The role of pre hospital thrombolysis

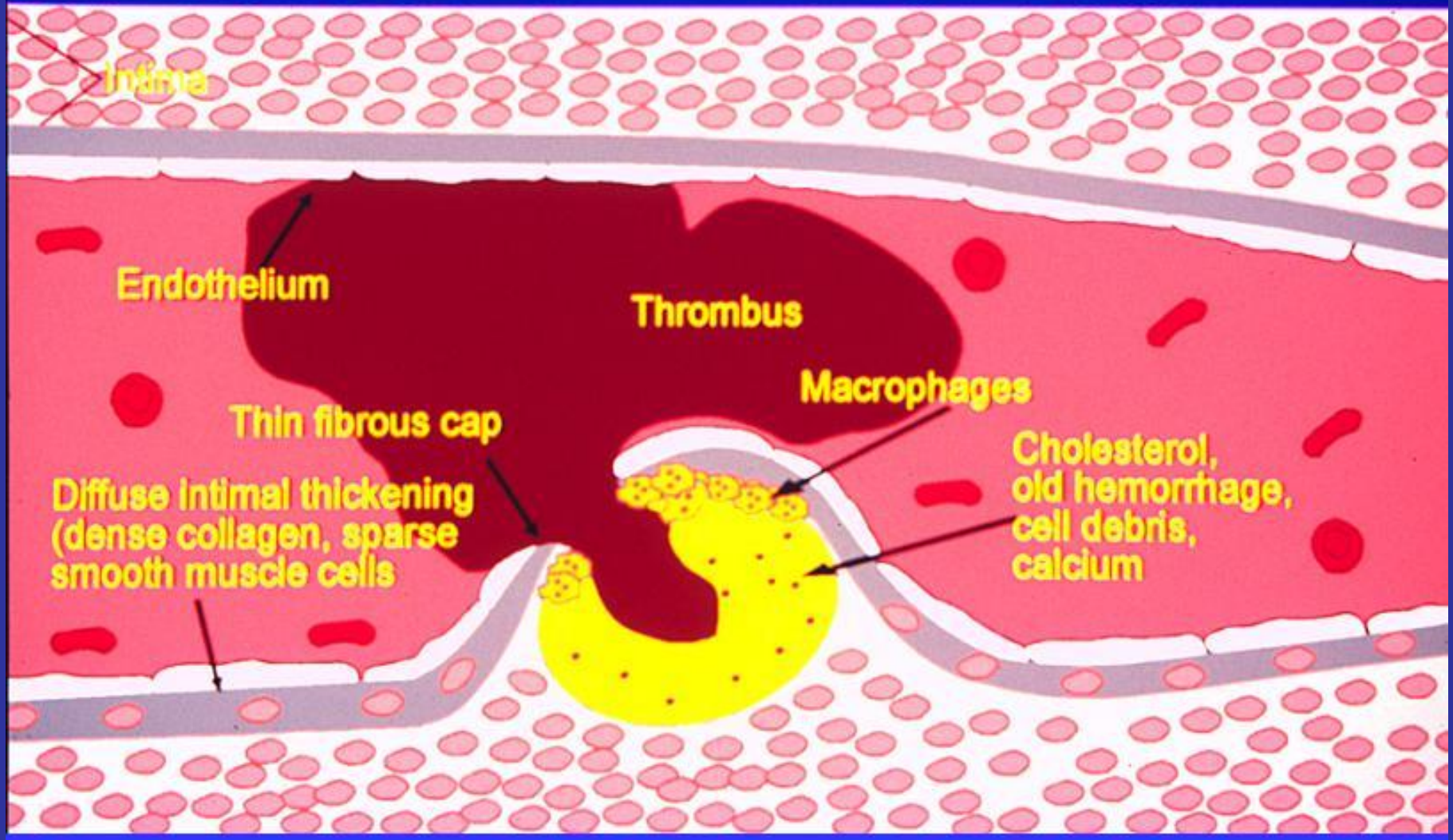
Aaron Frimerman
Hillel Yaffe Medical Center
Hadera
Israel

Is thrombolysis still valid?

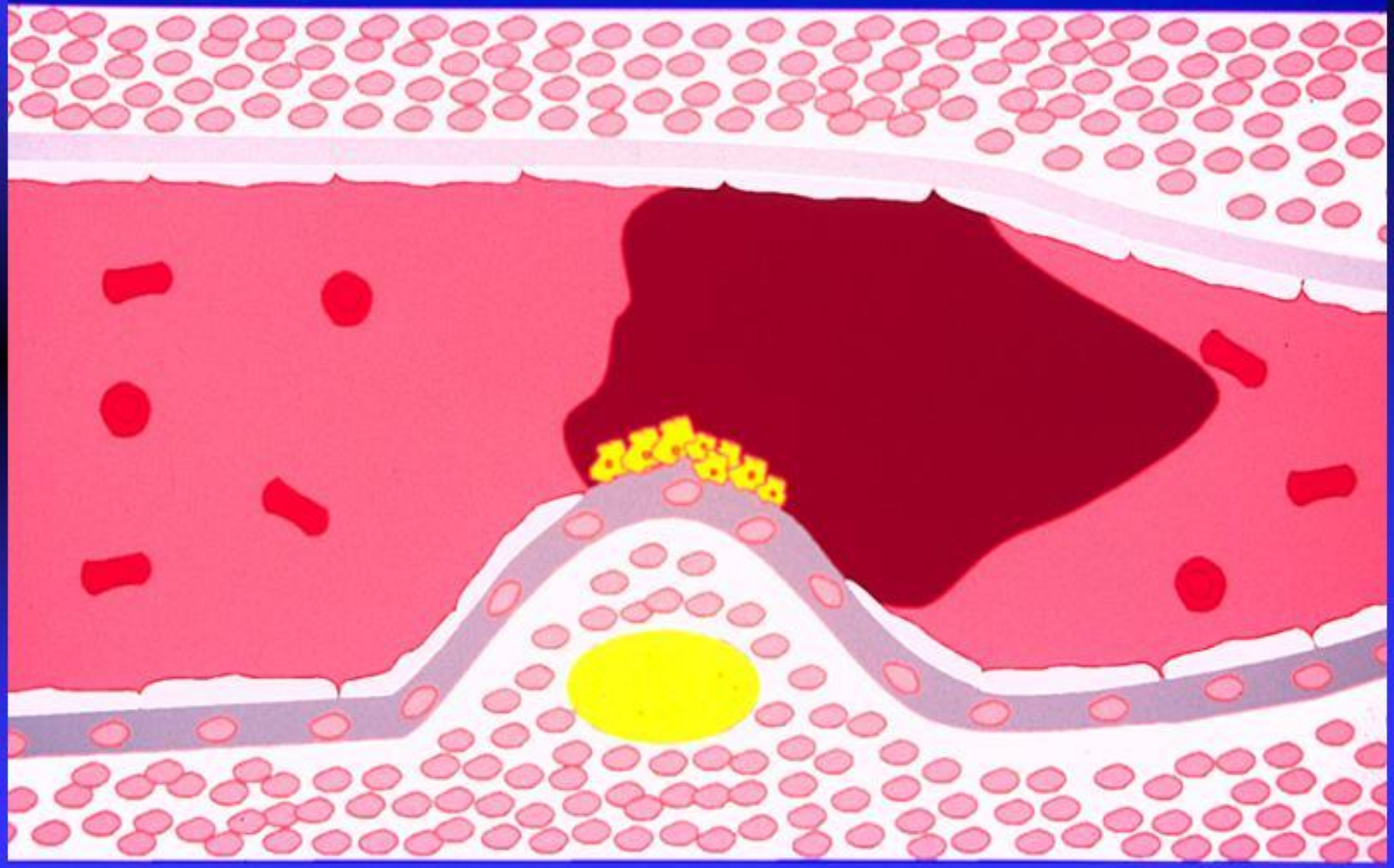
Disclosure

I am an Interventional Cardiologist

Anatomy of 60% of Fatal Myocardial Infarctions: Rupture



Anatomy of 30% of Fatal Myocardial Infarctions: Erosion



- **STEMI is mainly a thrombotic event**
- **It induces ischemia**
- **As a consequence: myocardial damage, CHF, death**
- **Our goal: to minimize all the above with a long-lasting effect**

Reperfusion-the treatment of STEMI

- **Goal**: rapidly achieving high quality perfusion at the **epicardial and microcirculatory vessels, and the myocytes** levels (which are not identical) and **preventing reocclusion** after initial success

- Is a prompt, fast, reperfusion beneficial for the patient?

Primary PCI vs Fibrinolysis
Reperfusion and Re-vascularization

- The artery dose not care how reperfusion is achieved as long as it is fast and long lasting
- **Primary PCI** (PPCI): Mechanical method-first reperfusion (balloon, thrombus aspiration), then re-vascularization (stent)
- **Fibrinolysis** (FL) (Thrombolysis-TL): Pharmacological method-reperfusion only

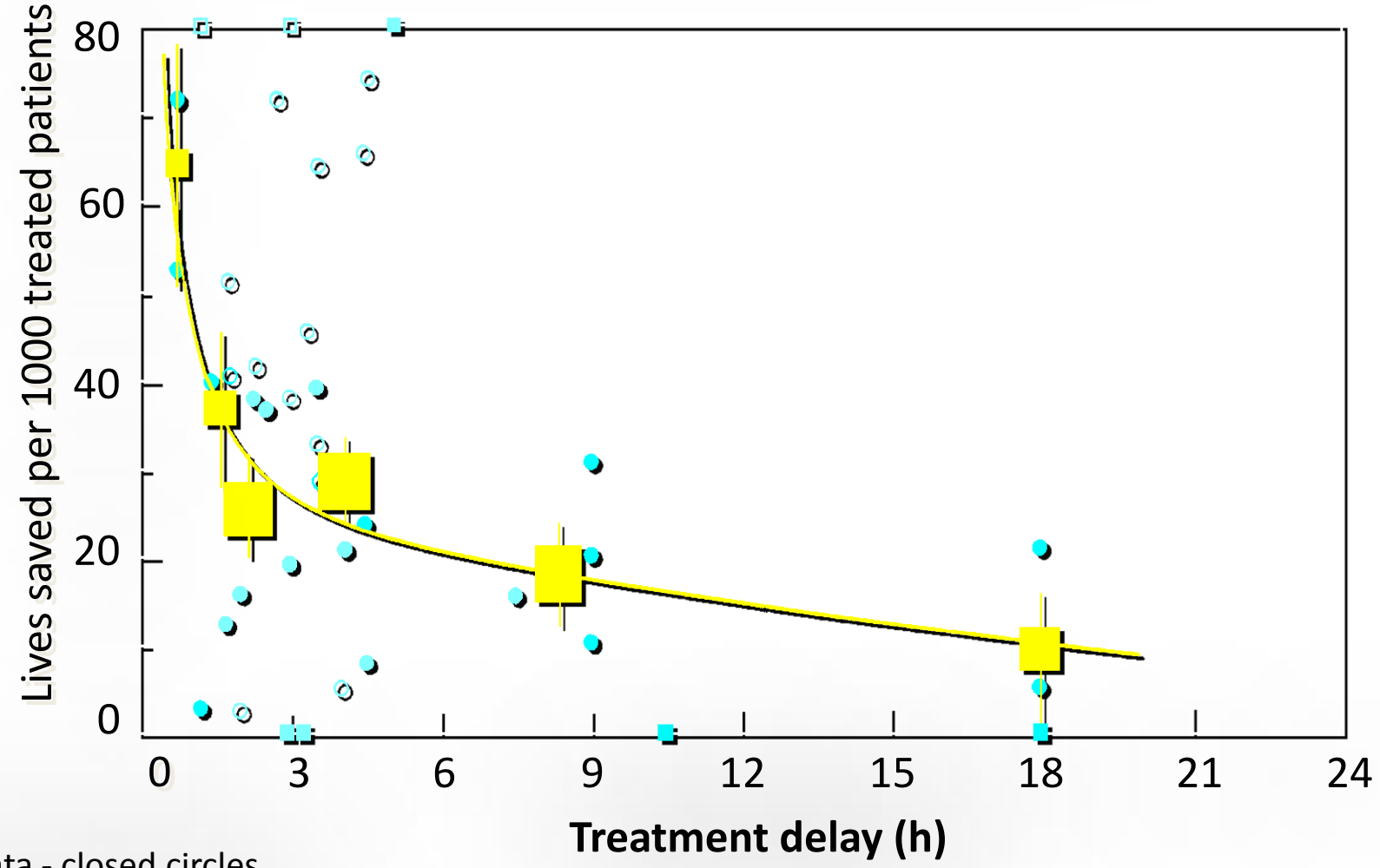
Reperfusion Factors

- **Patient:** age, co-morbidity, pt. time delay
- **Set up:** Cath. Lab. availability, hour of day
- **Time to reperfusion: "time is muscle, is survival"**
- **Lesion:** thrombus burden, complexity
- **What can we learn from the medical literature?**

“Time is muscle, is survival”

Reperfusion: the ‘golden hour’

Absolute reduction in 35 day mortality per 1000 patients treated



FTT data - closed circles
Smaller trials - open circles

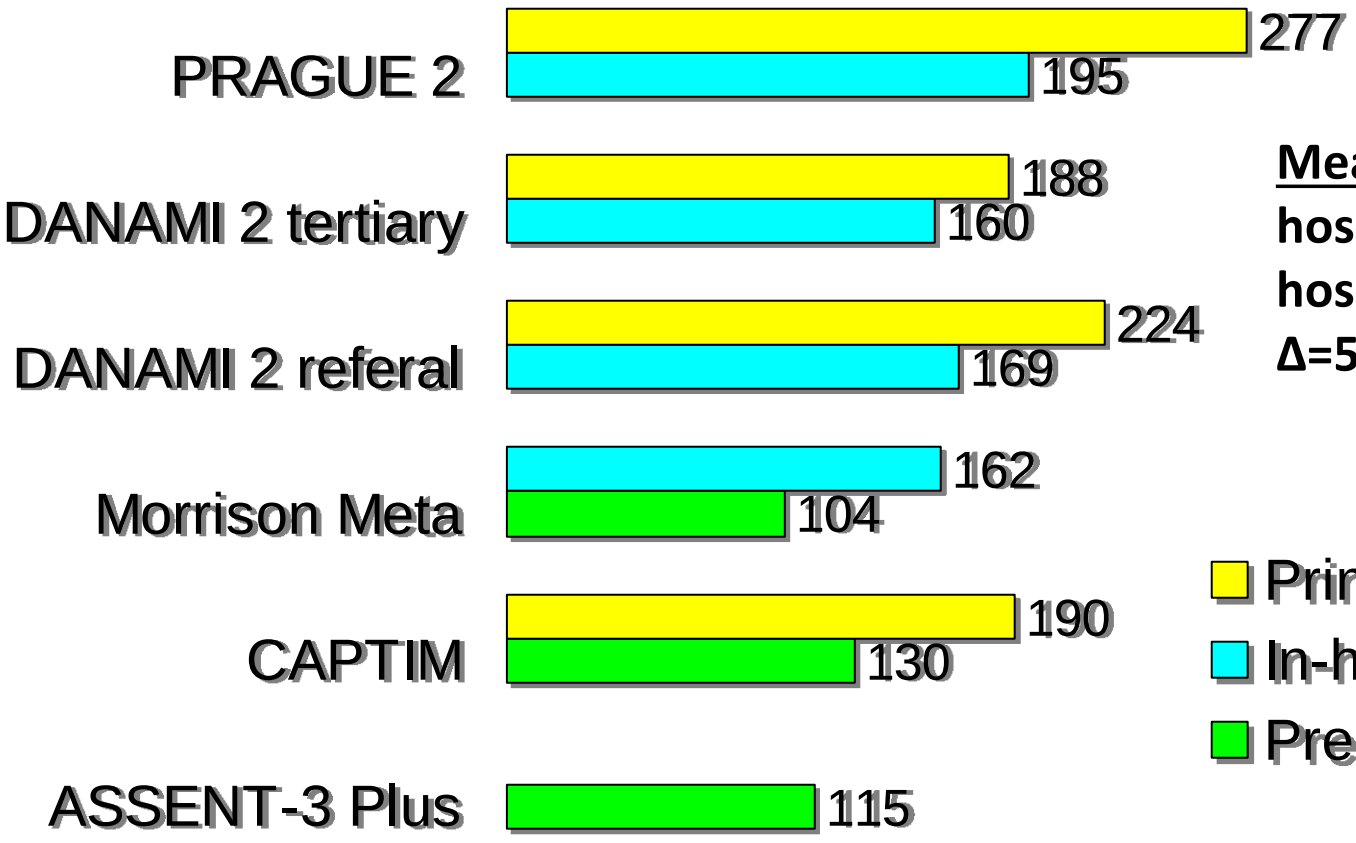
Boersma, Lancet 1996;348:771

PCI delay

Time difference between PCI vs TL, from symptom onset to treatment

Time from symptom onset to treatment in recent trials

PPCI delay=door to balloon minus door to needle

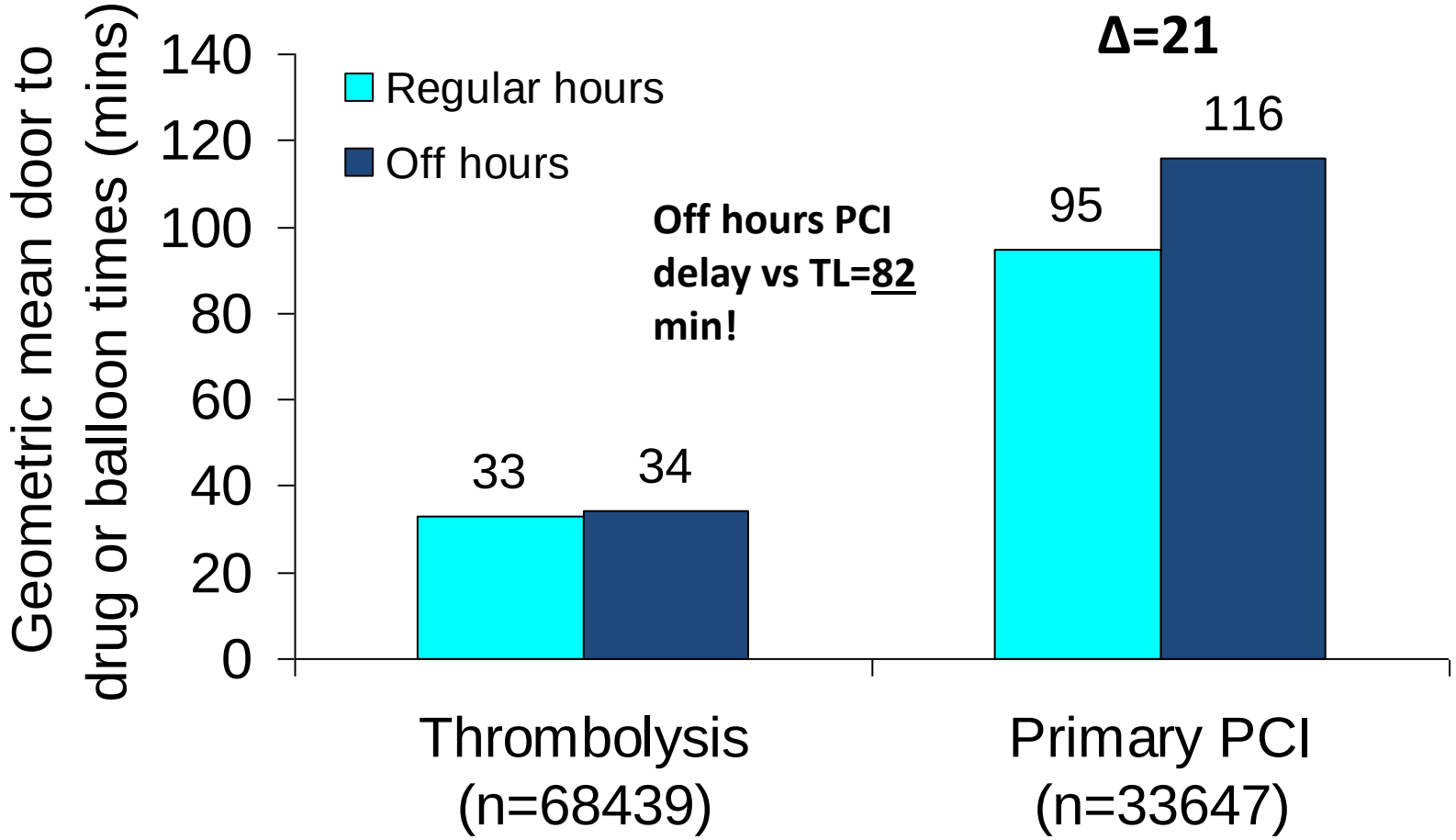


<u>Mean PCI delay</u>: in-hospital lysis=59, pre hospital lysis=114 min, Δ=55 min

“Time is muscle, is survival”

According to these studies, we can gain almost 2 hours by the pre-hospital TL approach compare to PPCI and theoretically save more heart muscle and improve survival

Relationship between time of day and time to reperfusion



Regular hours = weekdays 7am to 5pm

67.9% lysis and 54.2% PPCI were treated off hours

NRMI registry 1999-2002

Magid, JAMA 2005;294:803

ACSIS: Israeli registry 2000-2010

	Number	Symptoms to FMC (min)	Symptoms to reperfusion (min)
PPCI	899	108±38	179±235*
TL followed by PCI	383	106±37	122±45*

Mean PCI delay: 57 min

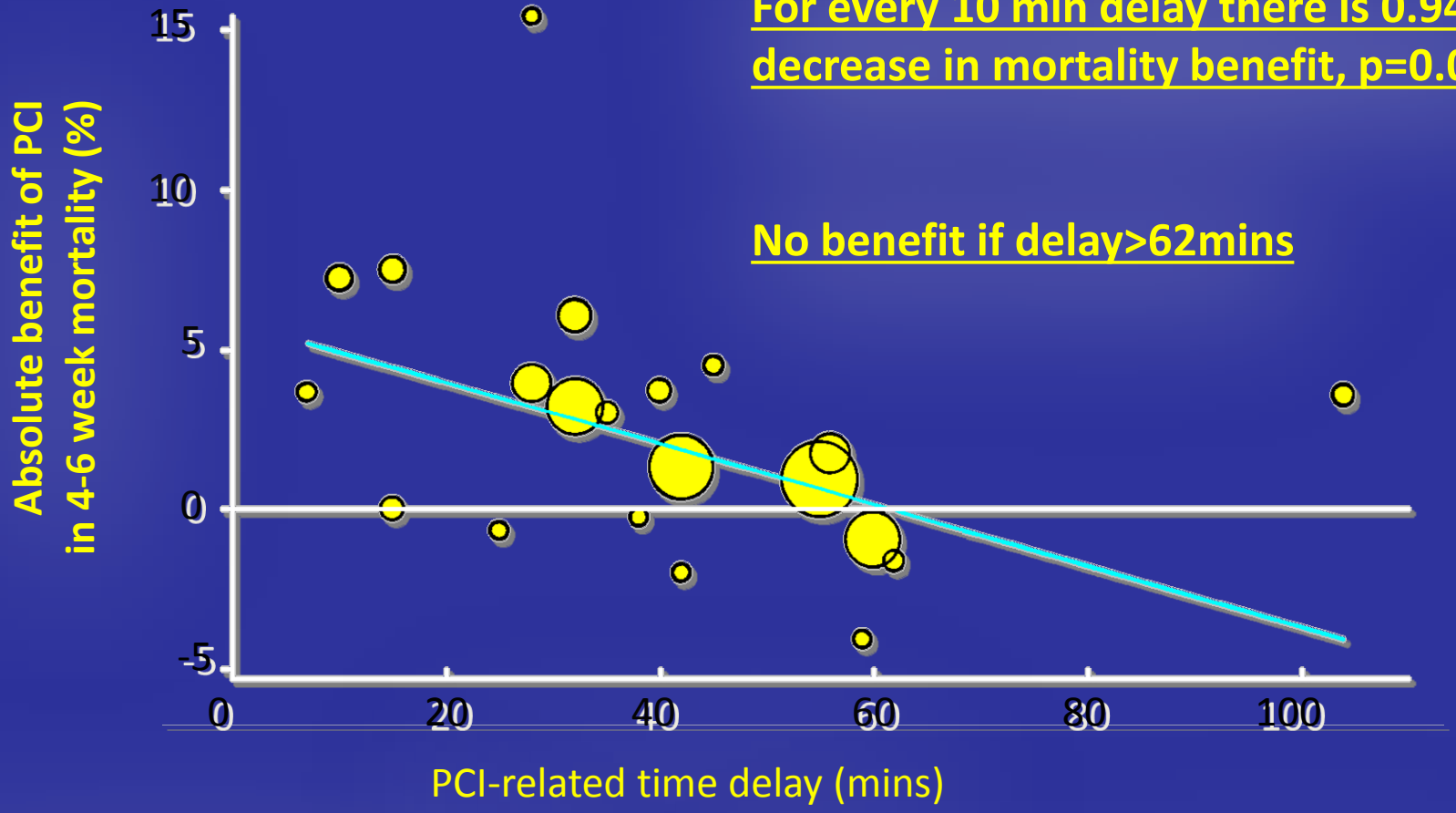
***P<0.001**

23 trials of PCI versus thrombolysis (n=7419)

Mean delay 39.5 min (SD 22.1)

For every 10 min delay there is 0.94% decrease in mortality benefit, p=0.006.

No benefit if delay>62mins



Circles reflect trial sample size

Blue line: weighted meta-regression

Nallamothu, Am J Cardiol 2003;92:824

Lesion factor

- PPCI is performed mainly at a totally occluded artery with high thrombotic burden

The challenge:

- Lesion crossing with guide wire
- Thrombus burden reduction-mechanical (TAPAS)? Pharmacological (INFUSE AMI)?
- Distal embolization-no solution so far
- Slow or no reflow-increases MACE tenfold
- Lethal reperfusion injury-permanent myocardium damage despite and maybe because, prompt and aggressive early reperfusion by PCI with good flow

N Engl J Med 2007; 357:1121

Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials

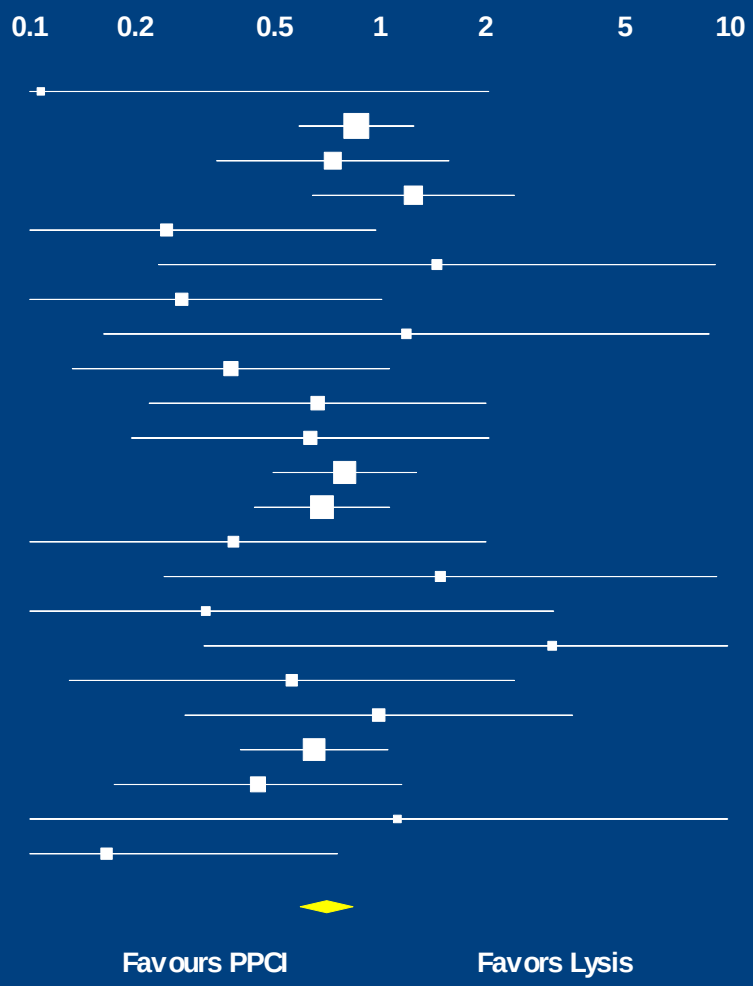
Ellen C Keeley, Judith A Boura, Cindy L Grines

Department of Internal Medicine, Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, TX, USA (E C Keeley MD); and William Beaumont Hospital, Royal Oak, MI (J A Boura MS, C L Grines MD)

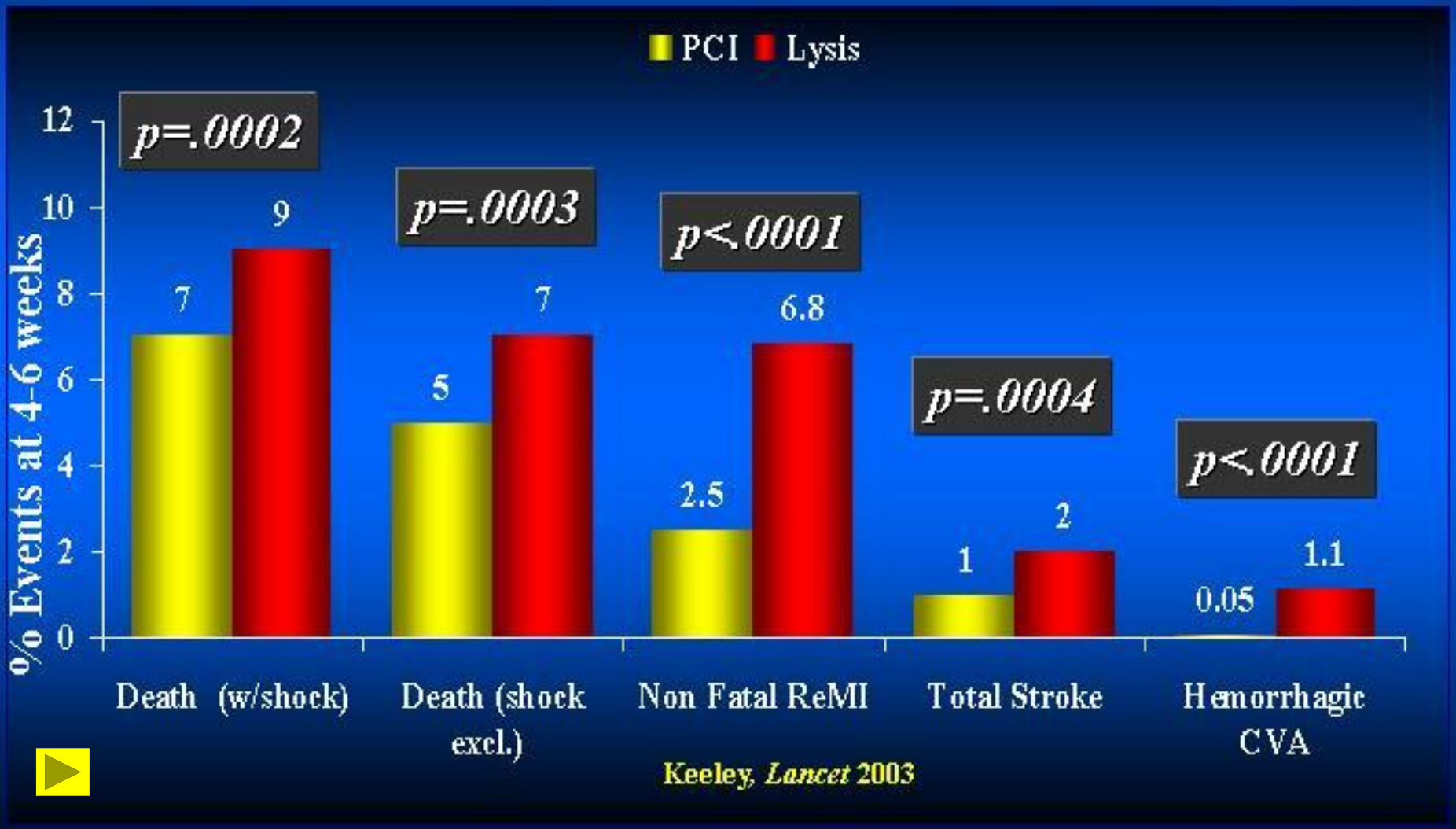
Lancet 2003; 361: 13–20

Primary PCI versus Thrombolysis - meta-analysis of 23 trials

Citation	Year	Treated	Control
Akhras	1997	0 / 42	4 / 45
Andersen	2002	52 / 790	59 / 782
Aversano	2002	12 / 225	16 / 226
Bonnefoy	2002	20 / 421	16 / 419
de Boer	2002	3 / 46	9 / 41
De Wood	1990	3 / 46	2 / 44
Garcia	1997	3 / 95	10 / 94
Gibbons	1993	2 / 47	2 / 56
Grines	1993	5 / 195	13 / 200
Grines	2002	6 / 71	8 / 66
Grinfeld	1996	5 / 54	8 / 58
GUSTO IIb	1997	32 / 565	40 / 573
Hochman	1999	71 / 152	84 / 150
Kastrati	2002	2 / 81	5 / 81
Le May	2001	3 / 62	2 / 61
Ribichini	1996	1 / 55	3 / 55
Ribiero	1993	3 / 50	1 / 50
Schomig	2000	3 / 71	5 / 69
Vermeer	1999	5 / 75	5 / 75
Widimsky	2002	29 / 429	42 / 421
Widimsky	2000	7 / 101	14 / 99
Zijlstra	1997	1 / 47	1 / 53
Zijlstra	1993	2 / 152	11 / 149
Combined (23)		**270 / 3872**	**360 / 3867**



Meta-Analysis of 23 Randomized Trials of PCI vs Lysis (n=7739)



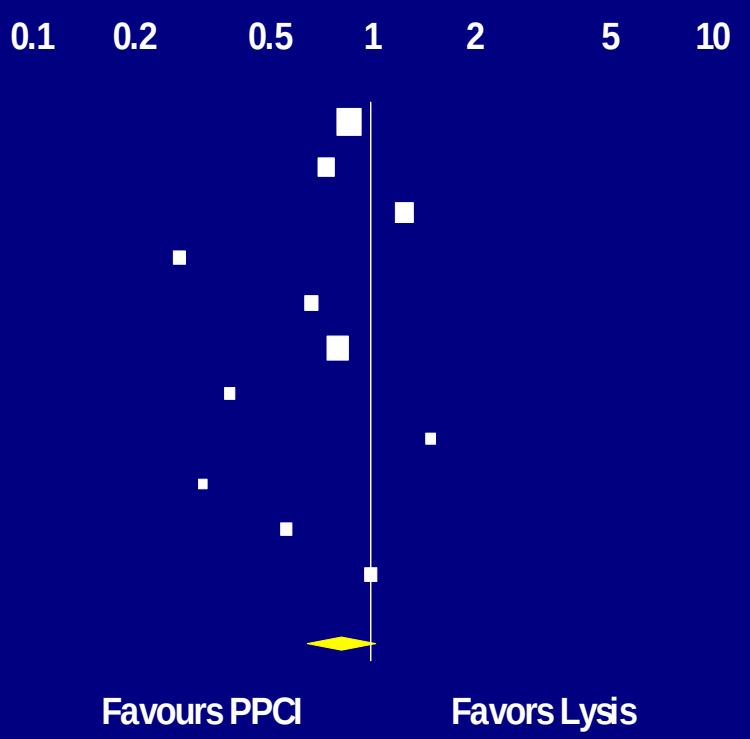
Keeley, *Lancet* 2003

Keeley meta-analysis of 23 trials
Some limitations…

- Suboptimal lytic strategies, many late comers...
  - The criterion for time to treatment was 6 h or less in 9 of the trials, 12 h in 13 trials, and up to 36 h in the SHOCK trial
    -streptokinase in 8 trials
- Many high risk patients with shock and CHF got lytic therapy! (mainly in the SHOCK trial with 63% in the lysis group)
- Most trials (15) had fewer than 200 patients
- 2% major bleeding and 0·4–2% need for vascular repair in PPCI patients
- Development of acute renal failure in 0·5–13% of PPCI patients
- PRAGUE-2: "The study results do not show difference between thrombolysis and PCI among patients with a **presentation time <3 hours".**

Primary PCI versus thrombolysis

	Citation	Year	Treated	Control
	Andersen	2002	52 / 790	59 / 782
	Aversano	2002	12 / 225	16 / 226
	Bonnefoy	2002	20 / 421	16 / 419
	Garcia	1997	3 / 95	10 / 94
	Grines	2002	6 / 71	8 / 66
	GUSTO IIb	1997	32 / 565	40 / 573
	Kastrati	2002	2 / 81	5 / 81
	Le May	2001	3 / 62	2 / 61
	Ribichini	1996	1 / 55	3 / 55
	Schomig	2000	3 / 71	5 / 69
	Vermeer	1999	5 / 75	5 / 75
Fixed	**Combined (11)**		**139 / 2511**	**169 / 2501**



Accelerated tPA trials, excluding Shock

OR 0.81, 95% CI 0.64-1.02, **P=0.07**

No routine revascularization after TL reperfusion!

- Most of the trials with no reference to post TL PCI or “NA”
- PRAGUE 2: “In the TL group, angiography was performed according to routine clinical indications: post MI angina, reinfarction, rescue PCI”. No numbers
- DANAMI 2: “PCI occurred in only **2.5%** of patients who got fibrinolysis”

Real scientific conclusions?

Most of the TL patients were left with no definitive re-vascularization that made them prone to re-MI and further MACE

For real scientific conclusions the comparison should have been between the PPCI patients and the TL patients that underwent early re-vascularization

Primary PCI in STEMI

	COR	LOE	References
Ischemic symptoms <12 h	I	A	(17,50,51)
Ischemic symptoms <12 h and contraindications to fibrinolytic therapy irrespective of time delay from FMC	I	B	(52,53)
Cardiogenic shock or acute severe HF irrespective of time delay from MI onset	I	B	(54–57)
Evidence of ongoing ischemia 12 to 24 h after symptom onset	IIa	B	(29,30)
PCI of a noninfarct artery at the time of primary PCI in patients without hemodynamic compromise	III: Harm	B	(58–60)

COR indicates Class of Recommendation; FMC, first medical contact; HF, heart failure; LOE, Level of Evidence; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

Fibrinolytic Therapy When There Is an Anticipated Delay to Performing Primary PCI Within 120 Minutes of FMC

	COR	LOE	References
Ischemic symptoms <12 h	I	A	(16,111–116)
Evidence of ongoing ischemia 12 to 24 h after symptom onset, and a large area of myocardium at risk or hemodynamic instability	IIa	C	N/A
ST depression except if true posterior (inferobasal) MI suspected or when associated with ST-elevation in lead aVR	III: Harm	B	(16,117–120)

COR indicates Class of Recommendation; FMC, first medical contact; LOE, Level of Evidence; MI, myocardial infarction; N/A, not available; and PCI, percutaneous coronary intervention.

Benefit to TL in “early comers”?

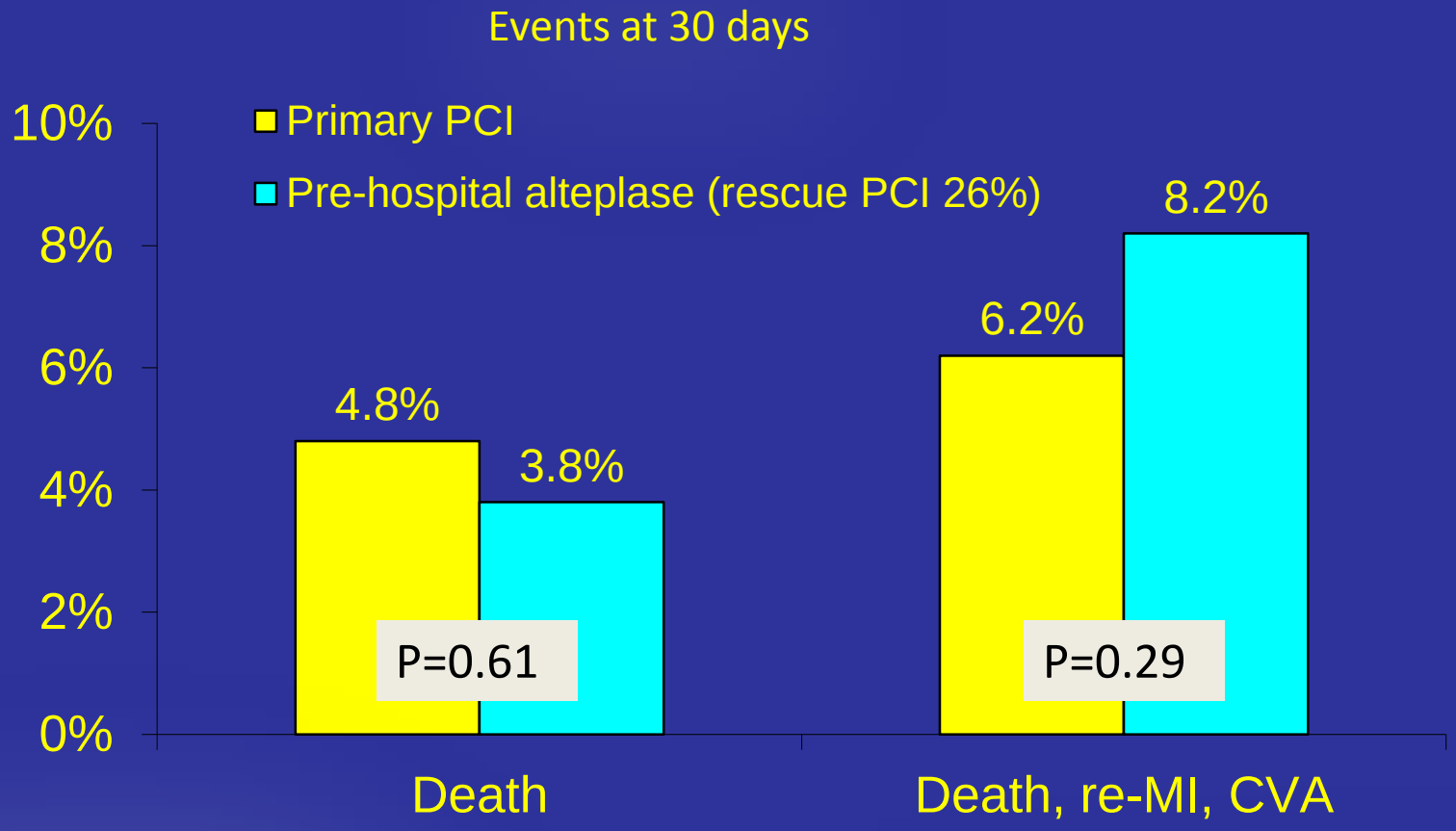
PPCI was accepted as superior to fibrinolytic therapy (TL) for STEMI, but there are more and more evidences that show otherwise in patients presenting soon after the onset of symptoms treated with TL

Smokers With ST-Segment Elevation Myocardial Infarction and Short Time to Treatment Have Equal Effects of PCI and Fibrinolysis

Thomas Rasmussen et al, *J INVASIVE CARDIOL 2012;24(8):401-406*

- 1572 patients with STEMI were randomized to either fibrinolysis or PCI for DANAMI-2
- 895 (57%) were identified as smokers
- Smokers with short time to treatment (<3 hours) benefited equally from PCI and fibrinolysis *P*=0.82
- There was a trend toward higher mortality in the PCI group

Comparison of primary PCI and prehospital thrombolysis in acute MI (CAPTIM n=840)



Planned 1200 patients
Symptoms to lysis 130 min
Symptoms to balloon 190 min

Bonnefoy, Lancet 2002;360:825

Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction-STREAM

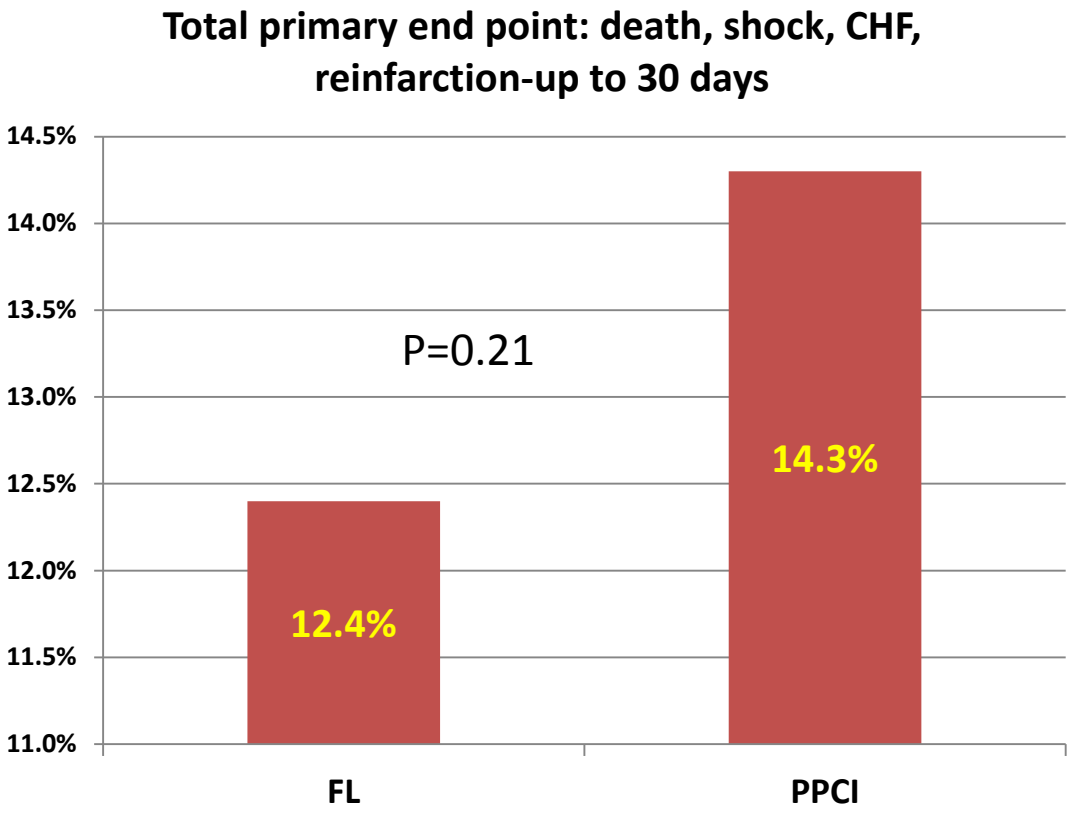
Paul W. Armstrong, M.D., Anthony H. Gershlick, M.D., Patrick Goldstein, M.D., Robert Wilcox, M.D., Thierry Danays, M.D., Yves Lambert, M.D., Vitaly Sulimov, M.D., Ph.D., Fernando Rosell Ortiz, M.D., Ph.D., Miodrag Ostojic, M.D., Ph.D., Robert C. Welsh, M.D., Antonio C. Carvalho, M.D., Ph.D., John Nanas, M.D., Ph.D., Hans-Richard Arntz, M.D., Ph.D., Sigrun Halvorsen, M.D., Ph.D., Kurt Huber, M.D., Stefan Grajek, M.D., Ph.D., Claudio Fresco, M.D., Erich Bluhmki, M.D., Ph.D., Anne Regelin, Ph.D., Katleen Vandenberghe, Ph.D., Kris Bogaerts, Ph.D., and Frans Van de Werf, M.D., Ph.D. for the STREAM Investigative Team

March 10,
2013, at NEJM.org

Methods

- **1892 patients** with STEMI, presented within **3 hours after symptom onset**
- Randomly assigned to undergo either PPCI or TL by TNK
- Emergency coronary angiography (Rescue) was performed if fibrinolysis failed
- Angiography and PCI was performed **6 to 24 hours after randomization**
- Primary end point: **death, shock, congestive heart failure, or reinfarction up to 30 days**

STREAM Results



TL patients underwent angiography at a **median of 17 hours** after randomization

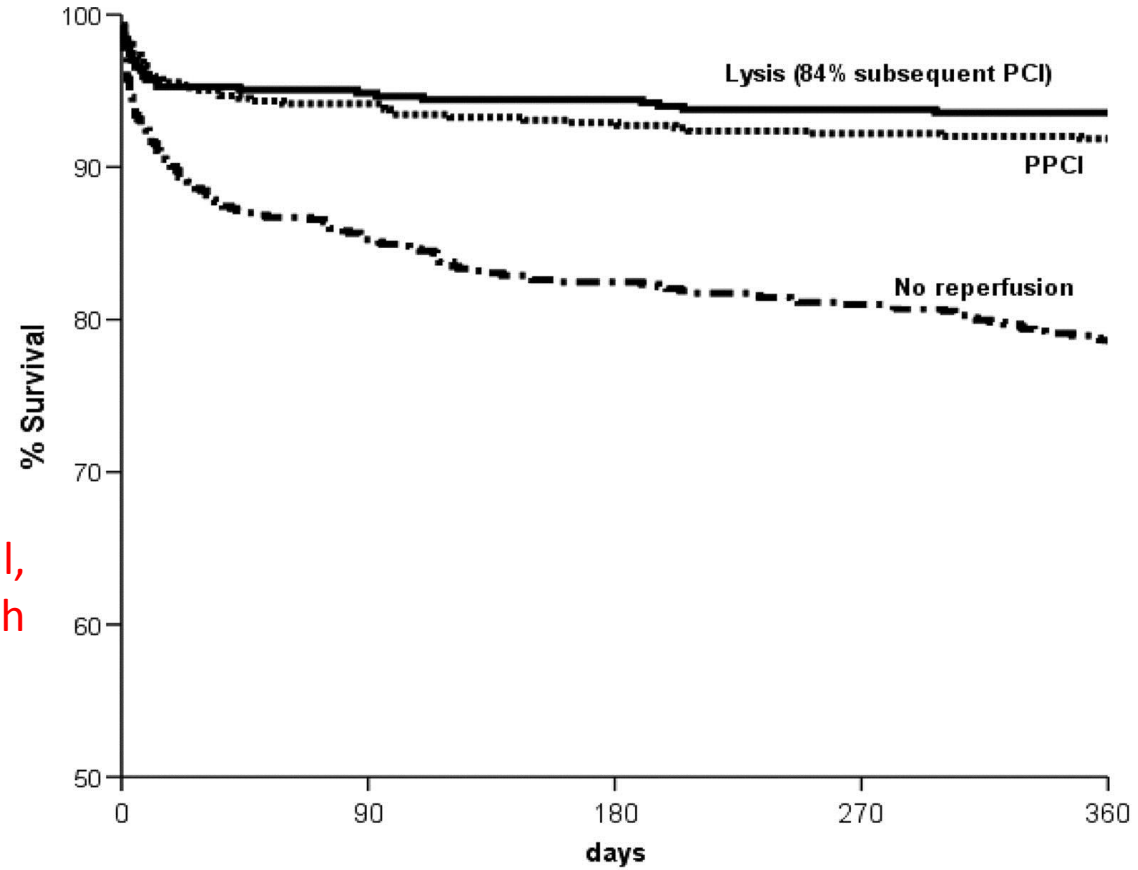
Lower rates of shock and heart failure, as well as **more complete surgical coronary revascularization**, among the patients undergoing fibrinolysis

FL: Fibrinolysis, PPCI: Primary PCI

Conclusion

"Prehospital fibrinolysis with timely coronary angiography resulted in effective reperfusion in patients with early STEMI who could not undergo primary PCI within 1 hour after the first medical contact"

French FAST AMI registry:
One-year survival according to use and type of reperfusion therapy



Lysis: 2/3 pre hospital,
70% treated <3h

# at risk				
No reperfusion	581	562	552	534
Thrombolysis	440	437	434	433
PPCI	529	522	518	512

Danchin, N. et al. Circulation 2008;118:268-276

Circulation

American Heart Association®

Learn and Live℠

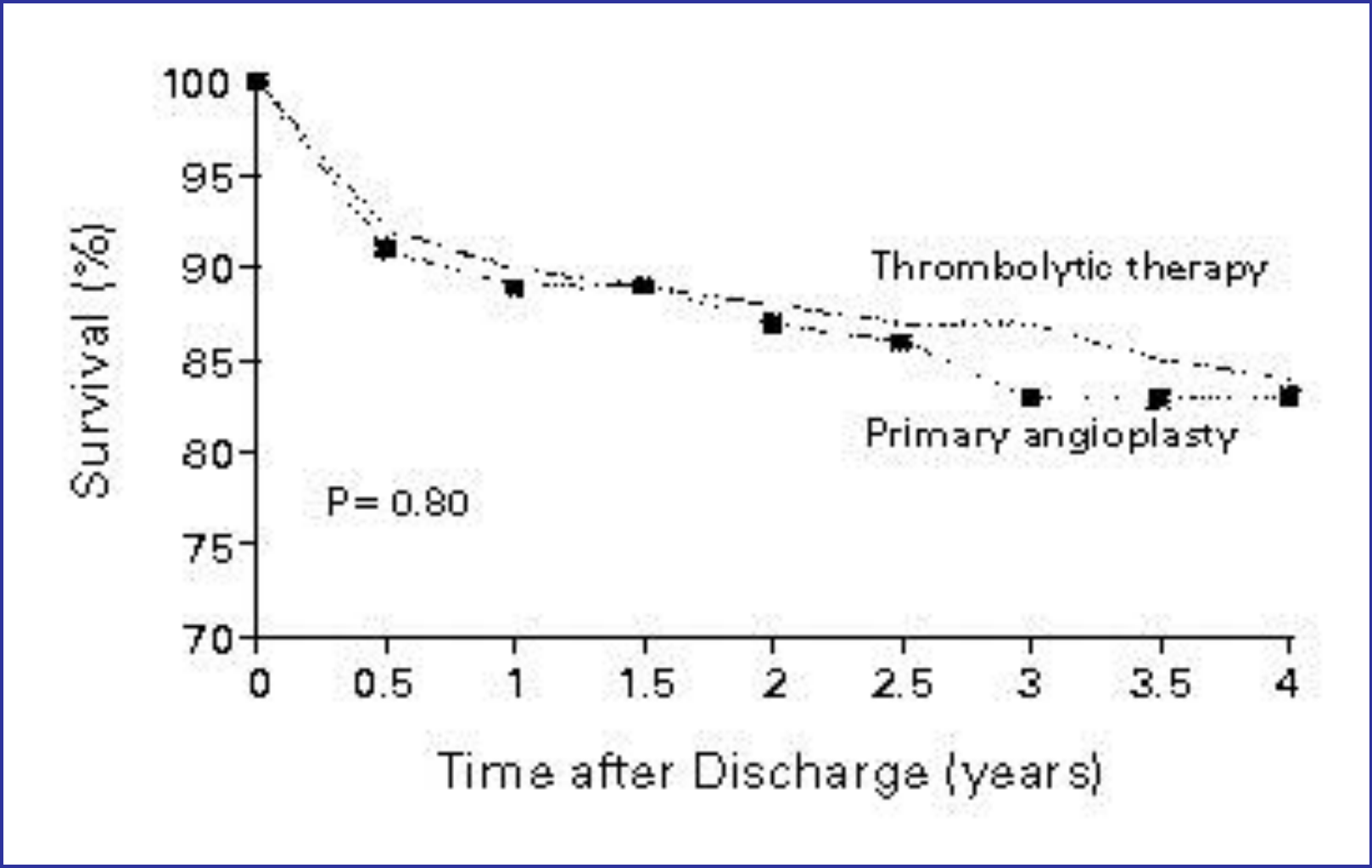
French FAST AMI registry

Conclusion

Pre-hospital lysis is as good as primary PCI, provided “rescue” procedures are available.

“**In early comers, pre hospital lysis is probably better than primary PCI**”

Cumulative Survival among 1050 Patients in the Primary-Angioplasty Group and 2095 Patients in the Thrombolytic-Therapy Group.

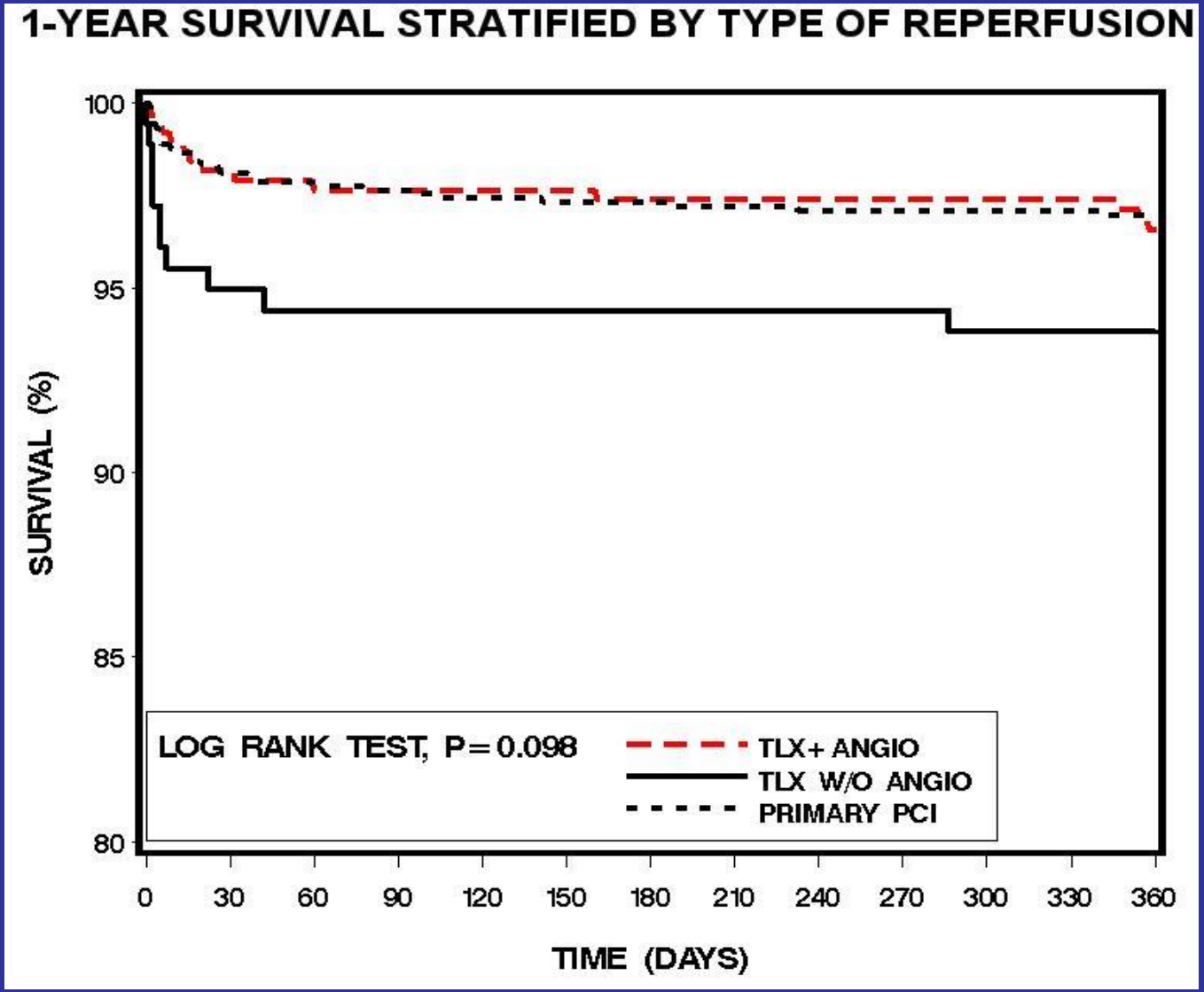


Every NR et al. N Engl J Med 1996;335:1253-1260.

MITI trial

The NEW ENGLAND JOURNAL of MEDICINE

ACSIS: Israeli registry 2000-2010



ESC Guidelines for STEMI

Thrombolysis – Recommendations

Recommendations	Class[a]	Level[b]
Fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications if primary PCI cannot be performed by an experienced team within 120 min of FMC.	I	A
In patients presenting early (<2 h after symptom onset) with a large infarct and low bleeding risk, fibrinolysis should be considered if time from FMC to balloon inflation is >90 min.	IIa	B
If possible, fibrinolysis should start in the prehospital setting.	IIa	A
A fibrin-specific agent (tenecteplase, alteplase, reteplase) is recommended (over non-fibrin specific agents).	I	B

Factors that increase the long term beneficial effect of TL in STEMI patients

- Patients presenting early (2-3 hr) after symptom onset
- Patients with no hemodynamic compromise
- Early definitive revascularization (6-24 hr after successful TL reperfusion) is <u>obligatory</u>

The PRER strategy

PRER: Prompt Reperfusion (TL) Followed by Early Revascularization (PCI) in Selected STEMI Patients

Early-arriving STEMI patients (2-3 hr after onset), with no signs of hemodynamic compromise, that come during off hour period, can benefit from prompt reperfusion by thrombolytic therapy, ASAP (pre hospital) followed by early IRA revascularization 6 to 24 hours after TL using TRA.

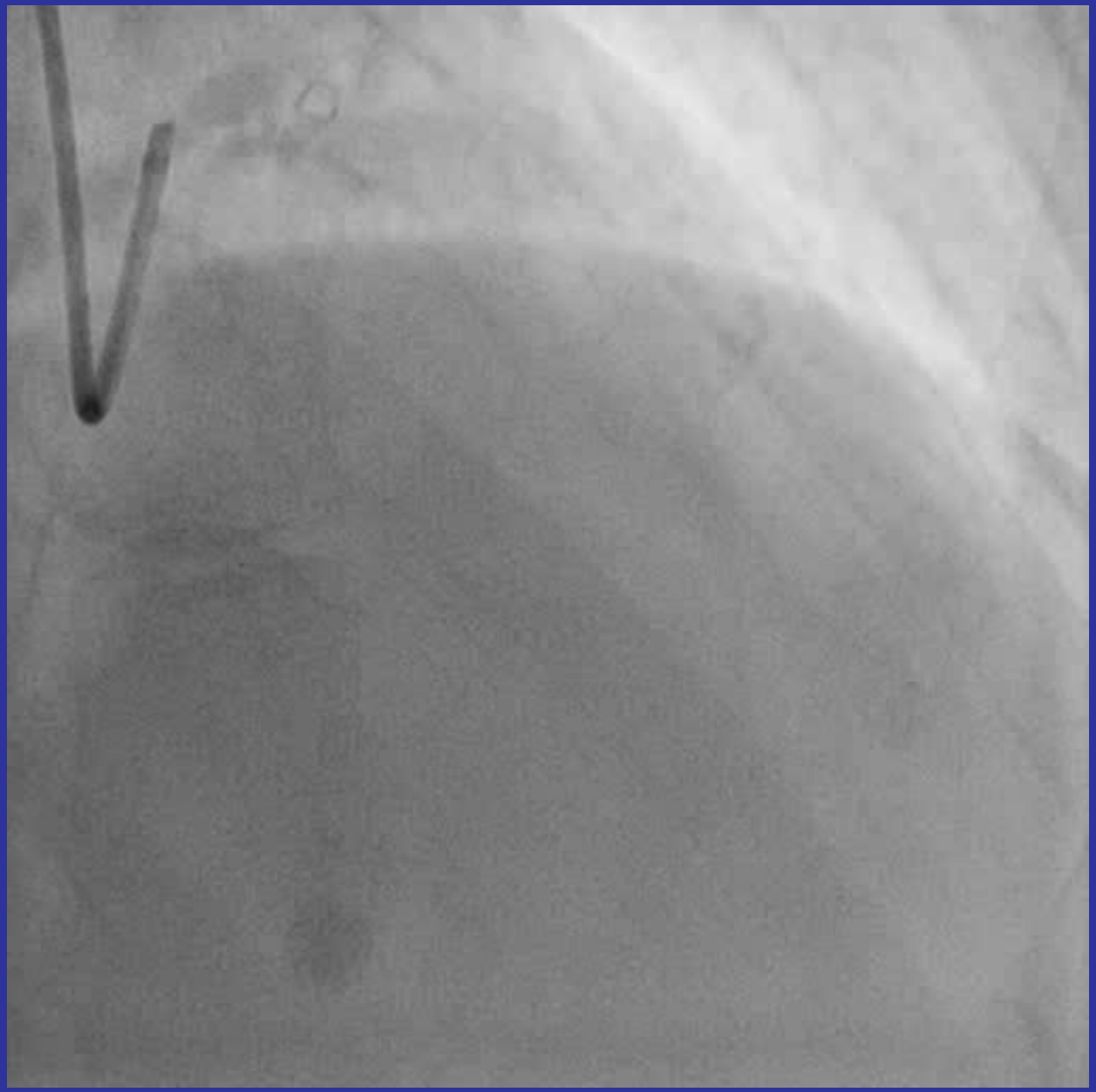
All the rest will be treated as PPCI.

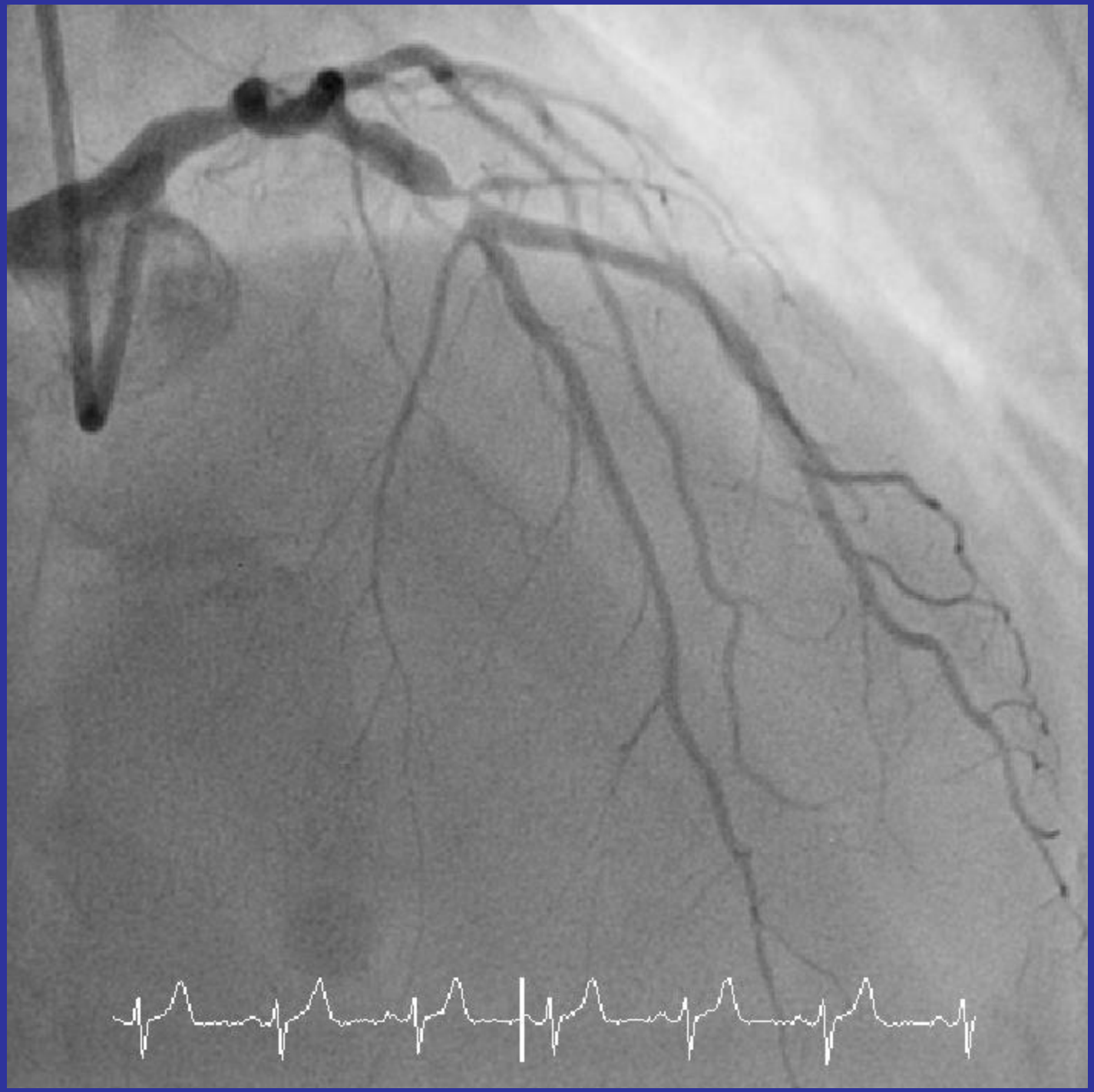
We call for a multi-center, prospective study, to substantiate the validity of this strategy.

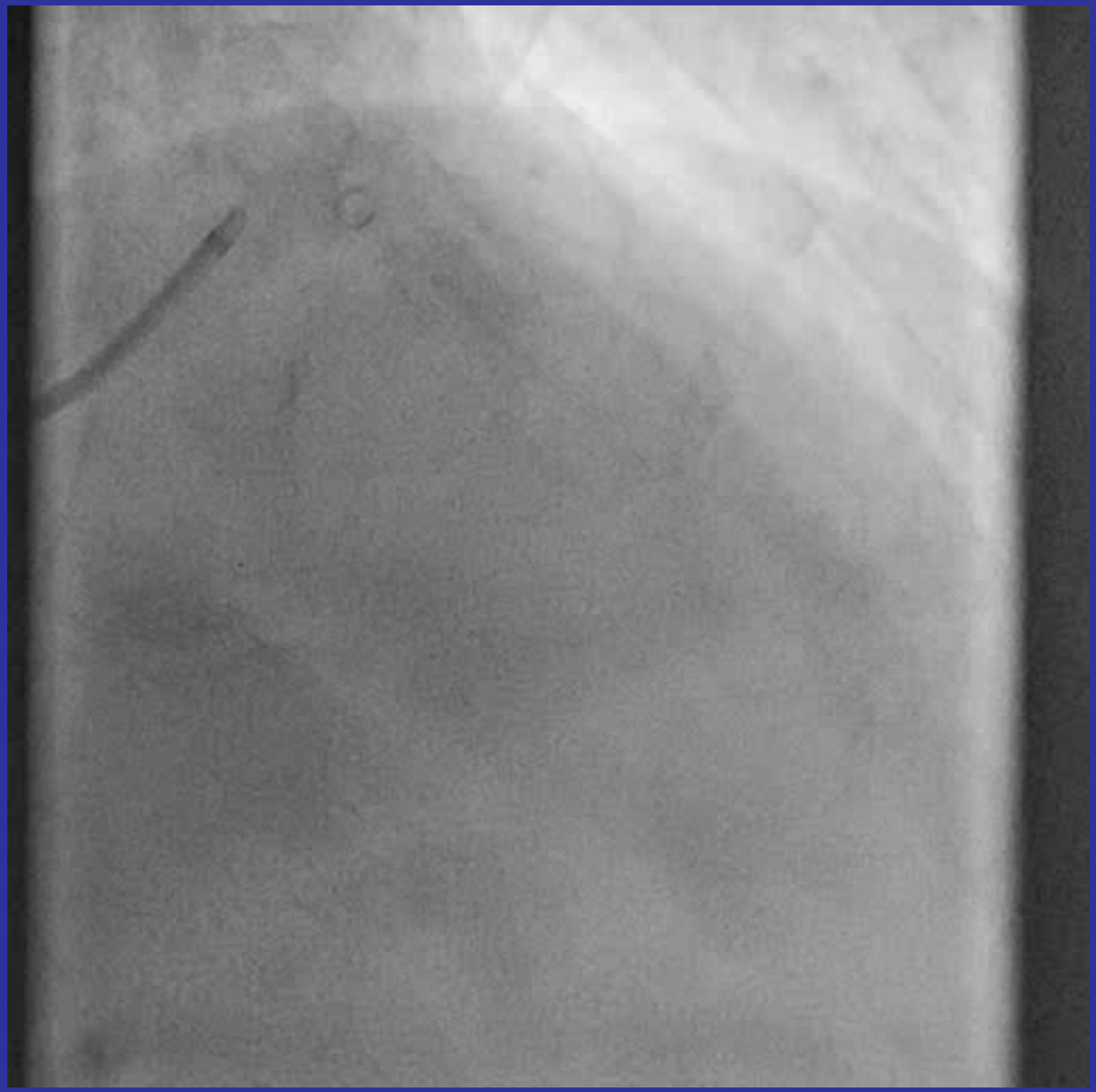
Prompt Pharmacological Reperfusion Followed by Early Mechanical Revascularization in Selected STEMI Patients *Frimerman et al*

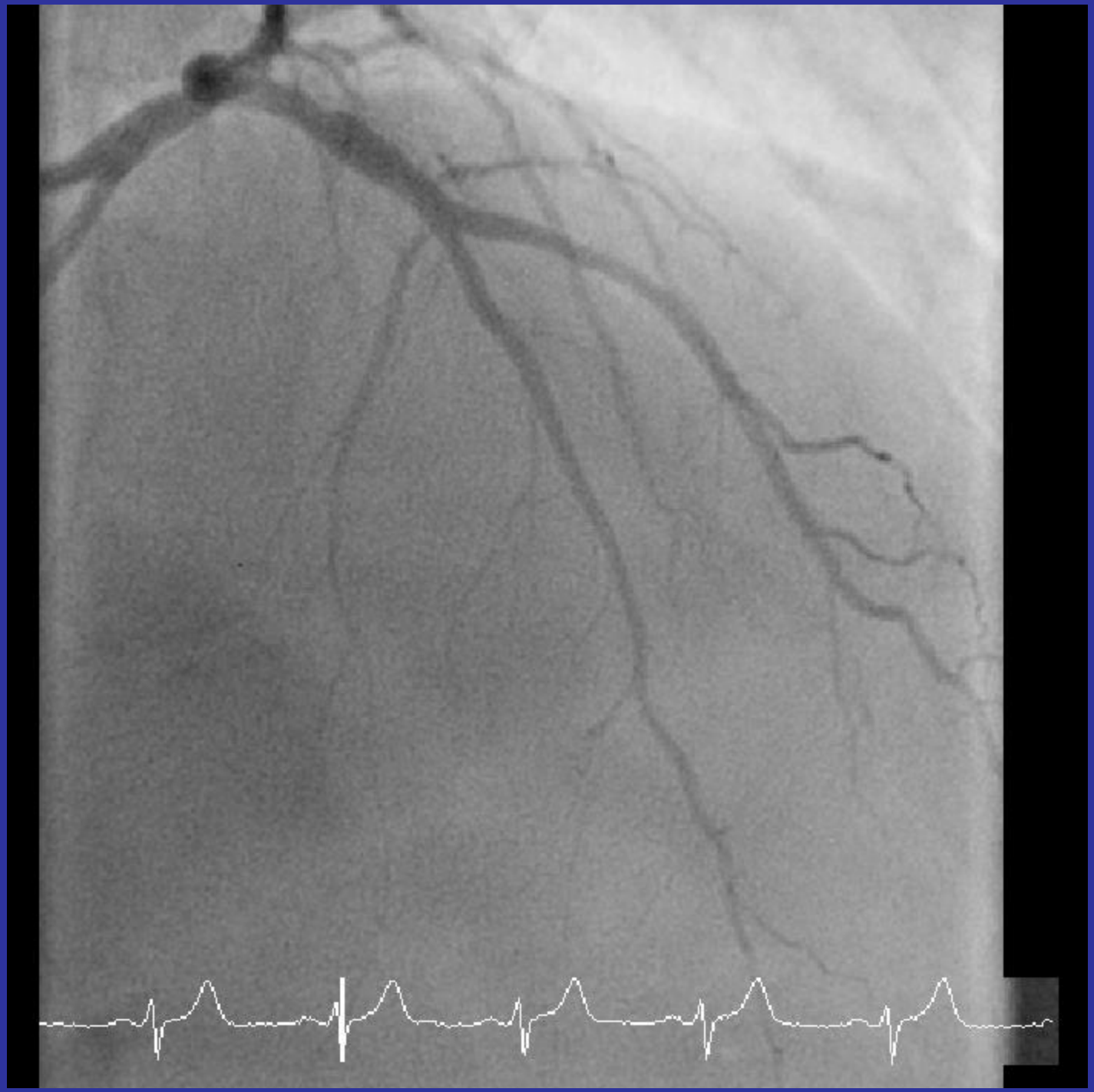
PRER

- 48 y.o. male, heavy smoker, admitted to ICCU at 02:30 with anterior STEMI.
- Symptoms begun one and a half hour prior to admission.
- 17 months ago he had lateral MI and a BMS was implanted in LCX.
- 10 minutes after arrival he got SK infusion.
- In 20 minutes the pain subsided and the ECG normalized.
- 10 hours later he was in the Cath. Lab.









“The reports of my death are greatly exaggerated.”

Mark Twain, 1897, cable from London to the Associated Press

Thank You

Our experience in 2010-2012

Early-arriving STEMI patients (2-3 hr after onset), with no signs of hemodynamic compromise, were treated by SK followed by PCI at 6-24 hr using trans-radial approach. In hospital, 1 month and 1 year mortality was compared to PPCI patients

Results

In-hospital, 1 month, and 1-year mortality of the PPCI patients versus the THR patients are presented in the table:

	Patient number (%)	In-hospital mortality	1-month mortality	1-year mortality
PPCI	183 (58%)	5 (2.7%)	11 (6%)	17 (9.3)
THR	133 (42%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
p-value		ns	0.016	0.001

PPCI: Primary PCI, THR: Thrombolysis

No intra-cranial hemorrhage occurred in the THR group.

Prompt Pharmacological Reperfusion Followed by Early Mechanical Revascularization in Selected STEMI Patients *Frimerman et al*

Thrombus causes complications during intervention

- 3X higher MACE – ischemic complications
- Lower procedural success (<75%): Type C lesions
- Higher distal embolization leading to slow flow or no re-flow
- High mortality (3-5%)
- ST-elevation
- Longer hospital stays

Zhao et al. Circulation 1999;100:1609 , White et al. Circulation 1996;93:253, Tan et al. JACC 1995;29:855, Myler et al. JACC 1992;19:1641, Violaris et al. JACC 1994;25:855

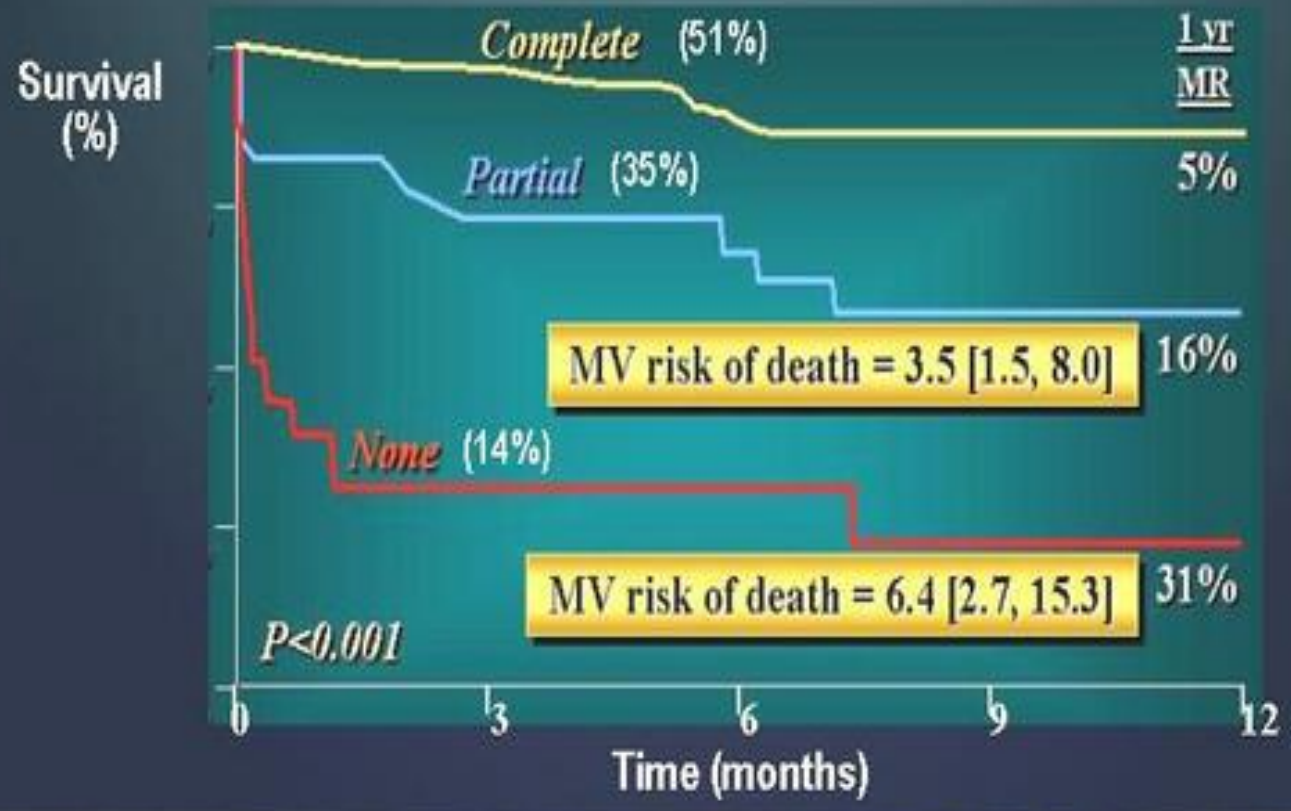
Benefit of an Open Artery on Arrival at the Cath Lab

	Closed Artery TIMI 0-1 (n = 1,214)	Open Artery TIMI 2-3 (n = 272)	p value
Procedural Outcomes			
Procedural Success	94%	97%	.02
Adverse Events	13.1%	5.0%	<.001
Hospital Outcomes			
30 Day Mortality	8.9%	4.8%	.02
Peak CK(U/L)	2,790	1,328	<.001
LV Function			
Acute EF	51.6%	54.3%	.05
6 Month EF	54.9%	59.2%	.004

Brodie AJC 2000; 25:13

Survival as a Function of ST-Segment Resolution

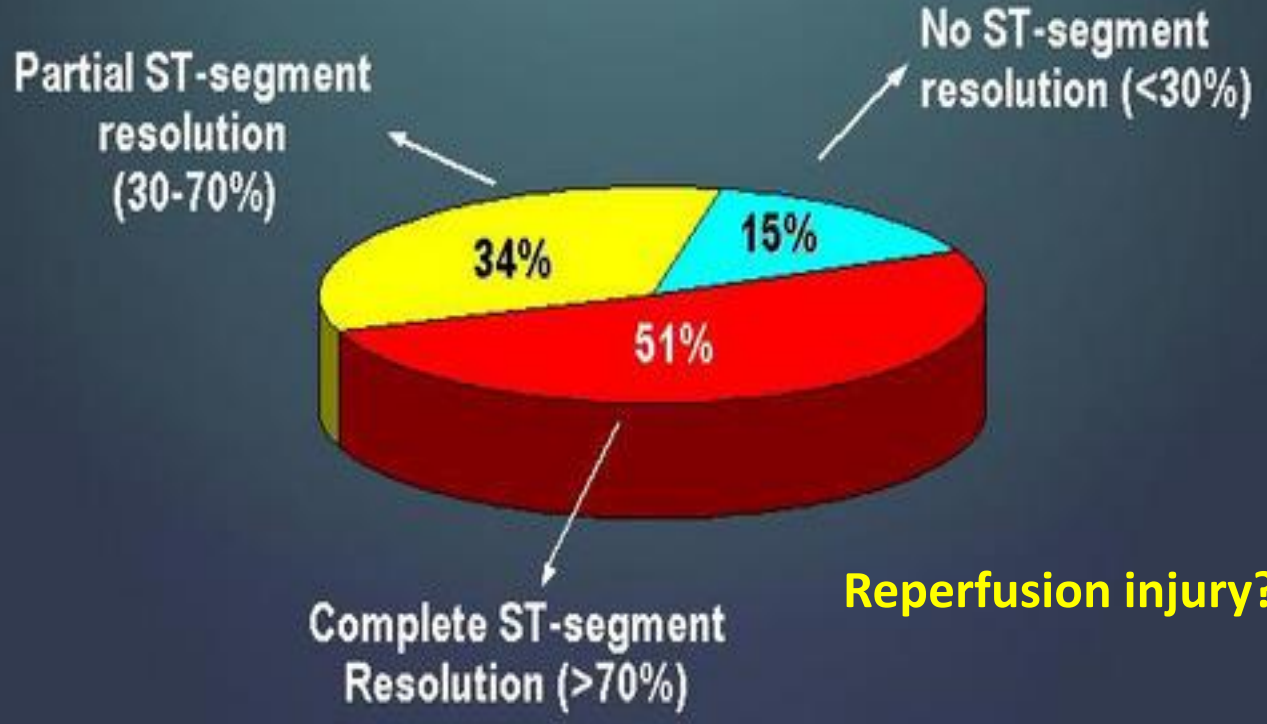
- In 403 patients with TIMI-3 flow after primary PTCA



Van't Hof et al. Lancet 1997;350:615

TIMI-3 Flow & ST-Segment Resolution

- In 403 consecutive patients with ST-segment elevation AMI achieving TIMI-3 flow after primary PTCA with ECGs before and after



Reperfusion injury?

Van't Hof et al. Lancet 1997;350:615