# ON-TIME

## On*going* T*irofiban* I*n* M*yocardial Infarction* E*valuation*

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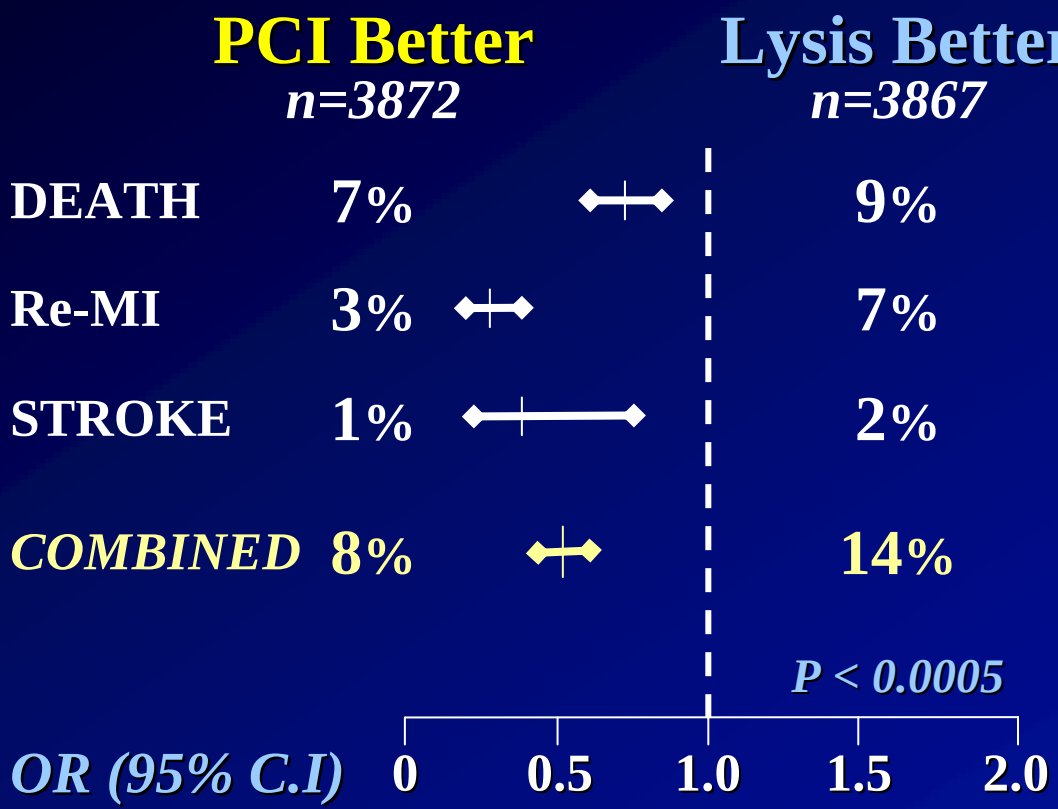
**Isala Klinieken, Zwolle, The Netherlands**
***On behalf of the ON-TIME Study Group***

# Primary PCI vs Thrombolysis for AMI

## 23 Randomized Trials (n=7739)

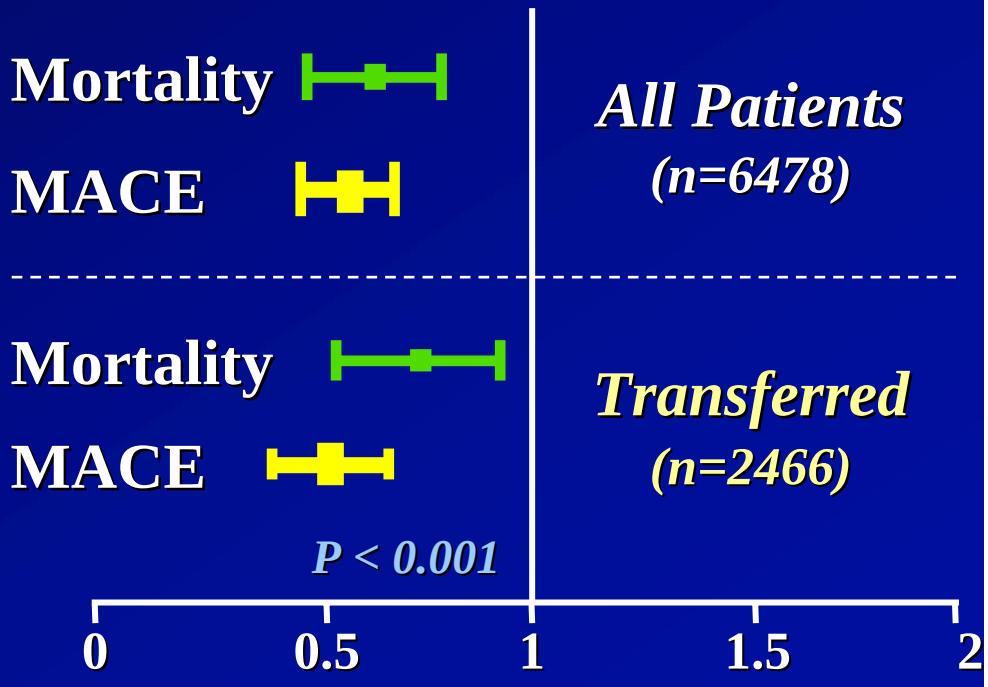
*Pooled Analysis - Outcome at 30-d*




Keeley et al. Lancet 2003

## Transferred for Primary PCI

*Pooled Analysis - OR (95% C.I)*

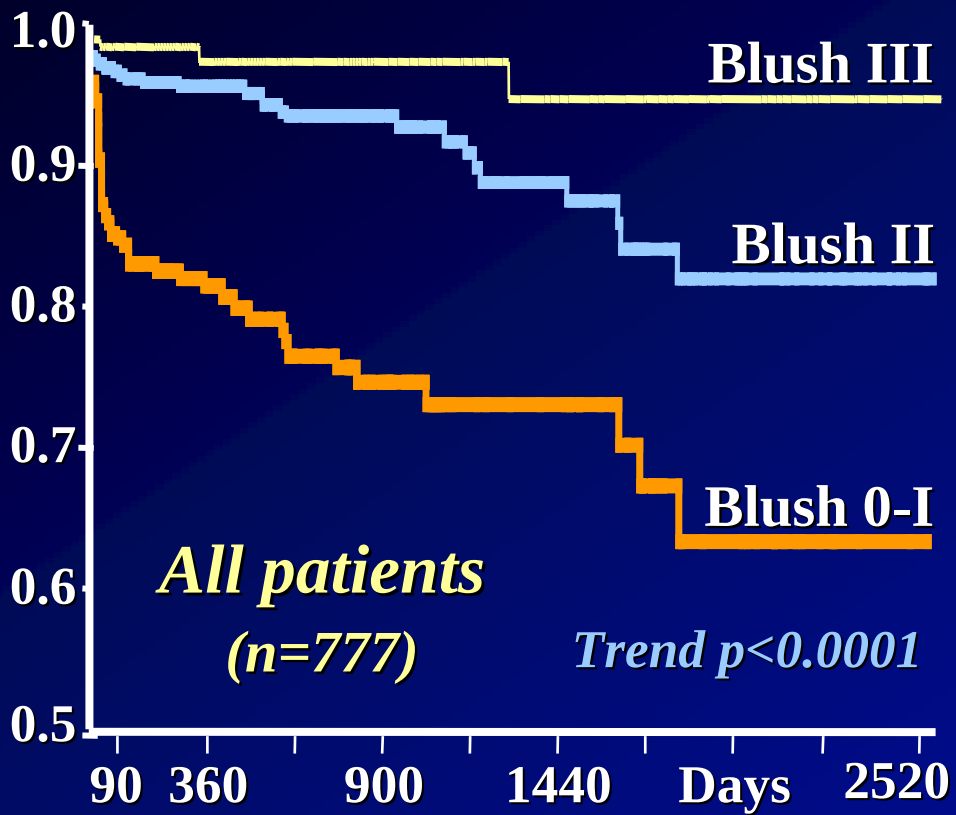



Zijlstra Eur Heart J 2003

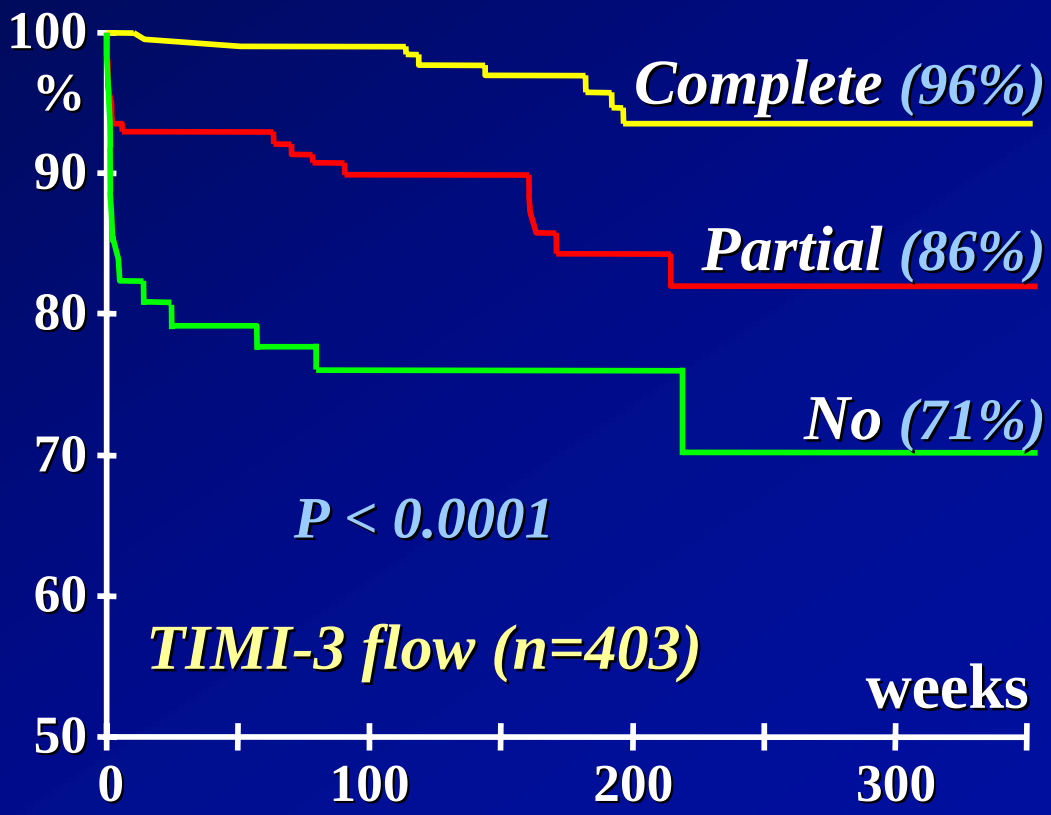
# Myocardial Blush Grade and ST-Segment Resolution

## *Zwolle Randomized Trial*

### MBG & Survival at 7 yrs




### ST Resolution & Survival at 7 yrs

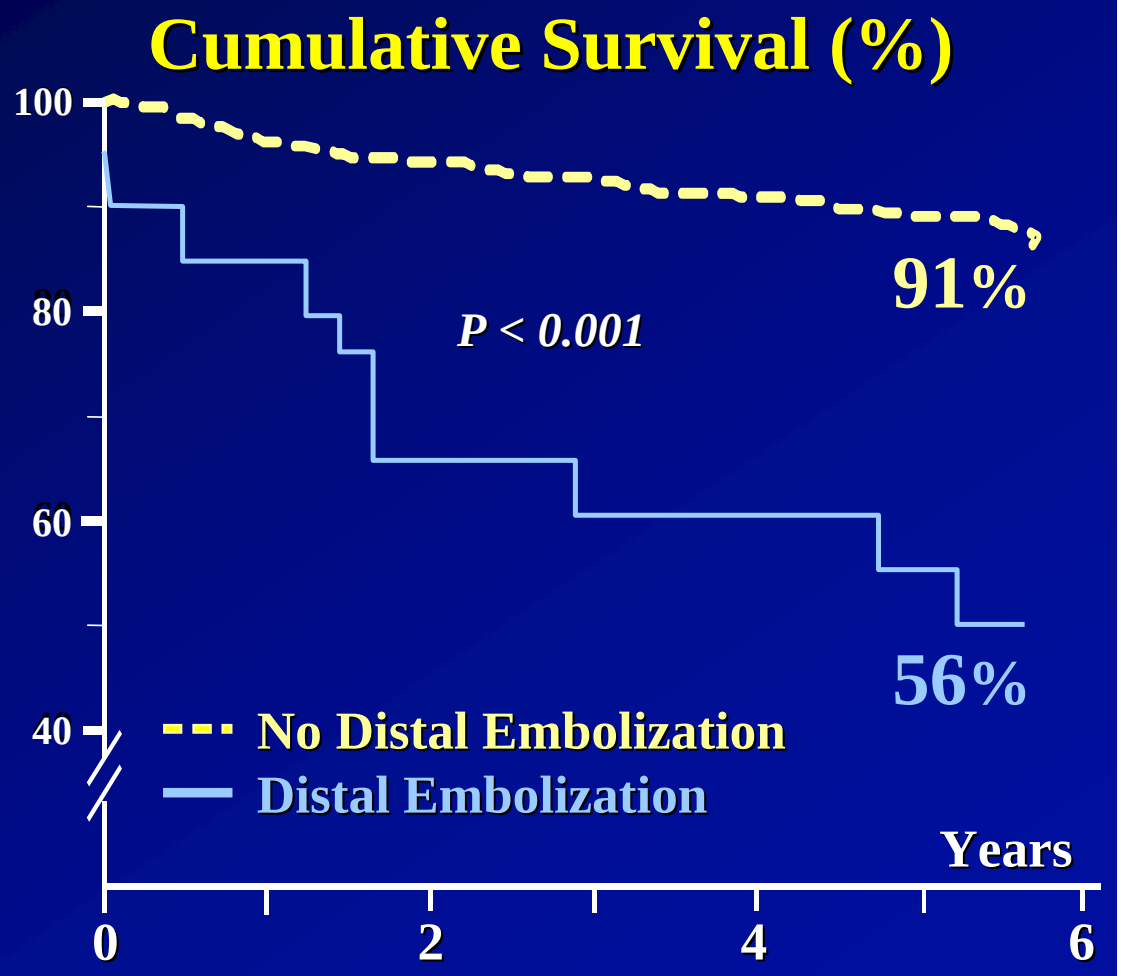



*A simple pair of ECG and initial angiogram are effective in assessment of reperfusion success, and in predicting long-term clinical outcome*

# *Zwolle Randomized Trial*
# Distal Embolization

| *Incidence: 16%* | *Emboli* (n=102) | *No Emboli* (n=529) |
|---|---|---|
| TIMI-3 flow (%) | 73 | 92 |
| MBG II-III (%) | 32 | 83 |
| ST resolution (%) | 9 | 60 |
| LVEF (%) | 42 | 51 |
| LDHQ72 (U/L) | 1612 | 847 |
| IIb/IIIa Inh (%) | 48 | 26 |
| Stent (%) * | 63 | 58 |

** ns*



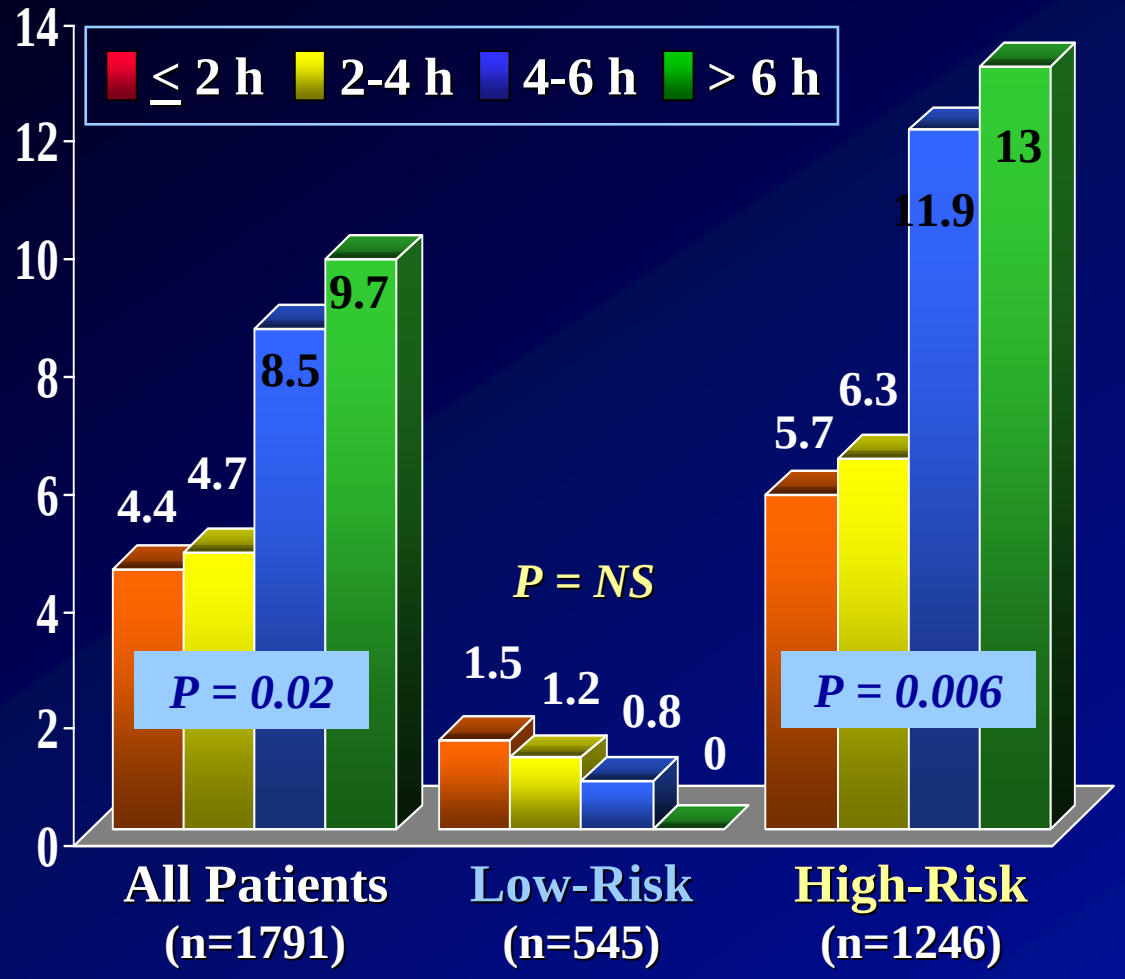

***Treatment strategy:*** • Mechanical approach *(Embolic Protection Devices)*
• Pharmacological approach *(GP-IIb/IIIa inh, lytics)*

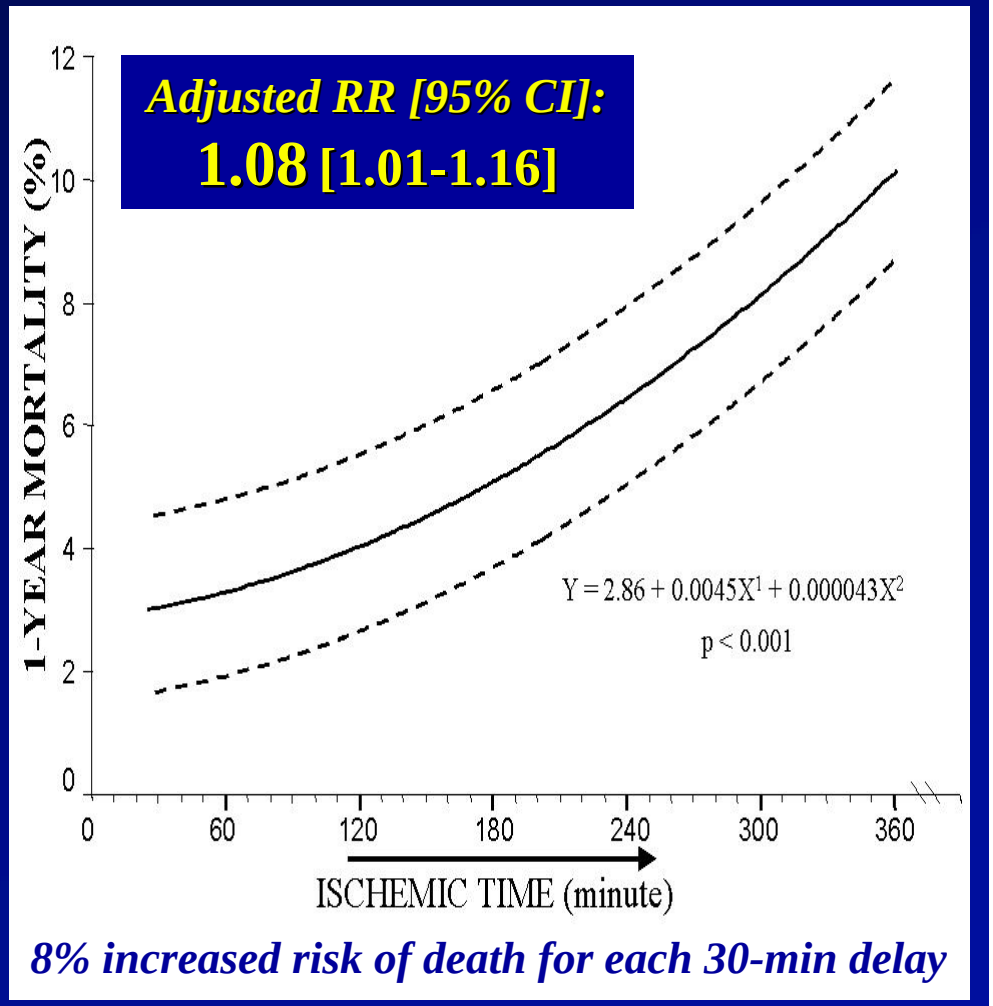
# *Zwolle Randomized Trial*
# Predictors of Impaired Myocardial Perfusion after Primary PCI

| ***Multivariate Analysis*** *(n=1527)* | *Odds Ratio [95% CI]* | | *P* |
|---|---|---|---|
| Pre-procedural TIMI 0-1 | 2.65 | [1.89-3.70] | <0.0001 |
| Anterior MI | 2.15 | [1.64-2.80] | <0.0001 |
| Ischemic Time (min) | 1.06 | [1.03-1.10] | <0.0001 |
| Killip class > 1 | 1.78 | [1.15-2.74] | 0.009 |
| Age (yrs) | 1.01 | [1.00-1.02] | 0.047 |

*De Luca, Suryapranata et. al. submitted*

# Zwolle Randomized Trial
# Symptom-To-Balloon and One-year Mortality (%)




*8% increased risk of death for each 30-min delay*

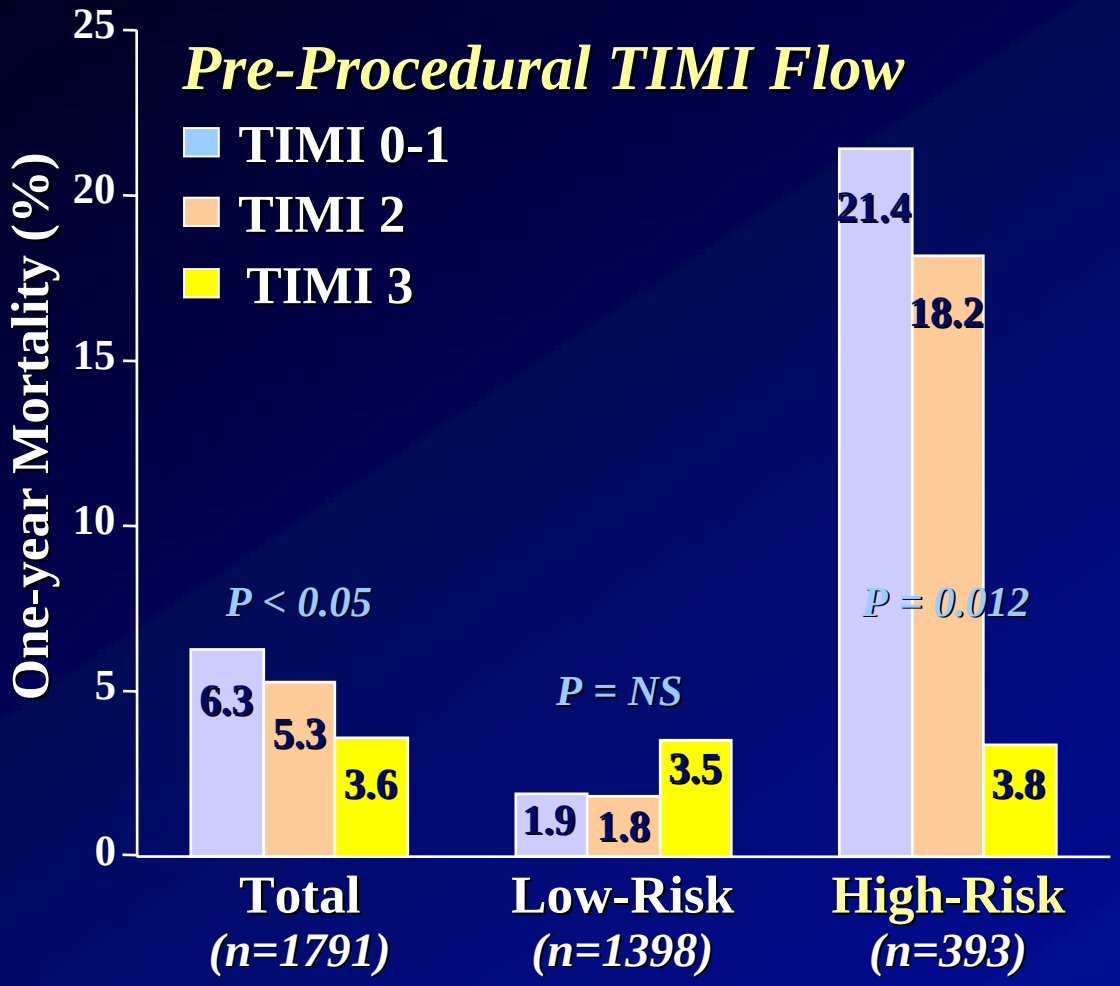
*De Luca, Suryapranata et. al. JACC 2003*

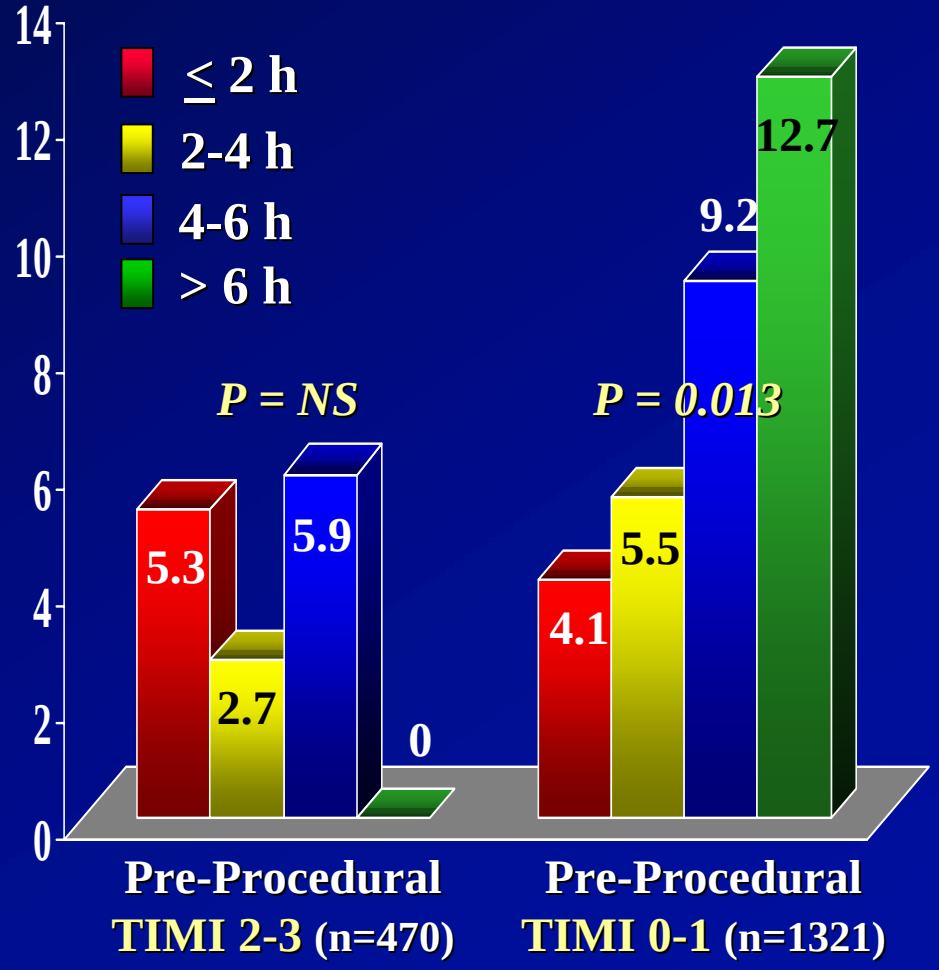
*De Luca, Suryapranata et. al. Circulation 2004*

***Every minute delay counts: not only for thrombolysis, but also for primary PCI***

# *Zwolle Randomized Trial*

# Pre-Procedural TIMI Flow and Mortality at One-Year



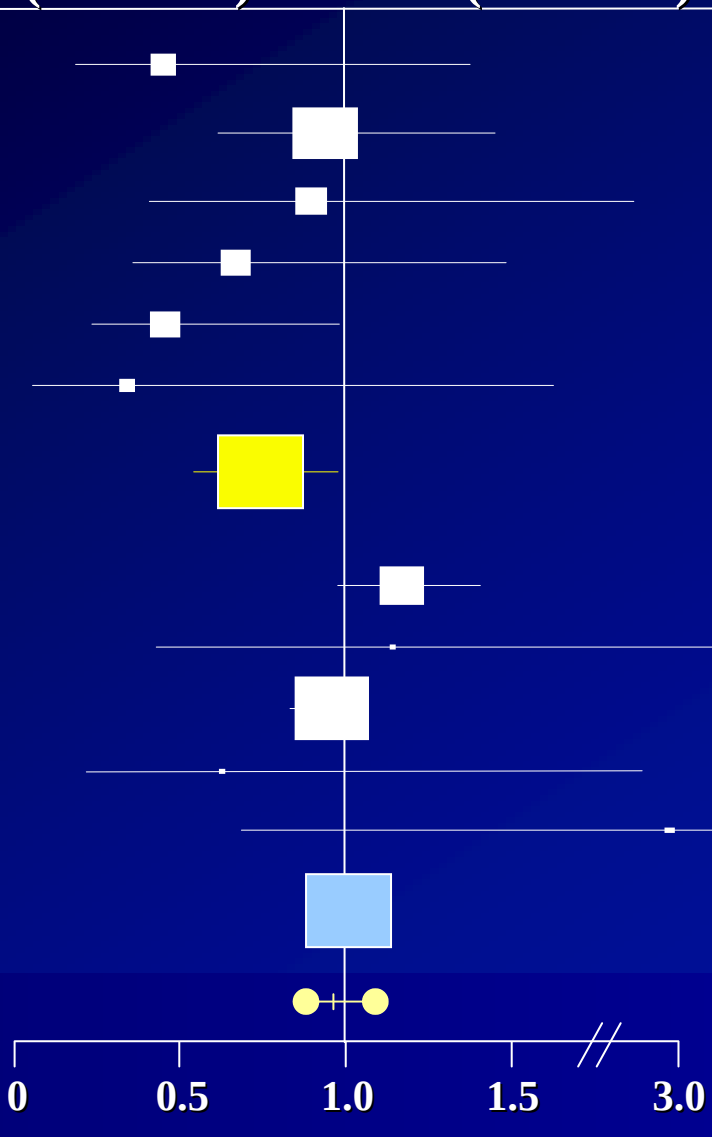




*De Luca, Suryapranata et. al. JACC 2004*

***The need for EARLY TIMI-3 flow BEFORE PCI procedure***

# *Meta-analysis: Adjunctive IIb/IIIa Inhibitor on 1-year Mortality*

| *Randomized Trials (n=27555)* | n | ABCIXIMAB (n=12835) | CONTROL (n=14720) | P | RR % | NNT |
|---|---|---|---|---|---|---|
| ADMIRAL | 300 | | | ns | 3.9 | 25.6 |
| CADILLAC | 2082 | | | ns | 0.2 | 500 |
| RAPPORT | 483 | | | ns | 0.4 | 250 |
| ISAR-2 | 401 | | | ns | 2.5 | 400 |
| ACE | 400 | | | 0.04 | 5.5 | 18.2 |
| Petronio et al | 89 | | | ns | 8.8 | 15.1 |
| ***All PCI*** | **3755** | | | **0.034** | **1.6** | **62.5** |
| ASSENT III | 6095 | | | ns | - | - |
| ENTIRE | 483 | | | ns | - | - |
| GUSTO V | 16588 | | | ns | 0.3 | 333.3 |
| SPEED | 300 | | | ns | 1.8 | 55.5 |
| TIMI 14 | 334 | | | ns | - | - |
| ***All Lysis*** | **23800** | | | **ns** | **-** | **-** |
| **OVERALL** | **27555** | | | **ns** | **0.4** | **250** |




*ODDS RATIO [95% C.I]*

*De Luca, Suryapranata; in press*


# *Ongoing Tirofiban In Myocardial Infarction Evaluation*

**A prospective multicenter randomized trial to compare *pre-hospital* vs *cathlab* initiation of Tirofiban on the initial IRV patency in pts with AMI who are candidates for primary PCI**

***ON-TIME Study Group***

# Ongoing Tirofiban In Myocardial Infarction Evaluation

**Acute Myocardial Infarction**
**identified in ambulance or referral center**

**Early** | **Late**

**Tirofiban** — *10 μgr/kg bolus, 0.15 μgr/kg/min*

*5000 IU heparin*
*500 mg aspirin i.v*

**Placebo**

**Transportation**

**Angiogram** — **PCI center** — **Angiogram**

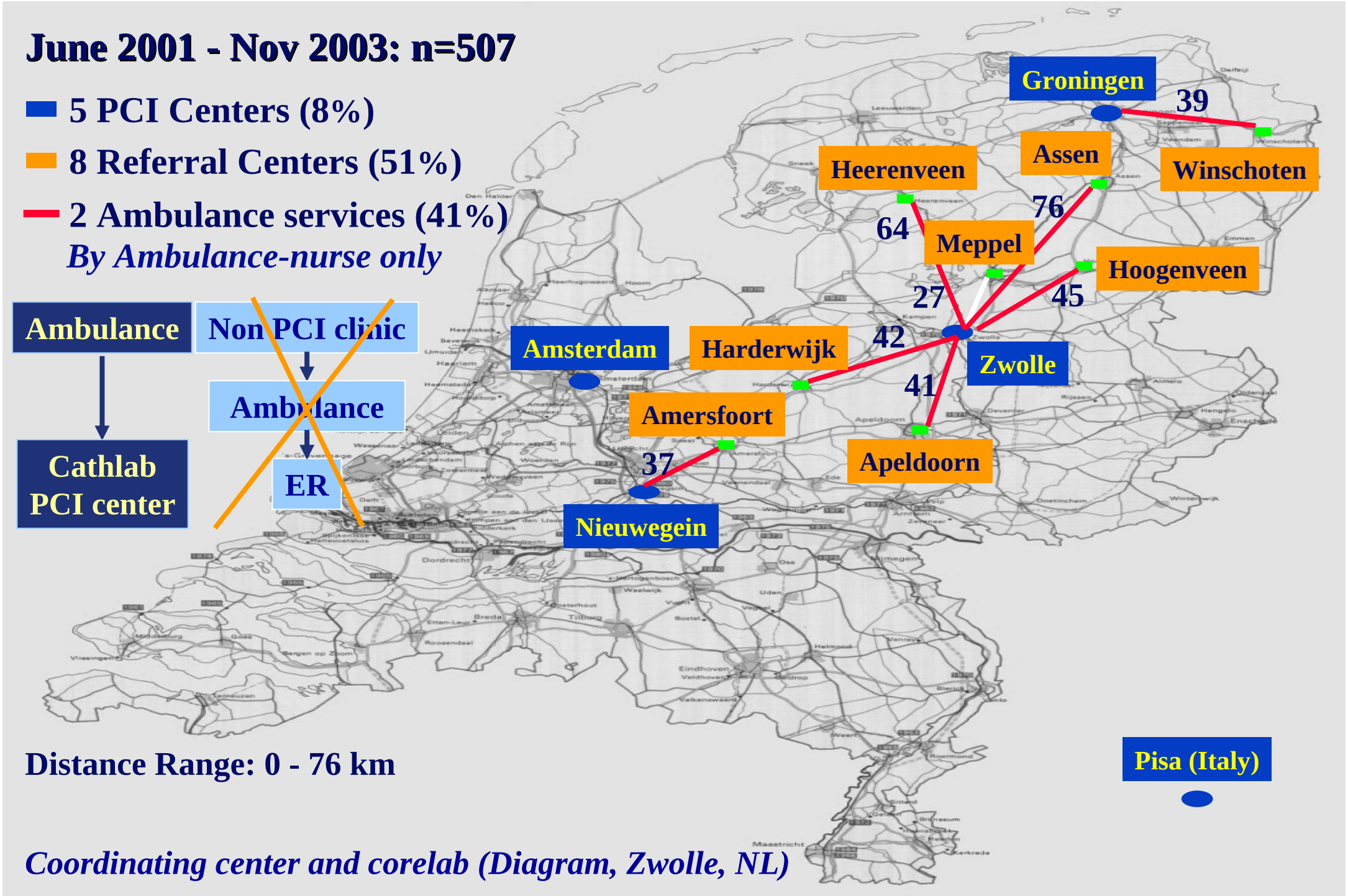
*Second bolus*

**Placebo** — **Tirofiban**

**PCI**

***Open label Tirofiban infusion (24h)***

*LMWH (48h), Clopidogrel (300mg loading + 75mg 30-d), aspirin, B-blocker, statin, ACE-inh*


June 2001 - Nov 2003: n=507
5 PCI Centers (8%)
8 Referral Centers (51%)
2 Ambulance services (41%)
By Ambulance-nurse only
Ambulance
Cathlab PCI center
Non PCI clinic
Ambulance
ER
Groningen
39
Winschoten
Heerenveen
Assen
64
76
Meppel
Hoogenveen
27
45
42
Amsterdam
Harderwijk
Zwolle
41
Amersfoort
Apeldoorn
37
Nieuwegein
Distance Range: 0 - 76 km
Pisa (Italy)
Coordinating center and corelab (Diagram, Zwolle, NL)

# Ongoing Tirofiban In Myocardial Infarction Evaluation

| Baseline Data | Early (n=251) | Late (n=256) |
|---|---|---|
| Age (mean, yr) | 63 | 61 |
| Male gender (%) | 79 | 80 |
| Prev MI (%) | 6 | 10 |
| Diabetes (%) | 10 | 11 |
| Hypertension (%) | 27 | 30 |
| Smoking (%) | 62 | 68 |
| Anterior MI (%) | 44 | 47 |
| Killip > 1 (%) | 16 | 15 |

**June 2001 - Nov 2003**

**507**

→ **No AMI (n=14)**
*Misinterpretation computer algorithm in the ambulance*

**493** **AMI confirmed**

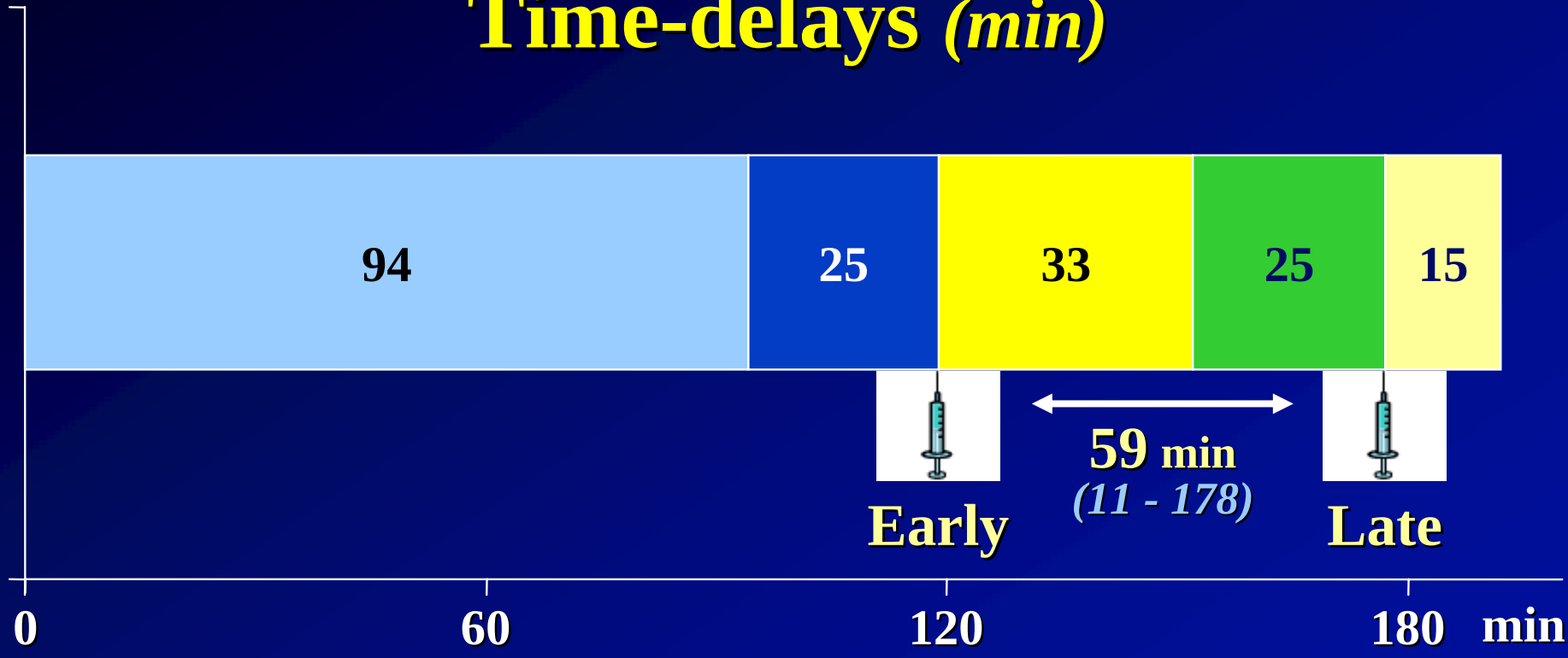
→ *2 died before angio*
*4 inadequate TIMI*

**487** **Primary Endpoint**
*(99%)*

ON-TIME
Tirofiban In Myocardial infarction Evaluation

# *Ongoing Tirofiban In Myocardial Infarction Evaluation*

## Time-delays *(min)*




*No difference in total time-delay between the groups (196 vs 199 min)*

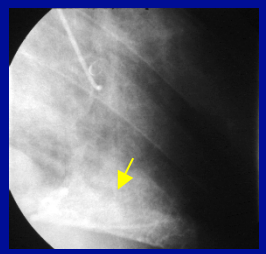
24/7 ON-TIME Tirofiban In Myocardial infarction Evaluation

*Ongoing Tirofiban In Myocardial Infarction Evaluation*

# Angiographic Results

| Pre-PCI | Early (n=243) | Late (n=244) | P |
|---|---|---|---|
| TIMI 3 (%) | 19 | 15 | 0.22 |
| TIMI 2 or 3 (%) | 43 | 34 | 0.04 |
| **TIMI 0 (%)** | **44** | **59** | **0.0013** |
| Thrombus (%) | 25 | 32 | 0.06 |
| Fresh Occl (%) | 35 | 41 | 0.20 |
| **Combined (%)** | **60** | **73** | **0.002** |

| Post-PCI | | Early (n=243) | Late (n=244) |
|---|---|---|---|
| TIMI-3 (%) | | 89 | 91 |
| MBG (%) | 0-I | 13 | 12 |
| | II | 37 | 35 |
| | III | 51 | 53 |
| CTFC (%) | | 27 | 26 |

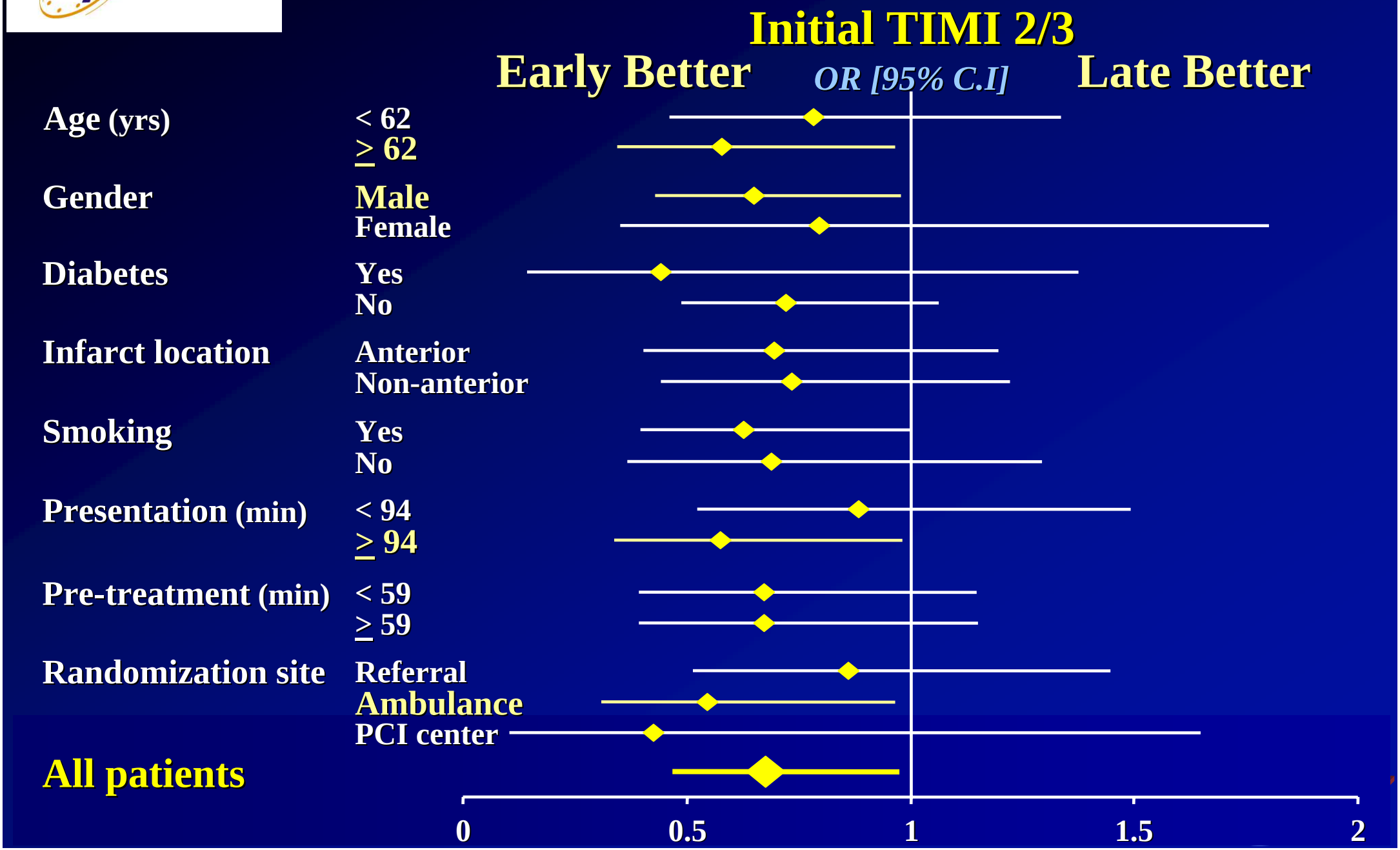


*Ongoing Tirofiban In Myocardial Infarction Evaluation*

# Angiographic Results

| | *Initial TIMI Flow* | | | | *Thrombus* | | |
|---|---|---|---|---|---|---|---|
| **Post-PCI** | **0-I** *(n=301)* | **II** *(n=104)* | **III** *(n=82)* | *p* | **Yes** *(n=323)* | **No** *(n=164)* | *p* |
| **TIMI-3** *(%)* | **89** | **92** | **97** | *0.109* | **89** | **94** | *0.07* |
| **MBG-3** *(%)* | **47** | **52** | **70** | *0.003* | **49** | **58** | *0.06* |
| **CTFC** | **28** | **26** | **22** | *0.035* | **28** | **24** | *0.07* |

# Ongoing Tirofiban In Myocardial Infarction Evaluation

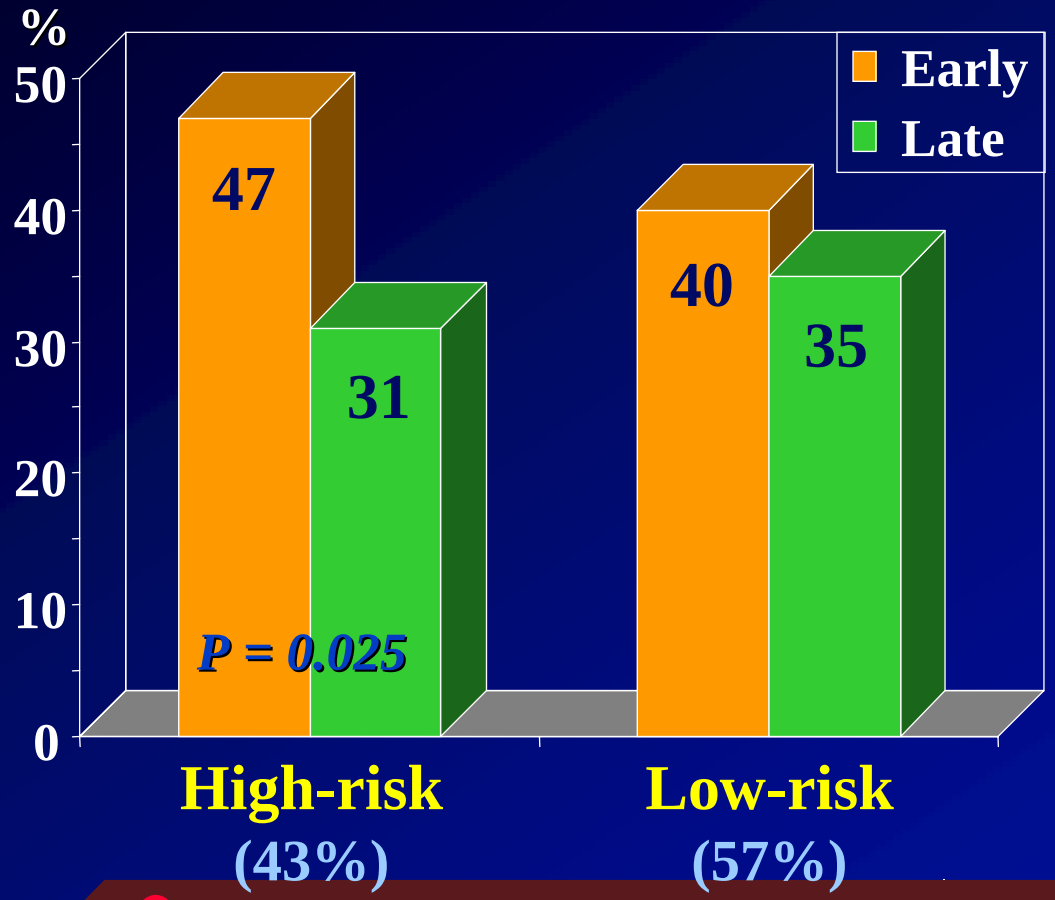


ON-TIME
Tirofiban In Myocardial infarction Evaluation

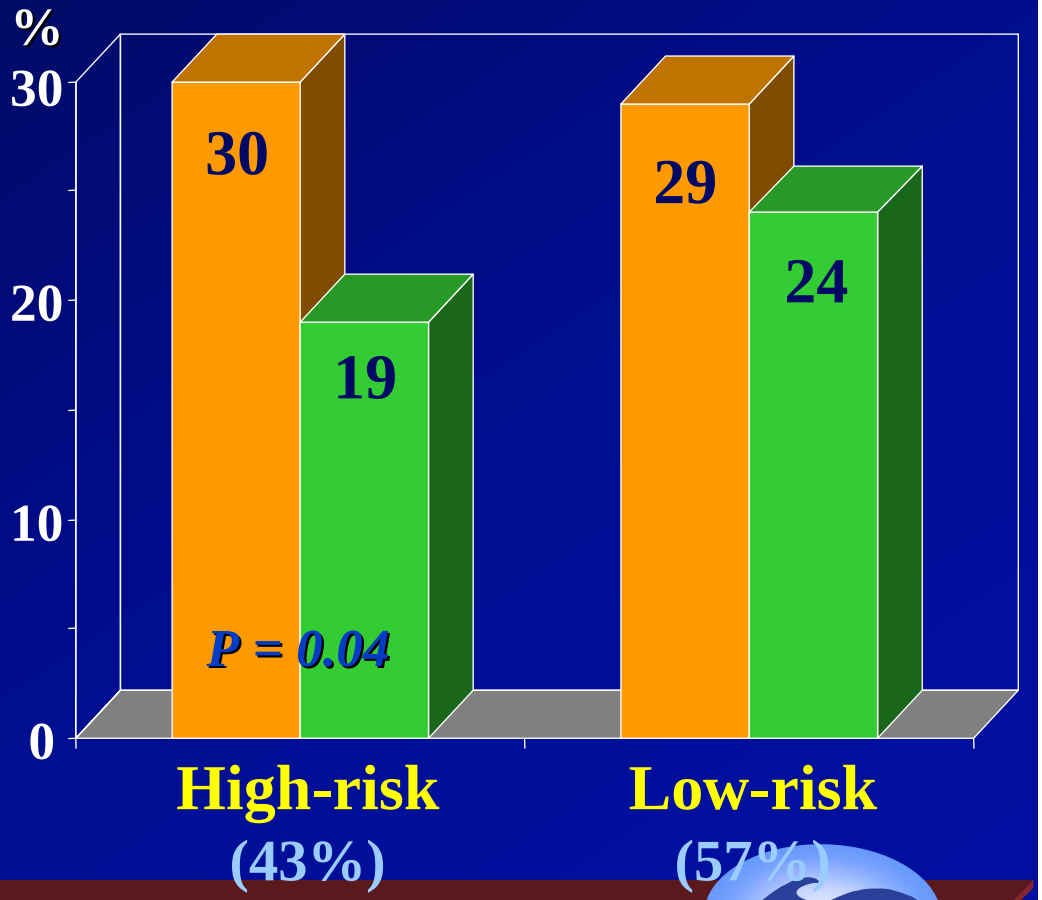
*Ongoing Tirofiban In Myocardial Infaction Evaluation*

# *Subgroup analysis:* High-risk vs Low-risk

## Initial TIMI 2/3

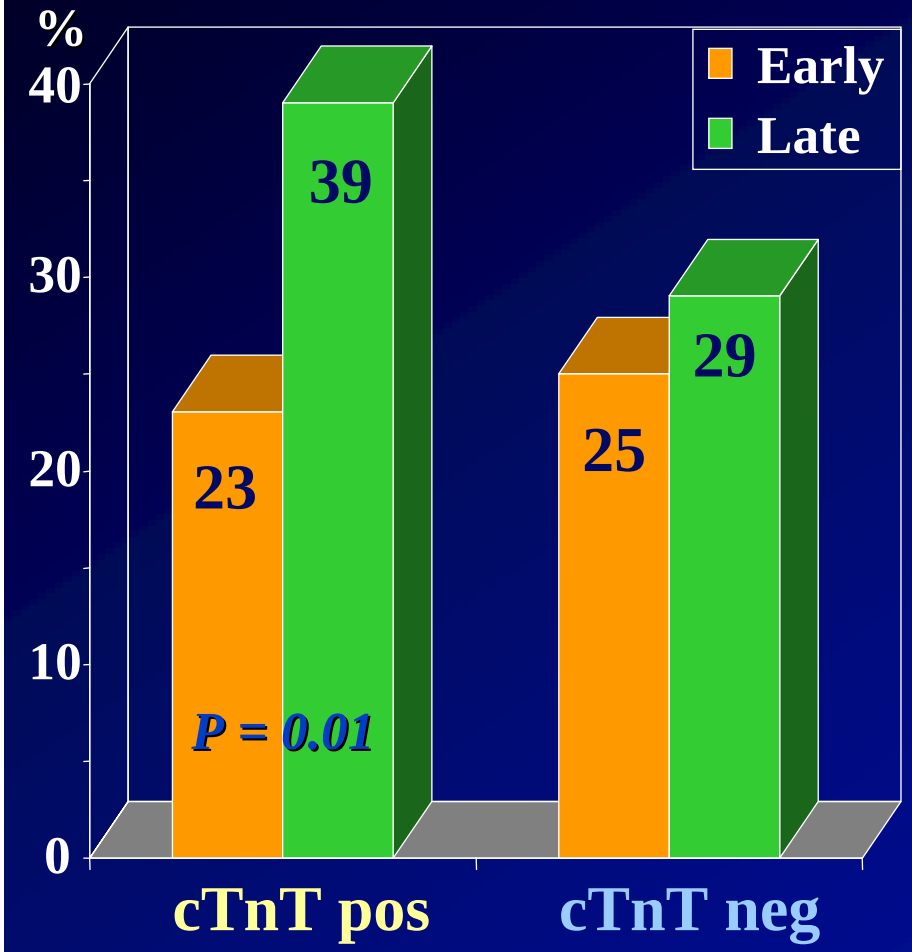



## MBG 2/3



# Ongoing Tirofiban In Myocardial Infaction Evaluation

## I.C. Thrombus



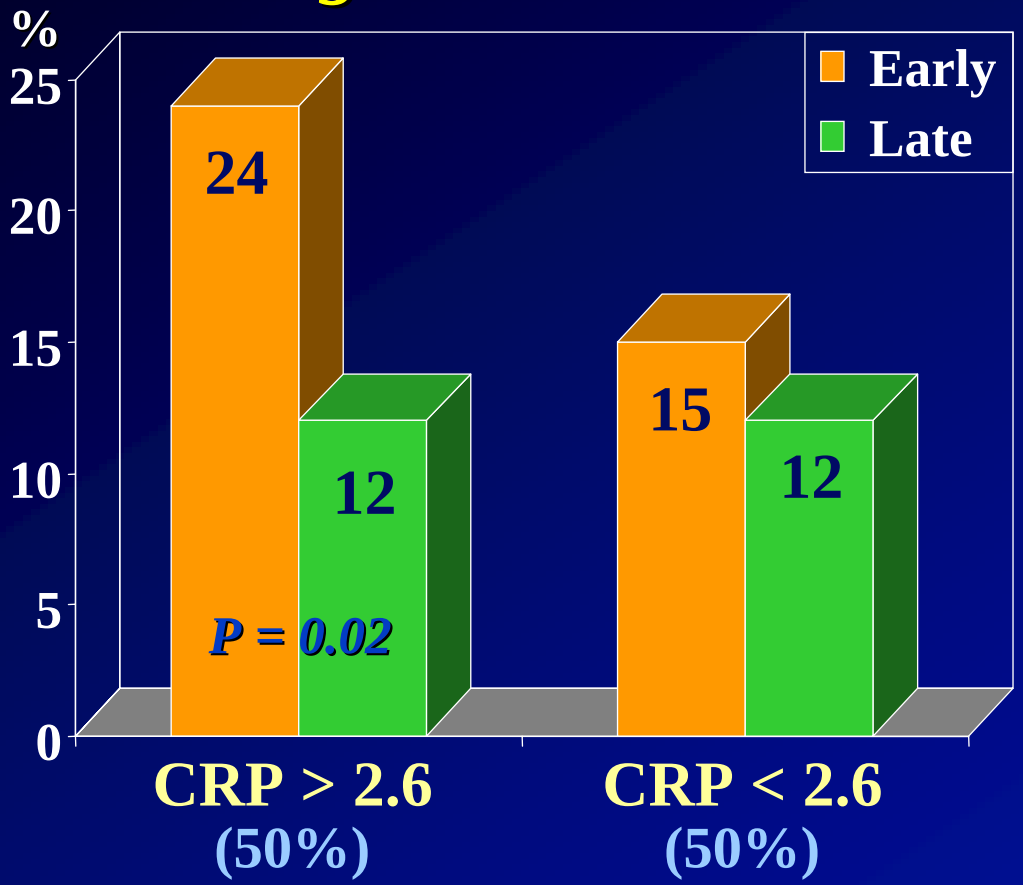

| Baseline Data | cTnT+ (n=208) | cTnT- (n=236) | P |
|---|---|---|---|
| Age *(mean, yr)* | 64 | 60 | 0.006 |
| Female *(%)* | 24 | 16 | 0.04 |
| Diabetes *(%)* | 13 | 8 | 0.09 |
| Time-delay *(min)* | 106 | 80 | <0.001 |
| Anterior MI *(%)* | 57 | 34 | <0.001 |
| Killip > 1 *(%)* | 22 | 11 | 0.003 |
| ***Outcome Data*** | | | |
| TIMI-3 flow | 87 | 93 | 0.04 |
| Death | 4.9 | 1.3 | 0.03 |

24/7 ON-TIME Tirofiban In Myocardial infarction Evaluation

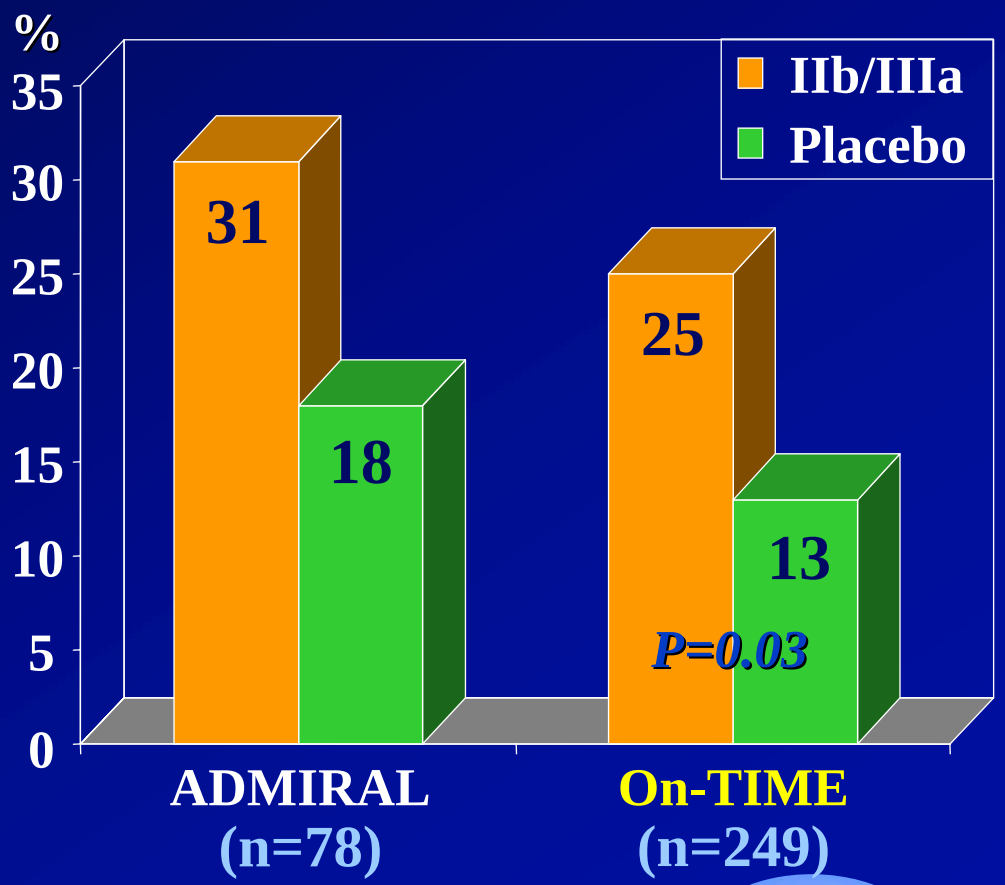
*Ongoing Tirofiban In Myocardial Infaction Evaluation*

# Pre-Procedural TIMI-3 Flow

## *High vs Low CRP*




## *Ambulance-ER Enrollment*



24/7 ON-TIME Tirofiban In Myocardial infarction Evaluation

*Ongoing Tirofiban In Myocardial Infaction Evaluation*

# Clinical Outcome at 30 days

| | | |
|---|---|---|
| **Mortality** | **11** | **(2.2%)** |
| **Recurrent MI** | **5** | **(1.0%)** |
| **Stroke** *(non-hemorrhagic)* | **1** | **(0.2%)** |
| **Major Bleeding** *(non CABG related)* | **19** | **(3.7%)** |

***Combined death, re-MI, or stroke only in 15 pts (3.1%)***

# Conclusion

**Early initiation of *Tirofiban* during transport for PCI**

- **Improvement in IRV patency *(TIMI 2/3)* and myocardial perfusion *(MBG 2/3)***
- **Significant reduction in i.c. thrombus**

**Particularly in *high-risk* pts enrolled in the *ambulance***

**Facilitation of primary PCI by Tirofiban results in a very low rate of mortality *(2%)* and re-MI *(1%)* at 30d**

**Safe and attractive for early facilitation of PCI in pts with AMI, who are transferred to a PCI center**