



Pre-Hospital Triage in AMI Intervention

On-Time-2 Randomized Trial

Early Administration of Tirofiban in PCI for STEMI

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Predictors of Impaired Myocardial Perfusion

Pre-procedural TIMI-3: Independent determinant of survival

Zwolle Multivariate Analysis (n=1527)

Predictors *Odds Ratio [95% CI]*

Pre-TIMI 0/1 **2.65 [1.89-3.70]**

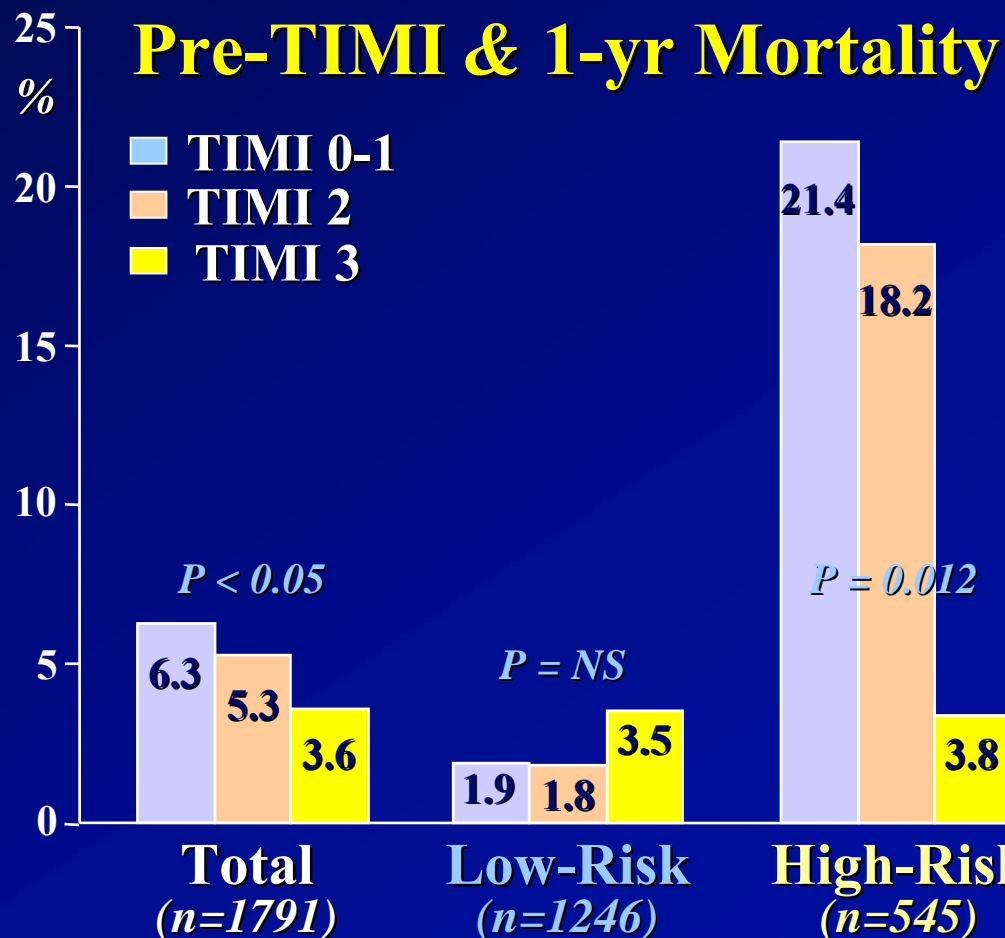
Anterior MI **2.15 [1.64-2.80]**

Time-delay (min) **1.06 [1.03-1.10]**

Killip class > 1 **1.78 [1.15-2.74]**

Age (yrs) **1.01 [1.00-1.02]**

De Luca, Suryapranata et al. Am Heart J 2005

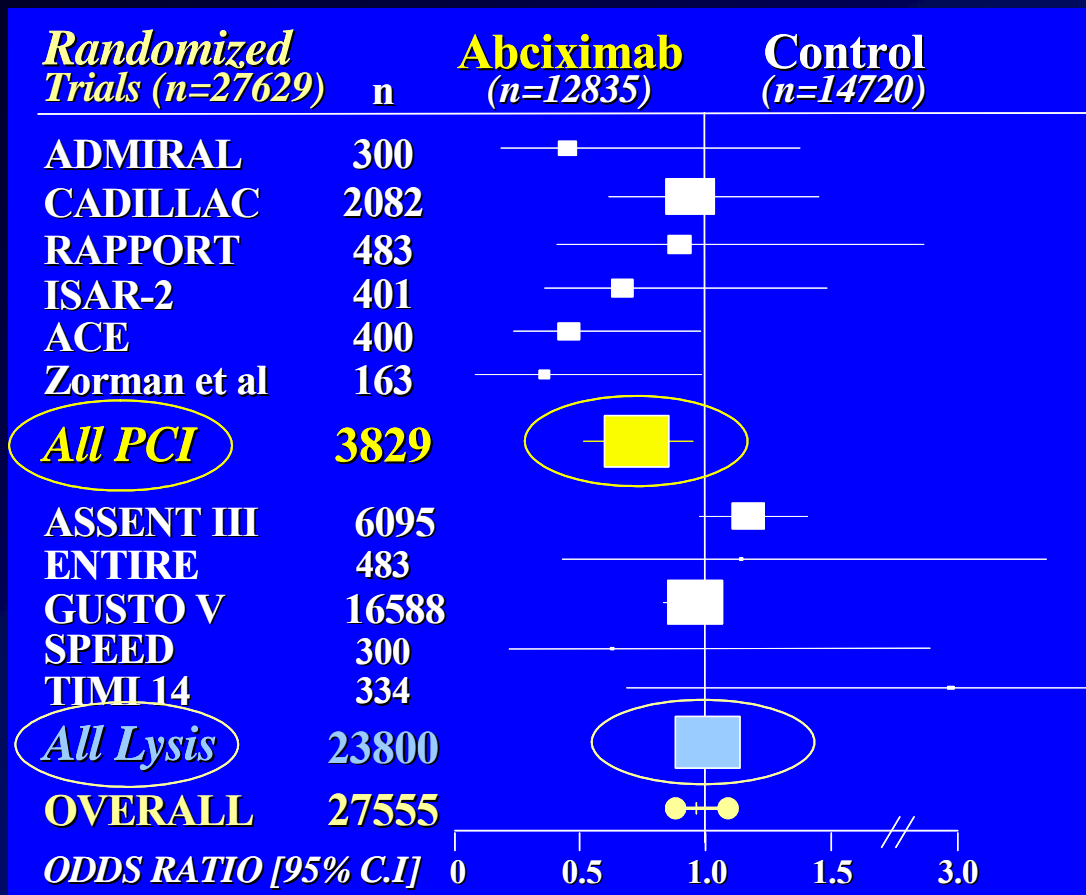


De Luca et al. JACC 2004

The need for EARLY TIMI-3 flow BEFORE PCI procedure

Adjunctive GP-IIb/IIIa Inhibitor in AMI Intervention

Meta-Analysis from RCTs: Adjunctive 2b/3a on 1-yr Mortality

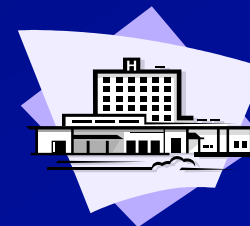


Adjunctive 2b/3a in STEMI

- Class 2A indication
- Registries: 2b/3a only in 25-30%
- No evidence in pts pre-treated with high-dose Clopidogrel
- **Timing of 2b/3a inhibitor?**



Pre-Hospital?



ER?



CathLab?

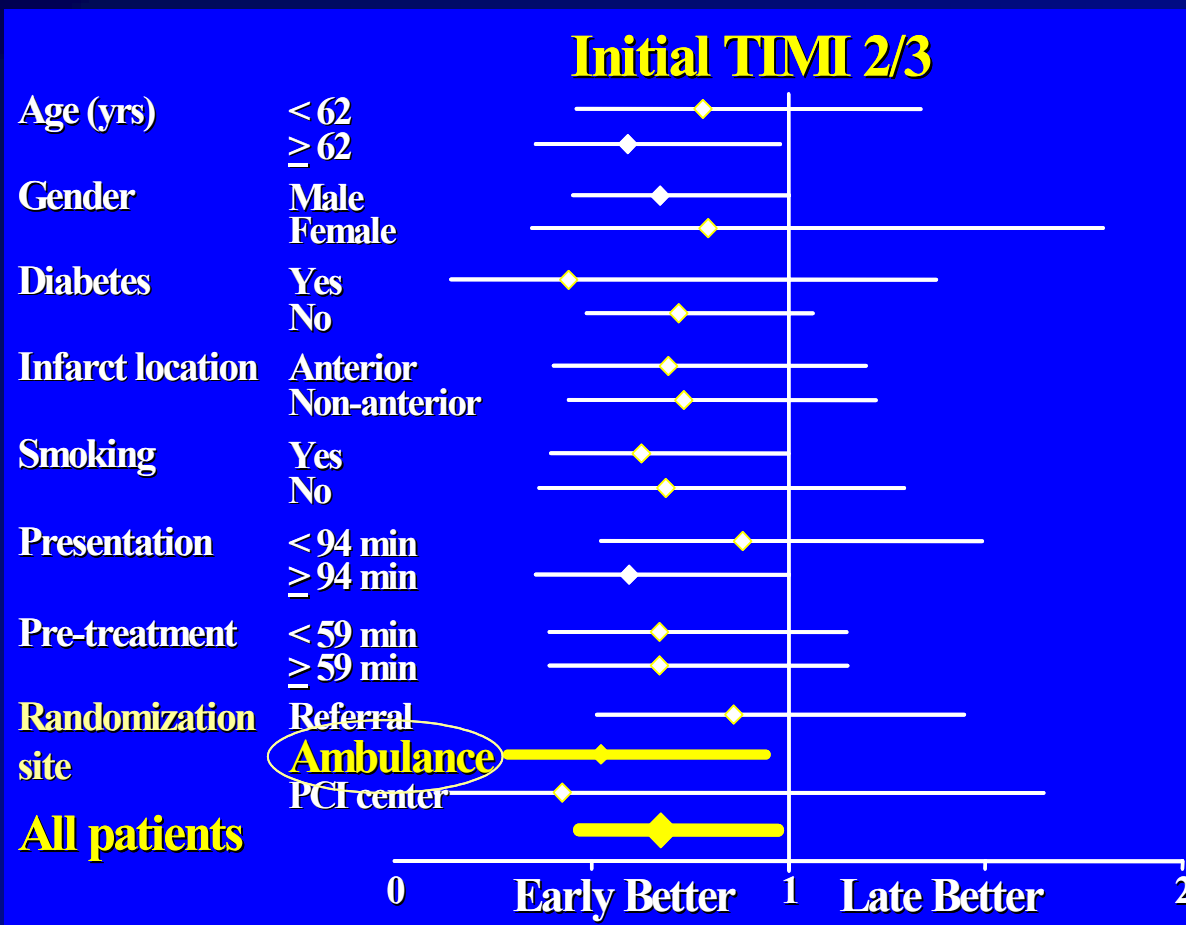
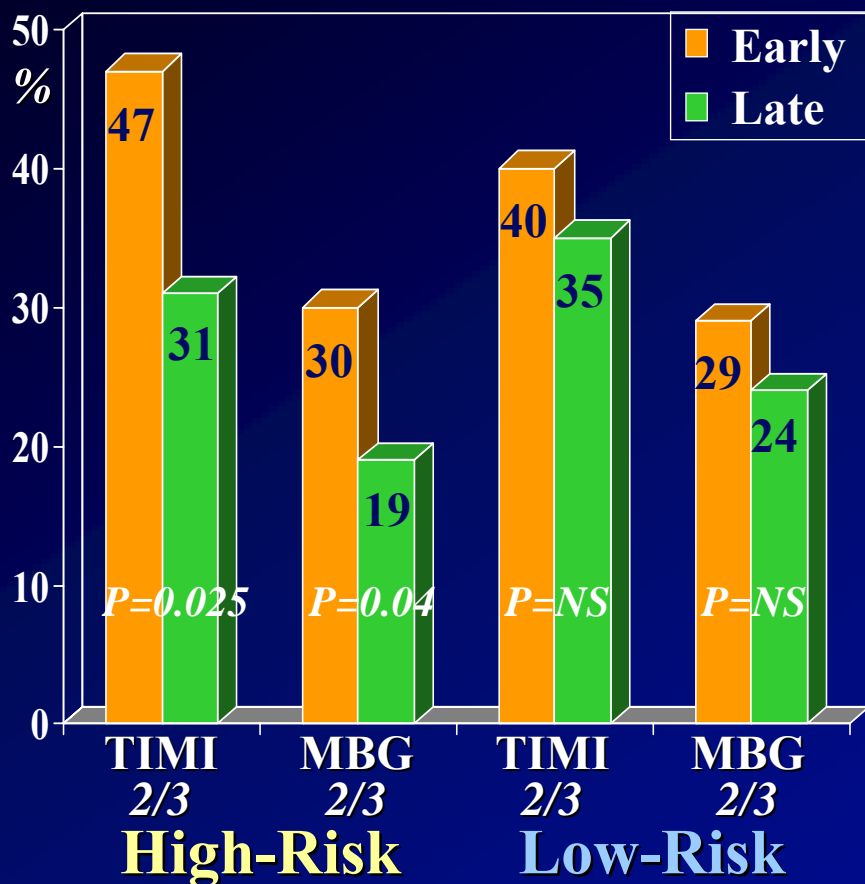
De Luca, Suryapranata, Stone et al. JAMA 2005



ONgoing Tirofiban In Myocardial Infarction Evaluation - 1

Early (Pre-hosp) vs Late (Cathlab) Tirofiban for STEMI

Initial TIMI and MBG



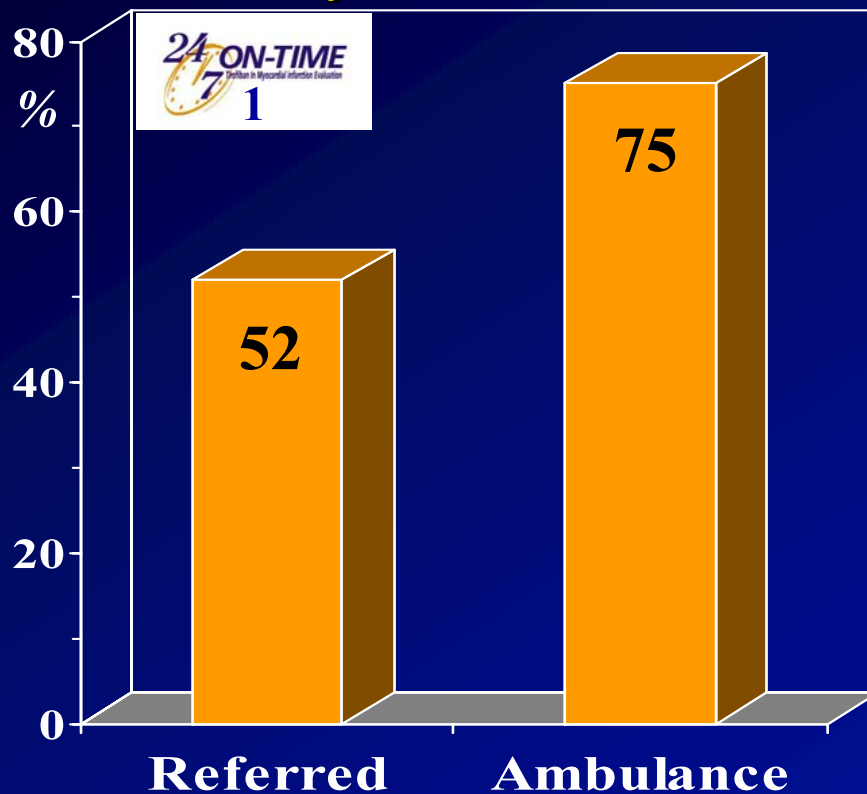
van 't Hof et al. Eur Heart J 2005

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

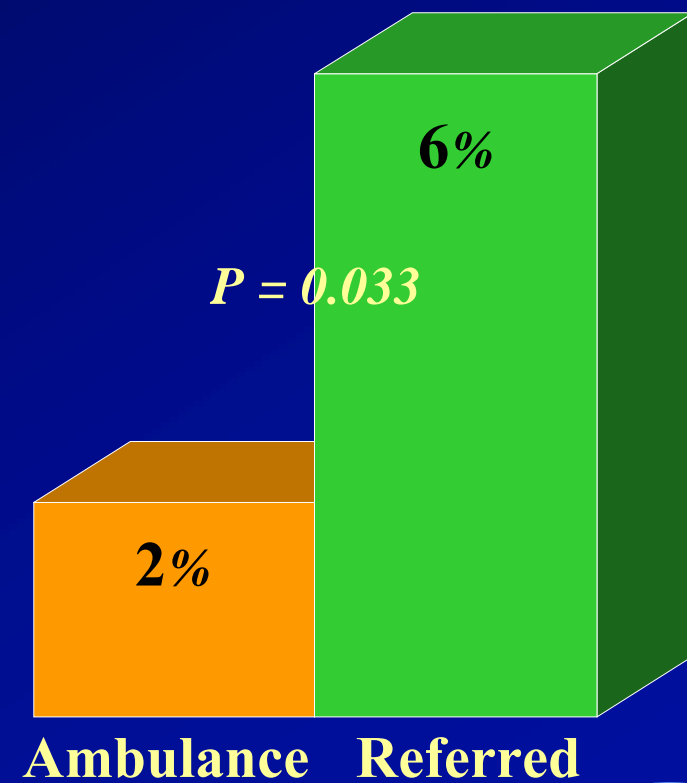
AHA/ACC Guidelines - *Pre-hospital Triage*

Primary PCI is preferred therapy when performed < 90 min after 1st contact by experienced operators with DTB < 60 min

Primary PCI < 90 min



1-year Mortality



Zwolle Pre-hospital Triage in Transferring patients for PCI

Zwolle **PHIAT** protocol (1998 -)
Pre-Hospital Infarct Angioplasty Triage

35 Ambulances + computer-assisted
12-lead tele-ECG, using algorithm

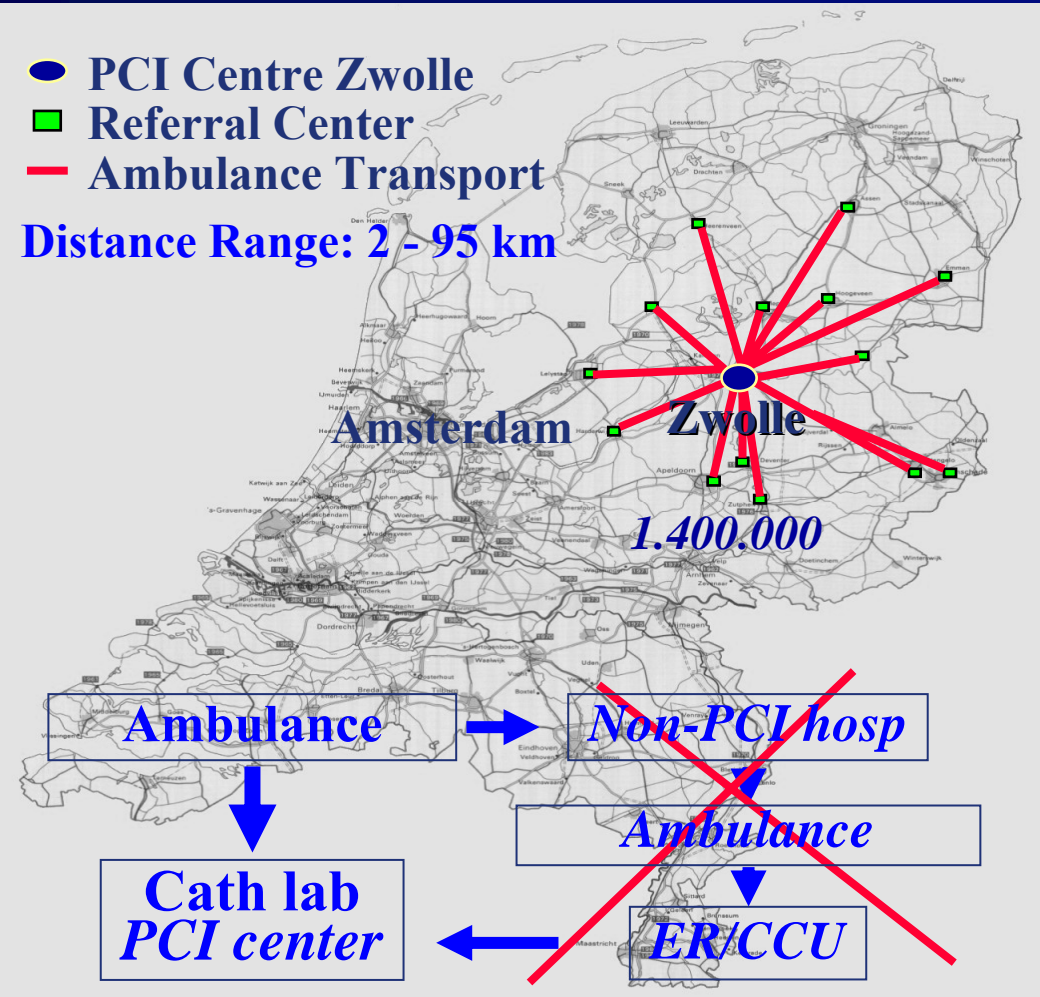


Identification of a large AMI
Ambulance nurse only, no physician



Immediate transfer to Cathlab
Rather than to nearest Hosp/CCU/ER

- PCI Centre Zwolle
 - Referral Center
 - Ambulance Transport
- Distance Range: 2 - 95 km



Symptom-Ambulance
91 min

Ambulance-Admission
49 min

Door-Balloon
38 min

Total
178'

ON-TIME-2 Multicenter Randomized Trial **ONgoing Tirofiban In Myocardial Infarction Evaluation - 2**

Multicenter double-blind placebo-controlled randomized trial to assess safety & efficacy of a high bolus Tirofiban vs Placebo on the extent of Myocardial Reperfusion in pts with STEMI who are transferred for primary PCI

Primary Endpoint:

- **Residual ST-segment deviation ($>3mm$) 1-hr post-PCI**

Key Secondary Endpoints:

- **Combined occurrence of Death, Re-MI, urgent TVR, or thrombotic Bail-out at 30 days follow-up**
- **Safety (major bleeding)**

On behalf of the On-Time Study Group

ON-TIME-2 Multicenter Randomized Trial

ONgoing Tirofiban In Myocardial Infarction Evaluation - 2

- **Open Label**: June 2004 - June 2006 ($n=414$) at 2 centers in Netherlands*
- **Double-Blind**: June 2006 – Nov 2007 ($n=984$)

25 Participating Centers

The Netherlands:

- | | |
|-----------------------------|------------------------|
| 1. Isala klinieken Zwolle * | Dr. A.W.J. van 't Hof |
| 2. Antonius Nieuwegein * | Dr. J. ten Berg |
| 3. UMC Utrecht | Drs. P.R. Stella |
| 4. Medisch Spectrum Twente | Dr. K. van Houwelingen |

Belgium:

- | | |
|-----------------------|-------------------|
| 1. AZ Sint-Jan Brugge | Dr. P. Coussement |
|-----------------------|-------------------|

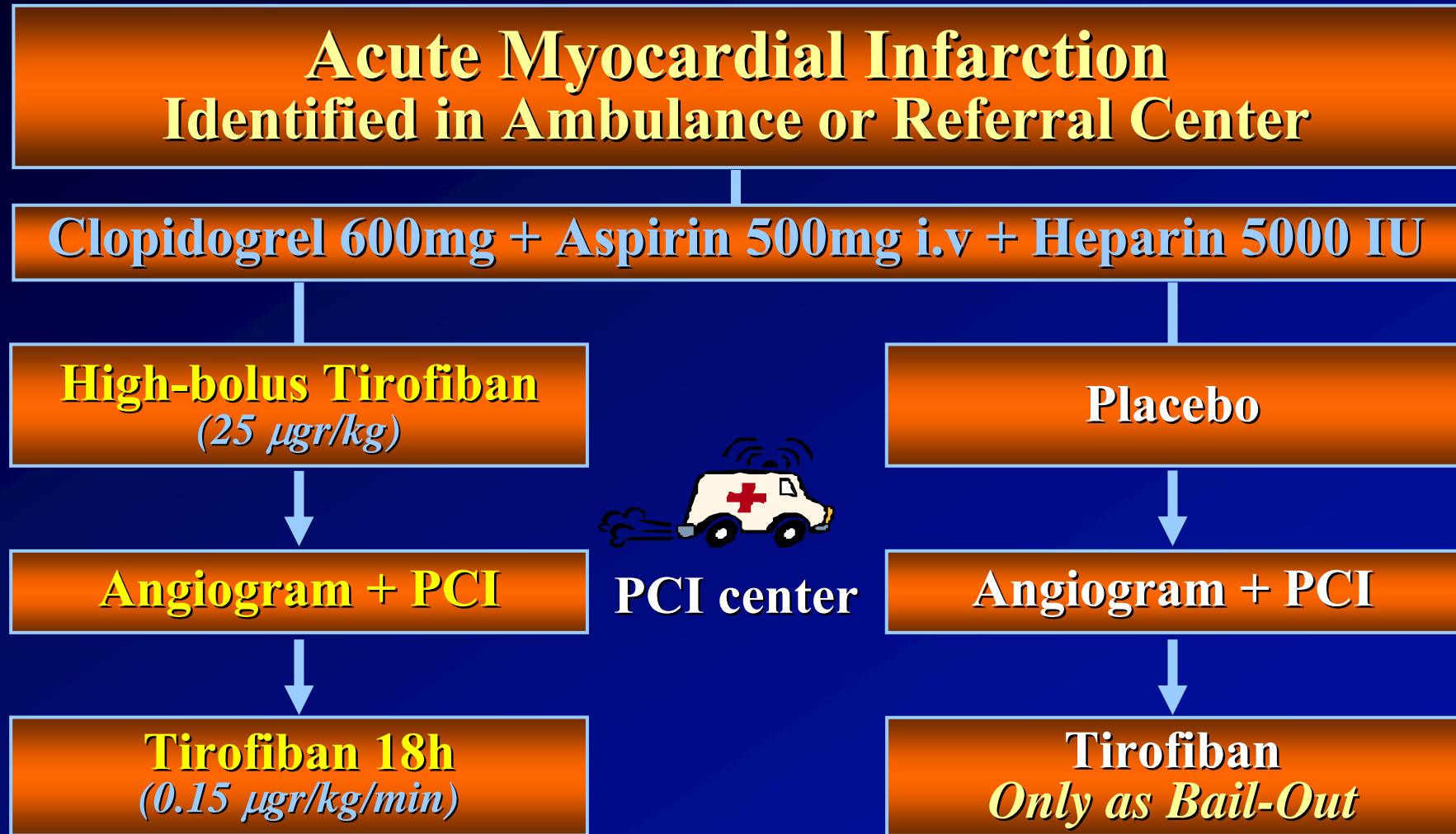
Germany:

- | | |
|------------------------------------|------------------------|
| 1. Kerckhoff-Klinik | Prof. Dr. C. Hamm |
| 2. Universitätsklinikum Heidelberg | Prof. Dr. H Katus |
| 3. St. Johannes Hospital Dortmund | Prof. Dr. Heuer |
| 4. Klinikum Coburg | Prof. Dr. J. Brachmann |
| 5. Klinikum Lüdenscheid | Dr. Lemke |
| 6. Segeberger Kliniken | Prof. Dr. G. Richardt |
| 7. Philipps Universität Marburg | Prof. Maisch |
| 8. Allgemeines Krankenhaus Celle | Prof. Dr. W. Terres |
| 9. Uni-klinik Giessen | Prof. Dr. H. Tillmanns |
| 10. Imtalklinik Pfaffenhofen | Prof. C. Firschke |
| 11. Med. Hochschule Hannover | Prof. Dr. Schieffer |
| 12. Uniklinik Mannheim | Dr. T. Süselbeck |
| 13. Uniklinik Lübeck | Prof. Dr. H. Schunkert |
| 14. Stätisches Klinikum Lüneburg | Prof. Dr. W. Kupper |
| 15. Zentralklinikum Suhl | Prof. W. Haberbosch |
| 16. Uni-Klinik Rostock | Prof. Dr. C.Nienaber |
| 17. Kreiskrankenhaus Bergstrasse | Dr. W. Auch-Schwelk |
| 18. Asklepios Klinik St. Georg | Prof. Dr. K.H. Kuck |
| 19. Klinikum Darmstadt | Prof Dr. G. Werner |
| 20. Evangelisches Holzminden | Dr. C. Beythien |



ON-TIME-2 Multicenter Randomized Trial

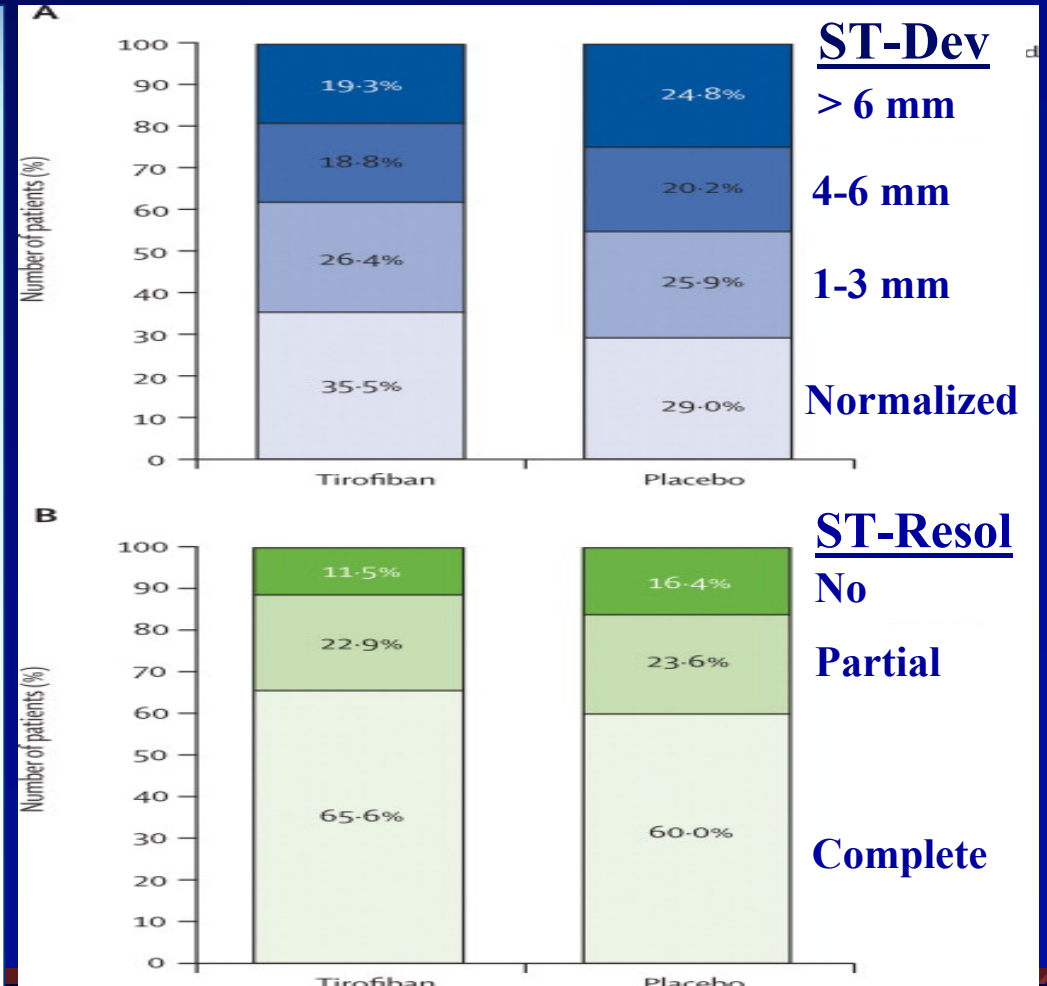
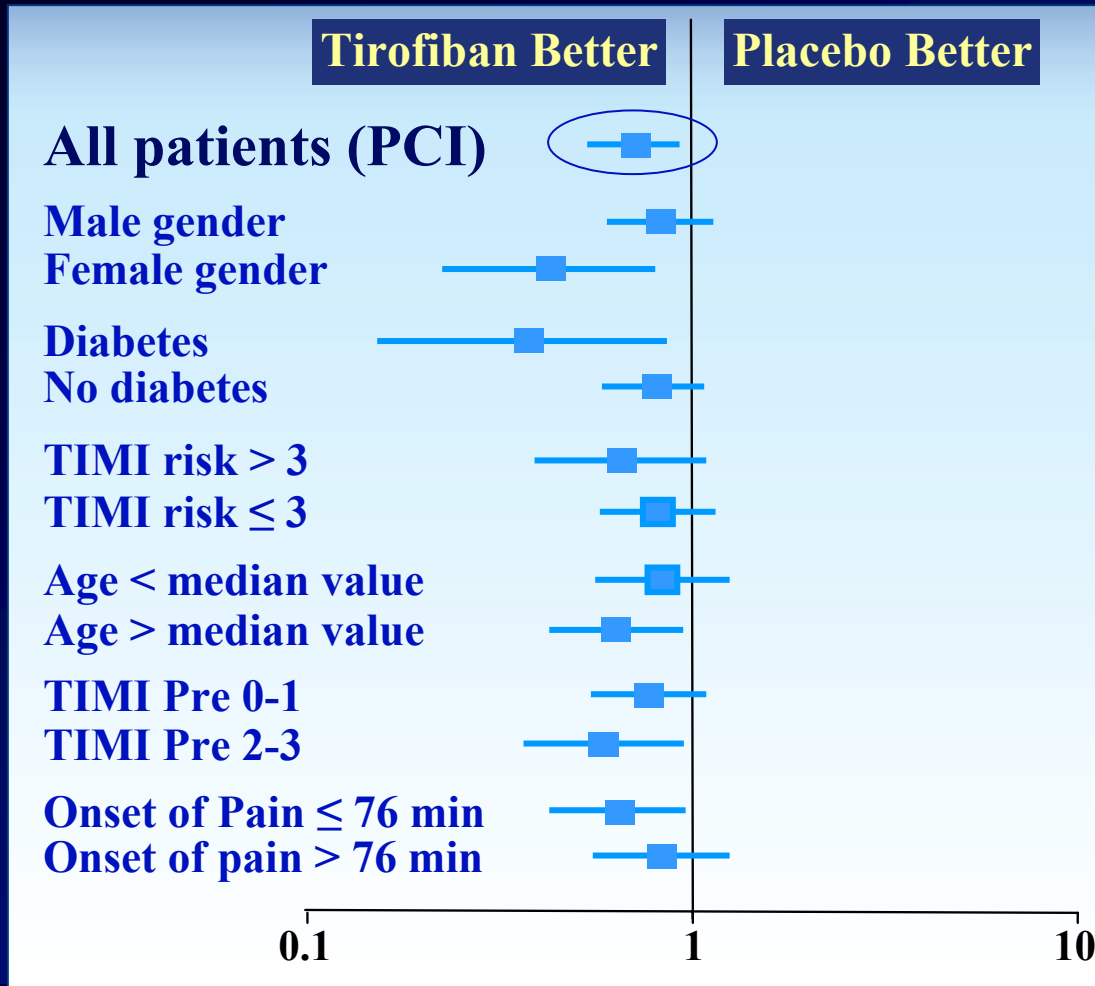
ONgoing Tirofiban In Myocardial Infarction Evaluation - 2



ON-TIME-2 Multicenter Randomized Trial

ONgoing Tirofiban In Myocardial Infarction Evaluation - 2

Double-Blind: Residual ST-Deviation >3mm (Primary Endpoint)

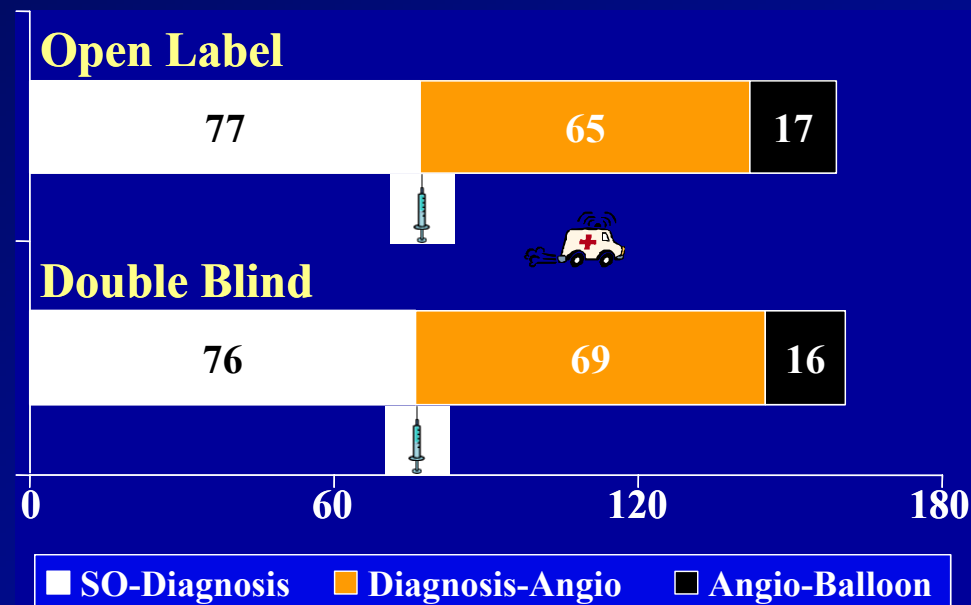


ON-TIME-2 Multicenter Randomized Trial

ONgoing Tirofiban In Myocardial Infarction Evaluation - 2

Baseline	Open Label (n=414)	Double-Blind (n=984)
Age (mean, yr)	62	62
Male (%)	77	76
Prev MI (%)	11	9
Diabetes (%)	11	12
Hypertension (%)	34	34
Smoking (%)	48	47
Anterior MI (%)	45	42
Killip > 1 (%)	13	12
Ambulance (%)	98	95

Ischemic Time (min)



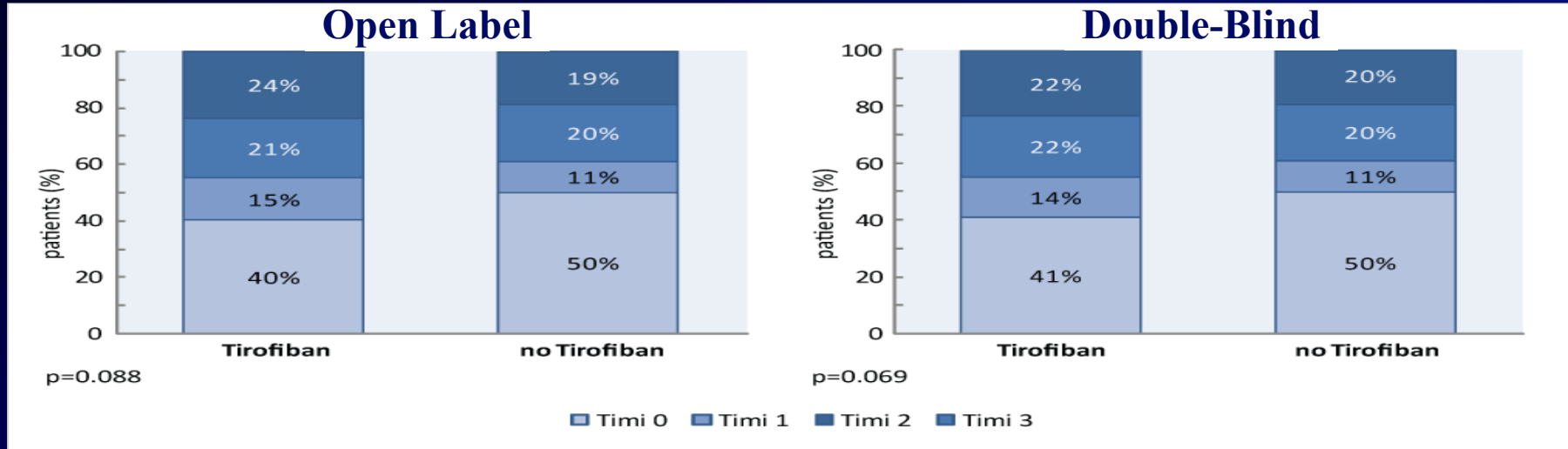
39% within 'Golden Hour'
Door-to-Balloon Time: 35 min



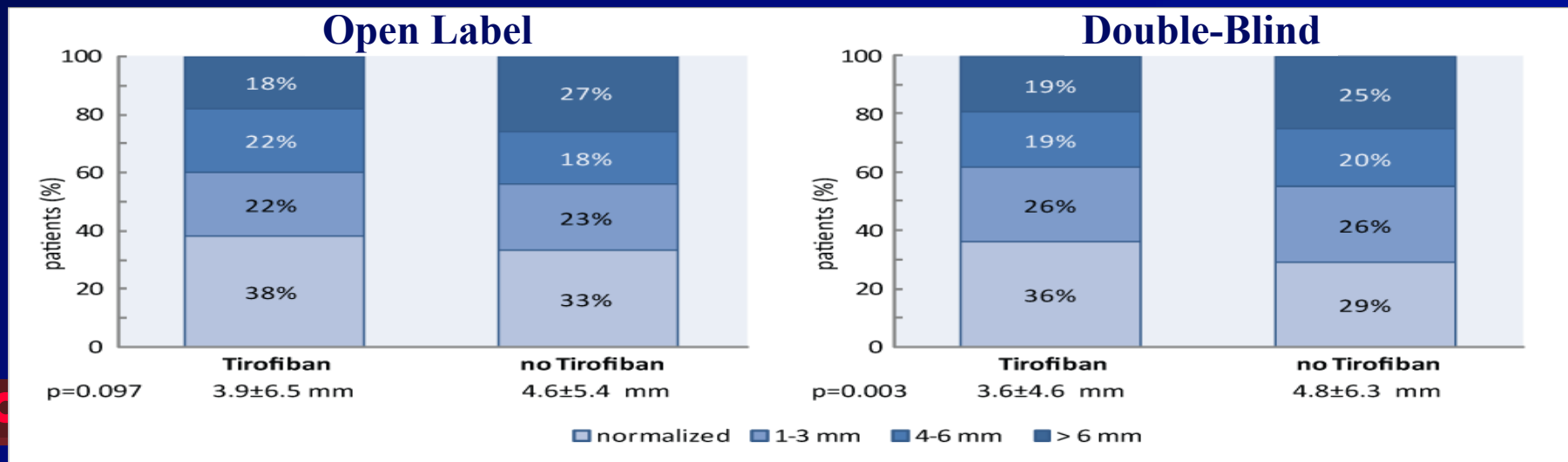
ON-TIME-2 Multicenter Randomized Trial

ONgoing Tirofiban In Myocardial Infaction Evaluation - 2

Initial TIMI-flow



Residual ST-Deviation after PCI



ON-TIME-2 Multicenter Randomized Trial

ONgoing Tirofiban In Myocardial Infarction Evaluation - 2

Pooled Analysis: Open Label and Double Blind (n=1398)

Baseline	Tirofiban (n=709)	Placebo (n=689)
Age (mean, yr)	62	62
Male (%)	77	76
Prev MI (%)	9	9
Diabetes (%)	12	11
Hypertension (%)	34	34
Smoking (%)	46	49
Anterior MI (%)	43	43
Killip > 1 (%)	11	14
Ambulance (%)	96	97

Primary Endpoint	PLACEBO (n=689)	TIROFIBAN (n=709)	P-value
Baseline ST-dev (mm)	14.2	14.6	0.645
Residual ST-deviation 1 hr post-PCI (mm)	4.8	3.7	0.001
Normal ECG @ 1hr (%)	30.0	36.1	0.003
ST-deviation >3mm (%)	45.0	38.7	0.024

Compl ST-Resolution Pre-PCI (%)

Tirofiban	Placebo	P-value
19.0	14.6	0.049

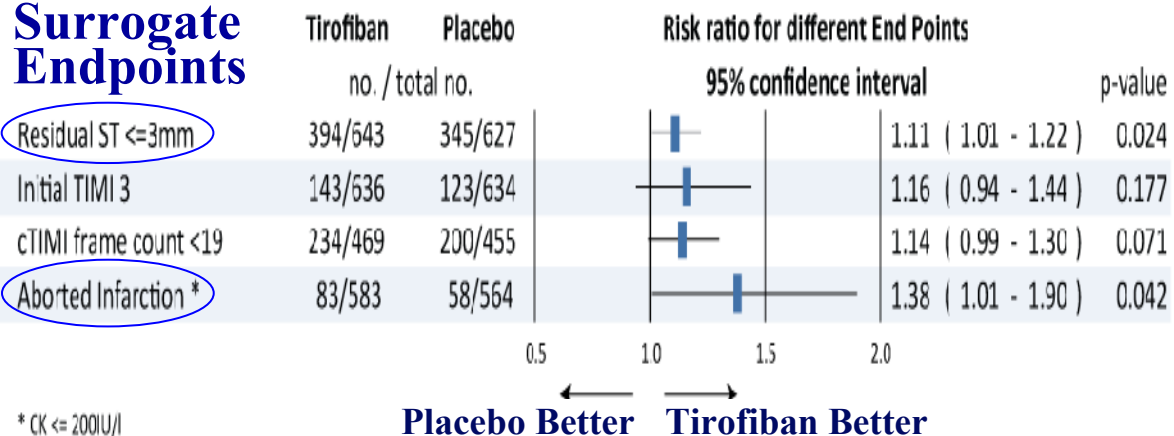


ON-TIME-2 Multicenter Randomized Trial

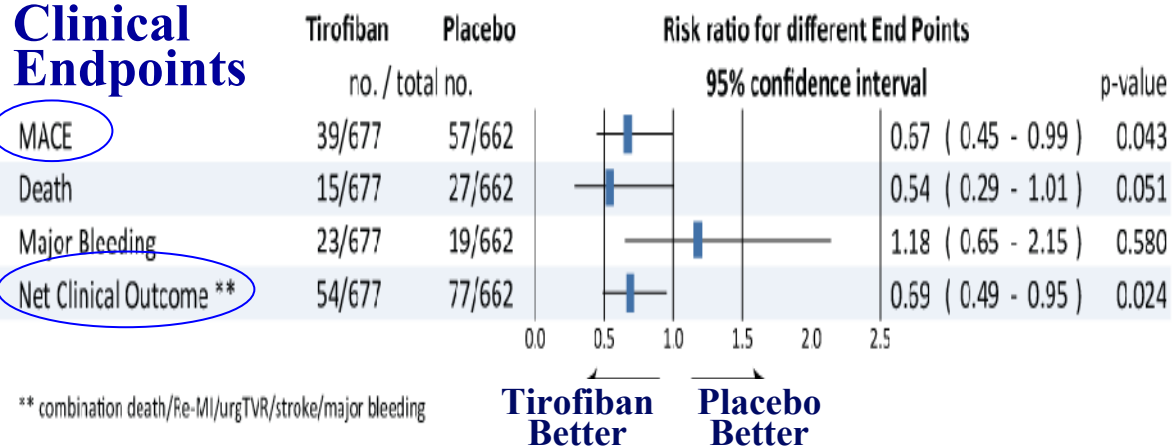
ONgoing Tirofiban In Myocardial Infarction Evaluation - 2

Pooled Analysis: Open Label and Double Blind (n=1398)

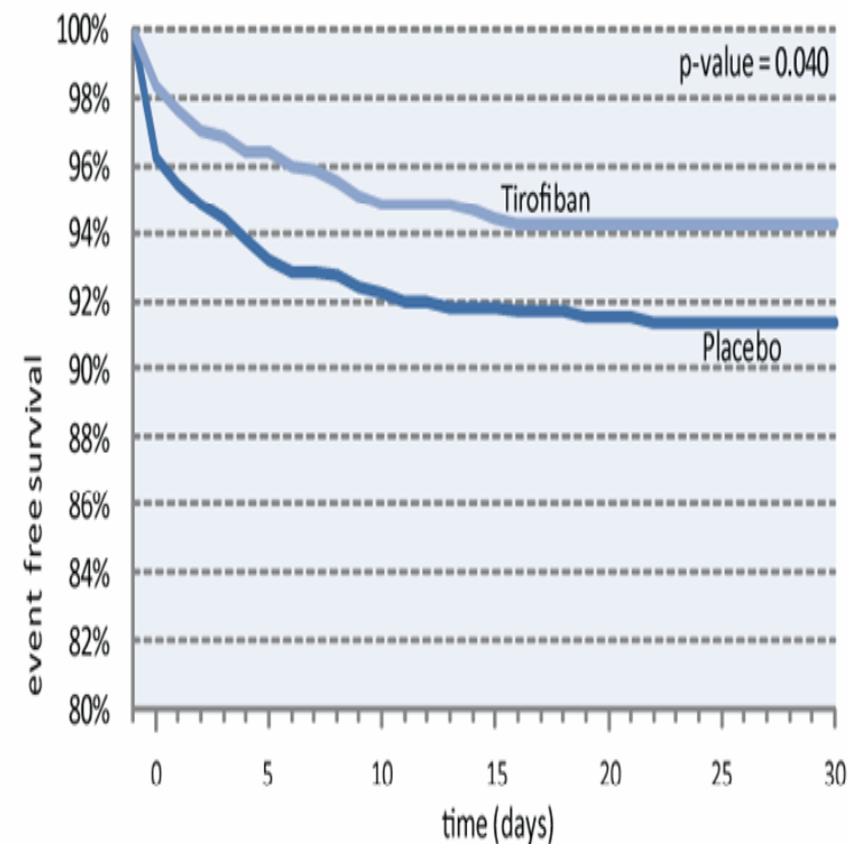
Surrogate Endpoints



Clinical Endpoints



Cumulative Event-free Survival

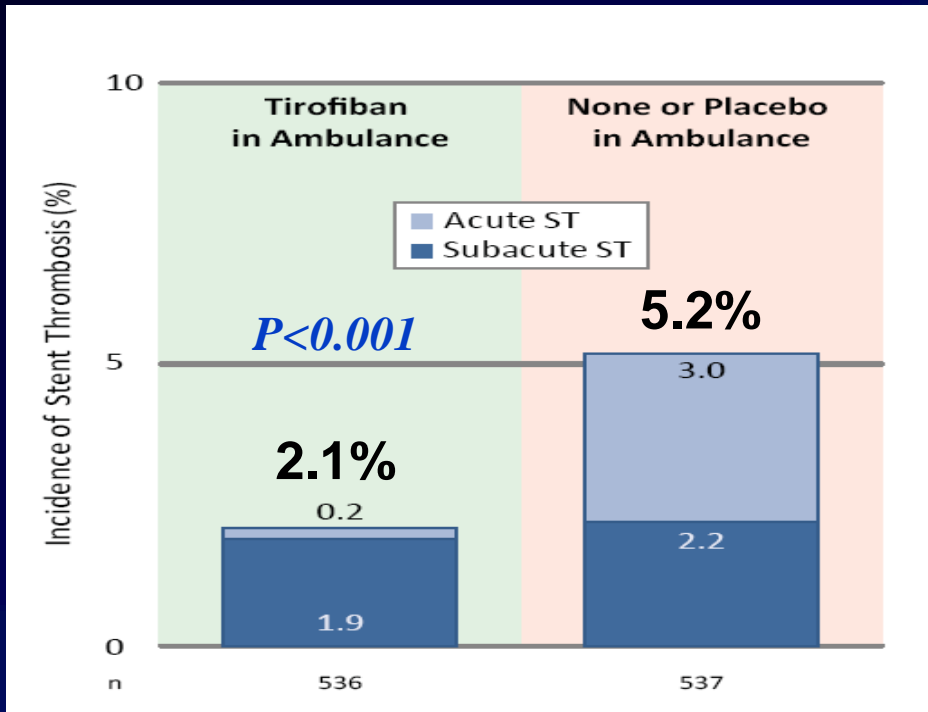


Net Clinical Outcome (Death/Re-MI/TVR/Major bleeding): 11.6% vs 8% (p=0.024)

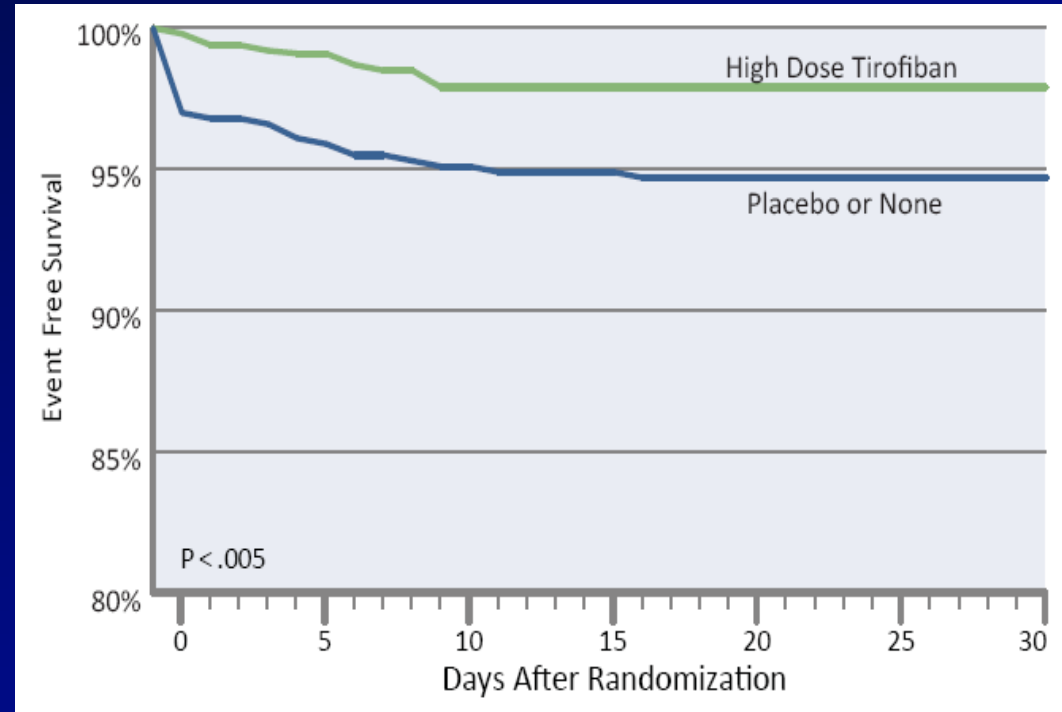
ON-TIME-2 Multicenter Randomized Trial

ONgoing Tirofiban In Myocardial Infaction Evaluation - 2

Early Stent Thrombosis



Event-free Survival



Independent Predictors of Stent Thrombosis

TIMI major Bleedings

OR (95% C.I)

P-value

Randomization to Placebo

9.0 (2.6-31.6)

0.001

Lower stent diameter/mm decrease

2.7 (1.3-5.7)

0.007

2.5 (1.06-5.92)

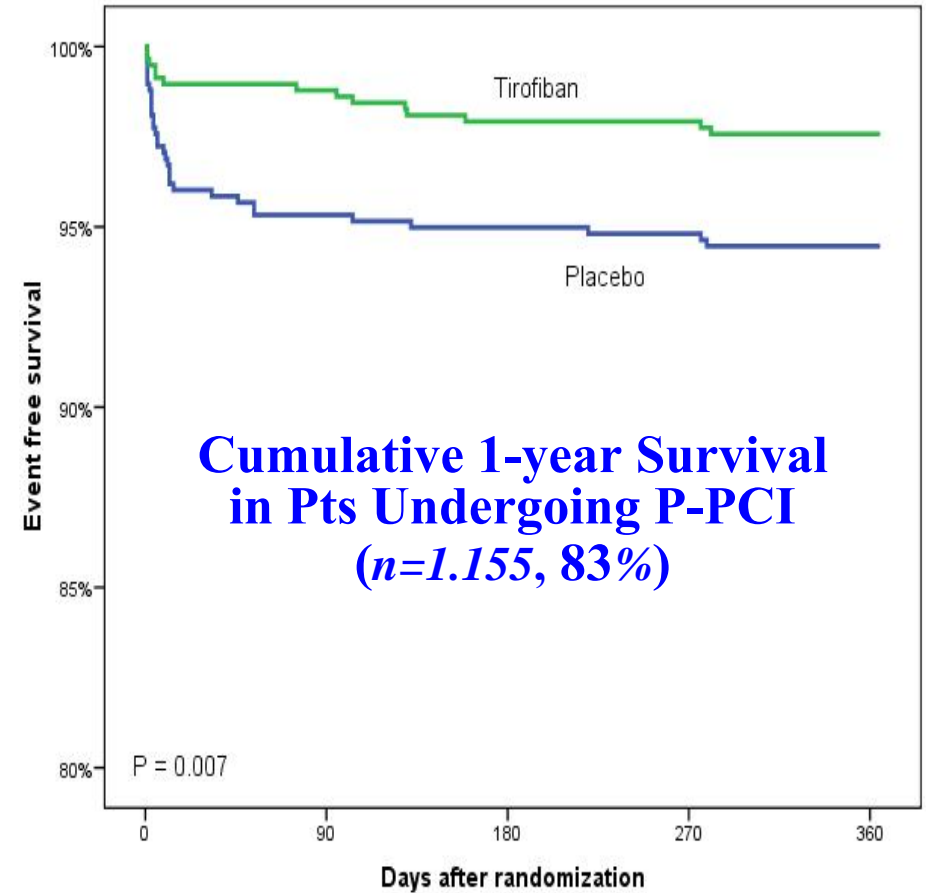
0.04

ON-TIME-2 Multicenter Randomized Trial

ONgoing Tirofiban In Myocardial Infarction Evaluation - 2

Pooled Analysis: Open Label and Double Blind (n=1398)

	Tirofiban no./total no.	Placebo no./total no.	Death within One Year Risk Ratio, 95% Confidence Interval	p-value
All patients	25/670	38/656	0.64 (0.39 - 1.05)	0.078
Sex				
Female	9/154	12/164	0.80 (0.35 - 1.84)	0.597
Male	16/516	26/492	0.59 (0.32 - 1.08)	0.083
Age(years)				
<= 61.6	7/337	6/327	1.13 (0.38 - 3.33)	0.822
> 61.6	18/333	32/329	0.56 (0.32 - 0.97)	0.035
Diabetes				
No	20/595	29/585	0.68 (0.39 - 1.18)	0.169
Yes	5/75	9/69	0.51 (0.18 - 1.45)	0.197
Location				
Anterior MI	12/253	20/259	0.61 (0.31 - 1.23)	0.164
Non anterior MI	11/343	14/331	0.76 (0.35 - 1.65)	0.483
Killip > 1				
No	15/587	19/554	0.75 (0.38 - 1.45)	0.385
Yes	6/69	18/87	0.42 (0.18 - 0.96)	0.039
Timi flow grade before PCI				
0-2	16/473	30/491	0.55 (0.31 - 0.99)	0.047
3	2/134	3/116	0.58 (0.10 - 3.39)	0.665
Time start study drug to balloon inflation/angiography				
<= 55	7/331	14/331	0.50 (0.20 - 1.22)	0.121
> 55	13/326	22/314	0.57 (0.29 - 1.11)	0.093
Time symptom onset to diagnosis				
<= 75	6/340	13/303	0.41 (0.16 - 1.07)	0.059
> 75	18/315	21/340	0.93 (0.50 - 1.70)	0.803
Primary PCI				
No	11/93	6/78	1.54 (0.60 - 3.97)	0.368
Yes	14/577	32/578	0.44 (0.24 - 0.81)	0.007



Conclusion

- **Early initiation of a high-bolus Tirofiban** (*on top of 600mg Clopidogrel*) in pre-hospital setting is safe and attractive for early facilitation of PCI in STEMI pts
- **Improves initial TIMI & ST-Resolution** (*pre & post PCI*)
- **More 'Aborted Infarction'** - Reduced MACE & Stent Thrombosis, without increase in major bleedings
- **Highest efficacy when Tirofiban is given early after symptom onset** (*ambulance*)

Do not wait with 2b/3a inhibitor until Cathlab arrival