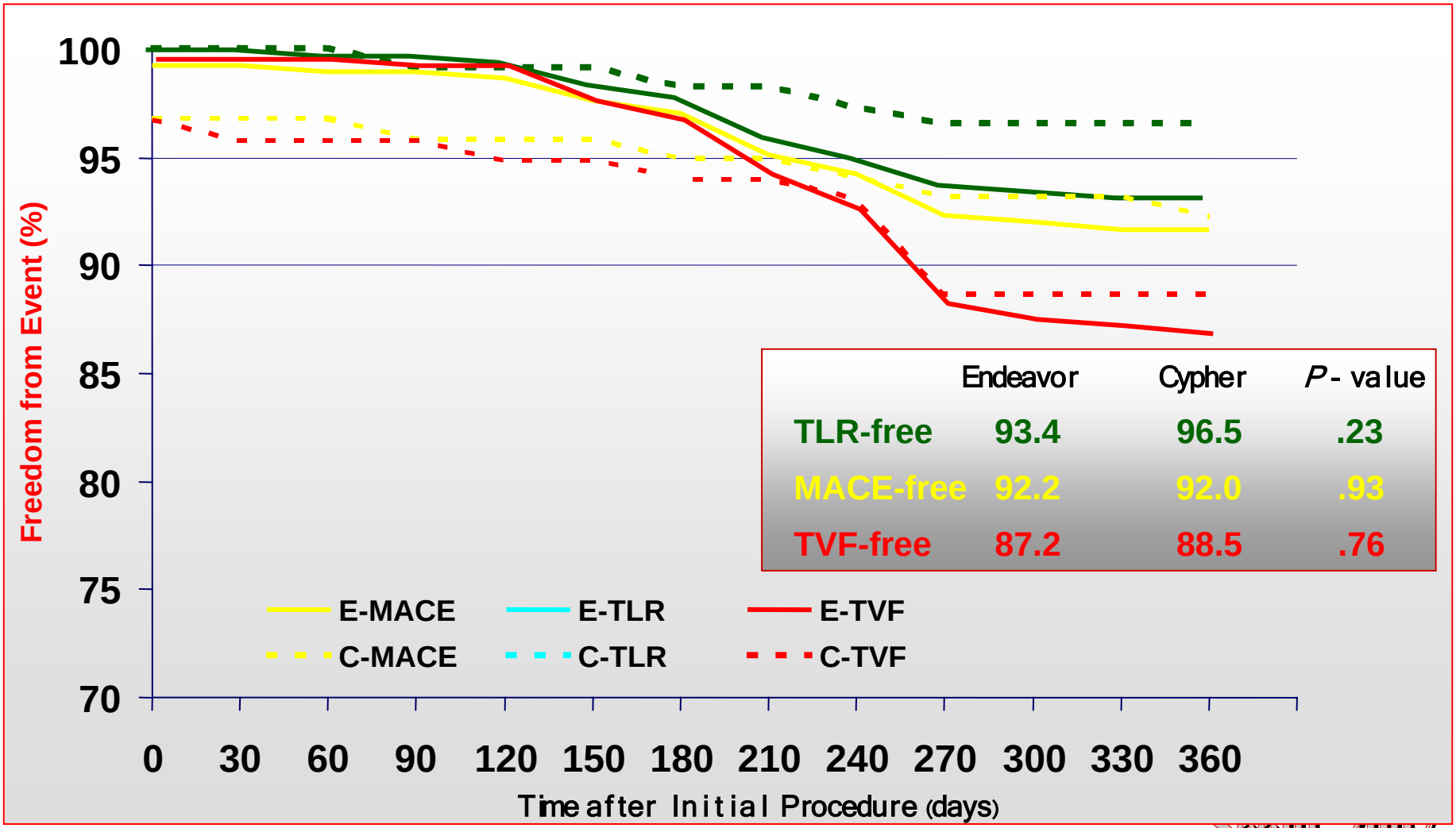
- **Observed Difference: 0.23 mm**



Kandzari et al. JACC Vol. 48, No. 12, 2006.

ENDEAVOR III

Event Free Survival to 360 Days

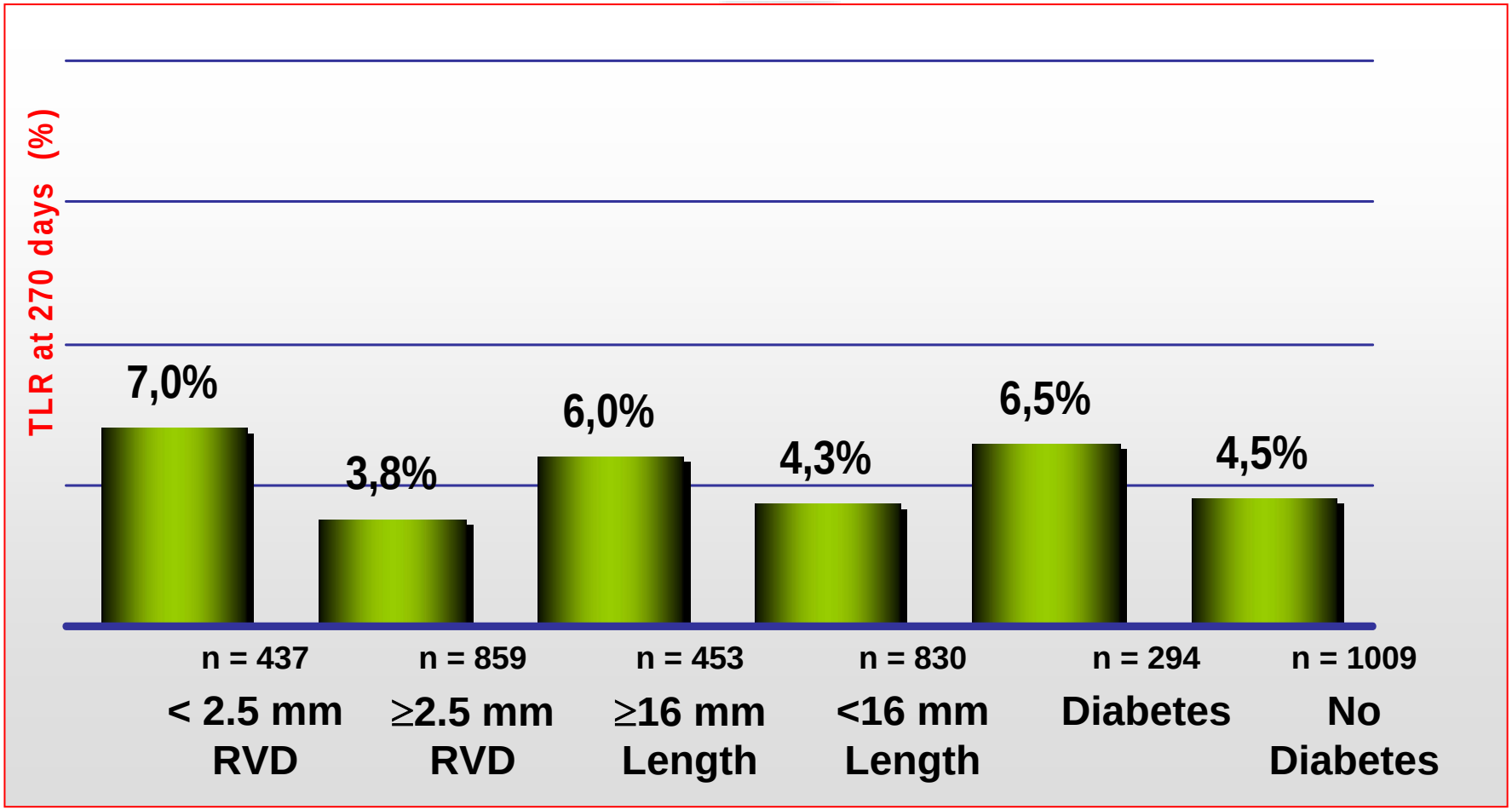


	Endeavor	Cypher	*P* - value
TLR-free	93.4	96.5	.23
MACE-free	92.2	92.0	.93
TVF-free	87.2	88.5	.76

Kandzari et al. ACC, 2006.

ENDEAVOR Clinical Program

TLR Across High Risk Groups EI, EII, EIICA and EIII



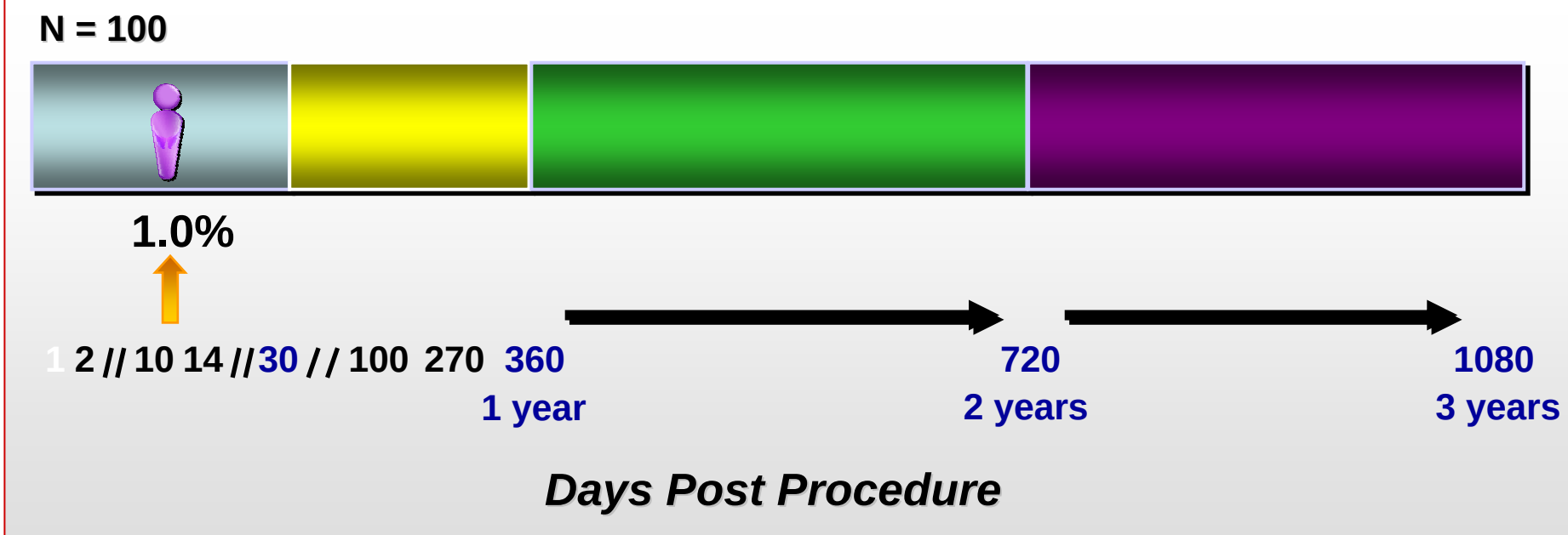
Kandzari et al. ACC, 2006.


Deliverability
Efficacy
Safety

ENDEAVOR I

Safety Profile

ENDEAVOR I Clopidogrel Therapy for ⩾3 months

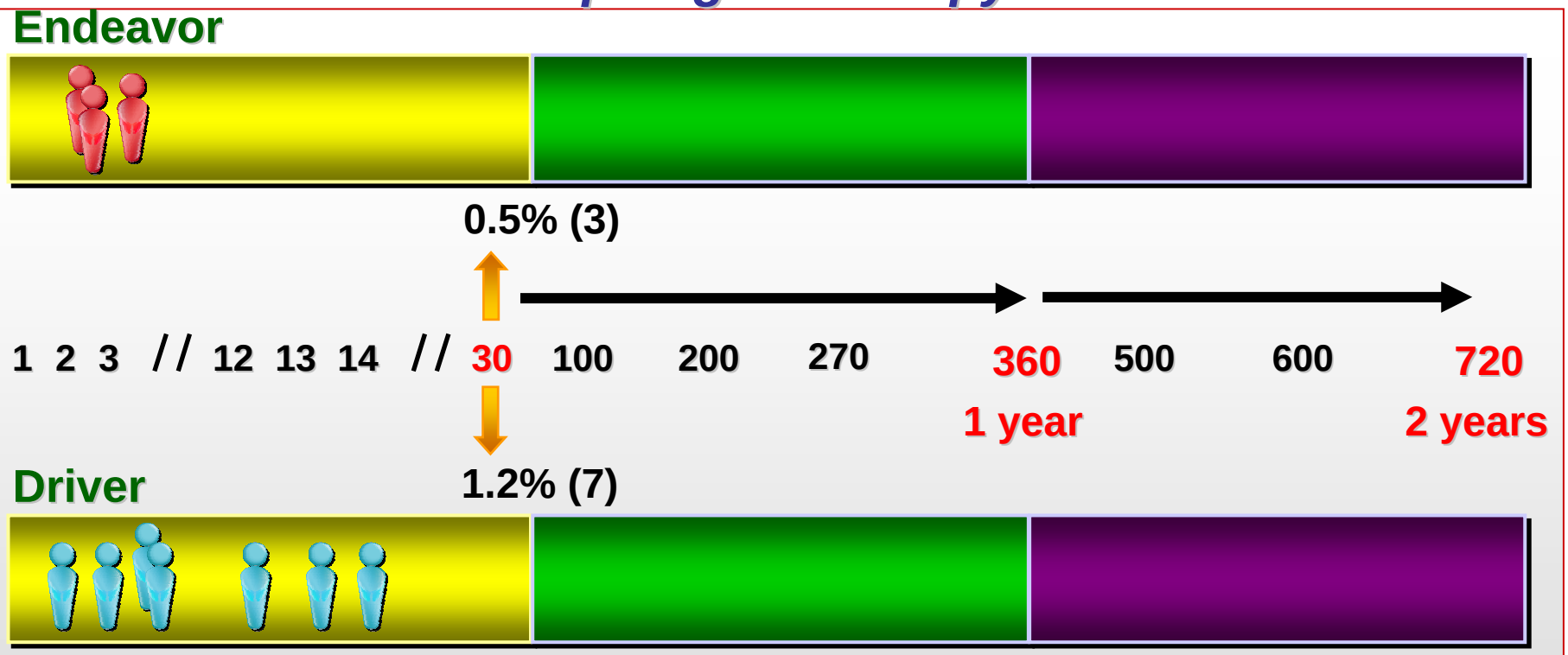


Defined as angiographic thrombus or subacute closure within the stented vessel at the time of the clinically driven angiographic re-study for documented ischemia (chest pain and ECG changes).
Any death not attributed to a non-cardiac cause within the first 30 days is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.

ENDEAVOR II

Safety Profile

ENDEAVOR II Clopidogrel Therapy for ⩾3 months



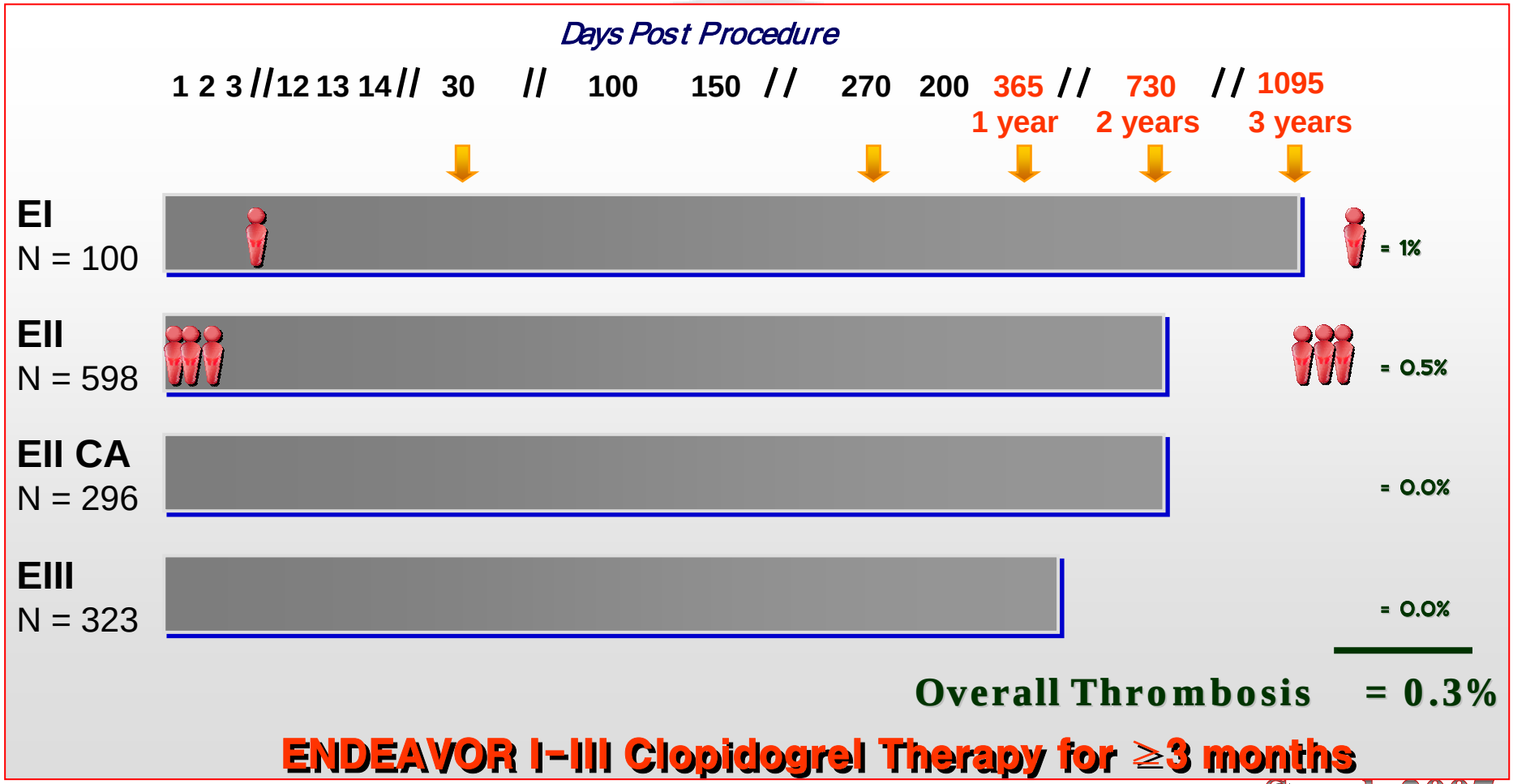
Days Post Procedure

Defined as angiographic thrombus or subacute closure within the stented vessel at the time of the clinically driven angiographic re-study for documented ischemia (chest pain and ECG changes).
Any death not attributed to a non-cardiac cause within the first 30 days is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.

Fajadet et al. *Circulation*. 2006;114:98-806.

Safety Profile

No Late Stent Thrombosis in Over 1300 Patients
No Late Stent Thrombosis in 994 Patients ³2 yr f/u



ENDEAVOR I–III Clopidogrel Therapy for ≥3 months

Fajadet et al. *TCT*. 2006.

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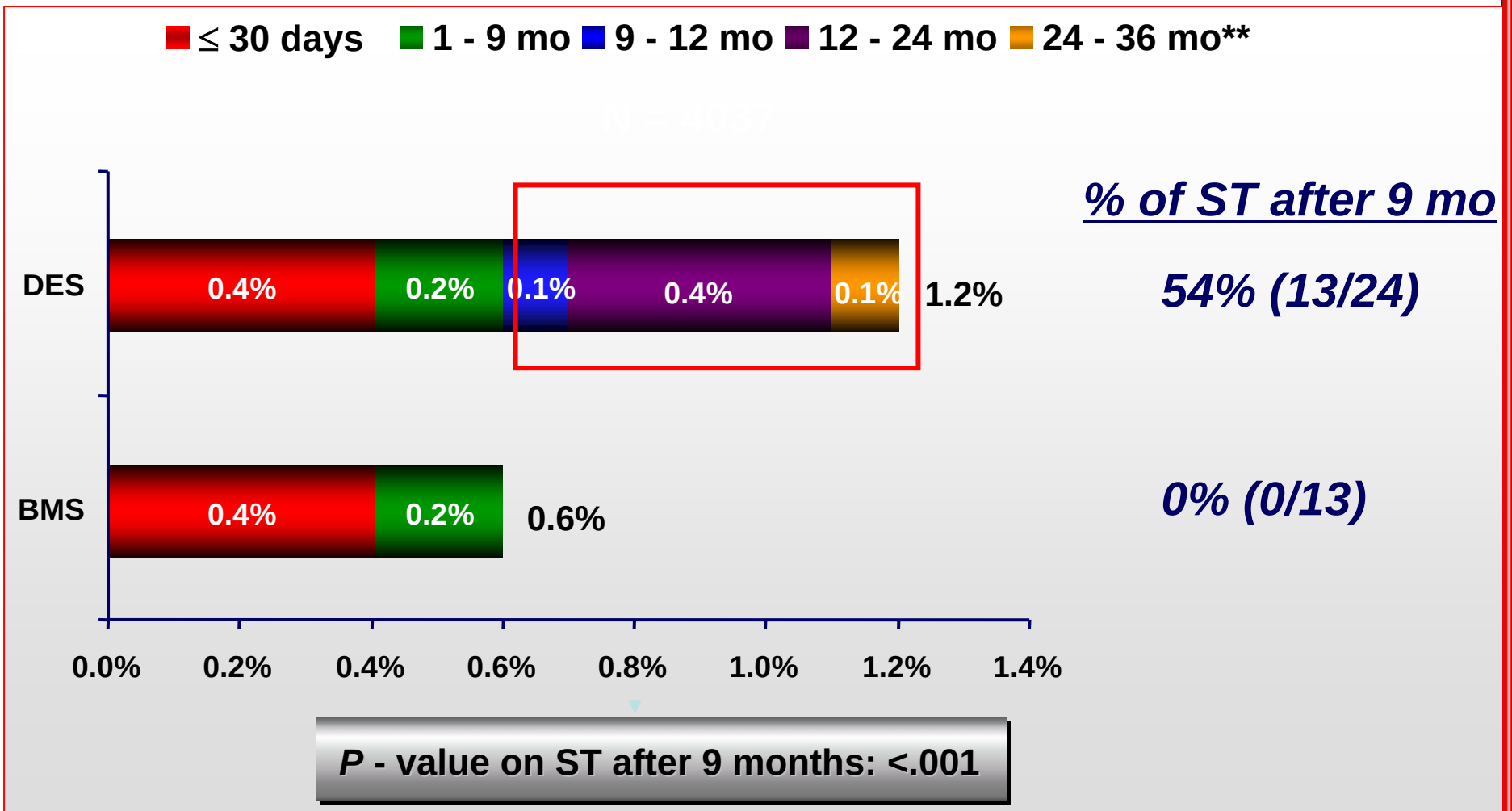
Cypher and Taxus

Combined Stent Thrombosis*



*TAXUS-II, TAXUS-IV, TAXUS-VI (2 yr); RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS (3 yrs).
**24-36 months for Cypher data only.

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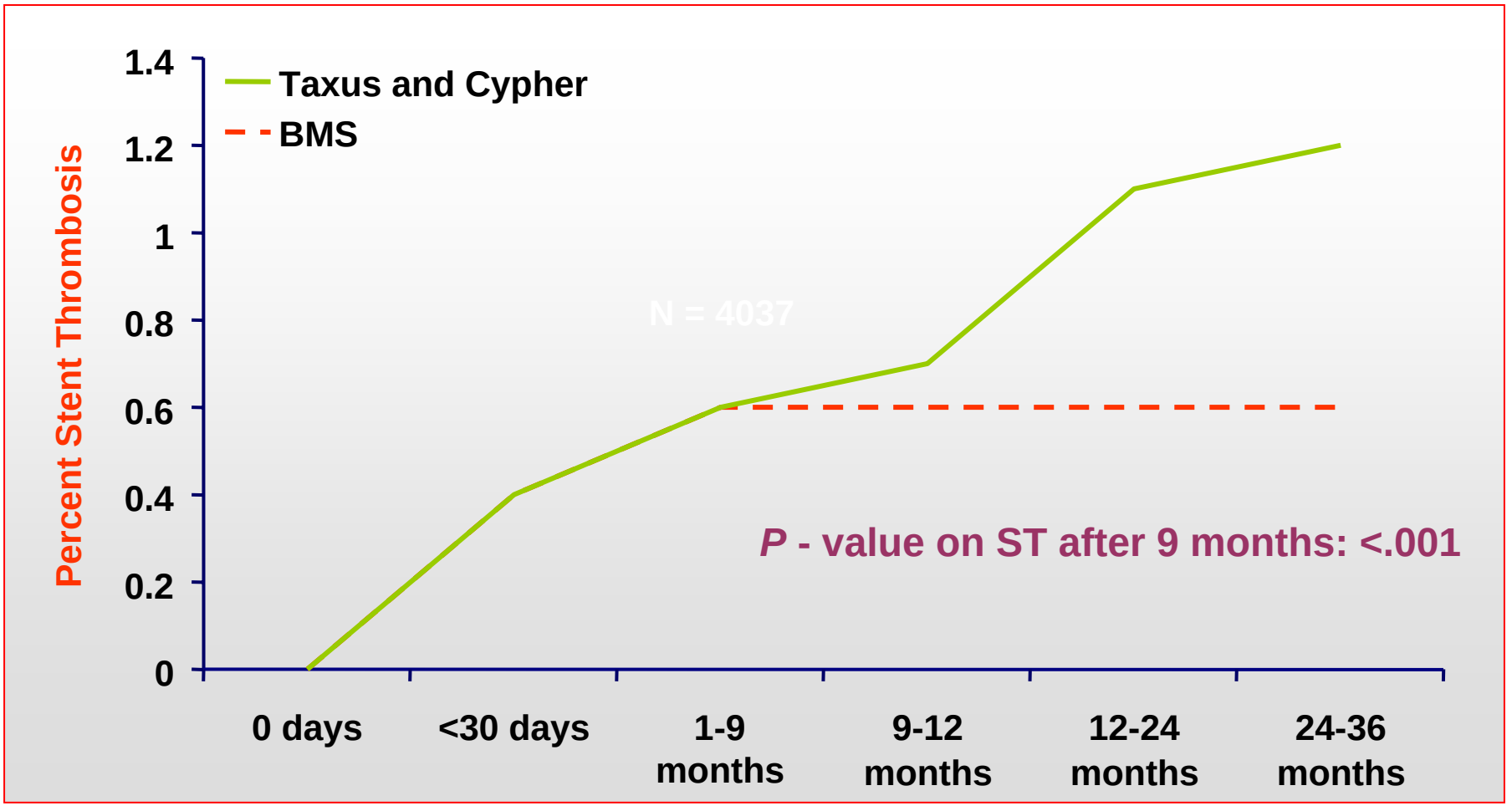
Meta-analysis of Published Data

Combined Stent Thrombosis: DES vs BMS



*TAXUS-II, TAXUS-IV, TAXUS-VI (2 yr); RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS (3 yrs).
** 24-36 months for Cypher data only.

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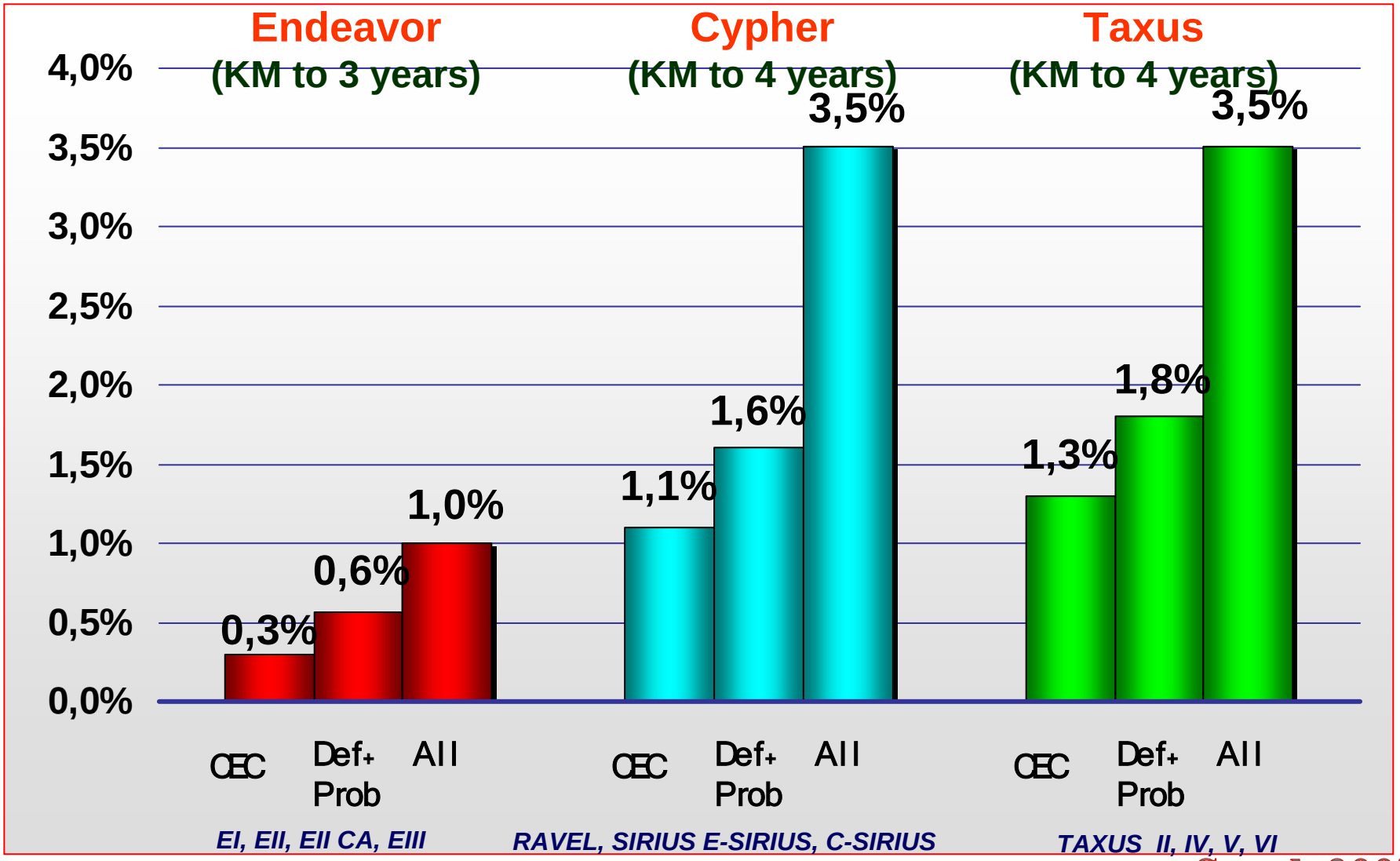
Total Stent Thrombosis Among DES HCRI CEC and ARC Definitions



Cutlip, HCRI, TCT 2006.
FDA Panel Meeting, 2006.

Clinical results are not suitable for comparison

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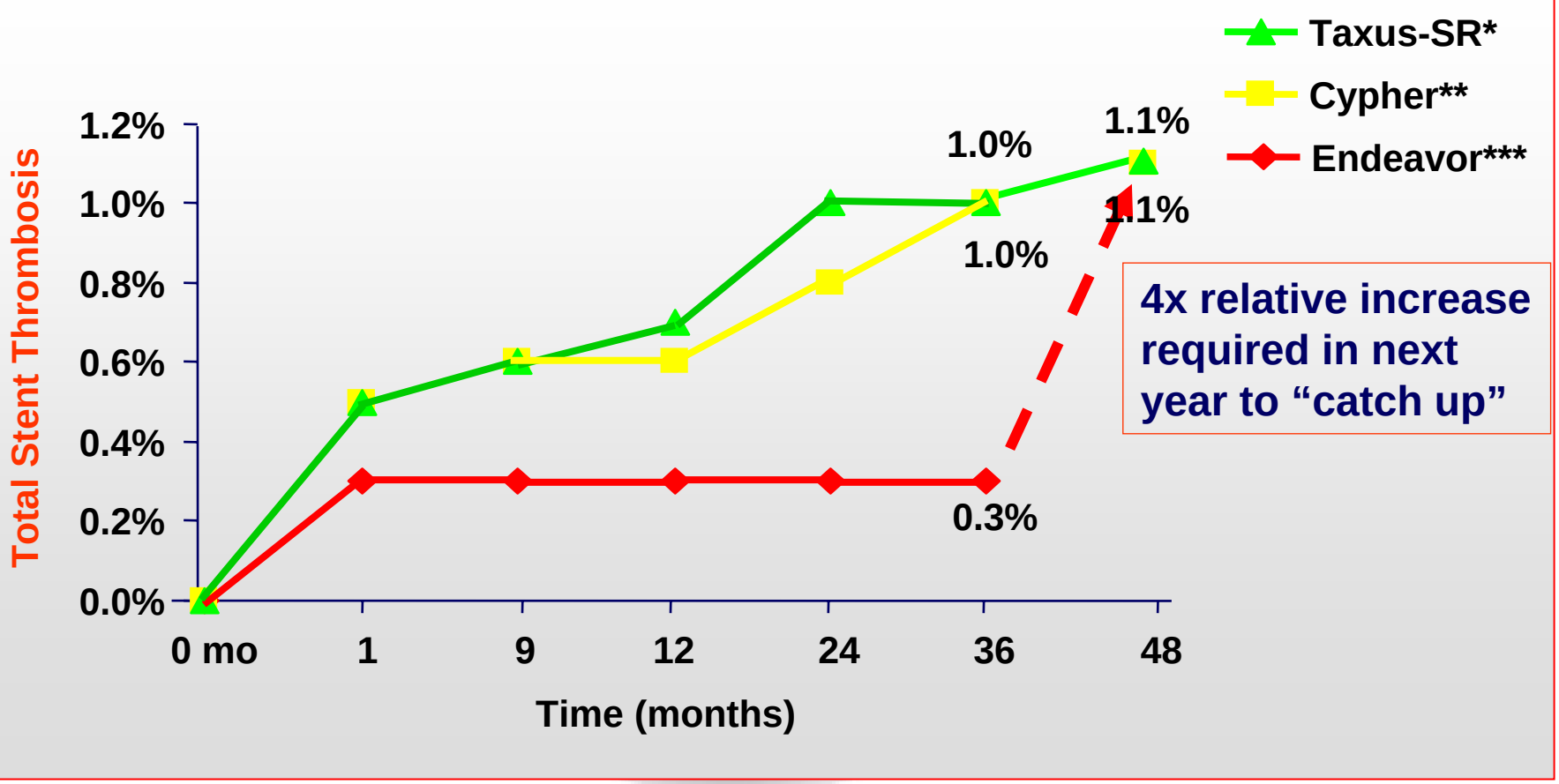
Stent thrombosis rates with DES

Pre-specified HCRI CEC Defined Stent Thrombosis



* TAXUS I, II SR, IV, V 1338 out to 3 years; 1217 to 4 years; 1.1% = 16 events / 1400 pts enrolled

** RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS; 741 pts to 4 years; 1.1% = 10 events / 878 pts enrolled

*** E-I, II, IICA, III 1206 pts out to 2 years; 690 patients out to 3 years; 0.3% = 4 events / 1316 pts enrolled

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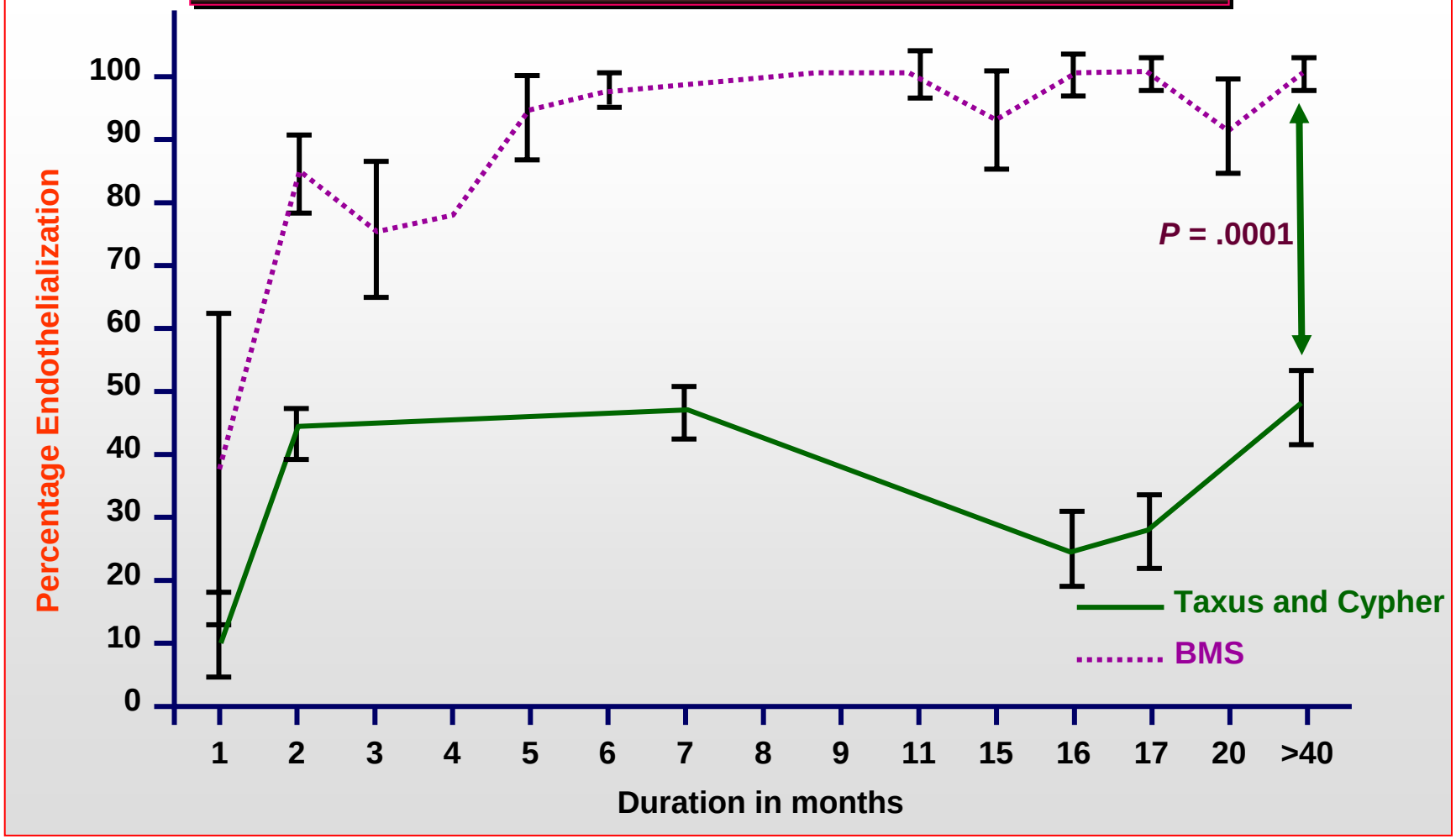
Clinical results are not suitable for comparison

Lack of Endothelial Strut Coverage

DES vs BMS >3 years in Humans



Joner, Virmani et al. *Circulation.* 2005;112:3210.

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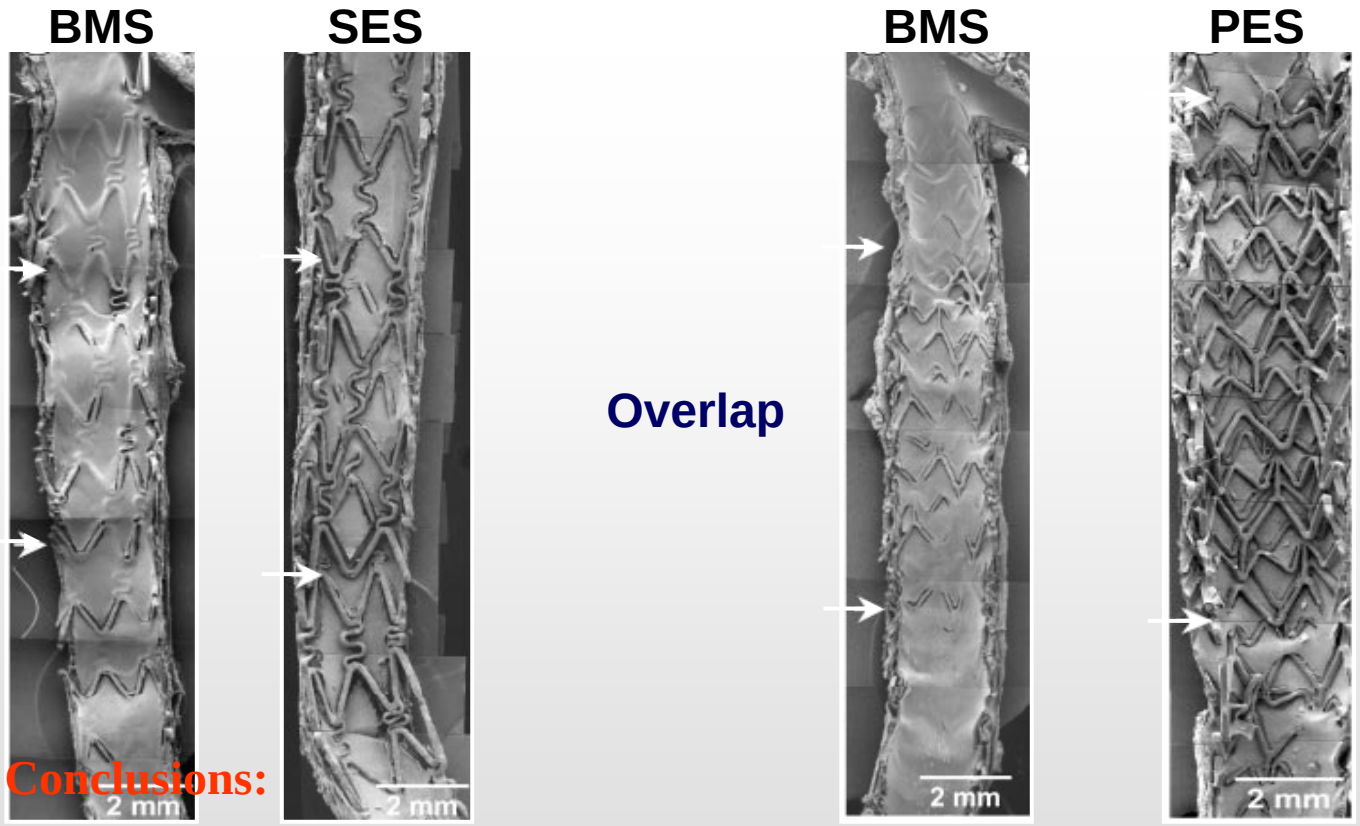
Delayed Endothelialization

Overlapping SES vs PES



Conclusions:

- BMS showed far greater endothelialization than DES
- Lack of coverage highlighted in areas of overlap
- Less surface coverage by endothelial cells in PES than SES

Finn et al. (Circulation. 2005;112:270-278.)

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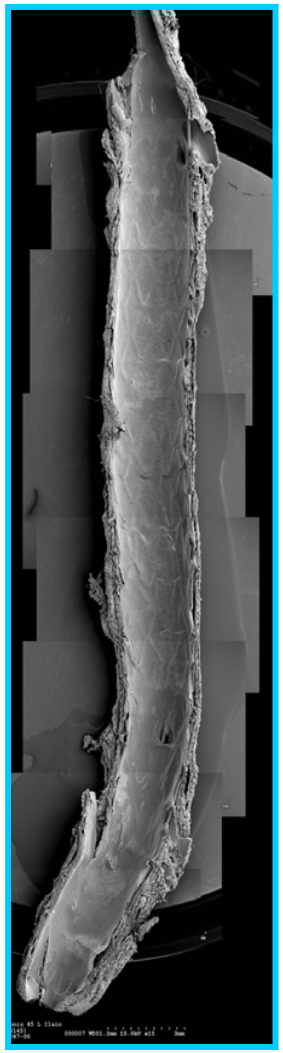
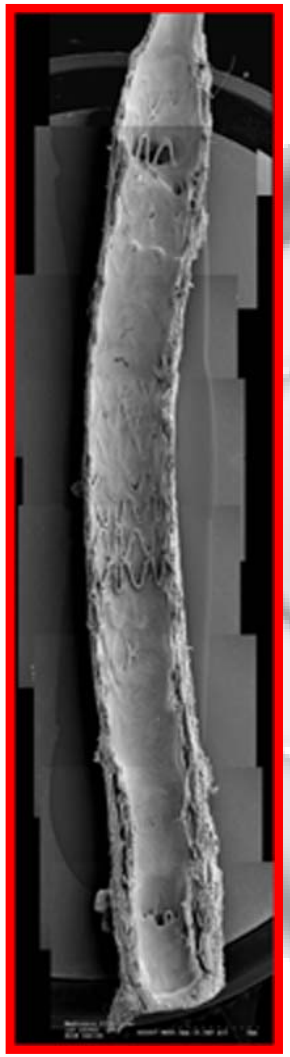
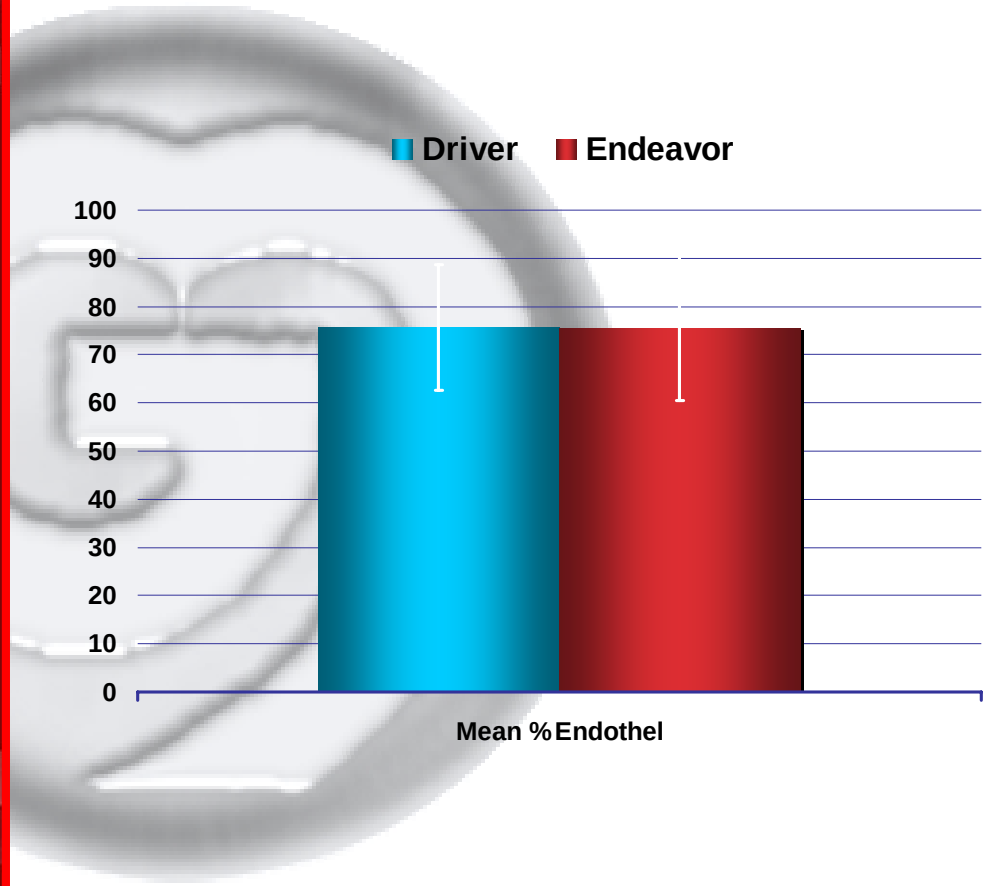
Strut Coverage and Endothelialization

Driver



Endeavor





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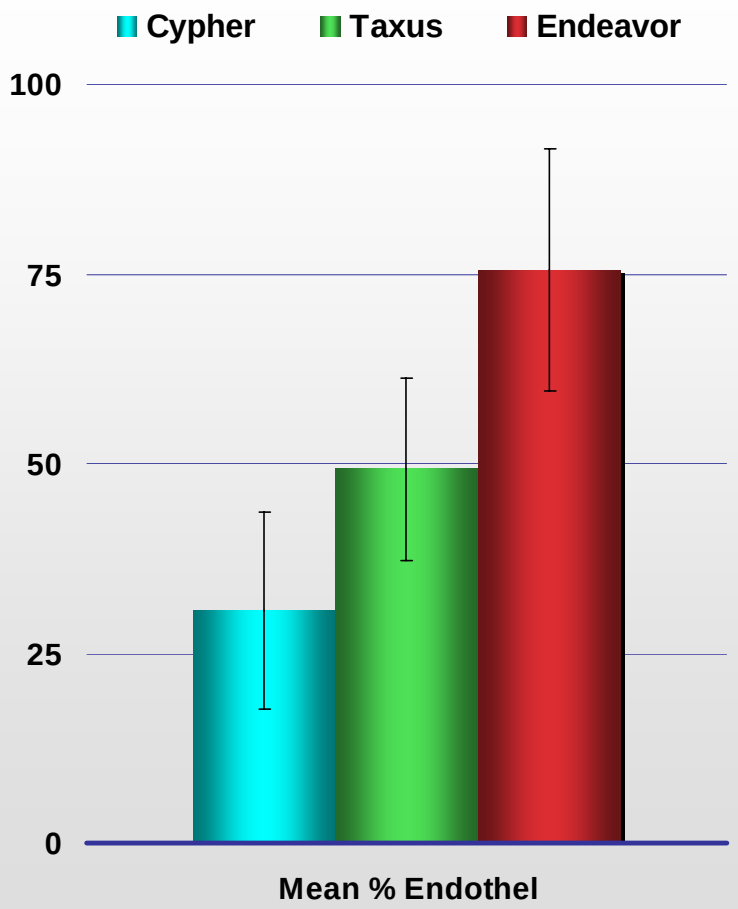
Strut Coverage and Endothelialization

Cypher

Taxus

Endeavor

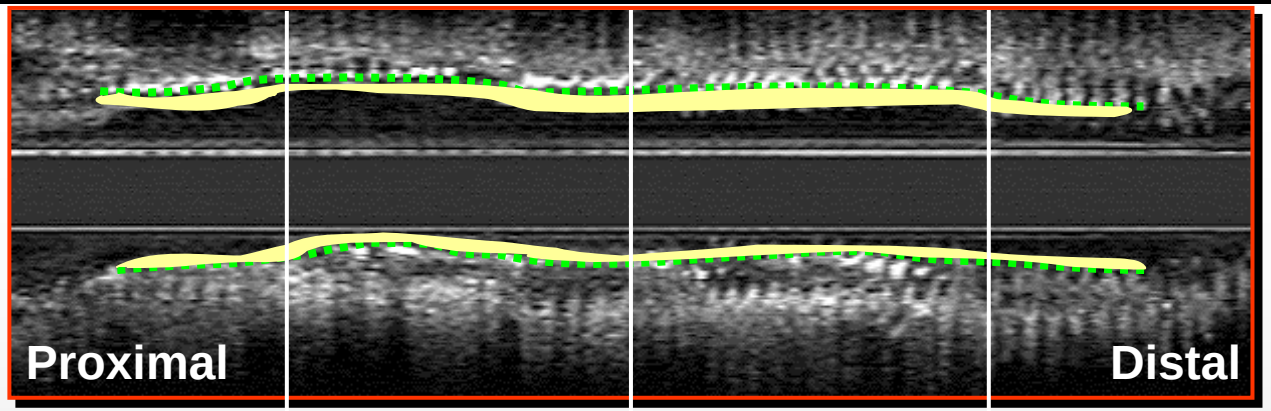
% of Struts Endothelialized

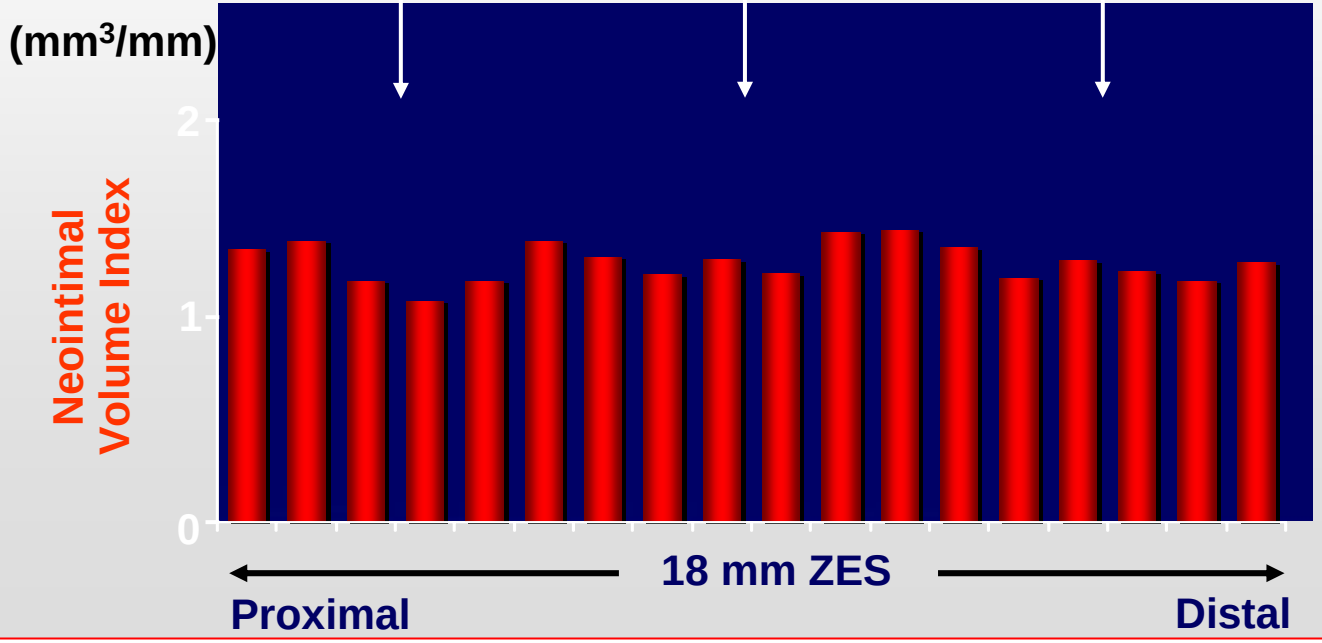


Virmani et. al; PCR 2006.
Rabbit Model at 21 days

Endeavor: "Complete" NIH

Smooth Lumen, Even Neointimal Distribution



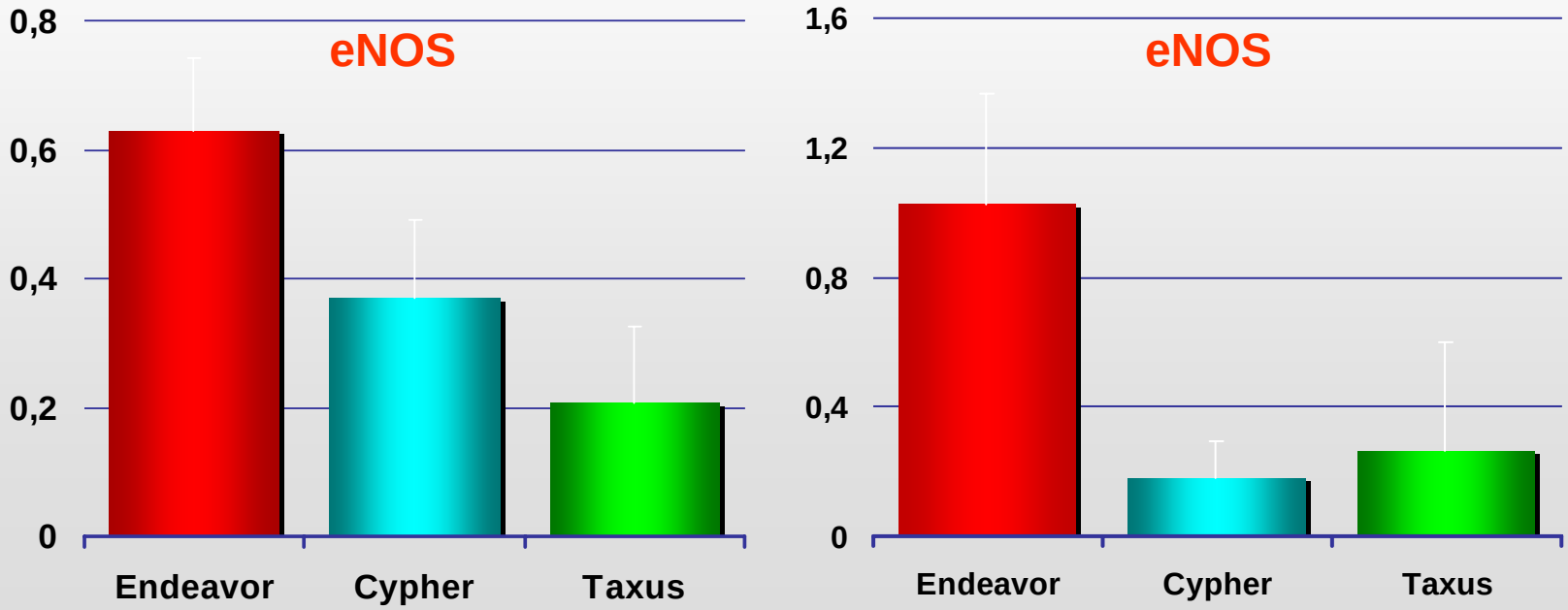


Source: Dr. Peter Fitzgerald EII 9 month (IVUS 8 months).

NO and Endothelial Cell Function

Endothelial Nitric Oxide Synthase (eNOS)

- eNOS is the protein that produces NO and is marker of endothelial cell function
- Both proximal and stent vessels have significantly more eNOS present than either Taxus or Cypher



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E-Five Registry

Interim Results: Procedural Outcomes on 8,260

Chaim Lotan, Ian Meredith and Martin Rothman on behalf of the E-Five Investigators

E-Five

Centers I

Country	Centers	Patients
Spain	31	1904
Germany	24	1220
Italy	16	813
India	7	586
Greece	7	451
United Kingdom	11	422
Netherlands	6	318
Malaysia	6	307
Israel	10	290
China	7	252
Austria	6	241

E-Five

Patient Demographics

	N=8260
Male Gender (%)	76.7
Age (years)	63.3±11.1
Prior MI (%)	33.6
Q wave MI	21.4
Non-Q wave MI	12.2
Prior PCI (%)	25.2
Prior CABG (%)	7.5
Diabetes Mellitus (%)	32.7
(Recent) MI (%)	21.8
Unstable Angina (%)	34.0

E-Five

Procedure Characteristics I

N=10259

Number Endeavor Stents / Lesion	**1.2**
1 Endeavor stent (%)	**84.7**
2 Endeavor stents (%)	**12.6**
3 Endeavor stents (%)	**2.3**
4+ Endeavor stents (%)	**0.4**
Overlapping Endeavor stents (%)	**74.8 (1172/1566)**
Only Endeavor stents (%)	**94.9**
Combination with other DES only (%)	**2.8**
Combination with other BMS only (%)	**2.1**
Combination with other DES and BMS (%)	**0.3**

The calculation includes all lesions with Endeavor stents implanted or attempted

E-Five

30-Day MACE – First Subset

n=1930	Non Hierarchical
MACE (%)	1.7
Death (all) (%)	0.9
MI (all) (%)	0.8
Q-wave	0.2
Non Q-wave	0.6
TLR (%)	0.4

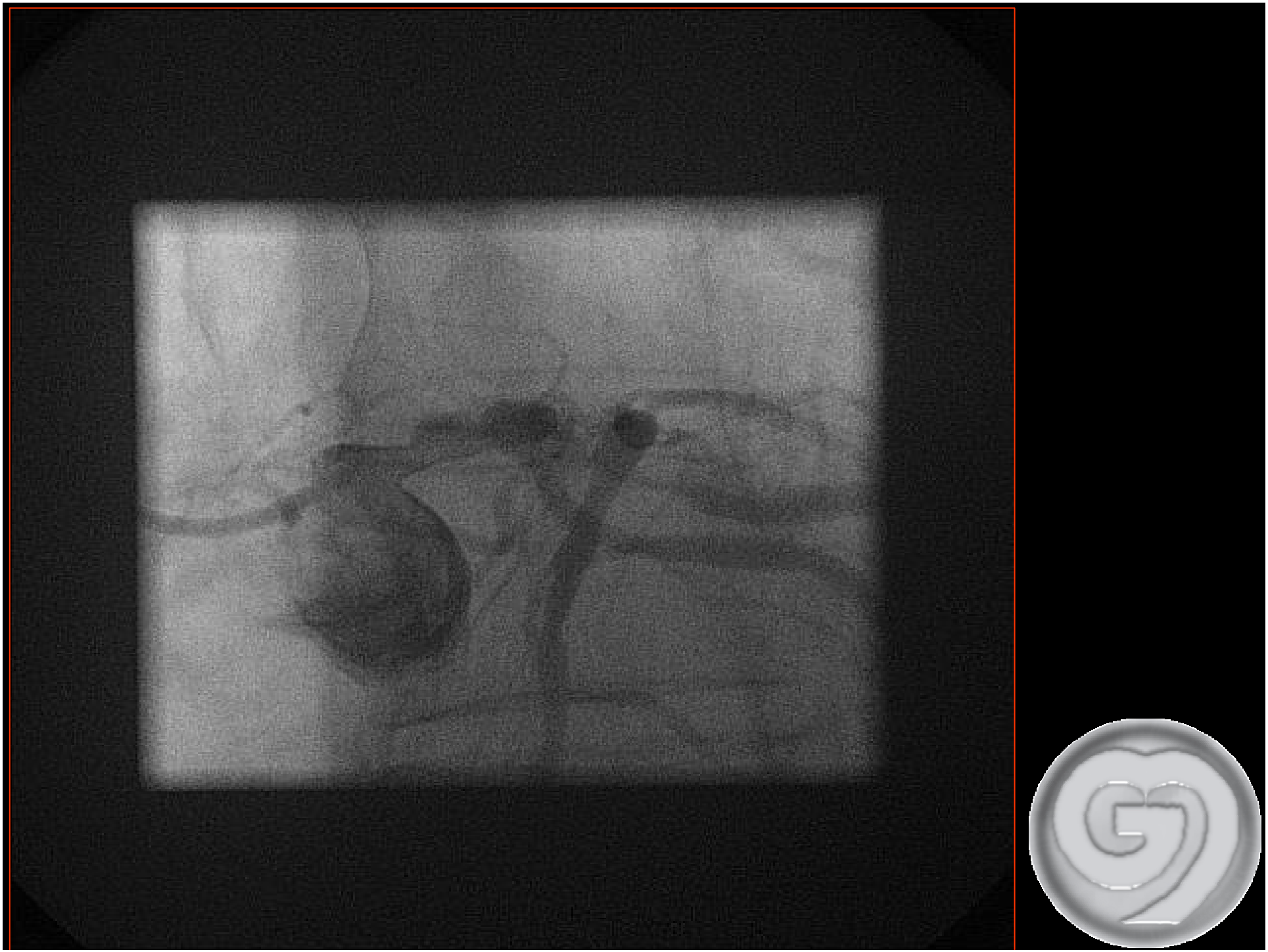
Re-adjudicated data

SAFETY & EFFICACY OF ENDEAVOR

- Fifty nine year old male admitted with chest pain .
- Risk factors : HTA & smoking
- ECG : ST depression V2-V6. Negative T waves V1-V6
- Echocardiogram : WNL. EF 50%

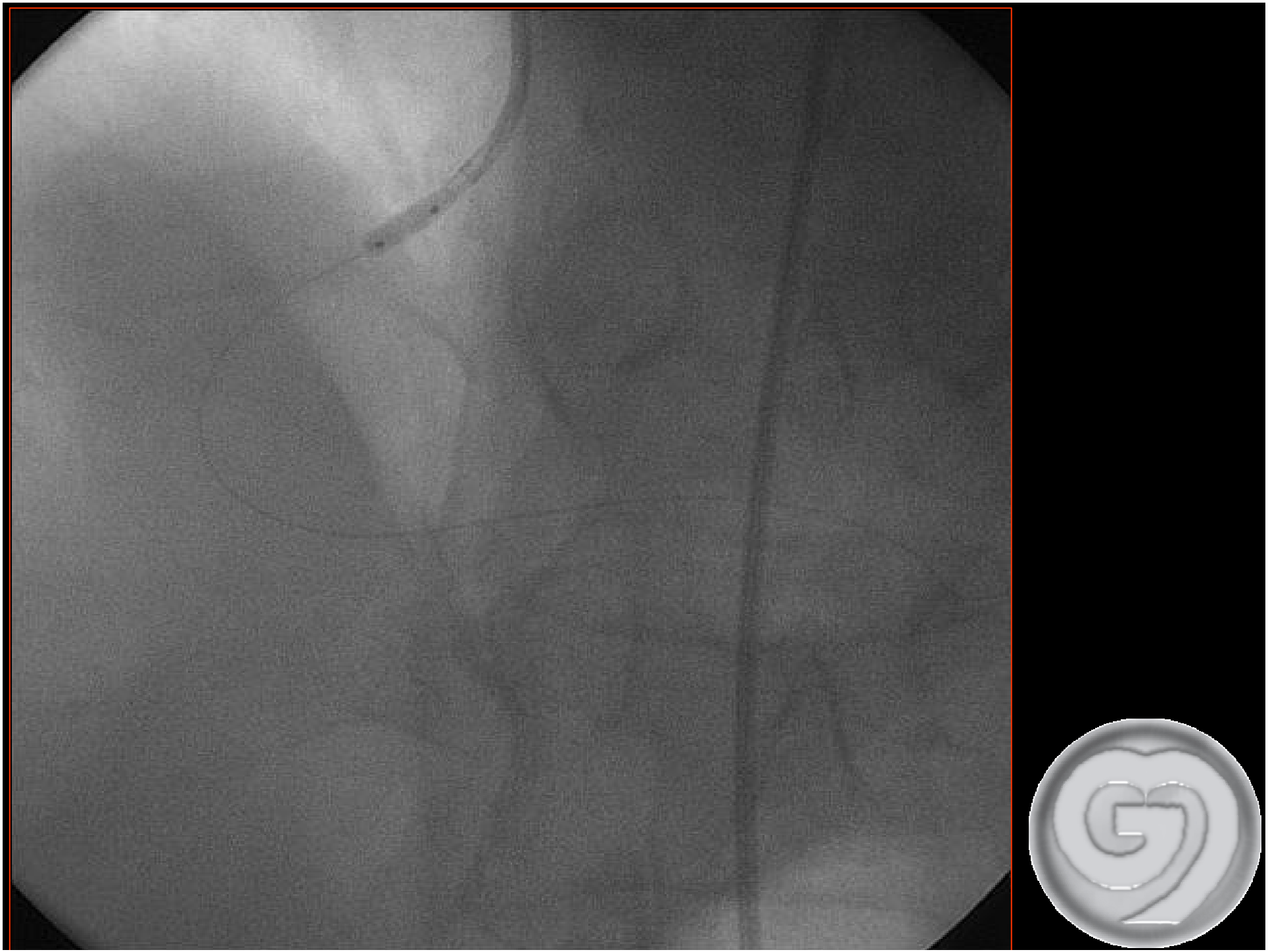
CORONARY ANGIOGRAM

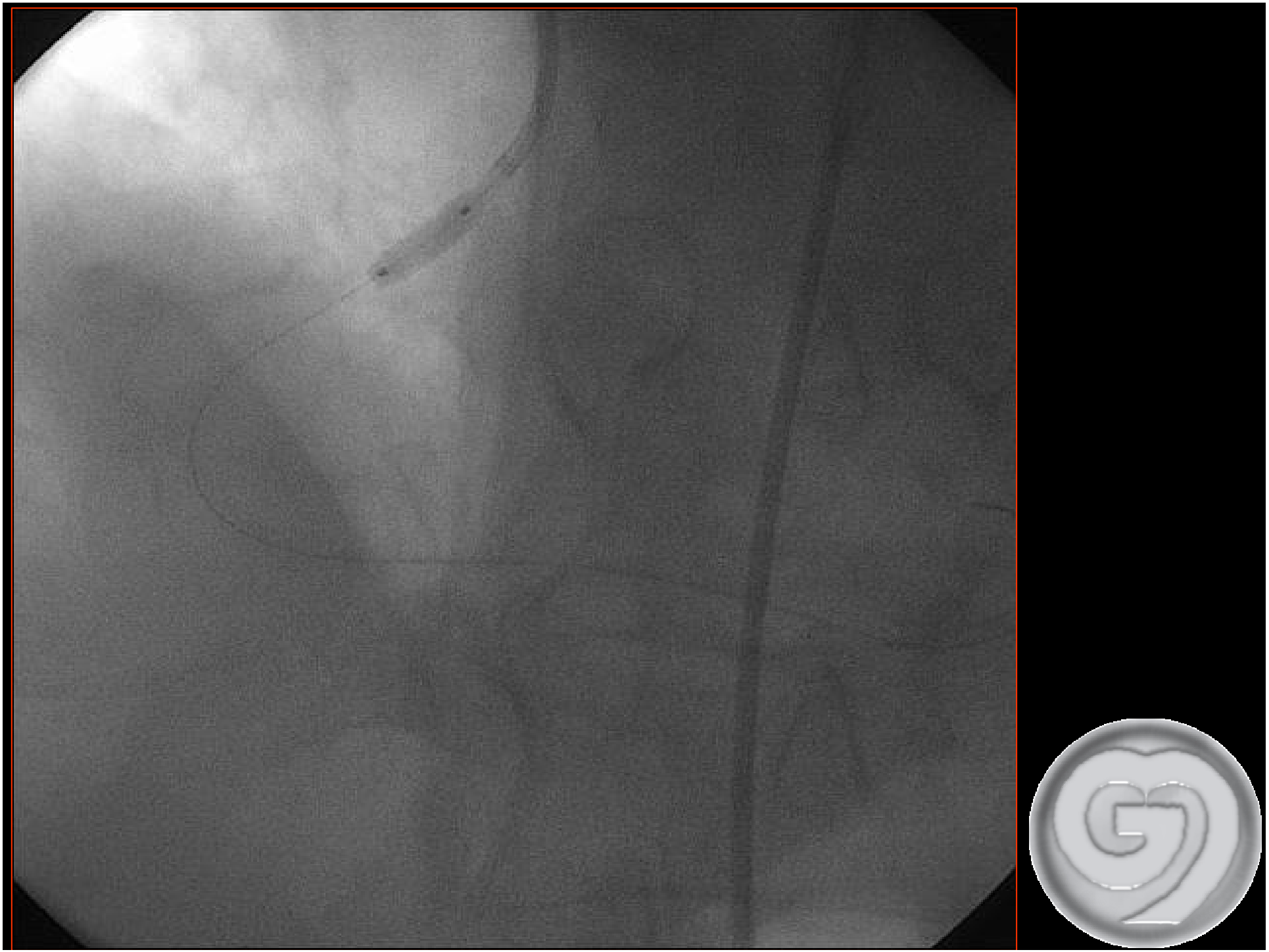
- **LM : ulcerated plaque w/o important compromise of the lumen**
- **LAD : Critical lesion proximal segment**
- **CX : Severe lesion OM1**
- **RCA : Ostial lesion**

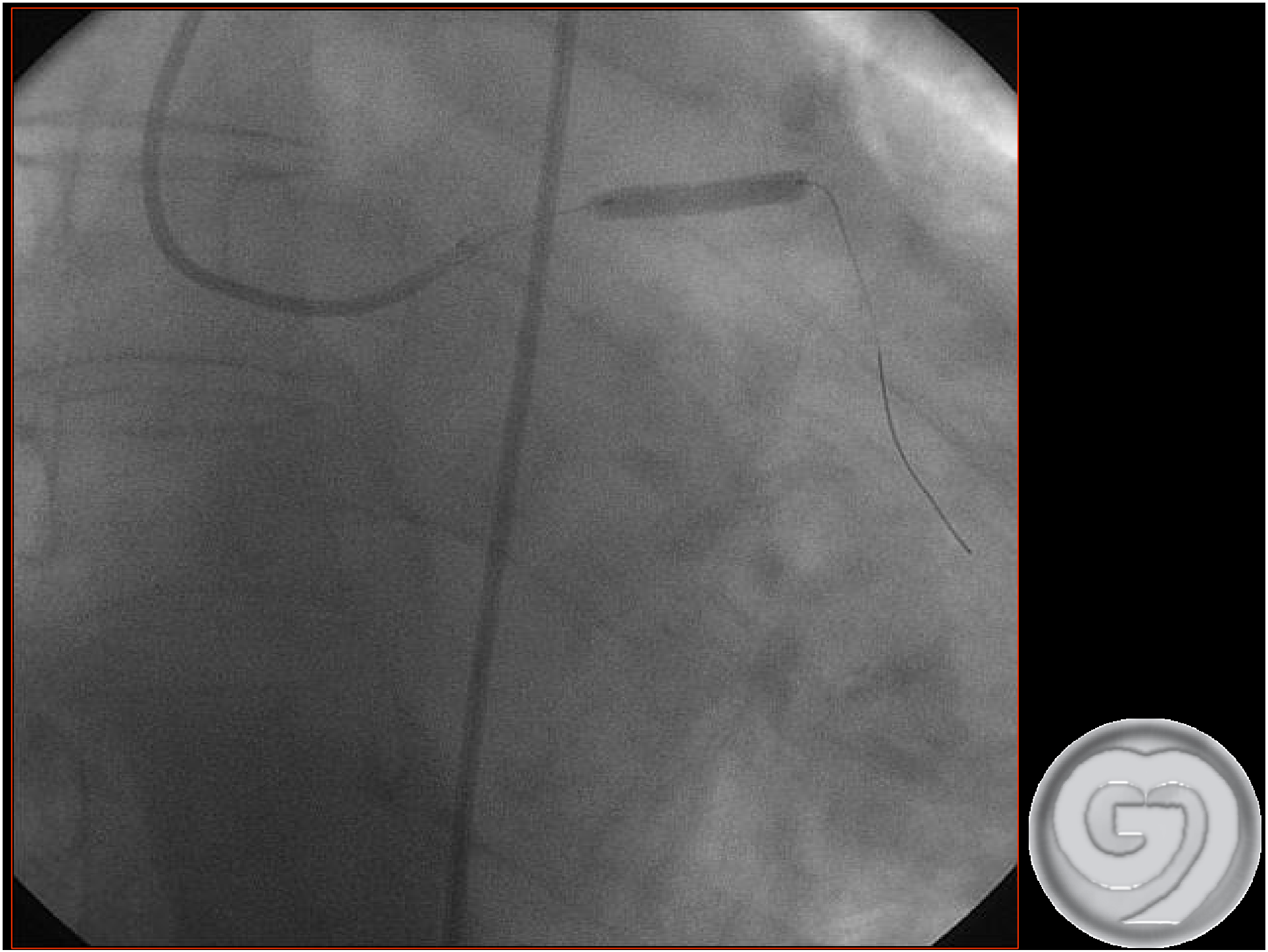


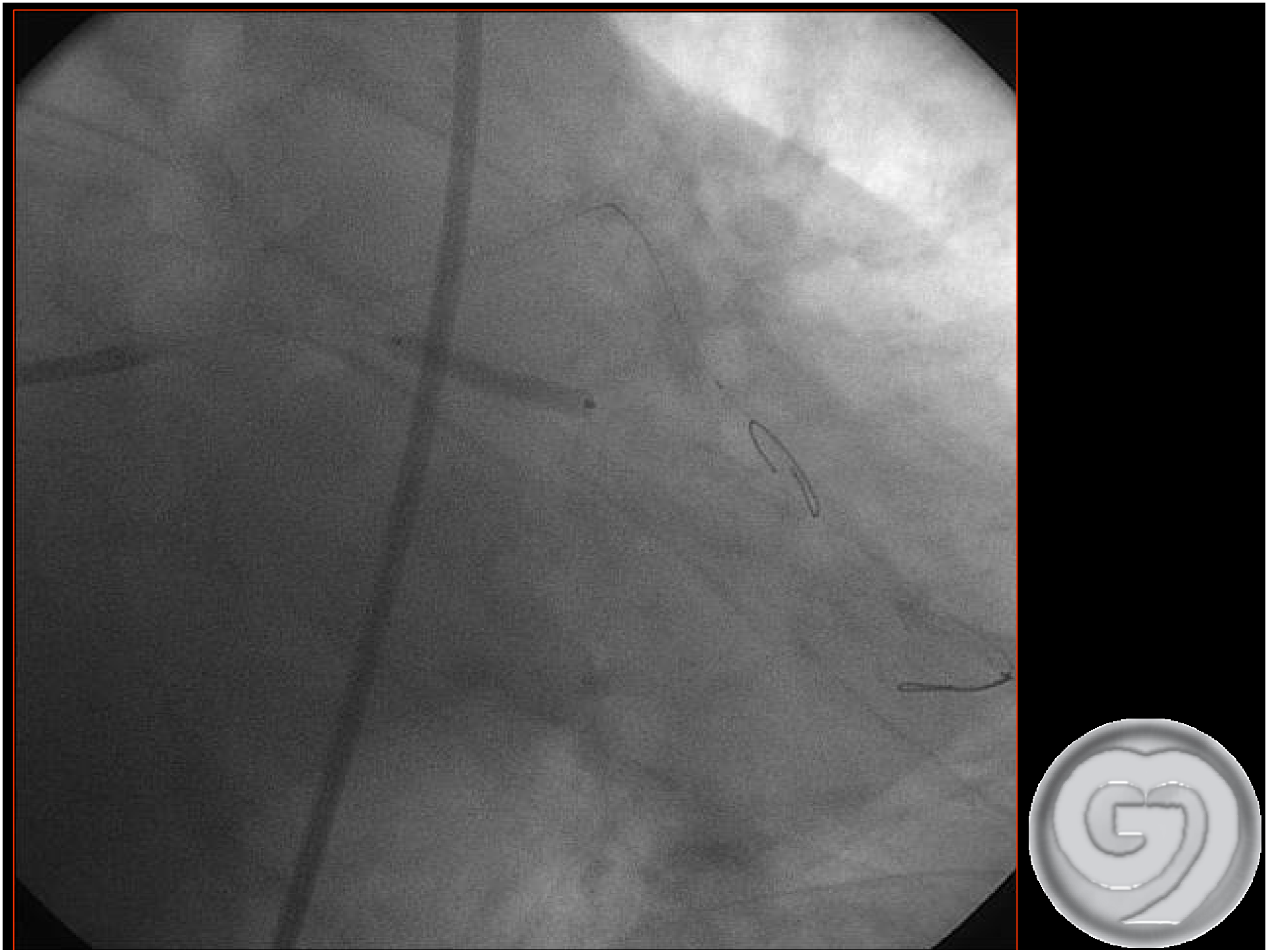
D.E.S.

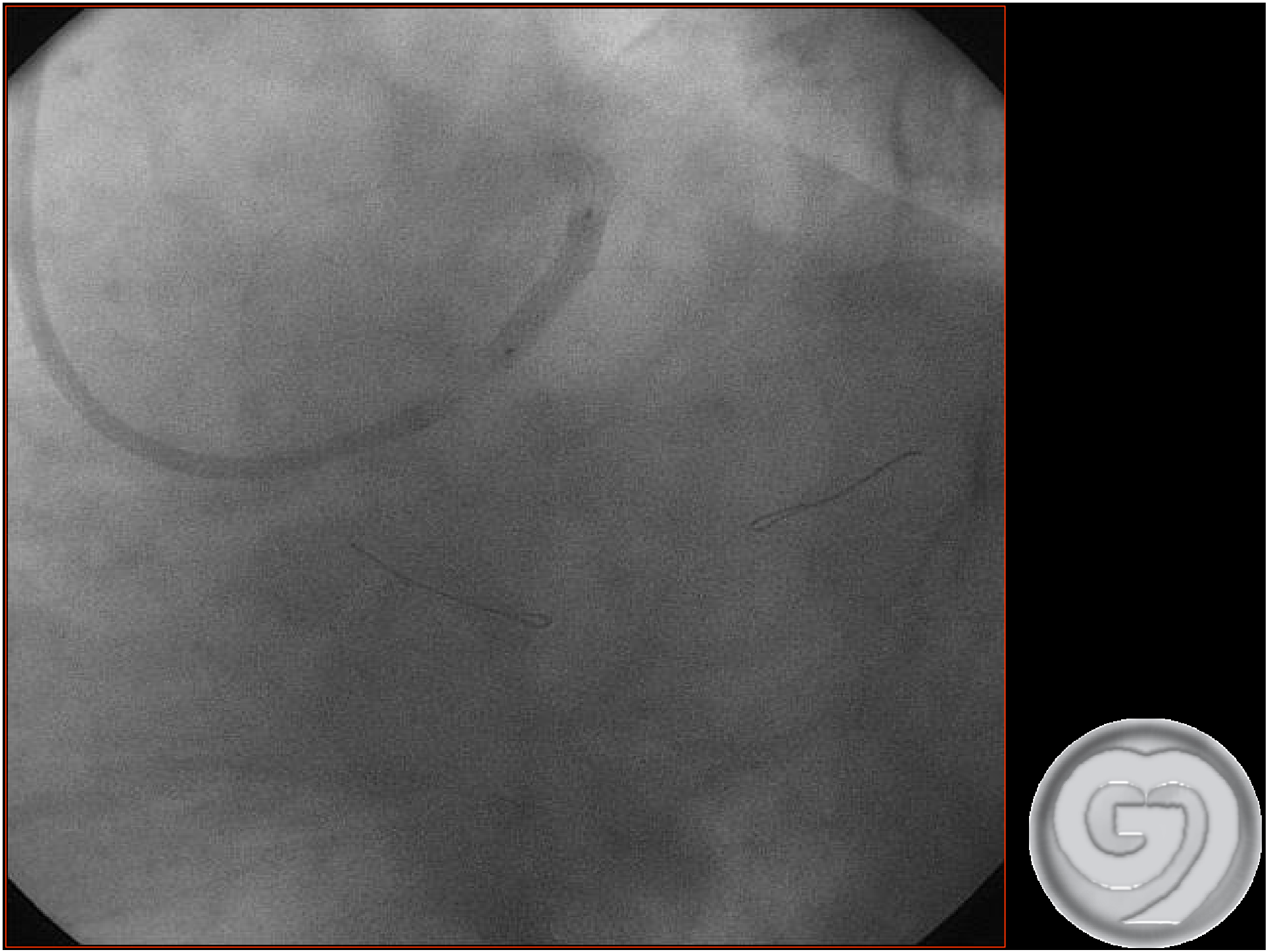
- Cutting balloon & stent Endeavor (3.5x10 mm) ostium RCA
- Stent Endeavor (3.5x24) in LAD
- Stent Endeavor (2.75x18mm) OM1
- Stent Endeavor (3.5x24 mm) LM-LAD
- Kissing balloon in LM-LAD-Cx











D.E.S.

- 6 mo. angiographic evaluation
- No restenosis in any of the stents

ENDEAVOR Program

Conclusions

- **Deliverability**
  - Endeavor drug-eluting stent deliverability documented in multiple patient populations and trials
- **Efficacy**
  - Efficacy of the Endeavor drug-eluting stent was maintained out to 24 months
- **Safety**
  - Safety of Endeavor stent may be unique among the DES programs

Ideal Scenarios for Endeavor Stent

- Lesions with reference vesel diameter ≥ 2.5 mm
- Patients with questionable compliance for antiplatelet therapy
- Lesions with high risk for restenosis and forseeable surgery
- ACS where the lesion principal component is thrombus
- STEMI ?