

**Adjunctive Platelet GP IIb/IIIa Receptor
Inhibition with Tirofiban before Primary
Angioplasty Improves Angiographic
Outcomes: Results of the TIGER-PA Pilot
Trial**

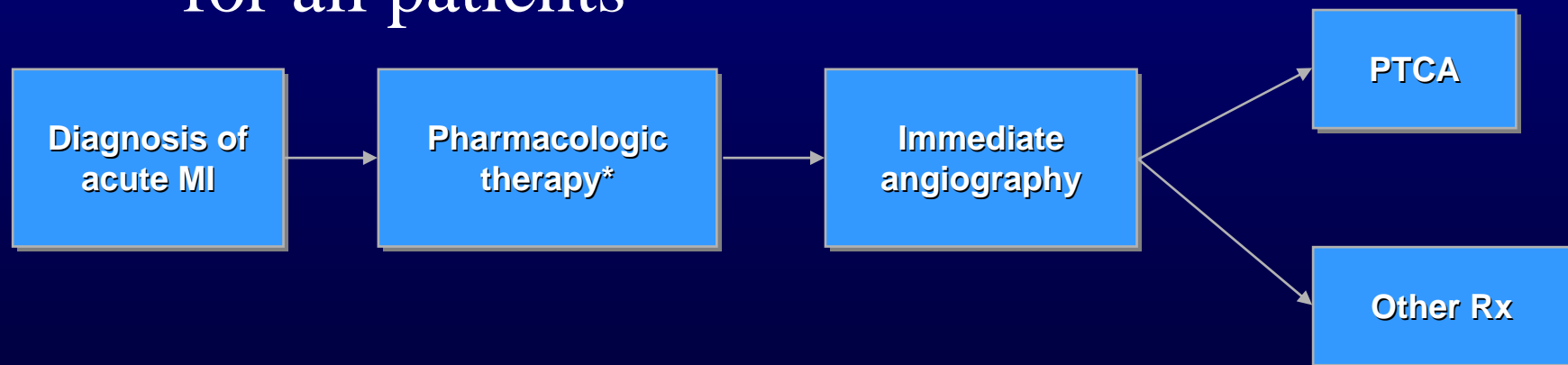
Alan C. Yeung, MD

Stanford University School of Medicine



“Prejunctive” Therapy

- A strategy to promote very early patency for some patients (drug responders) and very high final patency rates (assured by PTCA) for all patients



*Antithrombin agents, antiplatelet agents, and fibrinolytic agents.

Plasminogen-activator Angioplasty Compatibility Trial (PACT)

- Multicenter, randomized, double-blind trial
- 606 AMI patients
- ≤ 75 years old, low-risk infarctions
- 50 mg IV bolus of rtPA vs placebo
- Rescue PTCA if TIMI-3 flow not immediately achieved

Ross et al. (1999) *JACC* 34 (7):1954-62.

PACT

Reperfusion, LV function, and adverse events

	rtPA (n=302)	Placebo (n=304)
TIMI-3 flow immediately following drug treatment	33%	15%
%LVEF immediately following drug treatment	59.4 \pm 13.8 ₁	57.7 \pm 14.1 ₂
TIMI-3 flow achieved following rescue PTCA	78.6% ³	80.5% ⁴
Rate of major hemorrhaging	12.9%	13.5%

¹ ventriculogram available for analysis for only 220 patients

² ventriculograms available for analysis for only 224 patients

³ in 169 patients with TIMI 0, 1, or 2 flow after drug treatment

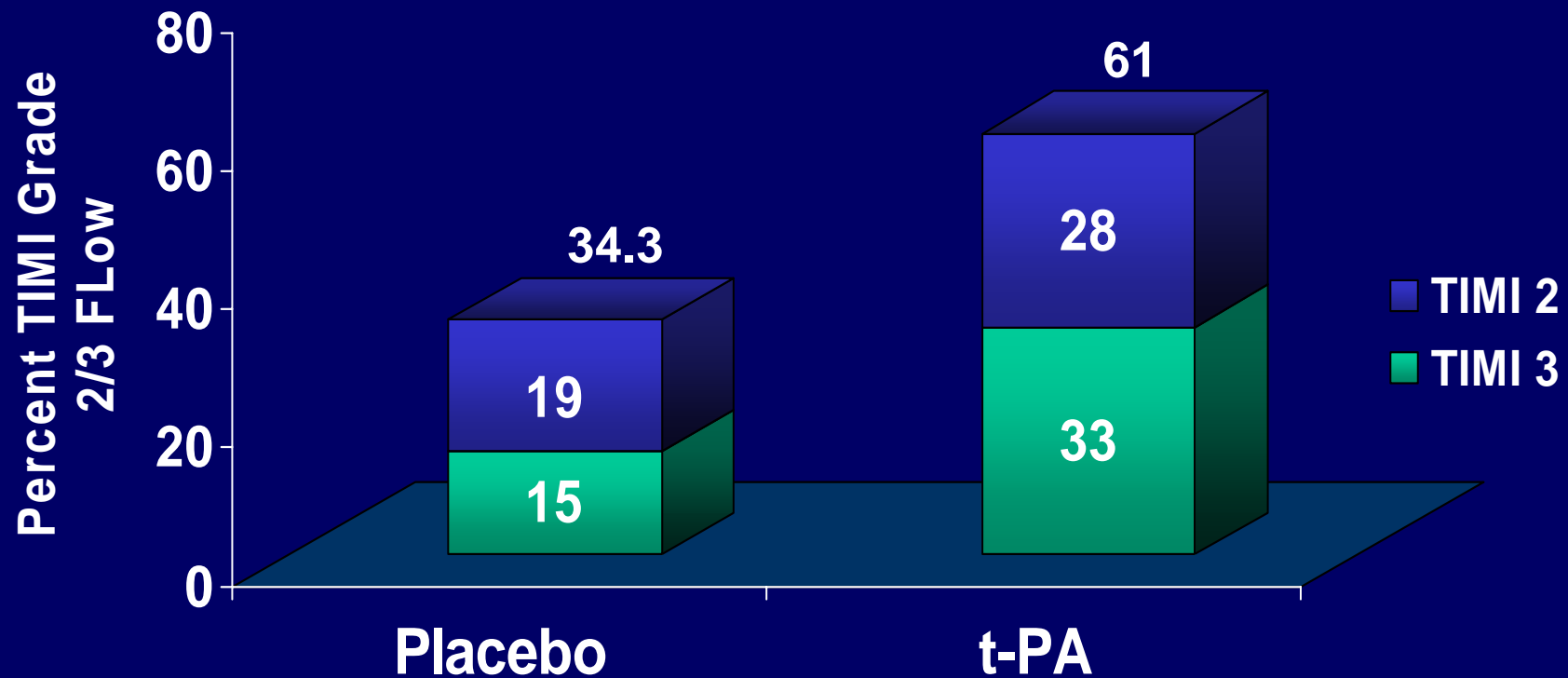
⁴ in 231 patients with TIMI 0, 1, or 2 flow after drug treatment

PACT: Adverse Events

Adverse Event	t-PA	Placebo	PValue
Major bleeding	12.9%	13.5%	0.84
<i>Stroke (any)</i>	<i>0.7%</i>	<i>0.7%</i>	<i>0.99</i>
Intracranial hemorrhage	0.3%	0.3%	0.99
Emergencyvascularization	7.3%	7.2%	0.98
Hospital death	3.6%	3.0%	0.64
30-day death	3.6%	3.3%	0.81

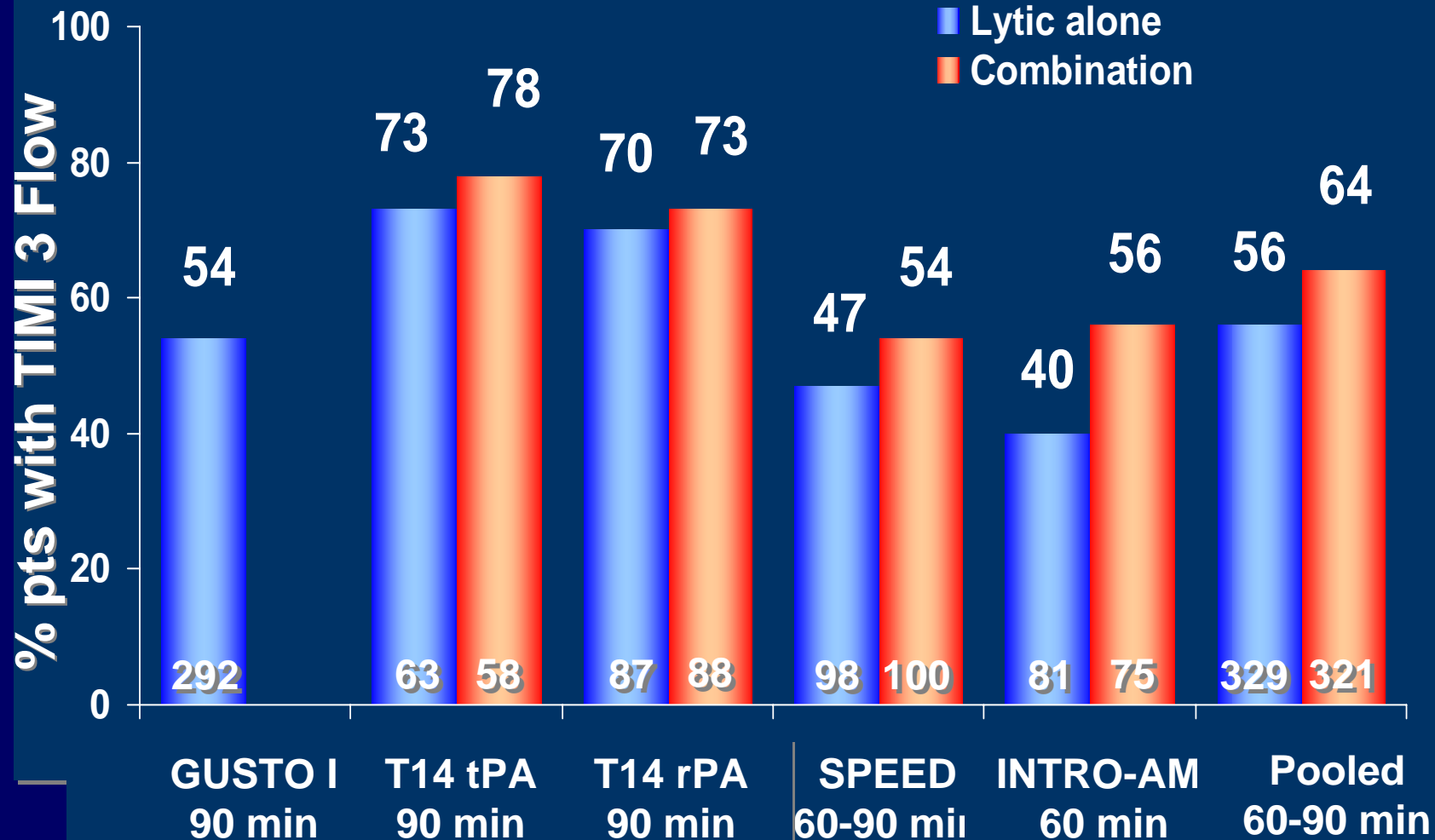
Adapted from Ross AM, et al. *J Am Coll Cardiol.* 1999;34:1954-1962.

Patency of the Infarct Artery on Catheter Laboratory Arrival (Core Laboratory)



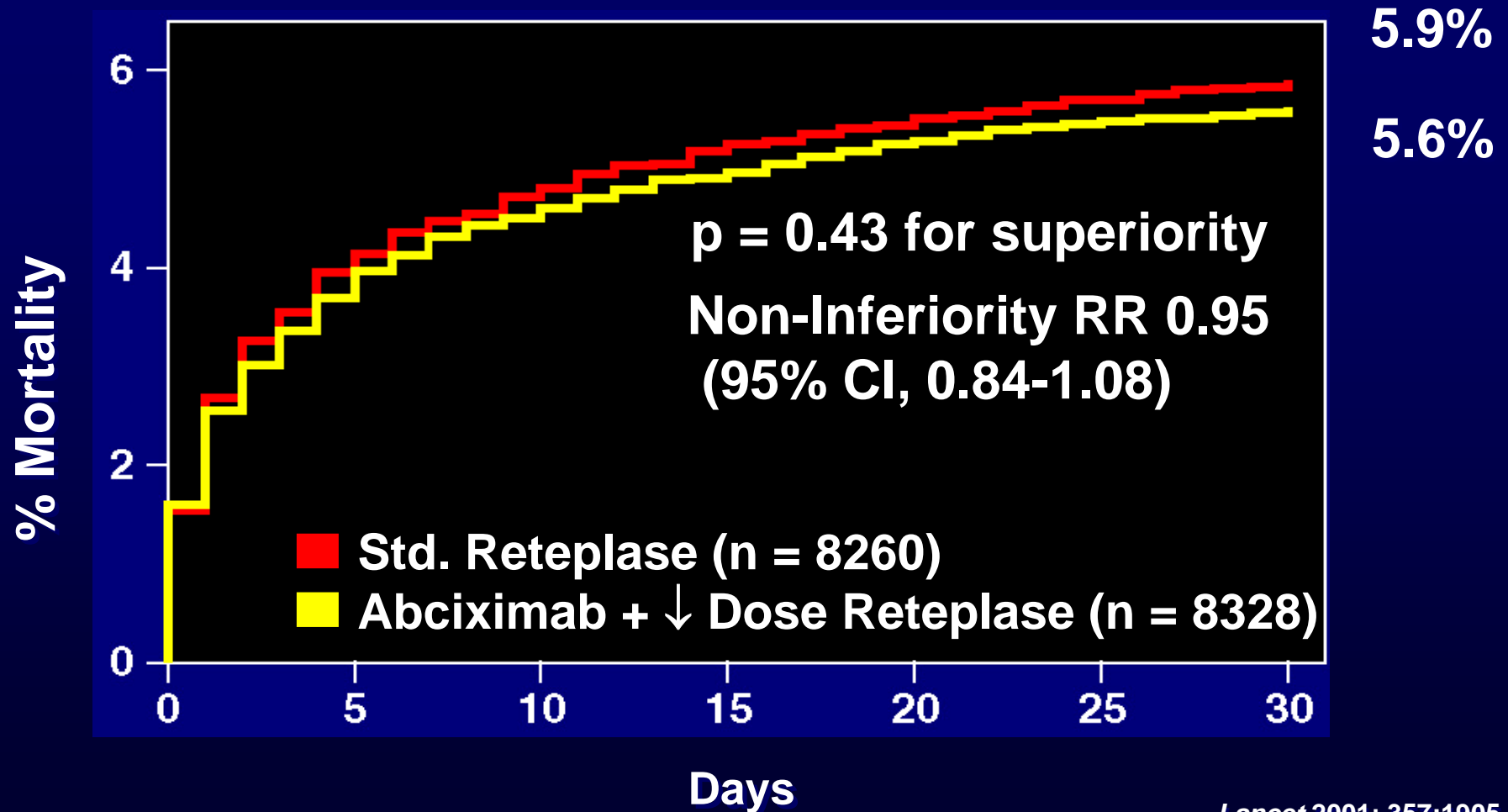
**All comparisons $P < 0.001$.*

Fibrinolytic + GP IIb/IIIa inhibitor

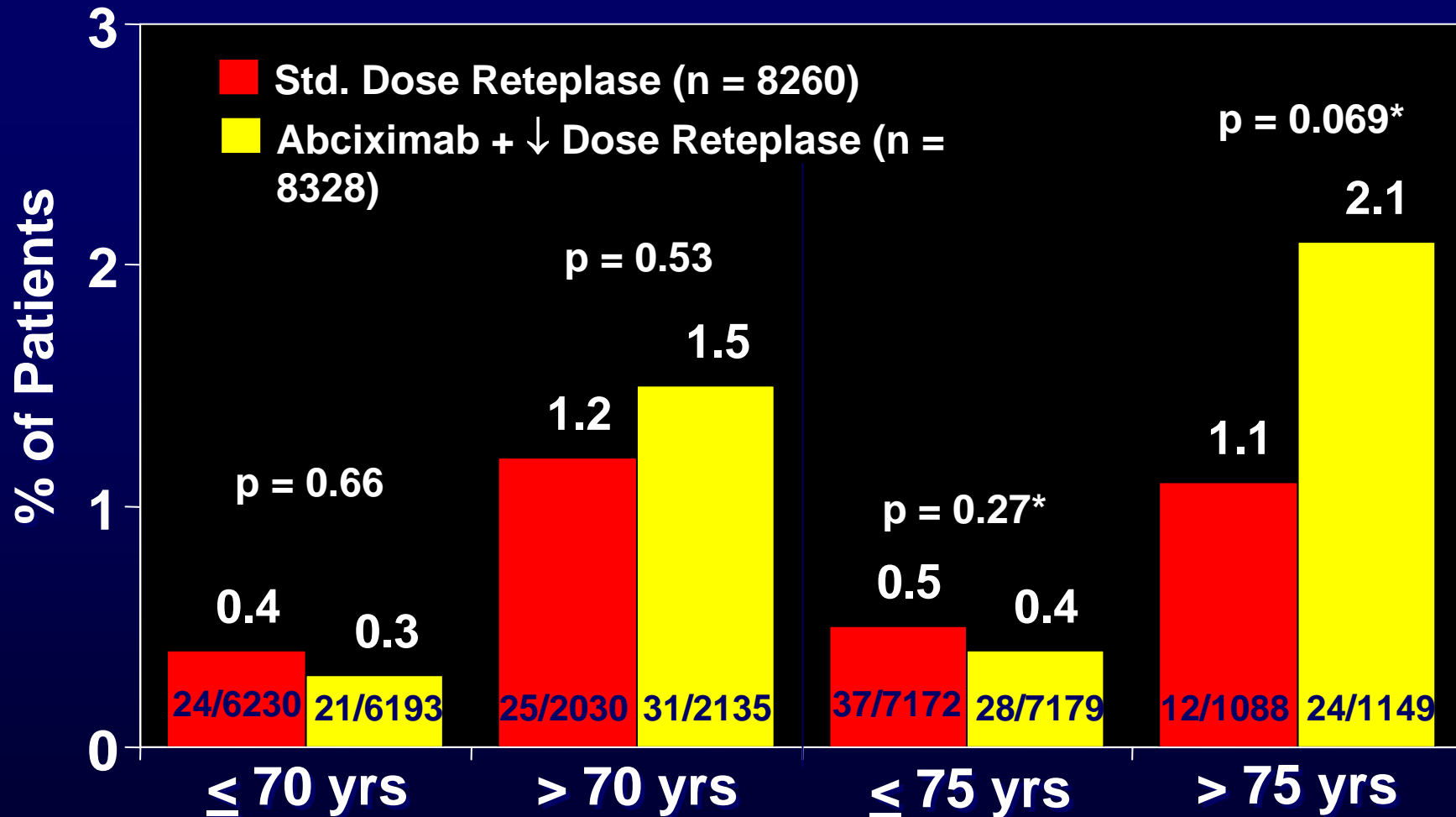


GUSTO-V

Primary Endpoint: 30 Day Death



GUSTO V: ICH by Age Group



* Significant treatment interaction for the age 75 dichotomy; $p = 0.033$; *Lancet* 2001; 357:1905-14

RAPPORT

ReoPro in Acute myocardial infarction and Primary PTCA Organization Randomized Trial

- N=483
- Abciximab in the ER or Cath Lab

30-day MACE	Any drug (n=409)	Int to treat (n=483)
Control	12.0	11.2
Abciximab	4.6	5.8
P value	0.005	0.038

- 6 month MACE: no difference

ADMIRAL

Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up

Event	*Abciximab (n=150)	Placebo (n=150)	p
Death, MI, urgent TVR at 30 d	10.7%	20.0%	0.03
*26% received in ambulance or ER			
TIMI-3 initial	21%	10%	<0.01
24 h	86%	78%	<0.03
LVEF 24 h	55%	51%	
30 d	63%	55%	

Tirofiban Given in the Emergency Room before Primary Angioplasty (TIGER-PA) Pilot Study

**David P. Lee, M.D., Alan C. Yeung, M.D.,
Donald Schreiber, M.D., Michelle Huston, M.D.**

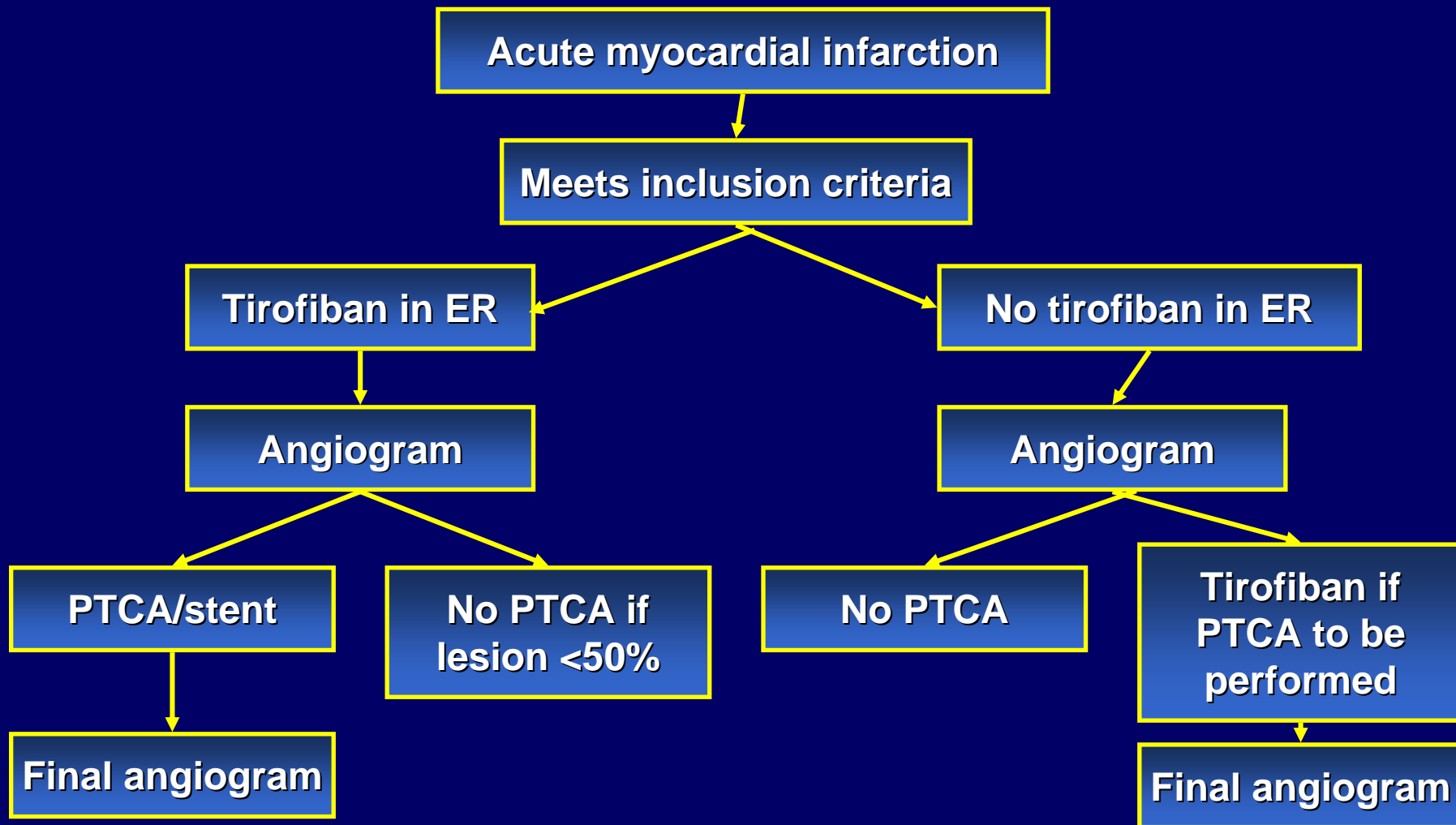
STANFORD



TIGER-PA



Pilot





TIGER-PA

Pilot



- **Dosing**
 - **Tirofiban: 10 $\mu\text{g}/\text{kg}$ over 3 minutes, then 0.15 $\mu\text{g}/\text{kg}/\text{min}$ x 24 hours**
 - **Heparin**
 - **Early: 70U/kg IV bolus, then 7.5 U/kg/hr**
 - **Delayed: 100U/kg IV bolus, then 10 U/kg/hr**
 - **All other medications including NTG, β -blockers at the investigator's discretion**



TIGER-PA

Pilot



- **Endpoints**

- **Primary endpoint**

- TIMI flow
 - TIMI frame counts

- **Secondary endpoint**

- **Bleeding**

- minor: Hct ↓ $\geq 10\%$ or Hb ↓ $\geq 3\text{g/dl}$
 - major: Hct ↓ $\geq 15\%$ or Hb ↓ $\geq 5\text{g/dl}$
 - Thrombocytopenia (PLTs < 90000)



TIGER-PA

Pilot



- **Endpoints**
 - **Tertiary endpoint (30 days)**
 - **Repeat coronary revascularization**
 - urgent vs. nonurgent
 - **Death (from any cause)**
 - **New MI (CPK>2x normal)**
 - **Hospitalization for refractory ischemia**



TIGER-PA

Pilot



- **Adjuvant therapy**
 - If a stent is placed, ticlopidine 250 mg POBID or clopidogrel 75 mg POQD $\times \geq 14$ d
 - Heparin may be stopped temporarily for early sheath removal



TIGER-PA

Pilot



- **Data analysis**
 - **Primary endpoint**
 - **Blinded observer for TIMI frame count and flow at baseline and after PTCA**
 - **Secondary endpoint**
 - **Data monitoring for CBC and CPKs**
 - **Safety monitor for bleeding events**
 - **Tertiary endpoint**
 - **Clinical follow-up by chart review and telephone**



TIGER-PA



Pilot

Demographics

<i>Characteristic</i>	<i>Early</i>	<i>Late</i>	<i>p</i>
Age (y)	63.5 ± 12.6	66.4 ± 14.3	NS
Gender (%male)	60	64	NS
%Diabetes	24	24	NS
%HTN	36	40	NS
%Hyperlipidemia	32	32	NS
%Prev CAD	12	10	NS



TIGER-PA

Pilot



Demographics

<i>Characteristic</i>	<i>Early</i>	<i>Late</i>	<i>p</i>
CP duration (h)	3.0 ± 2.0	3.0 ± 1.8	NS
Door-to-tirofiban (min)	55.7 ± 18.0	81.8 ± 17.7	<0.001
Door-to-balloon (min)	88.9 ± 20.7	82.7 ± 20.0	NS

33 minute mean from drug-to-balloon



TIGER-PA



Pilot

Angiographic Outcomes

<i>Characteristic</i>	<i>Early</i>	<i>Late</i>	<i>p</i>
<i>Culprit Vessel (%)</i>			
LAD	40	36	NS
LCX	20	20	NS
RCA	40	44	NS
<i>Initial TGF (%)</i>			
3	32	10	0.007
2	14	8	
1	10	2	
0	44	80	



TIGER-PA



Pilot

Angiographic Outcomes

<i>Characteristic</i>	<i>Early</i>	<i>Late</i>	<i>p</i>
Initial CTFC	44 ± 20	66 + 23	0.005
% Initial TMPG-3	32	6	0.001
% Final TGF-3	92	92	NS
Final CTFC	18 ± 8	16 ± 8	NS
% Final TMPG-3	50	40	NS

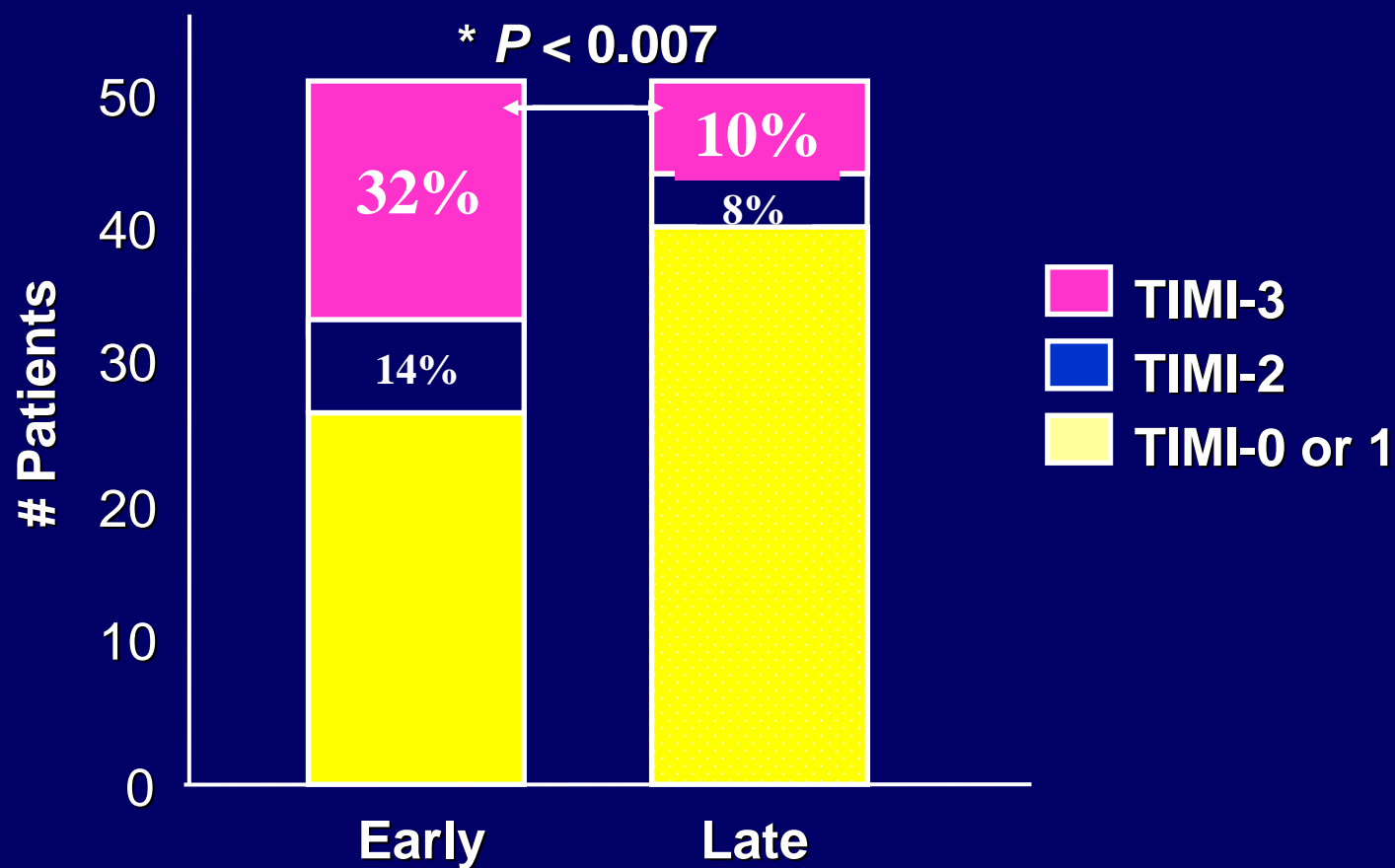


TIGER-PA



Pilot

Initial TIMI-Grade Flow



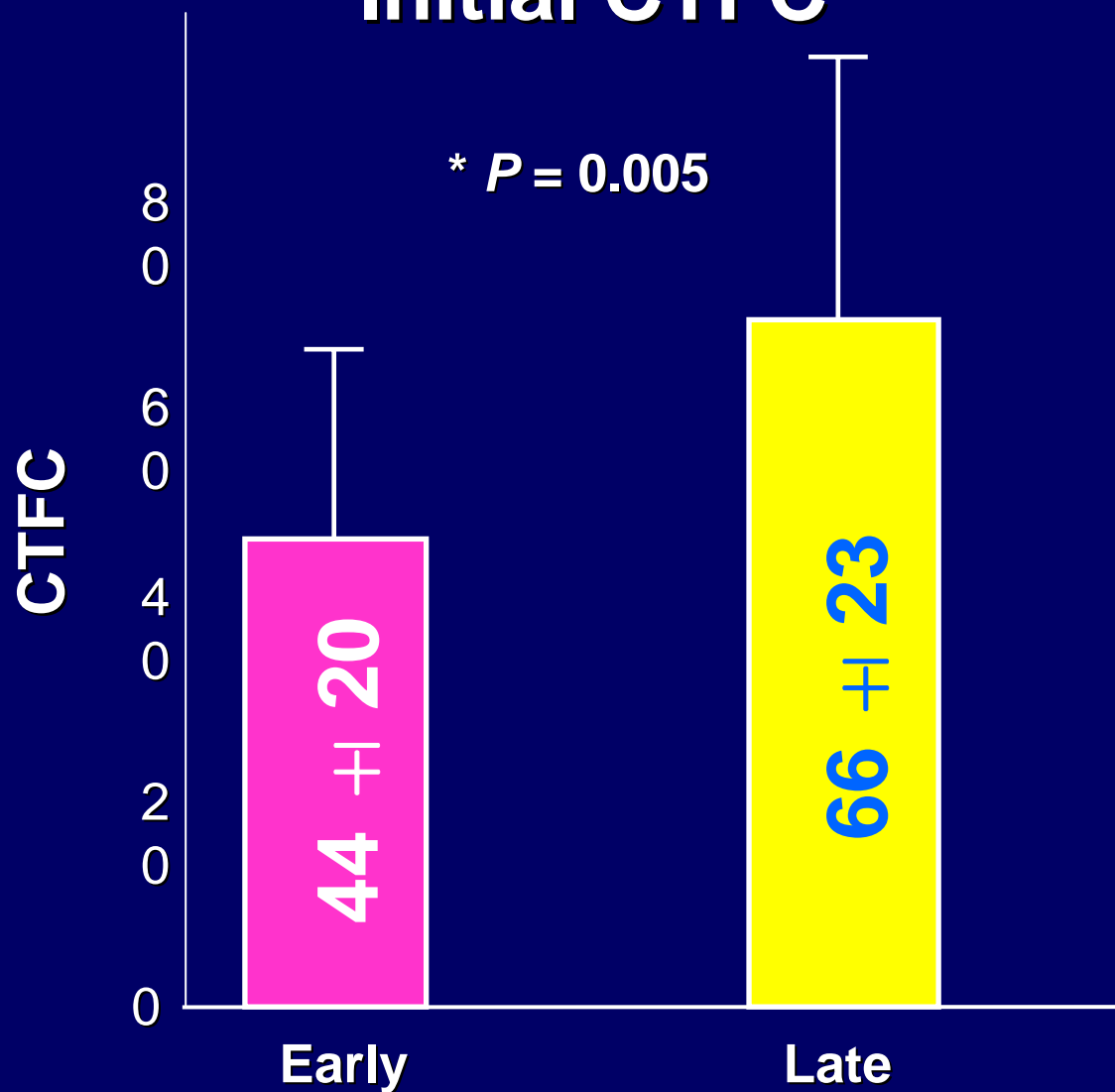


TIGER-PA



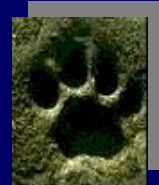
Pilot

Initial CTFC



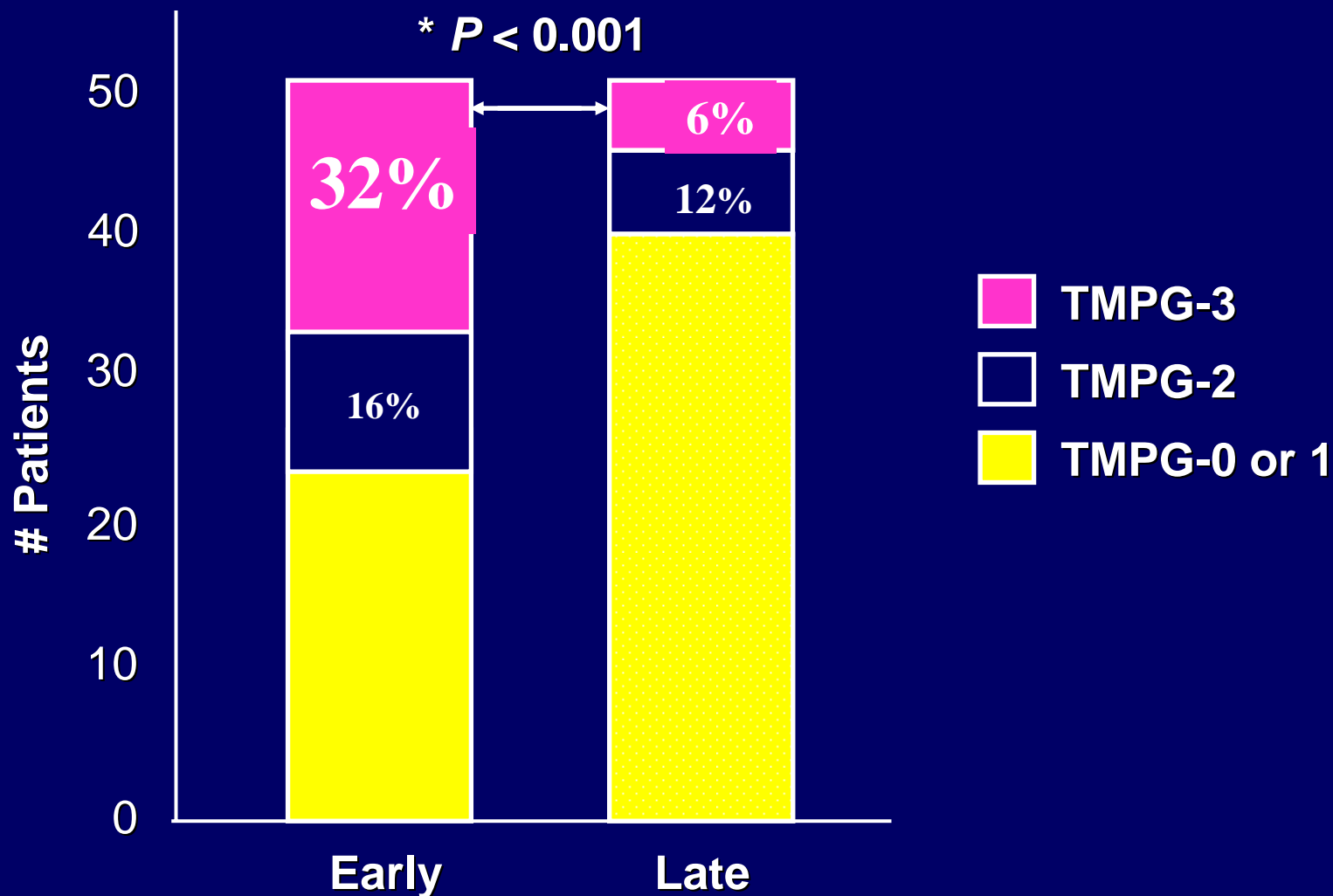


TIGER-PA



Pilot

Initial TIMI-Myocardial Perfusion Grade





TIGER-PA



Pilot

Clinical Outcomes

	Early	Late	p
Peak CPK	1924 ±	2260 ± 1959	NS
Time-to-peak	10.0 ¹⁶⁹⁹ ± 7.1	11.1 ± 6.5	NS
30-d Composite	6%	10%	NS
Death	2%	2%	NS
Re-MI	0	2%	NS
Rehosp	4%	6%	NS
Urgent TVR	0%	2%	NS



TIGER-PA



Pilot

Clinical Outcomes

	ER	Cath Lab	p
*Minor bleeding	10%	6%	NS
*Major bleeding	2%	2%	NS
Transfusions	10%	8%	NS
PLT < 100K	4%	0%	NS

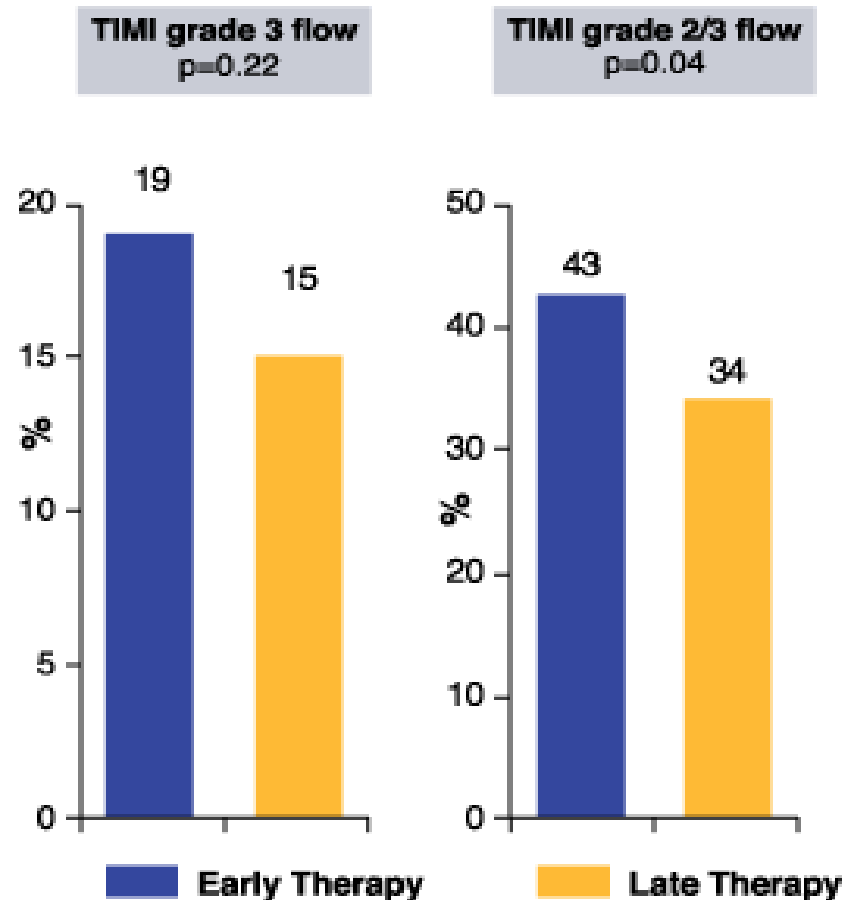
** TIMI-defined*

GP IIb/IIIa Summary

- **GP IIb/IIIa receptor inhibitors may be beneficial as an adjunct in AMI treated with primary angioplasty**
- **Safe and well-tolerated**
- **Is there a long-term benefit?**

ON-TIME

Trial Design: ON-TIME was a randomized trial of early (in ambulance or referral center; n=251) vs delayed (in the catheterization lab; n=256) tirofiban therapy in patients with ST elevation myocardial infarction undergoing percutaneous coronary intervention (PCI). The primary endpoint was TIMI grade 3 flow at initial angiography.



Results

- In early therapy arm, tirofiban administered mean of 59 minutes earlier than in late therapy arm
- No difference between treatment arms in primary endpoint of TIMI grade 3 flow, but patency (TIMI 2 or 3 flow) ↑ in early tirofiban arm (Figure)
- Thrombus presence ↓ in early tirofiban arm (25% vs 32%, p=0.06)
- No difference in post-PCI TIMI flow grade 3 (89% vs 91%), TIMI frame count (27 vs 26 frames) or myocardial blush grade 3 (51% vs 53%)

Conclusions

- Among ST elevation MI patients undergoing PCI, early administration of tirofiban therapy was not associated with a difference in primary endpoint of TIMI flow grade 3 compared with cath lab administration of tirofiban, but early therapy was associated with ↑ in patency (TIMI flow grade 2/3) and ↓ in thrombus

Presented at ESC 2003

www.cardiosource.com

On-Time

Trends positive:

- Thrombus 60% vs 73%
- Blush before PCI 30% vs 22%
- Ambulance patients mortality 3.7% vs 4.5%

ADVANCE-MI

↑ ST / LBBB
n = 5640

Eptifibatide + 1/2 TNK

Eptifibatide

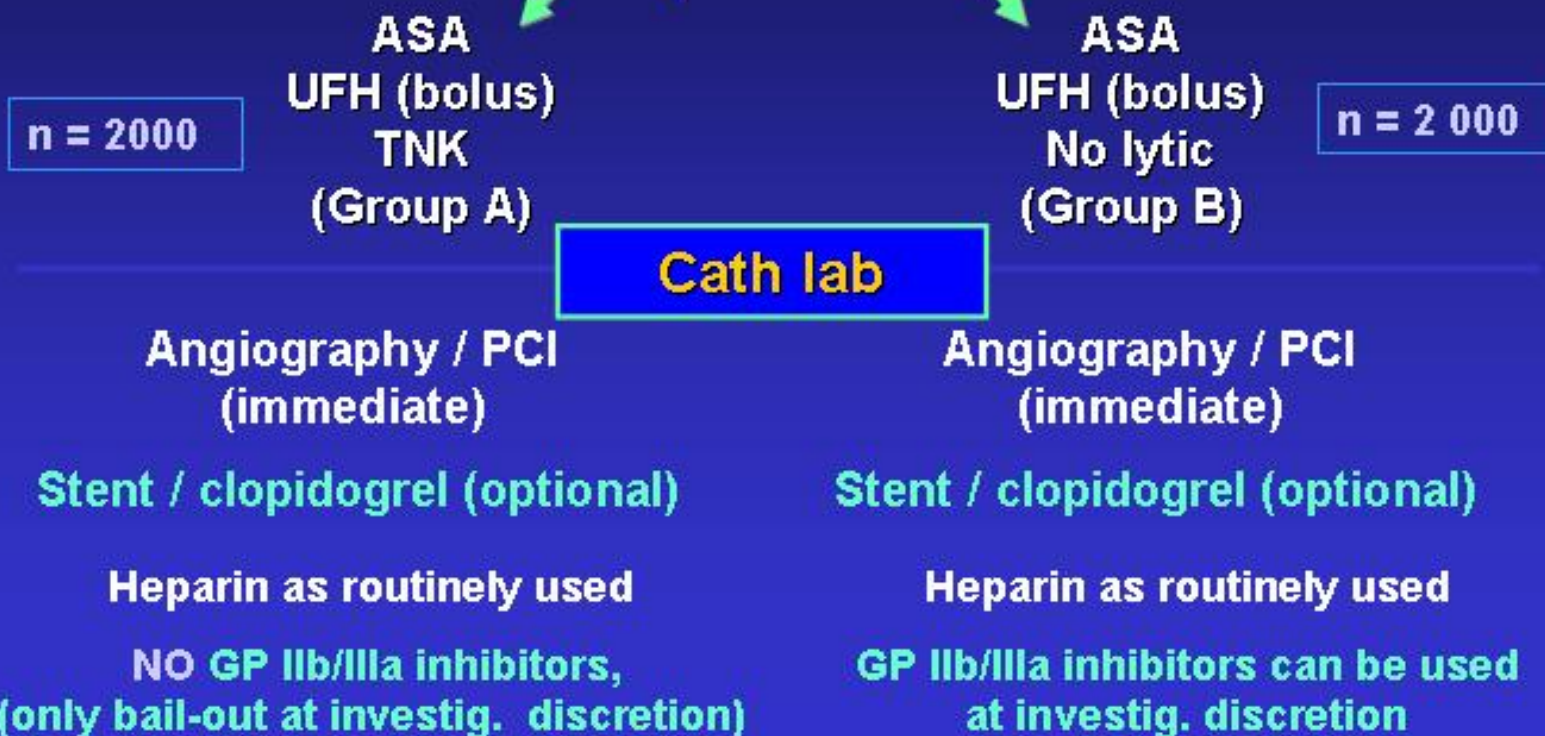
Primary angioplasty (LMWH or UFH)

*Primary endpoint at 30 days : death or
left ventricular failure*



Study design

Randomise
AMI
open label



CARESS IN AMI

(Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction)

N = 1800
AMI < 12 h

Medical Treatment

Half dosage r-PA 5 IU 30 min interval
plus full dose abciximab during 12 hours

↓
Transfer for PTCA only if
Sustained ischemia
< 50% ST segment resolution

Facilitated angioplasty

Half dosage r-PA 5 IU 30 min interval
plus full dose abciximab during 12 hours

↓
Direct transfer for
facilitated angioplasty

Primary endpoint at 30 days
Mortality, re-infarction and refractory ischemia

FINESSE

↑ ST / LBBB

Abciximab +
1/2 rt-PA

Abciximab
before angio

Abciximab
after angio

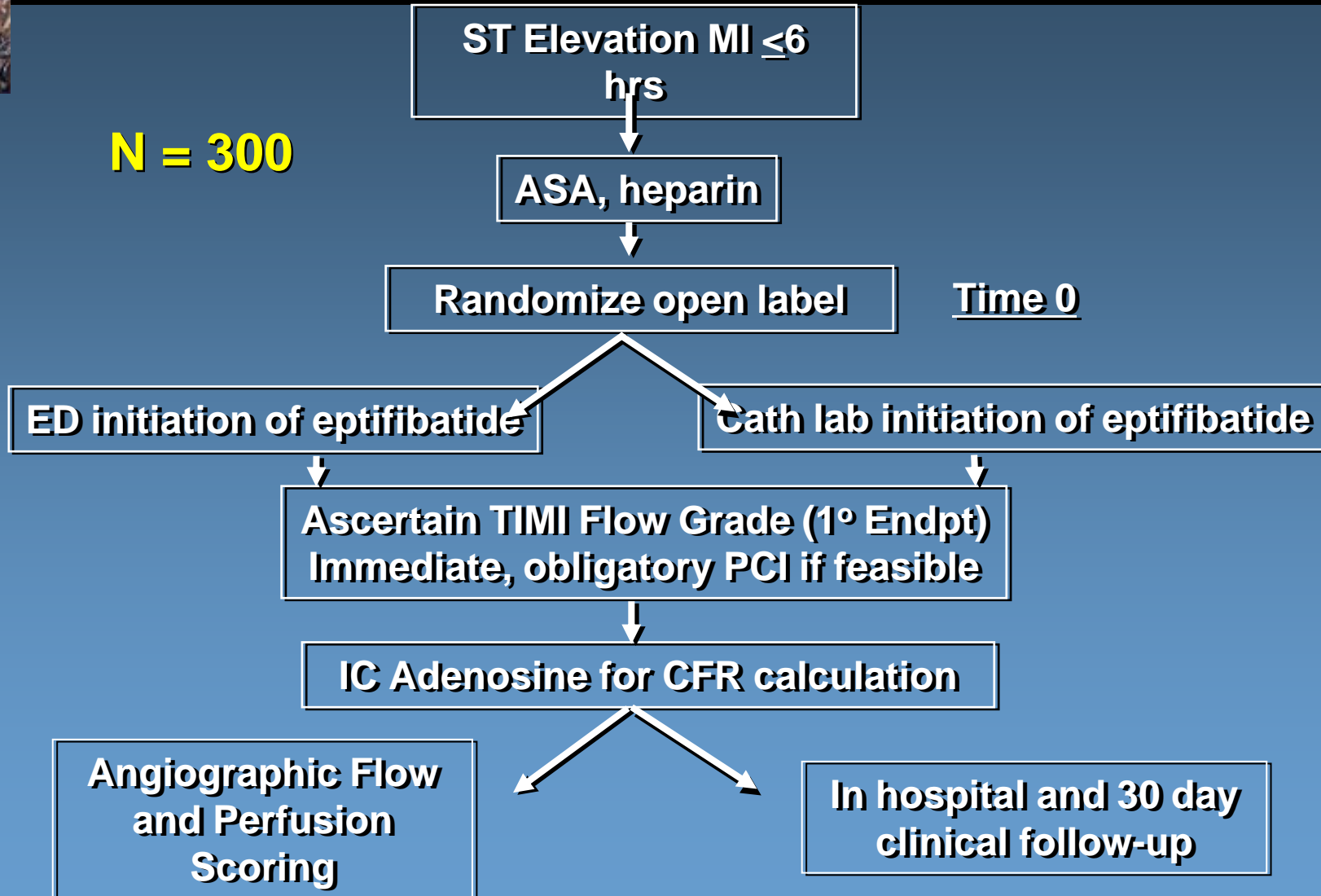
Primary angioplasty (LMWH or UFH)

*Primary endpoint at 30 days : death or
left ventricular failure*



TITAN: Design Overview

N = 300





TITAN: Study Procedures

STEMI < 6 HRS

ASA 160-325 mg pO

N = 300

HEPARIN 60 U/kg bolus (Max 4000U) and 7U/kg infusion (Max 800 U/hr)

**“EARLY
EPTIFIBATIDE”**

**RANDOMIZE
“= TIME ZERO”**

**“CATH LAB
EPTIFIBATIDE”**

**EPTIFIBATIDE
180/2.0/180**

**TRANSFER TO CATH
LAB**

DIAGNOSTIC ANGIO

**TRANSFER TO CATH
LAB**

DIAGNOSTIC ANGIO

**EPTIFIBATIDE
180/2.0/180**

ASCERTAIN PRIMARY ENDPOINT (TIMI Flow) & PERFORM PCI

**ANGIOGRAPHIC
PERFUSION SCORE**

**TIMI FLOW AND
CORONARY FLOW
RESERVE**

**IN-HOSPITAL AND 30
DAY CLINICAL
EVENTS**

What are the issues in Prejunctive Therapy ?

- The increase perfusion with IIBIIIa inhibitor is small but consistent so far.
- Will increase dose (different IIBIIIa) improve the results ?
- Will giving it in the ambulance provides better reperfusion ?
- Will use of LMWH or direct thrombin inhibitor helps ?

Stay tune.....TIGER-PA 2