Safety and Endeavor II Subsets

Richard Kuntz*
Brigham and Women's Hospital
Harvard Medical School

***no conflicts of interest declared**

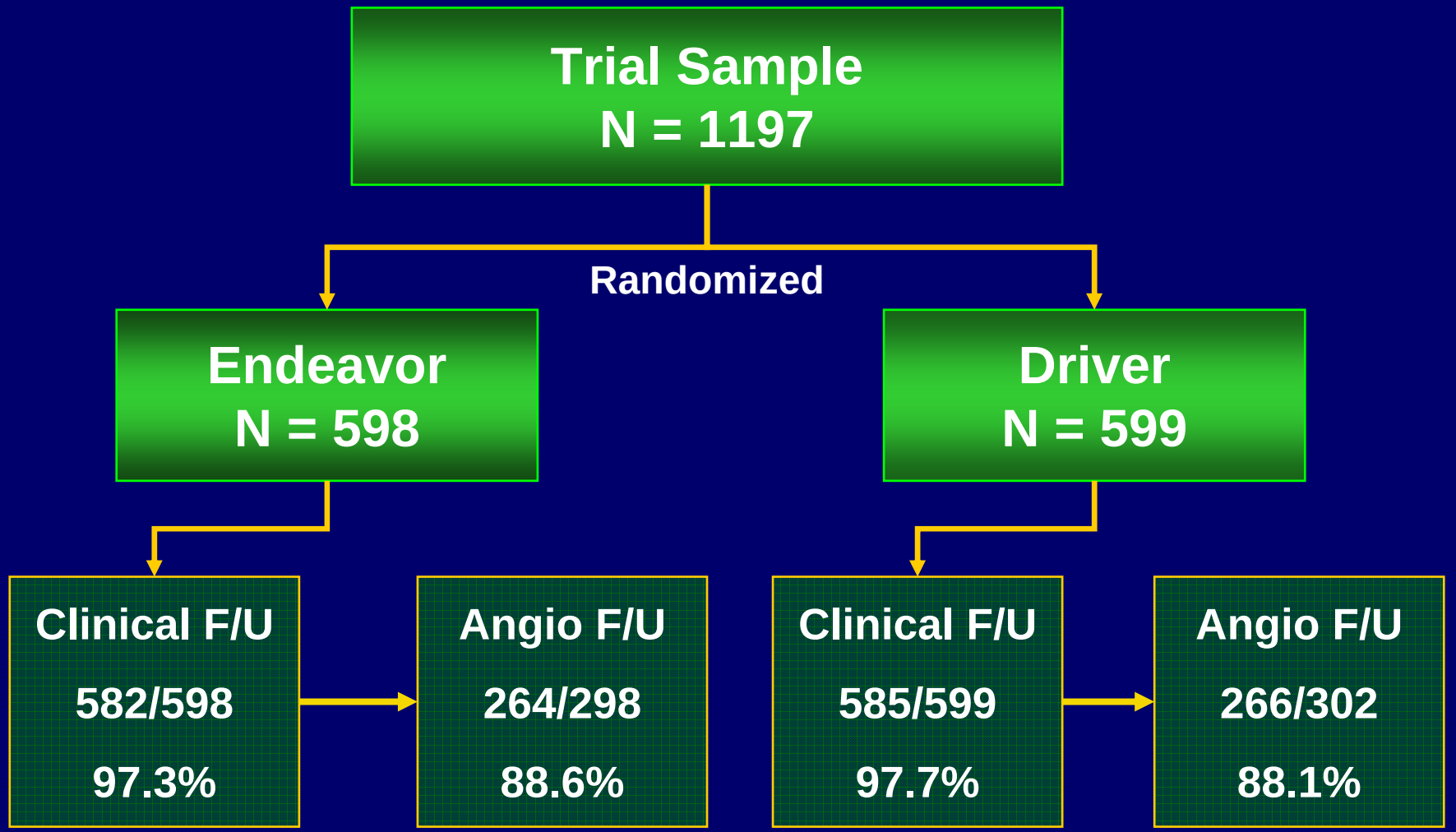
ENDEAVOR II
A Randomized Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesion

W. Wijns*, J. Fajadet* and R. Kuntz*

for the Endeavor II investigators

***no conflicts of interest**

ENDEAVOR II
Patient Flowchart

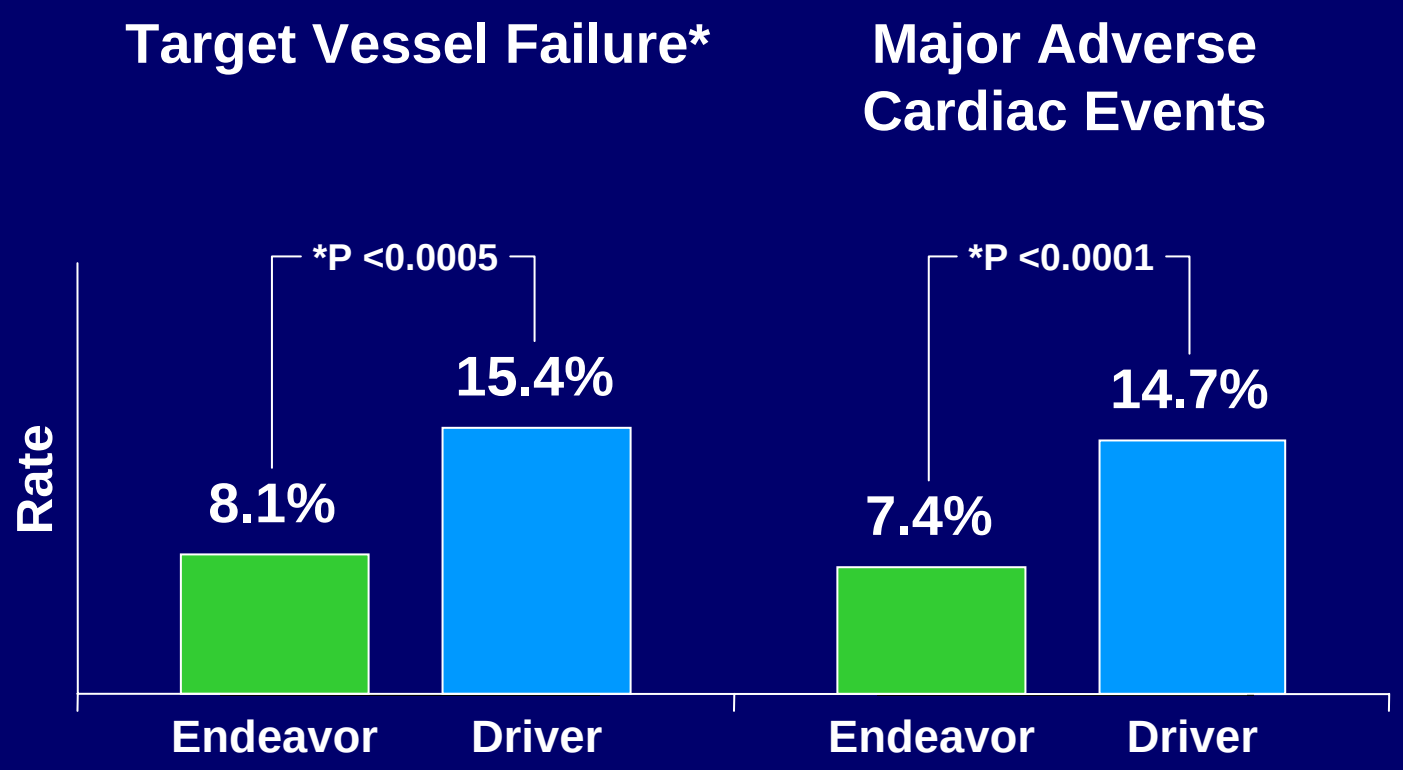


Procedure Characteristics

	Endeavor N = 588	Control N = 589	P Value
Stent Length:Lesion Length	1.84	1.79	ns
Stents per Lesion	1.12	1.11	ns
IIb/IIIa inhibitor use	13.2%	10.4%	ns
Lesion Success	99.8%	100%	ns
Device Success	99.3%	99.3%	ns
Procedure Success	97.4%	97.1%	ns

Lesion success	<50% residual in-segment percent diameter stenosis
Device success	<50% residual in-segment percent diameter stenosis with assigned stent
Procedure success	<50% residual in-segment percent diameter stenosis with assigned stent and without 30-day MACE

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

Clinical Results to 9 months

	Endeavor N = 582	Control N = 585	P value
Composite MACE (%)	7.4	14.7	<0.0001
Death	1.2	0.5	ns
Q-Wave MI	0.3	0.9	ns
Non Q-Wave MI	2.4	3.1	ns
CABG	0.0	0.0	ns
TLR	4.6	12.1	<0.0001
CABG	0.3	0.5	ns
PCI	4.3	11.6	<0.0001
TVR (%)	5.7	12.8	<0.0001
TVF (%) (Primary endpoint)	8.1	15.4	<0.0005

Endeavor II

9 month mortality

	Endeavor n = 582	Control n = 585	*P* value
Death	7 (1.2%)	3 (0.5%)	0.22
Cardiac*	5	3	
Non-Cardiac	2	0	

*Defined as death due to myocardial infarction, cardiac perforation or tamponade, arrhythmia, stroke within 30 days of the procedure or related to the procedure, death due to a complication of the procedure, and any death in which a cardiac cause cannot be excluded, as adjudicated by blinded clinical events committee.

ACC Late Breaking Trials, 6 March 2005

MDS 9m MACE Table 4

Endeavor II

*9 month cardiac mortality**

Treatment	Post-procedure day	Cause
Endeavor	1	Subacute stent thrombosis
Control	38	Acute respiratory failure
Control	92	Non-target vessel Q wave infarction
Control	134	Sudden death
Endeavor	175	Sudden death
Endeavor	182	Sudden death
Endeavor	229	Sudden death
Endeavor	243	Surgical death 1d post TLR-CABG

***As adjudicated by blinded clinical events committee.**

Endeavor II

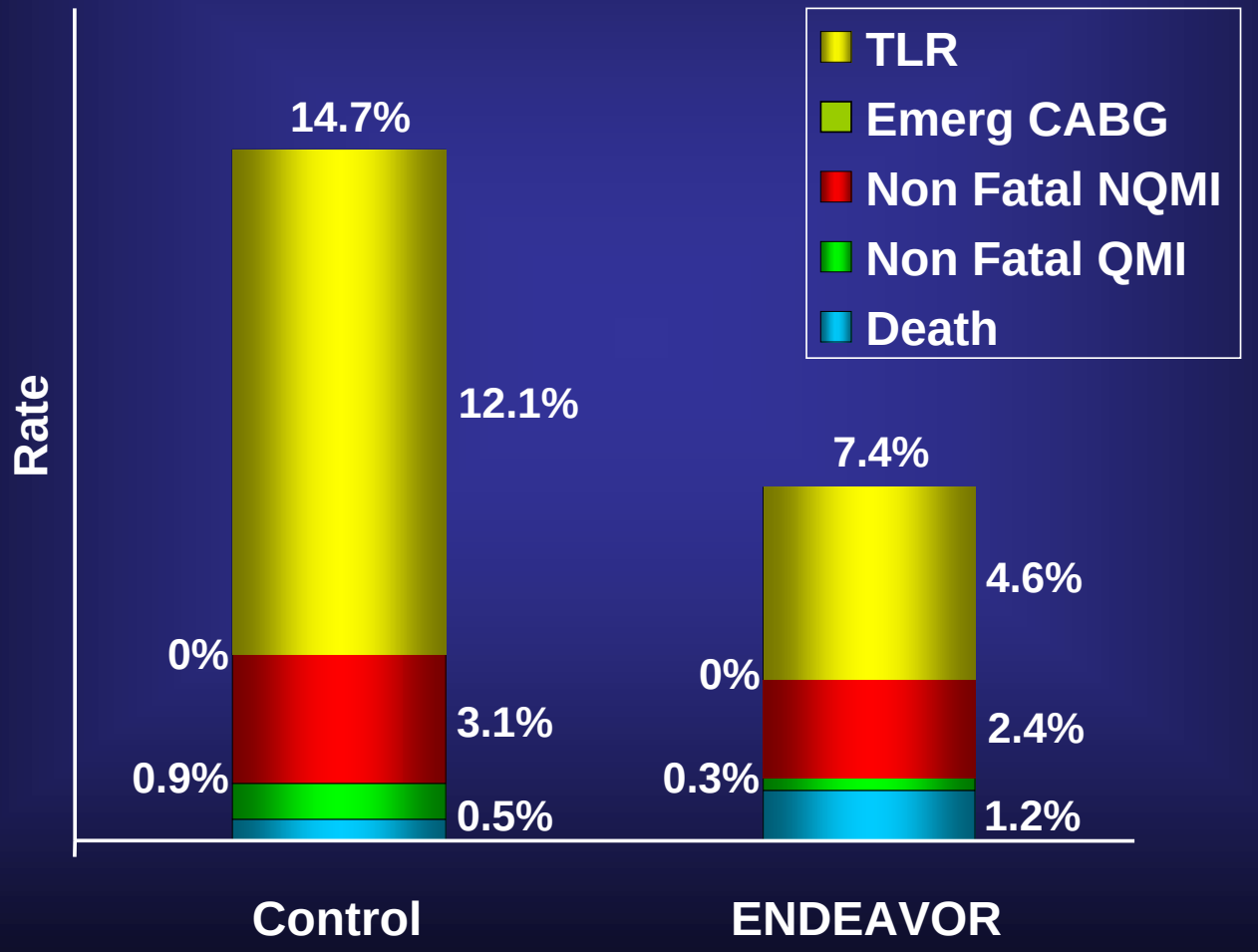
*9 month non-cardiac mortality**

Treatment	Post-procedure day	Cause
Endeavor	39	Metastatic lung cancer
Endeavor	262	Intracerebral hemorrhage

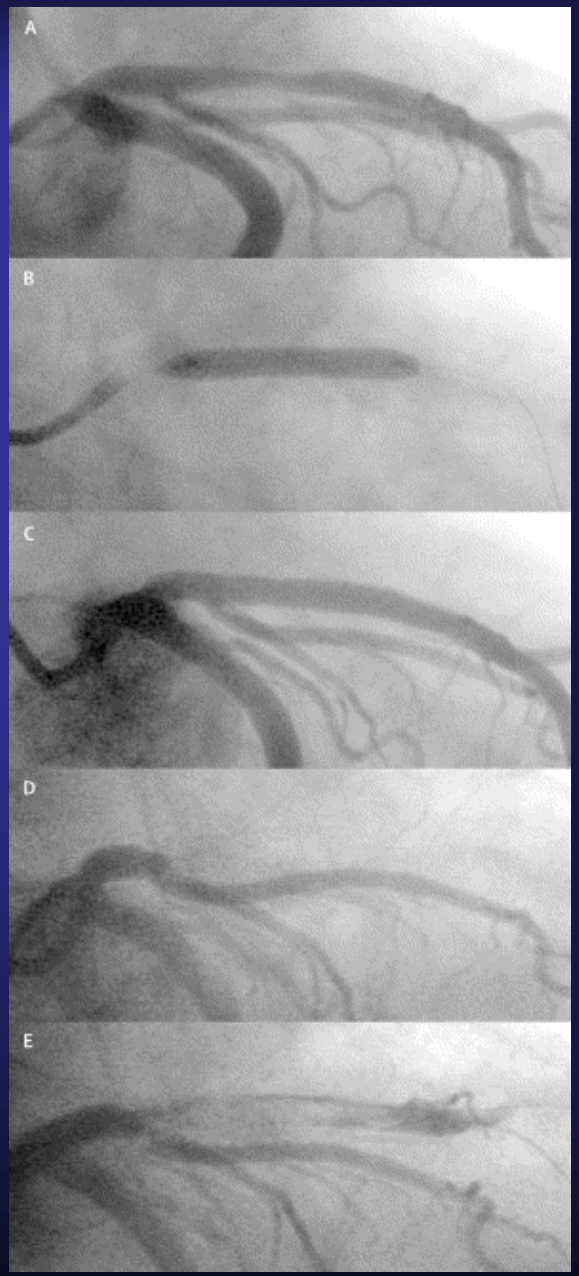
***As adjudicated by blinded clinical events committee.**

Endeavor II

Secondary Endpoint Results
Non-Hierarchical MACE to 9 months



DES
Late Stent Thrombosis



Drug Eluting Stent
Late Stent Thrombosis

- EP McFadden, E Stabile, E Regar, et. al. Research Letter, *Lancet* 2004: 364:1519
  - 4 cases of angiographically documented late stent thrombosis, accompanied by acute MI
    - SES (335, 375 days)
    - PES (343, 442 days)
  - All cases occurred soon after clopidogrel cessation

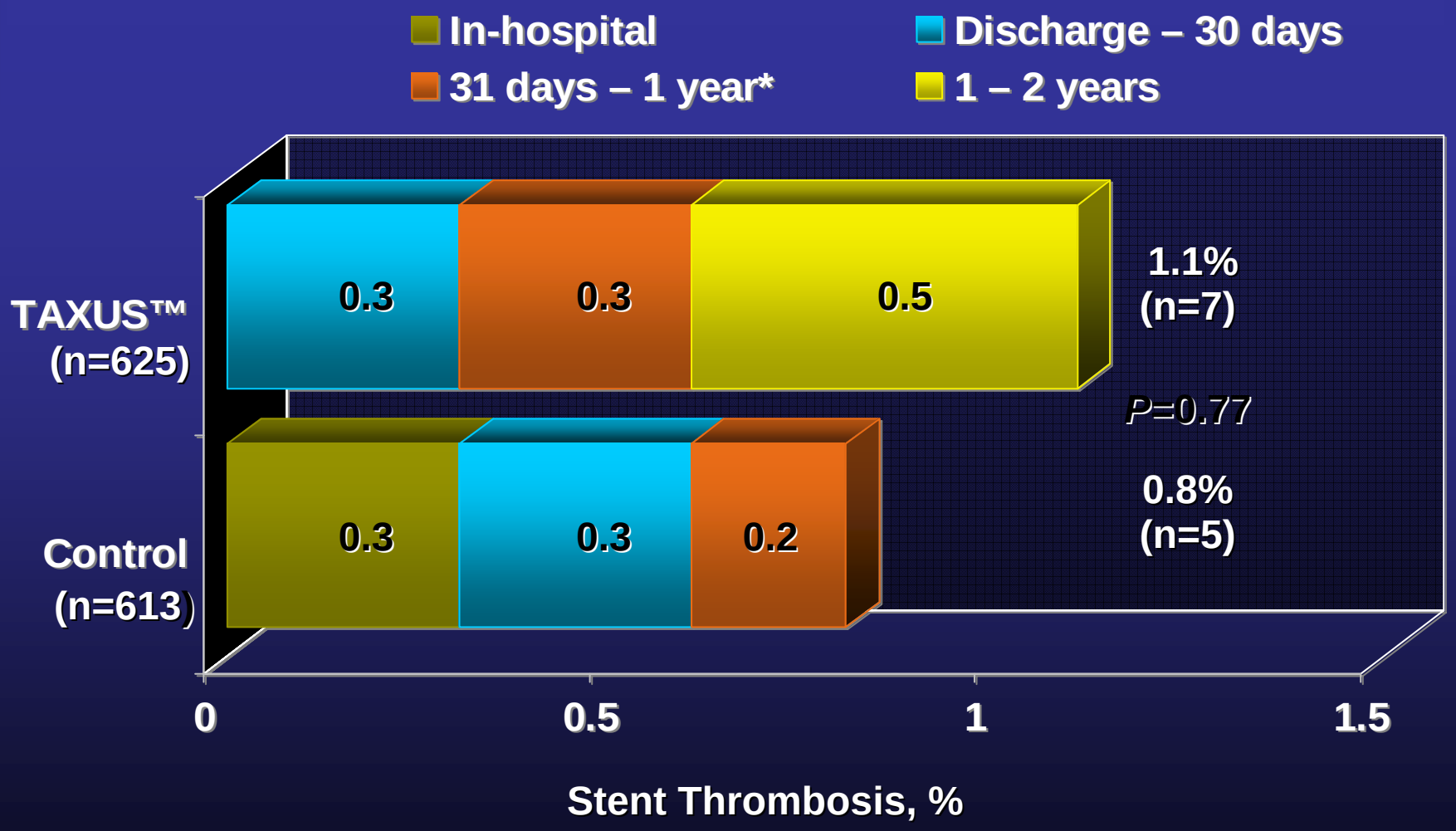
TAXUS II

Stent Thrombosis

	Combined Control (n=270)	TAXUS™ SR (n=131)	TAXUS™ MR (n=135)	*P*-Value SR vs Control	*P*-Value MR vs Control
≤1 d	0.0	0.8 (1/131)	0.0	NS	undef
2 d – 6 mo	0.0	0.0	0.0	undef	undef
6 mo – 1 yr	0.0	0.8 (1/130)	0.7 (1/134)	NS	NS
1 – 2 yr	0.0	0.8 (1/129)	1.5 (2/131)	NS	NS

A. Colombo, TCT 2004 : TAXUS™ II 2 year results.

TAXUS™ IV: Stent Thrombosis



*All within 1 – 6 months.

G.Stone, TCT 2004: TAXUS™ IV 2 year results.

SIRIUS

Stent Thrombosis (1080 days)

	Sirolimus (%) (n=533)	Control (%) (n=525)
Acute (≤ 24 hours)	0	0
Subacute (1-30 days)	0.2% (1)	0.2% (1)
Late (31-270 days)	0.2% (1)	0.6% (3)
Late (271-720 days)	0.2% (1)	0
Late (721-1080 days)	0.2% (1)	0
Total	***0.8% (4)***	***0.8% (4)***

Clinical Trials with CYPHER® Stent

All Late Thrombosis at 720 Days				
	Control		CYPHER®	
	Events/ # of Patients	%	Events/ # of Patients	%
RAVEL	0/118	0.0%	0/120	0.0%
SIRIUS	3/525	0.6%	2/553	0.4%
New SIRIUS	1/227	0.4%	1/225	0.4%
Total	**4/870**	**0.5%**	**3/878**	**0.3%**

Paclitaxel Stent Thrombosis

Bavry et al, *J Am Coll Cardiol* 2005

- Meta-anlysis of 8 PES/BMS trials

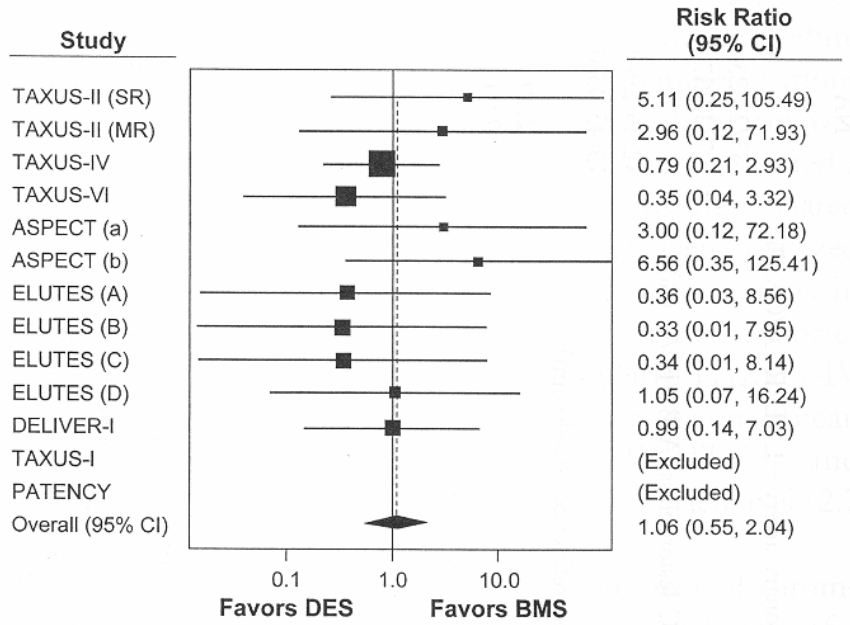


Figure 1. In trials with varying doses of paclitaxel, a = 1.3, b = 3.1, A = 0.2, B = 0.7, C = 1.4, and D = 2.7 μg paclitaxel/mm^2 of stent. BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; MR = moderate-release; SR = slow-release.

PES, SES, and BMS Thrombosis

Moreno et al, *J Am Coll Cardiol* 2005

10 RCT DES studies of 5030 patients pooled

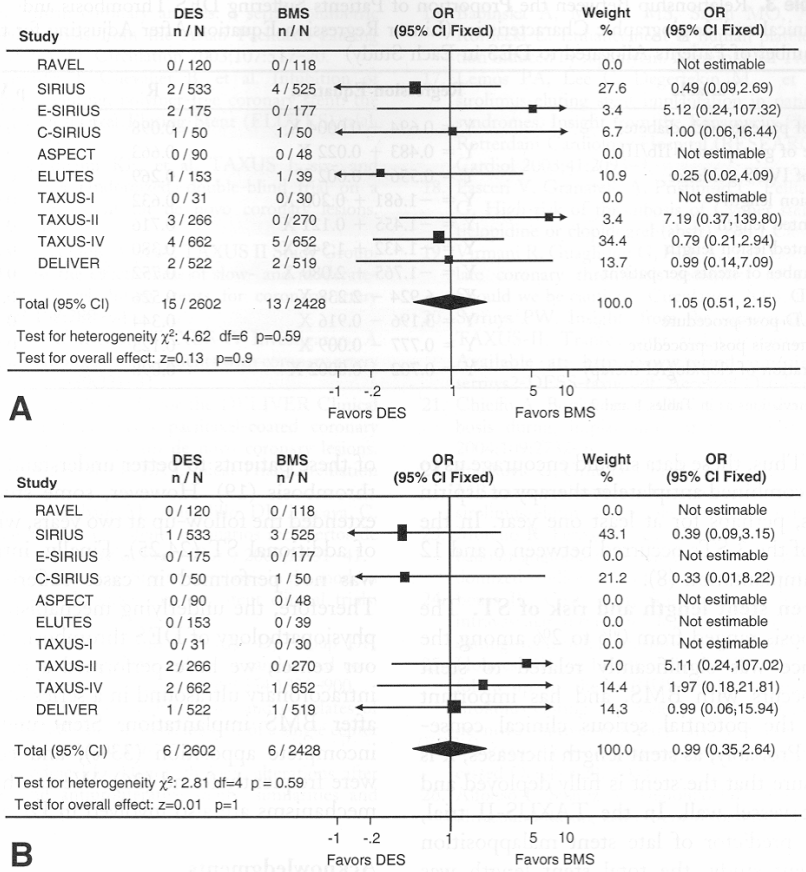
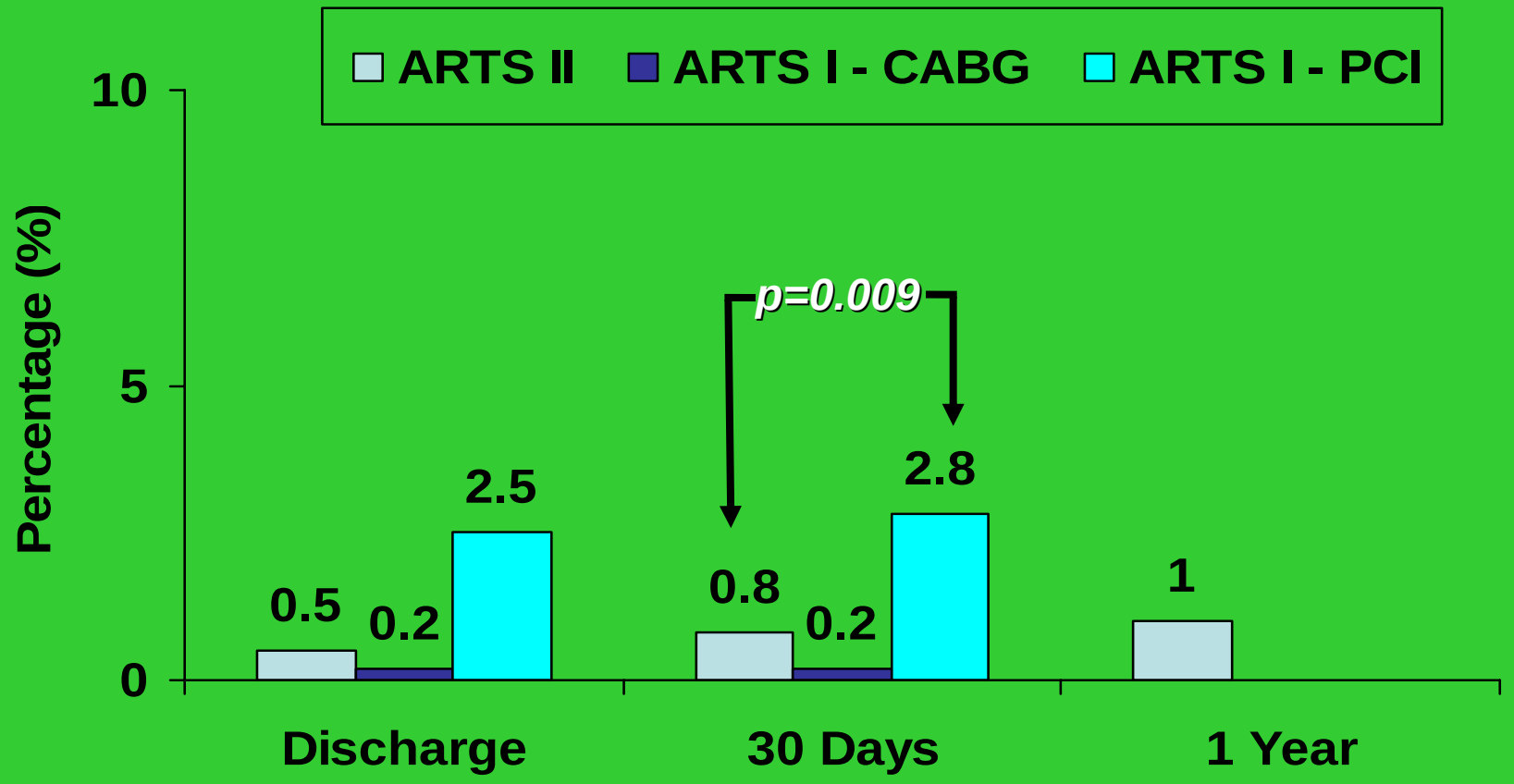


Figure 1. (A) Comparison between the rate of stent thrombosis in patients allocated to drug-eluting stents (DES) or bare-metal stents (BMS) in the randomized studies and in the pooled population. **(B)** Comparison between the rate of late stent thrombosis in patients allocated to DES or BMS in the randomized studies and in the pooled population. CI = confidence interval; OR = odds ratio.

ARTS II

Angiographic Occlusions

*** Definition of thrombotic occlusion: Angiographically proven occlusion (TIMI 0 or 1) or flow limiting thrombus (TIMI 1 or 2)**



ARTS II up to 1 year:
5 TLR (1 Q wave MI, 4 with substantial cardiac enzyme release)

Safety Results

Stent Thrombosis	Endeavor N = 582	Driver N = 585	P value
In-hospital	0.3% (2)	0.3% (2)	
Discharge to 30 days	0.2% (1)	0.9% (5)*	
>30 – 270 days	0	0	
Total at 270 days	0.5% (3)	1.2% (7)	0.34

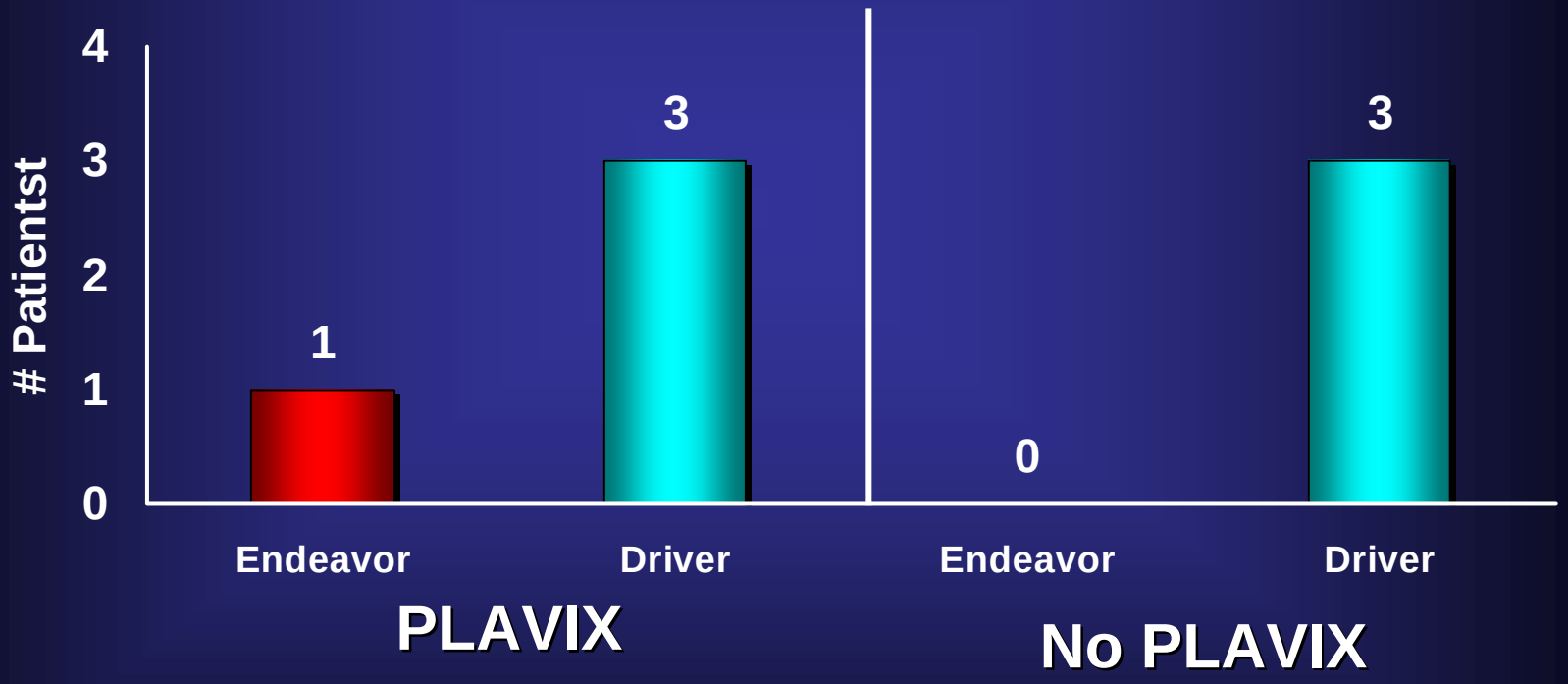
IVUS Results	Endeavor N = 100	Driver N = 83	P value
Late Acquired Stent Malapposition	0%	0%	ns
Late Aneurysm	0%	0%	ns

Stent thrombosis defined as angiographic thrombus or subacute closure in the stented vessel or any death not attributed to a non-cardiac cause within the 1st 30 days

*3/6 post-discharge stent thrombosis cases occurred in Driver arm when Plavix was stopped prematurely

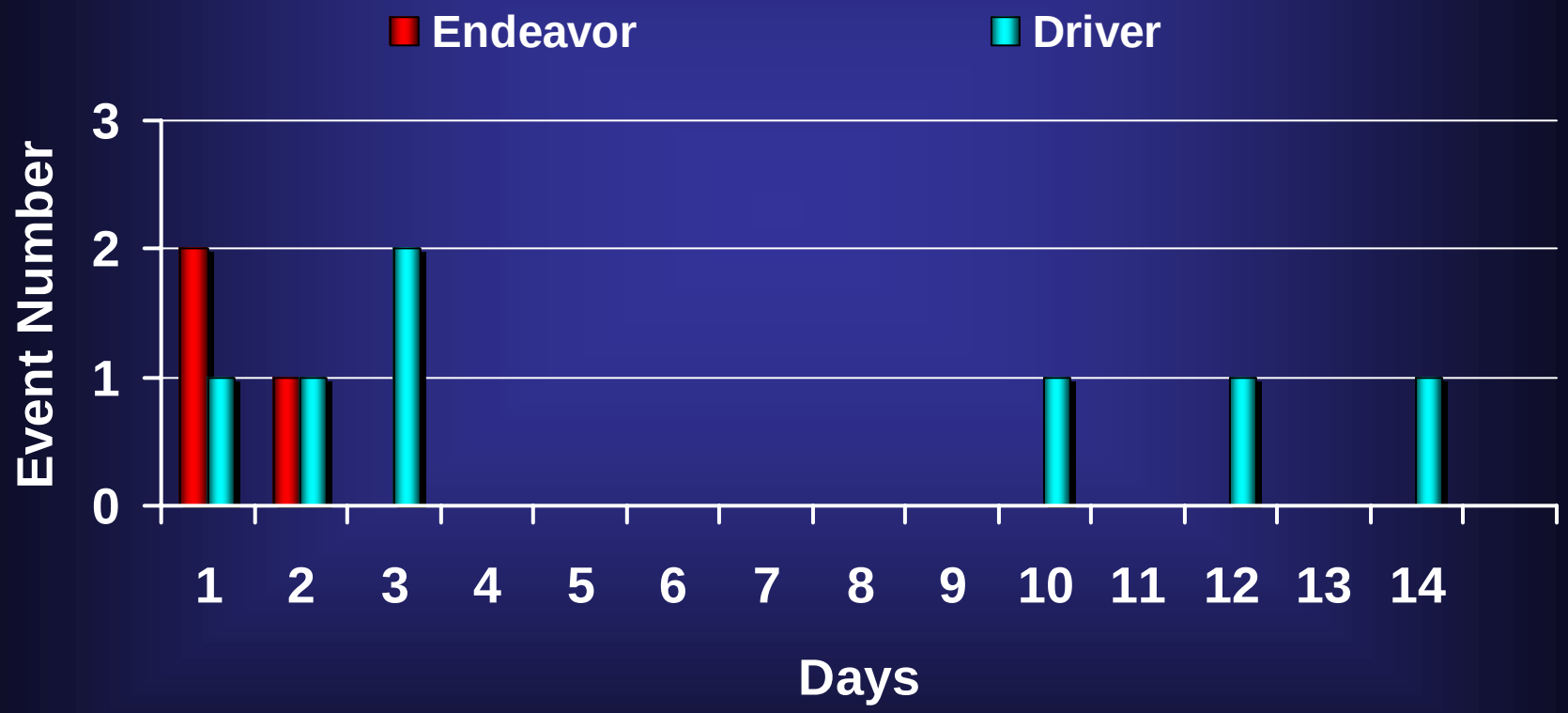
Endeavor II

Stent Thrombosis and Plavix Use After Discharge (> 1 Day)



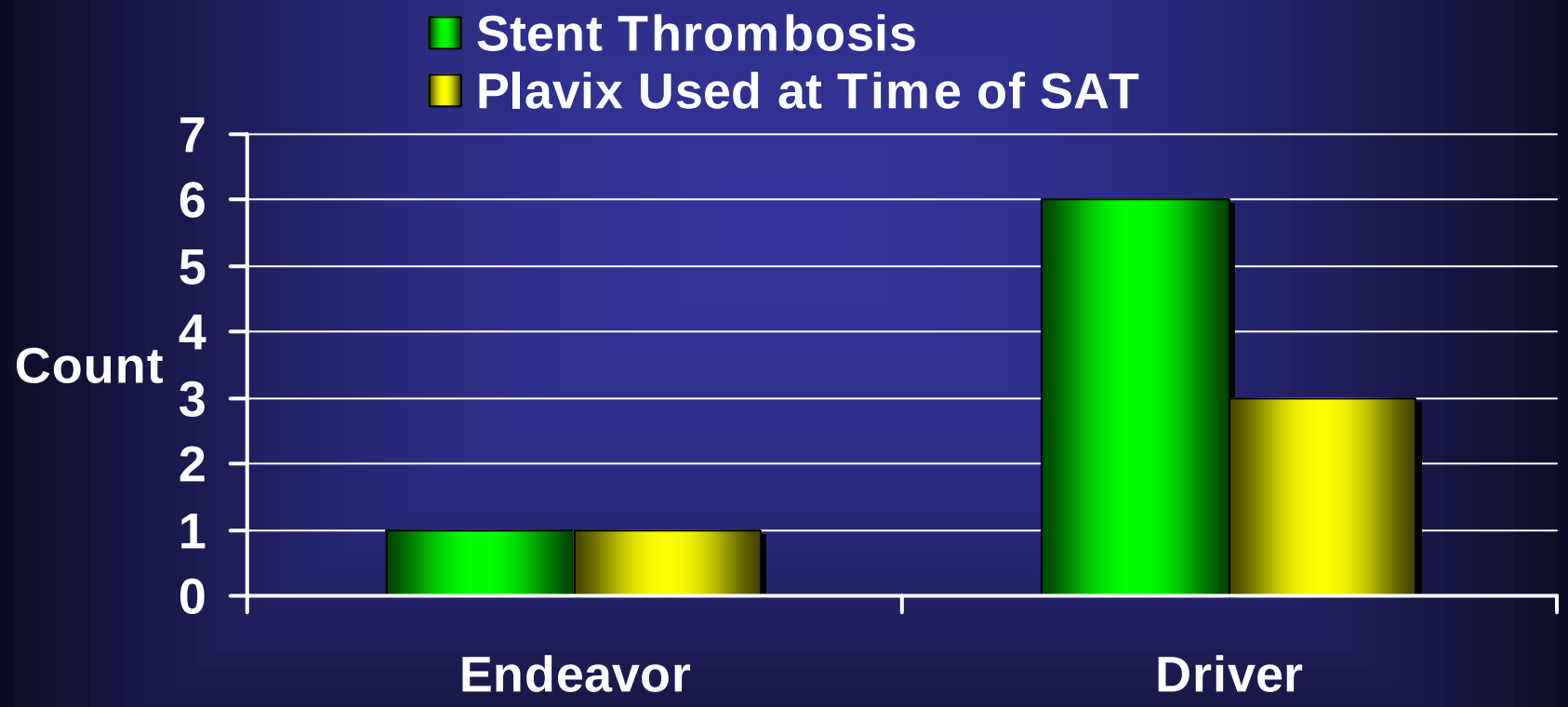
Endeavor II

Stent Thrombosis Timing



Endeavor II

Stent Thrombosis and Plavix Use After Discharge (> 1 Day)



Endeavor Safety

- Device success was >99%
  - *Driver has a good reputation for delivery and ease-of-use*
- Stent Thrombosis rate was 0.5%
- Clinical Restenosis rate was <5%

Conclusion: Endeavor is a Safe and Effective Stent

What about the higher, non-significant sudden death rate?

Endeavor II

9 month mortality

	Endeavor n = 582	Control n = 585	*P* value
Death	7 (1.2%)	3 (0.5%)	0.22
Cardiac*	5	3	
Non-Cardiac	2	0	

*Defined as death due to myocardial infarction, cardiac perforation or tamponade, arrhythmia, stroke within 30 days of the procedure or related to the procedure, death due to a complication of the procedure, and any death in which a cardiac cause cannot be excluded, as adjudicated by blinded clinical events committee.

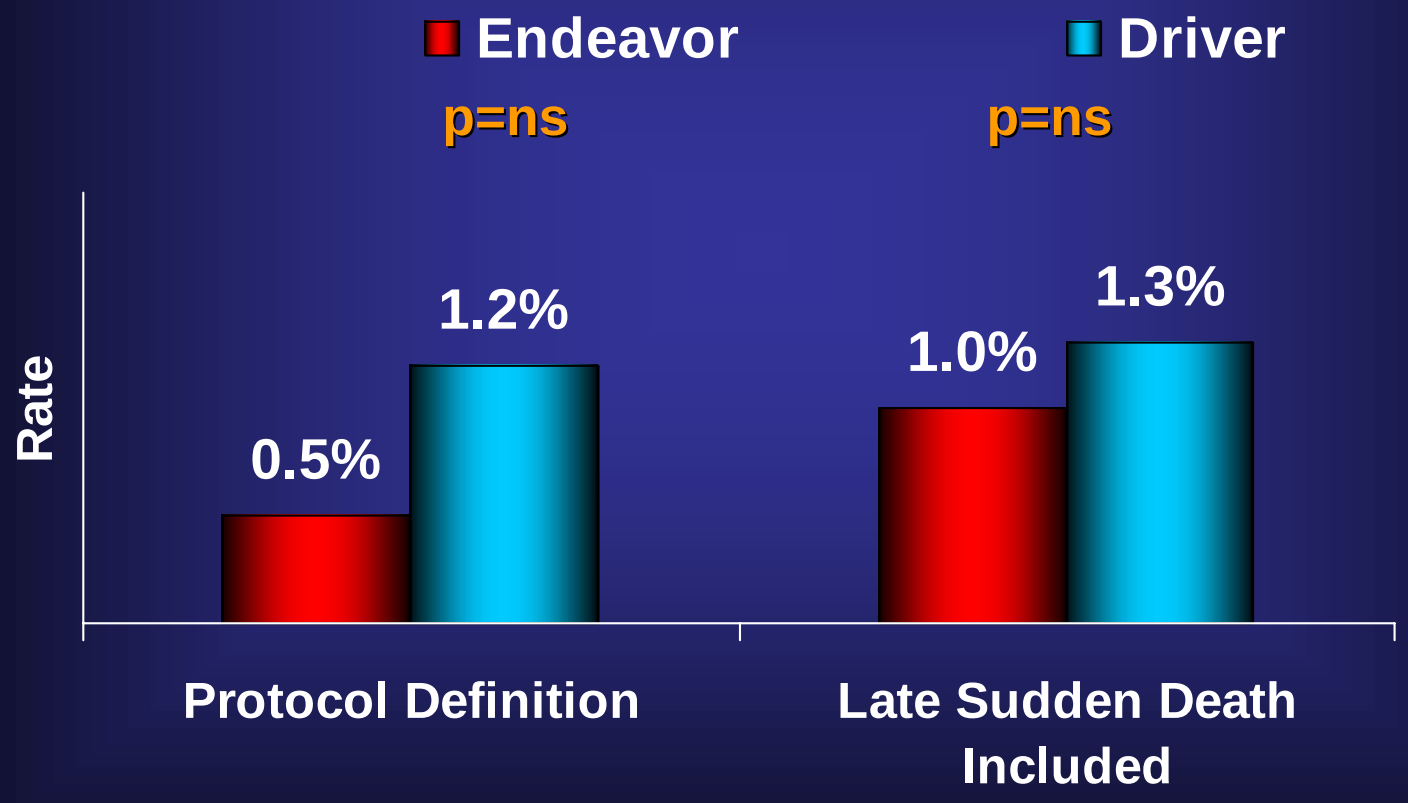
Sudden deaths in E2

- 4 late (>30 day) sudden deaths in Endeavor II
  - 3 in Endeavor arm
  - 1 in Driver arm
- How many ways can you divide up 4 deaths? Answer: 5
  - 4:0
  - 3:1
  - 2:2
  - 1:3
  - 0:4

Endeavor II

Stent Thrombosis Rates

Protocol Definition vs. Late Sudden Death Inclusive



Should We Include Late Sudden Deaths as Possible Stent Thromboses?

- What is the experience with stent thrombosis timing and clinical presentation?
- Is it common or possible to see stent thrombosis as sudden death only?
- Is it expected that at least 4 of 1197 patients with coronary disease will have sudden death over 9 month follow-up?

Definition of Stent Thrombosis

- Common definition:
  - Angiographic evidence of partial or total stent occlusion, or sudden cardiac death in 30 days, or MI not attributable to another non-target vessel

Stent Thrombosis and Mortality

Study	N	ST	Death	Mortality
[1]Leons 1653	38	1	2.6%	
[2]Cutlip	6186	53	10	18.9%
[3]Ong	2512	26	3	11.5%
[4]Fujii	C-Con	15	1	6.7%
Summary		**159***	**15**	**11.6%**

1 STARS Trial *NEJM* 1998
2 BMS Overview *Circulation* 2001
3 SES, PES and BMS pooled *J Am Coll Cardiol* 2005
4 Fujii Case-Control Study *J Am Coll Cardiol* 2005 (IVUS only patients)
*** Sum total does not included 3 pts counted twice in Leon and Cutlip**

Timing of ST in BMS

- Cutlip overview of 6186 patients: 51/53 ST occurred in the first week after PCI.
- Ong overview of 2152 PES/SES and BMS stent patients: 24 of 26 ST occurred by 11 days

PES, SES, and BMS Thrombosis

Ong et al, *J Am Coll Cardiol* 2005

- ST Timing in 2152 pts with overall 1.1% stent thrombosis rate

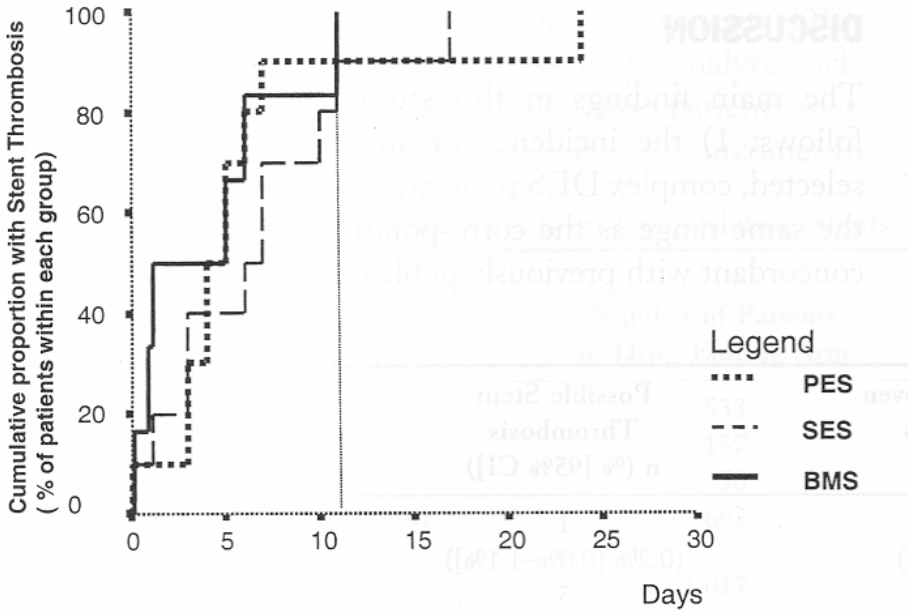
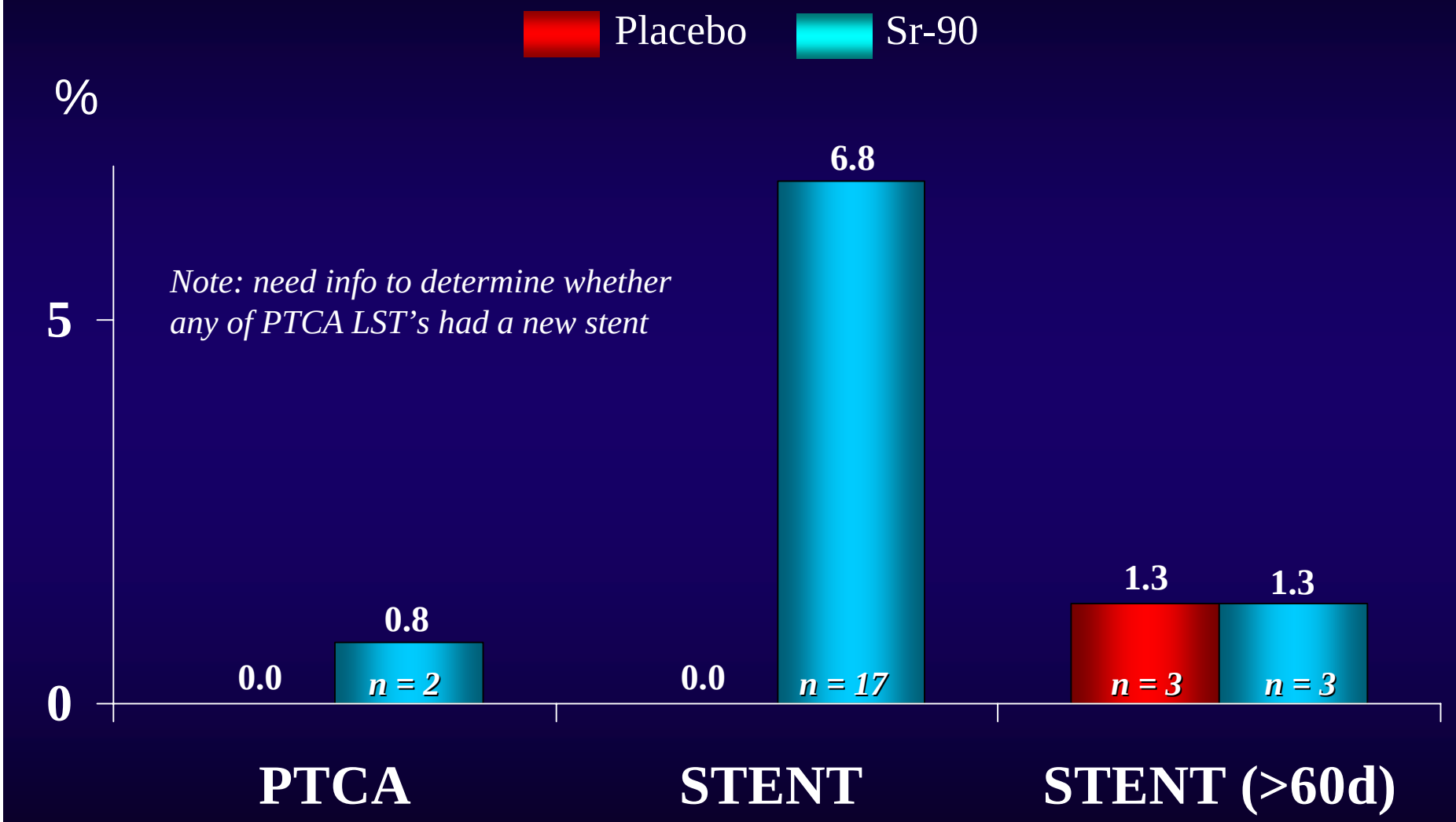


Figure 1. Cumulative incidence of angiographic stent thrombosis stratified by groups against time. **Vertical line** = day 11 on horizontal axis. BMS = bare-metal stents; PES = paclitaxel-eluting stents; SES = sirolimus-eluting stents.

Late Site Thrombosis
Beta-Cath Trial

	Sr-90	Placebo	P value
PTCA	**2 (0.8%)**	**0 (0.0%)**	
Stent	**17 (6.8%)**	**0 (0.0%)**	
Stent ≥ 60/90d	**3 (1.3%)**	**3 (1.3%)**	

Late Site Thrombosis



Sudden deaths in E2

- 4 late (>30 day) sudden deaths in Endeavor II
  - 3 in Endeavor arm
  - 1 in Driver arm
  - NO late stent thromoses seen!
- If these sudden deaths were caused by a stent thrombosis problem, we should have seen 4-8 times as many patients with non-fatal MI and Stent thrombosis
  - Similar to Beta Cath
  - **We would expect a ST rate of at least 3% if the sudden deaths represented the ST fatalities**
- The likelihood of late stent thrombosis manifesting as late sudden death alone: ~0%.

Endeavor and Safety Assessment

- The Enedavor stent has been studied in a rigorous fashion in E1 and E2
- The ST rate is 0.5%
- There are no other safety concerns

The combination of excellent safety, Driver ease-of-use, and low (<5%) clinical restenosis make the Endeavor stent a logical treatment choice for patients who suffer from coronary disease.