



ZWOLLE

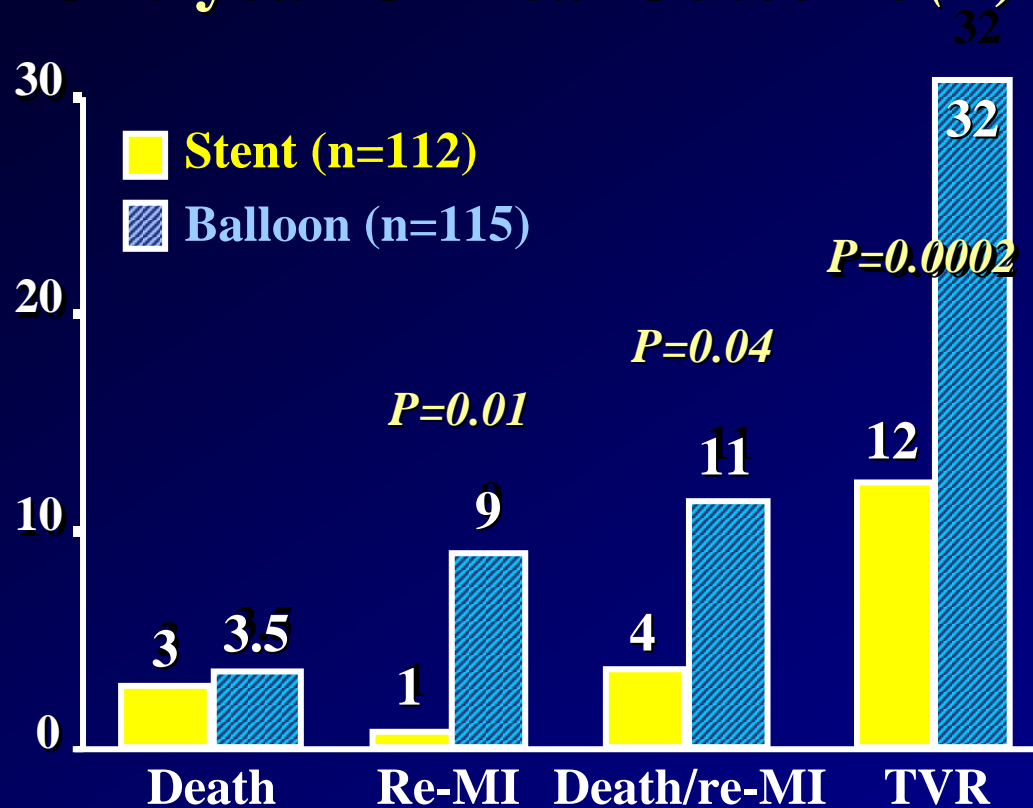
# **AMI Intervention** *in DES Era and Beyond*

**Harry Suryapranata**  
**ISALA Klinieken**  
**Hosp. De Weezenlanden**  
**Zwolle, The Netherlands**



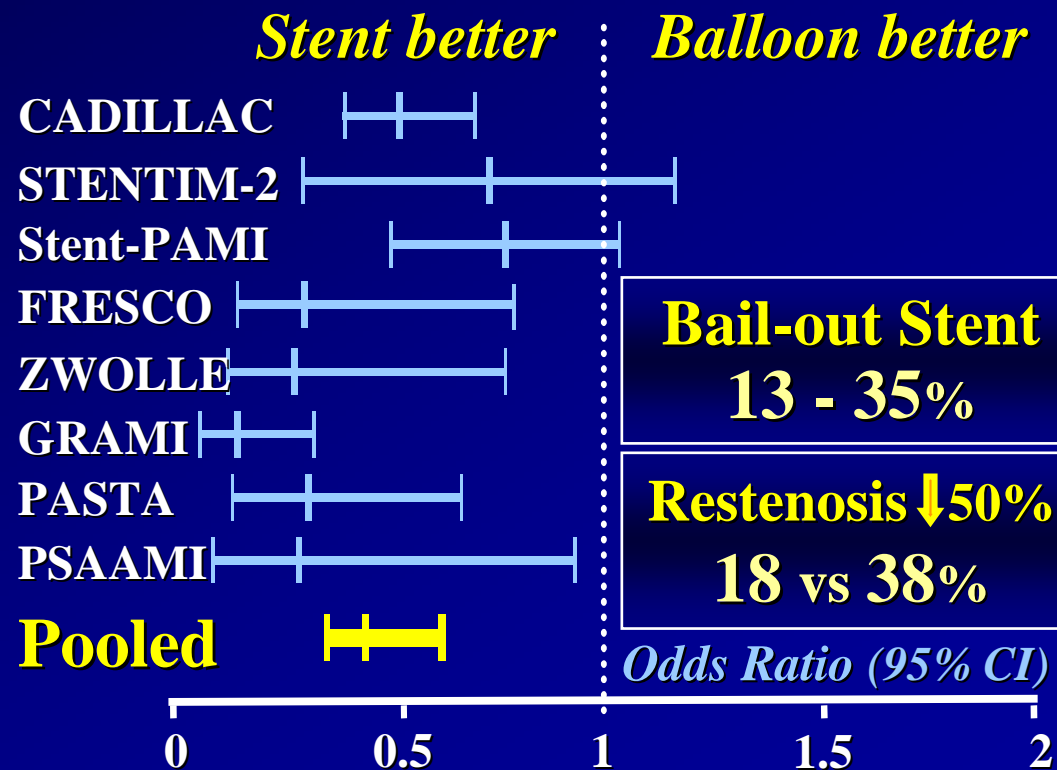
# Primary Stenting vs Balloon Angioplasty for STEMI

## Zwolle-5 Randomized Trial One-year Clinical Outcome (%)



Suryapranata et al. *Circulation* 1998

## Pooled Analysis Event-free Survival (n=3898)



Suryapranata et al. *Heart* 2001

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

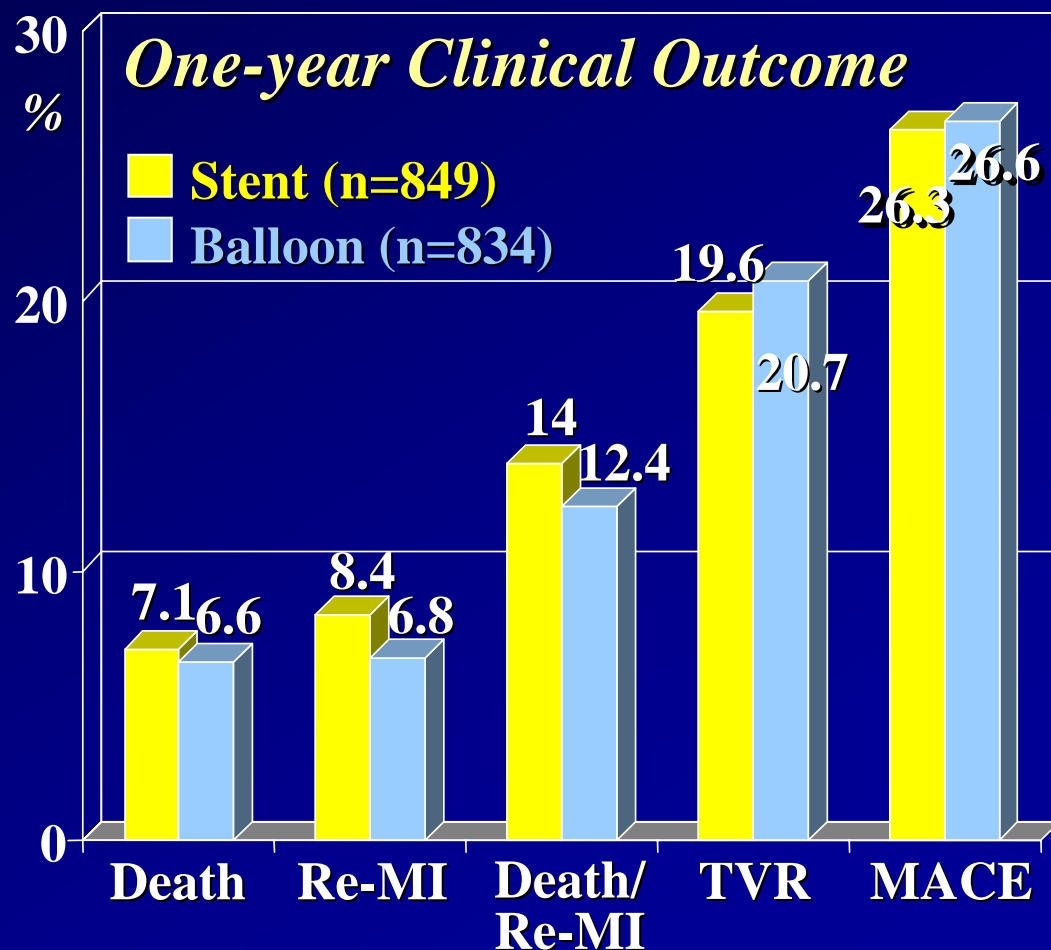
# Is Stenting for STEMI superior to Balloon angioplasty?

Zwolle-6 "Real World" Randomized Trial

## Routine Stent vs Balloon in a consecutive series of unselected pts

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
<b>WITHOUT ABCIXIMAB</b>						
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
<b>WITH ABCIXIMAB</b>						
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
<b>TOTAL (95% CI)</b>	<b>169/3298 (5.1%)</b>	<b>173/3298 (5.2%)</b>		<b>100.00</b>	<b>0.97 [0.78, 1.21]</b>	<b>0.81</b>

De Luca, Suryapranata et al. JACC 2006

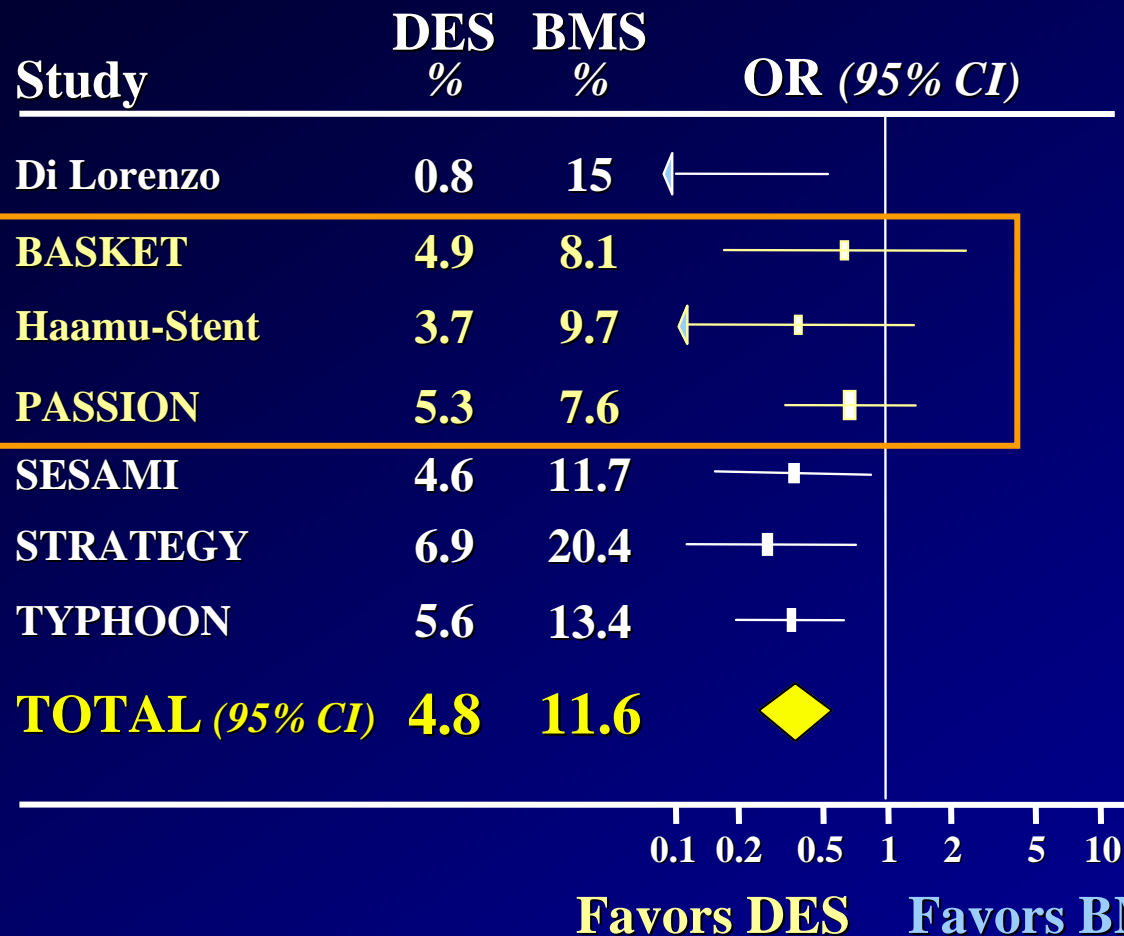
0.1 0.2 0.5 1 2 5 10

STENT BETTER

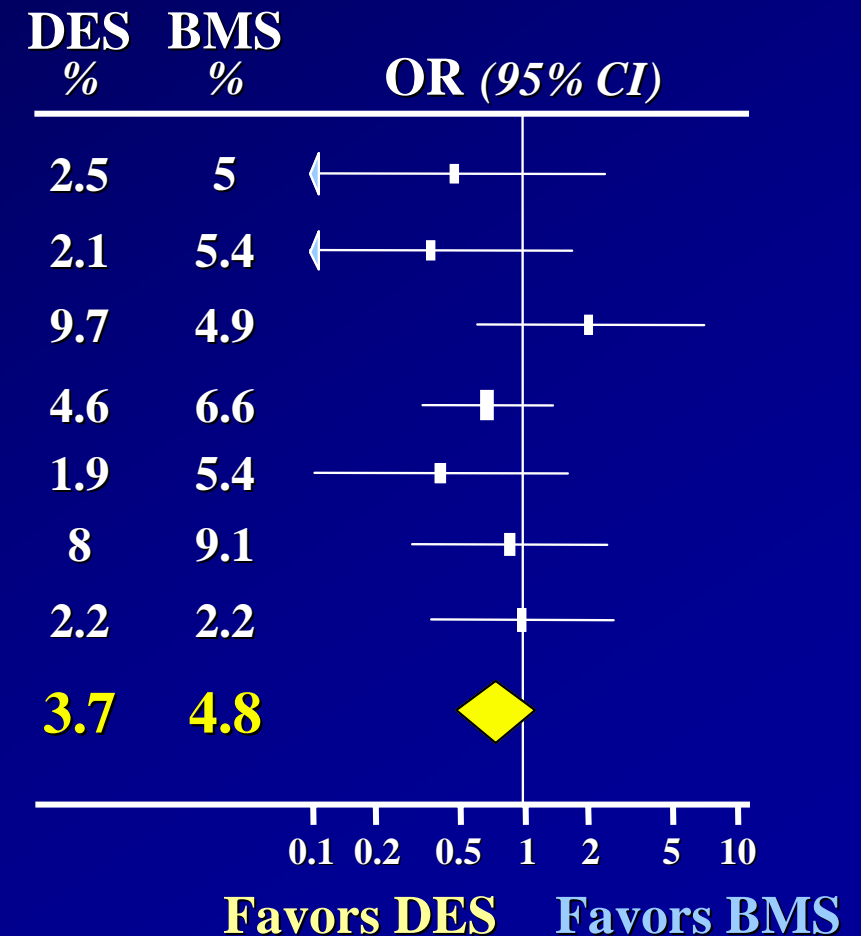
BALLOON BETTER

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

## TVR @ 12 Months



## Mortality @ 12 Months

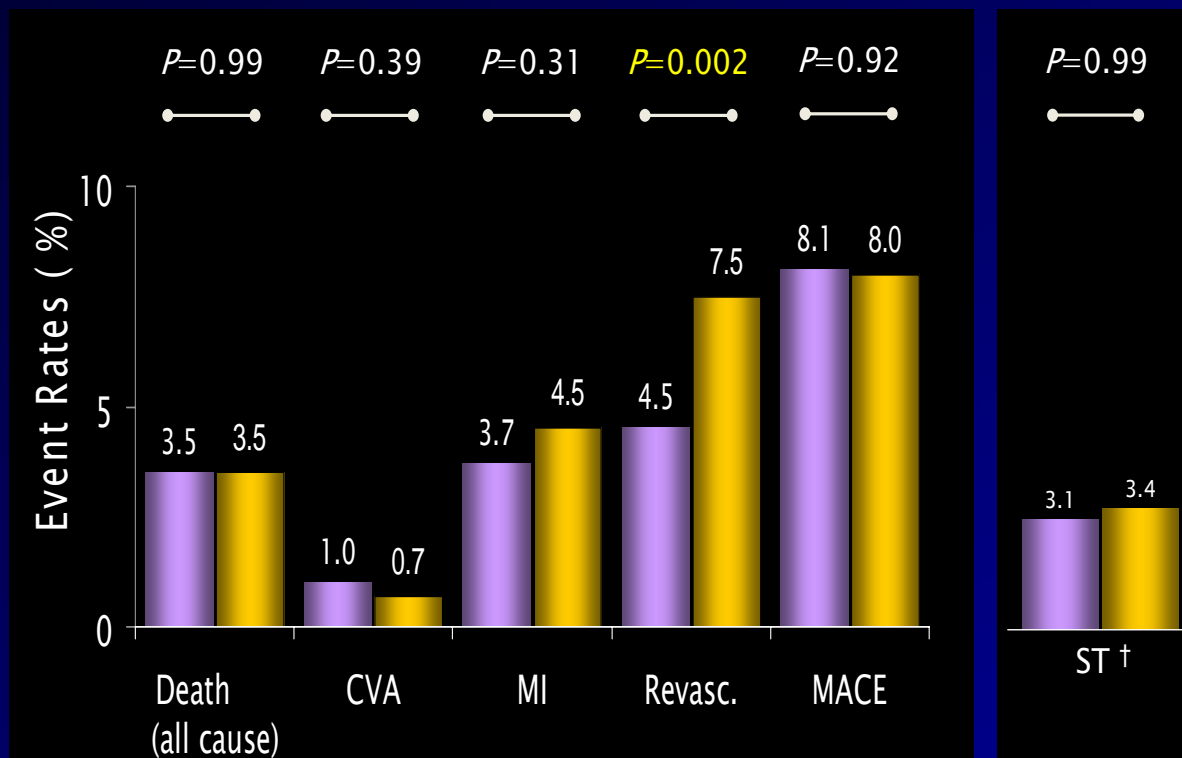


**No difference in Stent Thrombosis (1.2 vs 1.9%) or re-MI (2.3 vs 2.7%)**

# HORIZONSAMI

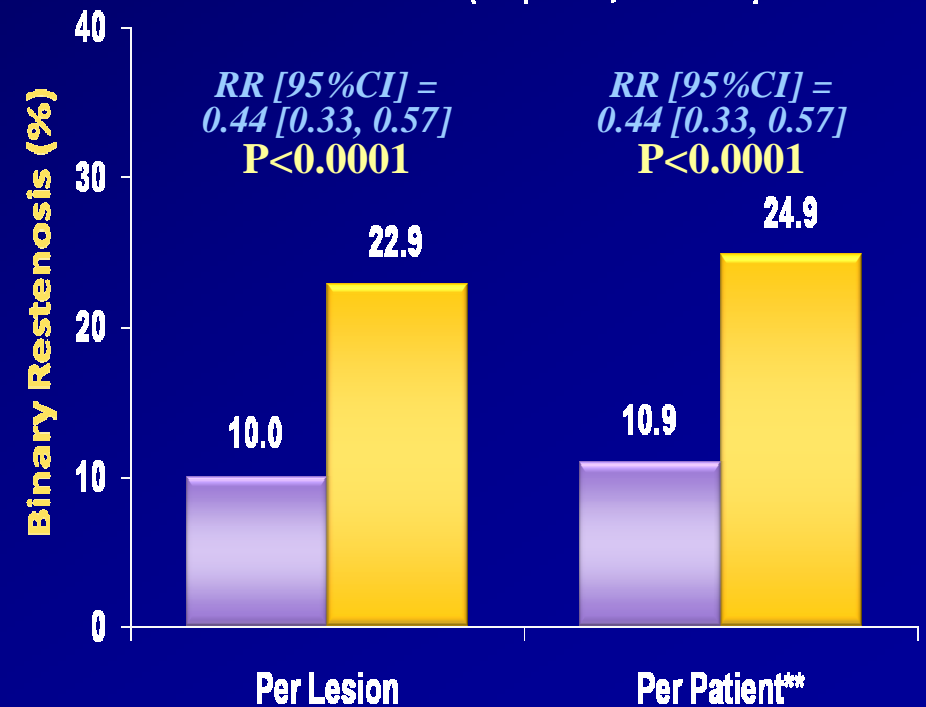
## Harmonizing Outcomes with Revascularization and Stents in AMI

■ TAXUS™ Express™ Stent (n=2,257) ■ Express™ Stent (n=749)



■ TAXUS DES (910 patients, 1081 lesions)

■ EXPRESS BMS (293 patients, 332 lesions)

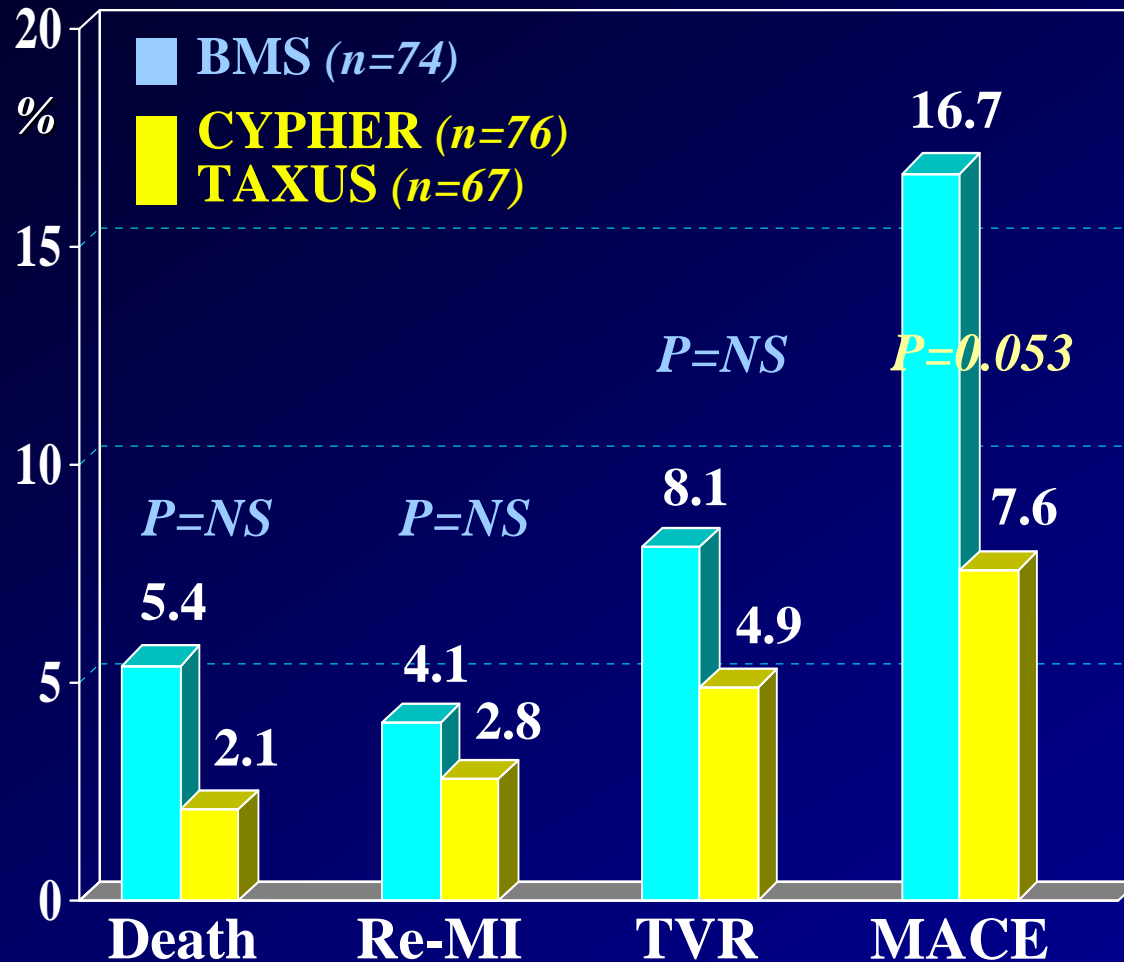


Stone, TCT 2008



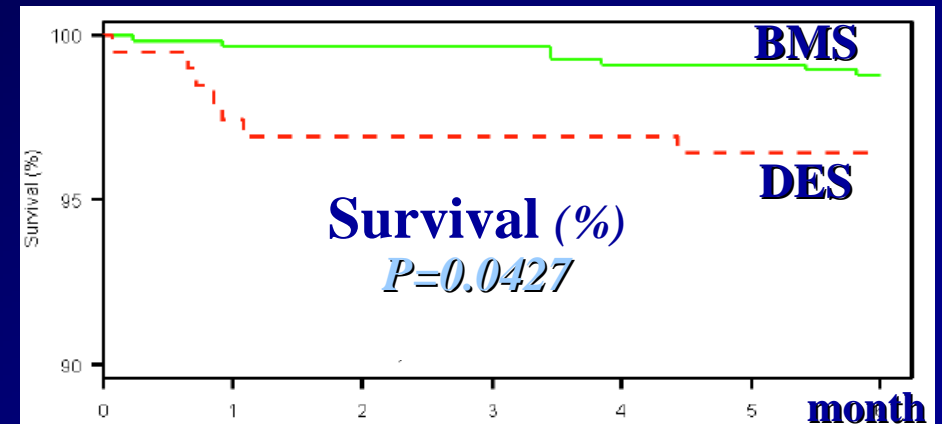
# Drug-Eluting Stent vs Bare Metal Stent for STEMI

## BASKET Trial

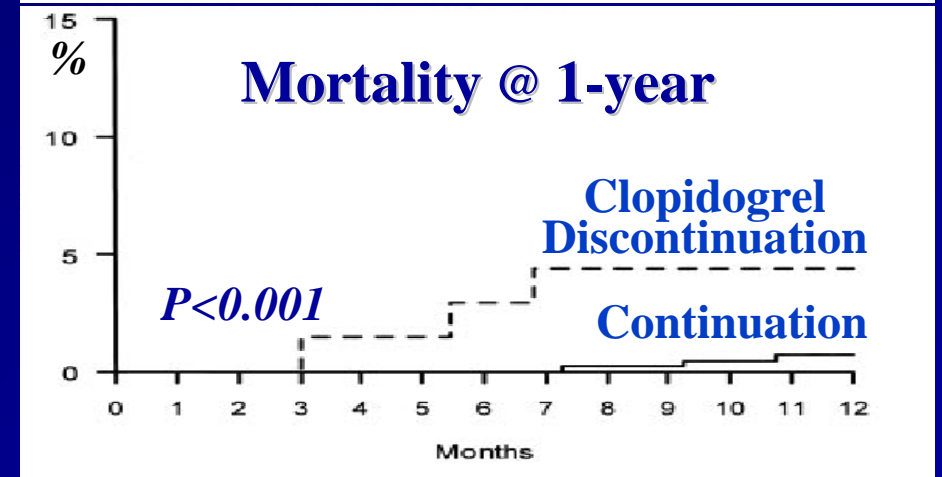


Pittl et al. WCC 2006

## PREMIER Registry



Kernis SJ et al. Am J Cardiol 2005



Spertus et al. Circulation 2006

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*

## Clinical Characteristics

<b>Baseline</b>	<b>TAXUS</b> (n=201)	<b>CYPHER</b> (n=199)	<b>Risk factors</b>	<b>TAXUS</b> (n=201)	<b>CYPHER</b> (n=199)
Age (mean, yrs)	<b>61</b>	<b>61</b>	Diabetes (%)	<b>7</b>	<b>11</b>
Male (%)	<b>74</b>	<b>69</b>	Hypertension (%)	<b>33</b>	<b>28</b>
Anterior MI (%)	<b>43</b>	<b>44</b>	Hyperchol (%)	<b>19</b>	<b>19</b>
Prev MI/PCI (%)	<b>12</b>	<b>13</b>	Smoking (%)	<b>55</b>	<b>50</b>
TIMI risk >3 (%)	<b>25</b>	<b>27</b>	Fam history (%)	<b>45</b>	<b>42</b>





# The **CEZAR** Trial

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

## Angiographic Characteristics

<b>Angio Data</b>	<b>TAXUS (n=201)</b>	<b>CYPHER (n=199)</b>	<b>PCI procedure</b>	<b>TAXUS (n=201)</b>	<b>CYPHER (n=199)</b>
<b>Primary PCI (%)</b>	<b>99</b>	<b>99</b>	<b>Stenting (%)</b>	<b>99</b>	<b>99</b>
<b>Single vessel (%)</b>	<b>69</b>	<b>63</b>	<b>Direct Stent (%)</b>	<b>35</b>	<b>32</b>
<b>IRV: LAD (%)</b>	<b>41</b>	<b>44</b>	<b>Stent size (mm)</b>	<b>3.2</b>	<b>3.2</b>
<b>CX (%)</b>	<b>17</b>	<b>15</b>	<b>Stent length (mm)</b>	<b>24</b>	<b>23</b>
<b>RCA (%)</b>	<b>42</b>	<b>41</b>	<b>Add devices (%)</b>	<b>5</b>	<b>6</b>

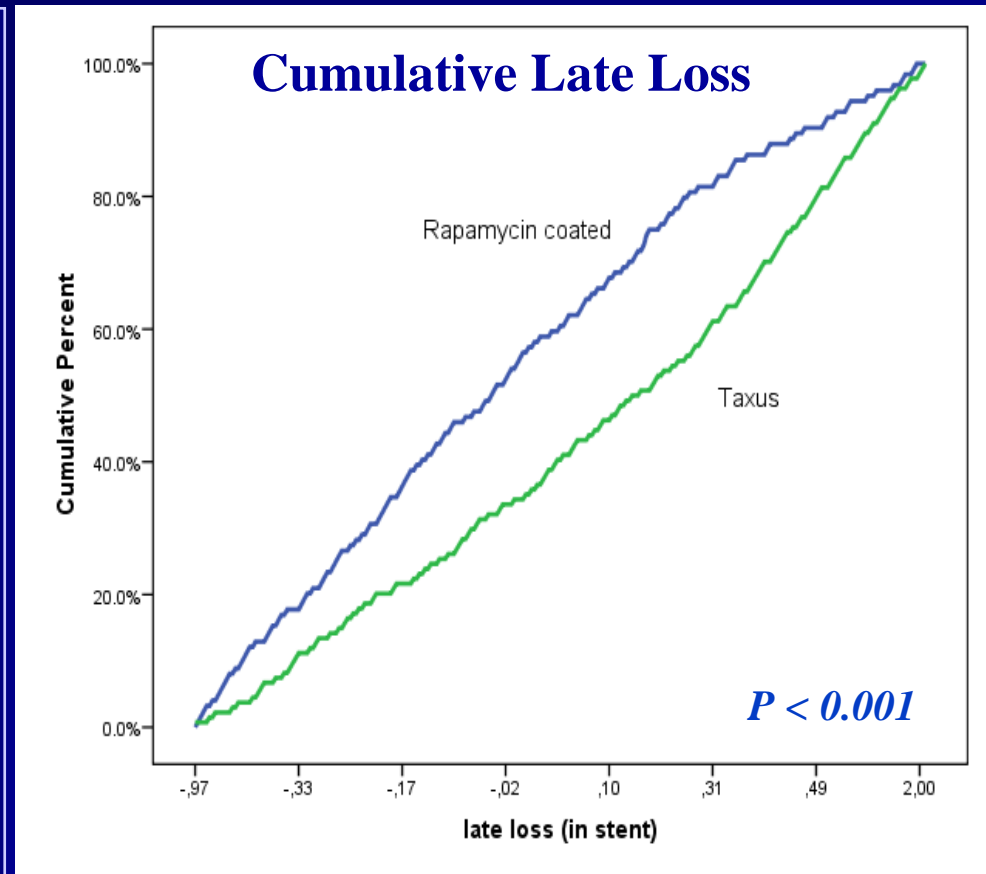


# The **CEZAR** Trial

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

## Quantitative Angiographic Results

<b>9-month F/U</b>	<b>TAXUS (n=136)</b>	<b>CYPHER (n=128)</b>
Mean MLD (mm)	2.26	2.40*
Diam Sten (%)	16.8	9.3#
Ref Diam (mm)	2.75	2.70
Lesion Length (mm)	19.2	18.7
<b>Late Loss (%)</b>	<b>0.21</b>	<b>0.01#</b>
Restenosis (%)	4.4	3.1



\*  $P = 0.22$  #  $P < 0.001$

# The **CEZAR** Trial

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

## Clinical Outcome

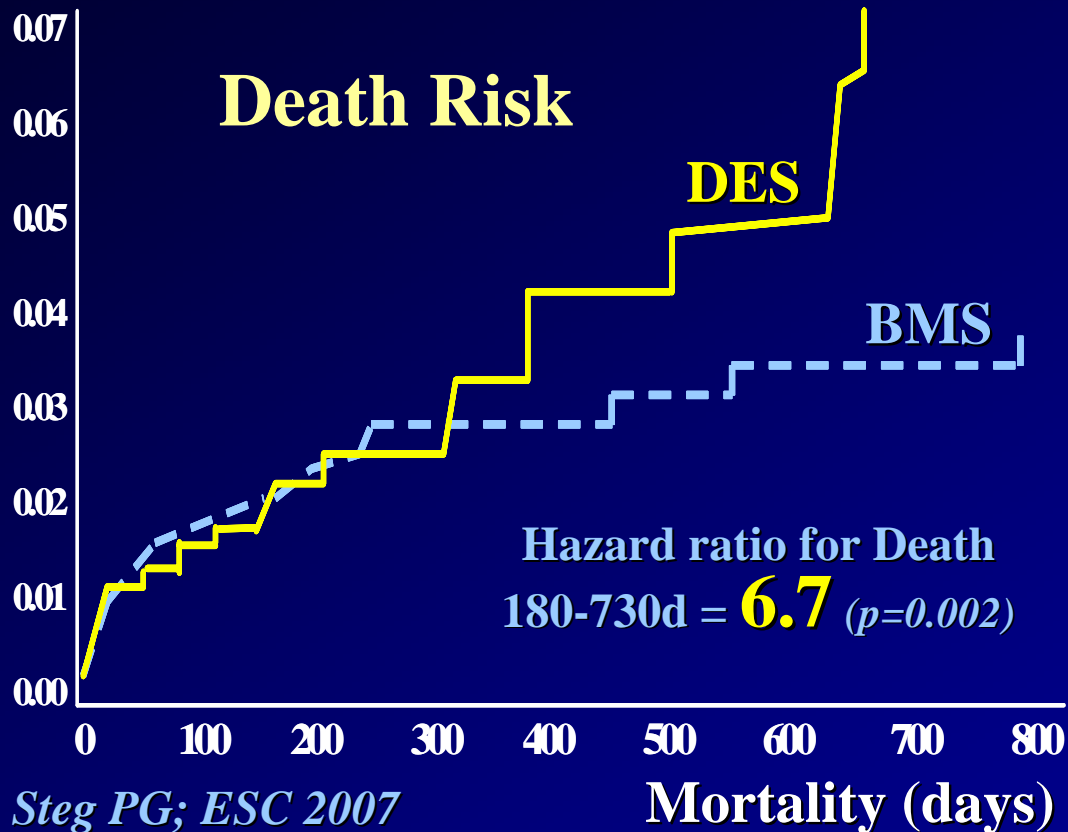
<b>@ 30-day F/U</b>	<b>TAXUS (n=201)</b>	<b>CYPHER (n=199)</b>	<b>@ 1-year F/U</b>	<b>TAXUS (n=201)</b>	<b>CYPHER (n=199)</b>
<b>Death (%)</b>	<b>1.5</b>	<b>1.5</b>	<b>Death (%)</b>	<b>2.7</b>	<b>3.9</b>
<b>Re-MI (%)</b>	<b>1.5</b>	<b>1.5</b>	<b>Re-MI (%)</b>	<b>2.7</b>	<b>2.8</b>
<b>Stent thromb (%)</b>	<b>2.0</b>	<b>2.1</b>	<b>Stent thromb (%)</b>	<b>2.5</b>	<b>2.7</b>
<b>TVR (%)</b>	<b>4</b>	<b>4</b>	<b>TVR (%)</b>	<b>7</b>	<b>6</b>
<b>MACE (%)</b>	<b>6</b>	<b>6</b>	<b>MACE (%)</b>	<b>9.8</b>	<b>10</b>

*Late Stent Thrombosis (30d - 1yr) is low (0.5 vs 0.6%), comparable to BMS*

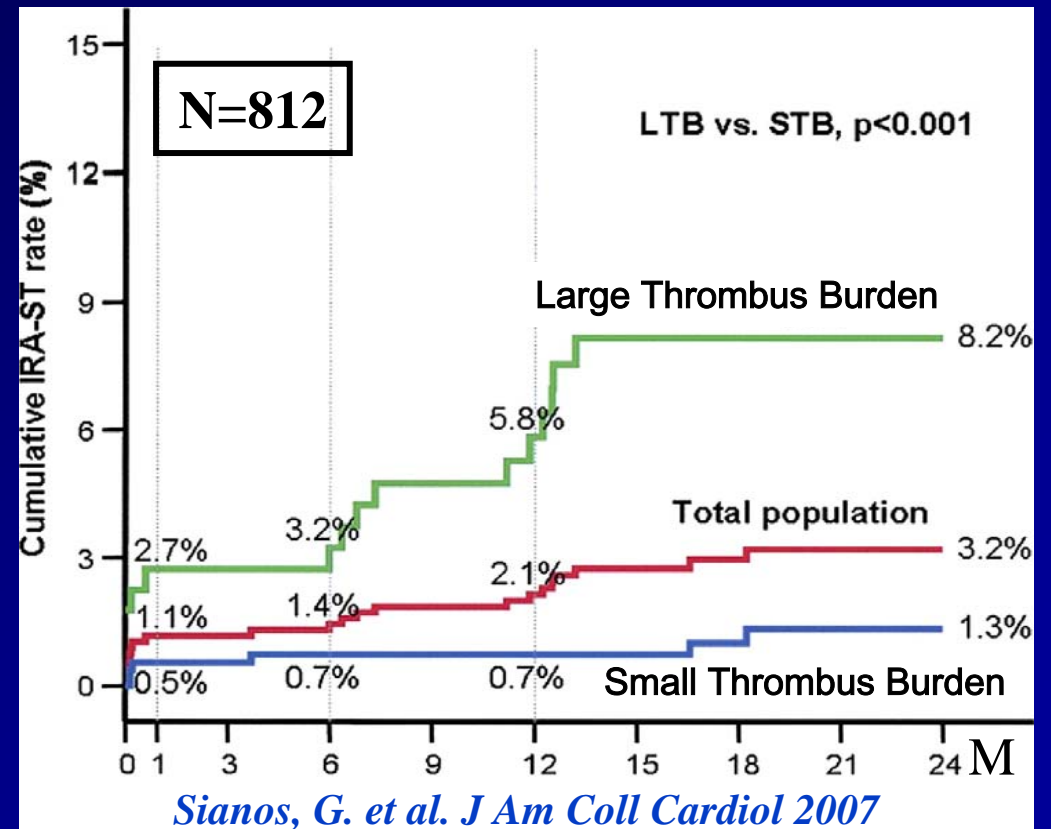
# DES in STEMI: Death Risk *and* Stent Thrombosis

*Inhibition of cell growth after DES may not be the answer in STEMI*

## GRACE Registry (n=2298)



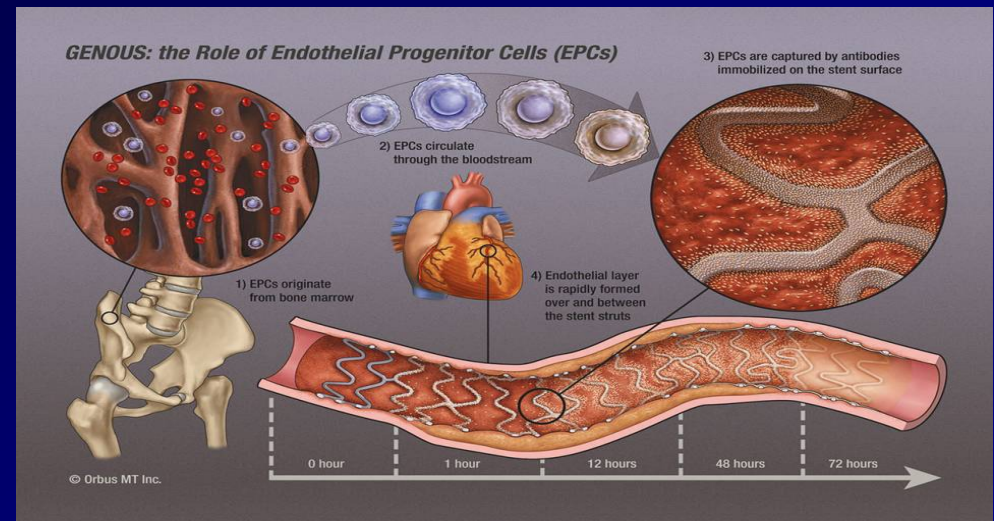
## Stent Thrombosis (%)



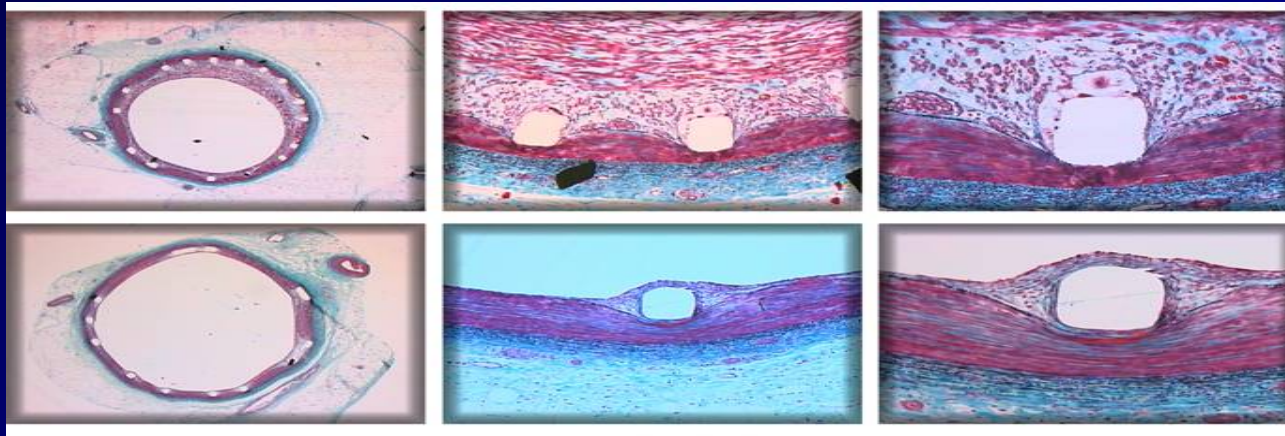
*DES issue on Late Thrombosis: Due to Impaired Re-endothelialization?*

# GENOUS *Endothelial Progenitor Cells* Capture Technology

- EPCs are bone marrow derived, present in circulating blood
- Ability to differentiate into mature endothelial cells, which may accelerate Healing process, protect against thrombus, and minimize restenosis, with safety profile over current *DES*

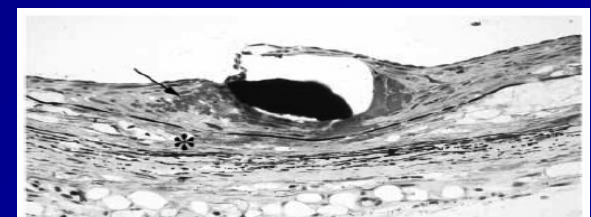
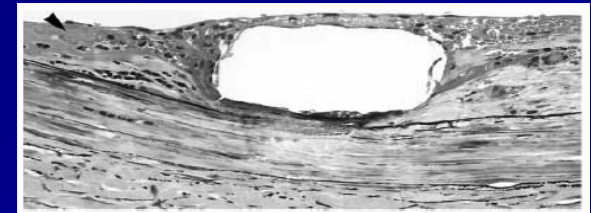


**BMS:** *Typical neo-intimal response to stent injury*



**Genous:** *Complete healing with mature neo-intima*

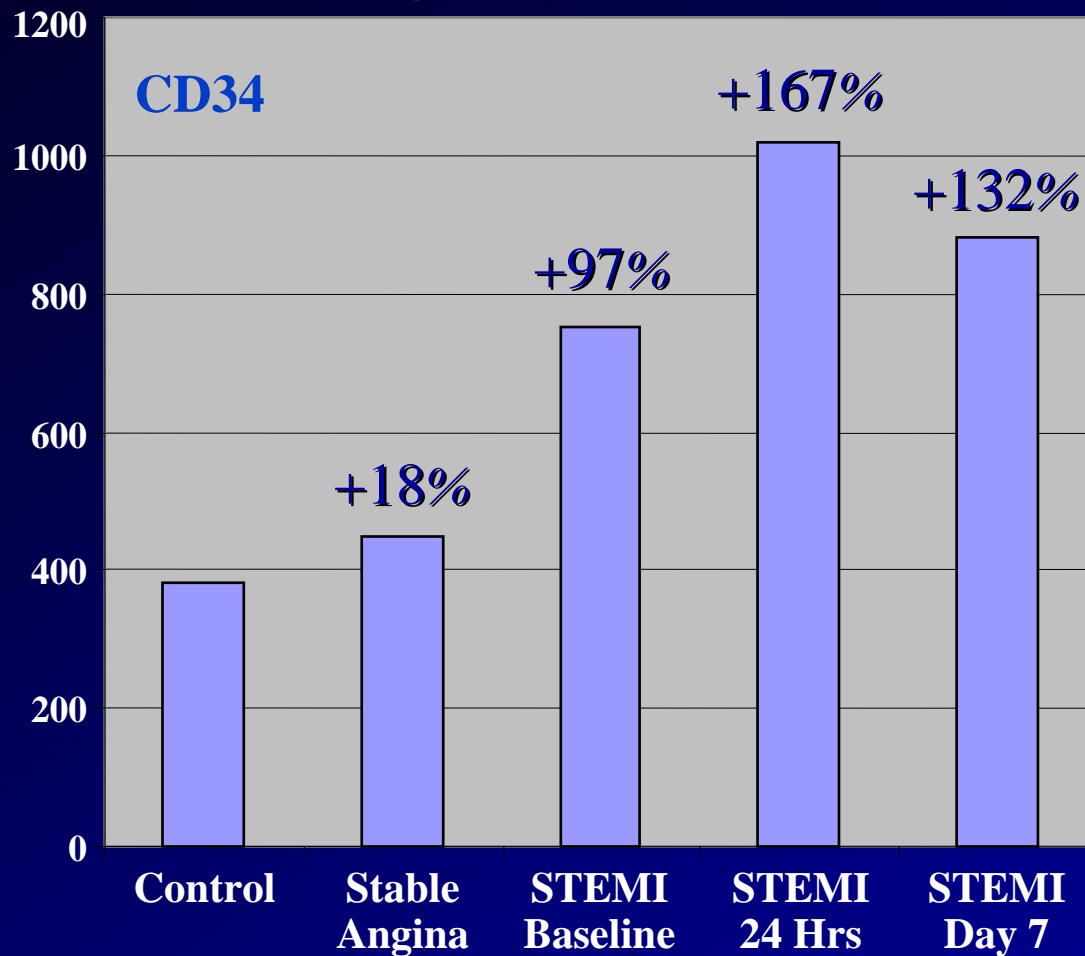
**Brachytherapy**



**Drug-Eluting Stent**

# Circulating *Endothelial Progenitor Cells* in AMI

## Circulating EPC Levels vs Control



- Endogenous Granulocyte-Colony Stimulating Factor (*G-CSF*) and Vascular Endothelial Growth Factor (*VEGF*) are significantly increased in acute phase of MI, and are directly correlated to circulating *CD34+* levels
- Independent predictors of increasing levels of circulating *CD34+* after AMI
  - patients treated with **statins** ( $p < 0.01$ )
  - Patients treated by **P-PCI** ( $P = 0.048$ )
- Associated with improvement in LV function and reduction in infarct size

Wojakowski W et al; Leone AM et al. *Eur Heart J* 2005; Leone AM et al. *International J Cardiol* 2005; Massa M et al. *Blood* 2005; Shintani S et al. *Circ* 2001; Numaguchi Y et al. *Circ* 2006

# Zwolle **GENOUS-AMI** Program

*Safety & feasibility of Genous in Consecutive Series of STEMI Pts  
Pre-treated with statin, aspirin, and clopidogrel (for only 30-d)*

## Interim Results

Baseline			Risk Factors		
Age (yrs)	60	(35-81)	Diabetes	49	11%
Male	343	77%	Hypertension	156	35%
Anterior MI	157	35%	Hyperchol	116	26%
Prev MI/PCI	38	8%	Smoking	174	39%
Killip class I	396	89%	Fam. History	142	32%

*January – October 2008 (n=446)*

# Zwolle **GENOUS-AMI** Program

*Safety & feasibility of Genous in Consecutive Series of STEMI Pts  
Pre-treated with statin, aspirin, and clopidogrel (for only 30-d)*

## Interim Results

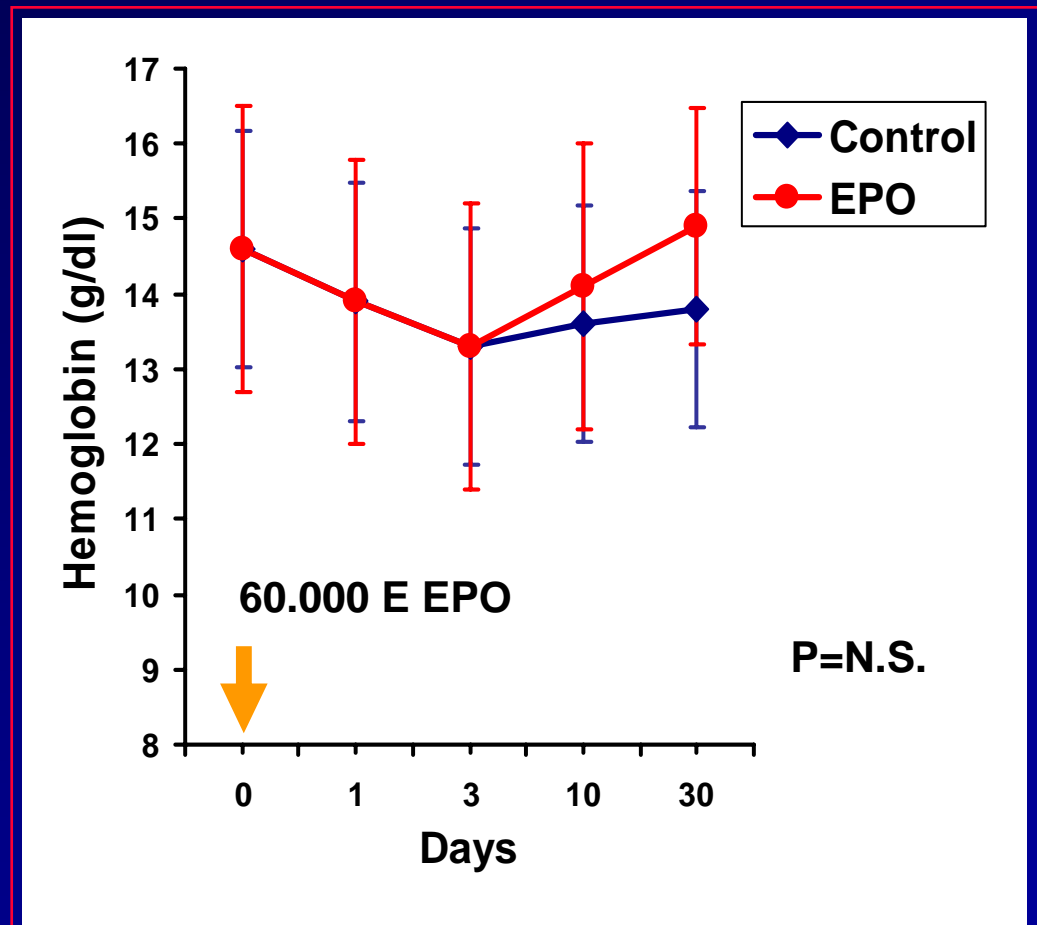
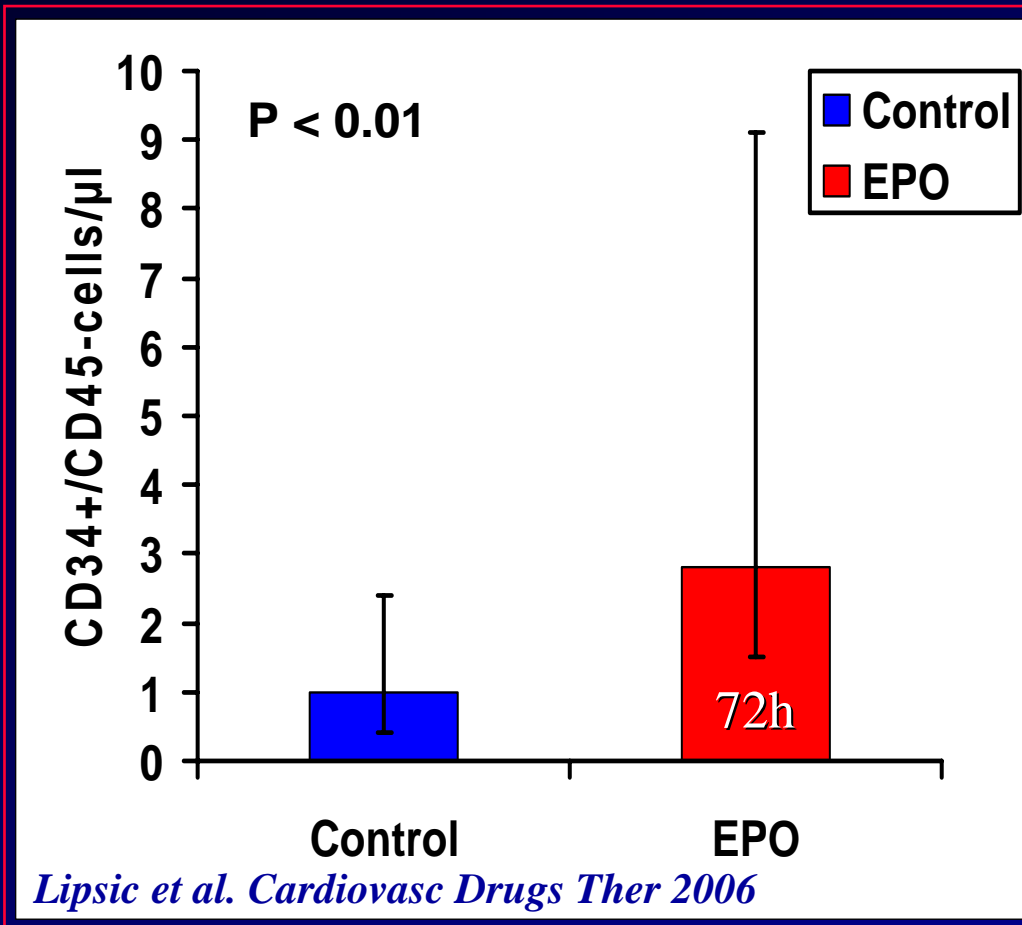
Angiographic Data			Clinical Outcome @ 30-d		
Single-vessel	263	59%	Death	10	2.2%
IRV: LAD	201	45%	Re-MI	3	0.7%
CX	68	15%	<b>SAT</b>	<b>1</b>	<b>0.2%</b>
RCA	177	40%	TVR	15	3.4%
TIMI-3 Post	420	94%	Major Bleeding	3	0.7%

*January – October 2008 (n=446)*



# Effects of a single bolus EPO on EPCs and Hemoglobin

*In PCI for STEMI (n=20)*



*Low dose EPO regulates EPCs without significant effects on RBC*

# **HEBE-III: A Dutch Multicenter Randomized Trial**

*To assess safety & efficacy of a single bolus EPO in STEMI*

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- **Pts undergoing PCI for a first STEMI are randomized to receive a single bolus Eprex (60.000 IU) or placebo, on top of standard therapy**
- **All patients receive the Genous stent, with post-stenting Clopidogrel for only 30-days**
- **Study Endpoints:**
  - **Radionuclide LV function at 6 wks**
  - **Late Loss at 6 month angio F/U**
  - **Infarct size and MACE**

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*Previous studies have shown safety of a single bolus EPO in STEMI*

**DEBORA: Drug Eluting Balloon Open Randomized trial in AMI**  
*Safety and Efficacy of the Genous EPC Capture Stent Pre-dilated with Paclitaxel-Eluting Balloon vs Conventional Balloon in STEMI Patients*

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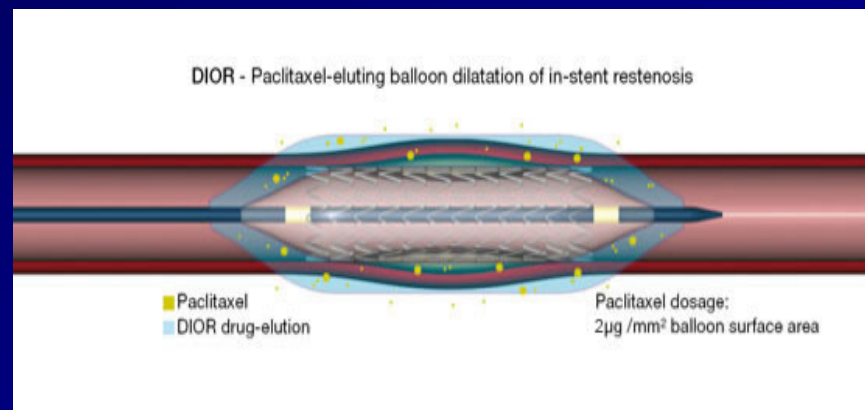
- A prospective single-center randomized trial to assess the safety & efficacy of the Genous EPC capture stent, pre-dilated with DEB vs conventional balloon in STEMI
- Patients undergoing PCI for STEMI are randomized to pre-dilatation with DEB (DIOR) *or* conventional balloon before Genous stent implantation (*Clopidogrel for 3 months*)
- Clinical F/U at 30-d, 9 and 12 months; F/U angio at 9M
- **Primary endpoint:** Late Loss @ 9-M angio F/U by QCA  
**Secondary endpoints:** MACE @ 30d, 9-12M; ISR @ 9-M



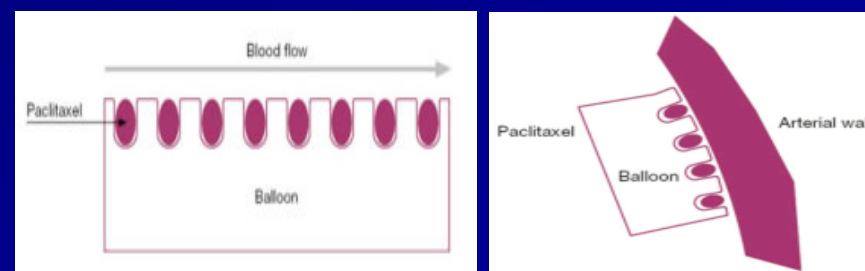
# DEBORA: Drug Eluting Balloon Open Randomized trial in AMI

## Safety and Efficacy of the Genous EPC Capture Stent Pre-dilated with Paclitaxel-Eluting Balloon vs Conventional Balloon in STEMI Patients

- DIOR - a Drug-Eluting Balloon - has recently been developed to reduce restenosis. This is a balloon catheter with microporous surface containing Paclitaxel (*2ug/mm<sup>2</sup> balloon surface*)
- Drug-Eluting Balloon has been shown to be safe & effective in pts with in-stent restenosis, bifurcation lesions, and in small vessels
- Therefore, the use of Genous EPC capture stent (*for rapid stent re-endothelialization*), after pre-dilatation with Paclitaxel-eluting balloon (*to reduce restenosis rate*), seems to be an ideal combination for the treatment of STEMI pts



### Microporous balloon surface structure



# CONCLUSION

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- Although DES for STEMI seems to be safe and feasible, the safety issue remains to be established
- DES implantation in a setting of large thrombus burden may result in an increased risk of subacute and late stent thrombosis, despite prolonged dual antiplatelet therapy
- EPC capture technology (*for rapid re-endothelialization by capturing patient's own EPCs*) promotes healing process, and may prevent these adverse events
- The healing process may be further enhanced by the use of Statins and Erythropoietin (*HEBE-3*); whereas the use of adjunctive DEB may reduce in-stent restenosis (*DEBORA*)

