

**Revascularization Strategies of Coronary Multiple
Vessel Disease In Drug Eluting Stent Era: One Year
Follow Up Results Of ERACI III Trial.**

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NO CONFLICT TO DISCLOSE

Angioplasty Summit 2006

TCT Asia-Pacific

Seoul, Korea, April 26- 28 ,2006.



BACKGROUND

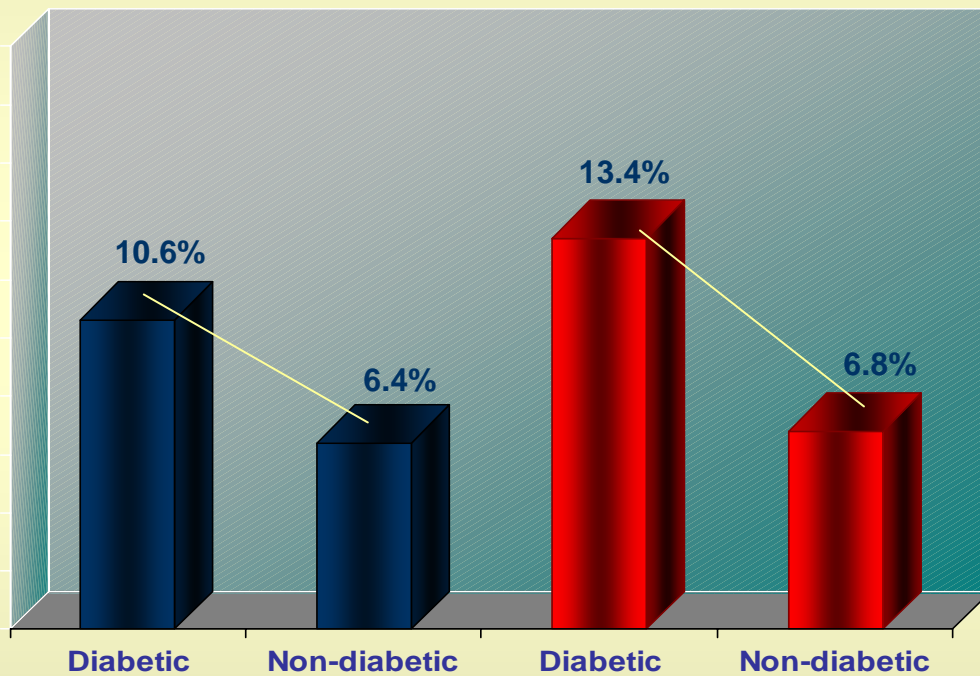
At 5 years of follow up ERACI II and ARTS showed similar incidence of death and non fatal myocardial infarction either in stent or CABG assigned patients.

However repeat revascularization procedures were significantly more frequent in PCI assigned patients (Rodriguez AE and Serruys PW, JACC 2005)

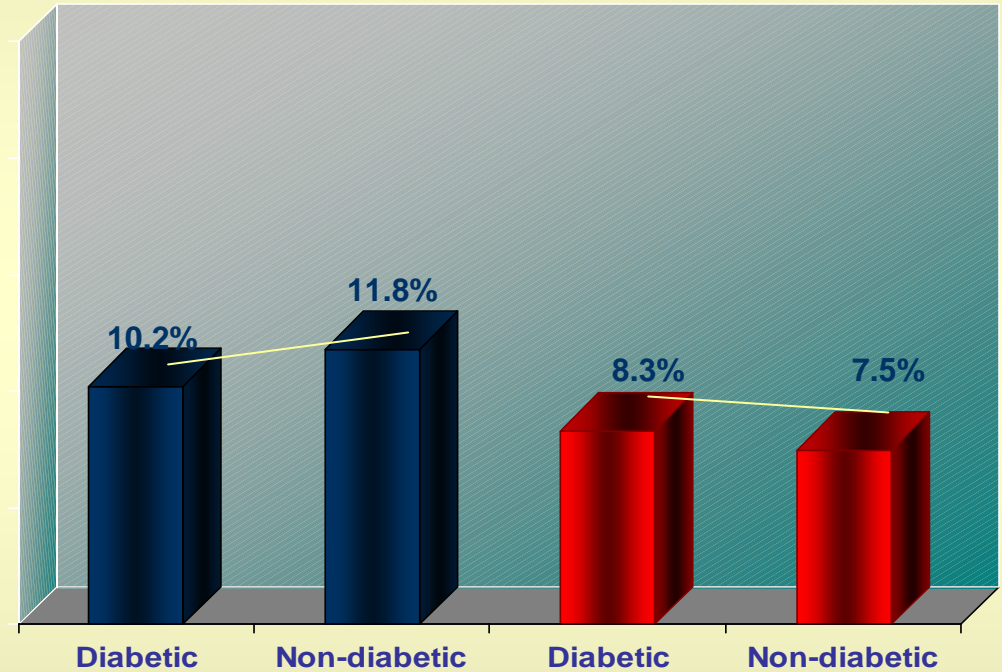
ERACI II & ARTS

Five Years Mortality
Diabetic vs. Non-diabetic

PCI ARM



CABG ARM



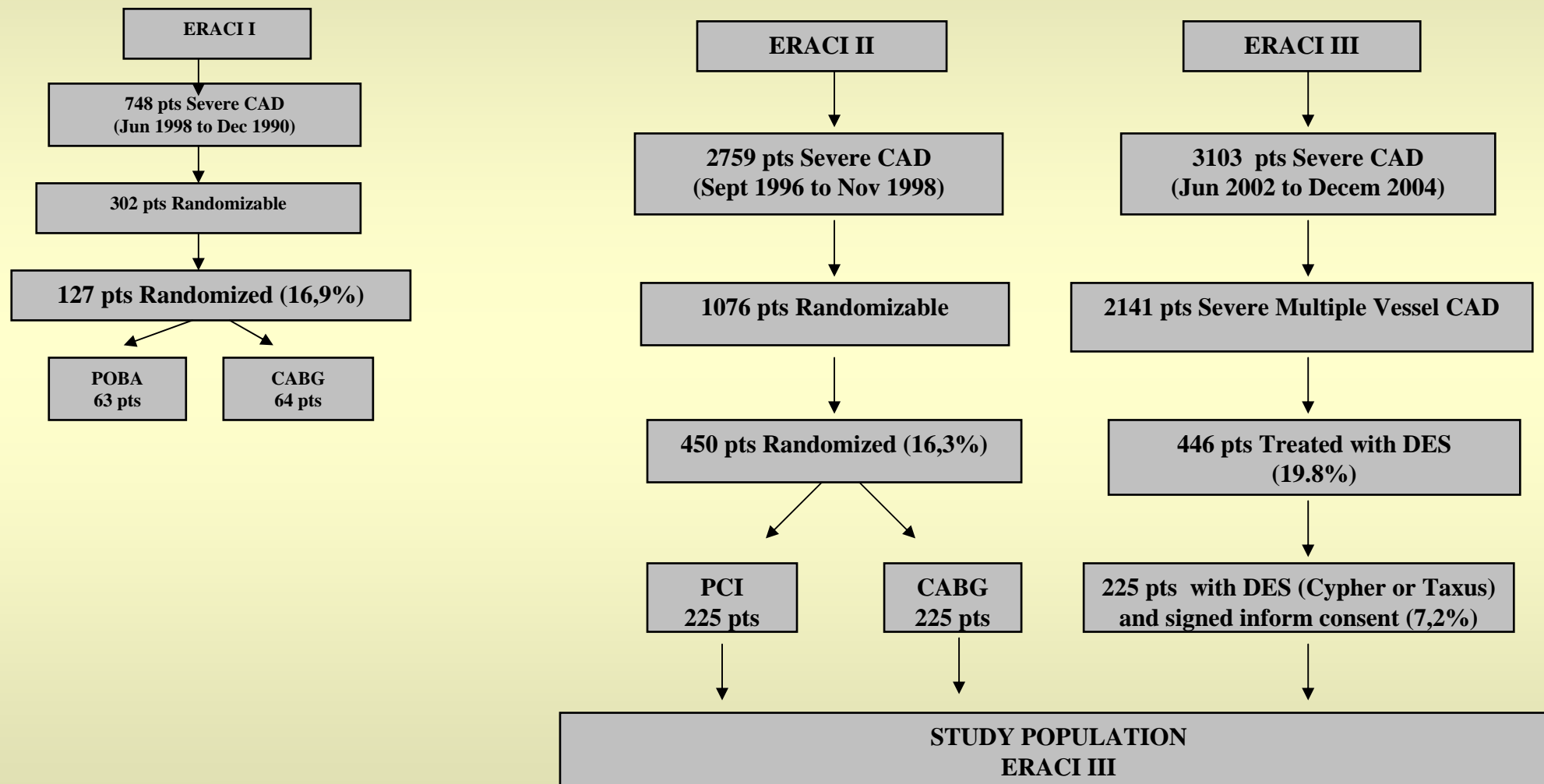
■ ERACI II
■ ARTS



Serruys PW, Rodriguez A, JACC2005

ERACI II and ERACI III

Study Population of ERACI Trials: 1988-2004



Methods

ERACI III is a multicenter, prospective, non randomized and open labeled study designated to evaluate the role of SES and PES use in patients with multiple vessel disease who meet angiographic and clinical criteria of the earlier ERACI II trial .

In order to obtain a comparable population and an equivalent revascularization strategy to that employed in ERACI II, the same centers and investigators (AE Rodriguez, W O'Neill and I Palacios), took part in ERACI III trial.

STATISTICS

The sample size of the study was determined using a test for trend analysis based on an estimation of MACCE at one year of follow up among patients treated with DES compared with ERACI II stent arm. In line with randomized data regarding DES treatment (SIRIUS ,E-SIRIUS,C-SIRIUS,TAXUS II and TAXUS IV) and also based on our previous ERACI trial data (35% of MACCE reduction among ERACI II with BMS versus ERACI I with POBA), **we predicted a 50% reduction of MACCE with DES therapy . Thus, based on the 22.3% incidence of MACCE at one year in the ERACI II-PCI arm, we expected a one year incidence of MACCE of 10 to 12% with DES.** Consistent with the above data and using a two-sided test for differences with an alpha level of 0.05, we calculated that approximately 210 patients treated with DES were required to guarantee a power of 80%.

END POINTS

Primary

- To compare incidence of MACCE and TVR at one, two, three, and five years at follow up between patients with multivessel disease treated with DES (ERACI III) versus similar cohort of patients included in ERACI II treated either with Bare stent or CABG

Secondary

- MACCE at 30 days.
- Incidence of MACCE in Diabetics and non Diabetics.
- Incidence of stent thrombosis in DES patients.
- Incidence of stent thrombosis in DES compared with ERACI II Bare stent patients.
- Cost and cost effectiveness.

ERACI II and ERACI III

Baseline Demographic, Clinical and Angiographic Characteristics

COVARIATE	BMS (n=225)	CABG (n=225)	DES (n=225)	p-Value
Sex (Male)	174 (78.2%)	183 (81.3%)	188 (83.6%)	n/s
Age (Years)	60.63±10.10	60.79±10.30	65.49±10.63	<0.001
Previous AMI	64 (28.4%)	62 (27.6%)	71 (31.6%)	n/s
Hypertension	160 (71.1%)	158 (70.2%)	179 (79.6%)	0.046
Hyperlipidemia	141 (62.7%)	134 (59.6%)	178 (79.1%)	<0.001
Diabetes	39 (17.3%)	39 (17.3%)	46 (20.4%)	n/s
Smoking	122 (54.2%)	111 (49.3%)	154 (68.4%)	<0.001
Stable Angina	17 (7.6%)	21 (9.3%)	58 (25.8%)	<0.001
Braunwald I/IIb	138 (61.3%)	141 (62.7%)	99 (44.0%)	<0.001
Braunwald Class IIIb	48 (21.3%)	42 (15.1%)	44 (19.6%)	n/s
Braunwald Class IIIc	22 (9.7%)	21 (9.3%)	24 (10.7%)	ns
Left Main	12 (5.3%)	9 (4.0%)	13 (5.8%)	n/s
Type C Lesions	34 (15.1%)	36 (16.0%)	83 (36.9%)	<0.001
2Vessel CAD	102 (45.3%)	95 (42.2%)	139 (61.8%)	<0.001
3Vessel CAD	123 (54.7%)	130 (57.8%)	86 (38.2%)	<0.001
No. of Stents	1.39±0.56	-	1.79±0.71	<0.001
Stented Length	25.7±13.23	-	36.16±8.89	<0.001

ERACI II and ERACI III

Univariate Analysis of Incidence of Primary and Secondary Endpoints by Subgroup (BMS,CABG and DES)

COVARIATE	BMS (n=225)	CABG (n=225)	DES (n=225)	p- Value
MACCE	50 (22.2%)	44 (19.6%)	27 (12.0%)	0.014
Death	7 (3.1%)	17 (7.6%)	7 (3.1%)	0.034
AMI	5 (2.0%)	14 (6.2%)	6 (2.7%)	0.048
Stroke	4 (1.8%)	2 (0.9%)	5 (2.0%)	n/s
TVR	38 (16.9%)	11 (4.4%)	20 (8.9%)	<0.001

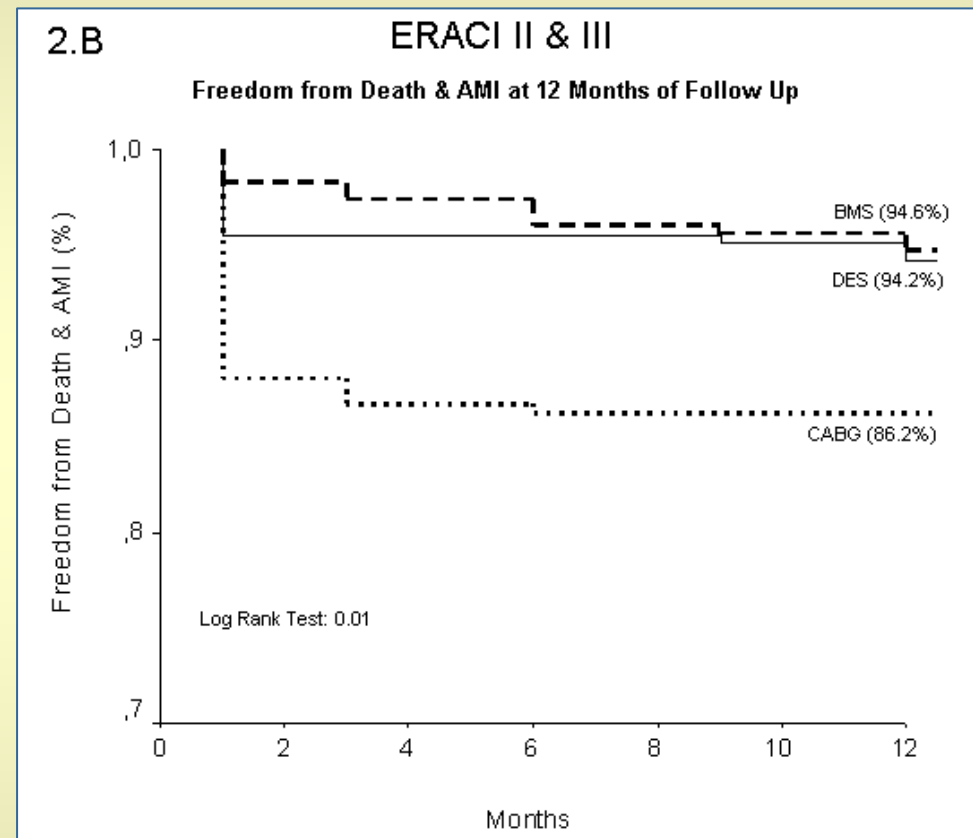
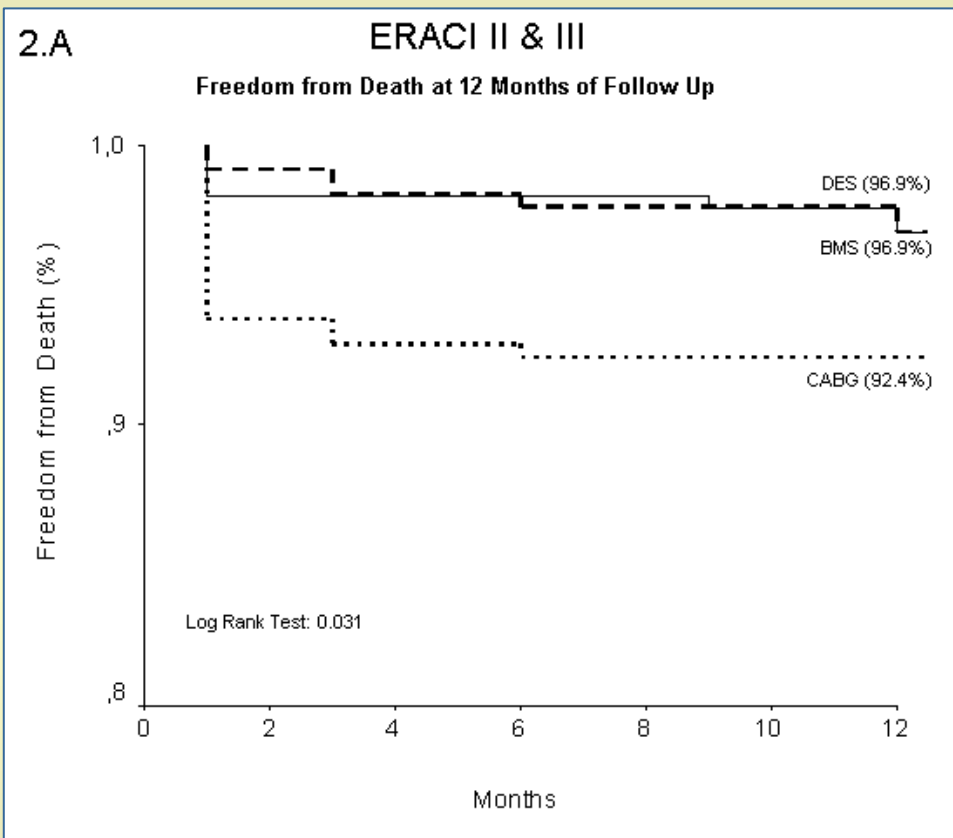
MACCE: Major Adverse Cardiac and Cerebrovascular Events.

AMI: Acute Myocardial Infarction

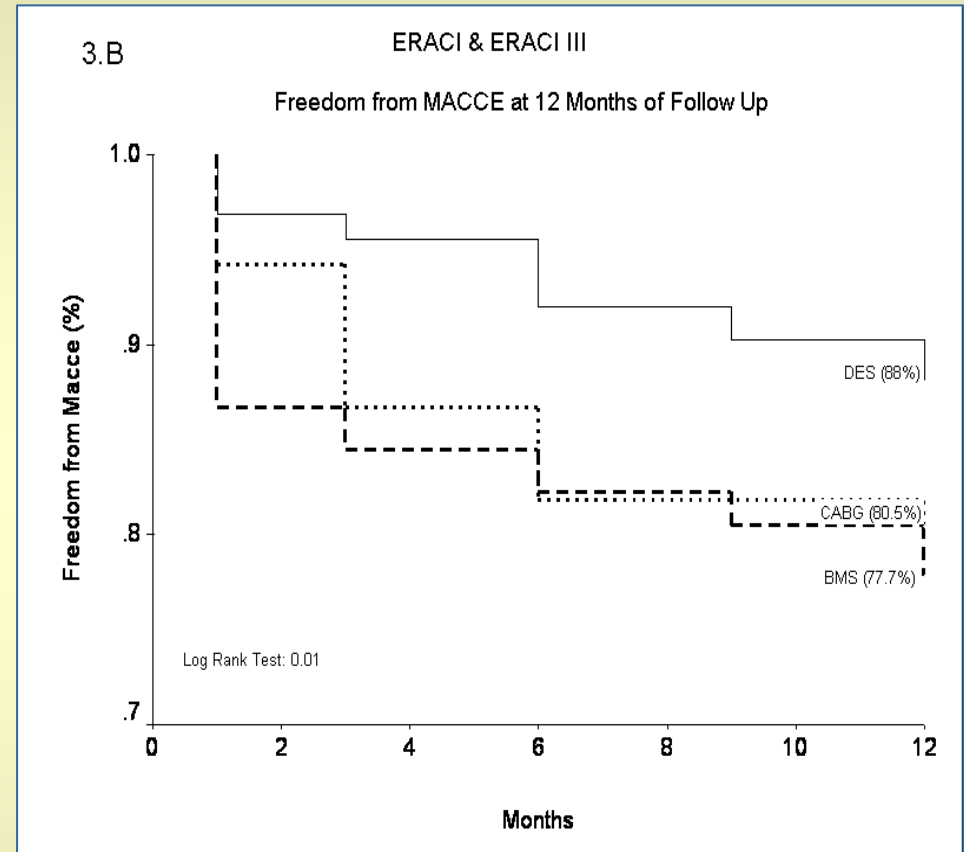
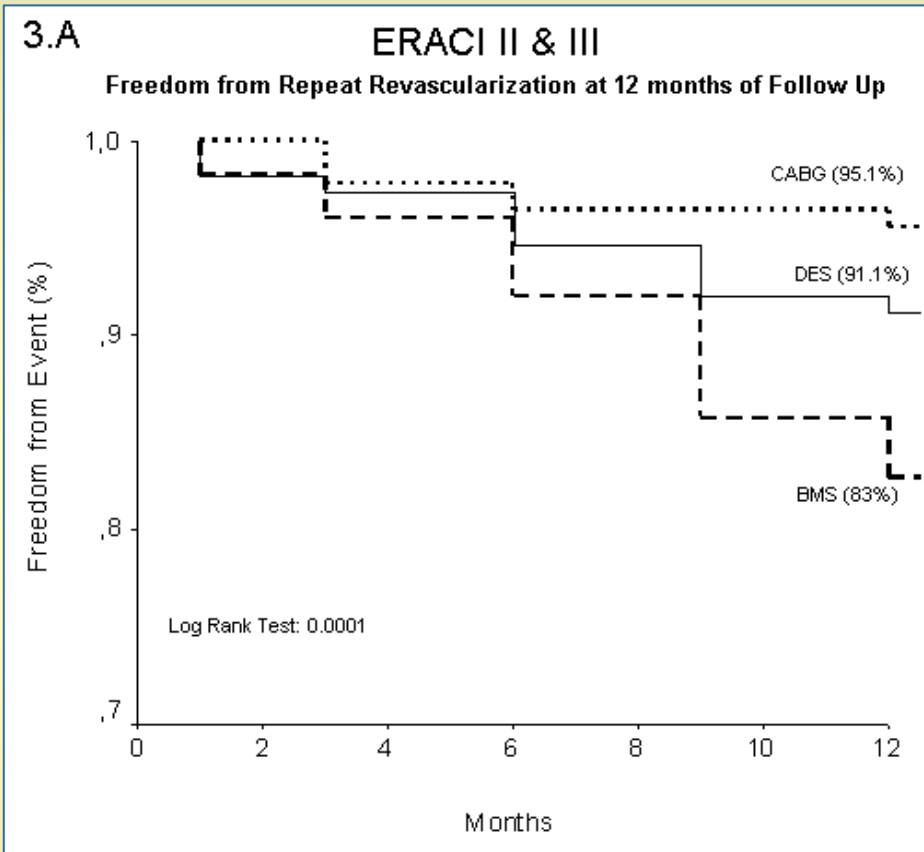
TVR: Target Vessel Revascularization

Rodriguez A et al EuroInterv, 2006

ERACI II and ERACI III



ERACI II and ERACI III



ERACI II and ERACI III

Multiple Variable Predictors of MACCE at Follow Up

VARIABLE	95.0% C.I for Exp (B)			
	Significance	Exp (B)	Lower	Upper
DIABETES	0.003	0.481	0.299	0.774
BMS vs DES	0.006	2.649	1.316	5.335
Dyslipidemia	0.014	0.557	0.349	0.887
CABG vs DES	0.038	2.679	1.055	6.801
BMS vs CABG	0.981	0.989	0.387	2.526
Sex	0.259	1.341	0.806	2.231
Age	0.404	1.009	0.988	1.030
Hypertension	0.678	1.105	0.689	1.773
Smokers	0.416	0.835	0.542	1.288
Braunwald IIb	0.558	0.859	0.516	1.429
Braunwald IIIC	0.399	0.652	0.241	1.763
No. Stents	0.729	1.091	0.666	1.789
Stented Length	0.992	1.000	0.967	1.034
Type C lesion	0.551	1.202	0.656	2.203
2 Vessels	0.569	0.886	0.583	1.345

BMS:Bare Metal Stents in ERACI II; **CABG:** Coronary Artery Bypass Graft in ERACI II; **DES:** Drug Eluting Stents in ERACI III

ERACI II and ERACI III

**One Year Follow Up MACCE and TVR
Univariate Analysis : Diabetics vs non Diabetics
DM (n=124)-non DM (n=551)**

MACCE	27.4 %	vs	15.8%	(p= 0.004)
TVR	18.5%	vs	8.3%	(p=0.002)

ERACI II and ERACI III

One Year Follow Up ERACI III Trial (DES) : Non Diabetic vs. Diabetic

	Non DM (n:178)	DM (n:47)	<i>p value</i>
Death	2.8%	4.2%	0.61
AMI	1.1%	8.5%	0.005
Death + AMI	3.9%	8.5%	0.4
Stroke	2.2%	2.1%	0.96
Repeat PCI/CABG	6.7%	17%	0.028
MACCE	9%	23.4%	0.038

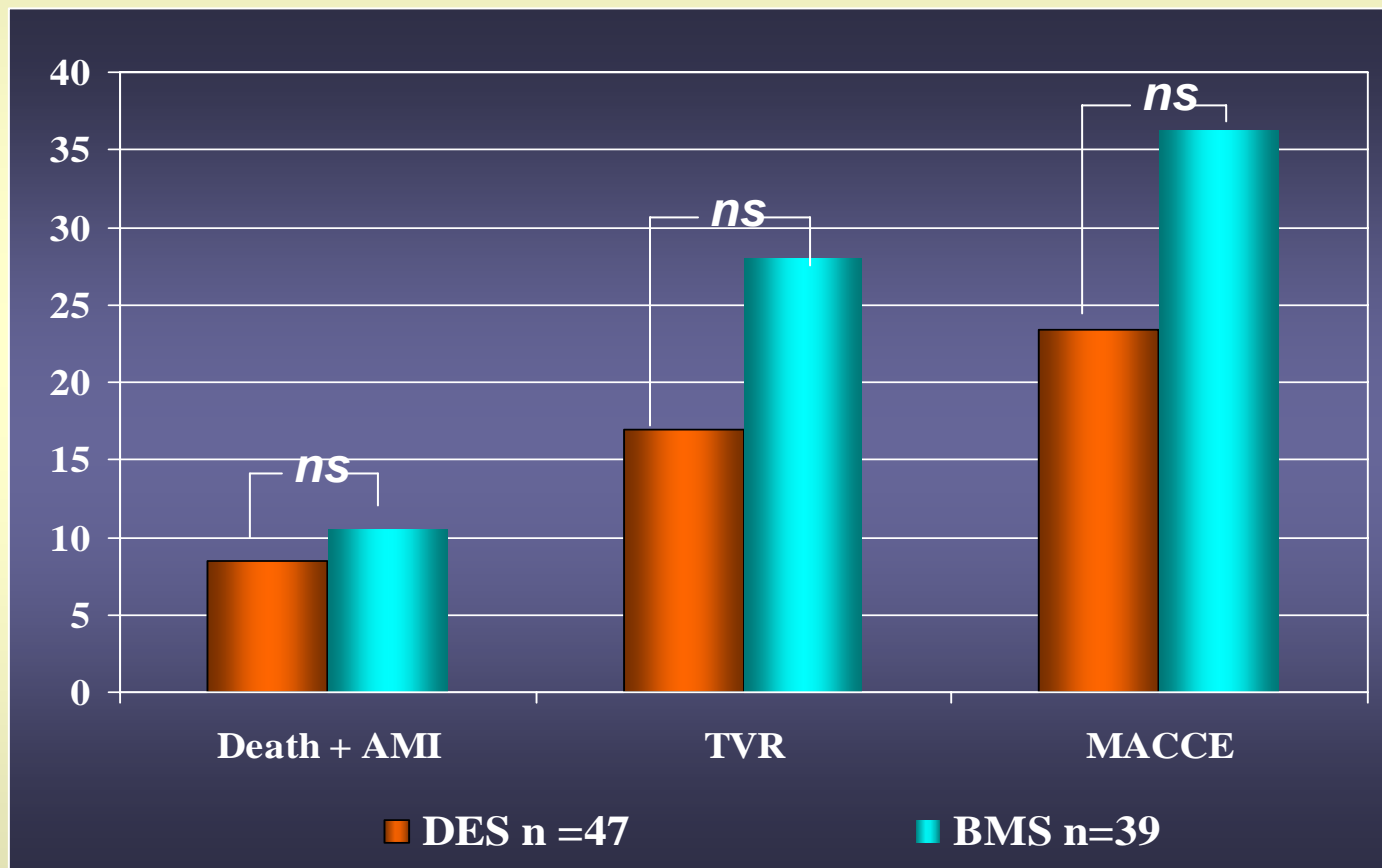
DM : Diabetics

MACCE: Major Adverse Cardiac and Cerebrovascular Events

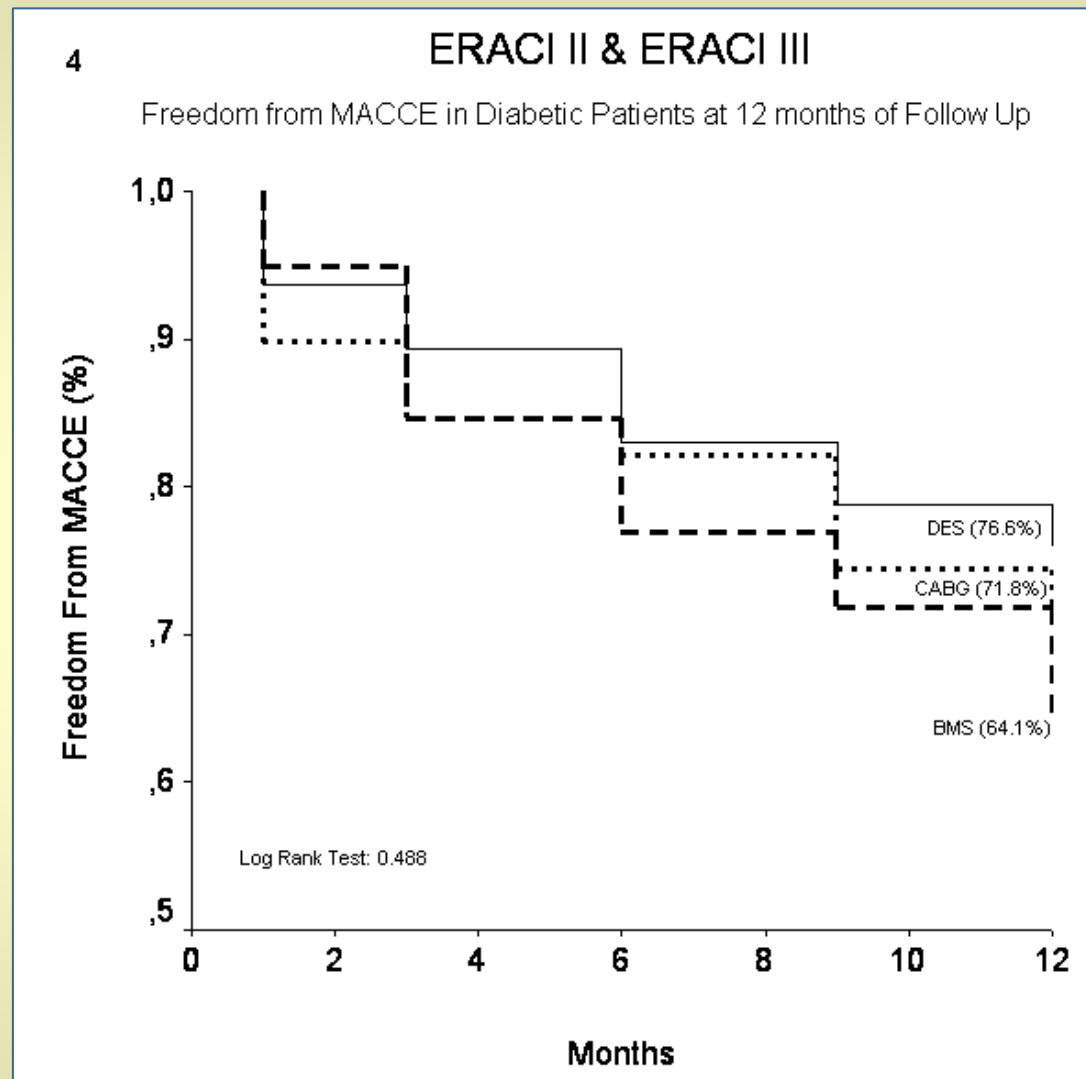
AMI: Acute Myocardial Infarction

ERACI II and ERACI III

One Year Follow Up Results in Diabetics: DES vs BMS



ERACI II and ERACI III



ERACI III

Coronary Stent Thrombosis (SET) was pre defined as:

Confirmed Stent Thrombosis (CST), when the patient had angiographically documented stent thrombosis with TIMI flow 0 or 1 or the presence of flow-limiting thrombus (TIMI flow 1 or 2).

Suspected Stent Thrombosis (SST), when the patient suffered unexpected cardiac or sudden death or had a segment elevation myocardial infarction (STEMI) which correlates with the area of DES placement. Patients having non STEMI or not able to reviewed the electrocardiogram at the moment of the acute event, were not included in this category. Patients who suffered cardiac or sudden death, were included as SST only if the event was certified by a physician present during or immediately after the acute event.

Stent Thrombosis ERACI II vs. ERACI III

	In Hospital	< 30 Days	One Year	Three Years	Overall
ERACI II (n = 225)	3/225	0/225	0/225	0/225	3/225*
ERACI III (n= 225)	1/225	3/225	3/225	1/225	8/225*

* p= 0.224

ERACI III – Stent Thrombosis

Pt. Nº	Age, Gender	CST/ SST	DES Design	Time to DES Implantation	Bare stent patent	Treated Vessel	Stent Diameter (mm)	Stent Length (mm)	Notes	Clinical Presentation	Clinical Outcome at Hospital Discharge
1	70, Male	CST	PES	7 days	YES	LAD	2.5	16	Clopidogrel stopped 3 days prior	STEMI	Death
2	73, Male	CST	PES	204 days	YES	LAD	3.0	24	AAS and clopidogrel stopped 7 days before surgery	STEMI	Alive
3	75, Male	CST	PES	49 days	YES	LCX	2.5	16	AAS and clopidogrel stopped 4 days for haematuria and surgery	STEMI	Alive
4	57, Male	CST	SES	3 days		LAD	3.0	33	Clopidogrel stopped 2 days prior	STEMI	Alive
5	63, Male	CST	SES	927 days	YES	LAD	2.5	33	AAS and clopidogrel stopped for 45 days for gastrointestinal hemorrhage and surgery	STEMI	Alive
6	60, Male	SST	SES	227 days		LAD and LCX	2.5	23	AAS and clopidogrel stopped 7 days prior	STEMI	Death
7	66, Male	SST	SES	5 days		LM	3.0	18	AAS and clopidogrel not stopped	APE	Death

STEMI = ST- segment elevation myocardial infarction, APE = Acute Pulmonary Edema, PES = Paclitaxel Eluting Stent, SES = Sirolimus Eluting Stent, CST = Confirmed Stent Thrombosis SST = Suspected Stent Thrombosis. LAD:Left Anterior Descending Artery, LCX Left Circunflex, LM: Left Main



BASKET LATE Randomized Trial

Drug Eluting Stent (n=499)

vs

Bare Metal Stent (n=244)

Late Stent Thrombosis

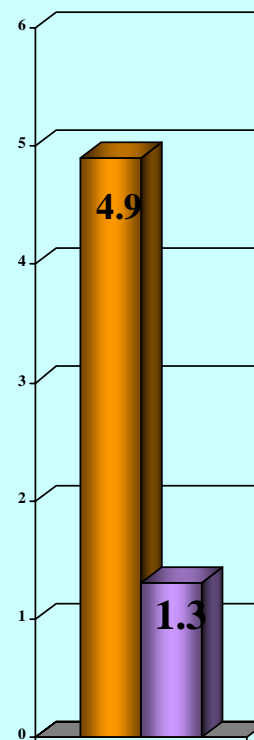
DES 2,6% vs BMS 1.3%

Conclusions

- Among patients with coronary artery disease treated with PCI, use of DES was associated with significantly higher rates of cardiac death or MI compared with BMS in the year following clopidogrel discontinuation.
- For every 100 patients treated with DES 3.3 of death or MI are induced for reduction of 5 cases of TLR.

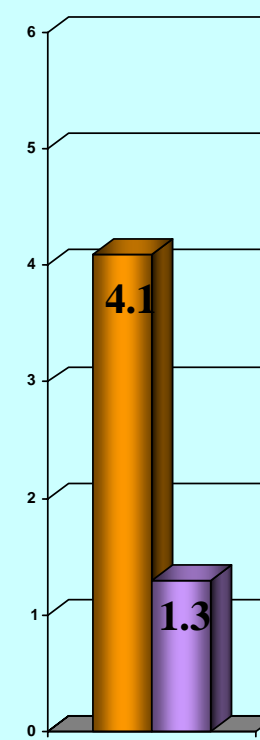
Cardiac death or MI

P= 0.01



MI

P= 0.04



■ Drug Eluting Stents ■ Bare Metal Stent

■ Drug Eluting Stents ■ Bare Metal Stent



Multivessel Stenting in Drug Eluting Stent Era: Results from ERACI II and ERACI III trials.

Study Limitations

First, it is a non-randomized study, and it's well known that randomized comparisons are the most appropriate study design to evaluate medical or surgical procedures in clinical practice.

Secondly, the study (ERACI II-BMS or CABG arms) was not performed with contemporary PCI equipment and techniques, including better secondary prevention practices which may have contributed to a beneficial effect in our ERACI III-DES study arm.

Thirdly, the high in-hospital rate of MACCE reported in the ERACI II-CABG arm may artificially inflate the relative benefit of DES use at one year.

Finally, we are presenting the one year follow up data, and do not know if the DES efficacy and safety findings will be sustained over a longer follow up period.



Multivessel Stenting in Drug Eluting Stent Era: Results from ERACI II and ERACI III trials.

Conclusions

In conclusion, this multicenter, prospective and controlled study in patients with multivessel disease treated either with SES or PES stents, demonstrated a significant reduction of MACCE and the need for repeat revascularization when compared to our previous PCI bare metal stent data from ERACI II.

Univariate analysis revealed that patients with diabetes, when all treatments BMS, DES and CABG were combined, had a significantly higher incidence of MACCE at one year when compared to non-diabetics (27.4% vs 15.8% $p=0.004$). Comparison of DM patients treated with DES in ERACI III and DM from the ERACI II-PCI arm failed to demonstrate a significant improvement in death and myocardial infarction, repeat revascularization or MACCE . Further analyses are required to establish if there is a significant improvement in outcome among diabetic patients (FREEDOM and SYNTAX).



Multivessel Stenting in Drug Eluting Stent Era: Results from ERACI II and ERACI III trials.

Conclusions (cont.)

The issue of late stent thrombosis with DES is a contentious one

Late stent thrombosis is usually a severe but rare event with bare metal stent design. The incidence associated with DES will require a considerably larger study than ERACI III.

However, the findings of ERACI III are in agreement with the worrisome data from those recently reported by BASKET LATE (ACC06), reporting higher rates of late SET following clopidogrel discontinuation in the DES treated patients, which translate to higher incidence of death and AMI.

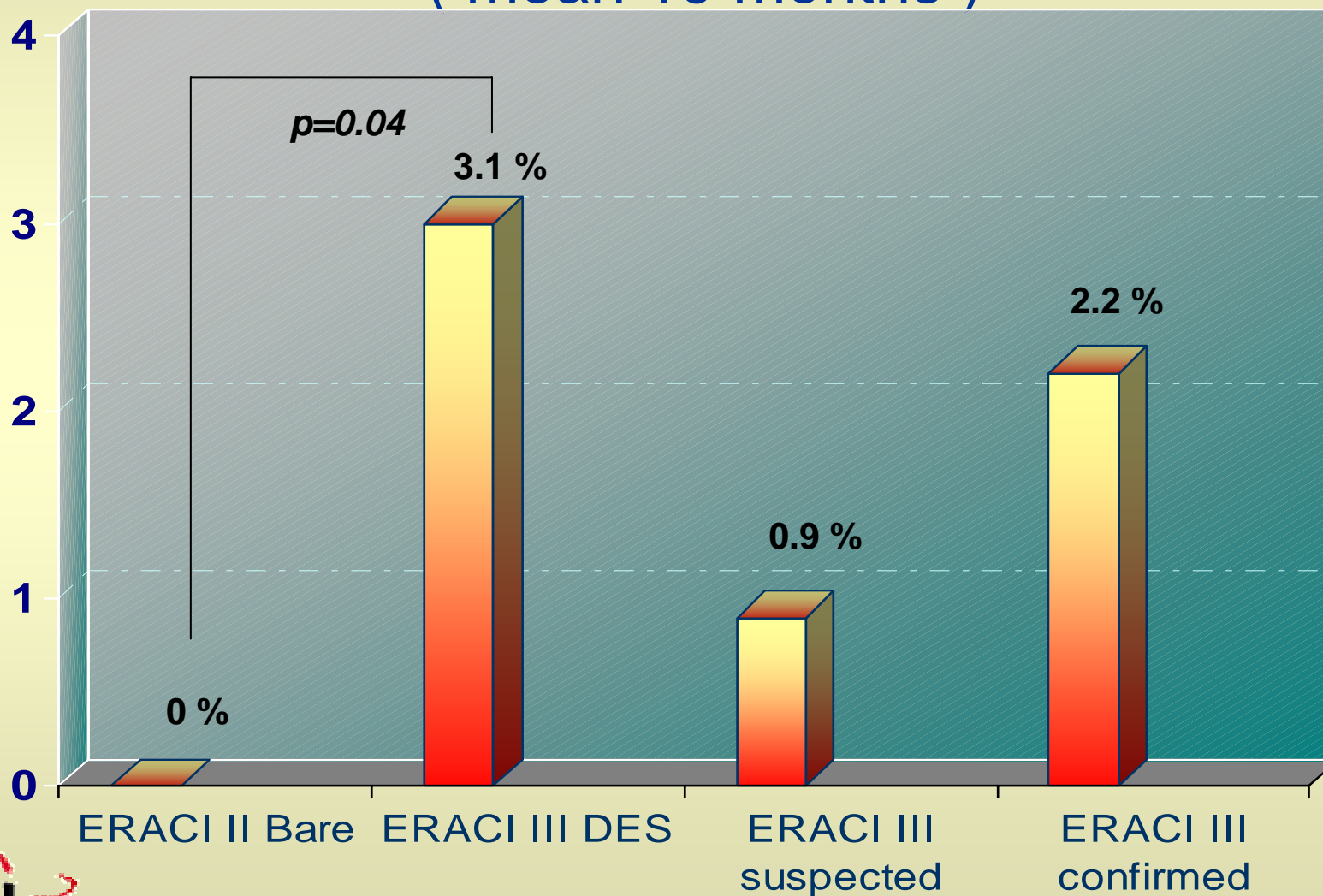
Thus, the incidence of late SET, nor TLR reduction, will determine in the near future, the final role of current DES designs during interventional procedures.

High late SET can not be the price to paid for less TLR, and dual antiplatelet therapy indefinitely might not be the solution !!



ERACI II and ERACI III

Out of Hospital Stent Thrombosis (mean 19 months)



ERACI II and ERACI III

Four Years Follow Up Pooled Analysis from SIRIUS Trials RAVEL,SIRIUS,E-SIRIUS,C-SIRIUS

	Cypher (n:878)	BMS (n:870)	<i>p value</i>
Death	6 %	4.6 %	0.230
TVF(1st end point)	19%	32%	<0.001
Stent Thrombosis	1.7%	1.6%	1.0
Very Late SET	0.6%	0%	0.073
DIABETES	22.2%	26.8%	0.026

Argentine Multivessel CAD Revascularization Studies: POBA, BMS or DES versus CABG (ERACI I-II-III) Trials.

- Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease (ERACI): In-Hospital Results and 1-Year Follow-Up. A Rodriguez, F Boullon, N Perez-Balino, C Paviotti, M Sosa-Liprandi, I Palacios; *J Am Coll Cardiol* 1993; 22:1060-7.
- Three-Year Follow-Up of the Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Surgery in Multivessel Disease (ERACI). A Rodriguez, E Mele, E Peyregne, F Boullon, N Perez-Balino, MI Sosa-Liprandi, I Palacios; *J Am Coll Cardiol* 1996;27:1178-84.
- Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients Wit Multiple-Vessel Disease (ERACI II): 30-Day and One-Year Follow-up Results. A. Rodriguez, V. Bernardi, J. Navia, J. Baldi, L. Grinfeld, J. Matinez, D. Vogel, R. Grinfeld, A. Delacasa, M. Garrido, R. Oliveri, E. Mele, I. Palacios. E. Mele, E. Peyregne, F. Boullon, N. Perez-Balino, M.I. Sosa-Liprandi, I. F. Palacios; *J Am Coll Cardiol* 2001;37:51-8.
- Coronary Stenting versus coronary bypass surgery in patients with multiple vessel disease and significant proximal LAD stenosis: results from ERACI II study. A. Rodriguez, M Rodriguez-Alemparte, J Baldi, J Navia, A Delacasa, D Vogel, R Oliveri, C Fernandez-Pereira, V Bernardi, W O'Neill, I Palacios; *Heart* 2003;89:184-188.
- Five-Year Follow-Up of the Argentine Randomized Trial of Coronary Angioplasty Wit Stenting Versus Coronary Bypass Surgery in Patients With Multiple Vessel Disease (ERACI II). A Rodriguez, J Baldi, C Fernandez-Pereira, J Navia, M Rodriguez-Alemparte, A Delacasa, F Vigo, D Vogel, W O'Neill, I Palacios. *J Am Coll Cardiol* 2005;46:582-8.
- Coronary Stent Thrombosis in Current Drug Eluting Stent Era: Insights From ERACI III trial. A. Rodriguez, J Mieres, C Fernandez-Pereira, CF Vigo, M Rodriguez-Alemparte, D Berrocal, L Grinfeld, I Palacios. *JACC*, 2006;47.
- Revascularization Strategies of Coronary Multiple Vessel Disease In Drug Eluting Stent Era: One Year Follow Up Results Of ERACI III Trial .Alfredo Rodriguez , Andrew O,Maree, Liliana Grinfeld, Carlos Fernandez-Pereira , Juan Mieres, Maximo Rodriguez Alemparte, Daniel Berrocal, Alfredo M Rodriguez-Granillo, Cesar F Vigo, Miguel Russo Felsen, William Oneill, Igor Palacios. *Eurointervention*,2006.

STUDY DESIGN

225 patients with multivessel coronary lesions

21.5% diabetic
30.2% Braunwald IIIb or C
37% type C lesions

Historical Controls from ERACI II: 450 patients with multivessel coronary lesions

17.3% diabetic
29% Braunwald IIIb or C
15 % type C lesions

Taxus and Cypher stents

1.8 stents per patient
Avg total length: 36 mm
n = 225

Bare Metal Stent

1.4 stents per patient
Avg total length: 25.7 mm
n = 225

CABG

n = 225

ERACI III

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PCI VS CABG IN MULTIPLE VESSEL DISEASE

TABLE 3. Independent Correlates of Primary End Point Within Interval of Time (Randomization to 1 Year and up to 3 Years) in Patients Treated by Stented Angioplasty or CABG

Variable	1 Year		Up to 3 Years	
	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)
Stent				
Diabetes mellitus	0.002	2.1 (1.34–3.30)	0.0009	1.81 (1.28–2.57)
Maximal balloon pressure*	0.002	0.95 (0.91–0.99)	0.002	0.92 (0.87–0.97)
No. of stents implanted in mid-RCA	0.004	1.43 (1.11–1.84)
Stenosis in mid-LCx	0.0043	1.85 (1.23–2.78)
Stenosis in distal RCA	0.02	4.53 (1.24–16.52)
Intention to treat distal (dominant) RCA	0.03	3.60 (1.15–12.36)
No. of unsuccessful treated segments	0.03	1.27 (1.02–1.58)
Use of digitalis	0.03	4.81 (1.33–22.572)
Previous MI	0.047	0.80 (0.65–1.00)
<i>c</i> Index		<i>c</i> =0.66		<i>c</i> =0.65
CABG				
Elevated CK-MB	0.0001	1.73 (1.33–2.26)
Increasing age	0.002	1.06 (1.02–1.10)
Use of heparin	0.003	2.66 (1.39–5.08)
Abnormal hematocrit	0.01	2.56 (1.22–5.39)
Intra-aortic pump	0.03	9.44 (1.16–76.87)
Anastomosis in distal RCA	0.04	0.4 (0.17–0.97)
Anastomosis in mid-LAD	0.006	0.55 (0.35–0.84)
Incomplete RCA revascularization (S2)	0.009	11.17 (1.06–242.00)
Intention to treat RCA stenosis	0.02	2.70 (1.24–5.69)
<i>c</i> Index		<i>c</i> =0.77		<i>c</i> =0.61

LCx indicates left circumflex coronary artery; CK, creatine kinase.

*Only in LAD for 1-year events; in all vessels for 3-year events.

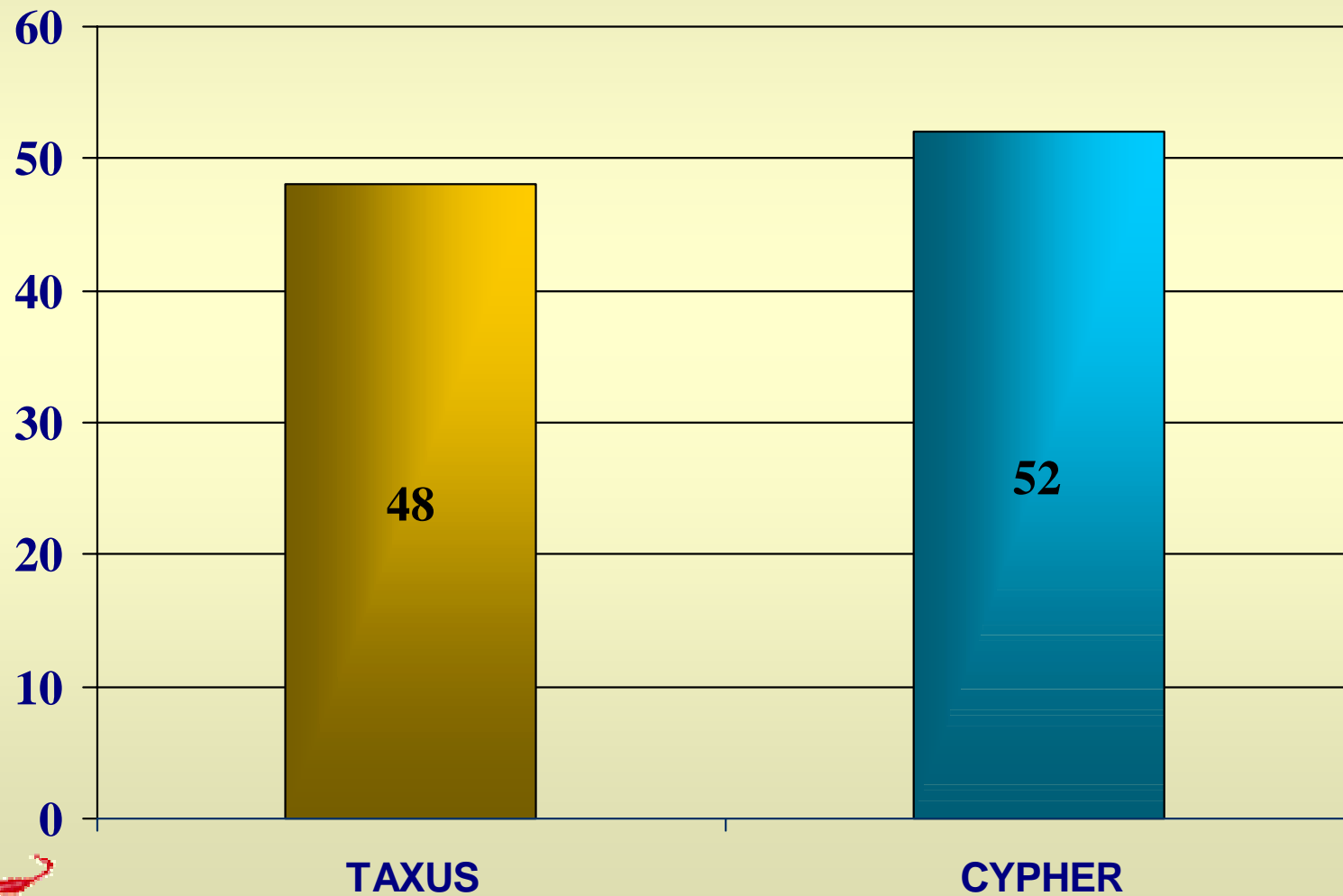


Purpose

We sought to compare in DES Era, incidence of TVR and MACCE at one, two, three, and five years at follow up between patients with multivessel disease prospectively included and treated with DES (ERACI III) versus similar cohort of patients included in ERACI II treated either with Bare stent or CABG. We are presenting here one year follow up results.

ERACI III

Stent Design %



Multivessel Stenting in Drug Eluting Stent Era: Results from ERACI II and ERACI III trials.

Conclusions (cont.)

The issue of late stent thrombosis with DES is a contentious one

Late stent thrombosis is usually a severe but rare event with bare metal stent design. The incidence associated with DES will require a considerably larger study than ERACI III.

However, the findings of ERACI III are in agreement with the worrisome data from those recently reported by BASKET LATE (ACC06), reporting higher rates of late stent thrombosis following clopidogrel discontinuation in the DES treated patients, which translate to higher incidence of death and AMI. Thus, the incidence of late stent thrombosis, nor TLR reduction, will determine in the near future, the final role of current DES designs during interventional procedures.

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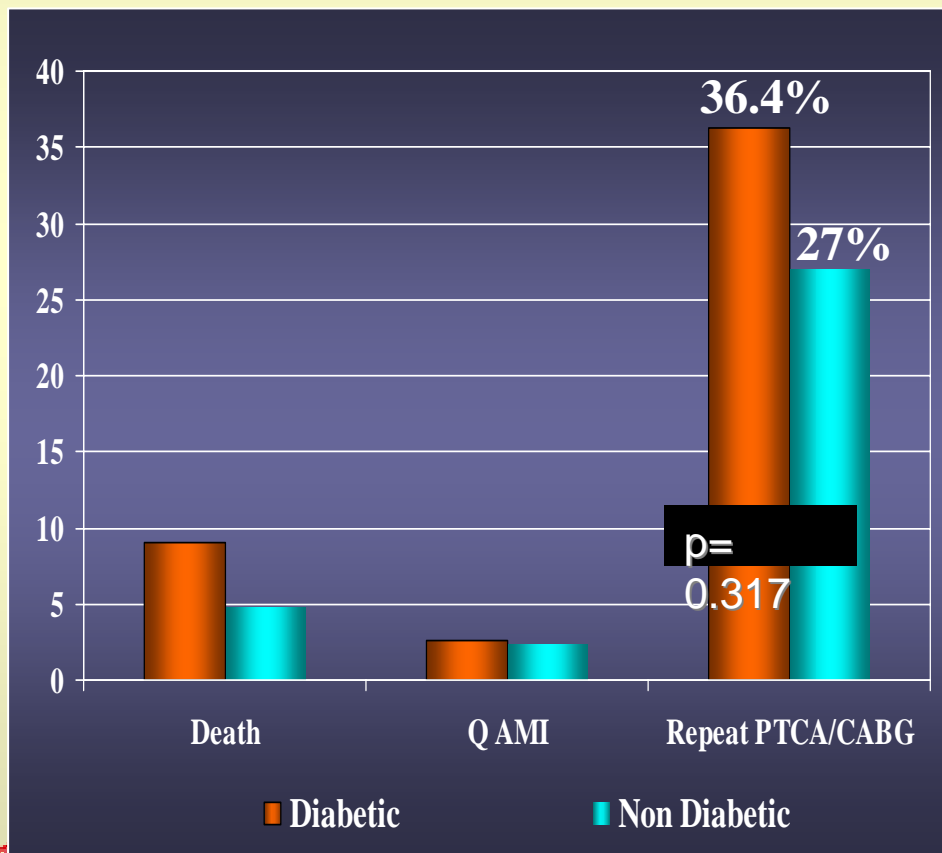
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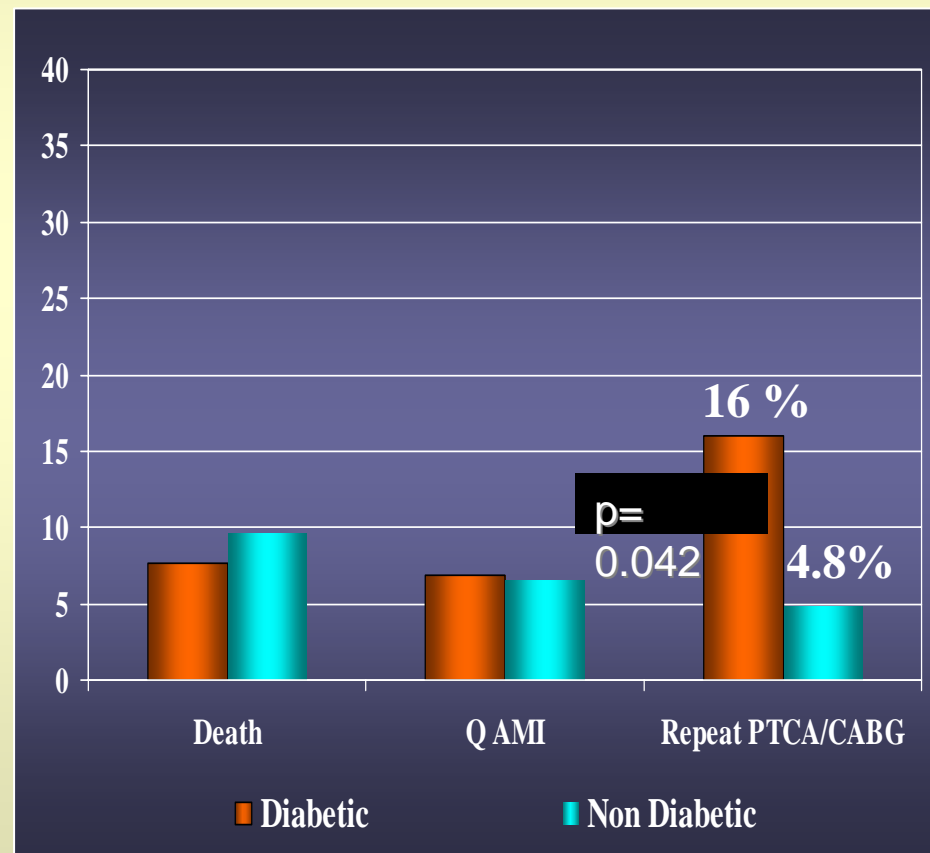


Diabetics vs. Non Diabetics ERACI I-II 3 Years Outcome

PTCR Arm



CABG Arm



PCI VS CABG IN MULTIPLE VESSEL DISEASE

TABLE 4. Total No. of Patients With Major Clinical Events at 3 Years Among Nondiabetes and Diabetes Subgroups

	Stent	CABG	Relative Risk (95% CI) Stent/CABG
Nondiabetes	n=488	n=509	
Death, n (%)	14 (2.9)	24 (4.7)	0.608 (0.318–1.162)
Cerebrovascular events, n (%)	14 (2.9)	13 (2.6)	1.123 (0.533–2.365)
MI, n (%)	32 (6.6)	27 (5.3)	1.236 (0.752–2.032)
Q-wave, n (%)	27 (5.5)	26 (5.1)	1.083 (0.641–1.829)
CABG, n (%)	40 (8.2)	5 (1.0)	8.344 (3.321–20.967)
PCI, n (%)	89 (8.2)	31 (6.1)	2.995 (2.029–4.420)
Event free, n (%)*	336 (68.9)	424 (83.3)	...
Diabetes	n=112	n=96	
Death, n (%)	8 (7.1)	4 (4.2)	1.714 (0.533–5.517)
Cerebrovascular events, n (%)	6 (5.4)	7 (7.3)	0.735 (0.256–2.112)
MI, n (%)	11 (9.8)	6 (6.3)	1.571 (0.604–4.090)
Q-wave, n (%)	9 (8.0)	4 (4.2)	1.929 (0.613–6.065)
CABG, n (%)	15 (13.4)	2 (2.1)	6.429 (1.508–27.406)
PCI, n (%)	31 (27.7)	6 (6.3)	4.429 (1.930–10.162)
Event free, n (%)*	59 (52.7)	78 (81.3)	...

* $P < 0.0001$ (Fisher's exact test).

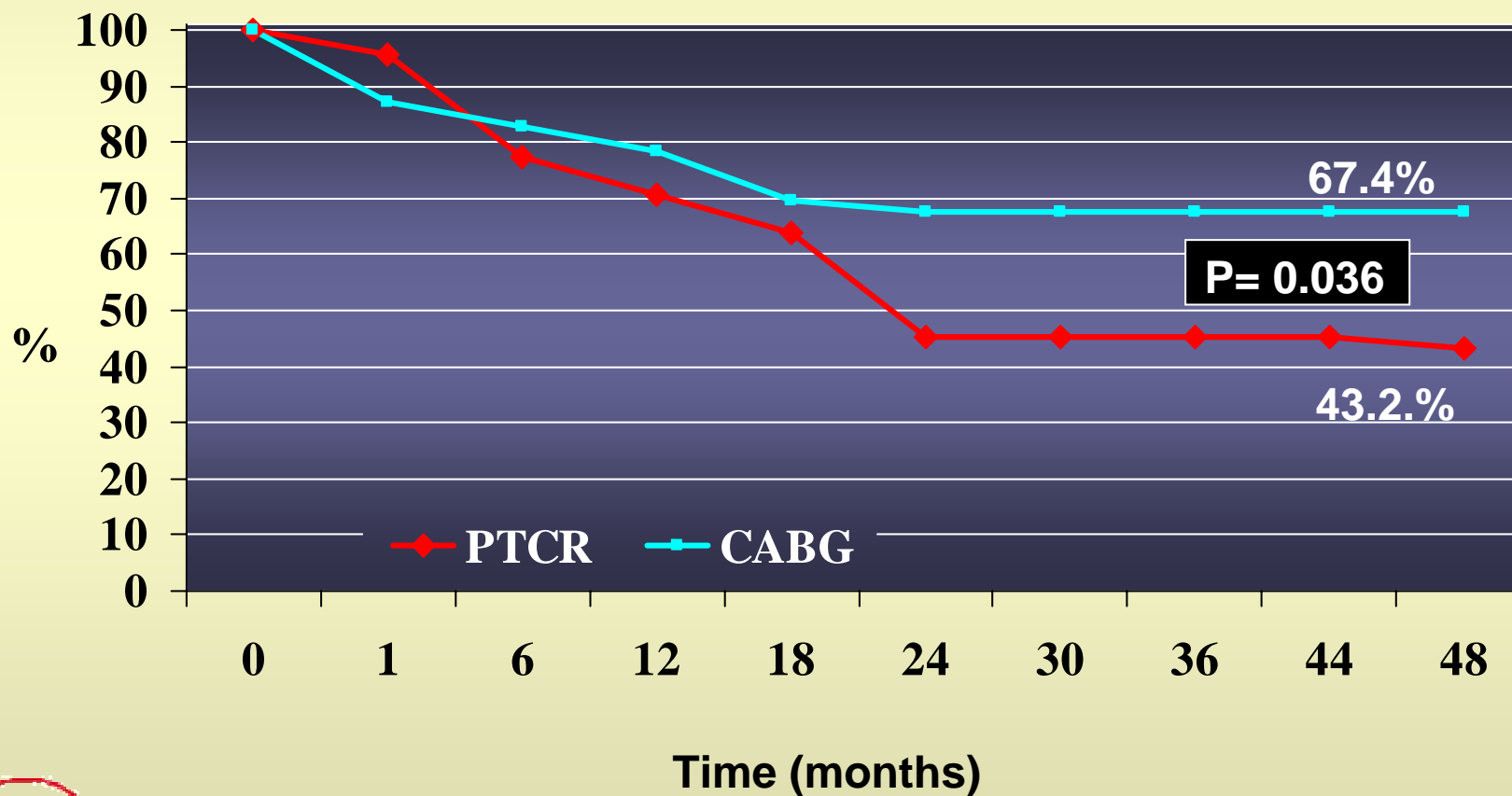


Increased risk for diabetics vs non diabetics at nine months after PCI in PRESTO

Outcome	Adjusted relative risk	95% CI	p
Death	1.87	1.31-2.68	0.01
MI	1.22	0.86- 1.73	0.26
TVR	1.27	1.14- 1.42	0.01
Death/ MI/ TVR	1.26	1.13- 1.40	0.01

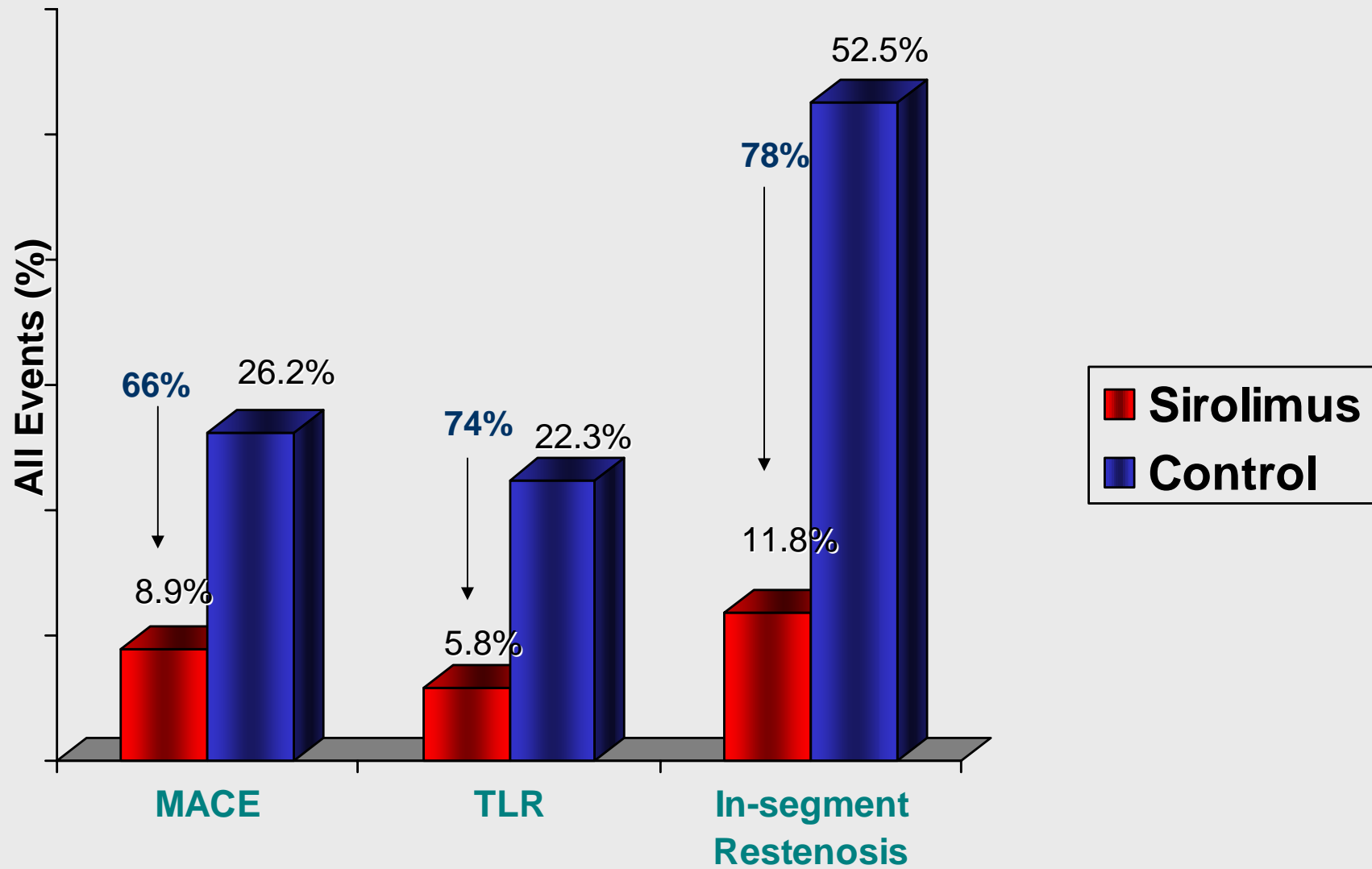
Diabetics Patients ERACI I- ERACI II

Freedom from Death, AMI, Repeat PTCA /CABG and Angina



Sirolimus Eluting Stent Trials

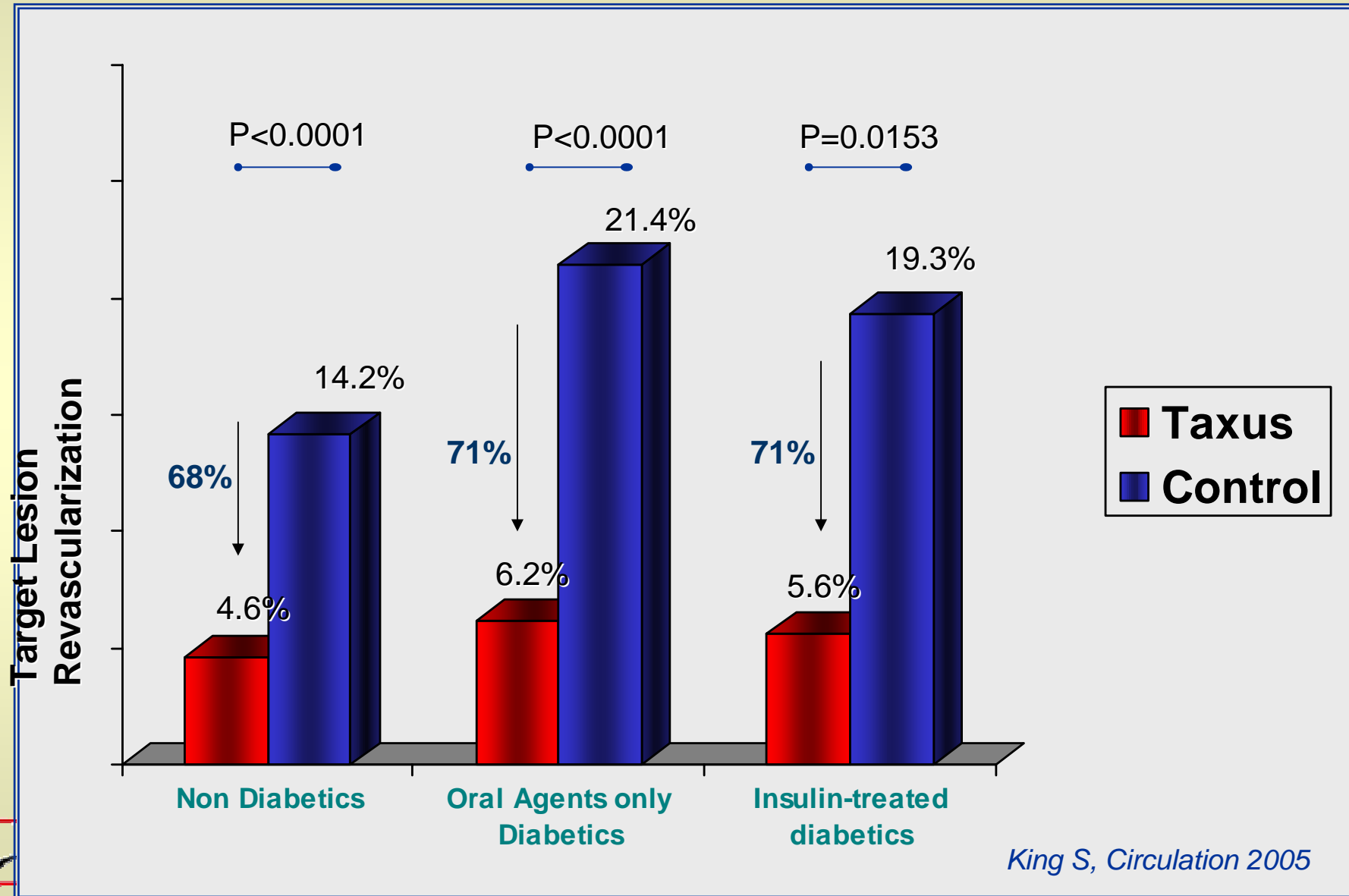
Results on Diabetic Patients



King S, Circulation 2005

Paclitaxel Eluting Stents Trials

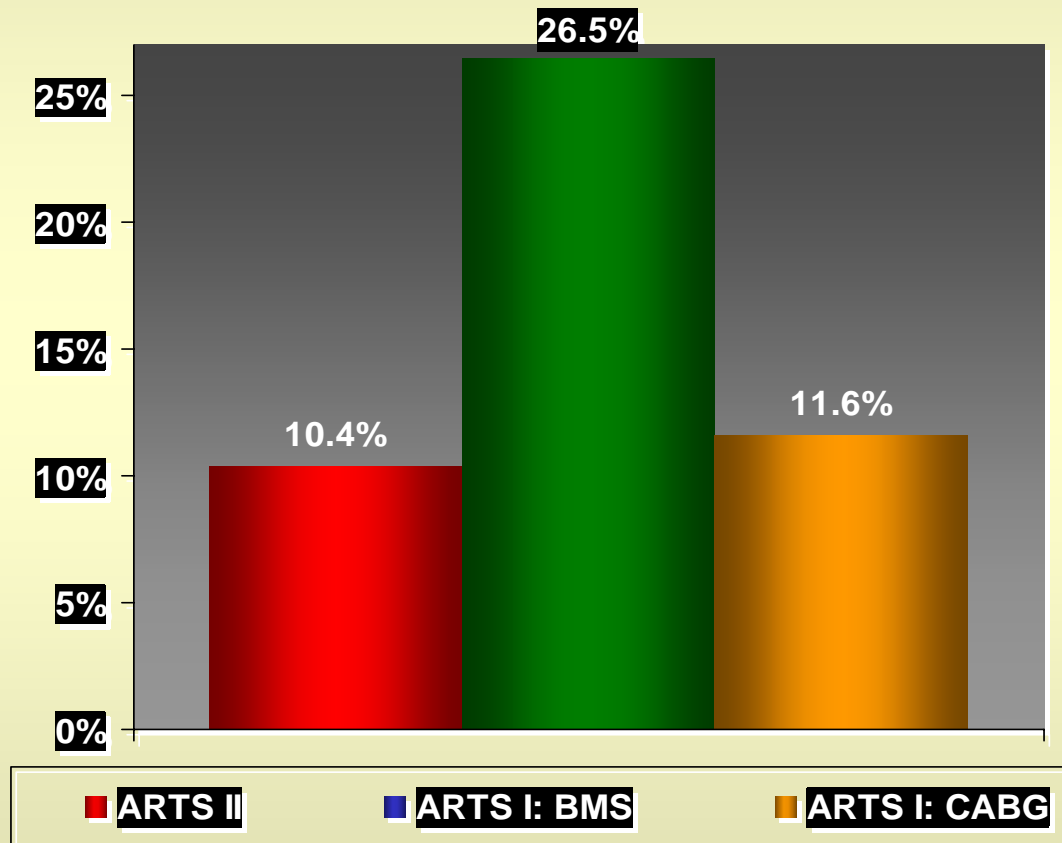
1 year TLR Results on Diabetic Patients.



King S, Circulation 2005

ARTS II: MACCE at one year

Overall MACCE at 1 year



- At 1 year, there was no difference in the incidence of MACCE between the ARTS II SES group and the ARTS I CABG group.
- The ARTS I bare metal stent group was associated with a significantly higher rate of 1 year MACCE compared to the other groups

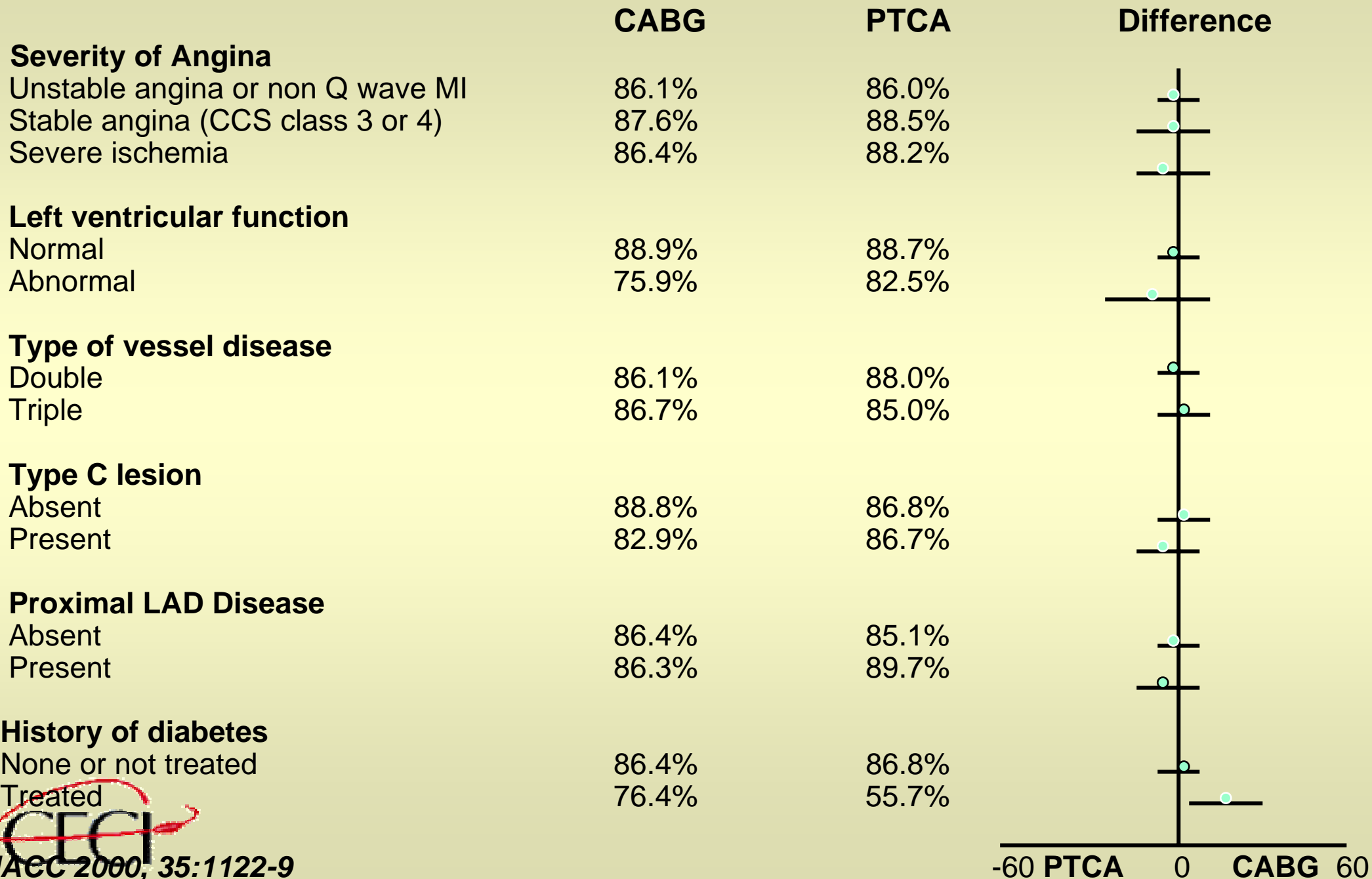
ERACI III – Out of Hospital Stent Thrombosis

	ERACI III (n=225)	Stent Thrombosis (n=7)
Age	65.5 +/- 10.9	68 +/- 7.25
Male (%)	83.5	100
Hypertension (%)	79.5	100
Diabetes (%)	20.4	28
Smoker (%)	68.4	85
Stable Angina (%)	26.3	42
Unstable Angina (%)	73.7	58
LM (%)	5.7	14
2 vessels (%)	61.7	42
3 vessels (%)	38.3	58
Stent Length per patient	36 mm	37 mm
Stent Diameter	2.93 +/-0.3mm	2.71 +/- 0.26mm
Stent per patient	1.8	2.1
Stent Design (%)		
Sirolimus Eluting Stent	52	58
Paclitaxel Eluting Stent	48	42

Table 1. Baseline Demographic, Clinic and Angiographic Characteristics of the Overall Population and with Stent Thrombosis



BARI TRIAL: Seven Year Survival



ERACI III – Stent Thrombosis

J.B., male, 63 years; presents with UA BII with anterior ischemia.

11/10/2002

PCI to LAD (cass 12) with Cypher® (2.5 x 33 mm)



ERACI III – Stent Thrombosis

21/10/2004

Patient was with SA and ischemia.

PCI to LAD (CASS14) with DES (2.5 X 23 mm)
and PCI to LCX (CASS19) with BMS.

ERACI III – Stent Thrombosis

10/01/2005

The patient presents with respiratory distress secondary to pneumonia, EKG with minor changes in anterolateral leads; repeat coronarioangiogram showing no intimal proliferation in both DES stents.

ERACI III – Stent Thrombosis

26/05/2005

Anterior AMI, with discontinuation of Clopidogrel for almost 45 days due to a Gastrointestinal haemorrhage and posterior surgery.

Univariate Predictors Of Cumulative DES Thrombosis

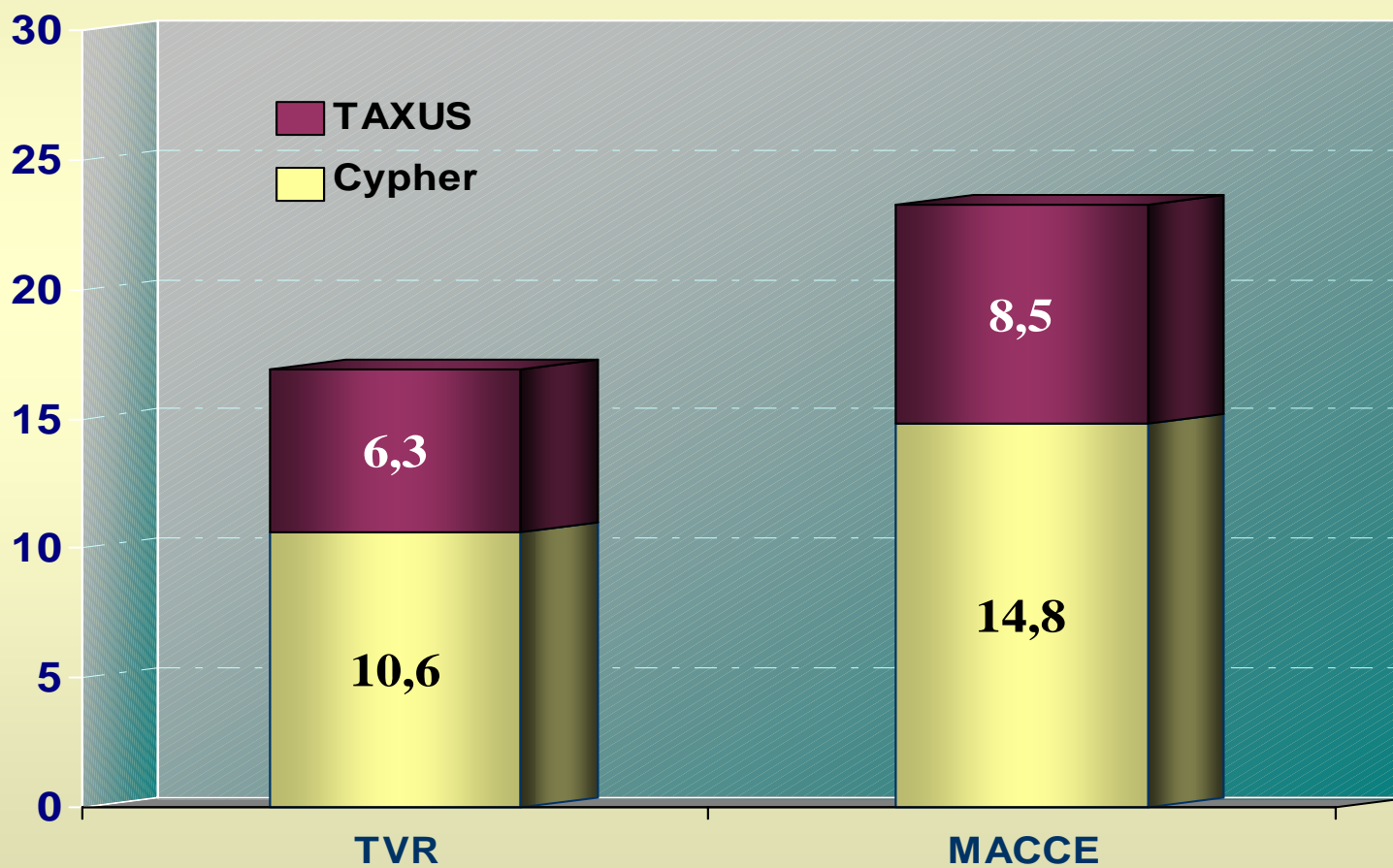
Variables	Incidence of Stent Thrombosis, No./Total (%)	Hazard Ratio (95% Confidence Interval)	P Value
Categorical Variables			
Premature antiplatelet therapy discontinuation	5/17 (29)	152 (52-442)	<.001
Prior brachytherapy	2/23 (8.7)	7.49 (1.78-31.49)	.006
Renal failure	8/127 (6.2)	11.67 (5.17-26.35)	<.001
Bifurcation with 2 stents	13/336 (3.9)	4.62 (2.22-9.62)	<.001
Bifurcation lesion	18/507 (3.6)	6.50 (3.02-13.98)	<.001
Unprotected left main artery	3/92 (3.3)	0.95 (0.67-1.36)	.81
Diabetes	15/591 (2.5)	3.45 (1.66-7.18)	<.001
Thrombus	1/50 (2)	1.58 (0.21-11.65)	.65
Unstable angina	8/590 (1.4)	1.24 (0.56-2.73)	.58
Male sex	22/1907 (1.2)	0.80 (0.30-2.11)	.66
B2 or C type	21/1698 (1.2)	1.19 (0.48-2.94)	.69
Calcification	4/392 (1)	0.74 (0.26-2.14)	.58
Sirolimus-eluting stent	9/1062 (0.8)	0.50 (0.22-1.10)	0.09

Independent Predictors Of DES Thrombosis

Variables	Hazard Ratio (95% Confidence Interval)	P Value
Subacute stent thrombosis		
Premature antiplatelet therapy discontinuation	161.17 (26.03-997.94)	<.001
Renal failure	10.06 (3.13-32.35)	<.001
Bifurcation lesion	5.96 (1.90-18.68)	.002
Diabetes	5.84 (1.74-19.55)	.004
Left ventricular ejection fraction per 10% decrease	1.12 (1.06-1.19)	<.001
Stent length, per 1-mm increase	1.03 (1.00-1.05)	.01
Late stent thrombosis		
Premature antiplatelet therapy discontinuation	57.13 (14.84-219.96)	<.001
Bifurcation lesion	8.11 (2.50-26.26)	.001
Left ventricular ejection fraction per 10% decrease	1.06 (1.01-1.12)	.03
Cumulative stent thrombosis		
Premature antiplatelet therapy discontinuation	89.78 (29.90-269.60)	<.001
Renal failure	6.49 (2.60-16.15)	<.001
Bifurcation lesion	6.42 (2.93-14.07)	<.001
Diabetes	3.71 (1.74-7.89)	.001
Left ventricular ejection fraction per 10% decrease	1.09 (1.05-1.13)	<.001

ERACI III

TVR and MACCE: Accorded Stent Design



Multivessel Stenting in Drug Eluting Stent Era: Results from ERACI II and ERACI III trials.

Conclusions (cont.)

The issue of late stent thrombosis with DES is a contentious one

Late stent thrombosis is usually a severe but rare event with bare metal stent design. The incidence associated with DES will require a considerably larger study than ERACI III.

However, the findings of ERACI III are in agreement with the worrisome data from those recently reported by BASKET LATE (ACC06), reporting higher rates of late stent thrombosis following clopidogrel discontinuation in the DES treated patients, which translate to higher incidence of death and AMI. SIRIUS trials pooled data (ACC06), also showed higher rate of very late stent thrombosis, in DES patients, with higher four years mortality in DES treated patients.

Thus, the incidence of late stent thrombosis, nor TLR reduction, will determine in the near future, the final role of current DES designs during interventional procedures.

We can not give dual antiplatelet therapy for ever!!!

Multivessel Stenting in Drug Eluting Stent Era: Results from ERACI II and ERACI III trials.

Conclusions

In conclusion, this multicenter, prospective and controlled study in patients with multivessel disease treated either with SES or PES stents, demonstrated a significant reduction of MACCE and the need for repeat revascularization when compared to our previous PCI bare metal stent data from ERACI II.

Univariate analysis revealed that patients with diabetes, when all treatments BMS,DES and CABG were combined, had a significantly higher incidence of MACCE at one year when compared to non-diabetics (27.4% vs 15.8% $p=0.004$). Comparison of DM patients treated with DES in ERACI III and DM from the ERACI II-PCI arm failed to demonstrate a significant improvement in death and myocardial infarction, repeat revascularization or MACCE . Further analyses are required to establish if there is a significant improvement in outcome among diabetic patients.



Univariate Predictors Of Cumulative DES Thrombosis

	Continuous Variables*		
Age, y	68 (10)	1.05 (1.01-1.09)	.004
Balloon diameter, mm	3.0 (0.3)	1.22 (0.54-2.72)	.62
Balloon-to-artery ratio	1.2 (0.2)	2.71 (0.82-8.97)	.10
Left ventricular ejection fraction per 10% decrease	45 (9)	1.07 (1.04-1.11)	<.001
Lesion length, mm	19.46 (13.43)	1.01 (0.98-1.03)	.39
Preintervention reference vessel diameter, mm	2.55 (0.44)	1.22 (0.54-2.72)	.22
Postintervention minimal lumen diameter, mm	2.30 (0.71)	0.58 (0.33-1.00)	.06
Stent length, mm	33.67 (23.24)	1.01 (0.98-1.03)	.32
Stent-per-lesion ratio	1.37 (0.6)	1.49 (0.85-2.63)	.16

ARTS-II Trial

607 patients with multivessel coronary lesions

26.2% diabetic
54% 3 vessel disease
13.9% type C lesions

Historical Controls from ARTS I: 1202 patients with multivessel coronary lesions

18.2% diabetic
28% 3 vessel disease
7.5% type C lesions

Sirolimus-eluting stent

3.7 stents per patient
Avg total length: 73 mm
n = 607

CABG

n = 602

Bare Metal Stent

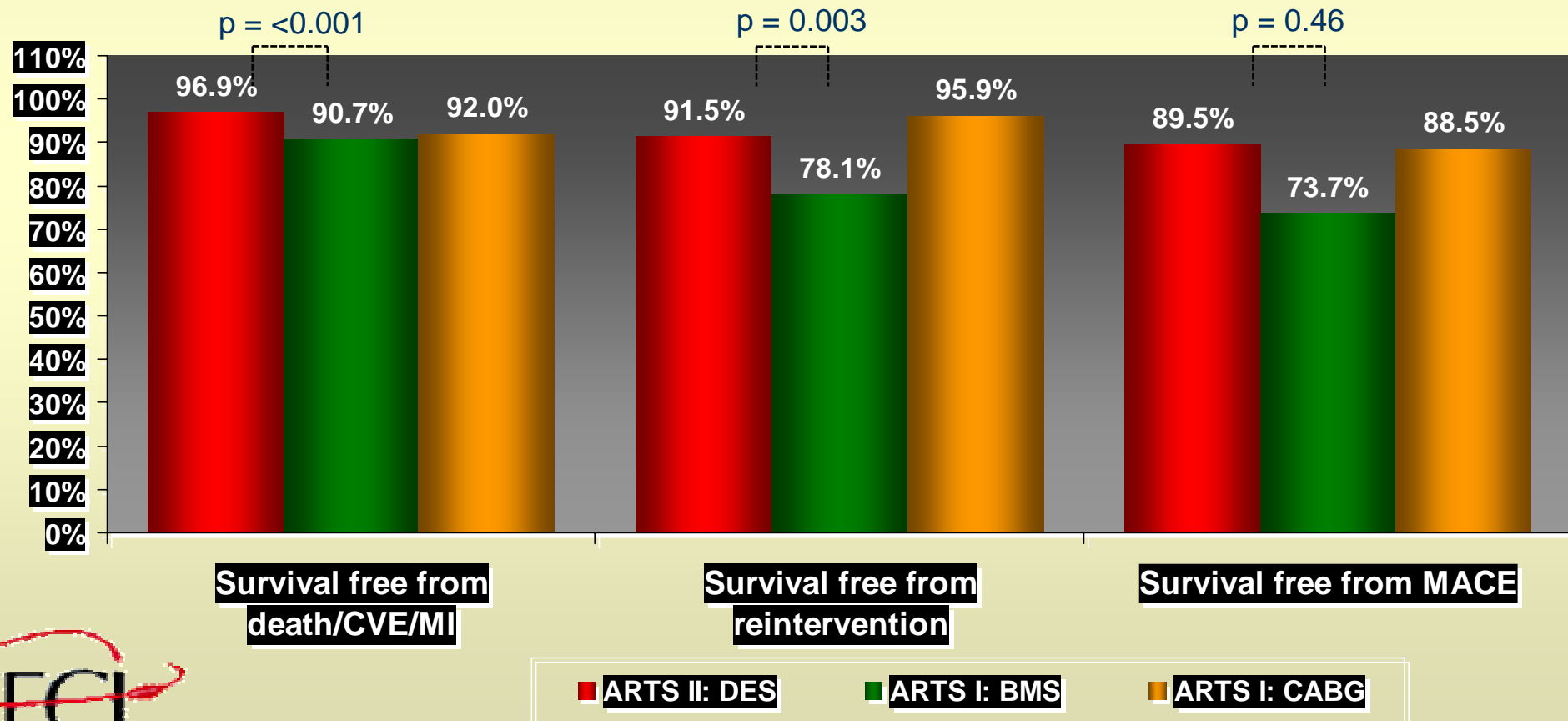
2.8 stents per patient
Avg total length: 48 mm
n = 600

Endpoints:

- **Primary** – Major adverse cardiac and cerebrovascular events (MACCE), including death, cerebrovascular event, myocardial infarction, and revascularization, at 1 year for the comparison of CABG treated patients in the ARTS I trial with sirolimus-eluting stent patients in the ARTS II trial
- **Secondary** – MACCE at 30 days, 6 months, 3 and 5 years.
 - Total cost at 30 days
 - Cost, cost effectiveness, quality of life at six mo, and 1, 3, and 5 years

ARTS II: Event free survival

At one year, there was no difference in event-free survival between the ARTS II SES group and the ARTS I CABG group. However, the ARTS II group showed significantly higher rates of survival free from cardiac death, MI, and reintervention than the ARTS I bare metal stent group. The groups were not significantly different in the primary endpoint of survival free from MACCE.



Death and Myocardial Infarction in Drug Eluting Stent Era:

**Survival and survival freedom from non fatal myocardial
infarction were not significant different between
DES and BMS (RAVEL, SIRIUS,
E- SIRIUS, C-SIRIUS, TAXUS II, TAXUS IV and TAXUS VI)**

Multivessel Stenting in Drug Eluting Stent Era: Results from ERACI II and ERACI III trials.

Conclusions (cont.)

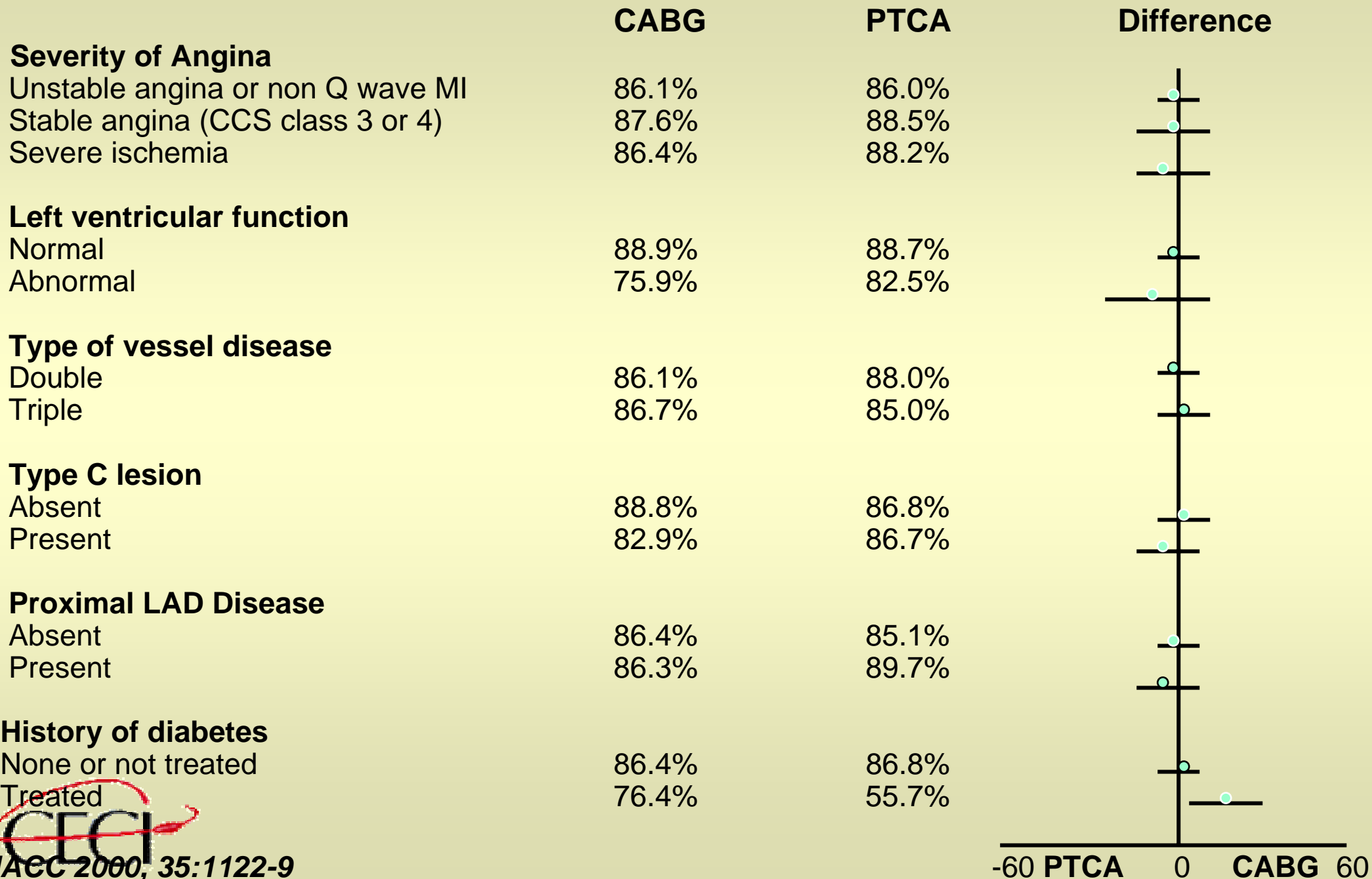
The issue of late stent thrombosis with DES is a contentious one

Late stent thrombosis is usually a severe but rare event with bare metal stent design. The incidence associated with DES will require a considerably larger study than ERACI III.

However, the findings of ERACI III are in agreement with the worrisome data from those recently reported by BASKET LATE and SIRIUS meta-analysis, reporting higher rates of late and very late stent thrombosis with DES, which translate to higher incidence of death and AMI.

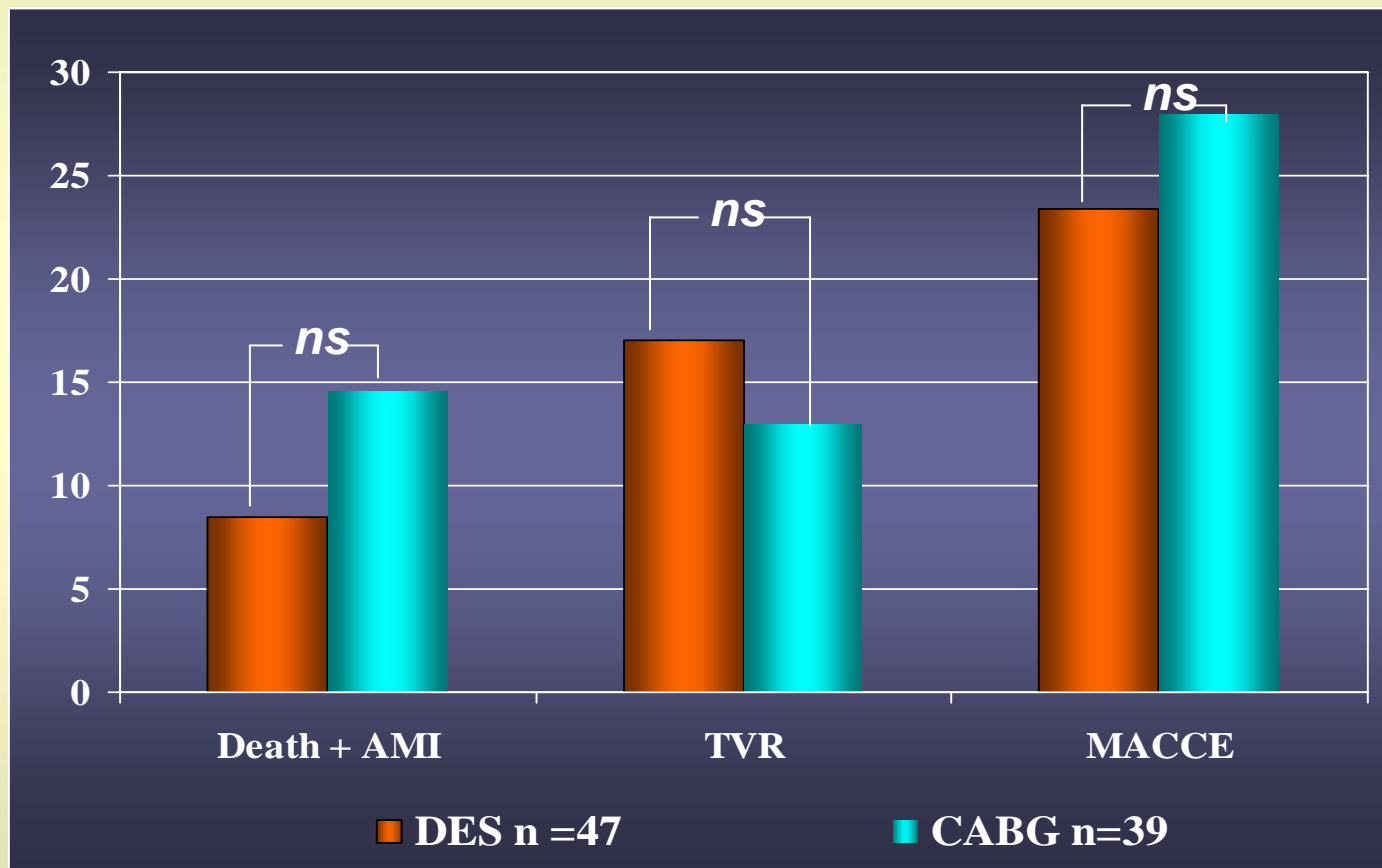
Thus, the incidence of late stent thrombosis, nor reduction of TLR, will determine in the near future, the final role of current DES designs during interventional procedures.

BARI TRIAL: Seven Year Survival



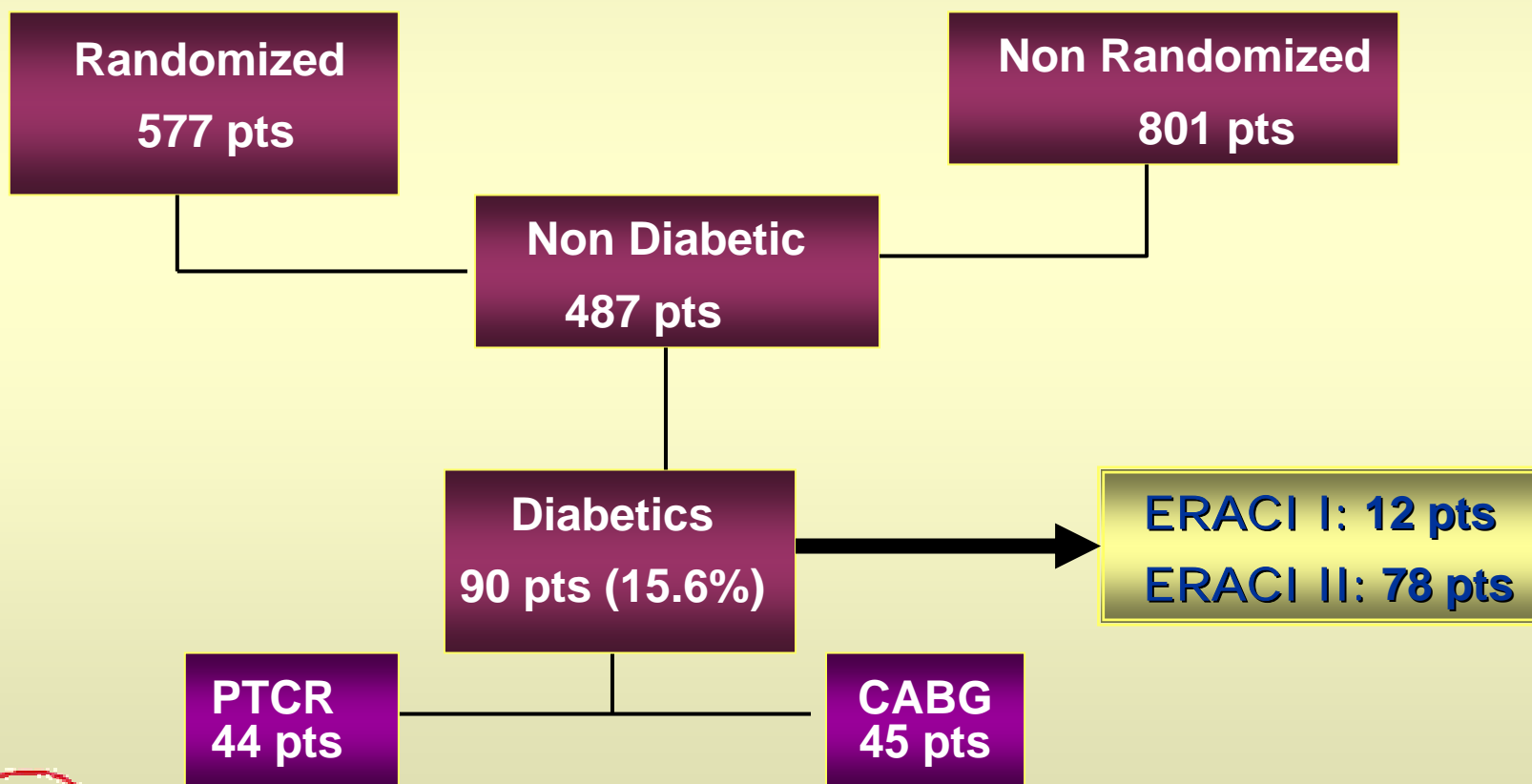
ERACI II and ERACI III

One Year Follow Up Results in Diabetics: DES vs CABG



Diabetics Patients ERACI I- ERACI II

Patient Population 1378 Randomizable Patients



STUDY POPULATION

Multivessel Stenting in Drug Eluting Stent Era: Results from ERACI 1, ERACI 2 and ERACI 3 trials.

Conclusions

Through all ERACI trials (ERACI 1,ERACI 2, and ERACI 3) there were a tendency to poor outcome in Diabetic patients compared to non Diabetic when they were treated with interventional procedures either POBA, BMS or DES.

With the introduction of DES (ERACI 3) , there was a trend to lower one year mortality and incidence of non fatal myocardial infarction,incidence of repeat revascularization procedures and total MACCE, compared with previous data with BMS design (ERACI 2).

At one year, Diabetic patients treated with DES had similar incidence of MACCE than those treated with CABG.

With DES therapy, stent thrombosis out of hospital discharge is a severe but rare event, associated with dual antiplatelet therapy cessation in the majority of the cases, but its real incidence, can not be determined but this study, the numbers are too small to draw any conclusion, in fact, death and myocardial infarction was lower with DES therapy.

ERACI II and ERACI III

Two Year Follow Up of DES, BMS and CABG

	ERACI III (n = 225)	ERACI II Stent Arm (n=225)	ERACI II CABG (n=225)
TVR	11.1 % * #	24.4 % *	7.0 % #
MACCE	16 **	28 % **	21 %
SET	3.5 % ##	1.3 % ##	

* p = 0.034 ** p = 0.019 # p = ns ## p = ns

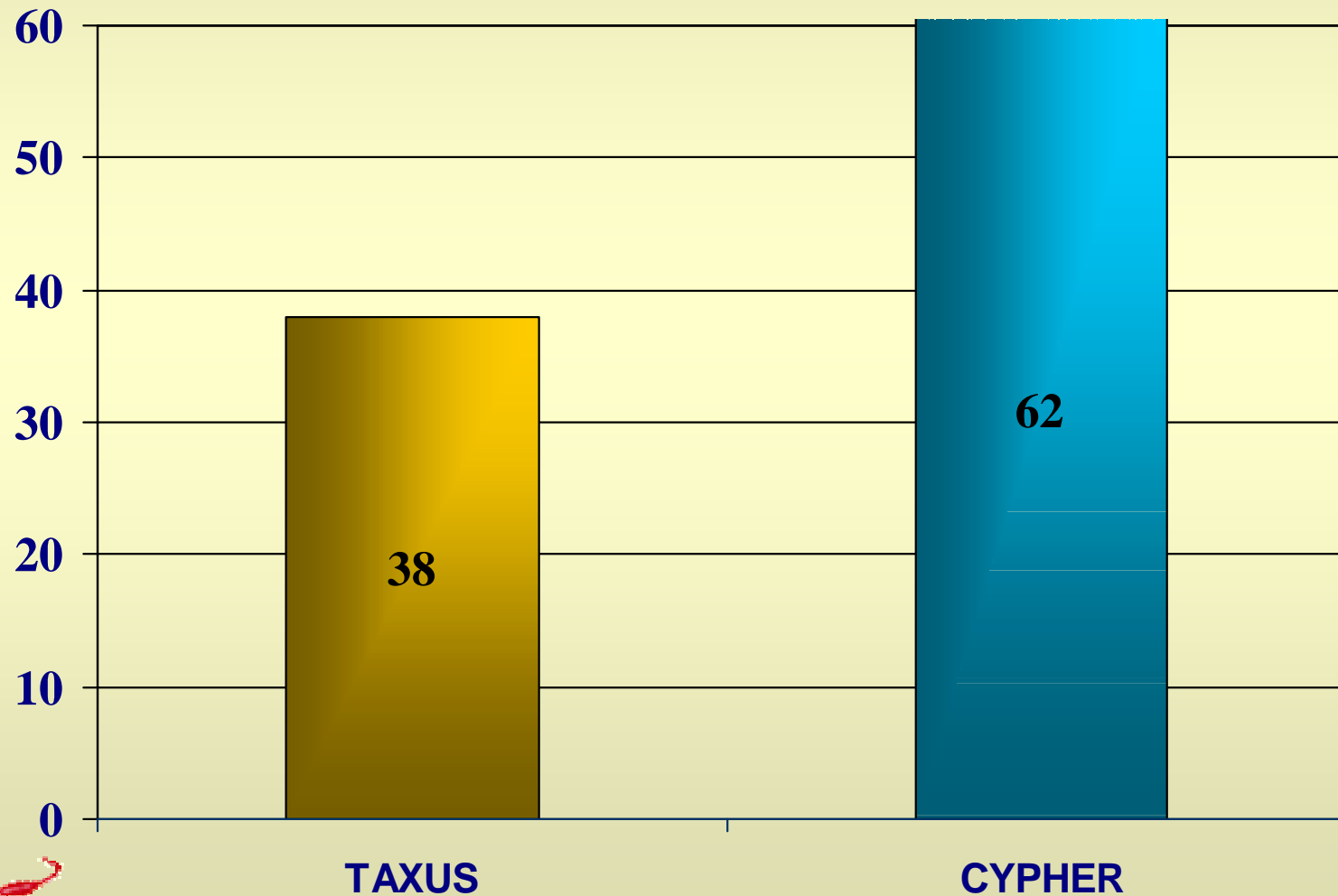
ERACI II and ERACI III

Cost Effectiveness of DES versus Oral Rapamycin plus BMS.

	DES group (n=270)	BMS group (n=94)	p value
Stent/pt	1.31	1.36	ns
Death %	3.7	2.1	0.7
AMI %	2.2	3.1	0.9
ST %	2.9	1	0.5
TVR %	10.1	10.1	0.8
MACCE %	16.2	15.9	0.94
Hospital Cost (u\$/pt)	7585 ± 2568	4416 ± 1423	< 0.0001
Follow up cost (u\$/pt)	1093 ± 1815	759 ± 1600	0.1
Overall cost (u\$/pt)	8678 ± 2501	5177 ± 2003	< 0.0001

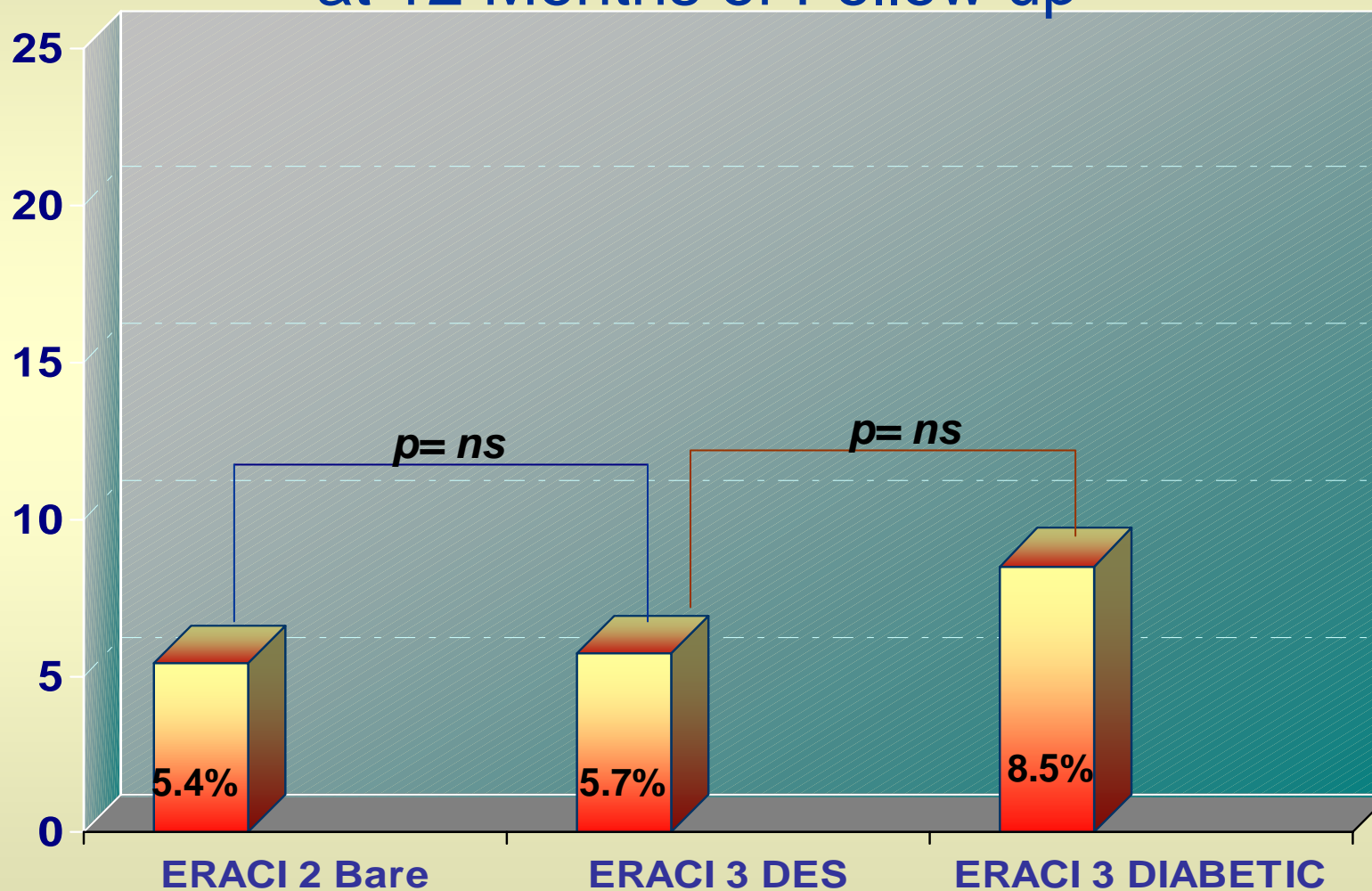
ERACI III

Stent Design Diabetic Group



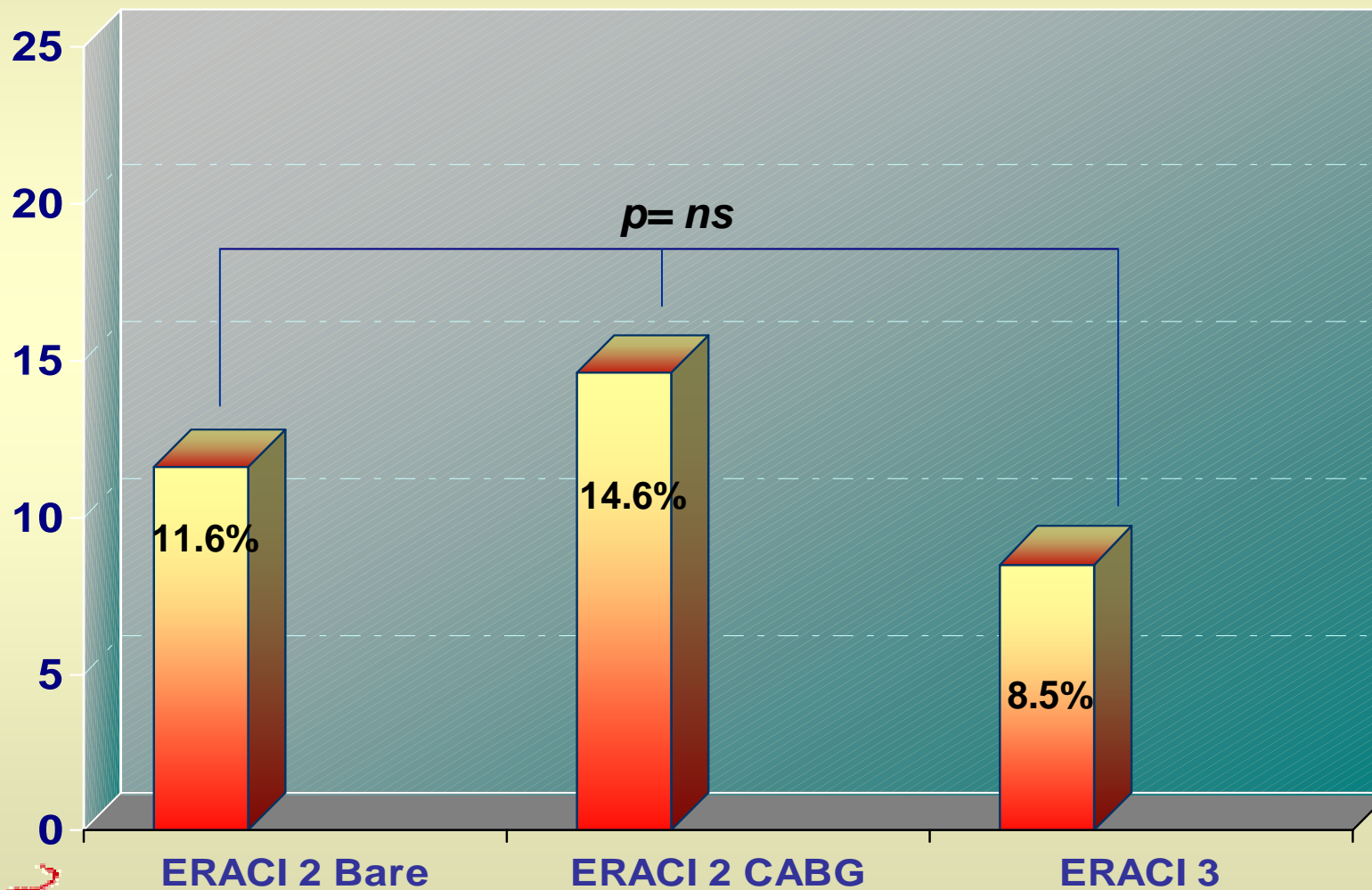
ERACI II and ERACI III

Death and Myocardial Infarction at 12 Months of Follow up



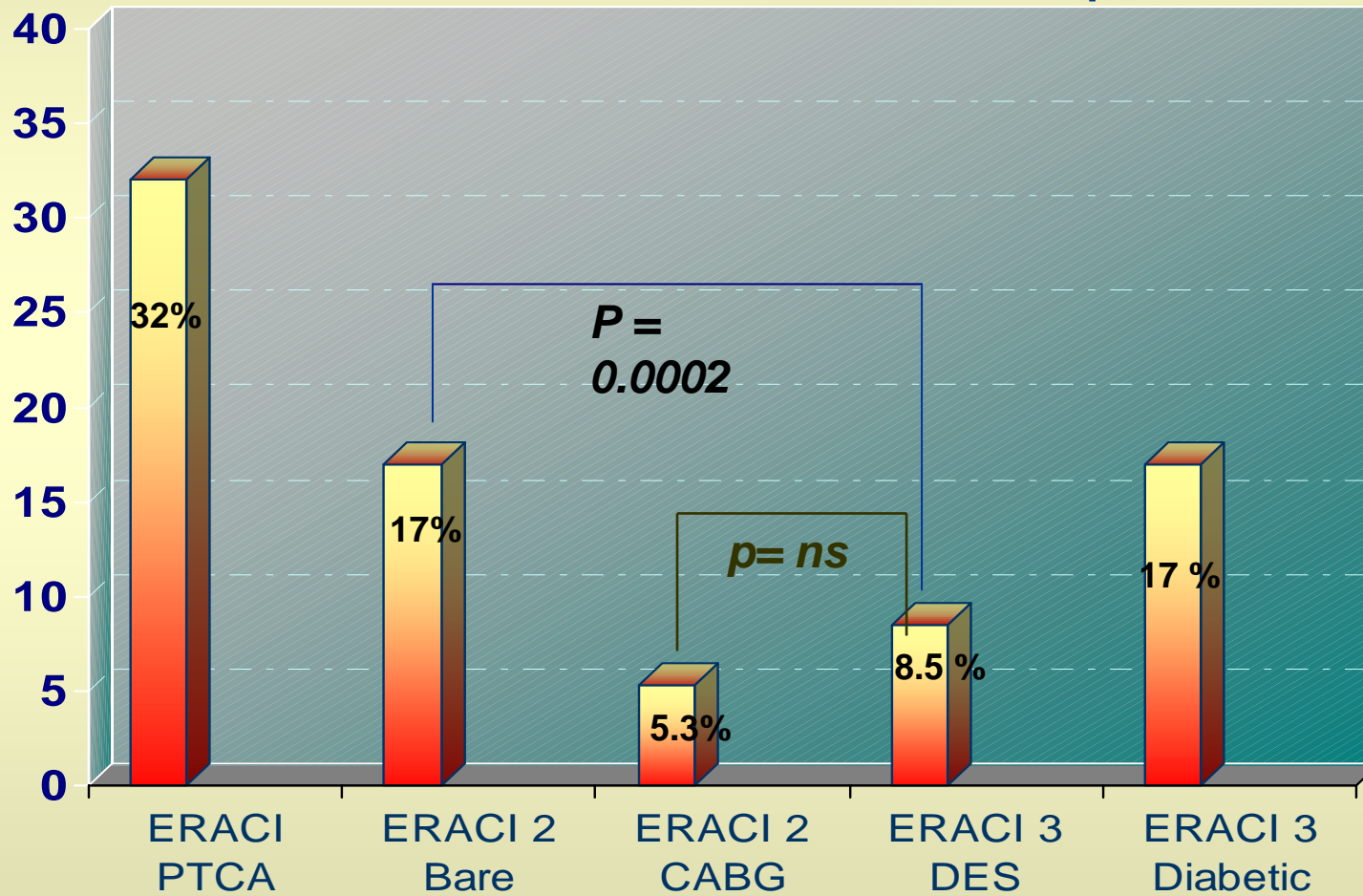
ERACI II and ERACI III

Death and Myocardial Infarction in Diabetics at 12 Months of Follow up



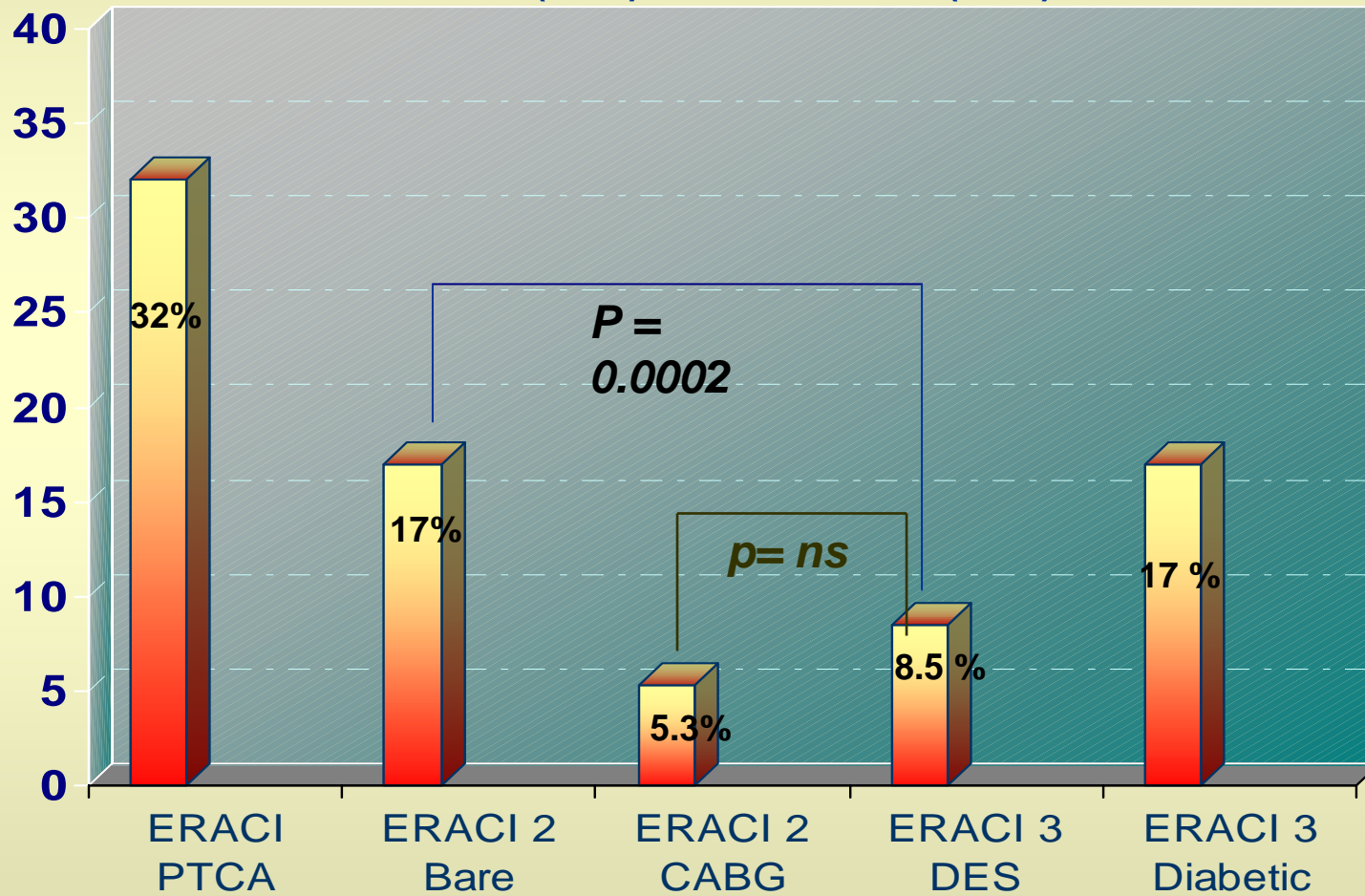
ERACI , ERACI II and ERACI III

Repeat PTCA and CABG
at 12 Months of Follow Up



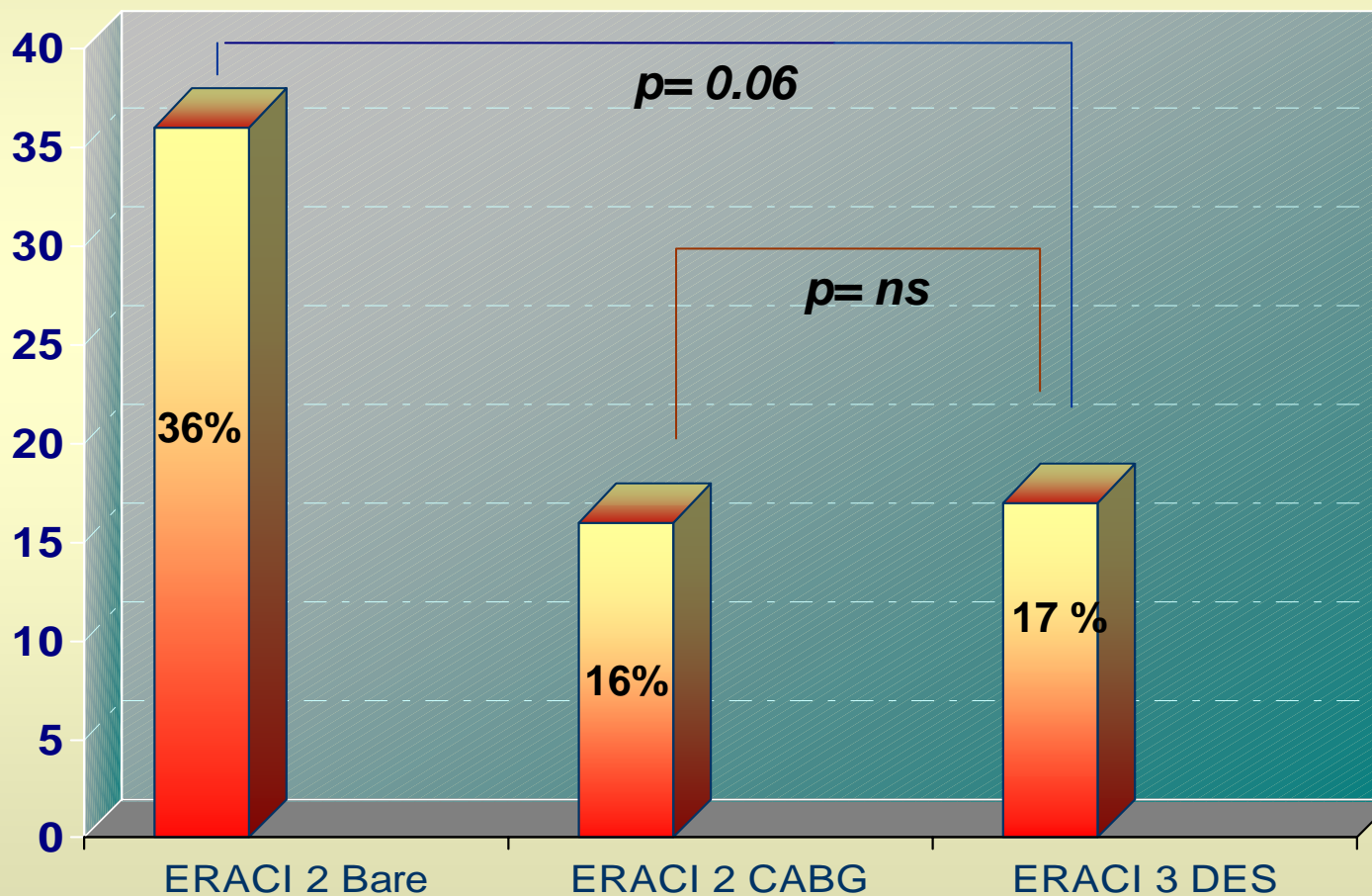
ERACI II and ERACI III

One Year Follow up results in Diabetics:
DES (47) vs BMS (39)



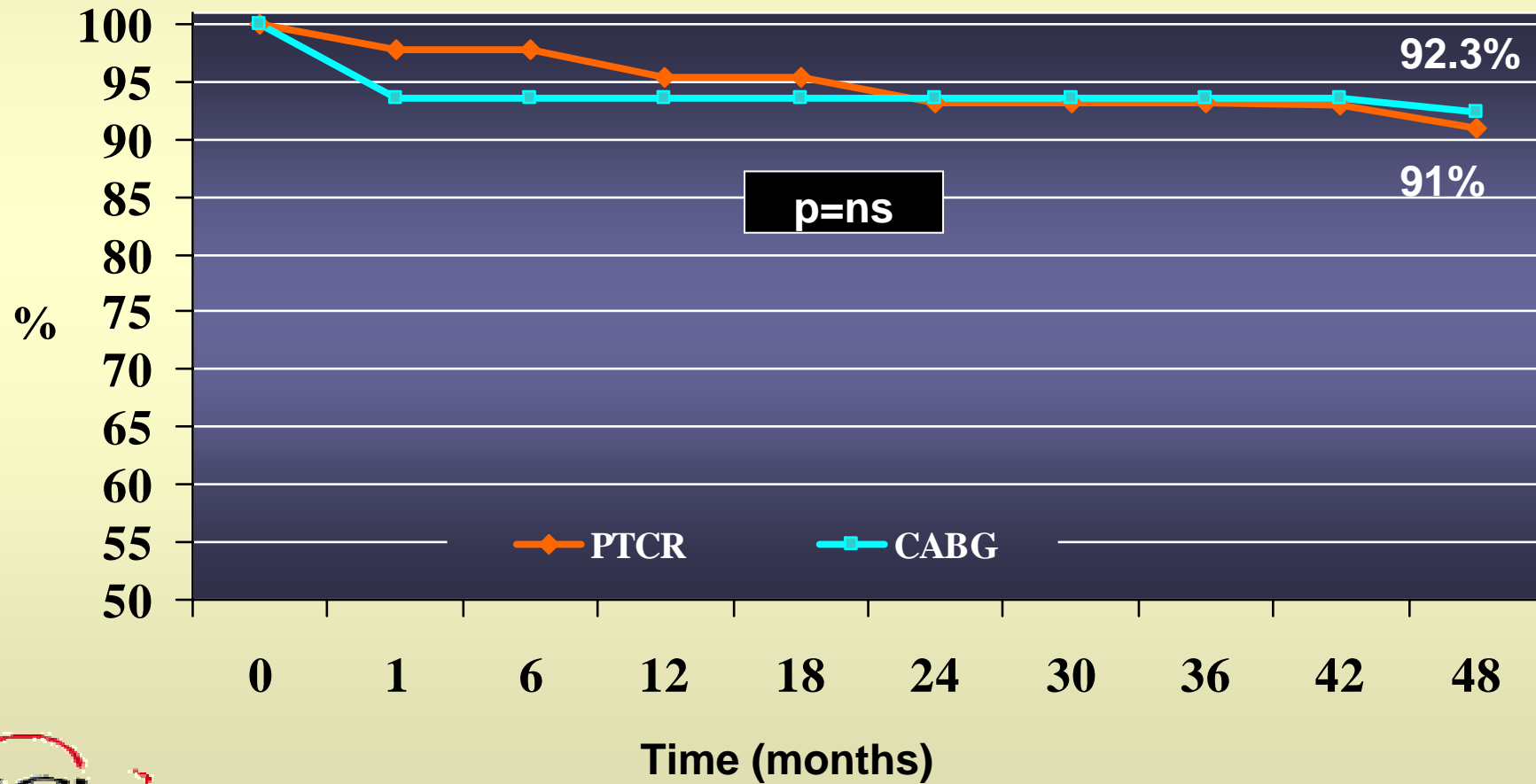
ERACI II and ERACI III

Repeat PCI and CABG in Diabetics at 3 Years (ERACI 2) and One Year (ERACI 3) of Follow Up



Diabetics Patients ERACI I- ERACI II

Follow Up Survival



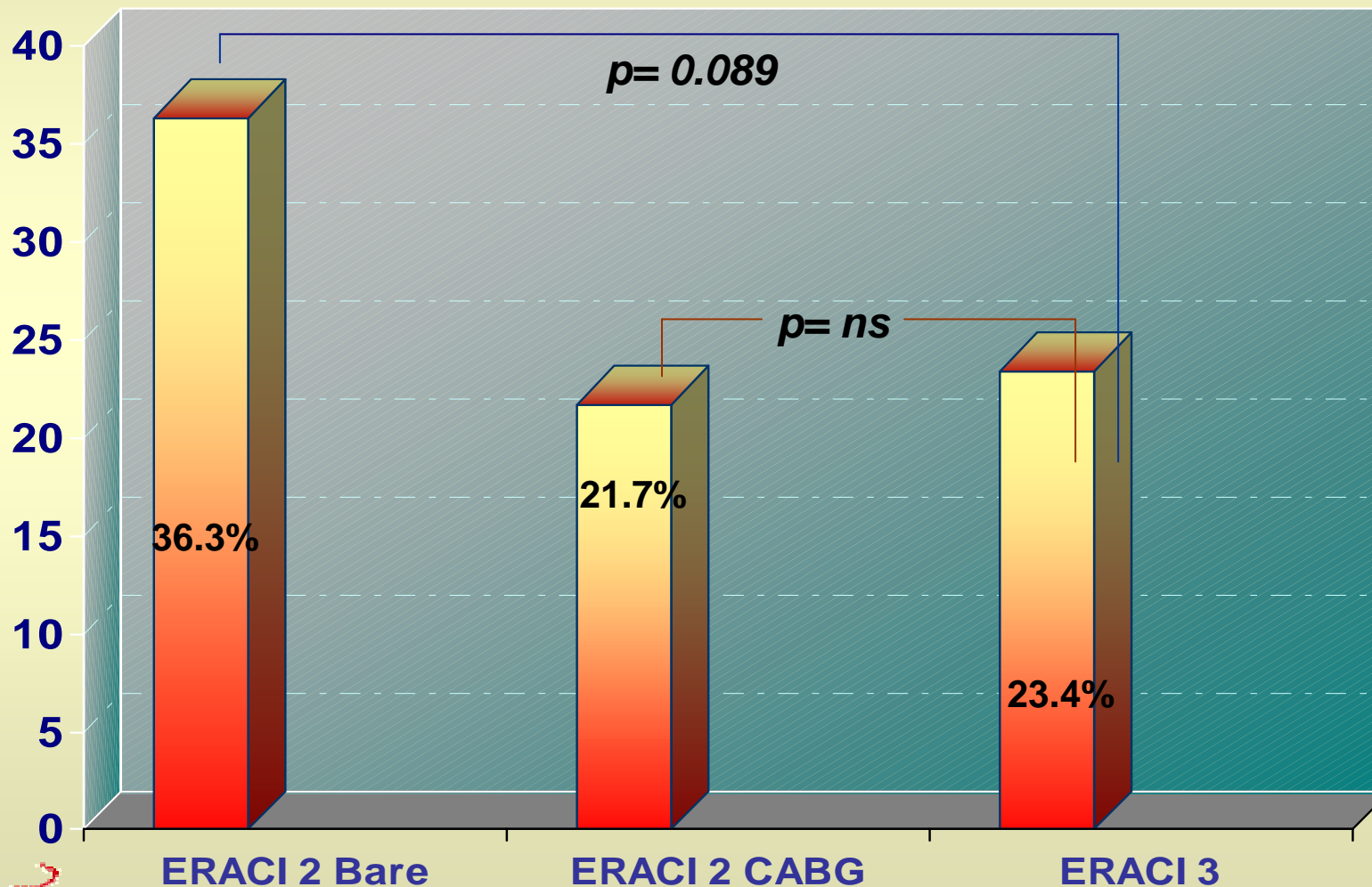
ERACI II and ERACI III

Baseline Demographic, Clinical and Angiographic Characteristics

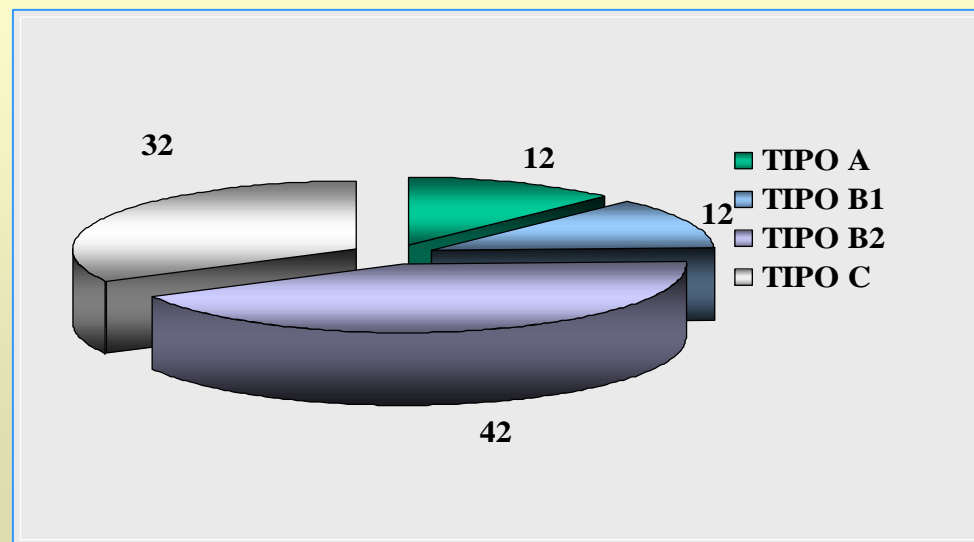
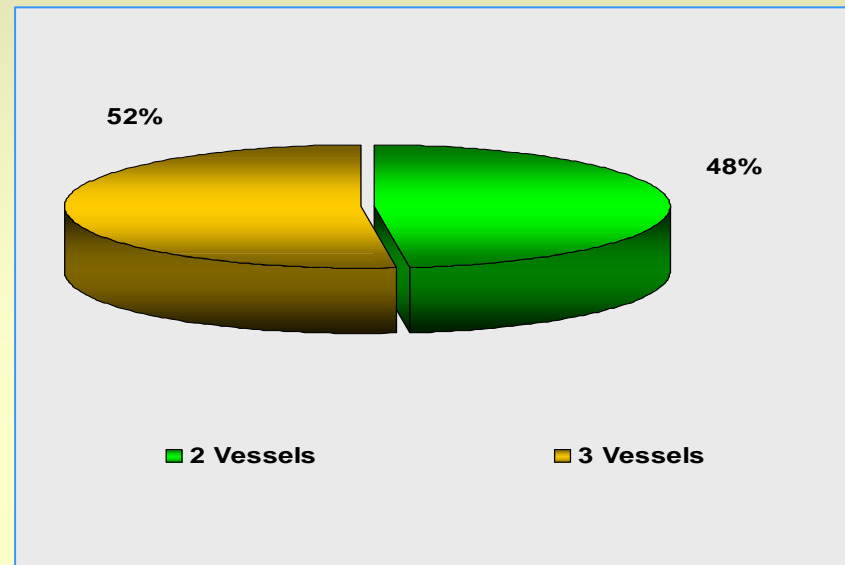
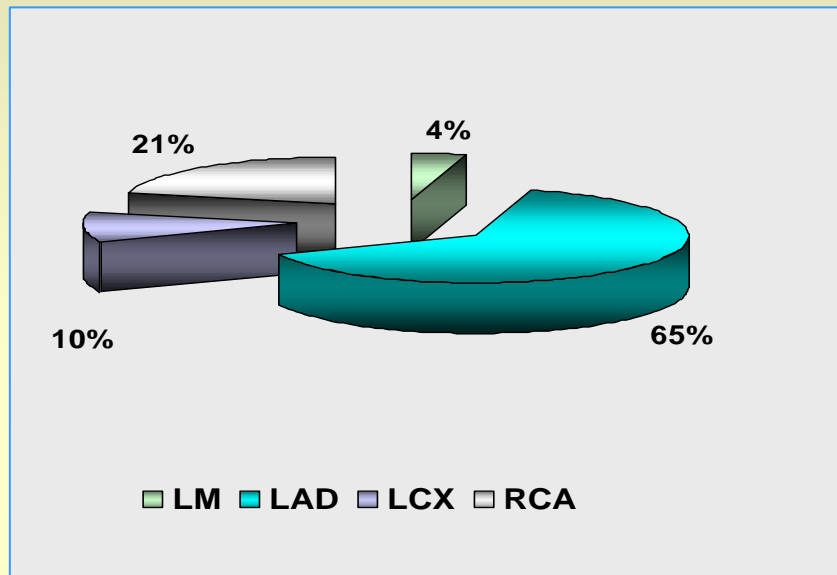
	ERACI II		ERACI III-DES	DBT	<i>p value</i>
	Bare Stent	CABG			
Age	62.5	61.4	65.1	67	<i>ns</i>
Male	77.3 %	81.4 %	79.5 %	78.7	<i>ns</i>
HTA	71 %	70.5 %	80 %	85 %	<i>ns</i>
Cholesterolemia	62.5 %	60.2 %	79 %	82 %	<i>ns</i>
Diabetes	17.3 %	17.3 %	21.5 %	100 %	<i>ns</i>
Smokers	54 %	49.5 %	69 %	51 %	<i>ns</i>
Stable Angina	7.9 %	9.3 %	25 %	23 %	<i>ns</i>
Unstable Angina	92.1 %	90.7 %	75 %	71 %	<i>ns</i>
LM	5.3 %	4 %	5.3 %	4.2 %	<i>ns</i>
2 vessels	40 %	38 %	45.3 %	48 %	<i>ns</i>
3 vessels	54.7 %	58 %	49.4 %	52 %	<i>ns</i>
Stent Length	25.7 mm	--	36 mm	41mm	<i>.0002</i>
Stent/ Patient	1.4	--	1.8	1.95	<i>.0002</i>

ERACI II and ERACI III

Major Adverse Cardiovascular Events (MACCE) in Diabetics at One Year at Follow Up



Baseline Angiographic Characteristics Diabetic Group



Stent Thrombosis ERACI II vs. ERACI III

	In Hospital	< 30 Days	One Year	Three Years	Overall
ERACI II (n = 225)	3/225	0/225	0/225	0/225	3/225*
ERACI III (n= 225)	1/225	3/225	3/225	1/225	8/225*
ERACI III DIABETIC (n = 47)	1/47		2/47		3/47



* p= 0.04

ERACI III

Baseline Demographic and Clinical Characteristics 47 patients in Diabetic Group

Age	67.14 ± 8.58
Male	78.7 %
HTA	85 %
Dislipemia	82 %
Diabetes	100 %
Smokers	51 %
Stable Angina	23 %
Unstable Angina	71 %
Asymptomatic	6 %

ERACI III

Procedural Outcome

	ERACI III	ERACI III DIABETIC GROUP
Procedural Success	99 %	97 %
Clinical Success	99 %	97 %
Previous PCI	32 %	31 %
IIb/IIIa Inhibitors	18 %	25 %
Stent/Patient	1.8	1.95 %
DES/Patient	1.4	1.51 %
Stent Length	36 mm \pm 8.8	41 mm \pm 5.8

ERACI III

In Hospital and One Year Follow up Diabetic Group

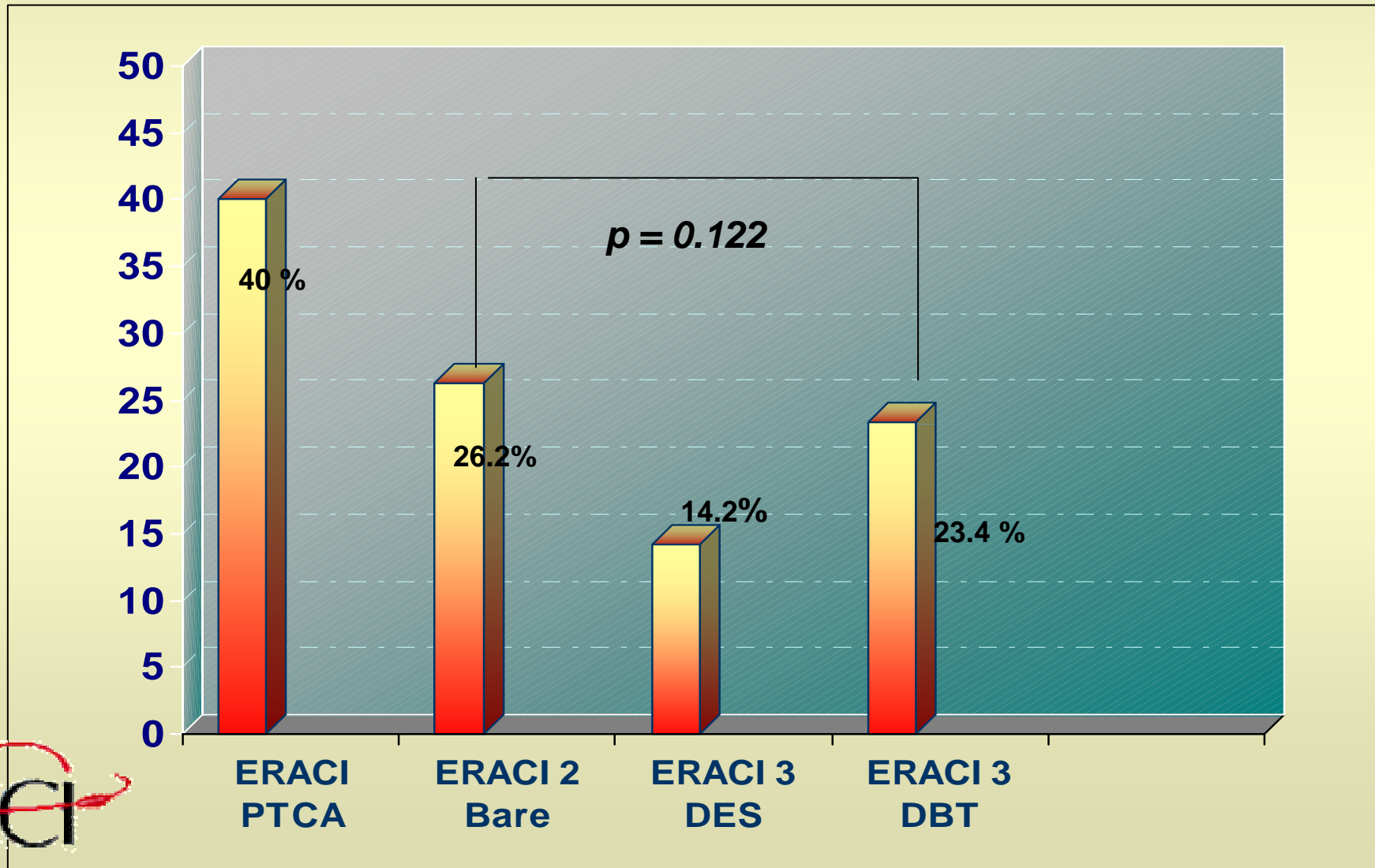
In-Hospital	
Death	2.1 %
AMI	4.2 %
Stroke	2.1 %
Urgent TVR	4.2 %
MACCE	6.3 %

One Year Follow up	
Death	4.2 %
AMI	8.5 %
Stroke	2.1 %
TVR	17 %
MACCE	23.4 %

ERACI , ERACI II and ERACI III

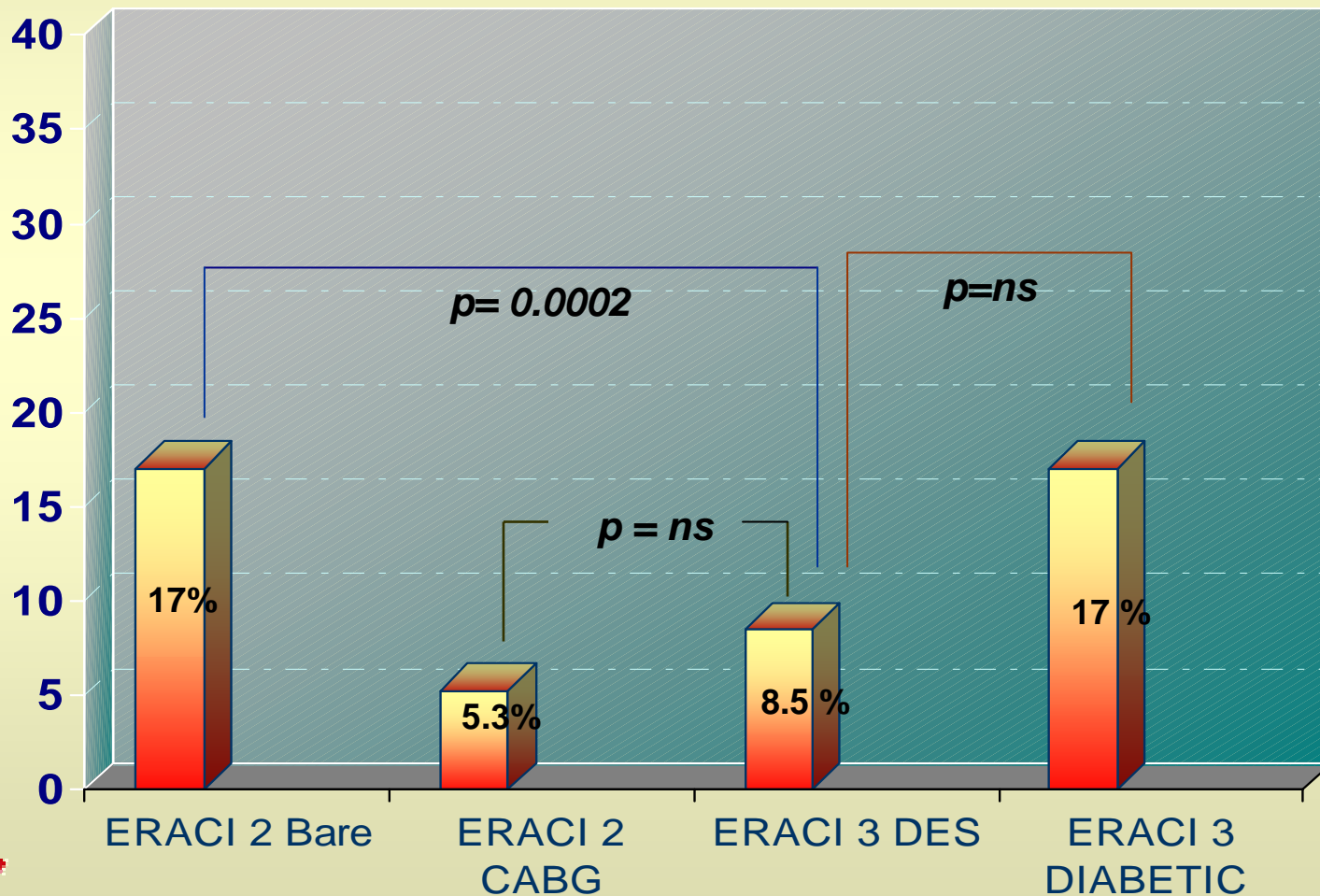
MACCE

at 12 Month at Follow Up



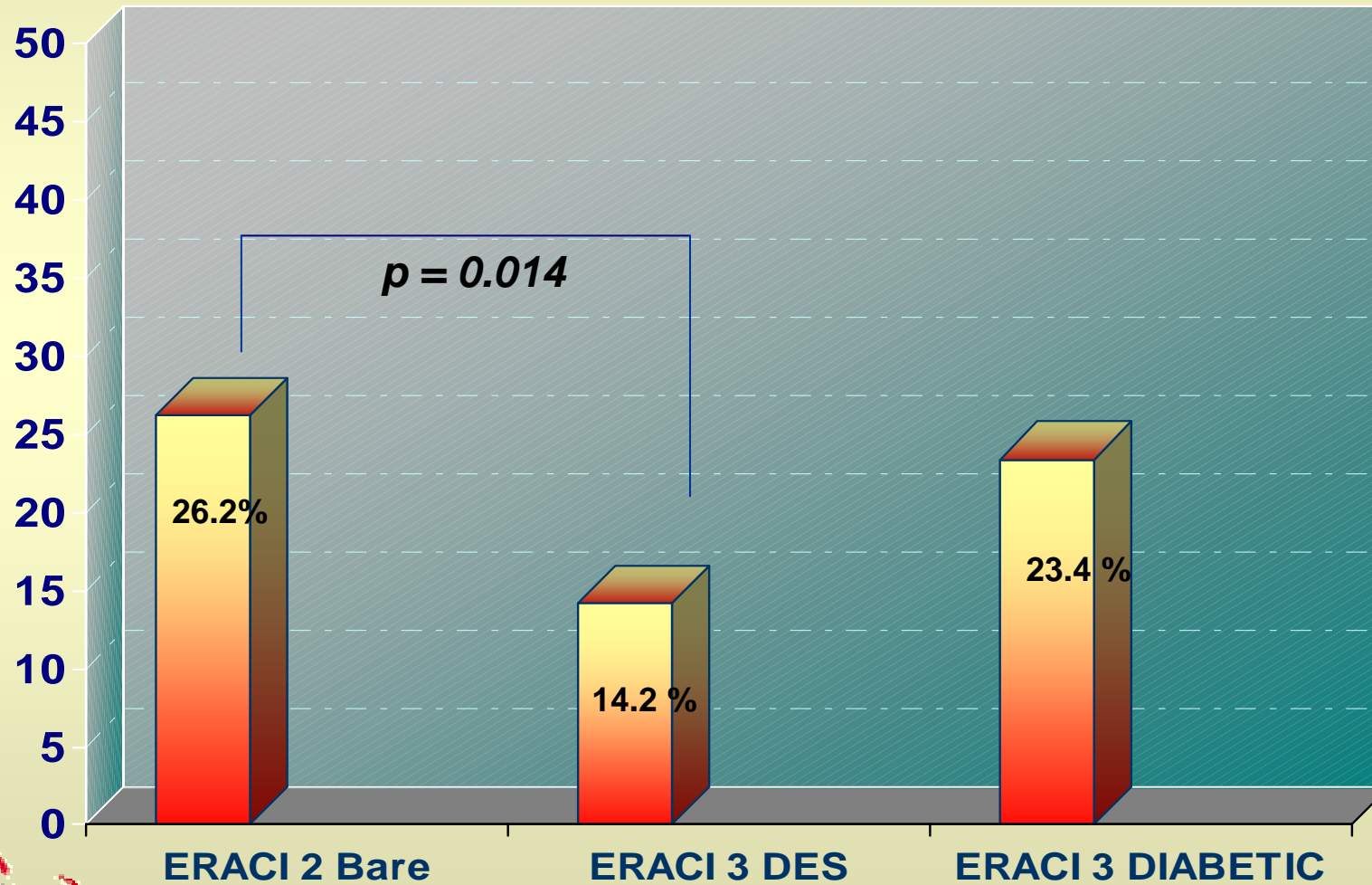
ERACI II and ERACI III

Repeat PTCA and CABG
at 12 Months of Follow up



ERACI II and ERACI III

MACCE
at 12 Month of Follow up



Multivessel Stenting in Drug Eluting Stent Era: Results from ERACI III trial.

Conclusions

Baseline clinical and angiographic characteristics among ERACI III and ERACI II , PCI and CABG arm, were similar.

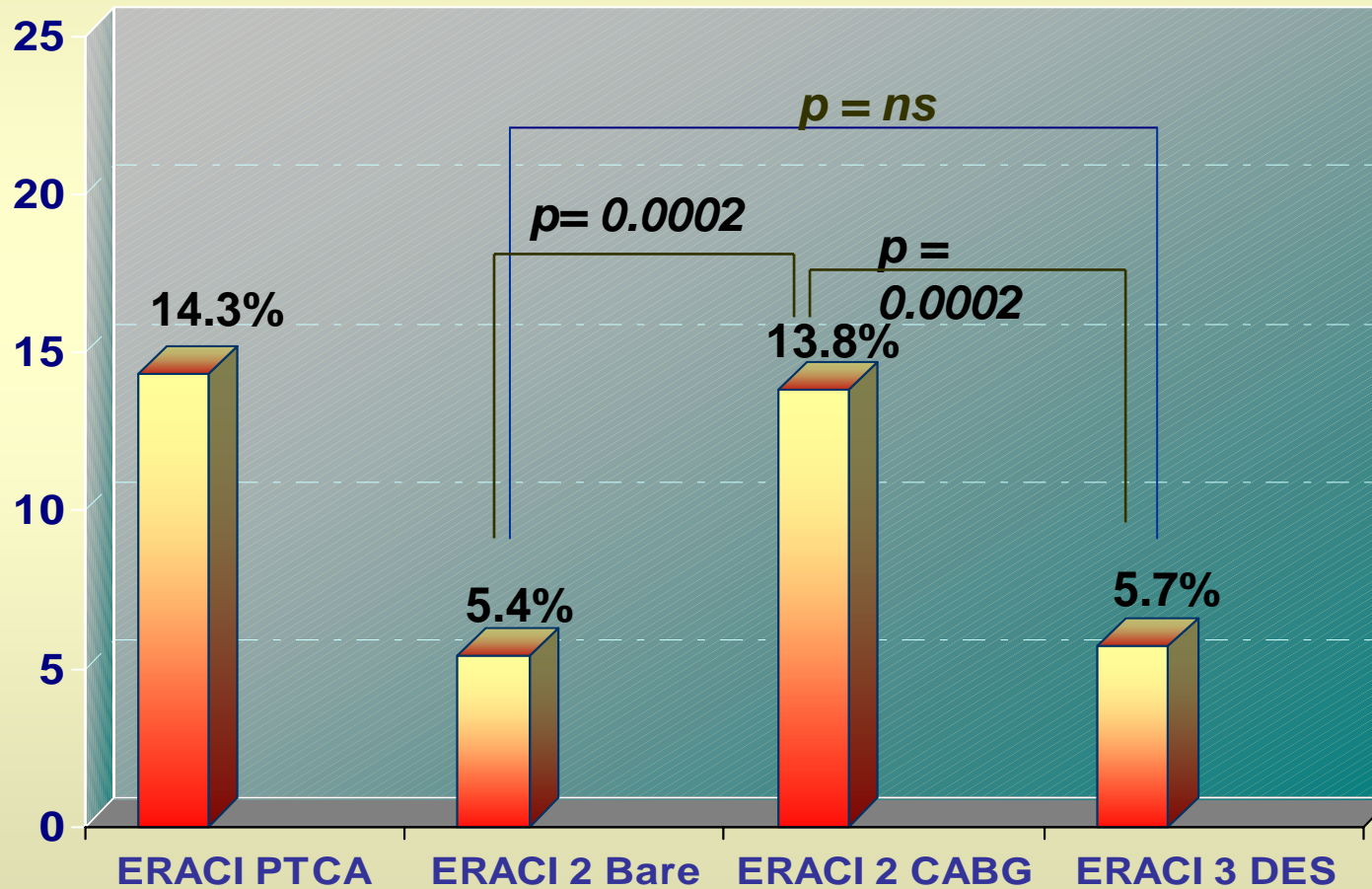
However, patients treated with DES had greater number and length of stent per patient compared with those treated with bare stent design ($p=0.002$).

There were a significant reduction of MACCE and TVR in patients treated with DES (ERACI III) compared with an equivalent population previously treated with bare stent design (ERACI II).

At one year of follow up, patients treated with DES showed in comparison with ERACI II, CABG arm, similar incidence of new revascularization procedures and MACCE, meaning a significant improvement in relation with bare stent design..

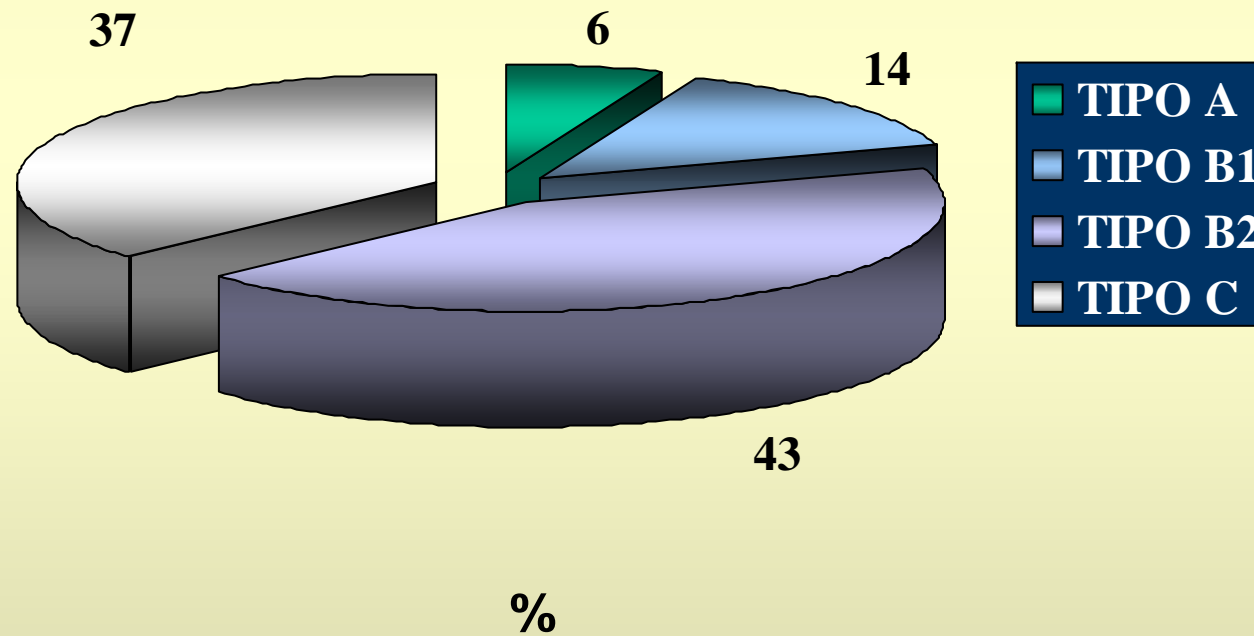
ERACI , ERACI II and ERACI III

Death and AMI
12 Month at Follow up

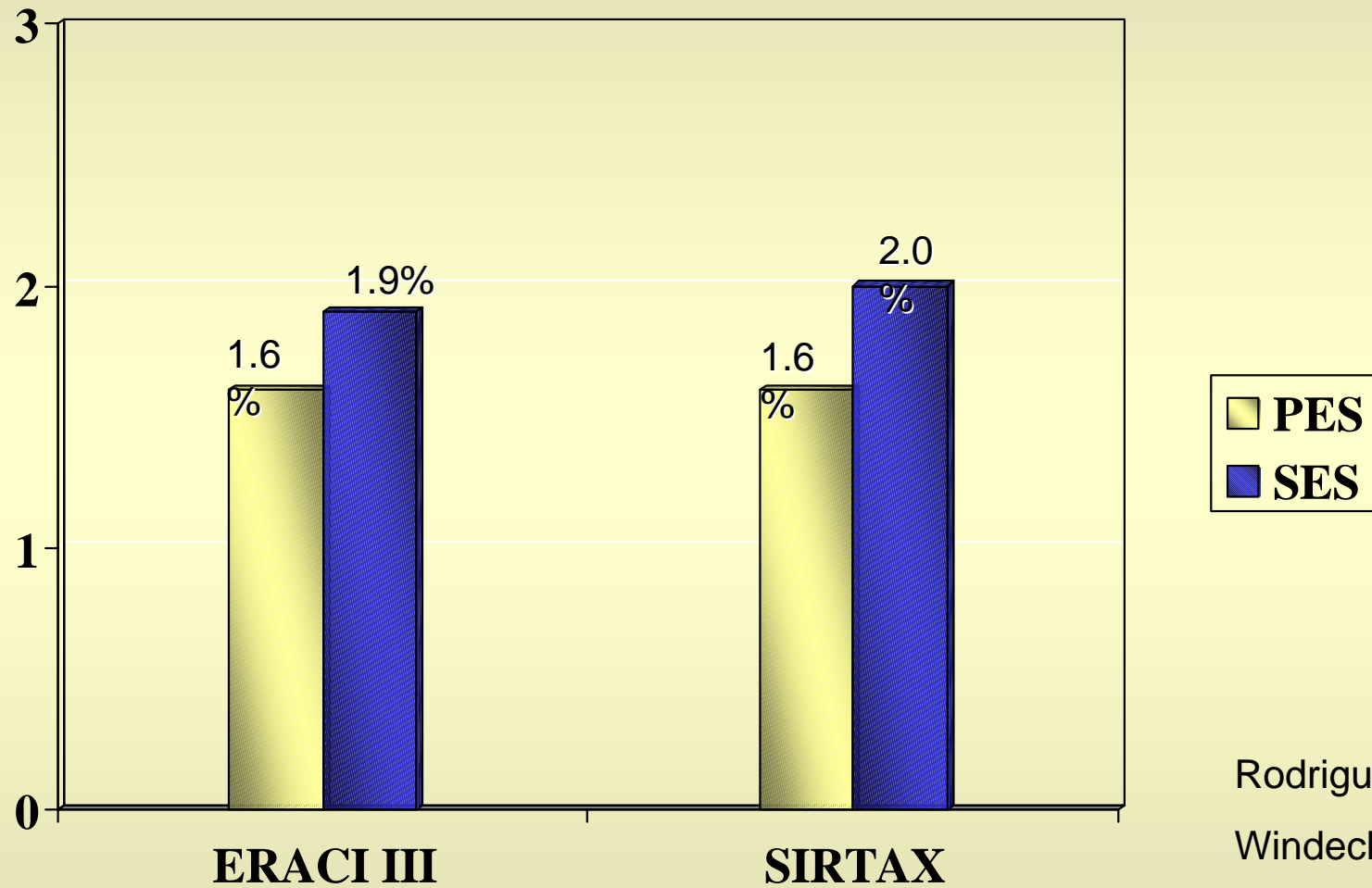


ERACI III

Angiographic Characteristics



Stent Thrombosis and DES Design



Rodriguez A, ESC 05
Windecker S, ACC 05

	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

Percent of patients (absolute counts)
NS, not significant

→ No significant difference in late stent thrombosis rates between groups

Reality Trial: One Year Follow up Results

	CYPHER (684)	TAXUS (669)	<i>p</i>
RD	2.4 mm	2.4 mm	<i>ns</i>
Lesion Length	16.9 mm	17.3 mm	<i>ns</i>
Post PCI	2.08 mm	2.16mm	<i>0.0001</i>
Late Loss	0.09 mm	0.31mm	<i>0.001</i>
AMI	4.8 %	5.5 %	<i>ns</i>
MACE	9.2 %	10.6 %	<i>ns</i>
TVF (1°End Point)	10.4 %	11.5 %	<i>ns</i>
Restenosis (2°End Point)	9.6 %	11 %	<i>ns</i>
Stent Thrombosis	0.4 %	1.8 %	<i>0.02</i>

Delayed Healing and Persistent Inflammation at Sites of Overlapping Sirolimus and Paclitaxel Drug – Eluting Stents

Aloke V Finn, Frank D Kolodgie, Eduardo Acampado, et al

Groups	Neointimal Thickness (mm)		N ^o struts surrounded by Fibrin		N ^o of eosinophils	
	28 days	90 days	28 days	90 days	28 days	90 days
SES	0.09±0.04	0.08±0.01	10 ± 5	3 ± 3 #	33.8±29.5	9.5 ± 18
PES	0.07± 0.03	0.13±0.01*	15 ± 5	6 ± 7 ^	89.5±64.1	52.3 ± 18.8 #
P value	ns	0.008	0.03	ns	0.03	0.03

28 days vs 90 days, * p = 0.02; # p=0.01;
^p=0.03



Should we worry about “new enemies” and late efficacy?

The “enemies”

Incomplete apposition

Aneurysm

Persistent restenosis

Delayed restenosis

Less efficacy in bifurcations

Late Stent Thrombosis ?

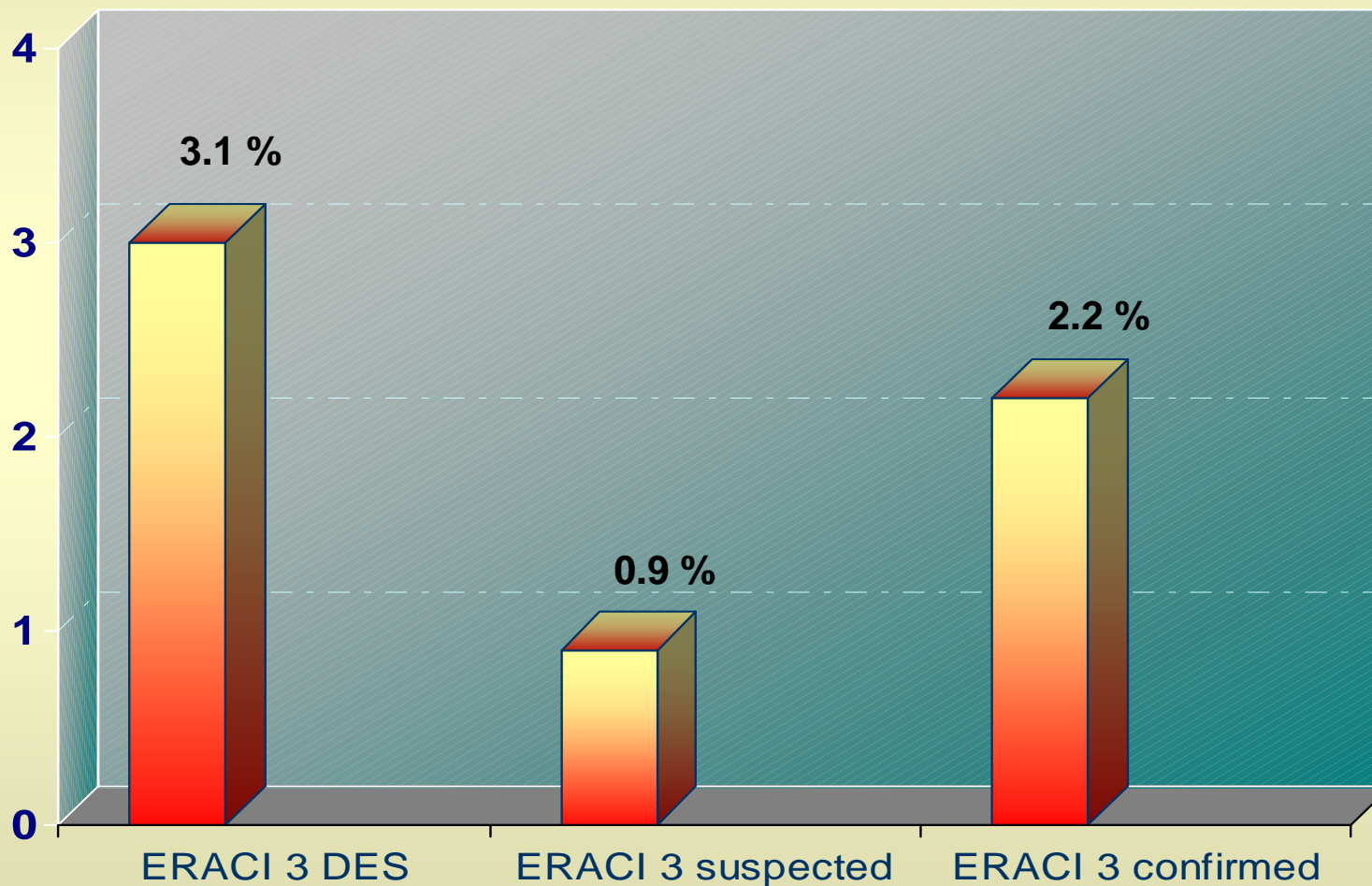
And... are the “old enemies”
defeated?



ERACI III – Stent Thrombosis

ERACI II and ERACI III

Follow Up Stent Thrombosis
(mean 19 months)

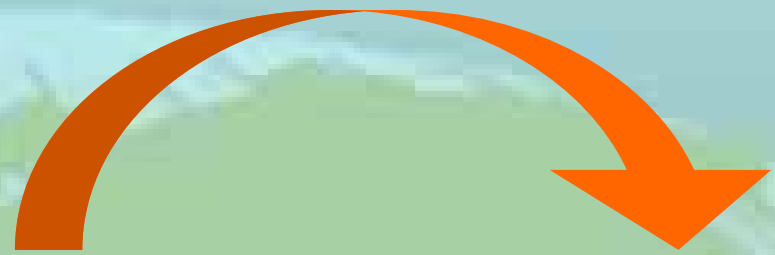




AWESOME



S.o.S



ARTS



MASS

ERACI II



1996-1999

STENT vs CABG

Multivessel Stenting in Drug Eluting Stent Era: One Year Follow-Up Results of ERACI III Trial

A. E. Rodriguez, L. Grinfeld, C. Fernandez Pereira, J. Mieres, D. Berrocal, CF. Vigo, W O'Neill, I. Palacios.

NO CONFLICT TO DISCLOSE

Otamendi Hospital, Buenos Aires School of Medicine, Buenos Aires, Argentina

Italian Hospital, Buenos Aires, Argentina

William Beaumont Hospital Royal Oak MI, USA

Massachussetts General Hospital, Boston, USA.

ESC CONGRESS 2005

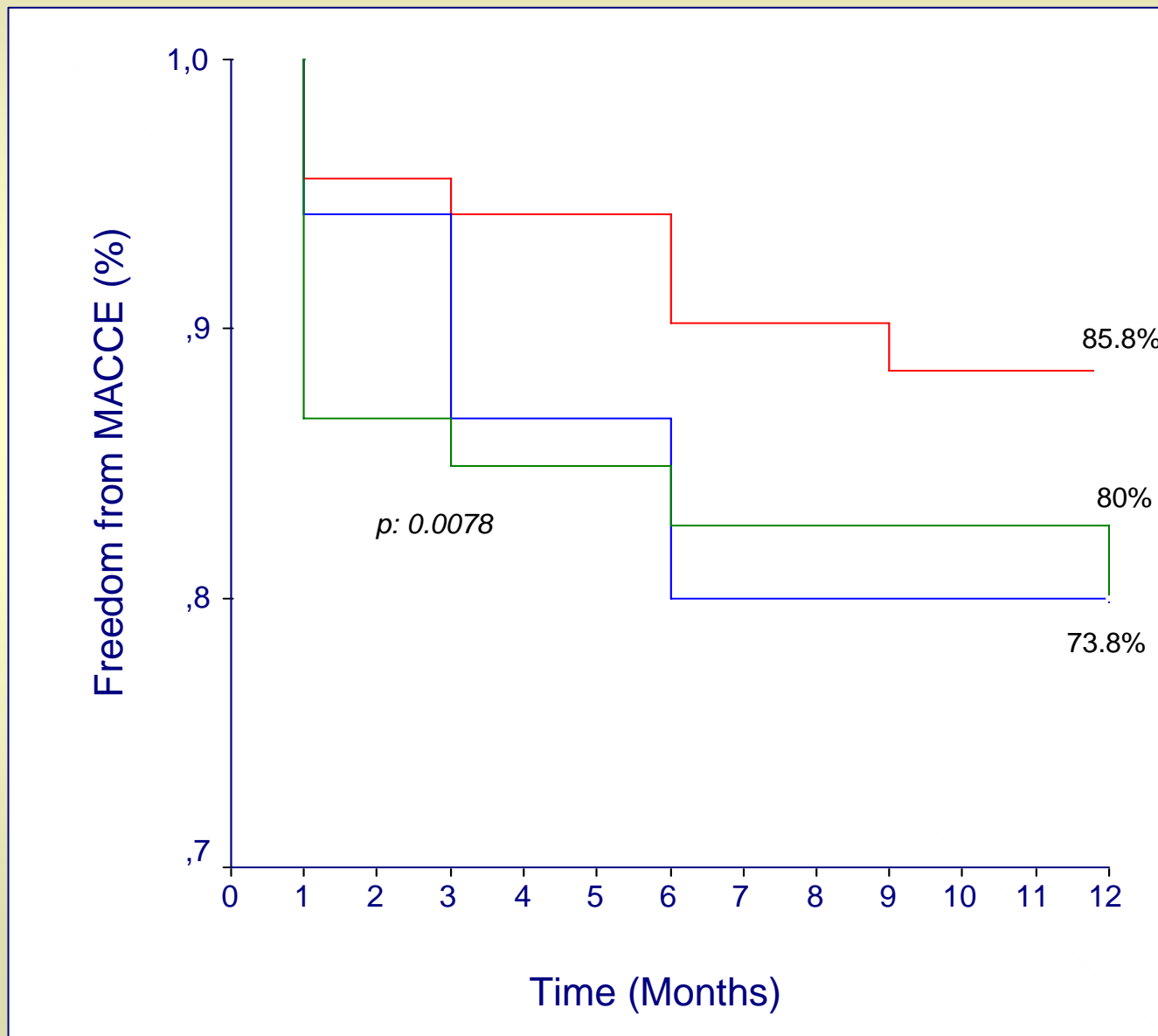
European Society of Cardiology

3-7 September -Stockholm, Sweden



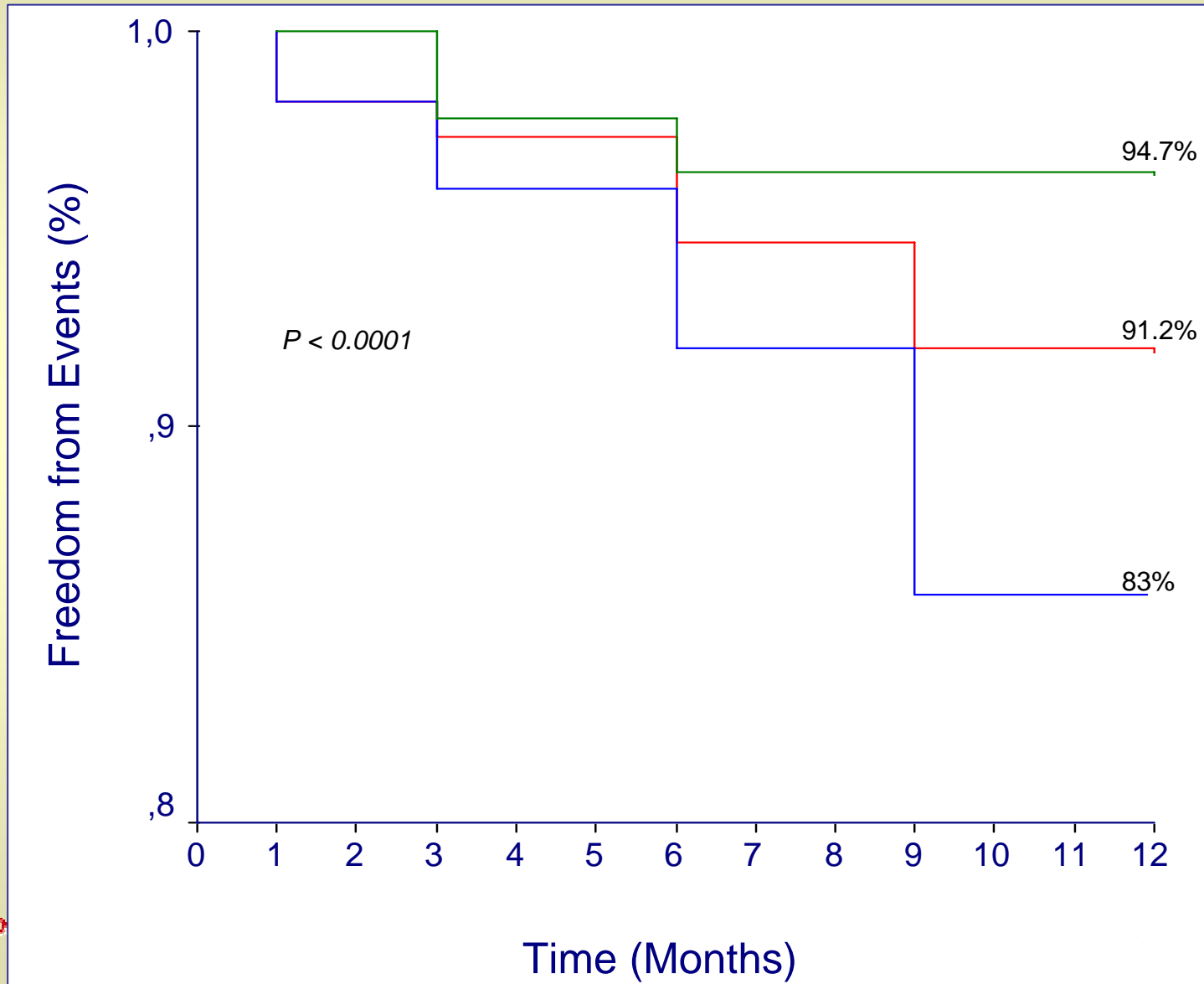
ERACI II & ERACI III

Freedom from MACCE at 12 Months of Follow Up



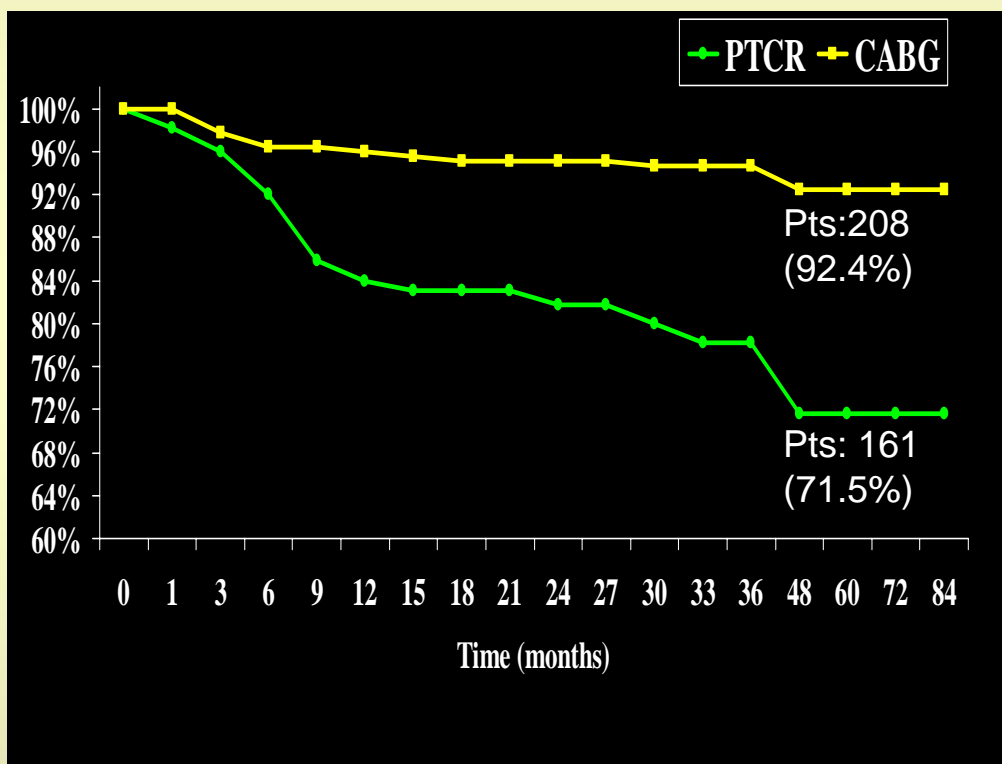
ERACI II & ERACI III

Freedom from Repeating Revascularization at 12 Months of Follow Up



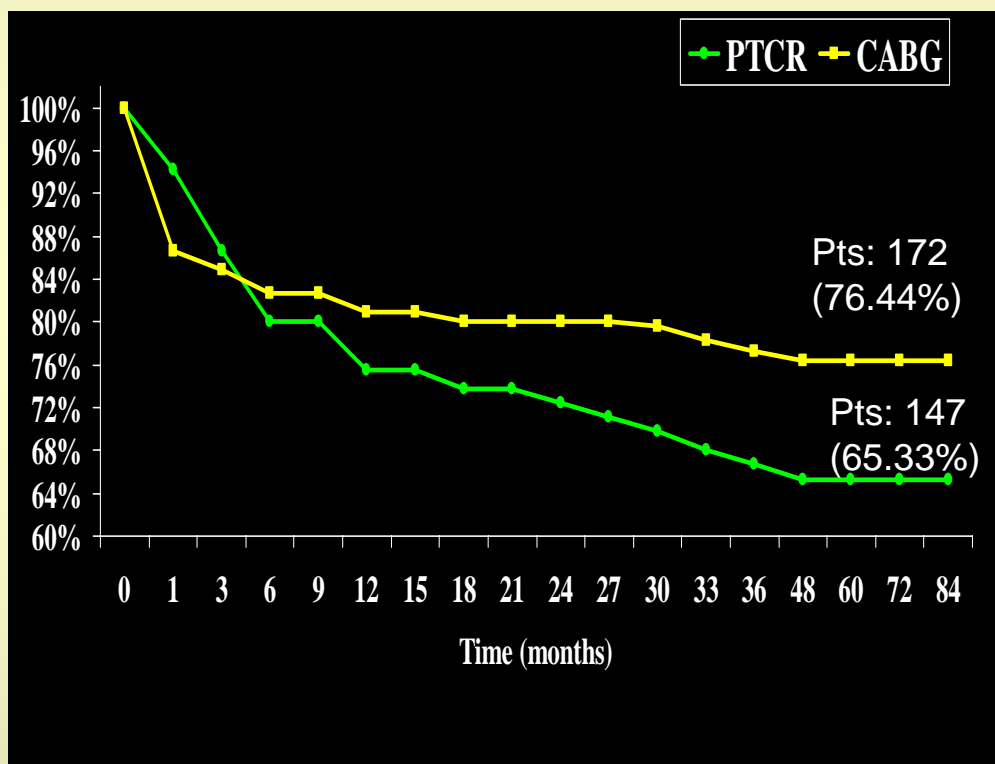
Five Years Follow Up of ERACI II

Freedom From Repeat PTCA/CABG



Log rank $p=0.00002$

Freedom From MACE



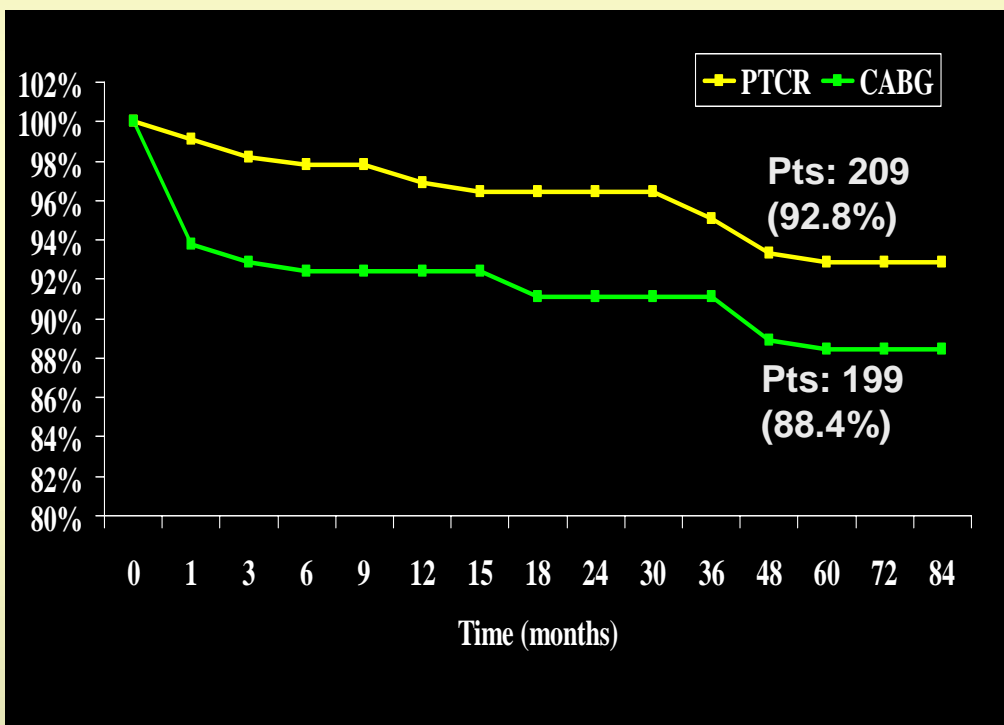
Log rank $p=0.019$



Five Years Follow Up of ERACI II

Freedom From Death

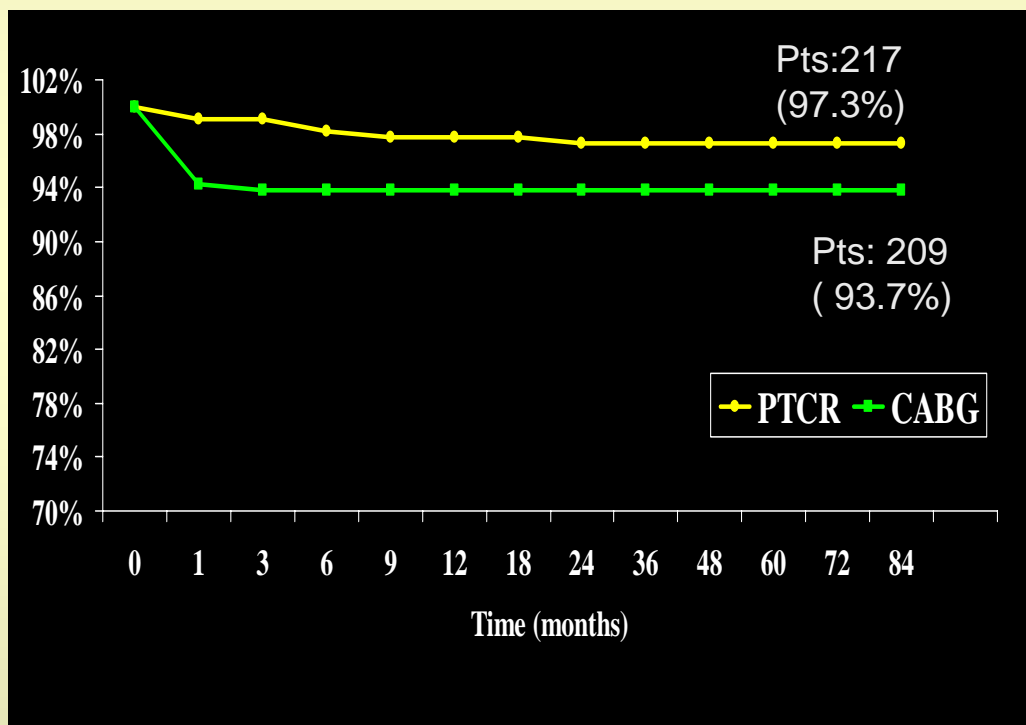
Cumulative Proportion Surviving (%)
Log Rank Test



Log rank $p=0.095$

Freedom from Non Fatal MI

Log Rank Test



Log rank $p=0.159$



Revascularizacion en Enfermedad Coronaria de Múltiples Vasos: Diabeticos vs No Diabeticos

Alfredo Rodriguez MD, Ph D, FACC, FSCAI

*Centro de Estudios en Cardiologia Intervencionista
(CECI)*

*Sanatorio Otamendi , Escuela de Medicina de Buenos
Aires , Argentina.*

NO CONFLICT TO DISCLOSE

**II Reunion en Prevencion y Tratamiento de
las Complicaciones en Intervencionismo
Coronario Percutaneo**

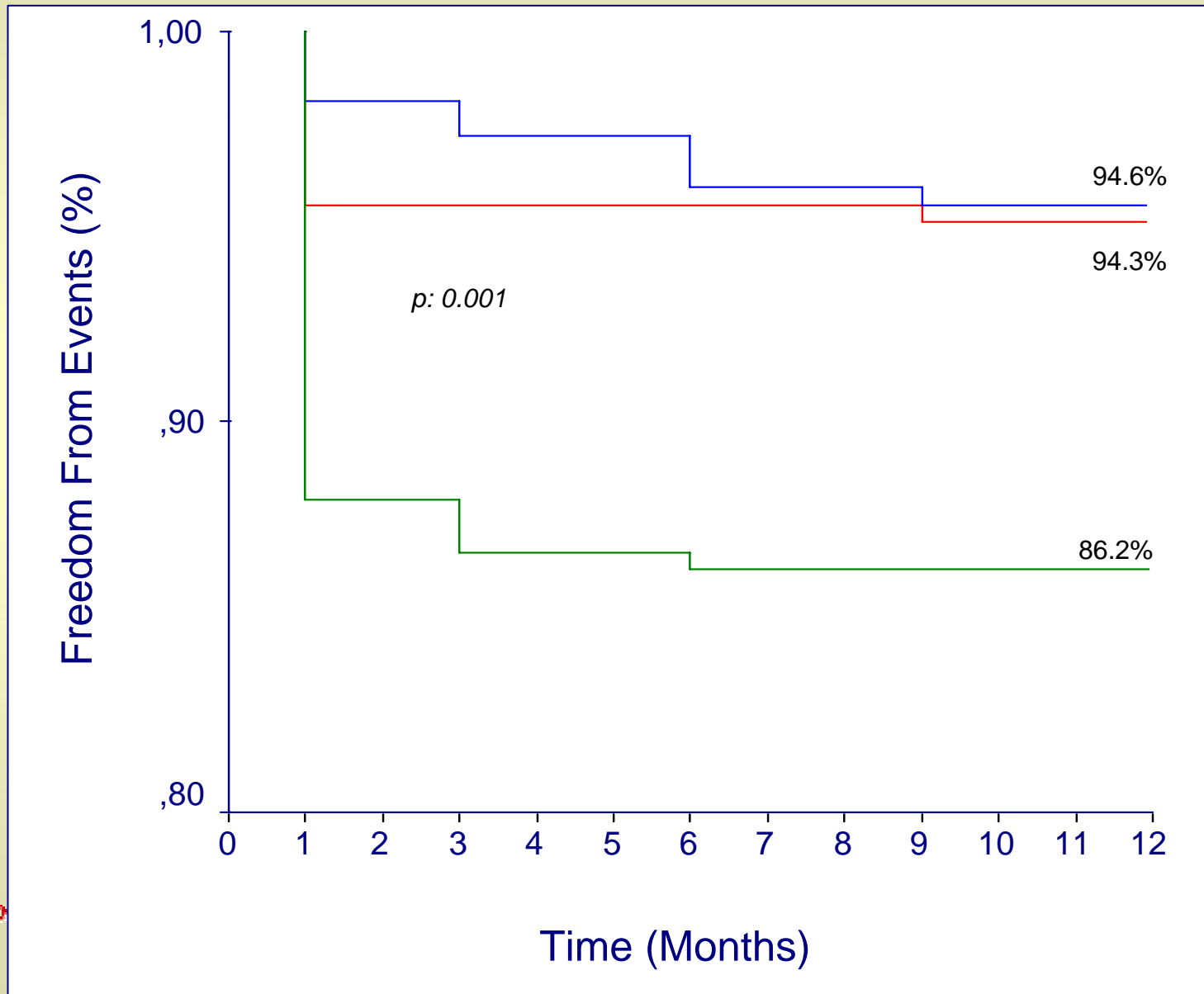
Barcelona, Espana

Abril 20 y 21, 2006



ERACI II & ERACI III

Freedom from Death or AMI at 12 Months of Follow Up



ERACI II & ERACI III

Freedom from Death at 12 Months of Follow Up

