Primary PCI *for* STEMI in DES Era & Beyond

Rationale & Initial Results of HEALING-AMI

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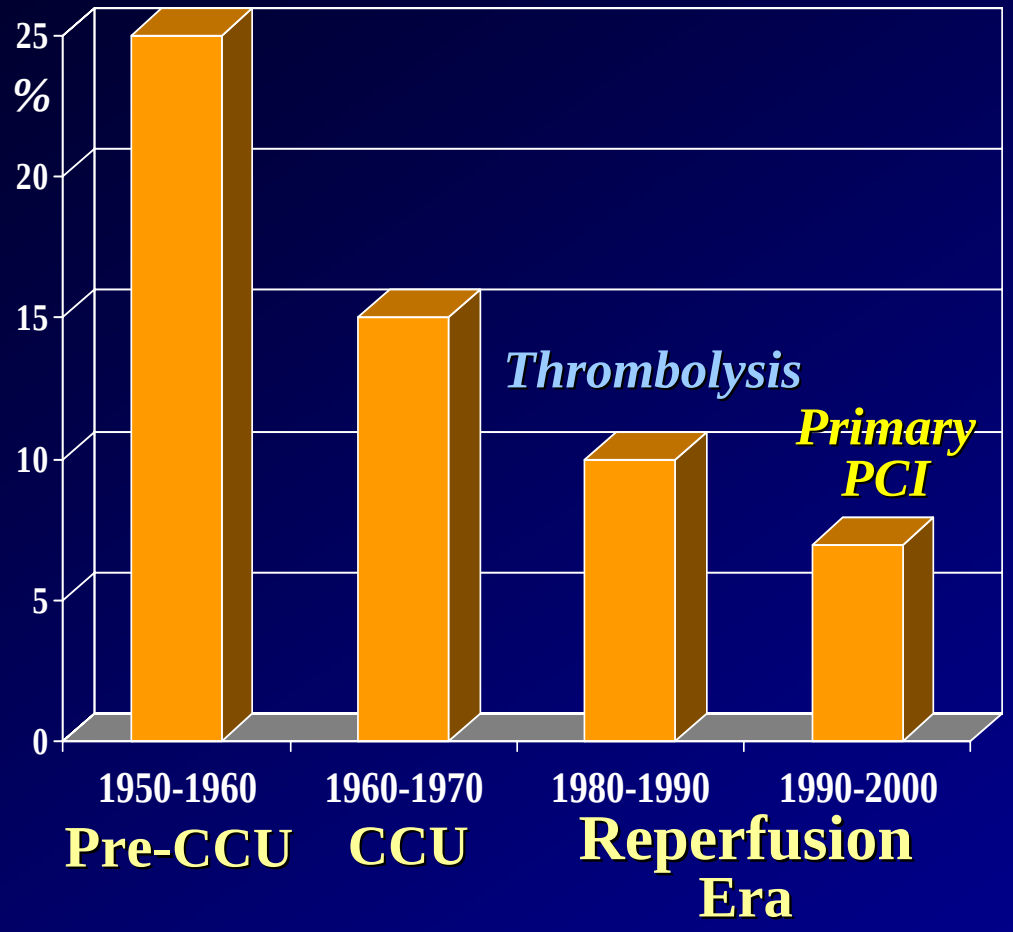
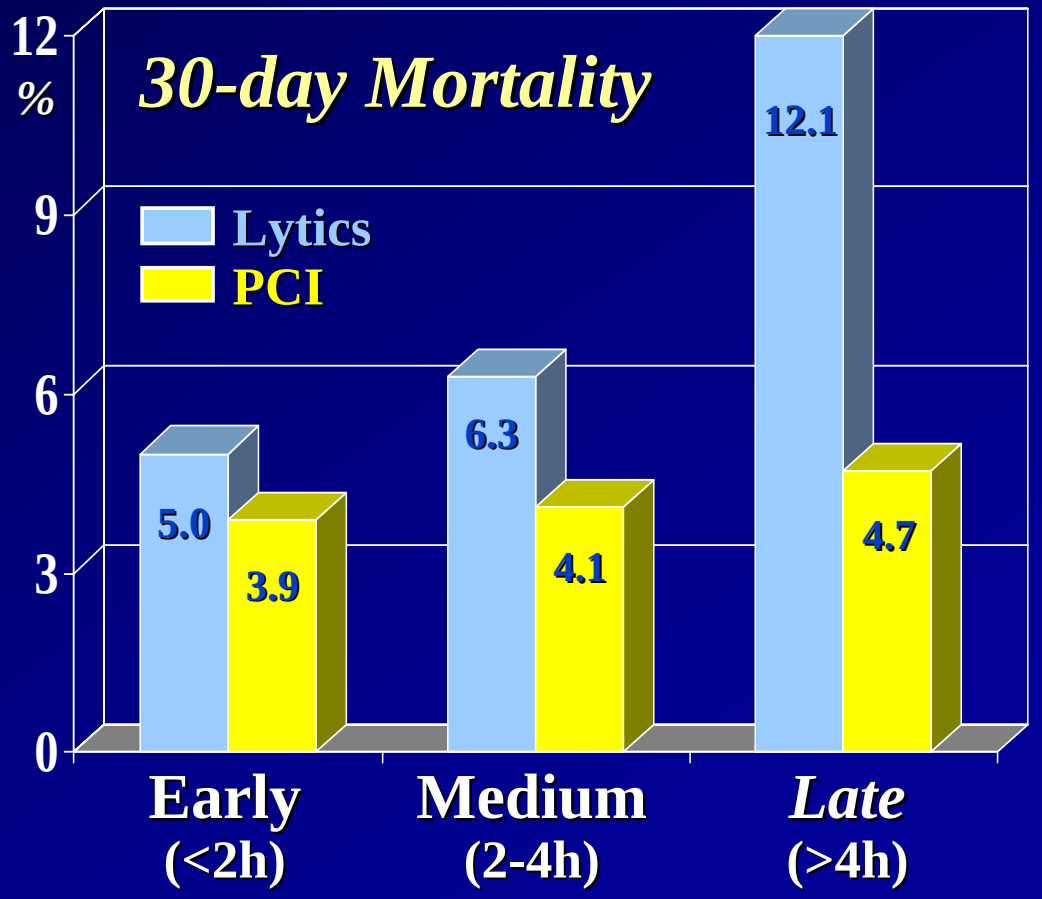
Reperfusion Therapy for STEMI

AMI Mortality in Netherlands



Pooled Analysis: PCI vs Lytics

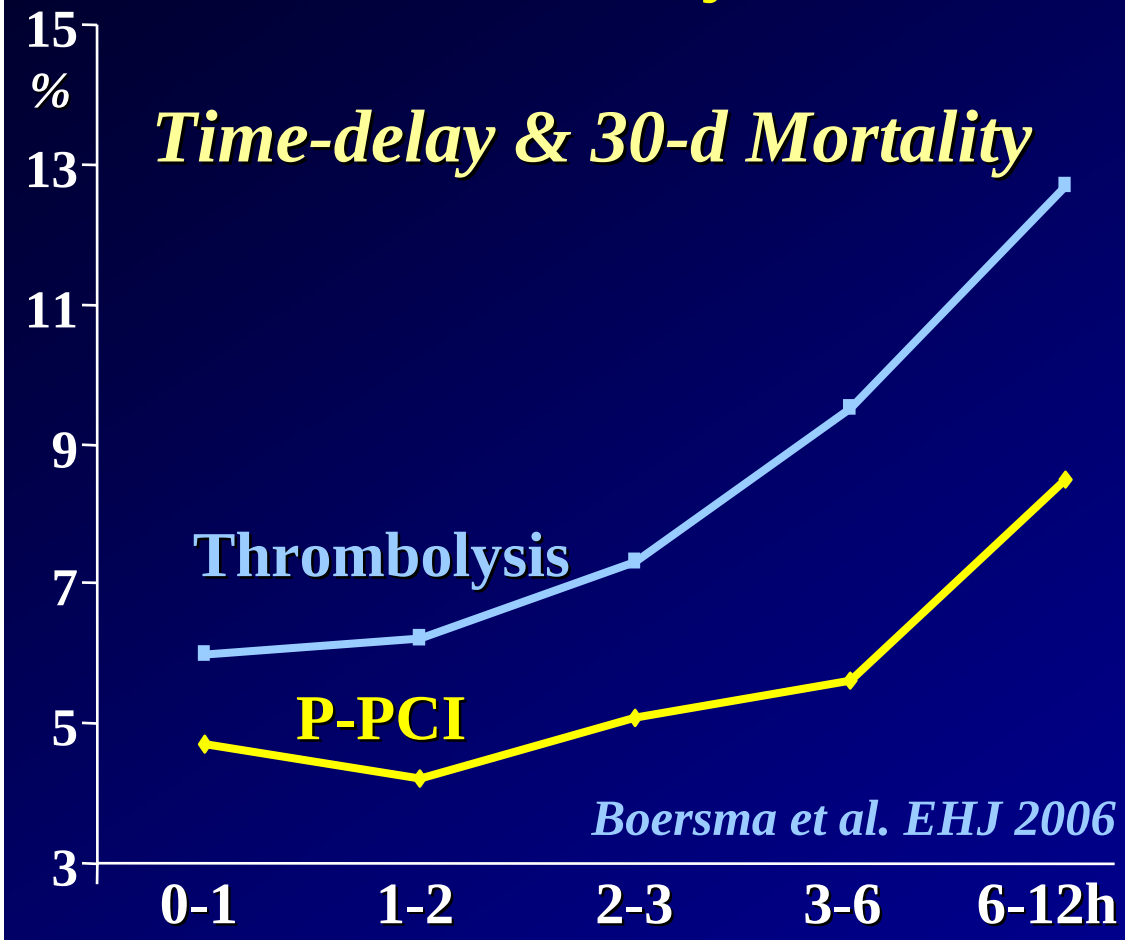


Zijlstra et al. Eur Heart J 2002

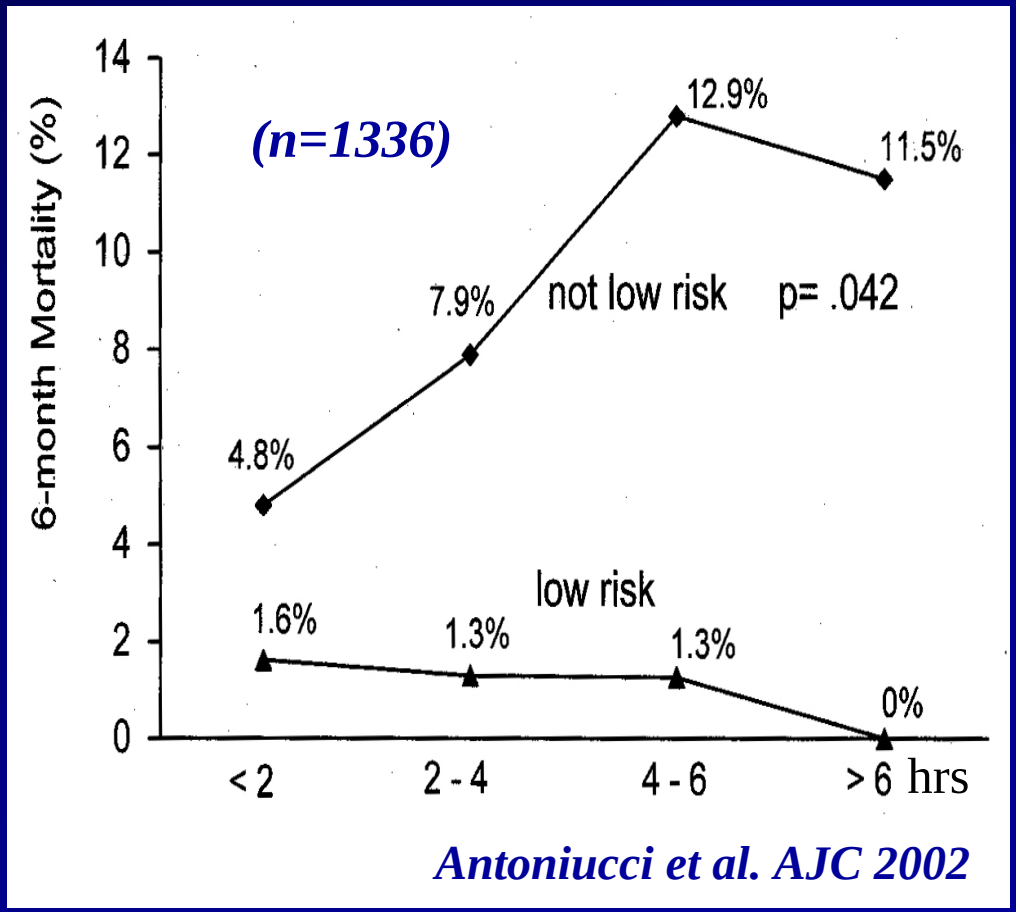
Are time-delays to Primary PCI really **NOT** *that important?*

Time-*to*-Reperfusion *and* Mortality

PCAT Meta-Analysis *(n=6763)*



High-Risk *vs* Low-Risk



Time-delay is related to mortality, not only for Lysis but also for PCI (high-risk)

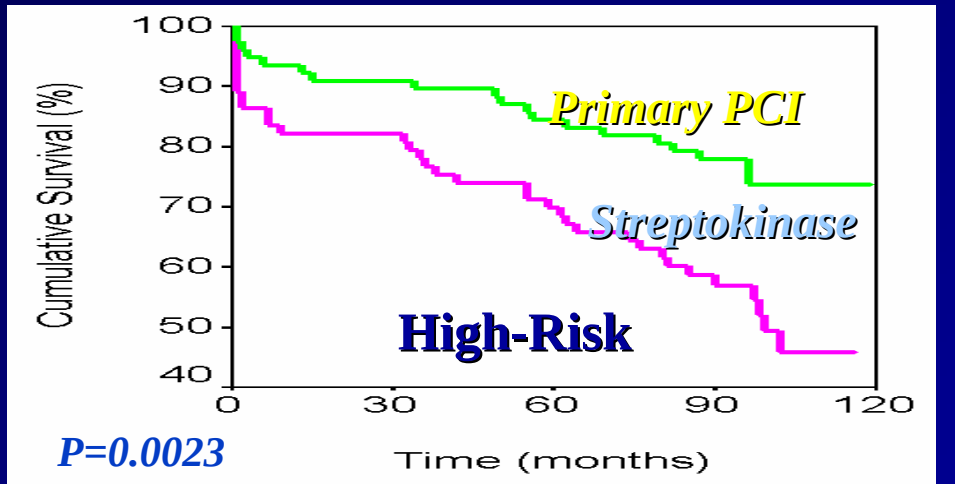
PCI for all STEMI's or only for *"High Risk"* Patients?

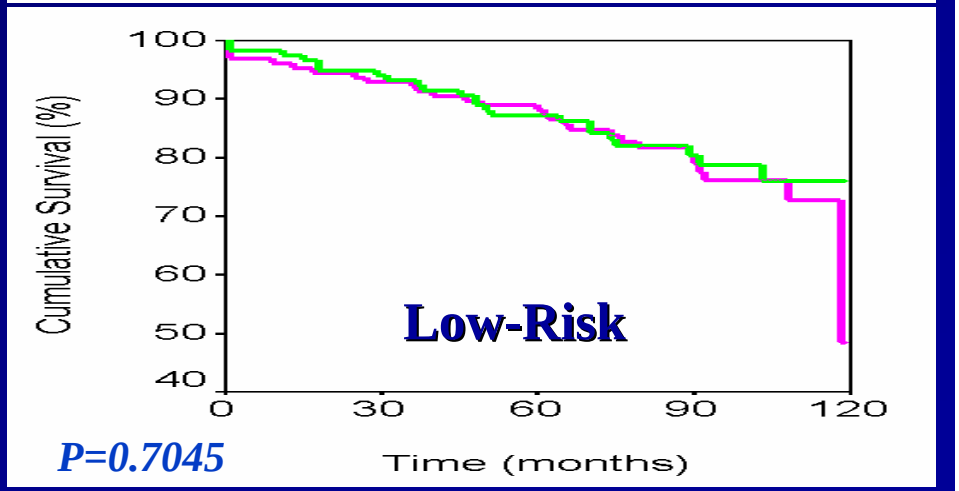
Zwolle Randomized Trial (1993-1995)

F/U @ 1-yr	High-Risk PCI (n=145)	Low-Risk PCI (n=45)	Low-Risk SK (n=50)
Mortality (%)	11	2	2
Stroke (%)	0	2	4
Re-MI (%)	3	3	16*
(Re)-PCI (%)	14	20	61*
CABG (%)	16	13	13
LVEF (%)	46	51	48

Zijlstra et al. JACC 1997

** p < 0.01*





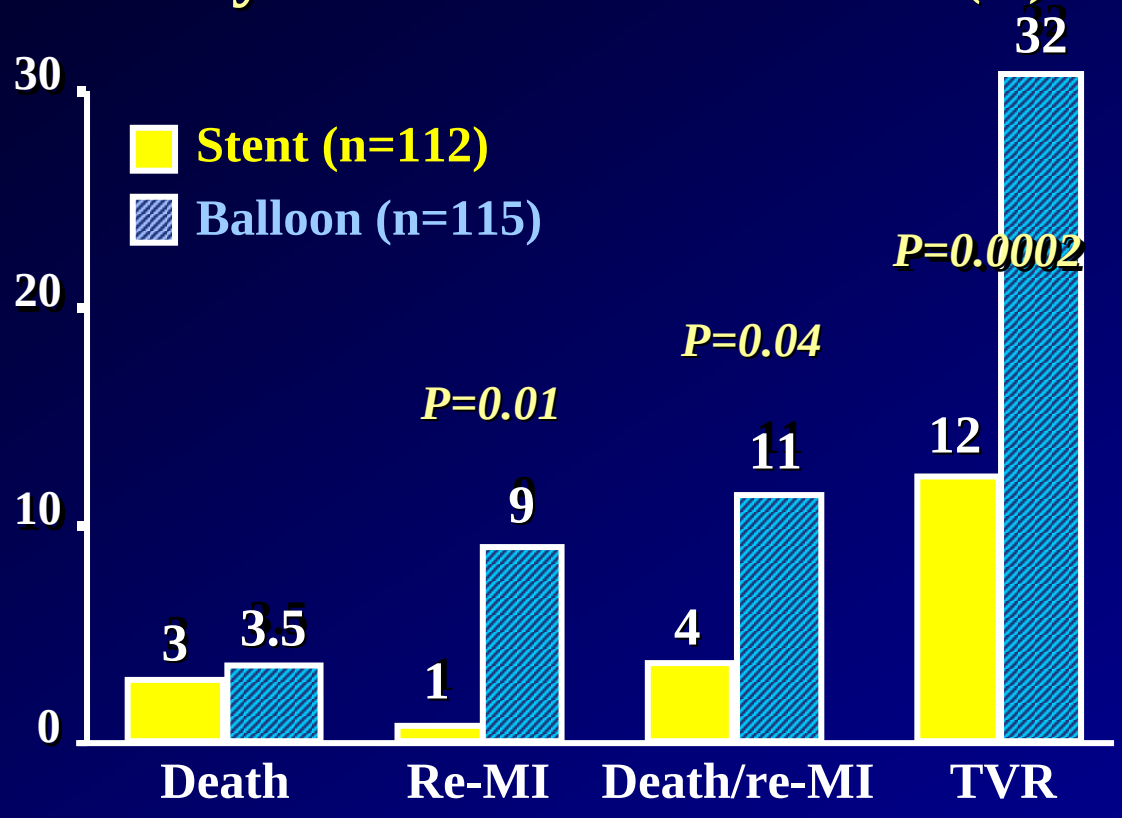
Henriques et.al. Heart 2006

PCI has never been shown to reduce mortality, except in subsets of pts with AMI

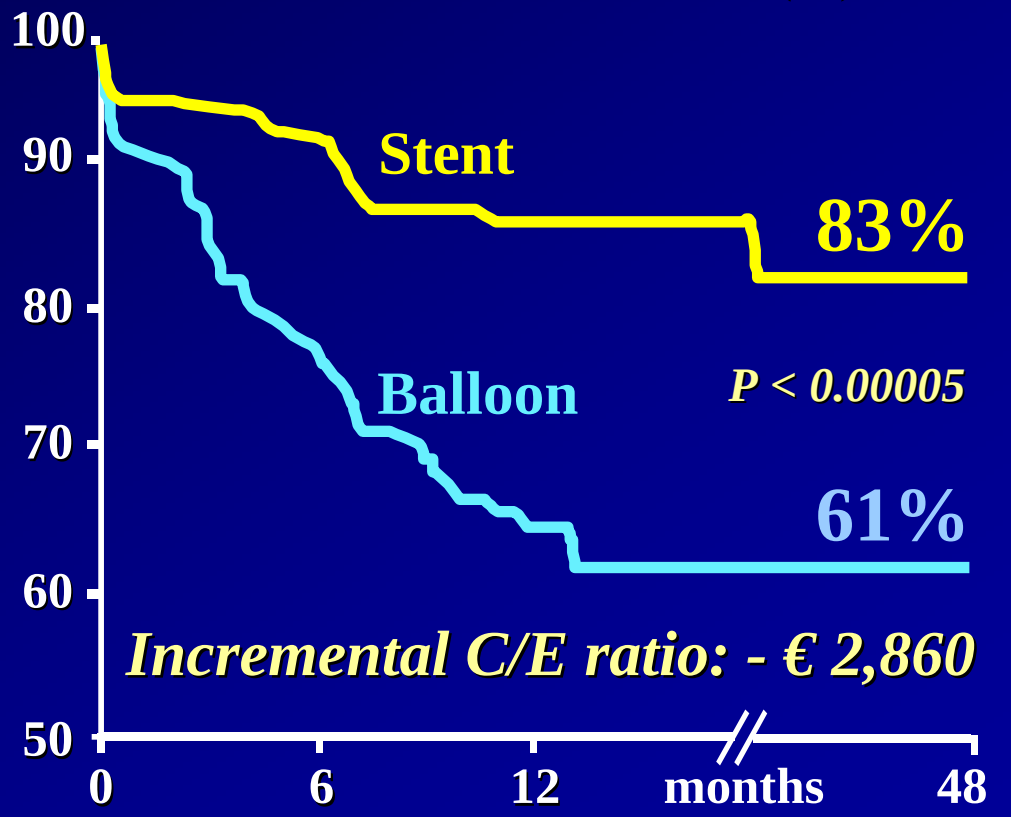
Primary Stenting vs Balloon Angioplasty for STEMI

Zwolle-5 Randomized Trial (1995-1997)

One-year Clinical Outcome *(%)*



Event-free Survival *(%)*



Suryapranata et al. Circulation 1998

Suryapranata et al. Heart 2001

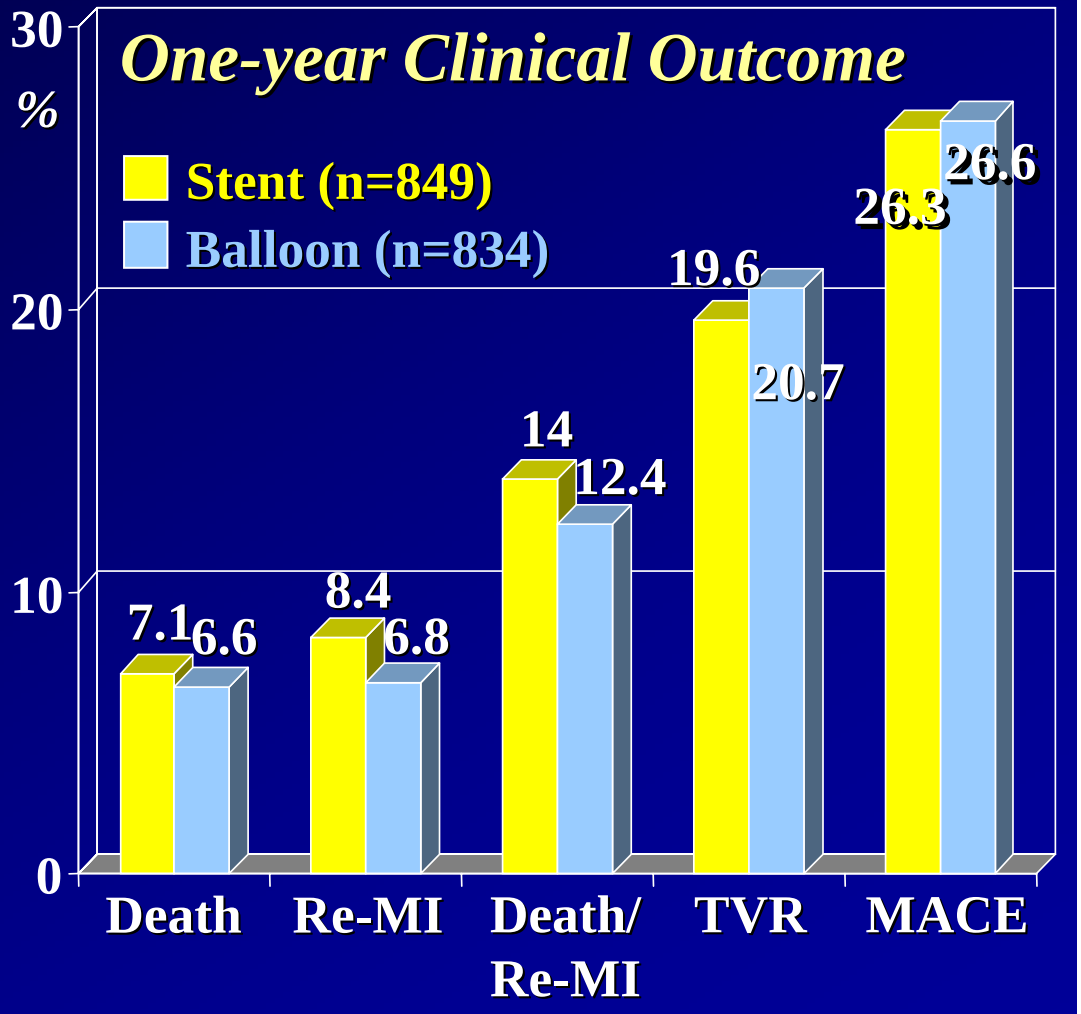
Involving highly selected patients **after** *the initial angiography*
Excluding many patients considered 'non-suitable' for stenting

Routine Stent vs Balloon in a consecutive series of unselected pts

Zwolle-6 "Real World" Randomized Trial

Post-PCI Results	Stent (n=849)	Balloon (n=834)
TIMI-3 Post *(%)*	88	88
MBG II-III *(%)*	81	80
Distal emboli *(%)*	14	18
Compl ST-res *(%)*	56	54
LVEF *(%)*	44	45
LDH Q48h *(U/L)*	1227	1286

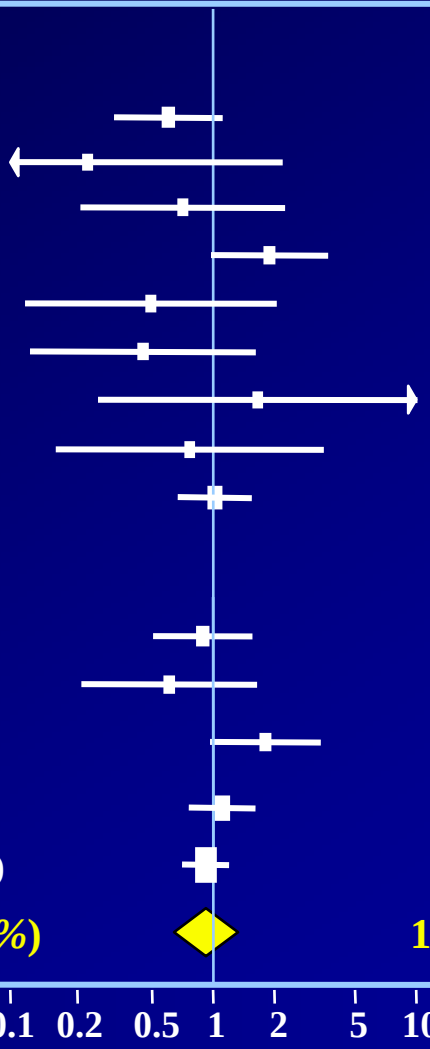
Suryapranata et al. Heart 2005



- *Stent doesn't improve epi-/myo-cardial reperfusion, unlike to reduce mortality*
- *Stent has never been shown to reduce mortality, as compared to balloon*

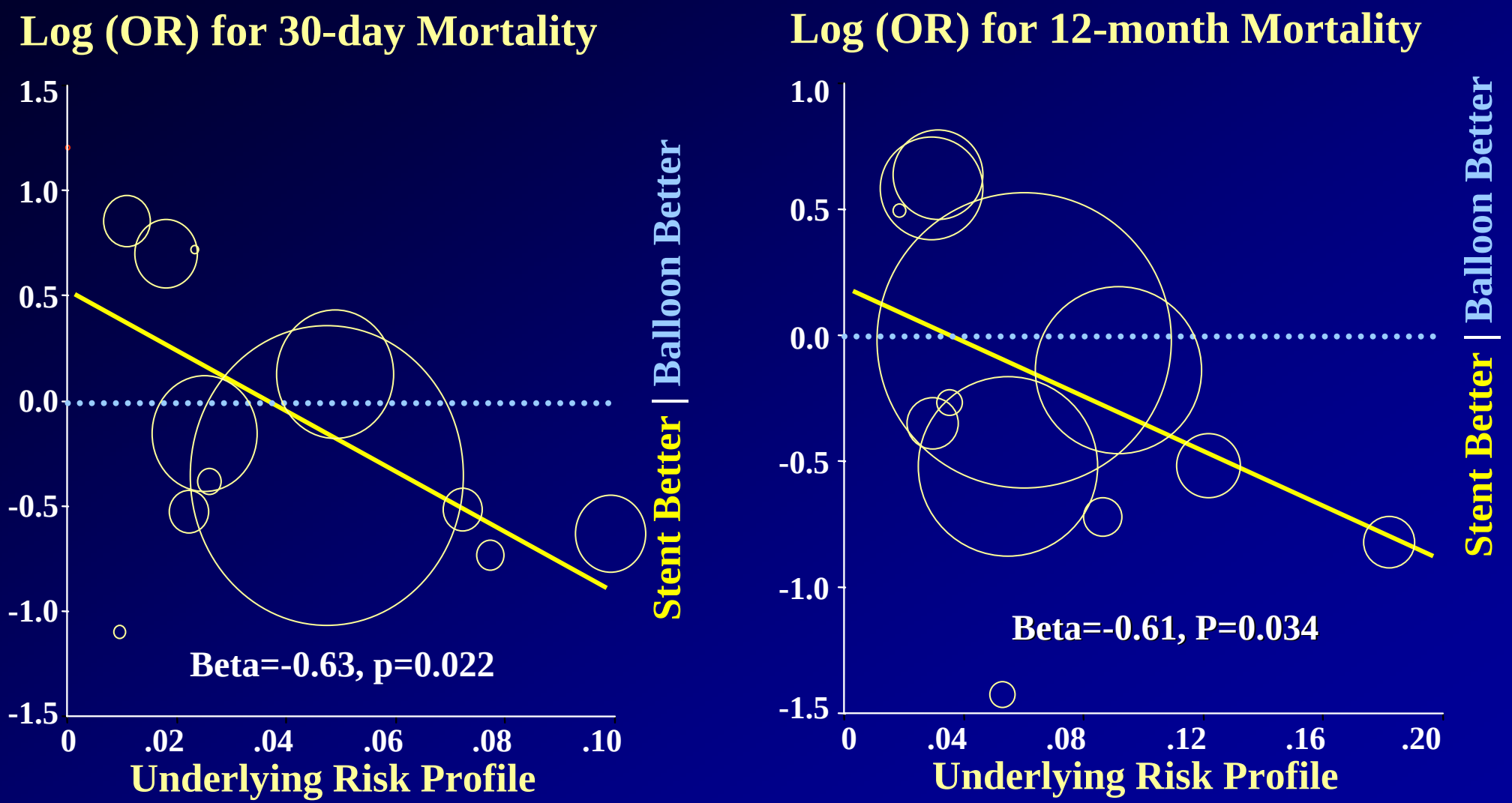
Meta-Analysis: Stenting *vs* Balloon for STEMI *(13 RCT's; n=6921)*
12-month MORTALITY

STUDY	STENTING n/N *(%)*	BALLOON n/N *(%)*	OR *(fixed)* 95% CI	Weight %	OR 95% CI	P value
WITHOUT ABCIXIMAB						
CADILLAC	17/512 (3.3%)	28/518 (5.4%)		16.47	0.60 [0.32, 1.11]	1.0
FRESCO	1/75 (1.3%)	4/75 (5.3%)		2.42	0.24 [0.03, 2.20]	0.36
Jacksch et al	5/231 (2.2%)	7/231 (3.0%)		4.19	0.71 [0.22, 2.26]	0.56
PAMI	26/452 (5.8%)	14/448 (3.1%)		8.11	1.89 [0.97, 3.67]	0.056
PASTA	3/67 (4.5%)	6/69 (8.7%)		3.46	0.49 [0.12, 2.05]	0.49
PSAAMI	4/44 (9.1%)	8/44 (18.2%)		4.45	0.45 [0.12, 1.62]	0.35
STENTIM-2	3/101 (3.0%)	2/110 (1.8%)		1.14	1.65 [0.27, 10.1]	0.58
ZWOLLE-5	3/112 (2.7%)	4/115 (3.5%)		2.35	0.76 [0.17, 3.49]	1.0
ZWOLLE-6	47/785 (6.0%)	45/763 (5.9%)		26.26	1.02 [0.67, 1.55]	0.94
WITH ABCIXIMAB						
STOPAMI-3	25/305 (8.2%)	28/306 (9.2%)		15.71	0.89 [0.50, 1.56]	0.67
STOPAMI-4	7/90 (7.8%)	11/91 (12.1%)		6.21	0.61 [0.23, 1.66]	0.33
CADILLAC	28/524 (5.3%)	16/528 (3.0%)		9.23	1.81 [0.97, 3.38]	0.061
ABCIXIMAB	60/919 (6.5%)	55/925 (5.9%)		31.25	1.10 [0.76, 1.61]	0.6
CONTROL	109/2379 (4.6%)	118/2373 (5.0%)		68.75	0.92 [0.70, 1.20]	0.5
TOTAL *(95% CI)*	**169/3298 (5.1%)**	**173/3298 (5.2%)**		**100.00**	**0.97** [0.78, 1.21]	**0.81**



De Luca, Suryapranata et al. JACC 2006

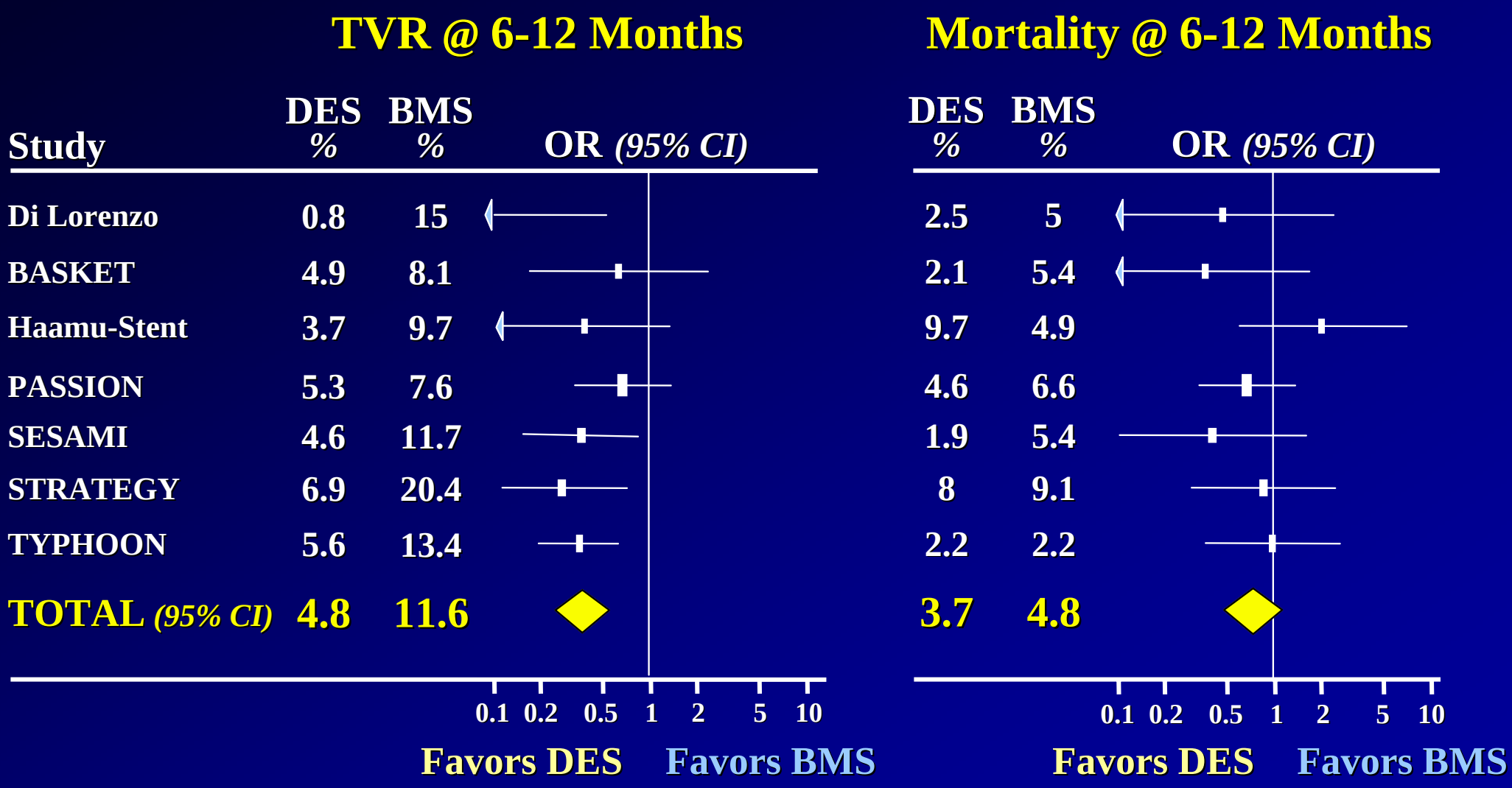
Meta-Regression Analysis: *Stenting vs Balloon for AMI (n=6921)*



De Luca, Suryapranata et al. JACC 2006

The higher the risk profile, the greater the benefits from Stenting

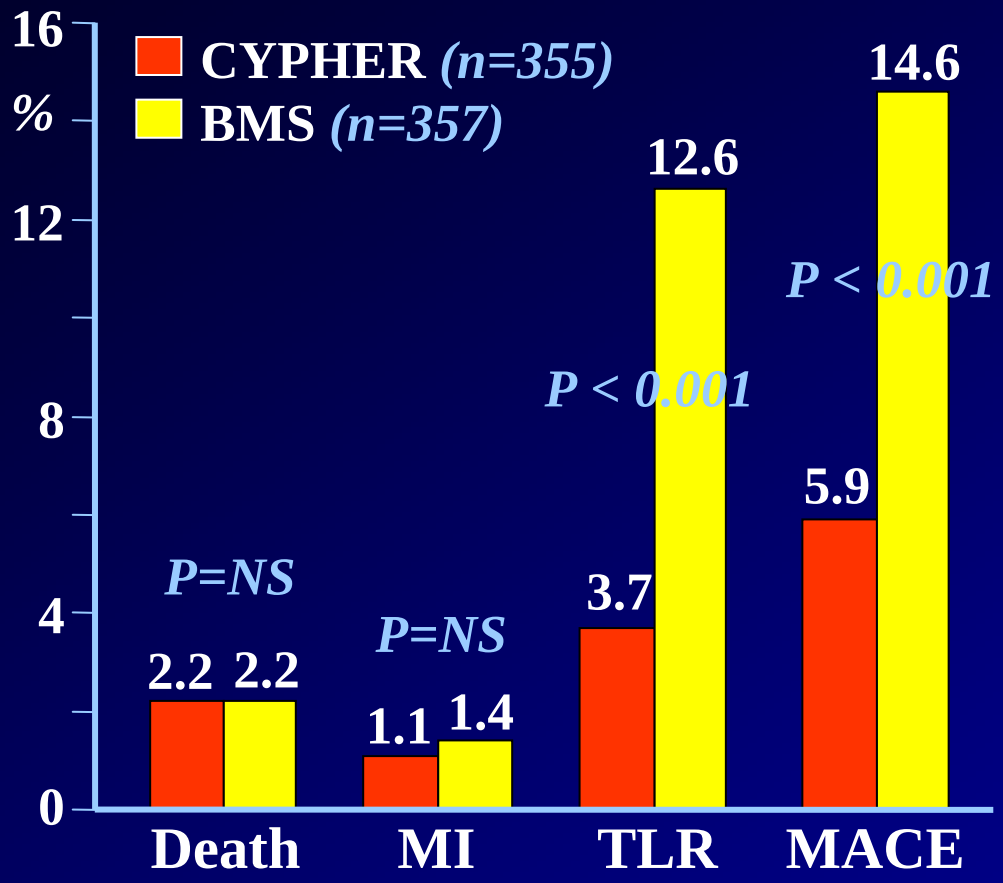
Meta-Analysis: DES *vs* BMS *for* STEMI *(n=2360)*



No difference in Stent Thrombosis *(1.2 vs 1.9%)* or re-MI *(2.3 vs 2.7%)*

Randomized Trials: DES *vs* BMS *for* STEMI @ 1-year F/U

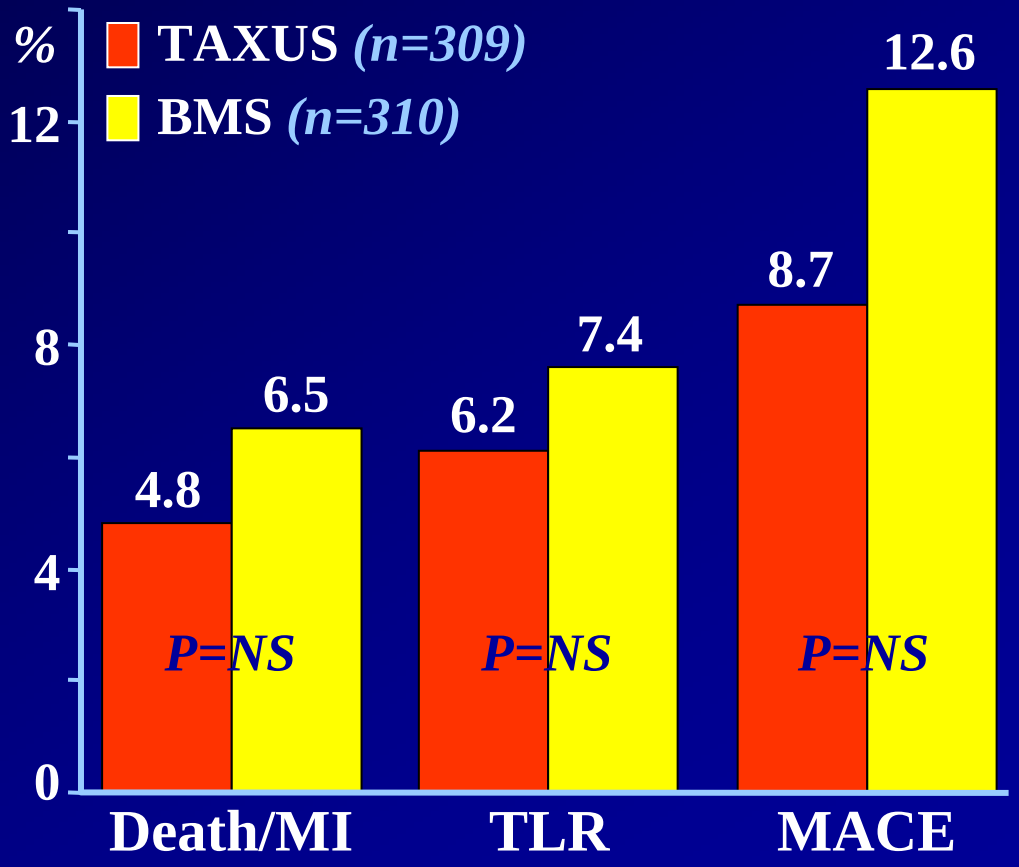
TYPHOON



Stent Thrombosis: 3.4 *vs* 3.6%

Spaulding et al. NEJM 2006

PASSION



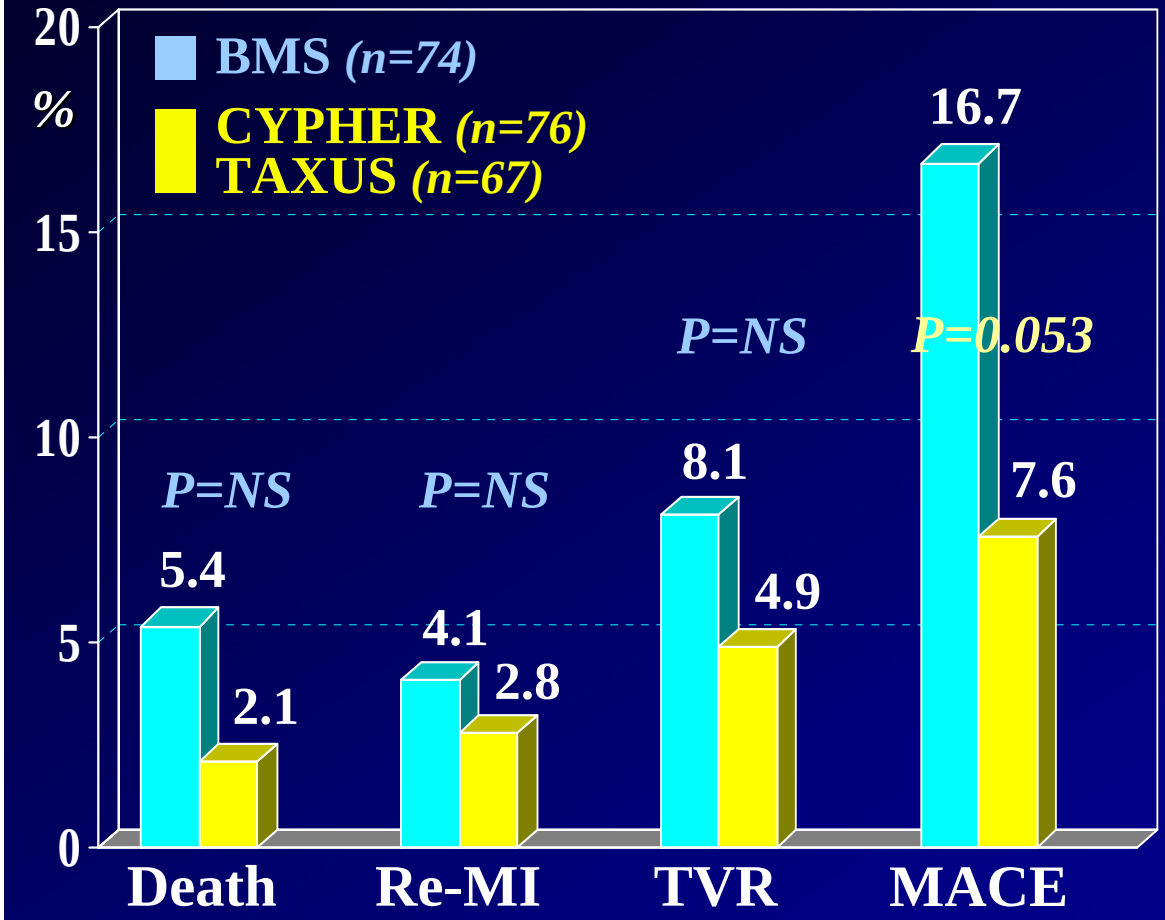
Stent Thrombosis: 1%

Laarman et al. NEJM 2006

No difference in Mortality or re-MI @ 1-year F/U

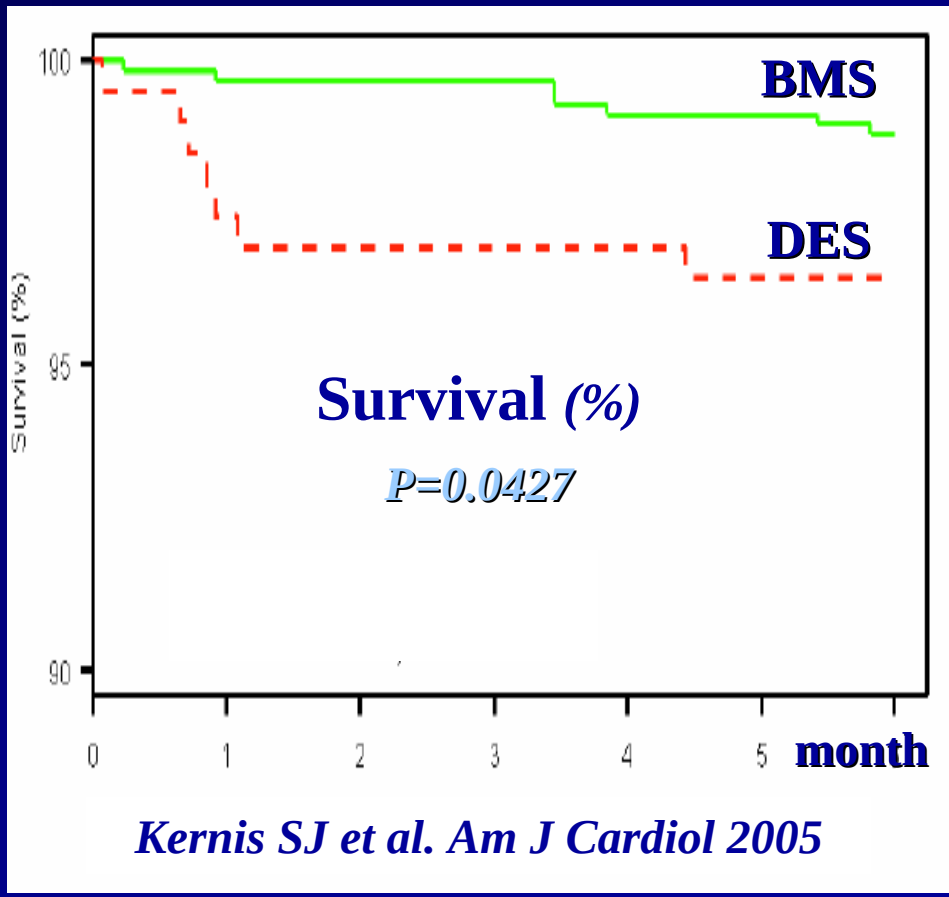
DES *vs* BMS *for* STEMI @ 6-month F/U

BASKET Trial



Pittl et al. WCC 2006

PREMIER Registry



Kernis SJ et al. Am J Cardiol 2005

The safety & efficacy of DES *for* STEMI remain to be established

The CEZAR *Trial*

Cypher vs Taxus drug-Eluting stent: A Zwolle AMI Randomized trial

Interim Analysis

Baseline	*TAXUS (n=134)*	*CYPHER (n=135)*
Age *(mean, yr)*	60	61
Male *(%)*	72	70
Prev MI *(%)*	7	5
PCI/CABG *(%)*	9	6

Risk Factors	*TAXUS (n=134)*	*CYPHER (n=135)*
Diabetes *(%)*	12	11
Hypertension *(%)*	32	28
Hyperchol *(%)*	53	59
Smoking *(%)*	36	35

Interim results as of August 31, 2006 (n=269)

The CEZAR *Trial*

Cypher vs Taxus drug-Eluting stent: A Zwolle AMI Randomized trial

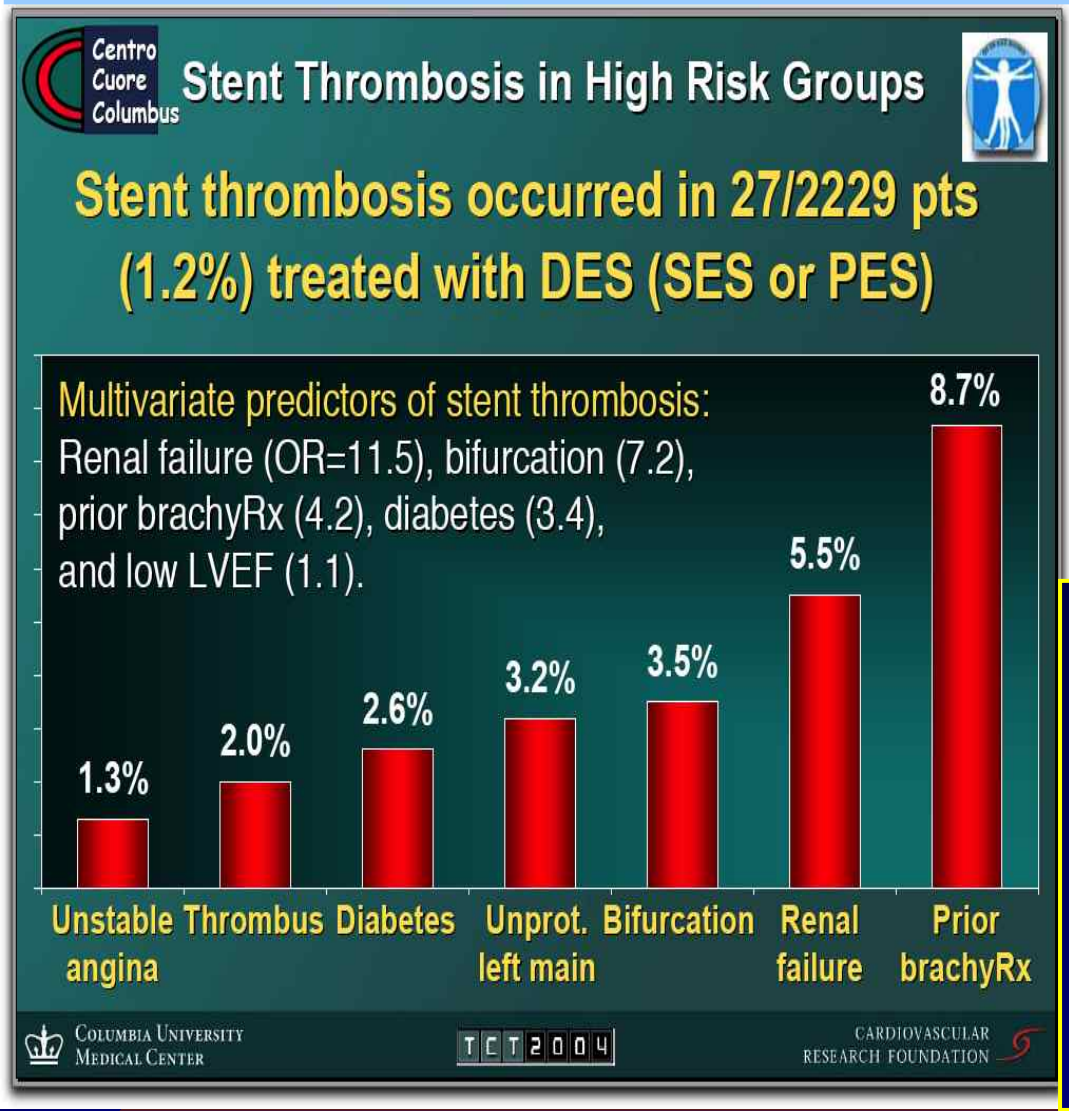
Initial Results

QCA-Post	*TAXUS (n=115)*	*CYPHER (n=114)*
RD *(mm)*	2.69	2.63
Length *(mm)*	16	17
MLD *(mm)*	2.62	2.59
DS *(%)*	4.7	4.5

F/U @ 30d MACE	*TAXUS (n=134)*	*CYPHER (n=135)*
Death	2	3
Re-MI	4	3
CABG	1	0
SAT/TLR	4 (*4%*)	5

DES for AMI seems to be feasible and even more effective in reducing TVR
Safety issue of DES on SAT, particularly in *AMI's*, remain to be established

Predictors of Late Stent Thrombosis
After Successful DES Implantation



Predictors of six-month major adverse cardiac events

Chu: AJC 2006

Variable	Hazard Ratio	95% Confidence Interval	p Value
Univariate predictors			
ACC/AHA type C lesion	2.22	1.24–3.97	0.007
Acute MI on admission	1.86	1.03–3.36	0.041
≥3 SES implantations	4.00	2.11–7.57	<0.0001
Cardiogenic shock	4.75	1.48–15.23	0.009
Previous MI	1.80	1.04–3.13	0.036
Acute renal insufficiency	4.40	1.59–12.17	0.004

Predictors of Late Stent Thrombosis	**Hazard *Ratio***	***95% C.I***	***P value***
Premature antiplatelet discontinuation	**89.78**	**29.9-269**	***< .001***
Renal failure	**6.49**	**2.60-16.2**	***< .001***
Bifurcation lesion	**6.42**	**2.93-14.1**	***< .001***
Diabetes	**3.71**	**1.74-7.89**	***.001***
EF per 10% decrease	**1.09**	**1.05-1.13**	***< .001***

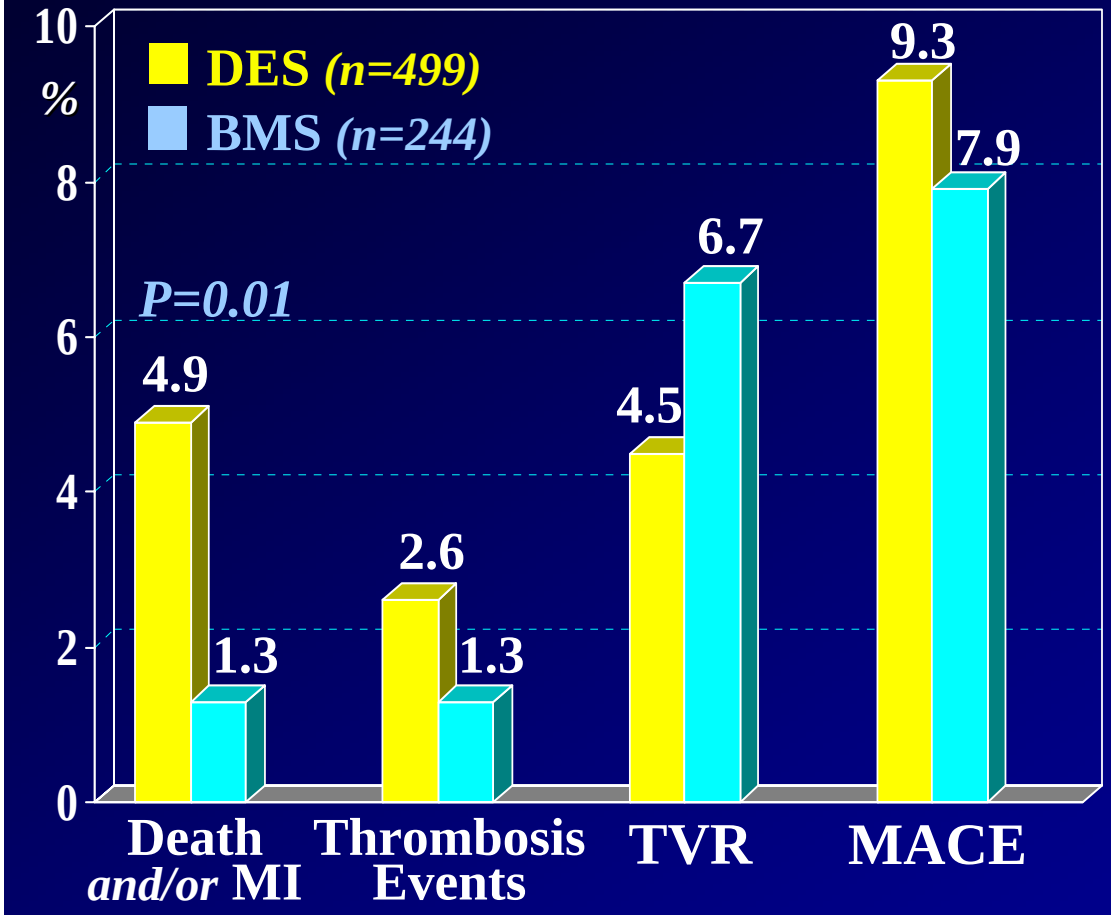
Iakovou et al. JAMA 2005

Late Stent Thrombosis is assiociated with 50% Mortality

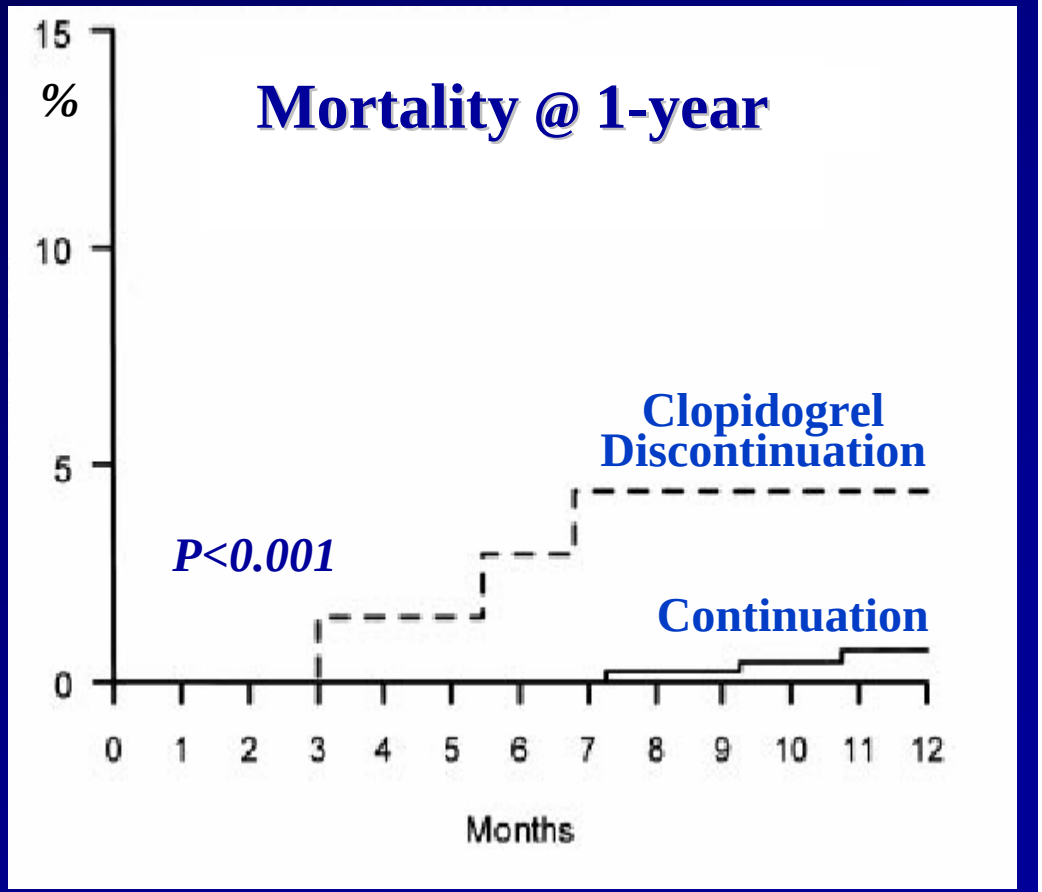
Drug-Eluting Stent *vs* Bare Metal Stent

Late Thrombotic Events @ 1-yr after Clopidogrel Discontinuation

BASKET LATE



PREMIER Registry



Pfisterer et al. JACC 2006

Spertus et al. Circulation 2006

Scientific papers on Late Thrombosis *after* DES
…. and the list is growing rapidly

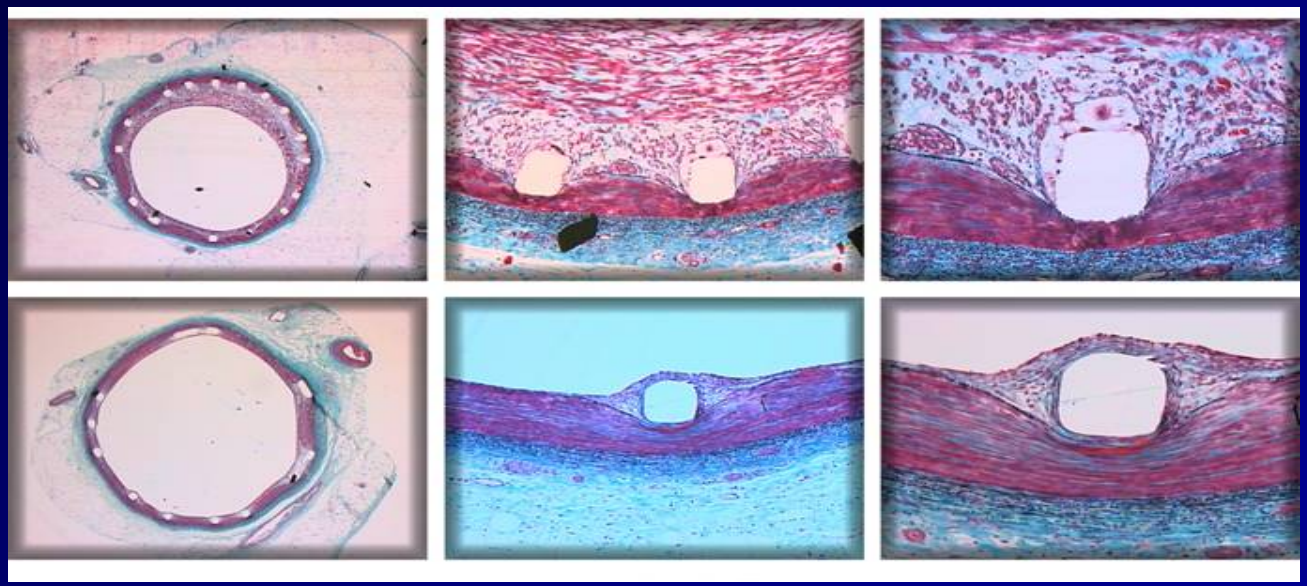
1. Virmani R *et al.* Circulation 2004: Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus eluting stent, should we be cautious
2. McFadden E *et al.* Lancet 2004: Late thrombosis in drug eluting coronary stents after discontinuation of antiplatelet therapy
3. Iakovou I *et al.* JAMA 2005: Incidence, predictors, and outcome of thrombosis after successful implantation of drug eluting stents
4. Biondi-Zoccai GG *et al.* Am J Cardiol 2005: Validation of predictors of intraprocedural stent thrombosis in the drug eluting stent era
5. Ong AT *et al.* JACC 2005: Late angiographic stent thrombosis (LAST) with drug eluting stents
6. Nilsen DW *et al.* Intern J Cardiol 2005: Late complications following the deployment of DES
7. Waters RE *et al.* Cathet Cardiovas Intervent 2005: Late thrombosis following treatment of in-stent restenosis with drug eluting stents after discontinuation of antiplatelet therapy
8. Derghazarian S, Eisenberg MJ. Am Heart Hosp J 2005: Late thrombosis associated with DES
9. Ong AT, Serruys PW. Texas Heart Institute Journal 2005: Drug eluting stents

DES issue on Late Thrombosis: Due to Impaired Re-endothelialization?

GENOUS *Endothelial Progenitor Cells* Capture Technology

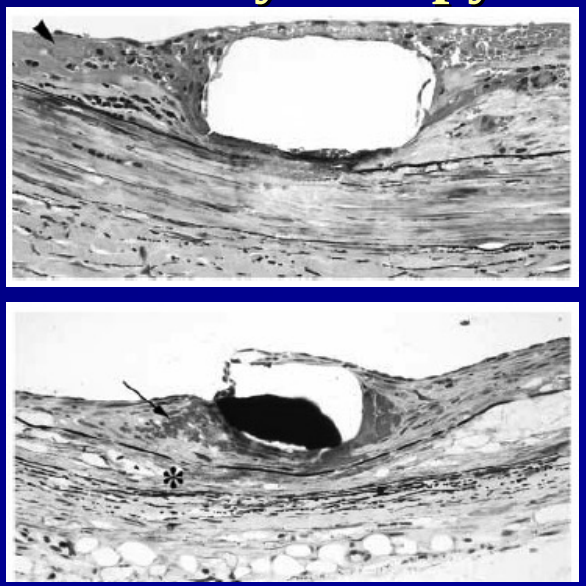
- **EPCs are bone marrow derived, present in the circulating blood,** *(First described by Asahara in 1996)*
- **They have the ability to differentiate into mature endothelial cells, which may accelerate Healing process, protect against thrombus, and minimize restenosis, with safety profile over current *DES***

BMS: *Typical neo-intimal response to stent injury*



Genous: *Complete healing with mature neo-intima*

Brachytherapy



Drug-Eluting Stent

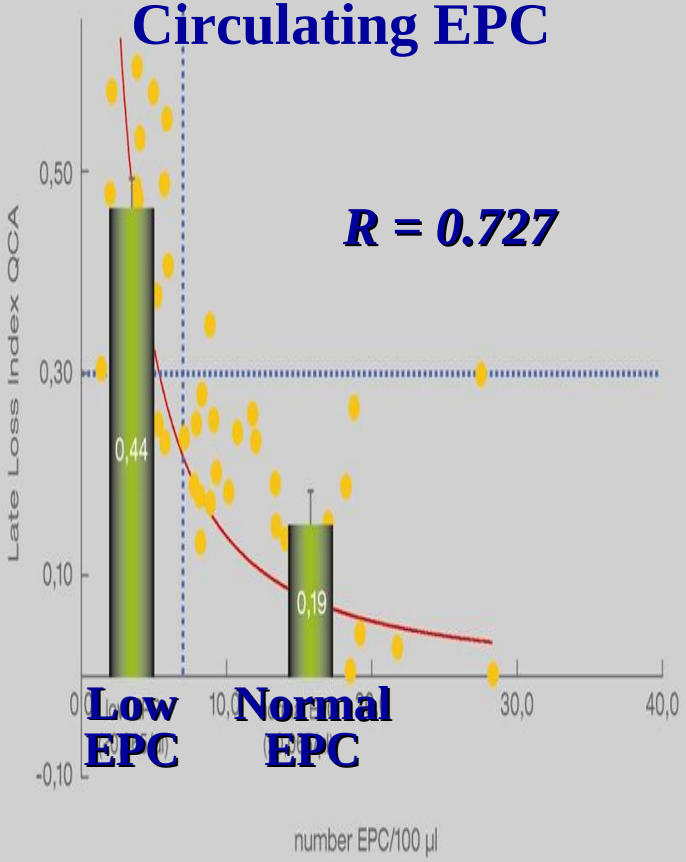
M. Kutryk, MD, PhD, St Michael's Hospital, Toronto, Canada

Virmani et. al. Herz 2002

Late Loss Index, Circulating EPC, and Statin Therapy

Initial Results from HEALING II Study

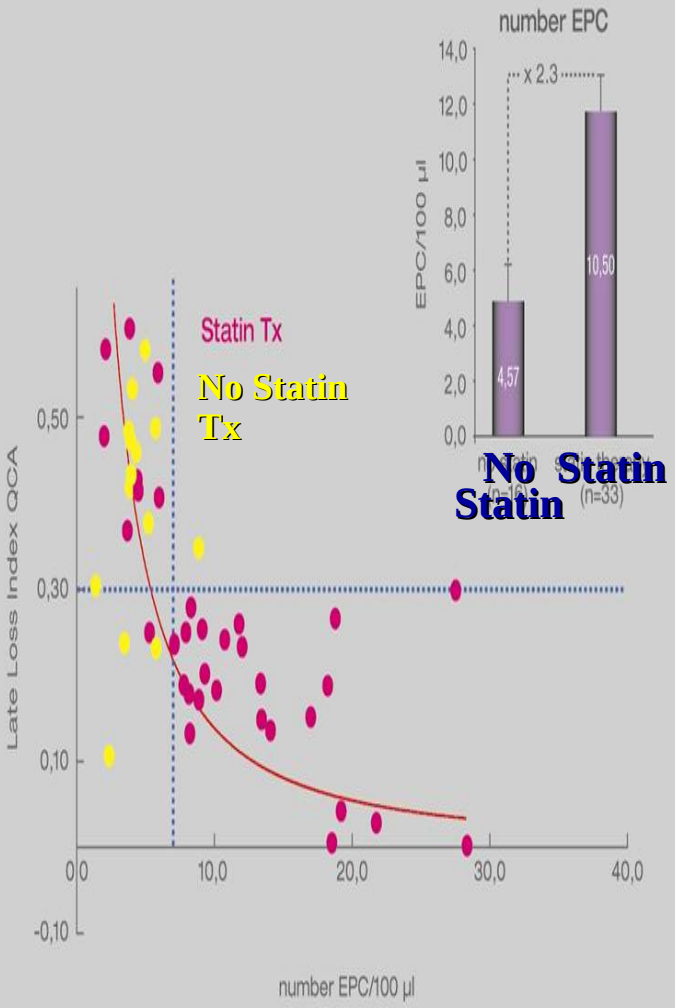
Late Loss Index and Circulating EPC



R = 0.727

Low EPC **Normal EPC**

PW Serruys & HH Duckers, TCT 2005



Clinical F/U Healing-II @ 9 months

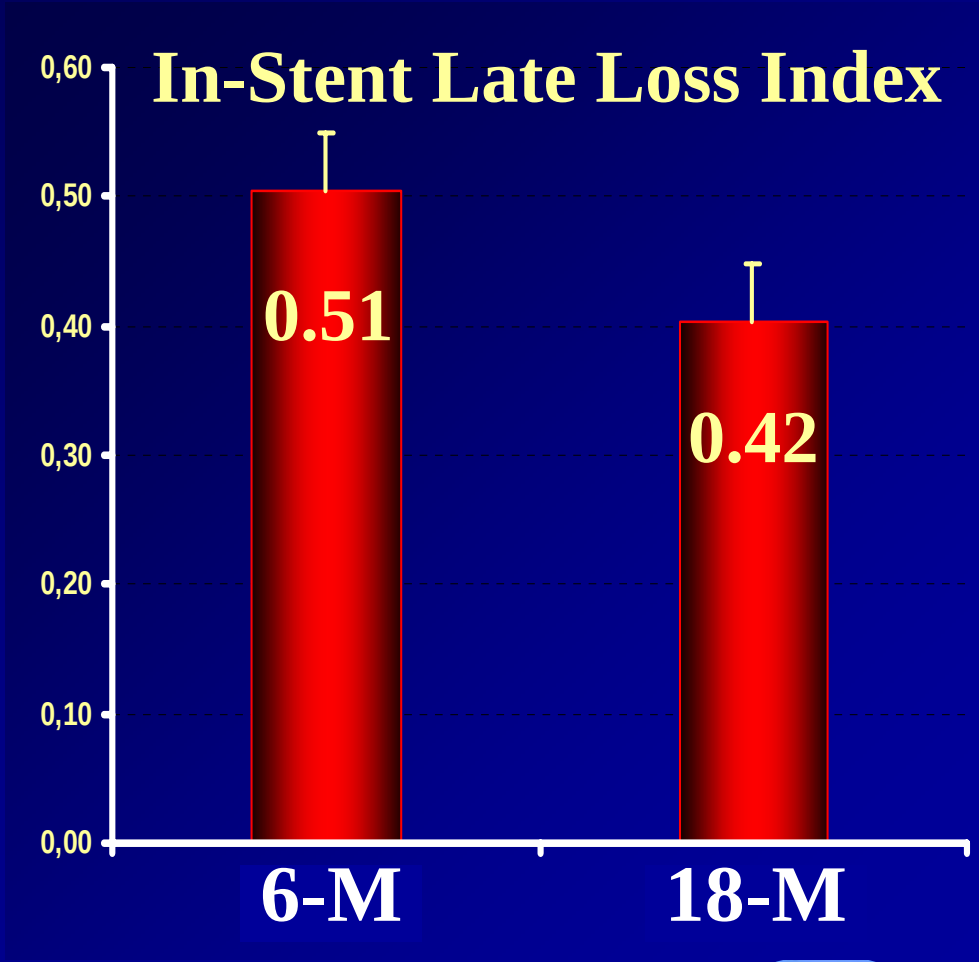
EPCs	Low *(n=24)*	Normal *(n=25)*
Death *(%)*	0	0
MI *(%)*	0	0
SAT *(%)*	0	0
TLR *(%)*	8	0
ISR *(%)*	17	0

The higher the circulating EPC levels, the lower the Late Loss Index

The HEALING-II *Trial*
Serial QCA Analysis at 6 & 18 months F/U

QCA-F/U	6-*month* (n=30)	18-*month* (n=30)
RD *(mm)*	2.49	2.58
MLD *(mm)*	1.69	1.81
DS *(%)*	31.5	29.2
Late Loss *(mm)*	0.71	0.58

Duckers, euroPCR 2006



Zwolle **HEALING-AMI** *Study*

A Safety Evaluation of Genous Bio-engineered R-Stent for AMI

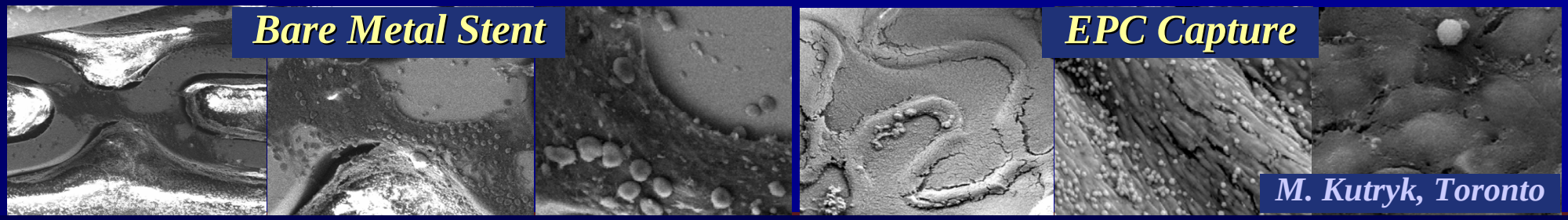
- **A prospective single-center pilot study on the safety and feasibilty of Genous Bio-engineered *R*-stent in 50 AMI's**
- **Clinical F/U at 30-d, 6 and 12 months; F/U angio at 6 M**
- **Blood samples for EPCs at baseline, 30-d and 6-months**
- **A loading dose of atorvastatin *(80mg)*, aspirin *(300mg)* & clopidogrel *(300mg)*, followed by clopidogrel *(75mg)* for 30-d, atorvastatine *(80mg)* and aspirin *(100mg)* for ≥ 6-M**
- **Primary endpoint: SAT at 30 days F/U**
  Secondary endpoints: MACE @ 30d, 6-12M; ISR @ 6M

P.I: H. Suryapranata *CRO & CoreLab: Cardiovascular Research Foundation*

Zwolle HEALING-AMI *Study*

RATIONALE

- **Although DES seems to be safe & feasible, *Stent Thrombosis* remains high despite prolonged dual antiplatelet therapy**
- **Rapid re-endothelialization, *by capturing Pt's own EPCs,* may reduce inflammation, ST & ISR, despite 30d clopidogrel**
- **The higher the circulating EPCs, the lower the late loss**
- **High EPC levels in AMI setting & in patients on Statin**
- **Serial QCA (6-18M) revealed 20% reduction in Late Loss**



Rapid and complete stent re-endothelialization 48hrs after Genous stent

Zwolle HEALING-AMI *Study*

A pilot trial on safety & feasibility of Genous R-Stent for AMI Pre-treated with statin, aspirin, and clopidogrel (for only 30-d)

Initial Results

Baseline		
Age *(yrs)*	57	*(35-81)*
Male	37	*74%*
LAD	18	*36%*
RCA	18	*36%*
CX	14	*28%*

Risk Factors		
Diabetes	7	*14%*
Hypertension	17	*34%*
Hyperchol	13	*26%*
Smoking	29	*58%*
Fam. History	25	*50%*

As of March 31, 2007 (n=50)

Zwolle **HEALING-AMI** *Study*

A pilot trial on safety & feasibility of Genous R-Stent for AMI Pre-treated with statin, aspirin, and clopidogrel (for only 30-d)

Clinical Outcome @ 30-*days*

• Cardiac death	1	• Re-PCI	1*
• Recurrent MI	1*	• CABG	3*
• Stent Thrombosis	1*	• MACE	4

* *Same patient due to edge dissections*

Initial results as of March 31, 2007 (n=50)

CONCLUSION

- Routine stenting in unselected STEMI pts does not seem to improve clinical outcome, when compared to balloon
- Stenting has never been shown to reduce mortality rate, but it is only associated with a reduction in TVR/TLR
- Although DES for AMI seems to be feasible & effective in reducing TVR, safety issue remains to be established
- The potential role of Genous stent for *STEMI*, to further reduce SAT and ISR, is currently being investigated

AMI Intervention

Take home message

- √ The Early The Better
- √ The Higher The Risk
  The Greater The Benefit

Enhancement of Engine Power in Ambulances is more effective than any Pre-hospital Therapy