

DES THROMBOSIS RESULTS FROM CONTEMPORARY REGISTRIES At the Washington Hospital Center

Ron Waksman, MD

Director of Experimental Angioplasty

Associate Chief of Cardiology

Washington Hospital Center, Washington, DC

**Assistant Professor of Medicine, Georgetown
University Medical Center**

Disclosure

- Consultant and speaker or research grant Support from Medtronic, Boston Scientific, Biotronik, GSK, Sanofi, BMS
- Educational Grant Support for CRT from variety of device and drug companies
- You will find this presentation on

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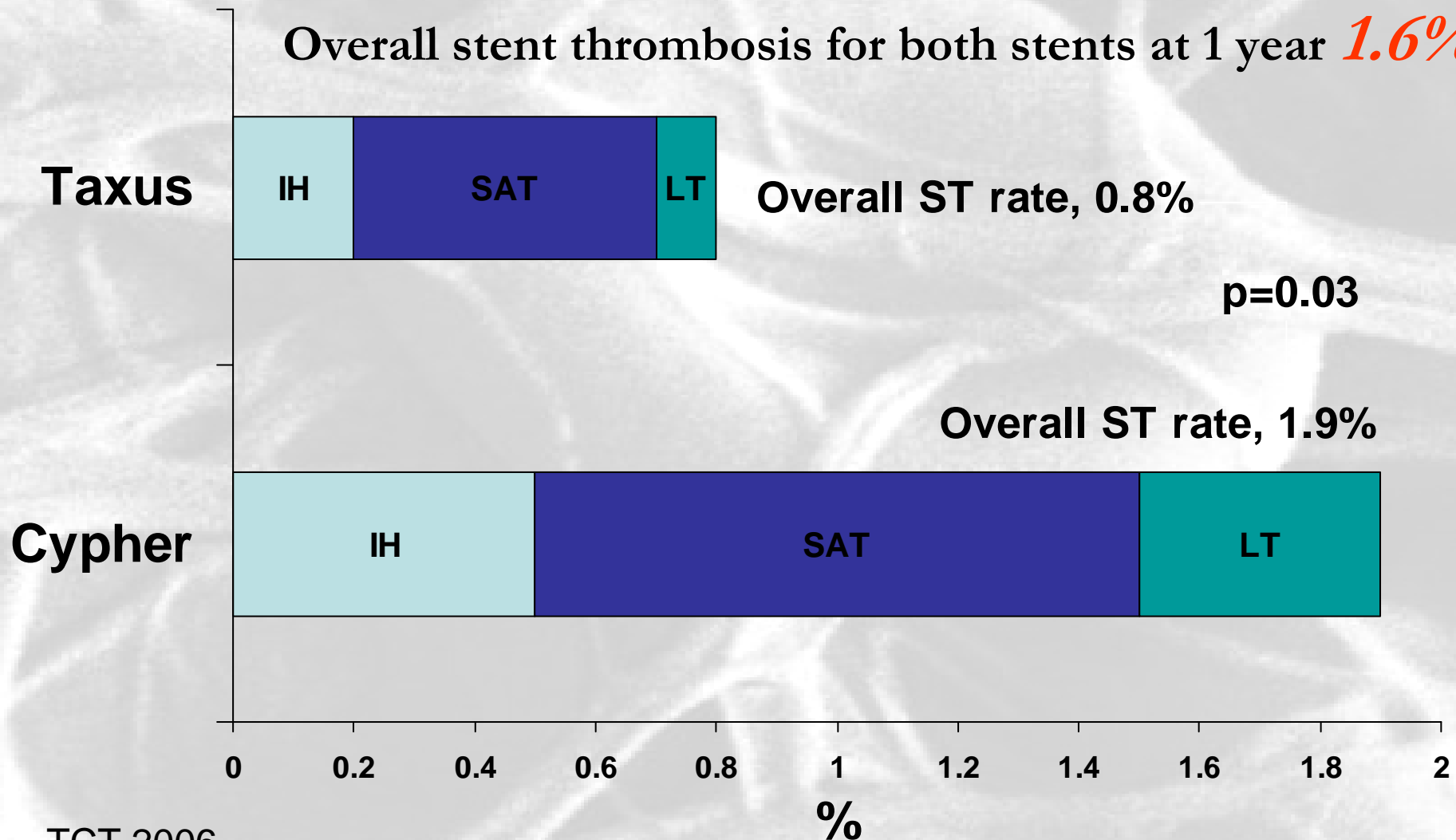
- **Single Center with 11 cath labs**
- **31 independent Interventional cardiologists**
- **Registries conducted under local IRB approval**
- **All patients underwent PCI per standard of care at the Washington Hospital Center**
- **IVUS guided PCI performed in 70% of interventions**
- **All patients were discharge on dual antiplatelet therapy for a minimum of 6-12 months with detailed instructions on the importance of long-term antiplatelet compliance**

- **Data on 7266 patients undergoing PCI (1135 lesions) with DES collected based on ACC database**
- **Patients followed at 30 days 6 months 12 months 24 months by office visit or telephone contact**
- **Events are adjudicated by independent committee**
- **All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).**
- **A p-value <0.05 denotes statistical significance**
- **Predictors of stent thrombosis were identified by proportional Cox or logistic regression analysis – stepwise multivariate regression models with an entry of 0.2 and a stay of 0.05 were used**

Cumulative Stent Thrombosis (Angio) – 12 Months

2769 patients 100% Follow-up at 1 year

Overall stent thrombosis for both stents at 1 year **1.6%**



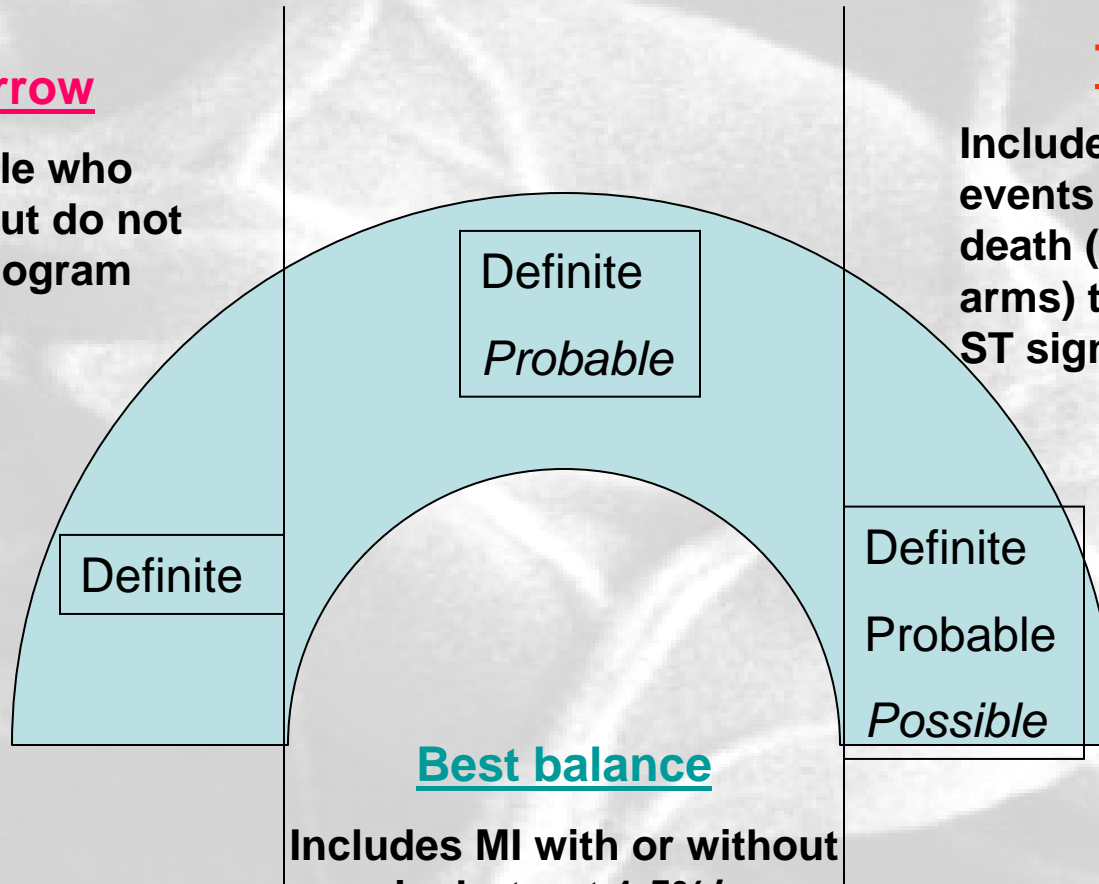
The ARC

Too narrow

Misses people who have an MI but do not have an angiogram

Too broad

Includes natural history events 1,5%/year natural death (equal in both arms) that dilute out true ST signal*



Best balance

Includes MI with or without angio, but not 1.5%/year natural history deaths

Will underestimate the ST Rates

Will Inflate the ST Rates
require modification

Why Possible should be dropped?

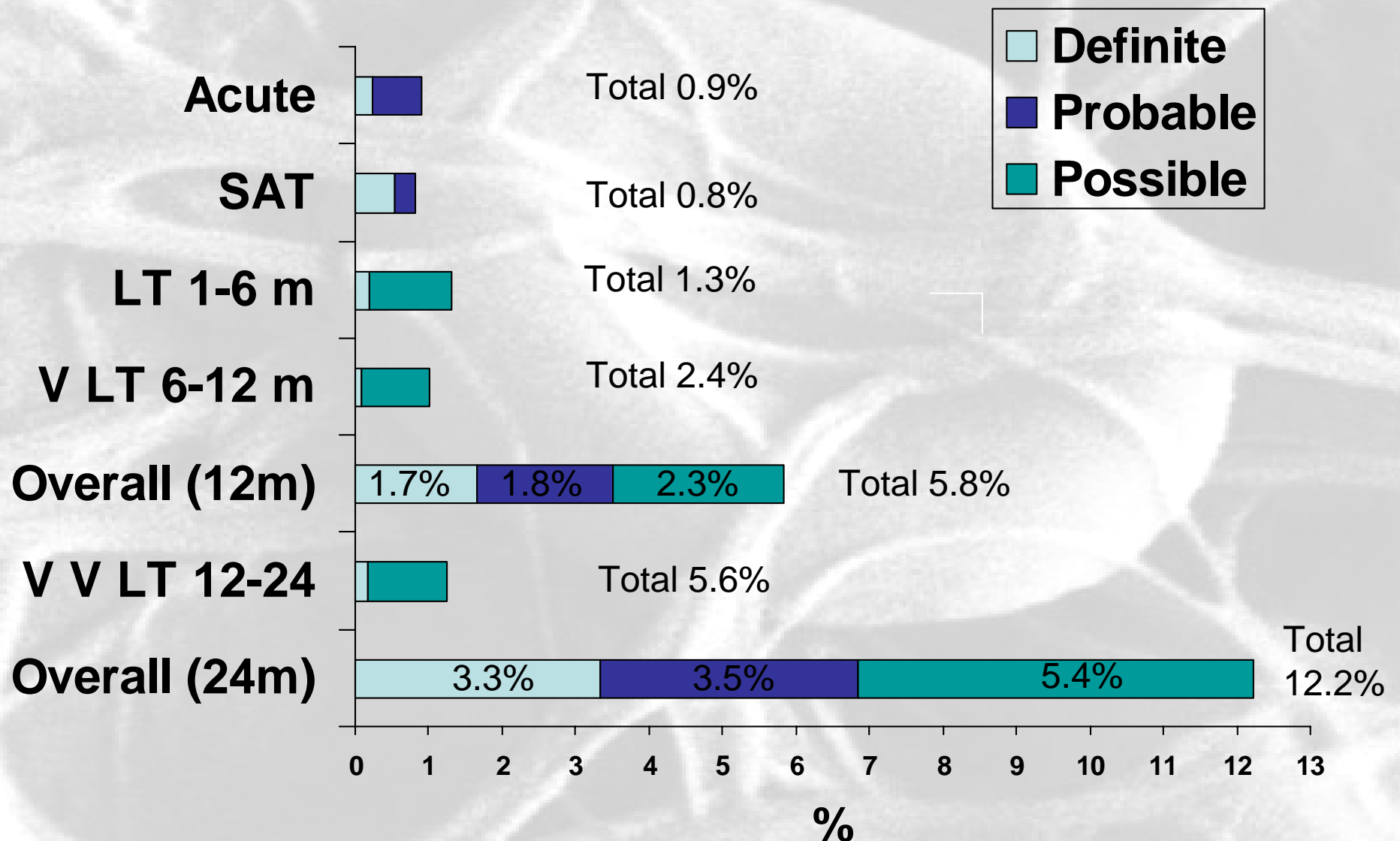
Unknown Cause of Death

- Unable to locate cause of death for a patient
- Unexplained non-cardiac cause of death
- Unexplained or sudden cardiac death (30-60% of all cardiac deaths)
 - Of which 10-50% are attributed to unexplained, atherosclerotic, or acute ischemic heart disease.

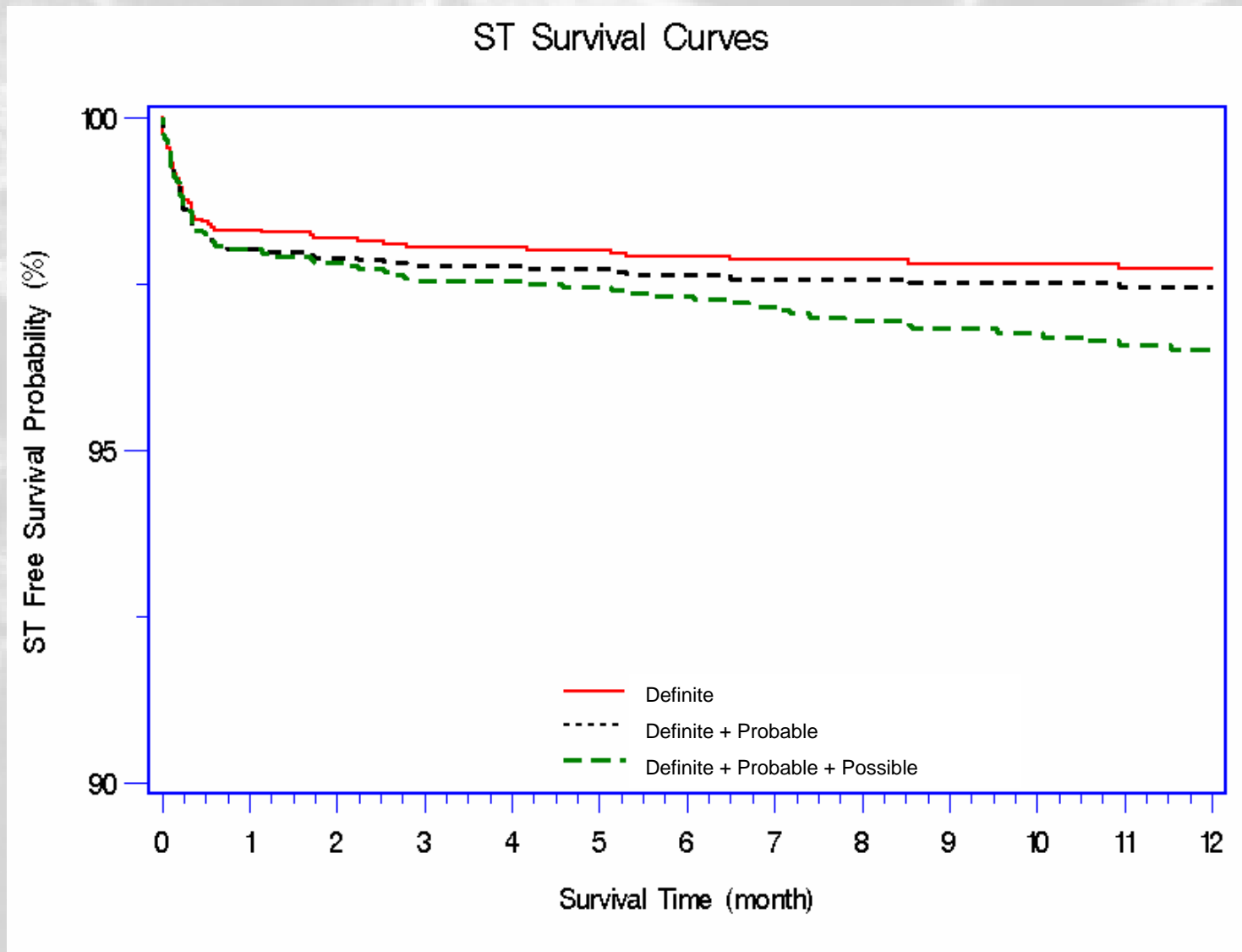
Thom T et al., Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006 Apr 11;113(14):e696.

Kuller et al. *Circulation* 1966;34;1054-68.; Albert et al. *Circulation* 2003; 107;2096-2101.; Zheng et al. *Circulation* 2001; 104:2158-63.; Hinkle et al. *Circulation* 1982; 65;457-64.

Stent Thrombosis



KM Curve for ST Definitions 12 months



Modified ARC

- Based on epidemiological studies and questions in accuracy of stent thrombosis detection resulting in unexplained death, different weights should be applied to each of the definitions
- Definite 1.0
- Probable 0.8
- Possible 0.3

$$\text{Cumulative ST} = \text{Definite ST} + 0.8 * \text{Probable ST} + 0.3 * \text{Possible ST}$$



Suggested Cumulative ST Definition from WHC

Cumulative ST = Definite ST + 0.8*Probable ST + 0.3*Possible ST

% (n)	Full ARC Analysis	Mod Arc Analysis
In Hospital	0.9 (68)	0.8 (58)
30 Days	2.1 (112)	1.8 (99)
6 Months	3.8 (171)	2.7 (123)
12 Months	5.8 (207)	3.8 (136)
6-12 Months	1.0 (36)	0.4 (12.9)
12-24 Months	1.1 (20)	0.4 (8.1)
24 Months	12.2 (227)	7.7 (144)

Endeavor Clinical Trial Program

definite + probable + possible

Thrombosis	Endeavor n=1316	Driver n=596
Early (Any)	4 (0.3%) 4 (0.3%)	7 (1.2%) 7 (1.2%)
Definite	4	7
Probable	0	0
Late (Any)	6 (0.5%) 4 (0.3%)	4 (0.7%) 2 (0.3%)
Definite	2	1
Probable	0	0
Possible	4	3
Very Late (Any)	2 (0.2%) 1.1 (0.1%)	3 (0.6%) 1 (0.2%)
Definite	0	0
Probable	1	0
Possible	1	3
Totals	12 (1.0%) 8.3 (0.6%)	14 (3.3%) 9.8 (1.6)

Cypher Clinical Trial Program

definite + probable + possible

Thrombosis	Cypher N=878	Bx Velocity N=870
Early (Any)	4 (0.5%) 3.8 (0.4%)	3(0.3%) 2.4 (0.3%)
Definite	3	0
Probable	1	3
Late (Any)	2 (0.2%) 1.5 (0.2%)	11 (1.3%) 8.1 (0.9%)
Definite	1	4
Probable	0	4
Possible	1	3
Very Late (Any)	23 (2.8%) 12.1 (1.4%)	14 (1.7%) 6.8 (0.8%)
Definite	6	3
Probable	2	1
Possible	15	10
Totals	29 (3.5%) 17.2 (2.0%)	28 (3.3%) 17.3 (2.0%)

Source Don Cutlip, HCRI, TCT 2006. 4 yr follow up from RCT (SIRIUS, E SIRIUS, C SIRIUS and RAVEL)

How long should We Prescribe Plavix???

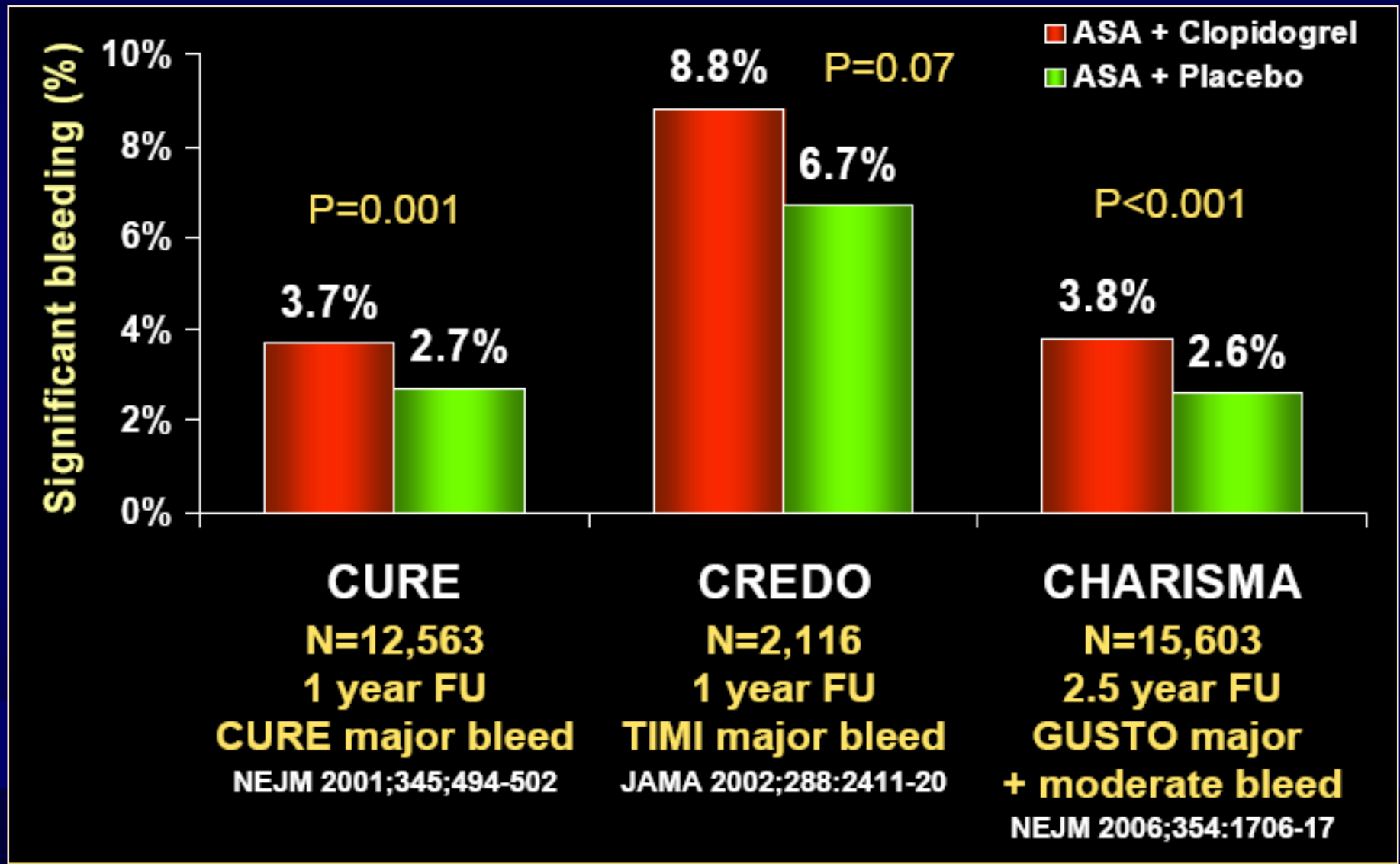
- **Can High Clopidogrel Compliance Post Drug-eluting Stent Implantation be Obtained and What is the Impact on Stent Thrombosis?**

**Rebecca Torguson, Kimberly Smith, Ashesh Buch,
Natalie Gevorkian, Augusto D. Pichard, Lowell
Satler, Kenneth Kent, Ron Waksman**

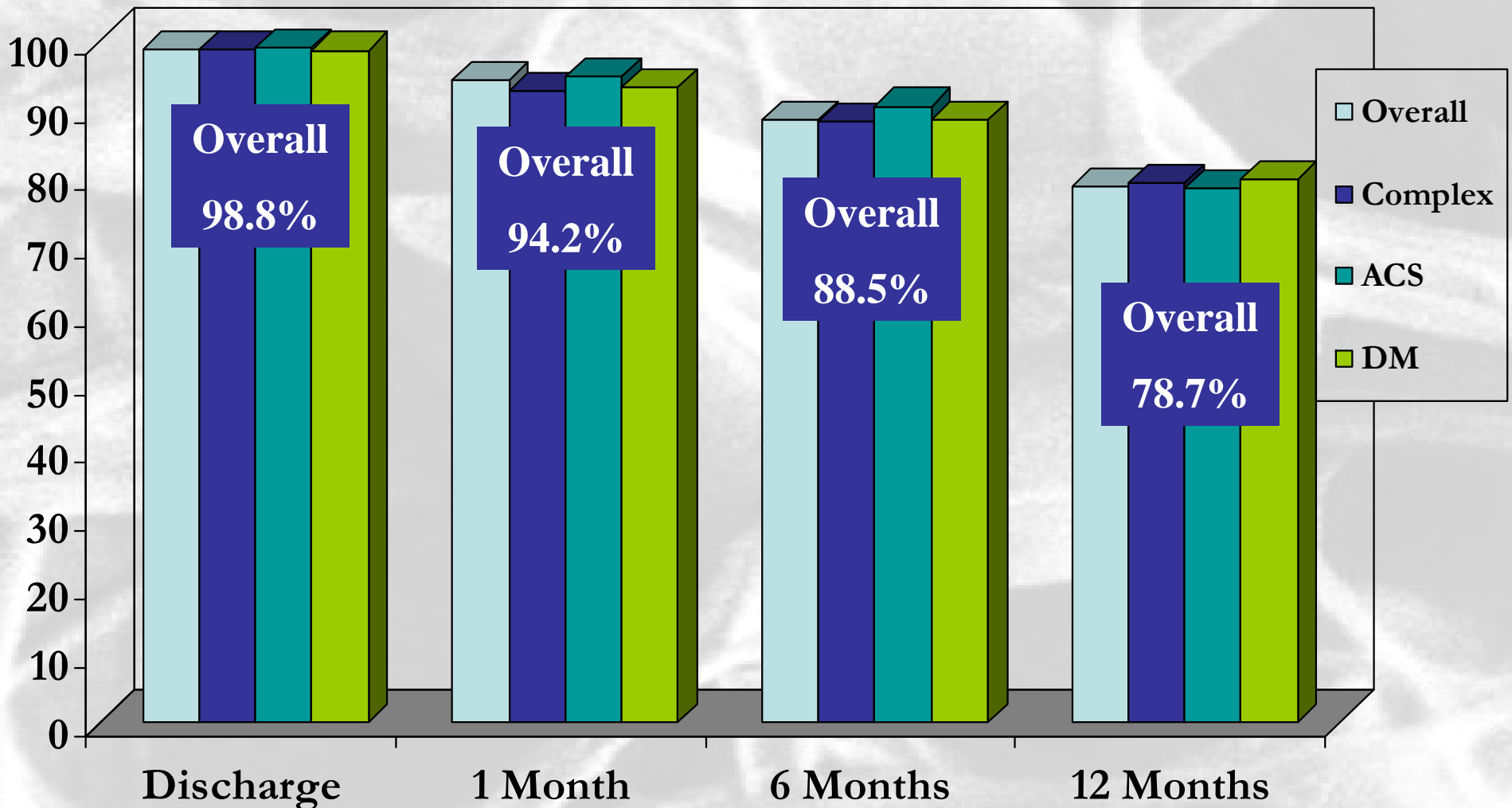
Washington Hospital Center, Washington, DC

Safety of Long-Term Clopidogrel

3 Placebo Controlled Trials



Clopidogrel Compliance



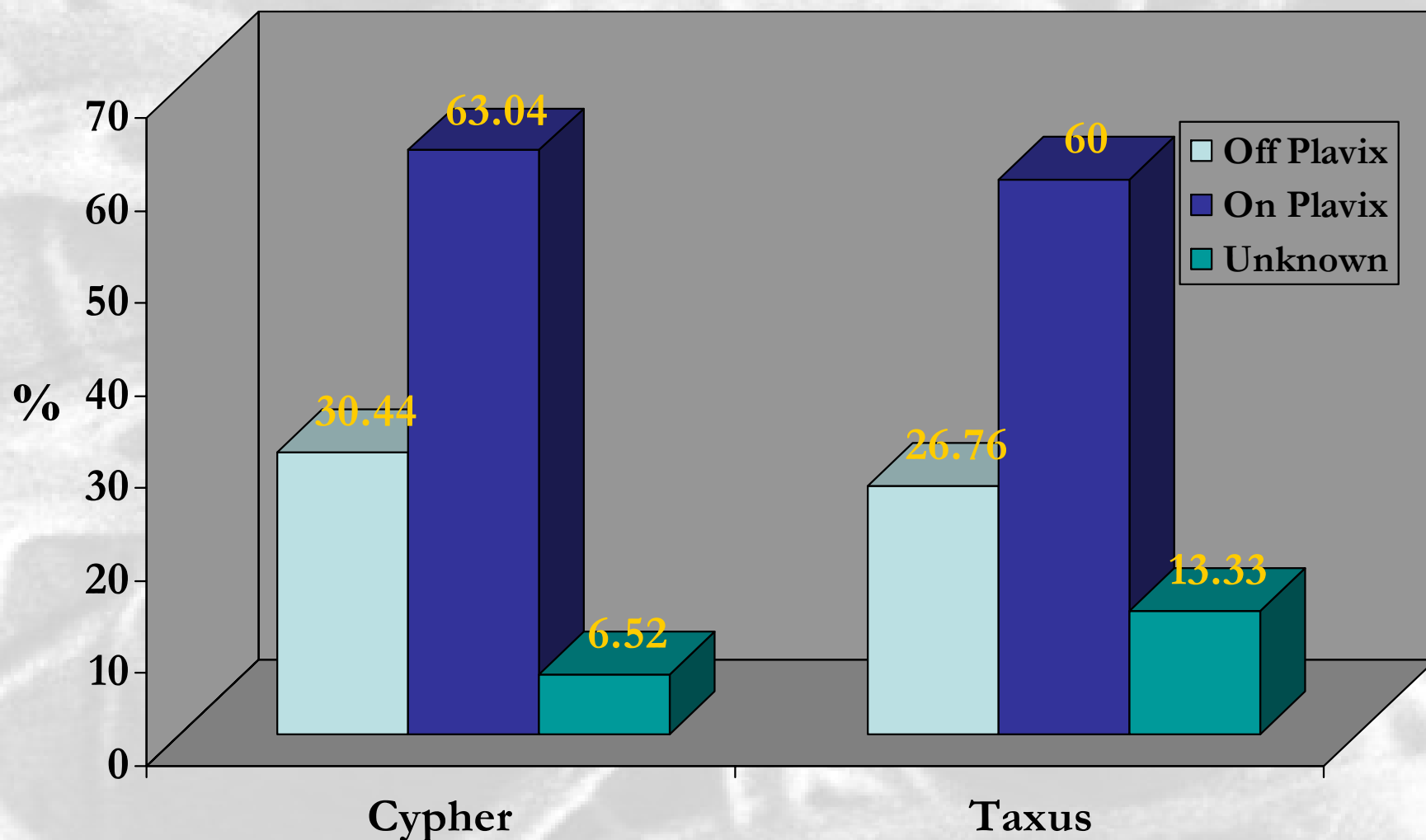
- 1) Overall population (n=2497)**
- 2) Complex Patients and Lesions (n=1439)**
defined as at least one of the following:

Ostial lesion	Type C lesion	AMI
ISR	CTO	IDDM
Non-native artery lesion	2+ DESs	On Chronic Dialysis
Long lesion (>33mm)		Prior CABG

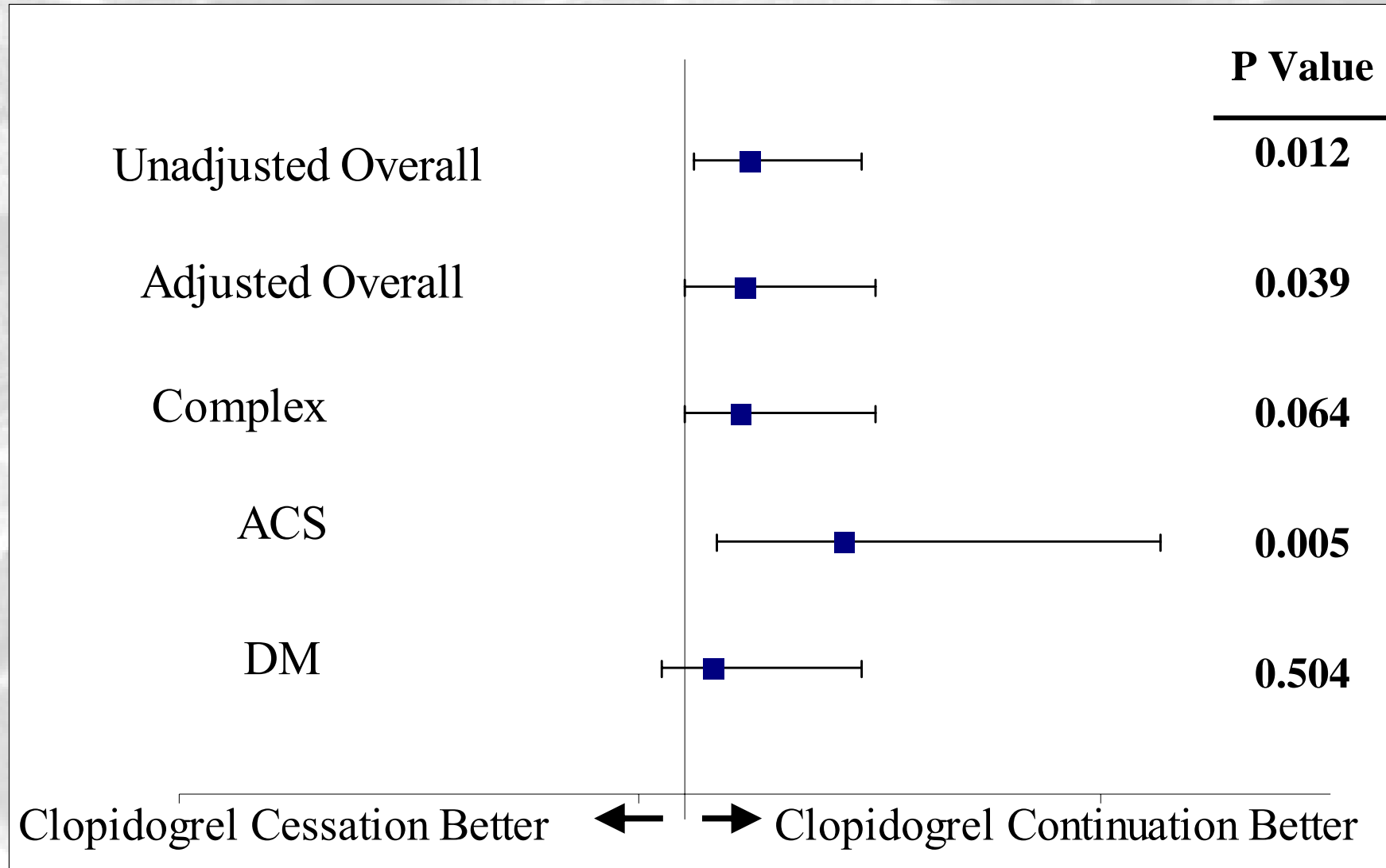
- 3) Presentation with Acute coronary Syndrome (n=1155)**
- 4) Diabetes Mellitus (n=837)**

REWARDS

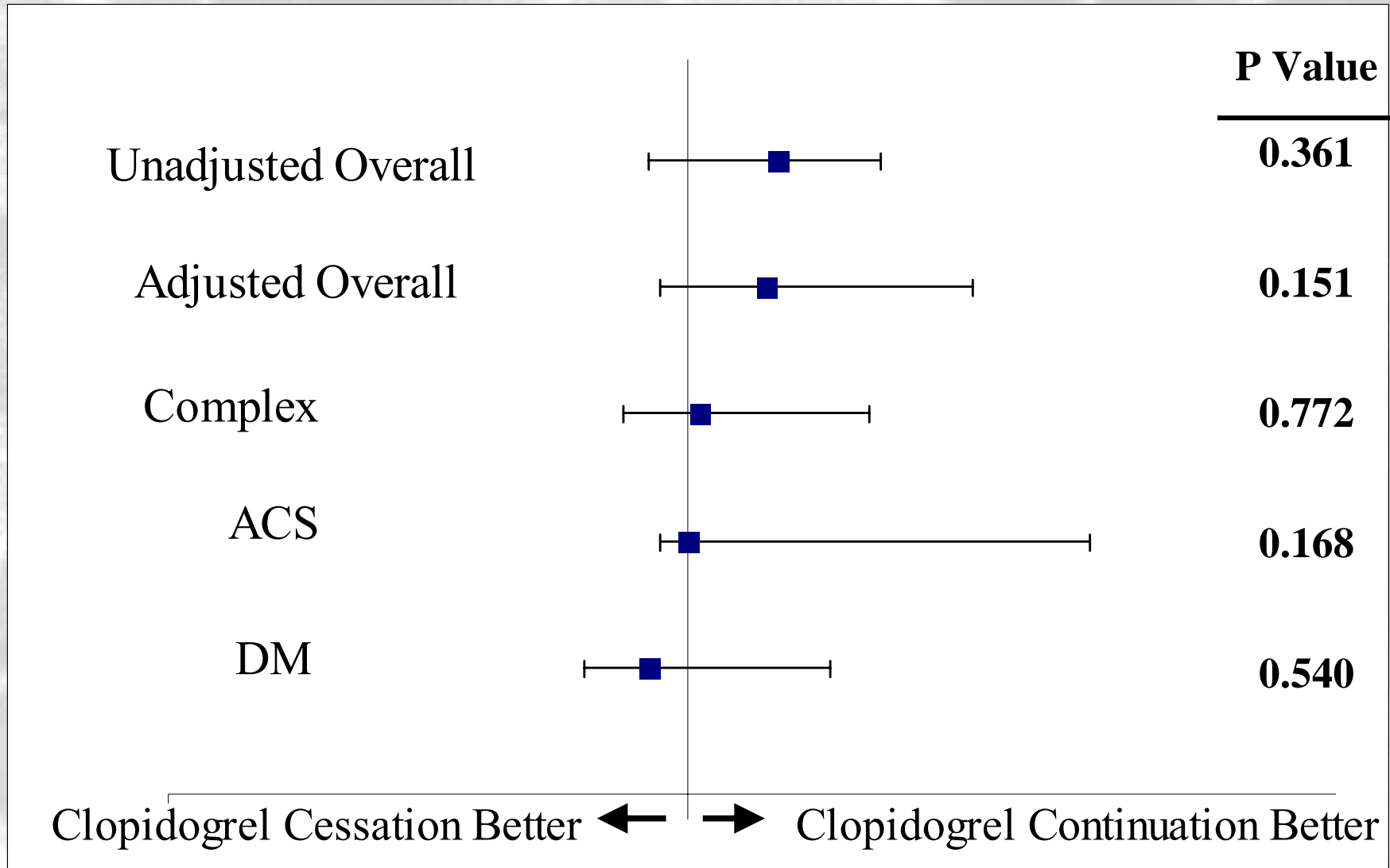
Clopidogrel Compliance at the Time of Stent Thrombosis



Cumulative ST (≤ 6 months) Definite Stent Thrombosis



Cumulative ST (≤ 12 months) Definite Stent Thrombosis



Additional Independent Predictors of Cumulative ST at 12 Months

Definite Stent Thrombosis

Female Gender

Presentation with MI

Type C Lesion

Number of Implanted DES

Probable Stent Thrombosis

Female Gender

History of DM

History of CRI

Presentation with MI

Type C Lesion

Lack of IVUS Guidance

Number of Implanted DES

Possible Stent Thrombosis

Female Gender

History of DM

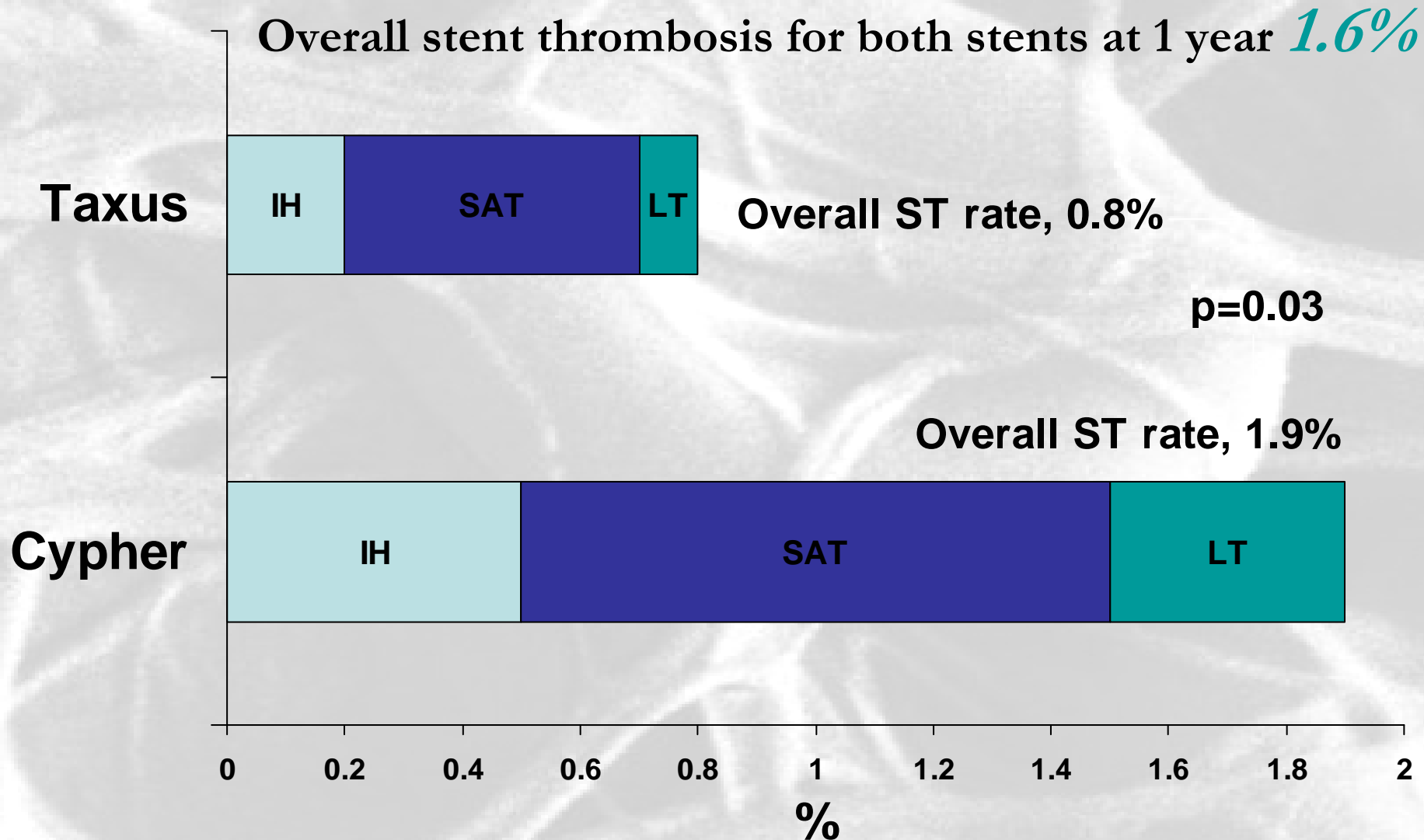
History of CRI

Presentation with MI

Type C Lesion

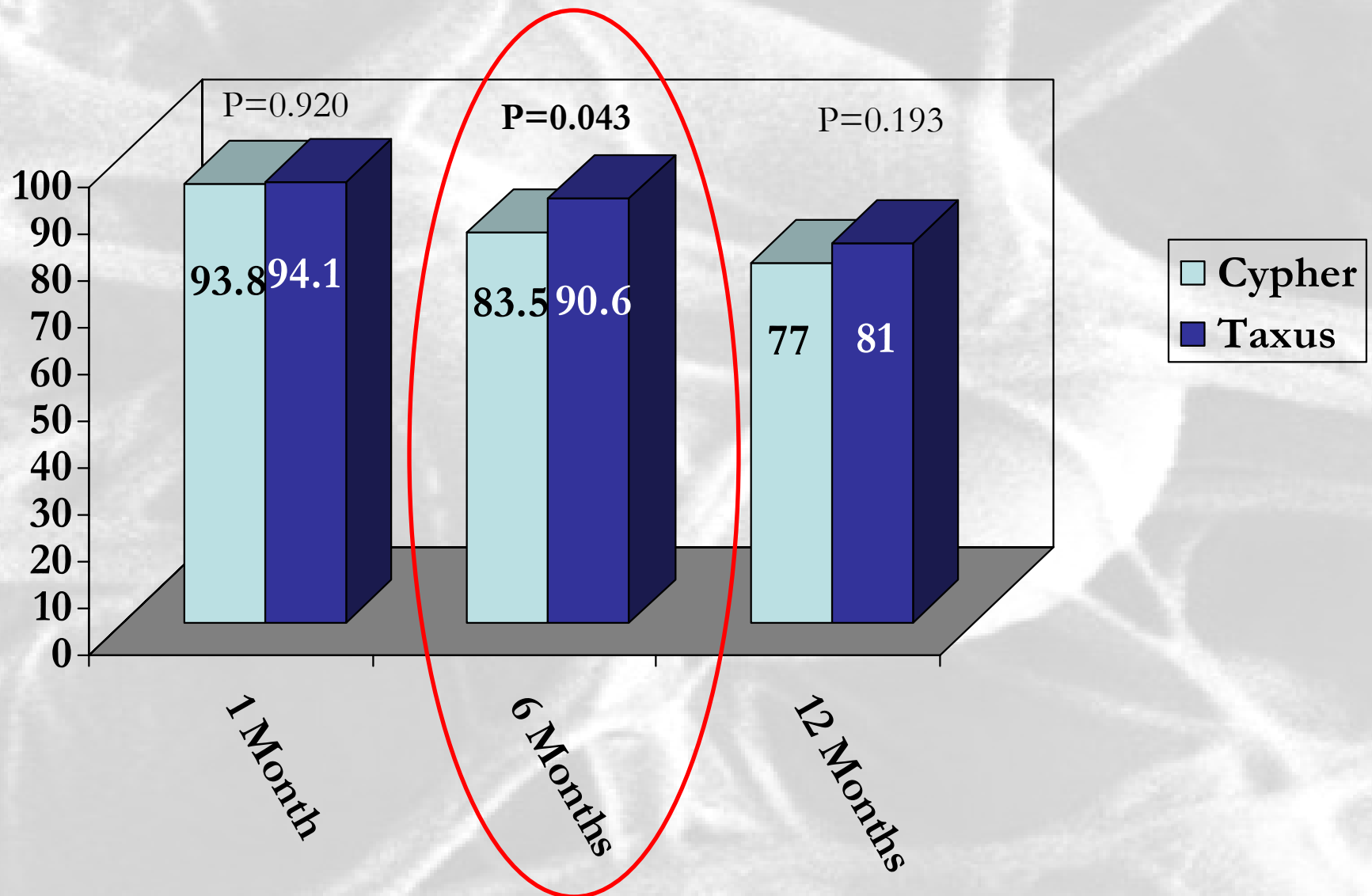
Number of Implanted DES

Cumulative Stent Thrombosis – 12 Months

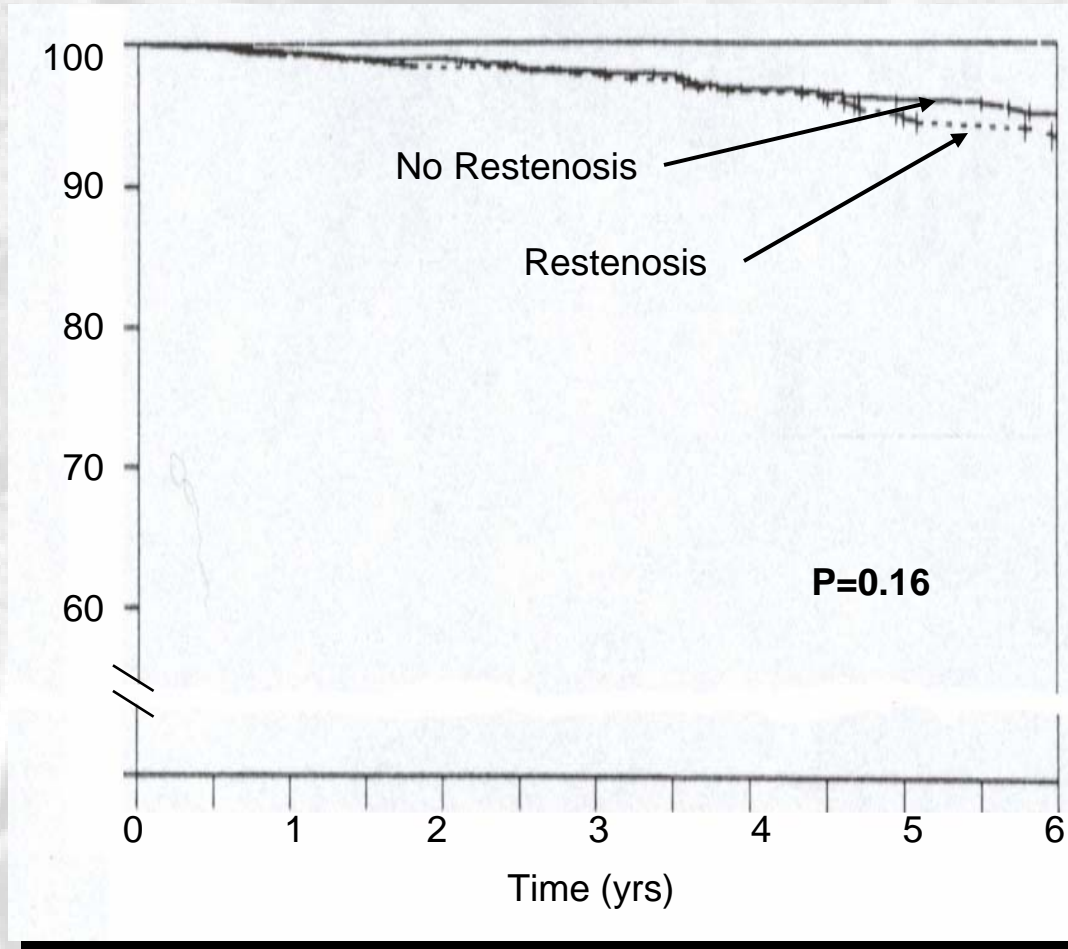


REWARDS

Clopidogrel Compliance



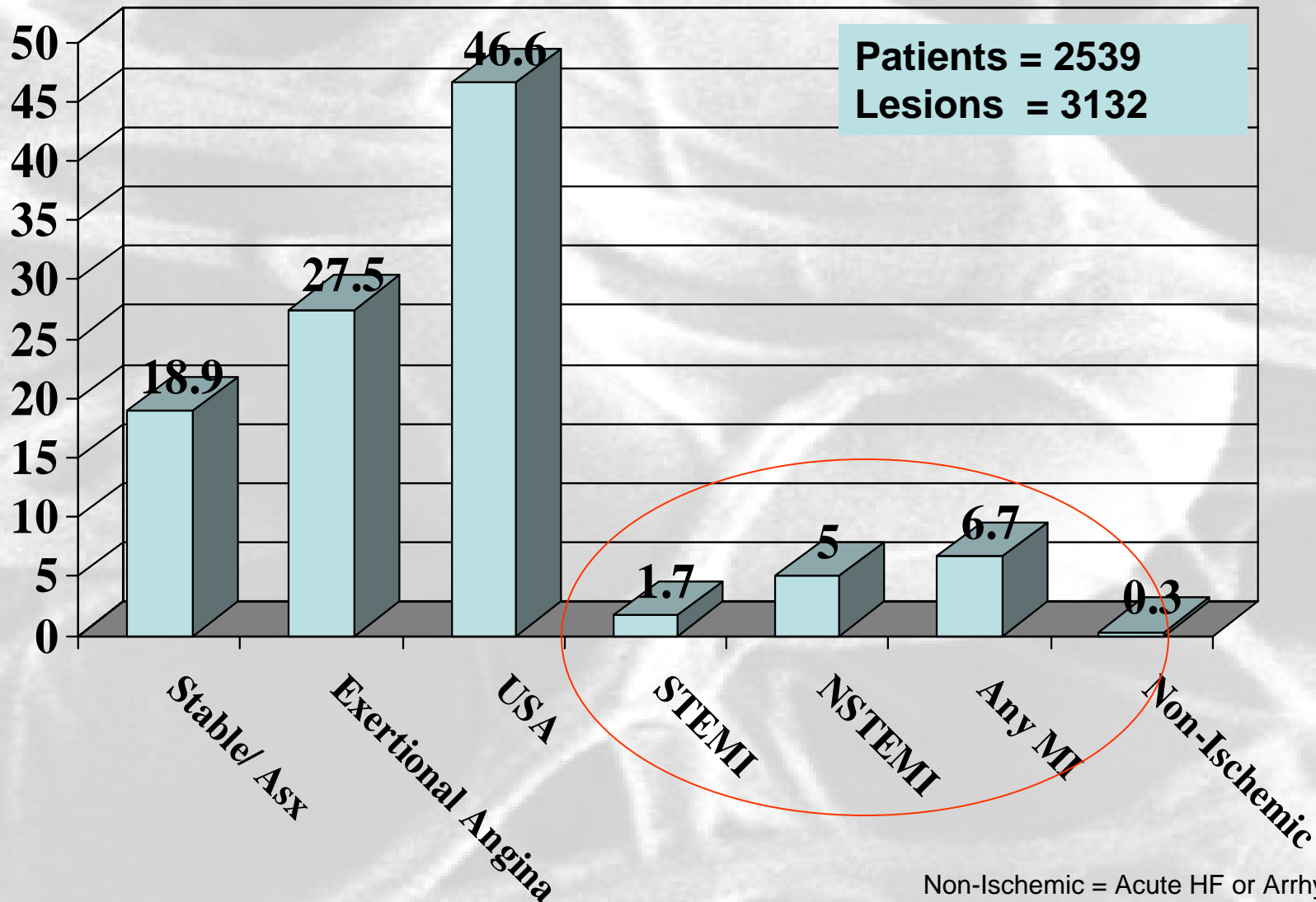
Does Restenosis Increase Late Mortality?



Emory Study POBA

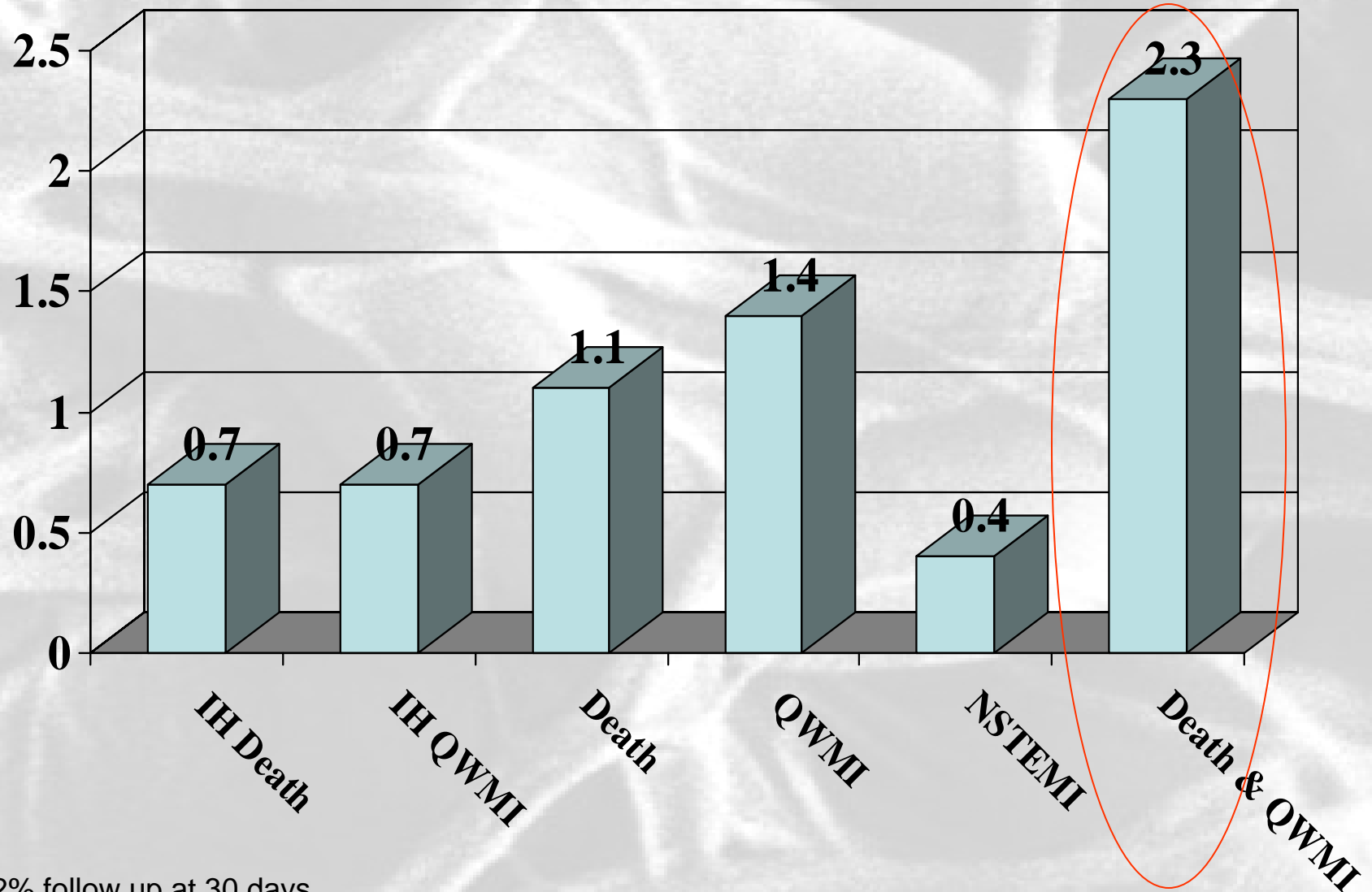
- 3363 pts who underwent angiographic restudy after successful PTCA
- No difference in 6 yr mortality according to status at angiographic follow-up

WHC BMS ISR Clinical Presentation



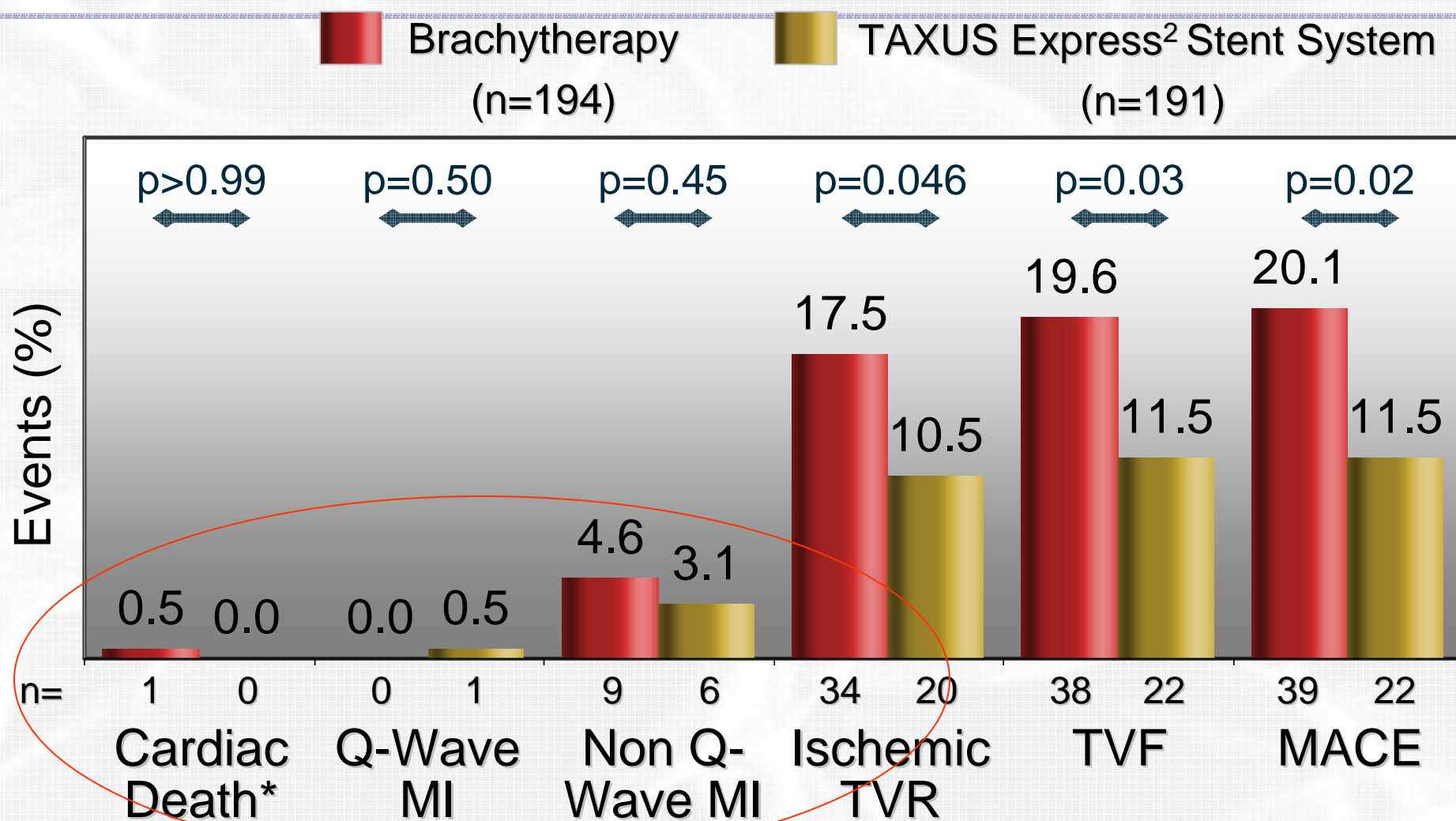
WHC BMS ISR

In-Hospital & 30 Day Events



87.2% follow up at 30 days

9 Month MACE Composition

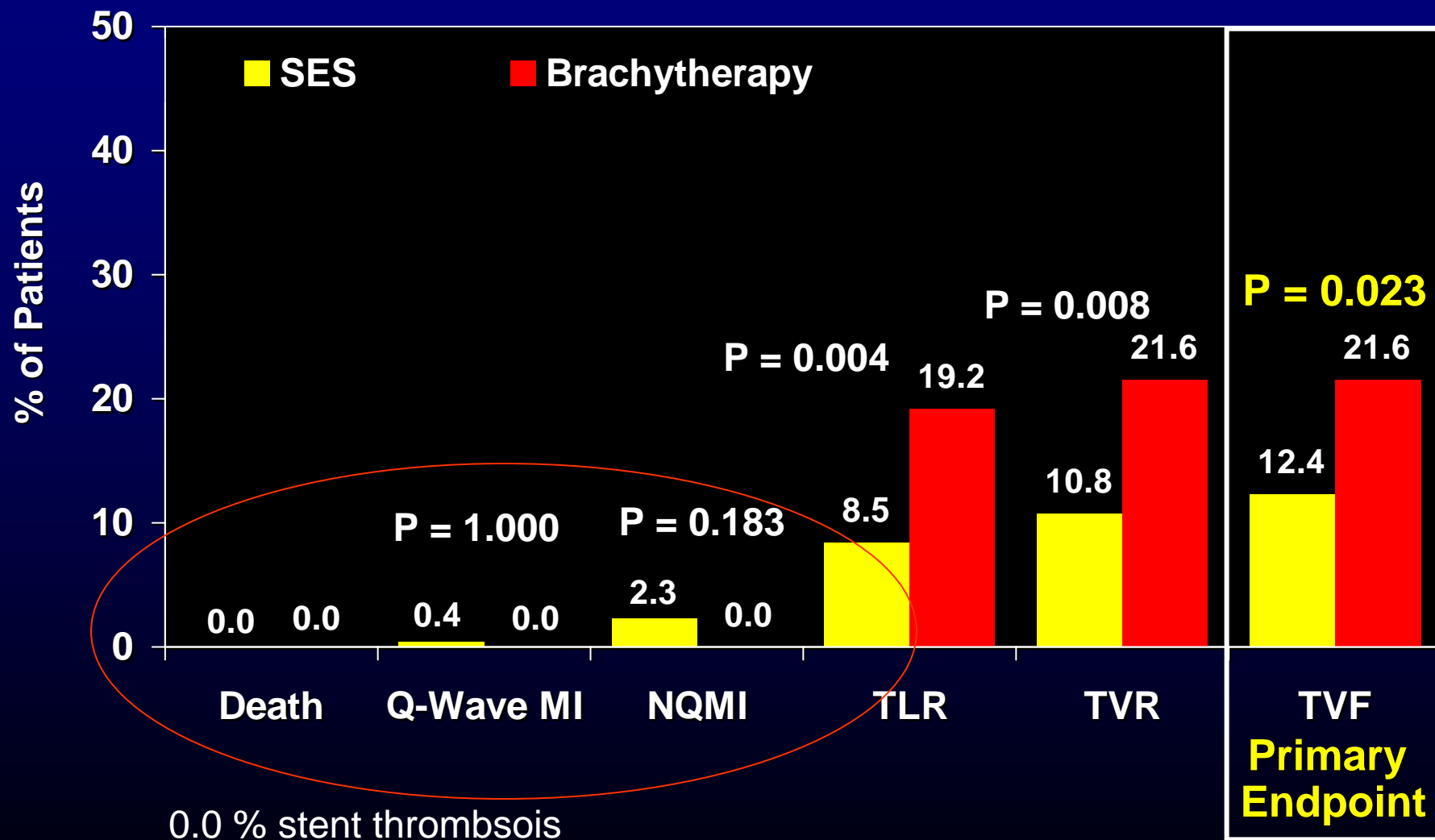


*Non-cardiac death: n=0 for both groups

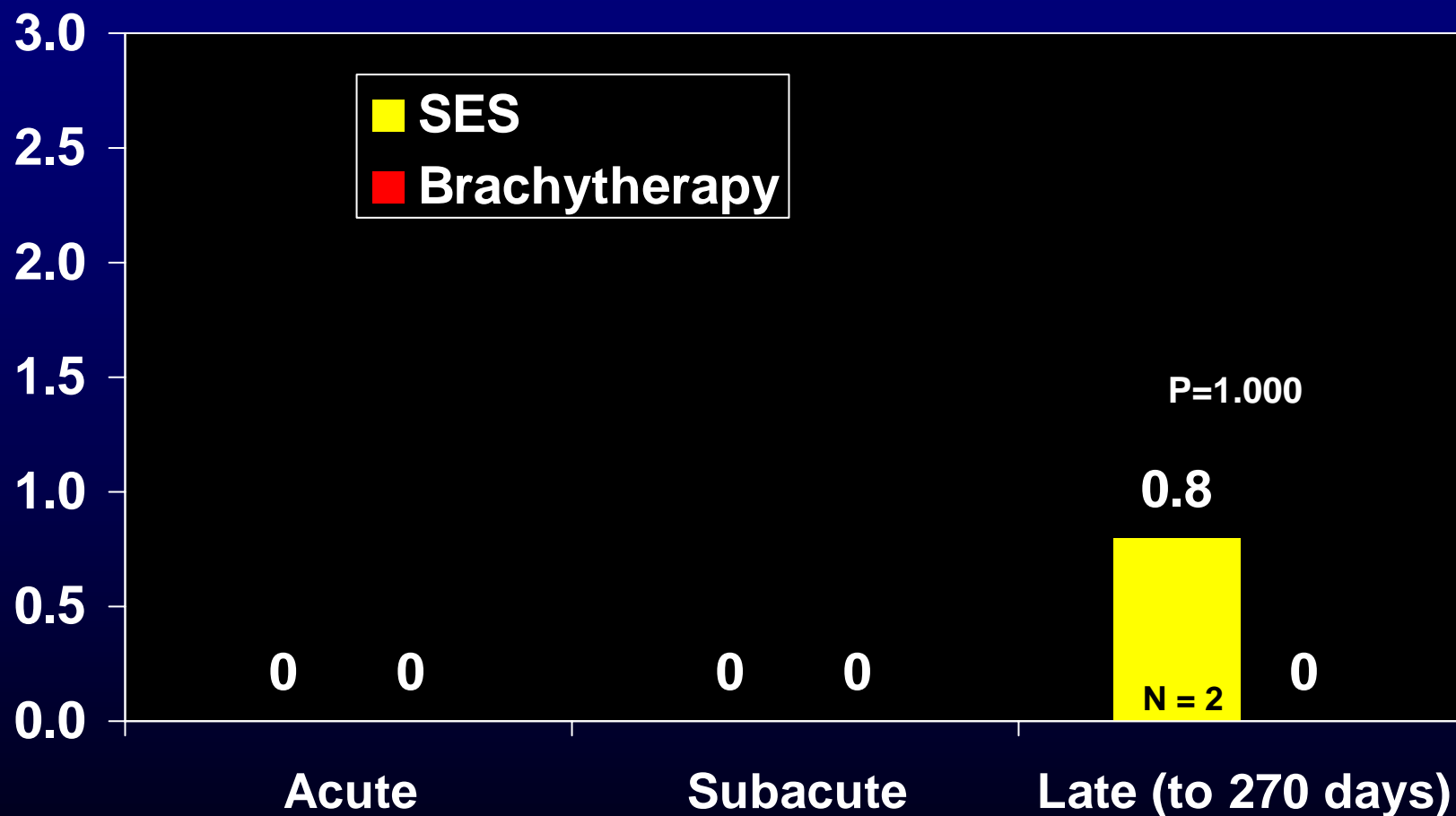
Stone GW et al. JAMA 2006;295:1253-63

*CAUTION : The TAXUS Express² paclitaxel eluting stent system is considered investigational in the United States for use in treating in-stent restenosis & for this indication is limited by Federal Law to investigational use only.

Clinical Outcomes Through 9 Months



Stent Thrombosis at 9-Month Follow Up



- **Study population**

On Label 1773 patients (2228 lesions)
Off Label 1365 patients 2428 lesions)
45%

- “Off label” inclusion criteria

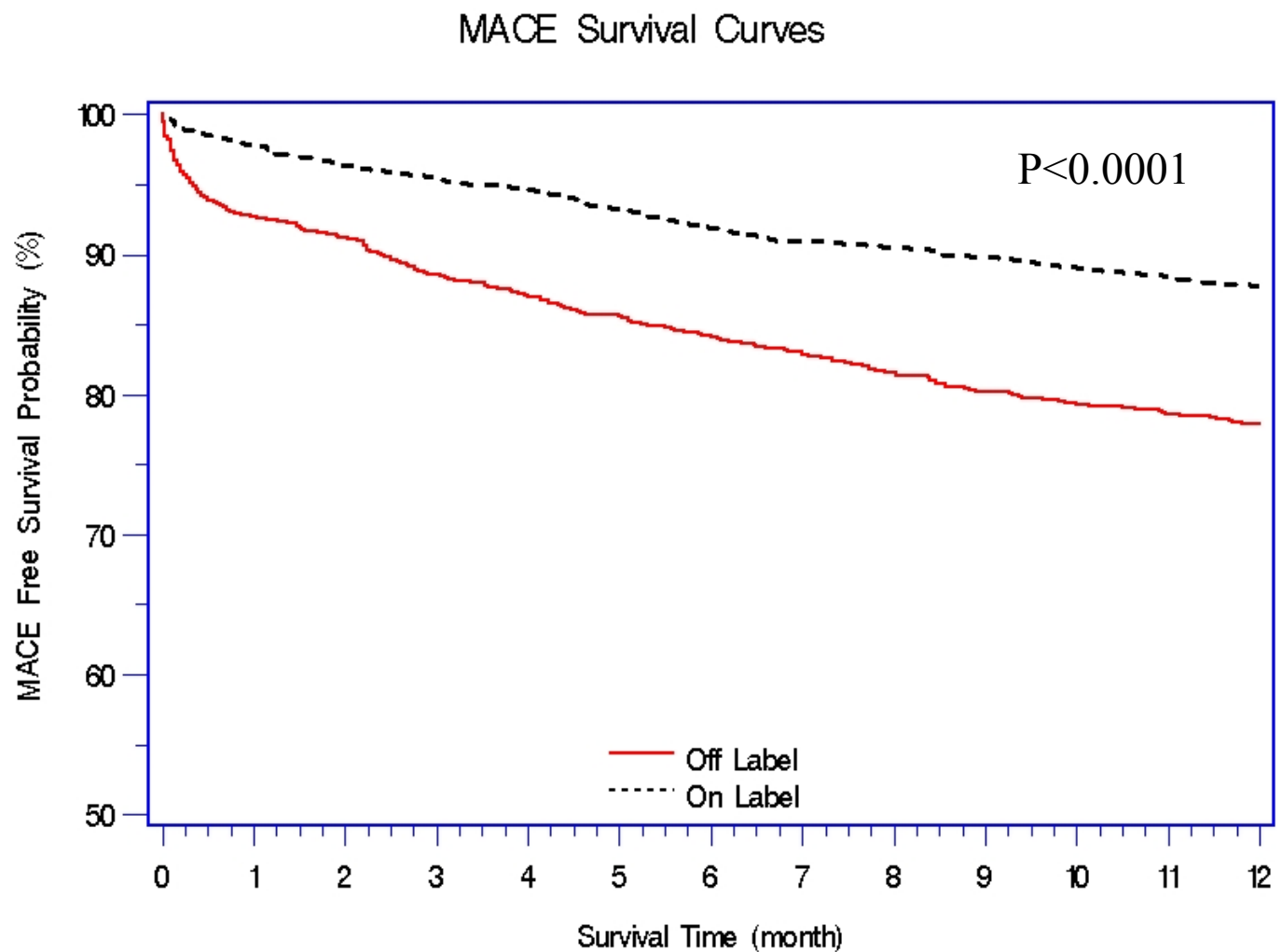
- Total stented length >33mm (inclusive of diffuse disease)
 - In-stent restenotic lesions
 - Bypass graft lesions
 - >2 stents per patient (inclusive of >2 overlapping stents)
 - Acute myocardial infarction
 - Unprotected left main coronary artery lesions
 - Chronic Total Occlusion

- **End Points: MACE**

Baseline Characteristics

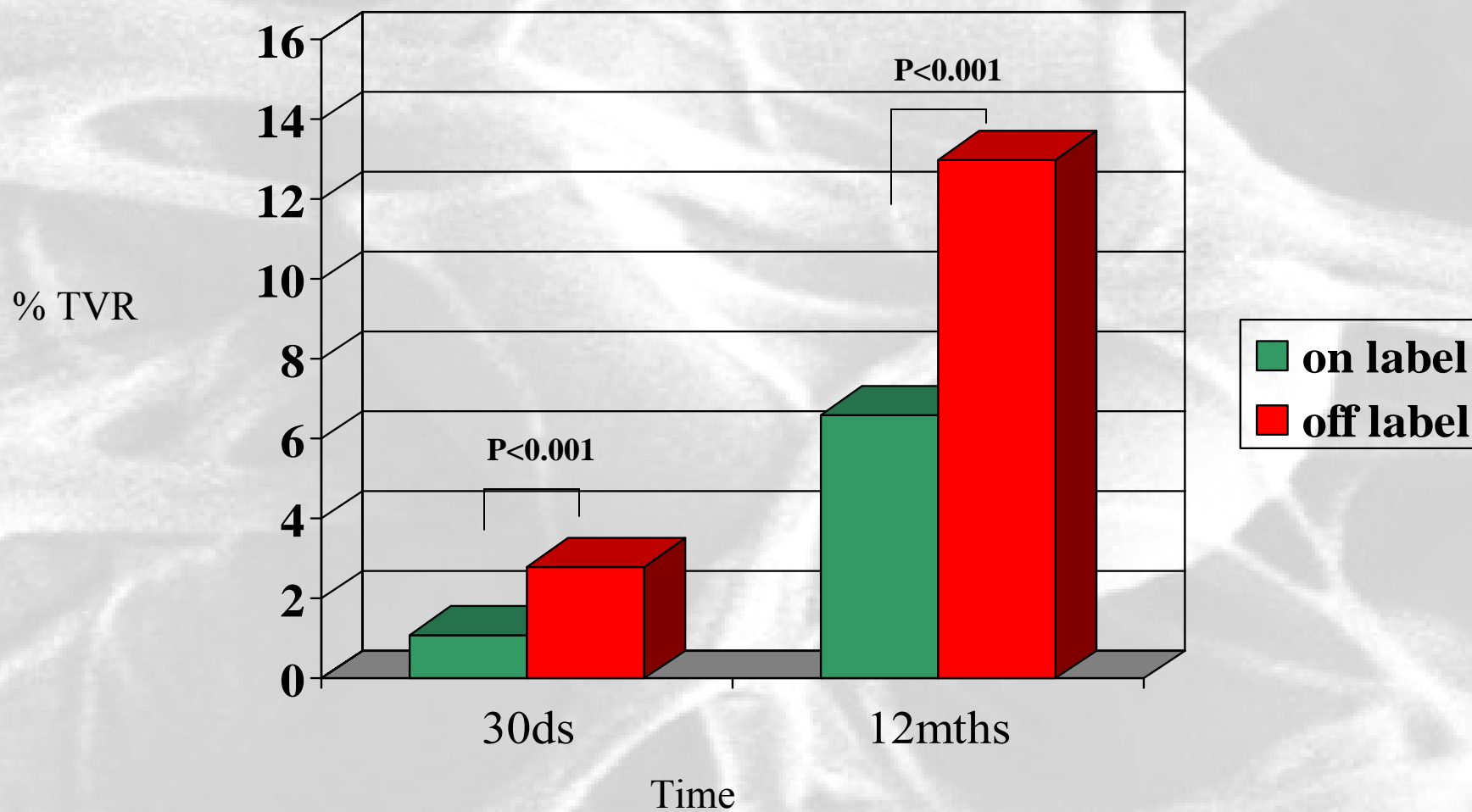
Variable	“Off label” use (n=1365)	“On label” use (n=1773)	p Value
Male, %	67.1	63.4	0.03
Age, yrs	65.6 ±11.9	65.0±11.2	0.17
Diabetes, %	37.9	34.0	0.02
Insulin requiring diabetes, %	12.0	11.1	0.44
Current smoking, %	17.9	18.1	0.87
Hypertension, %	82.0	78.0	0.006
Dyslipidaemia, %	87.0	83.9	0.015
Renal insufficiency, %	14.2	10.9	0.005
Peripheral vascular disease, %	16.7	14.3	0.07
Previous CABG, %	24.0	12.0	<0.001
Previous PCI, %	34.2	22.3	<0.001
Left ventricular ejection fraction, %	0.46±0.1	0.49±0.1	<0.001
Clinical presentation			
Unstable angina, %	40.4	46.9	<0.001
Acute myocardial infarction, %	27.0	0	<0.001
Cardiogenic shock, %	5.4	1.2	<0.001

MACE-free survival 12 Months

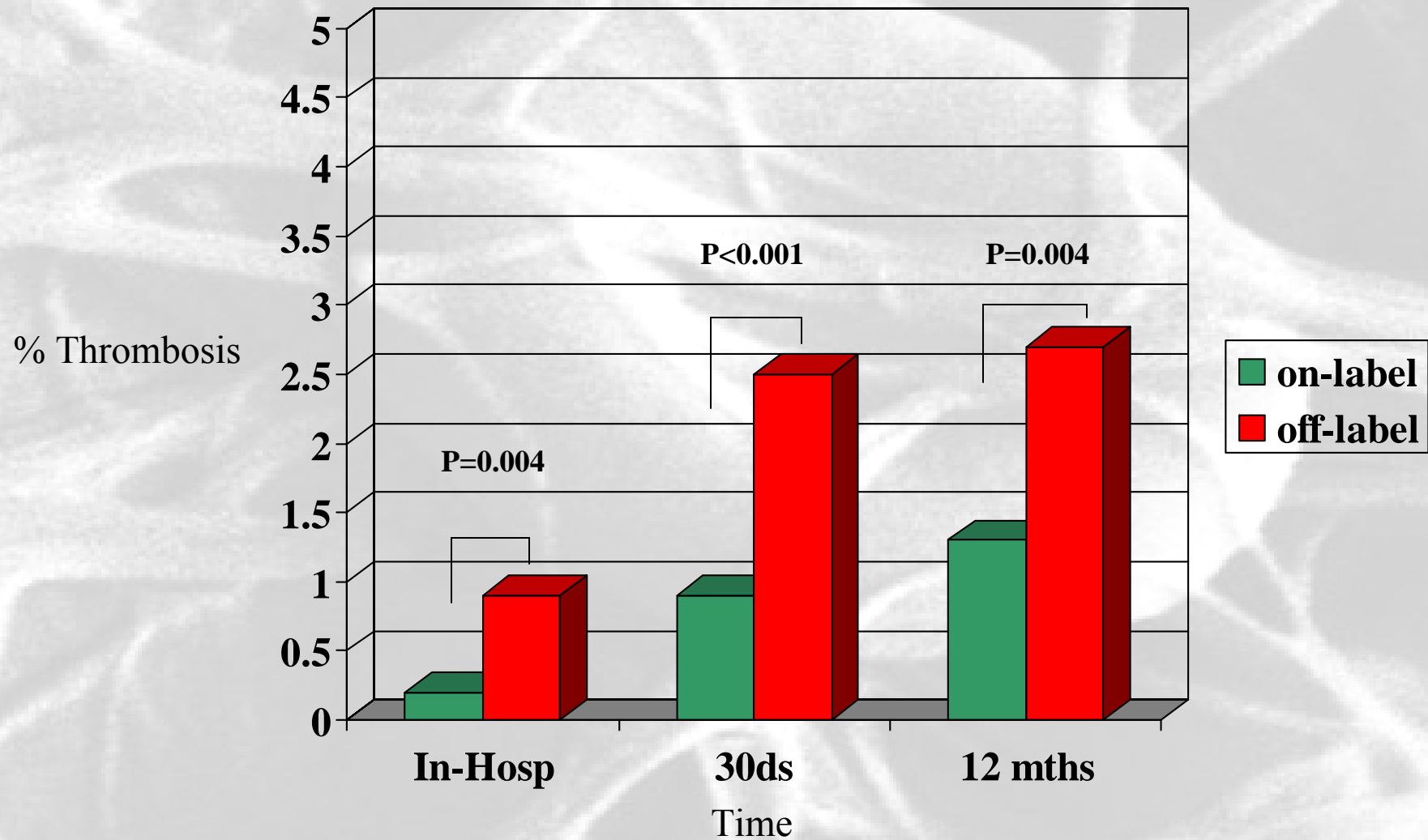


MACE: Death, QWMI, TVR

TVR Rates



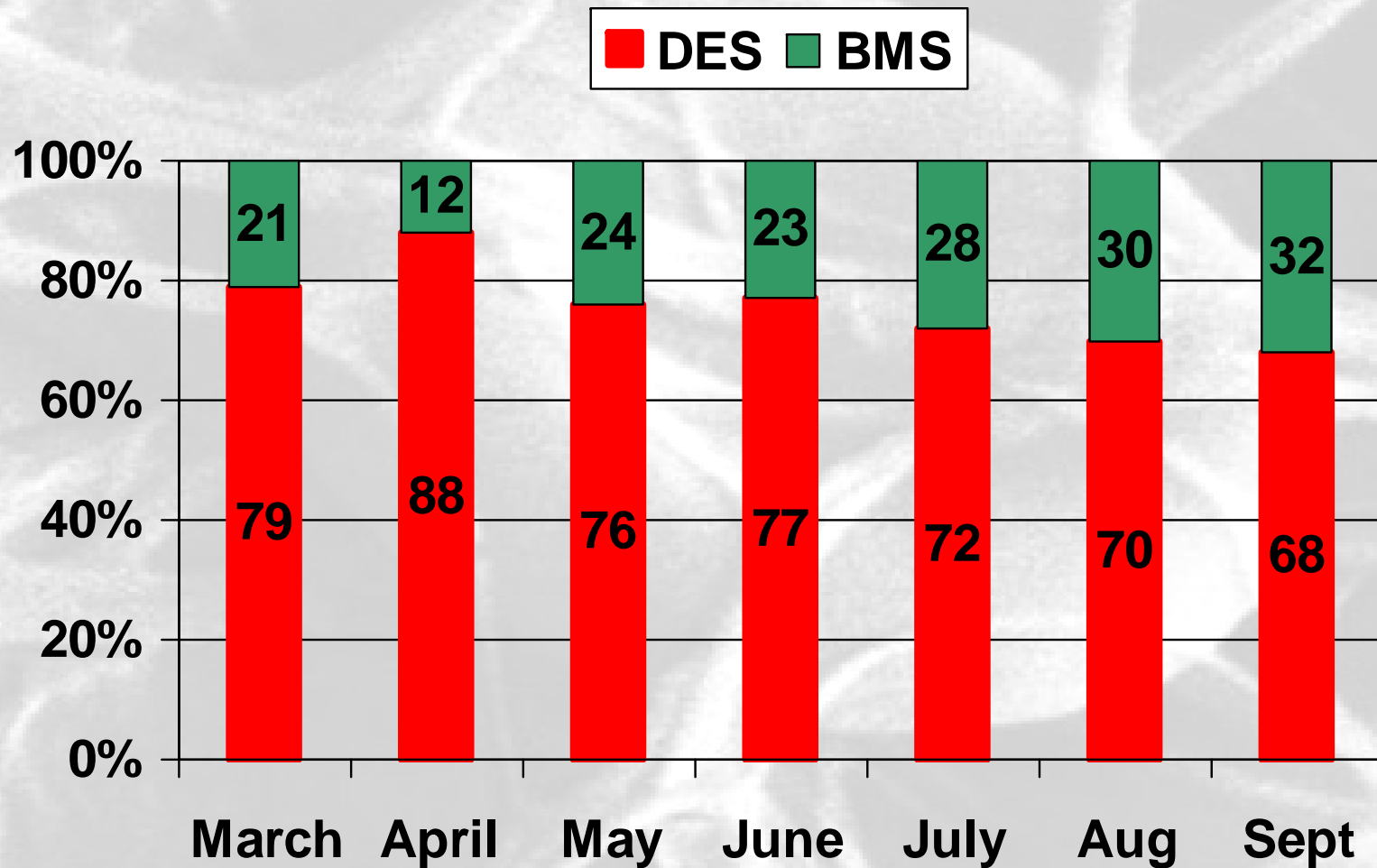
Angio Stent Thrombosis Rates



Predictors of MACE – 12 Months

	Hazard Ratio	95% CI	P value
Age	1.009	1.001-1.018	0.036
Diabetes requiring treatment	1.224	1.006-1.488	0.043
Hypertension	1.393	1.054-1.842	0.020
Chronic renal insufficiency	1.606	1.265-2.039	<0.0001
Cardiogenic shock	2.891	1.979-4.225	<0.0001
Left main coronary artery	2.056	1.366-3.094	0.0006
Saphenous vein graft	1.409	1.011-1.962	0.043
Smaller stent diameter	1.852	1.420-2.415	<0.0001
Number of implanted stents	1.135	1.042-1.235	0.0035
“Off label” use	1.439	1.161-1.782	0.0009

DES vs BMS at WHC



Final Comments and Recommendations

- DES stent thrombosis in off label use is higher when compared to the label use or to BMS
- **The ARC definition inflates the rate of LST and should be modified we propose to drop the possible or to weight adjust it. (changing the definition will not resolve the problem)**
- Stent Thrombosis of DES is associated with high mortality (30%) and morbidity (non fatal MI 60%)
- **Restenosis of BMS although associated with low rates of death or AMI is not the sole explanation of the discordance between thrombosis and death and MI**

Final Comments and Recommendations

- Careful patients selection for DES is mandatory and off label use should be reconsidered or restricted.
- **DES should be contraindicated for patients with poor compliance or allergic to Plavix or Aspirin, and need for upcoming surgery**
- Warning label of late thrombosis should be considered for the current DES devices, Cypher and Taxus when used off label
- **Diabetic patients with multivessel disease should be liberally referred to CABG**

Final Comments and Recommendations

- **Dual antiplatelet therapy beyond 6 months is not proven to be prohibitive of late stent thrombosis and more studies should be directed to view the optimal duration as longer is not necessarily better**
- Post marketing studies should be performed by **independent investigators and CRO's** to address these open ended questions.

Thank You