NO REFLOW – THE ACHILLES HEEL OF REPERFUSION

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Background

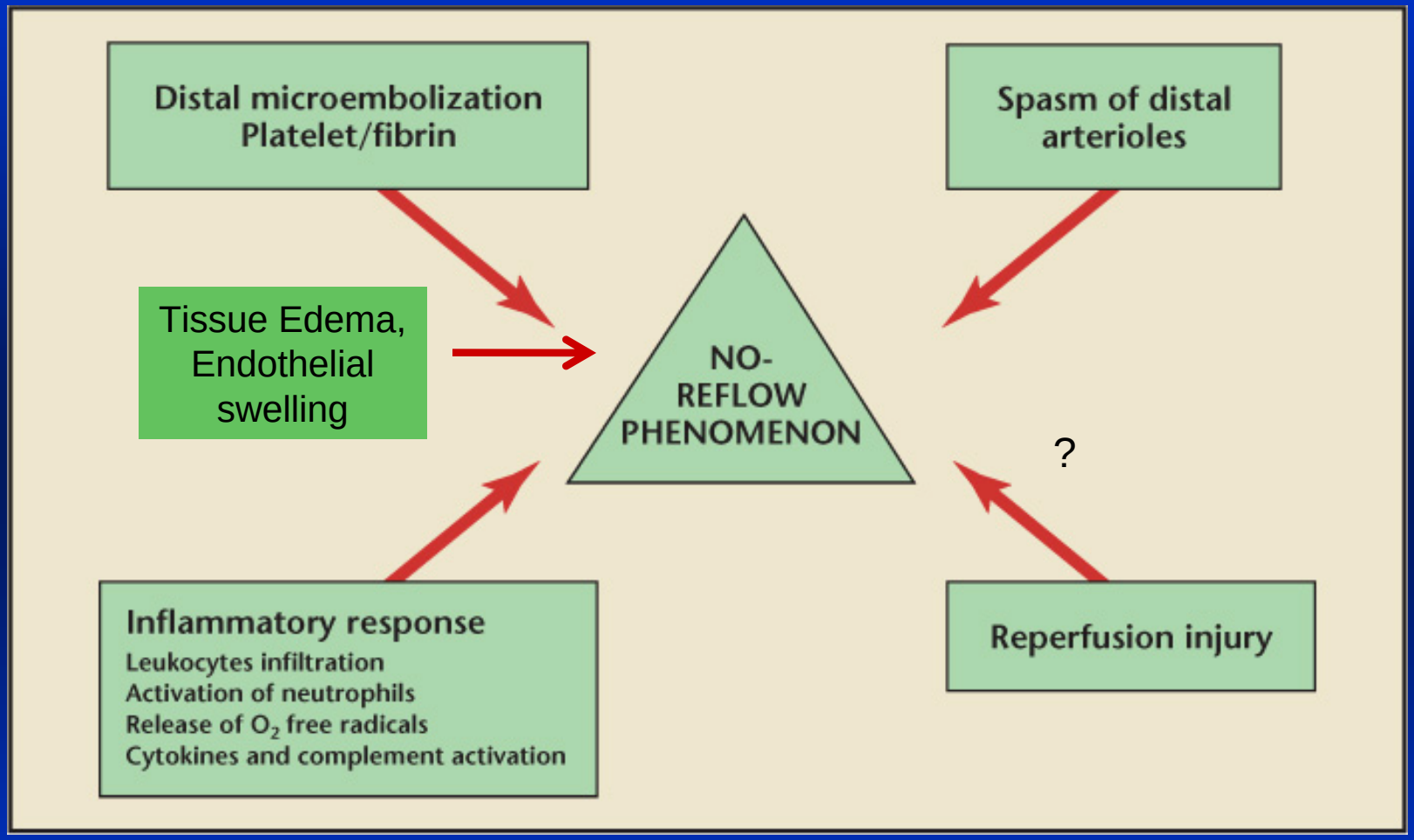
- Reperfusion therapy has dramatically improved the outcome of patients with ST elevation MI.
- Major limitations of reperfusion therapy are failure of epicardial reperfusion (more common with thrombolysis) and failure of tissue level reperfusion ("no reflow") .

FAILED TISSUE REPERFUSION - THE NO REFLOW PHENOMENON

A profound reduction in antegrade coronary blood flow in the absence of residual epicardial flow limitation or distal macroembolization.

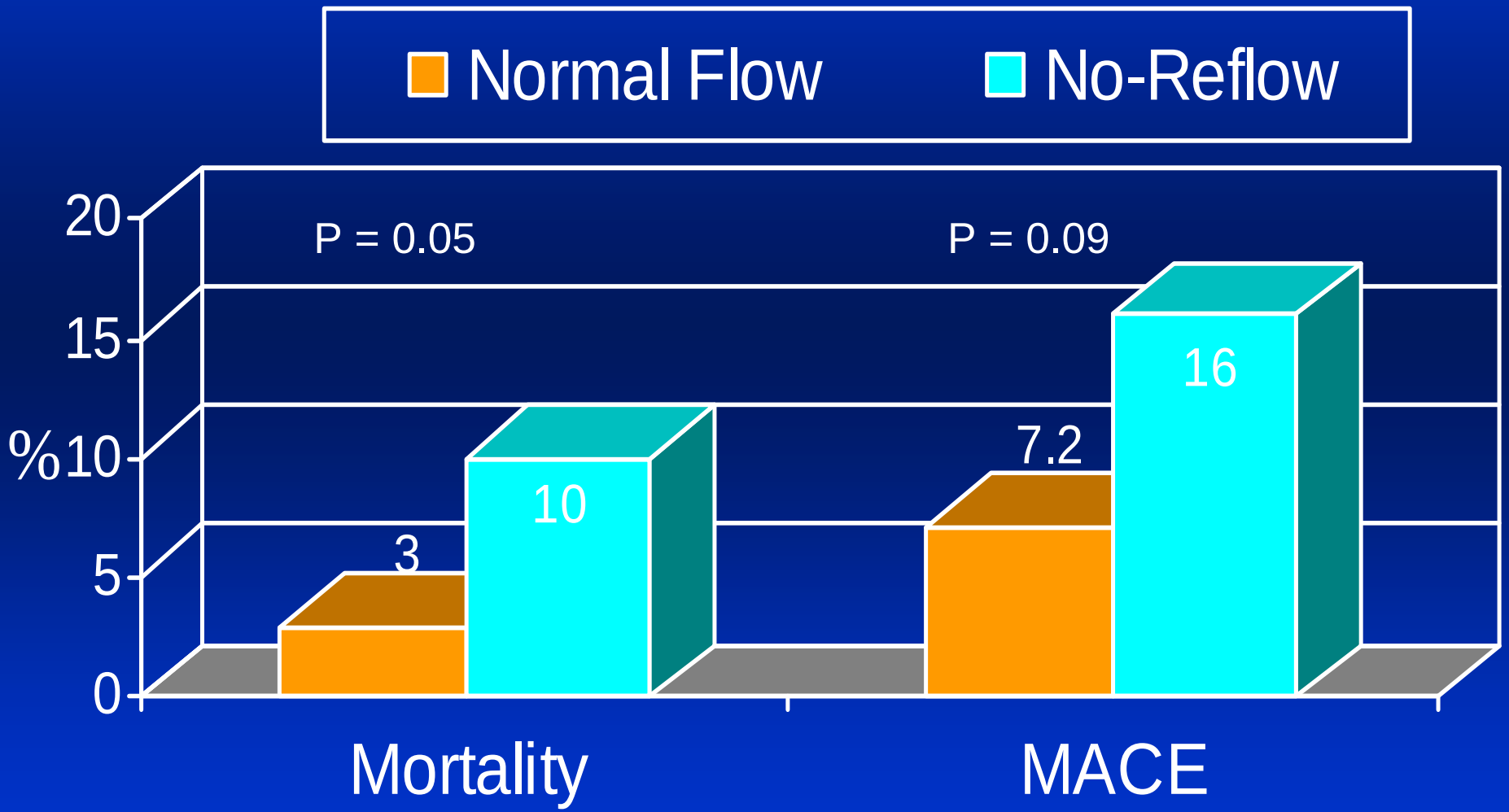
NO REFLOW

- Mechanisms
- Prognosis
- Recognition
- Pharmacologic management
- Interventional management



Pathophysiology of microvascular dysfunction after epicardial perfusion in patients with acute myocardial infarction.

30-days Mortality & MACE



Brosh et al. Am J Cardiol 2007;99:442

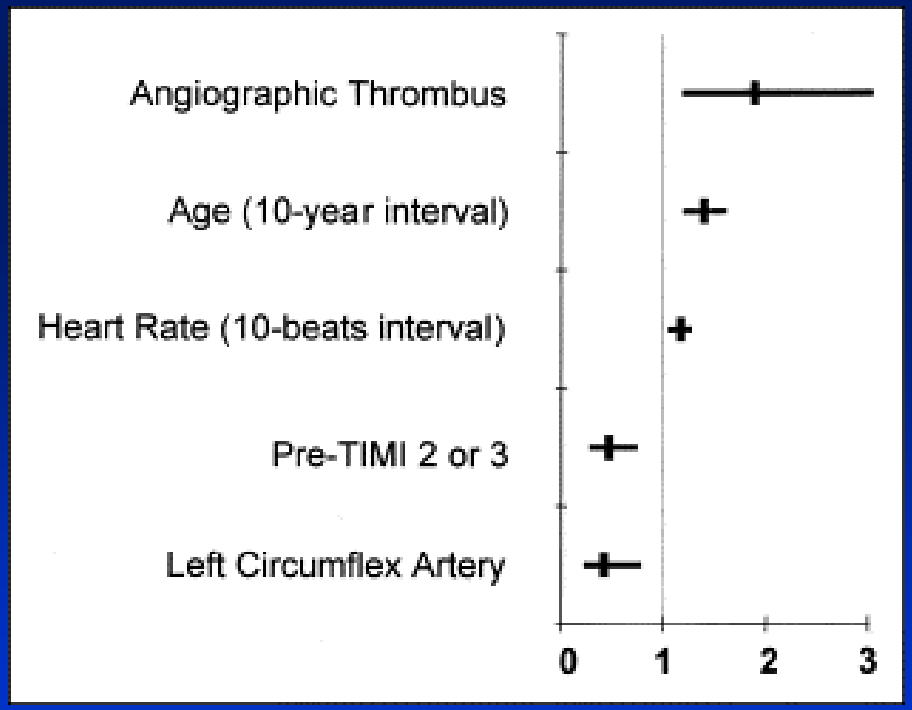
PREVALENCE & PREDICTORS OF NO REFLOW

- 232/3362 STEMI patients enrolled in the PAMI trials had TIMI ≤ 2 flow (6.9%).
- Predictors of TIMI ≤ 2 flow :
  - Age >70
  - Diabetes
  - Delayed reperfusion
  - Initial TIMI 0/1
  - LVEF <50%

Mehta et al. JACC 2003;42:1739

PREVALENCE & PREDICTORS OF NO REFLOW (2)

- 891 PPCI patients enrolled in GUSTO IIb & RAPPORT
- TIMI ≤ 2 flow achieved in 19%



Cura et al. AJC 2001;88:124

NO REFLOW

- Increases with age
- Probably more common in LAD infarcts
- Largely reflects the extent of damage sustained PRIOR to reperfusion (time to treatment, LVEF, Q waves, occluded vessel prior to PCI). Whether reperfusion itself contributes to this damage remains controversial.

Can no reflow be predicted on admission?

- Predicting reperfusion success is important for selection of reperfusion modalities and ancillary therapies.
- Multiple investigators studied admission characteristics as predictors of epicardial recanalization but very few assessed the ability to predict myocardial reperfusion on admission.

Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 38, No. 2, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(01)01405-X

Predictive Factors for Development of the No-Reflow Phenomenon in Patients With Reperfused Anterior Wall Acute Myocardial Infarction

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Table 2. Univariate and Multivariate Predictors of the No-Reflow Phenomenon

	Univariate Analysis		Multivariate Analysis		
	Chi-Square*	p Value	Chi-Square*	p Value	OR (95% CI)
Age	1.92	0.16	1.17	0.28	1.02 (0.98–1.06)
Gender	1.76	0.18	0.34	0.56	0.76 (0.30–1.90)
Diabetes mellitus	0.26	0.61	0.001	0.98	0.99 (0.39–2.48)
Hypertension	0.73	0.39	0.84	0.36	1.60 (0.60–4.12)
Hyperlipidemia	0.08	0.78	0.61	0.43	0.64 (0.21–1.96)
Smoking	0.52	0.47	0.34	0.56	0.78 (0.33–1.81)
Symptom onset to reflow time	0.67	0.41	2.28	0.13	0.93 (0.85–1.02)
Absence of pre-infarction angina	7.03	0.008	4.52	0.03	2.15 (1.06–4.37)
Killip class	6.46	0.01	3.01	0.08	1.77 (0.93–3.36)
No. of Q-waves on ECG	20.1	<0.0001	12.4	0.0004	1.52 (1.20–1.92)
Transient ST segment re-elevation	1.91	0.17	0.71	0.40	1.40 (0.65–2.97)
WMS	18.4	<0.0001	7.31	0.007	1.12 (1.03–1.21)
TIMI flow grade 0 at initial coronary angiography	14.2	0.0002	5.17	0.02	2.90 (1.16–7.23)
Culprit lesion in proximal LAD	3.57	0.06	0.40	0.53	0.79 (0.38–1.65)
Good collateral channels†	0.59	0.44	0.62	0.42	0.70 (0.30–1.66)

Admission EKG analyzed only for Q waves

Grade of Ischemia

- Terminal QRS distortion (grade of ischemia [GOI]) reflects the severity of ischemia and is a strong independent prognostic factor in patients with STEMI.

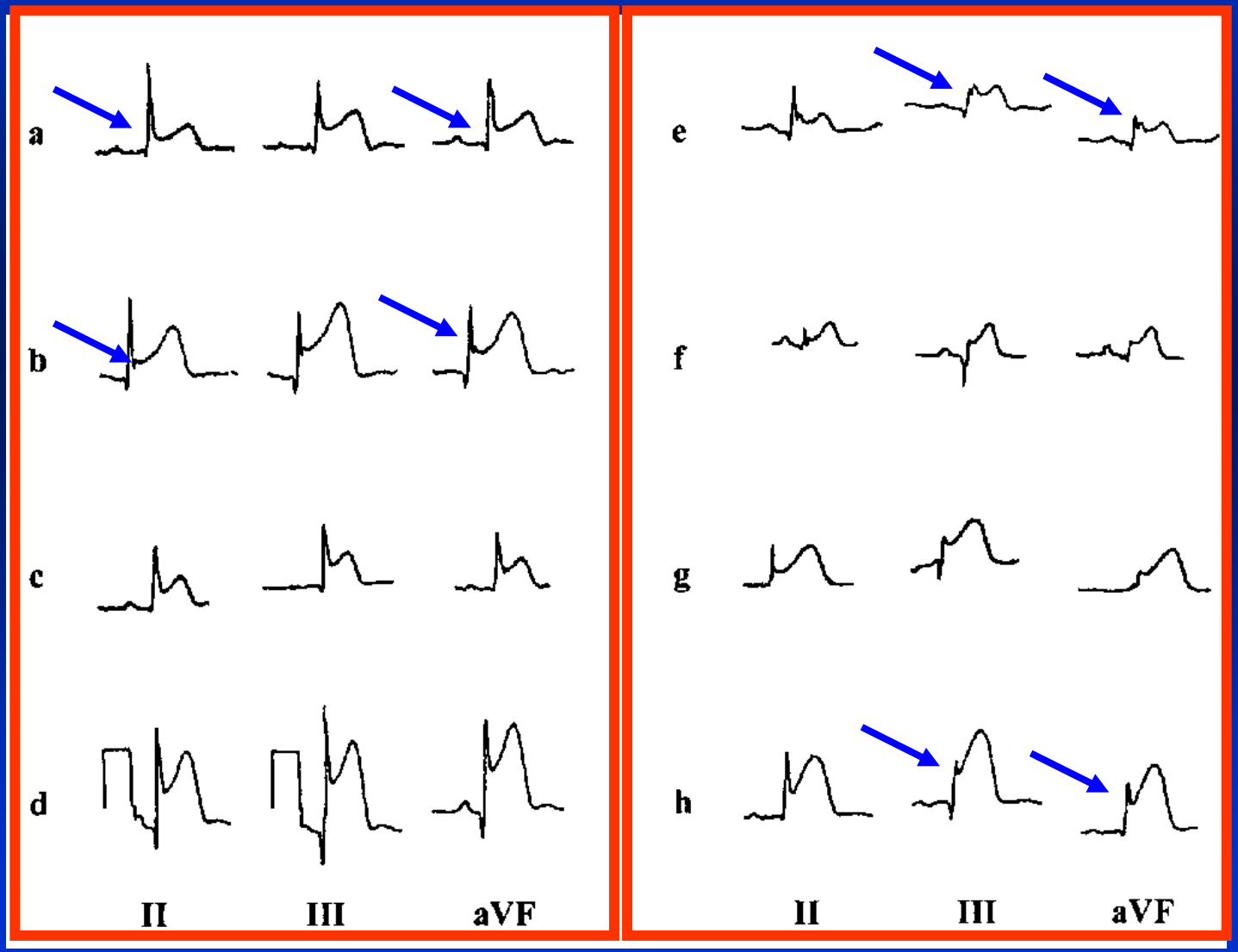
Grade of Ischemia (Sklarovsky – Birnbaum)

- Grade 1(G1I)
  - No ST elevation.
- Grade 2 (G2I)
  - ST-segment elevation which does not meet criteria for grade 3.
- Grade 3 (G3I)
  - Absence of S waves below the isoelectric line in leads that usually have a terminal S configuration (V1-V3).
  - ST J-point amplitude $\geq$50% of the R-wave amplitude in other leads.
  - Grade 3 criteria in 2 adjacent leads required.

Grade of Ischemia

GRADE 2

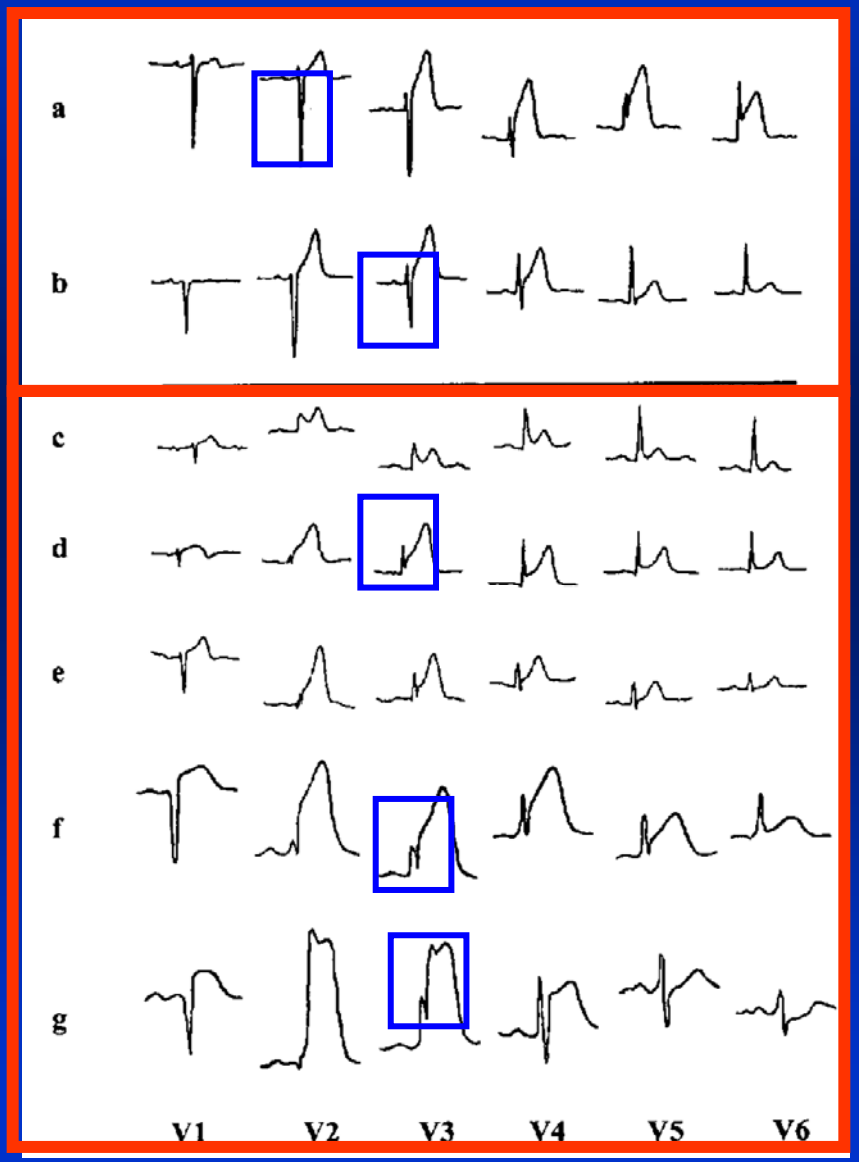
GRADE 3



Grade of Ischemia

GRADE 2

GRADE 3



Features of Grade 3 Ischemia

- Larger infarct size in comparison to G2I patients despite a similar area at risk and independent of the success of epicardial reperfusion.
- Higher reinfarction rate.
- Higher mortality rate.
- The mechanism responsible for the worse prognosis associated with G3I is unknown.

GRADE 3 ISCHEMIA ON THE ADMISSION ELECTROCARDIOGRAM PREDICTS FAILURE OF ST RESOLUTION FOLLOWING THROMBOLYTIC THERAPY FOR ACUTE MYOCARDIAL INFARCTION

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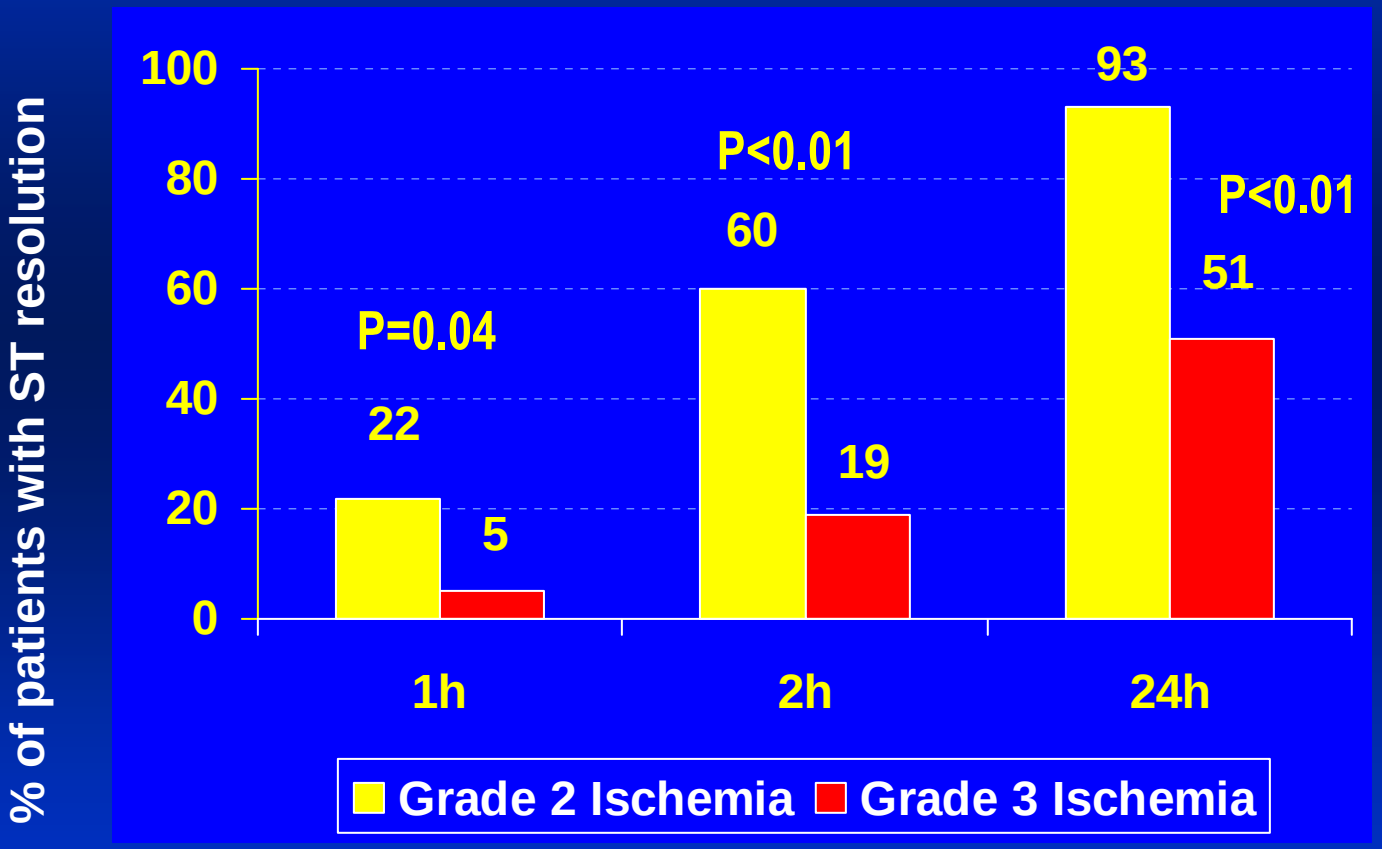
Int J Cardiol 2005;104:131-7

CAN NO REFLOW BE PREDICTED ON ADMISSION?

- 180 patients with first anterior MI undergoing thrombolysis
- Multiple factors available on admission assessed as predictors of complete ST resolution @ 1,2 & 24 h as a surrogate of no reflow
- Independent factors:
  - Grade 3 ischemia on admission
  - No prior use of beta blockers
  - Previous use of aspirin

Grades of ischemia and ST resolution following thrombolysis



CONCLUSIONS

- **Grade 3 ischemia is the strongest admission predictor of failure of ST resolution and of the need for rescue PCI in STEMI patients scheduled for thrombolysis.**

Grade 3 Ischemia on the Admission Electrocardiogram Predicts Failure of ST Resolution and of Adequate Flow Restoration Following Primary Angioplasty for Acute Myocardial Infarction

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Am Heart J 2007;153:410

Objectives

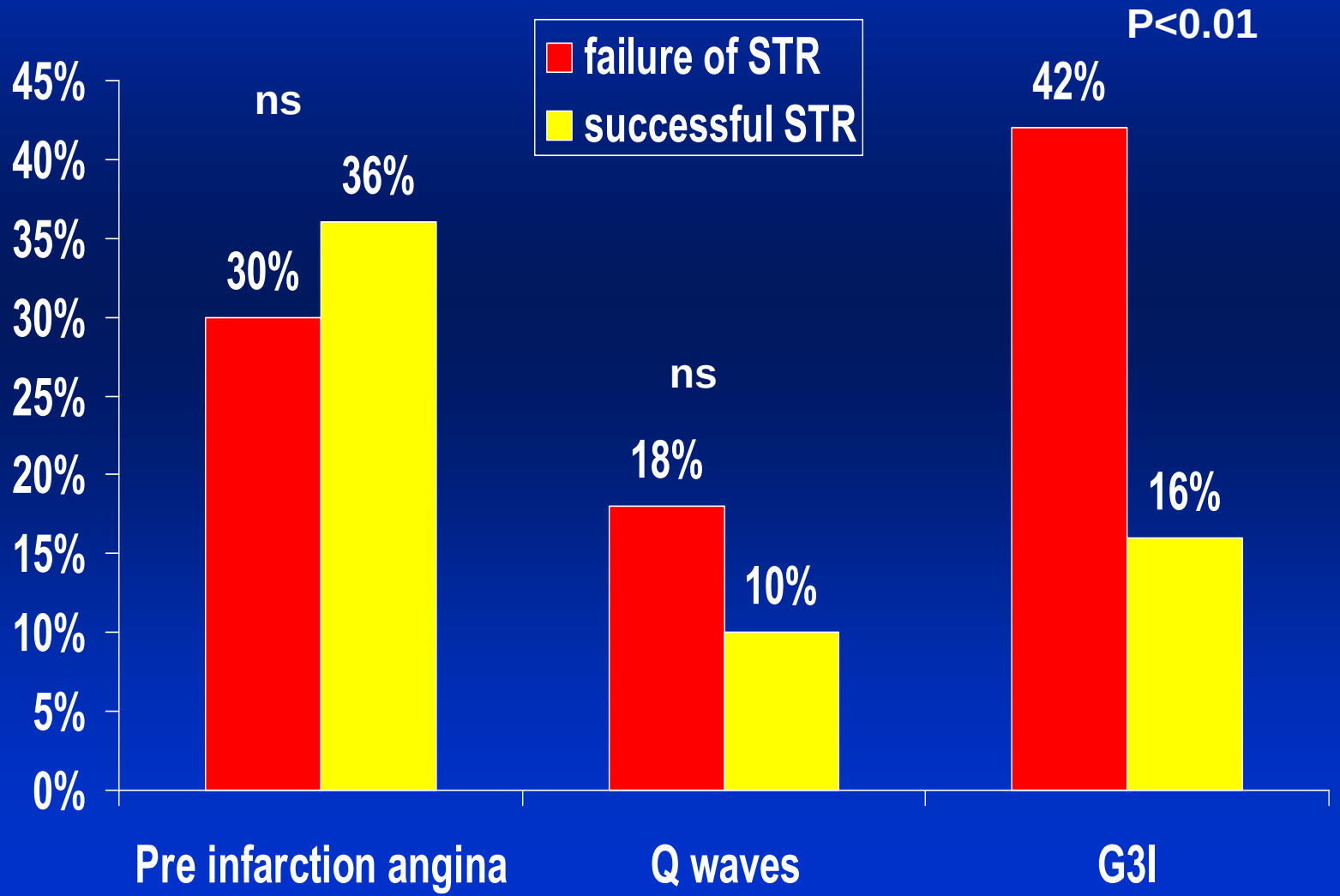
- To determine whether failure of ST resolution following primary angioplasty can be predicted on admission

- To determine whether the adverse outcome associated with G3I is mediated through impaired tissue reperfusion.

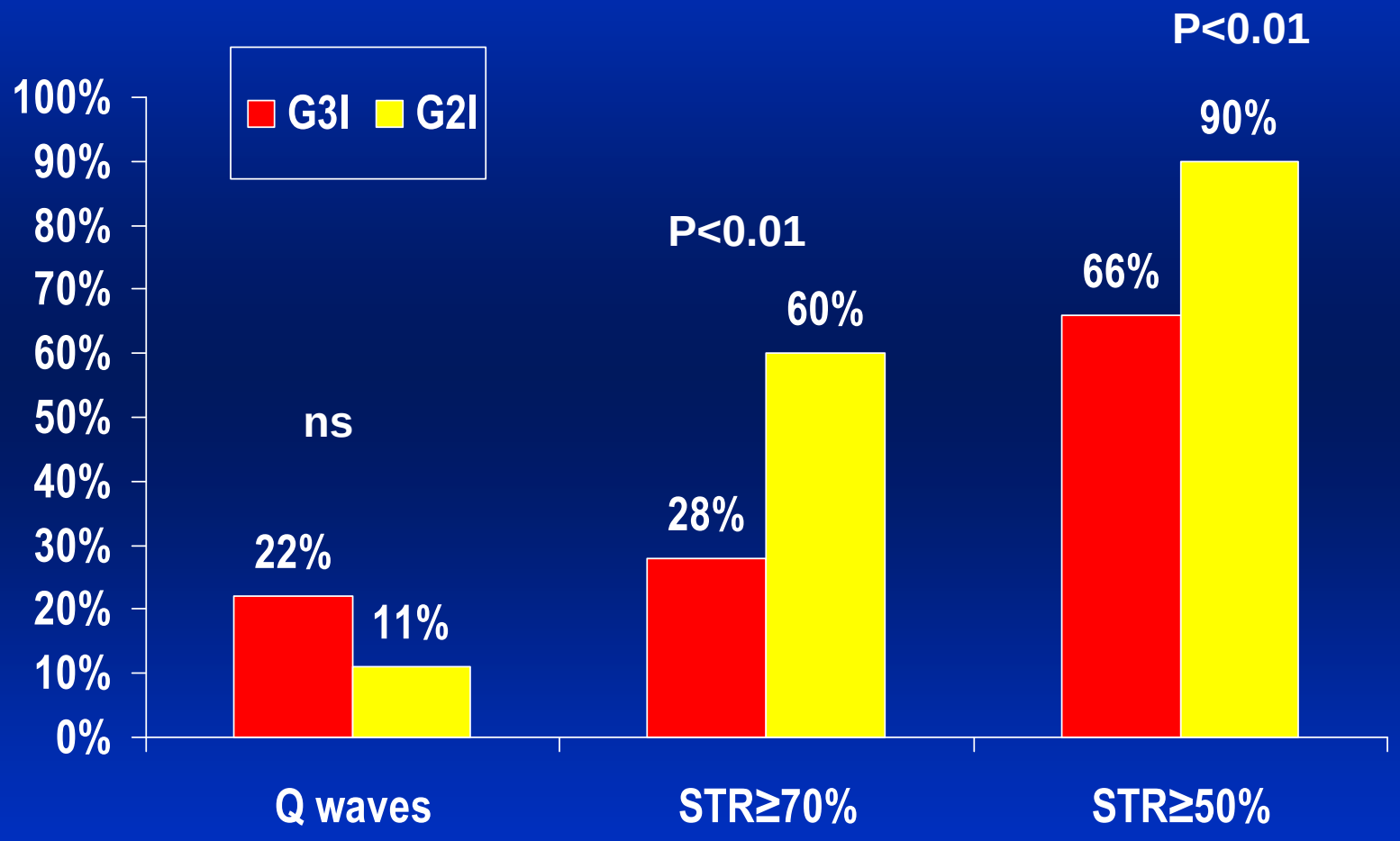
Methods (1)

- A prospective observational study.
- Study population (N=100):
  - Inclusion criteria:
    - Consecutive patients admitted for a first STEMI and scheduled for PPCI.
  - Exclusion criteria:
    - > 12h from symptoms onset.
    - LBBB
    - Paced or ventricular rhythm
    - Negative T waves in $\geq$ 2 adjacent leads with maximal ST elevation
    - Incomplete or uninterpretable ECG data.

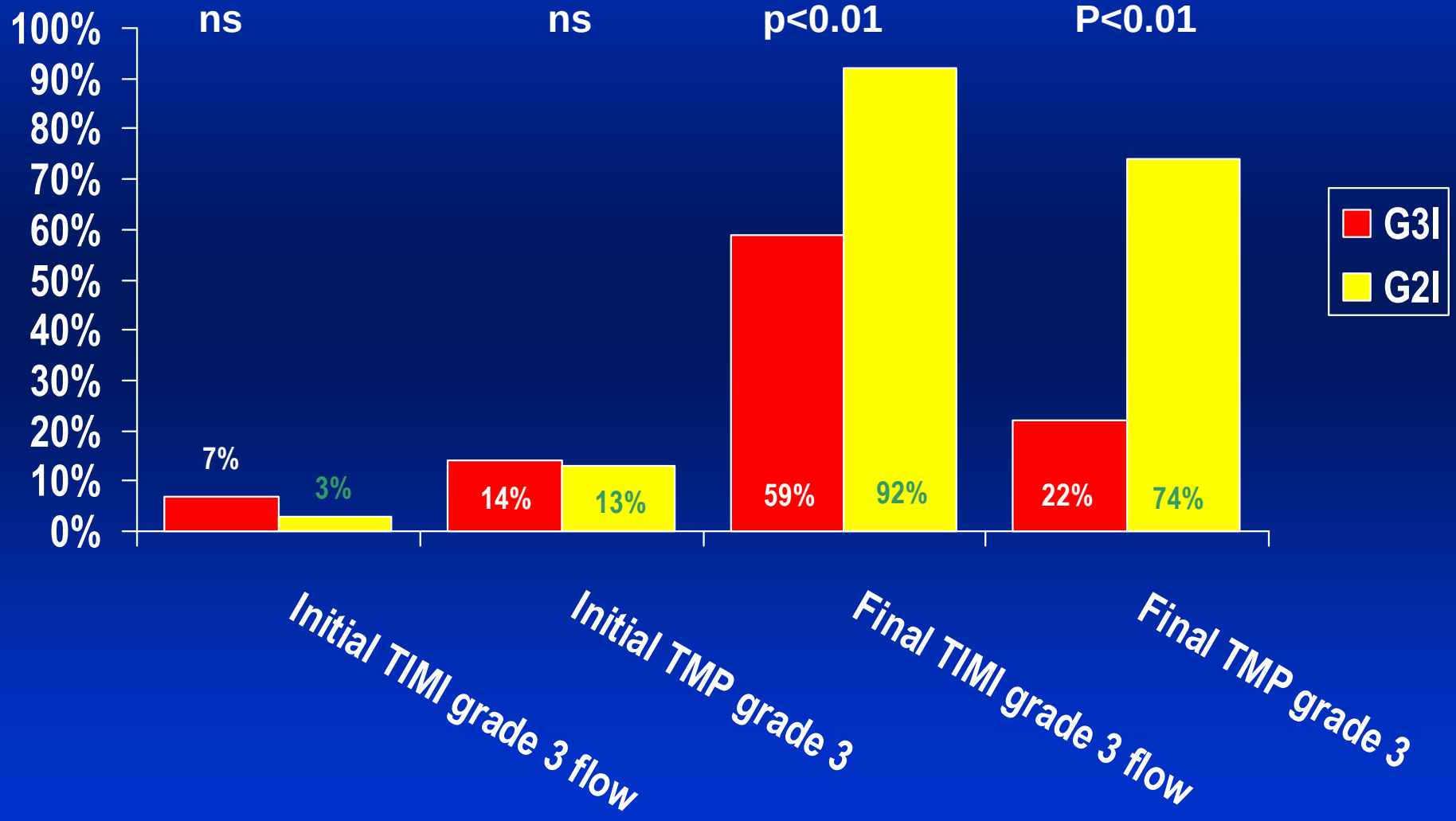
Failure of STR vs. successful STR



G3I vs. G2I


G3I
G2I
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
ns
22%
11%
P<0.01
28%
60%
P<0.01
66%
90%
Q waves
STR≥70%
STR≥50%

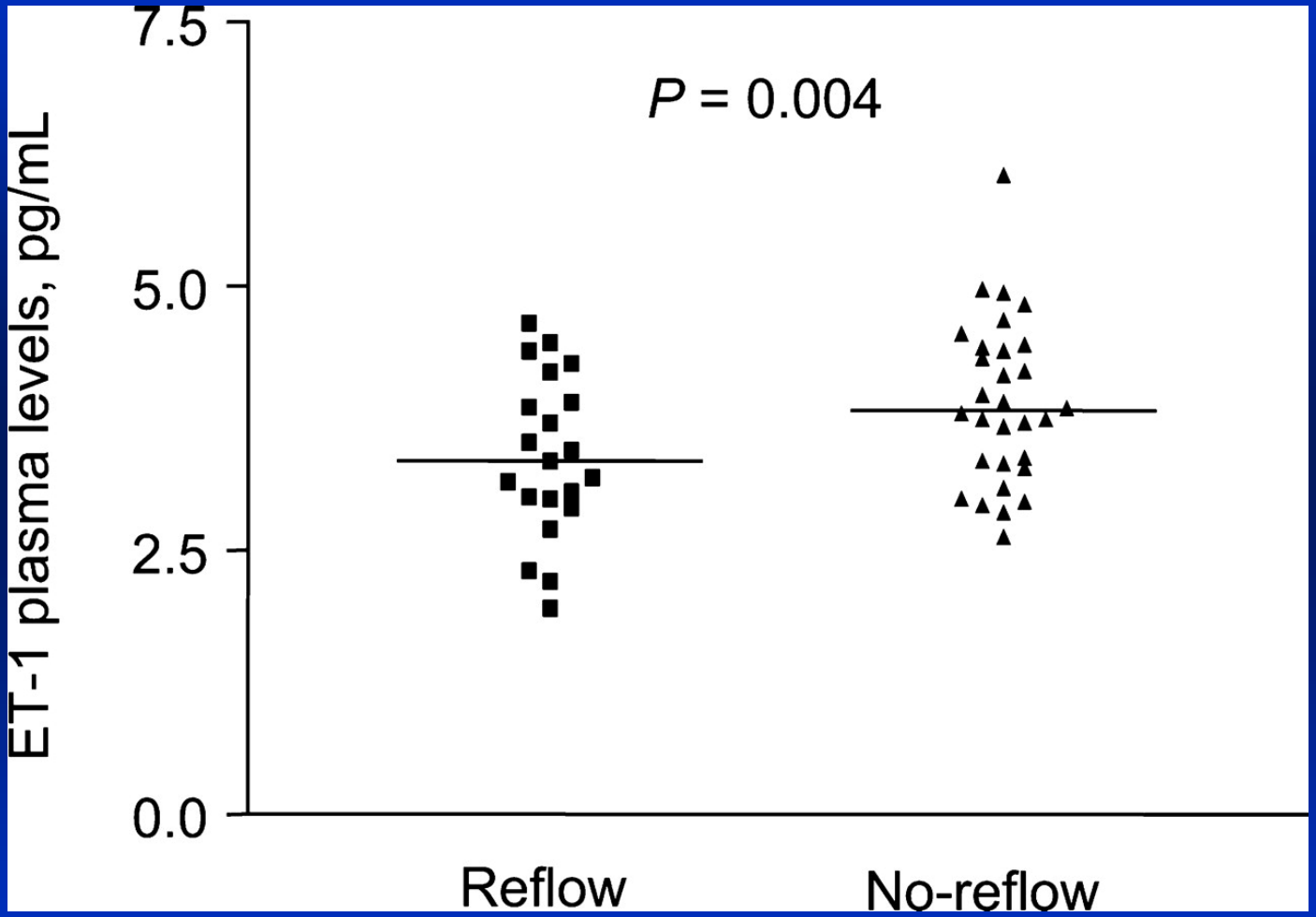
G3I vs. G2I angiographic results



Conclusions

- **G3I is the strongest independent predictor available on admission of failure to achieve myocardial reperfusion as assessed both electrocardiographically and angiographically**
- **Grade 3 ischemia probably reflects severe ischemic damage to the microvasculature.**
- **This observation may allow future investigators to identify on admission patients who are at high risk for failure of myocardial reperfusion.**

Individual values of ET-1 plasma levels according to no-reflow occurrence



Niccoli, G. et al. Eur Heart J 2006 27:1793-1798; doi:10.1093/eurheartj/ehl119

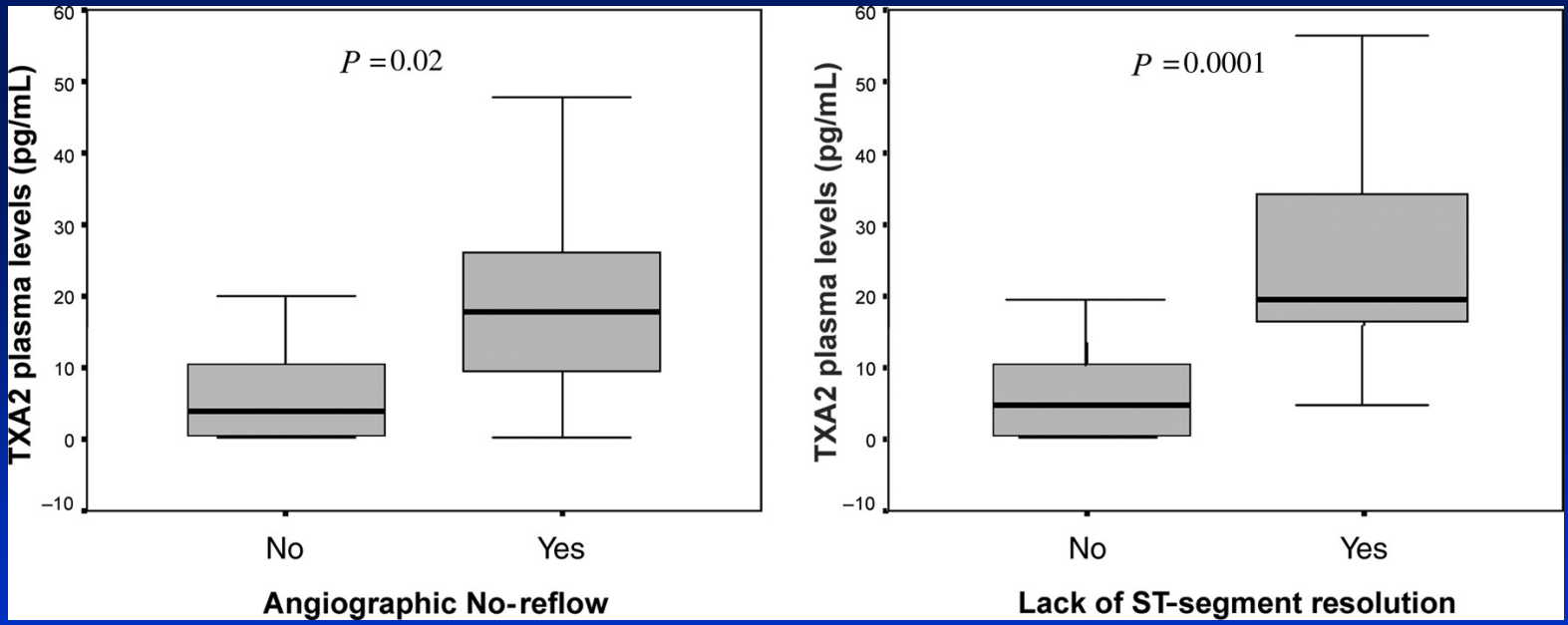
European Heart Journal

European Heart Journal (2008) 29, 1843–1850
doi:10.1093/eurheartj/ehn325

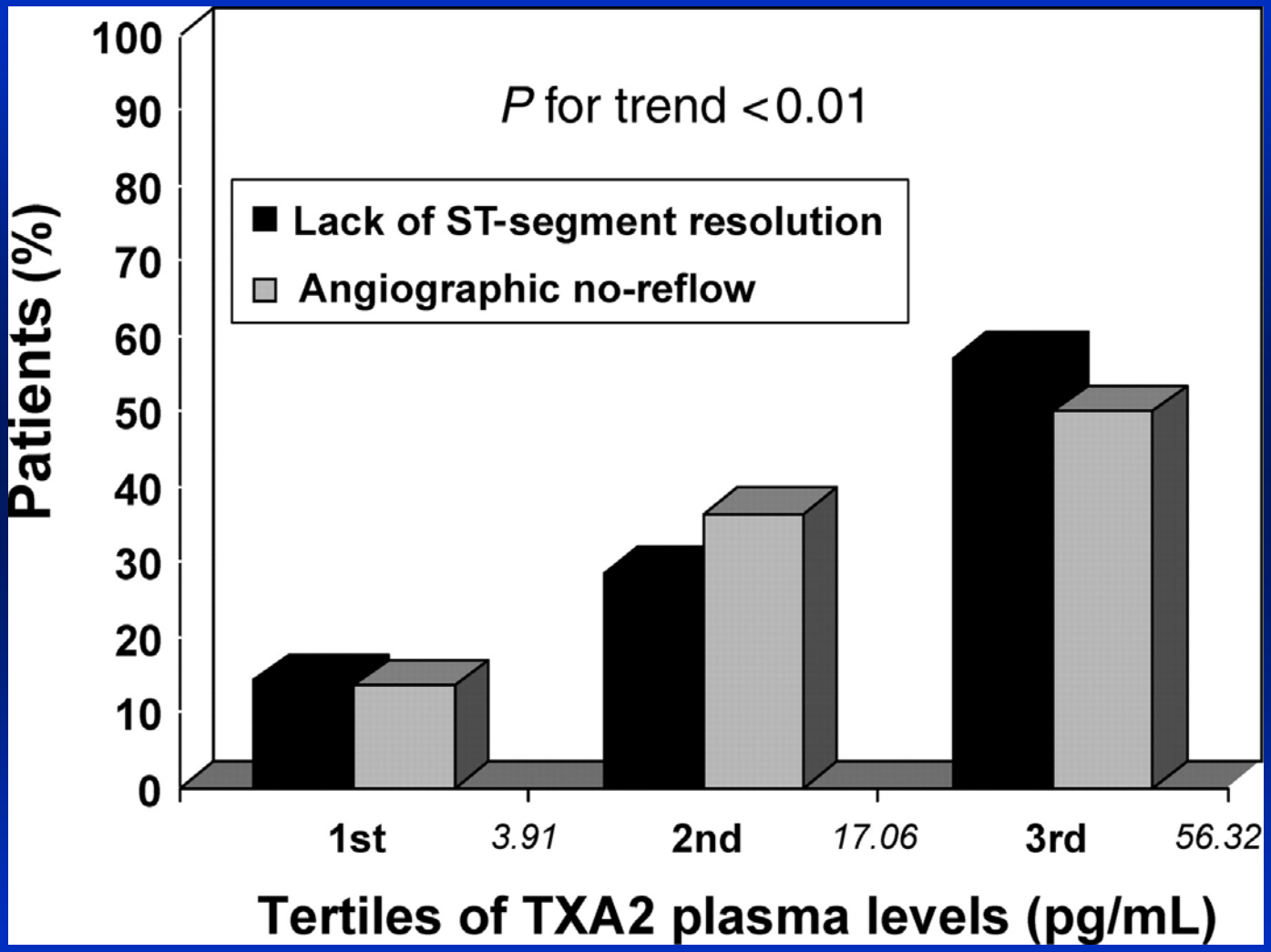
CLINICAL RESEARCH
Coronary heart disease

Plasma levels of thromboxane A2 on admission are associated with no-reflow after primary percutaneous coronary intervention

Giampaolo Niccoli[1*], Simona Giubilato[1], Eleonora Russo[1], Cristina Spaziani[1], Andrea Leo[1], Italo Porto[1], Antonio M. Leone[1], Francesco Burzotta[1], Silvia Riondino[2], Fabio Pulcinelli[2], Luigi M. Biasucci[1], and Filippo Crea[1]



European Heart Journal



Niccoli, G. et al. Eur Heart J 2008 29:1843-1850; doi:10.1093/eurheartj/ehn325

European Heart Journal

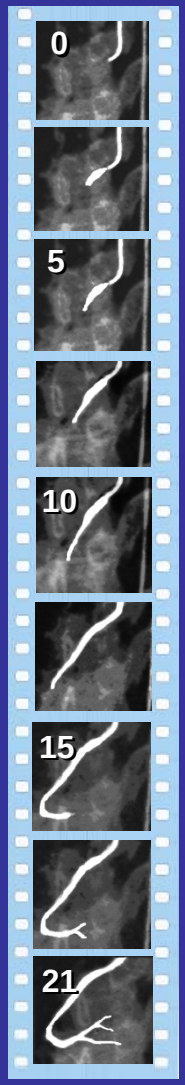
CONCLUSIONS

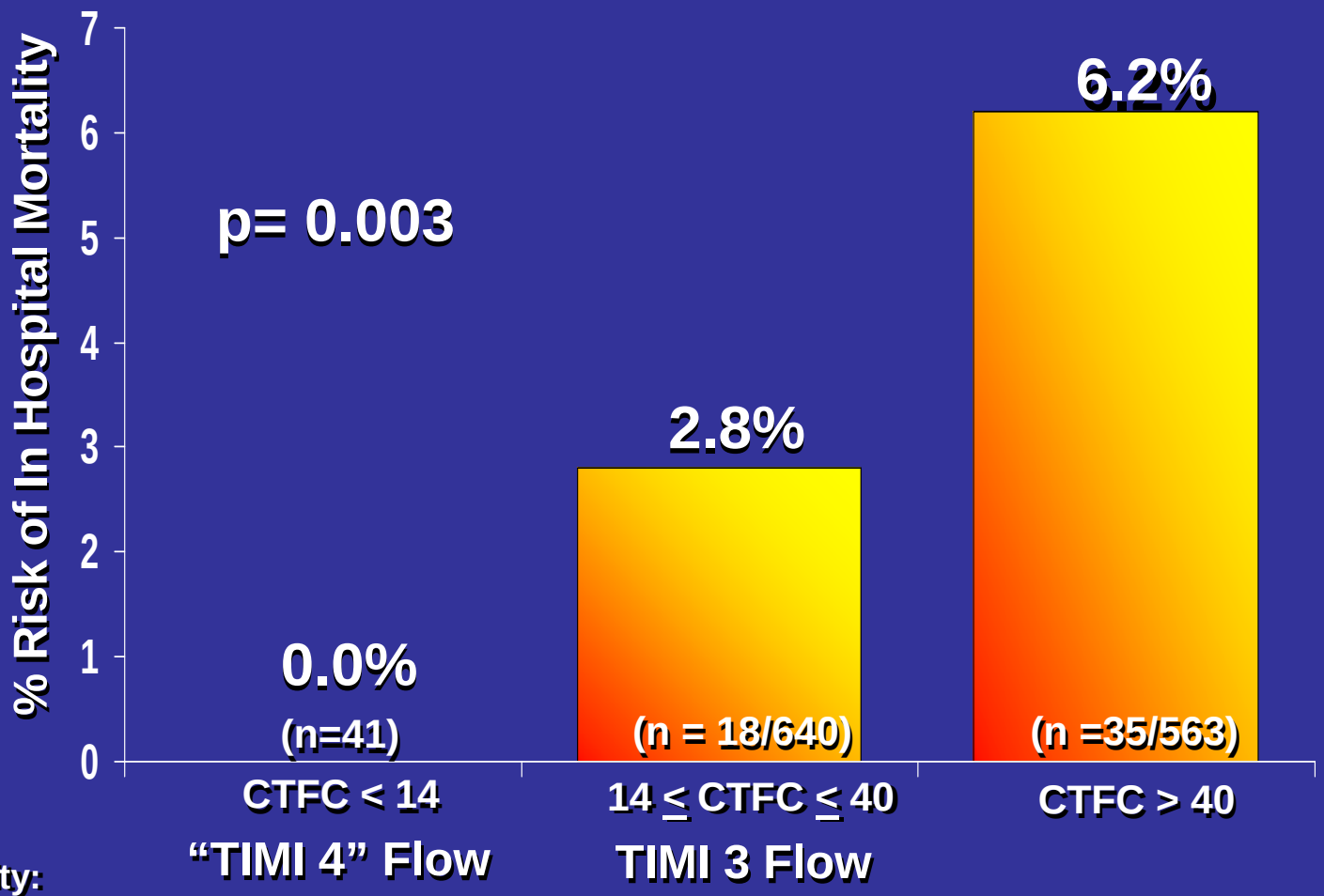
- No reflow can be predicted on admission by:
  - High ET1 and, better, by high TXA2 levels
  - Grade 3 ischemia on the admission EKG
- The EKG is the most readily available tool for this purpose and therefore is probably the best method available at present for this purpose.

HOW CAN FULL REPERFUSION BE DETECTED?

- **Bedside signs of reperfusion:**
  - Resolution of symptoms
  - Rapid release of biomarkers
  - ST resolution
  - Reperfusion arrhythmias
- **TIMI flow grade and CTFC**
- **Myocardial blush - TMPG**
- **Coronary Doppler wire**
- **Non invasive imaging: MRI, Contrast echo**

Even Faster Epicardial Coronary Blood Flow is Better

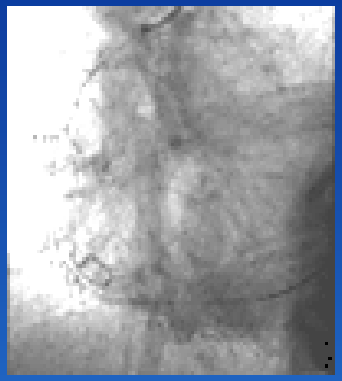
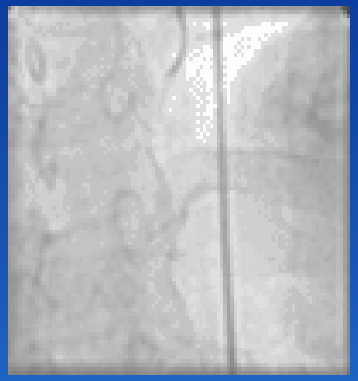




Reproducibility:
r = 0.97 between readers
Accuracy:
r=0.88 vs Doppler velocity

Gibson, Circulation 1999; 99: 1945-1950

TIMI Myocardial Perfusion (TMP) Grades


TMP Grade 3

Normal ground glass appearance of blush
Dye mildly persistent at end of washout

TMP Grade 2

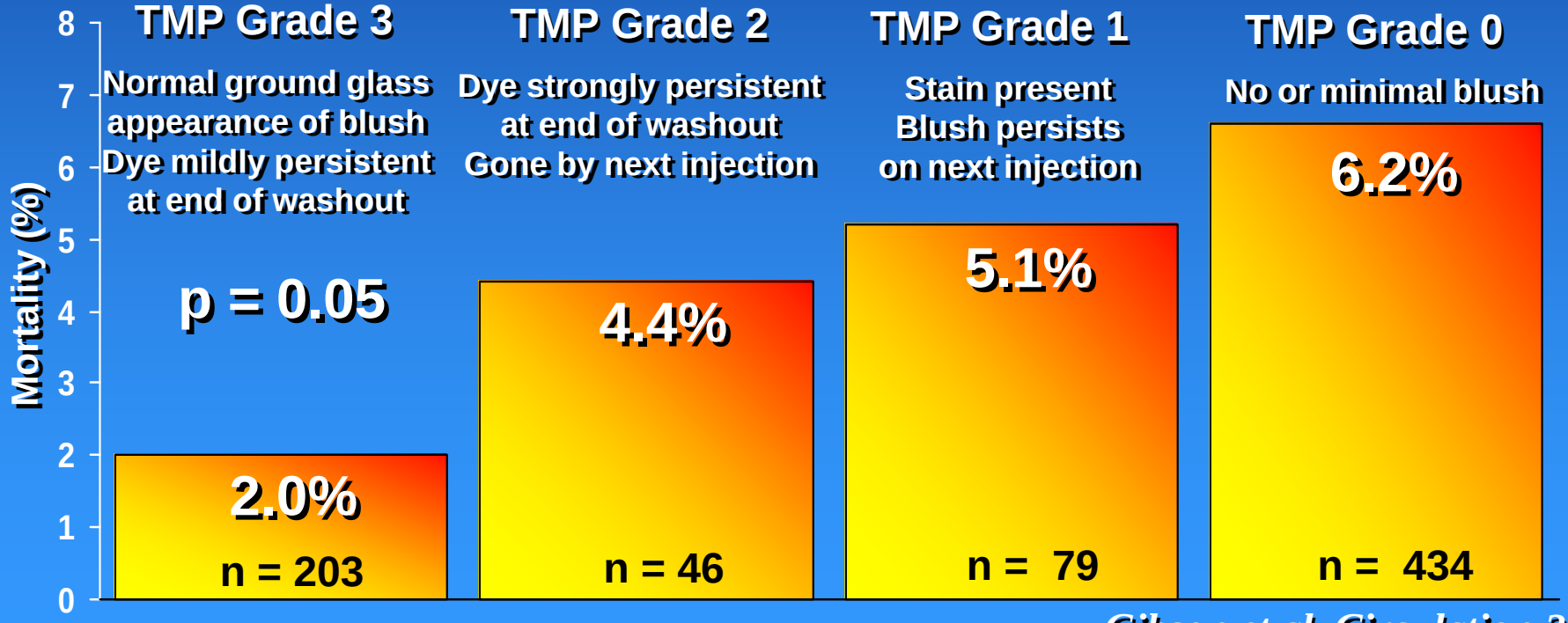
Dye strongly persistent at end of washout
Gone by next injection

TMP Grade 1

Stain present
Blush persists on next injection

TMP Grade 0

No or minimal blush

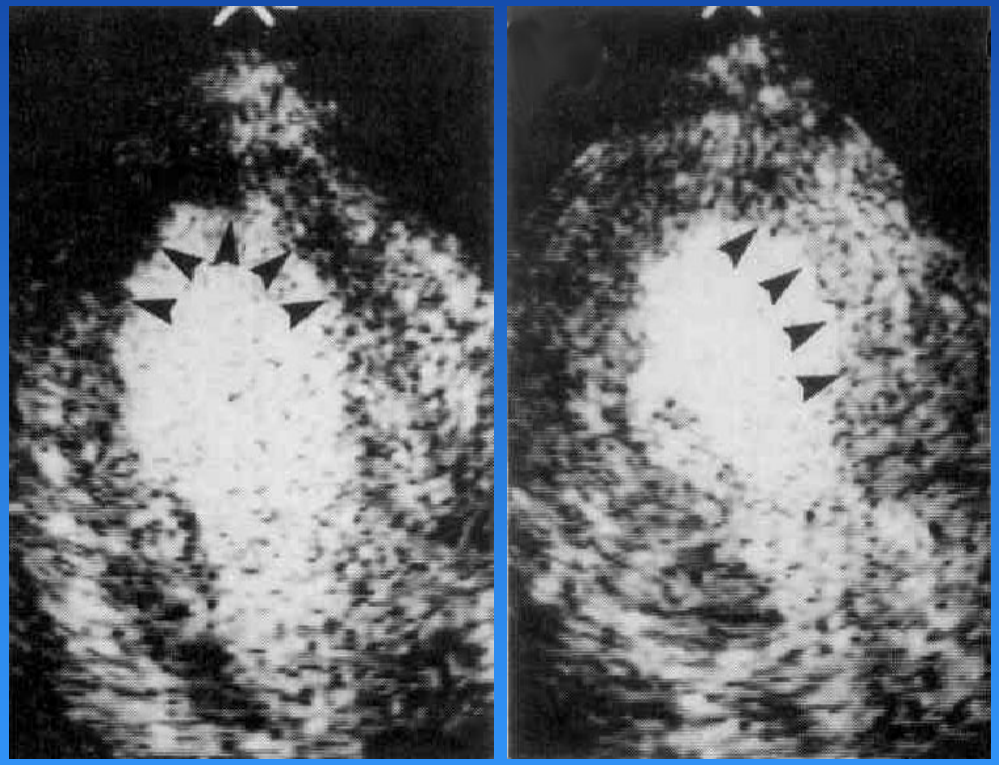


Gibson et al, Circulation 2000

Coronary Doppler wire

- Indicators of no reflow:
  - Systolic retrograde flow
  - Diminished systolic antegrade flow
  - Rapid deceleration of diastolic flow

Tissue Level Perfusion by Myocardial Contrast ECHO & Outcomes

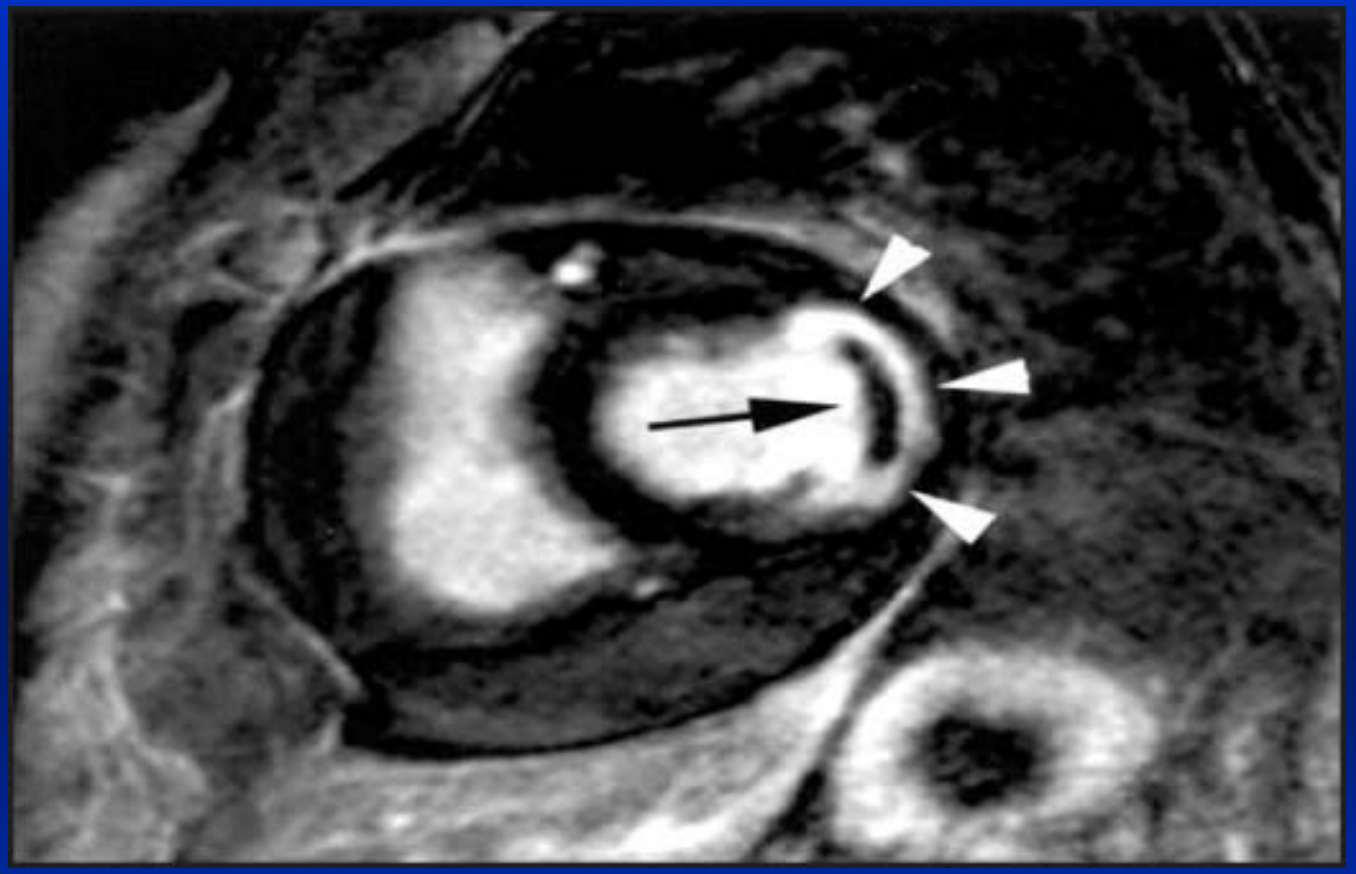


No Reflow Reflow

	No Reflow	Reflow	p value
Arrhythmia	40%	18%	0.005
CHF	21%	12%	0.001
In Hospital Death	6%	1%	0.15

Porter et al. Am J Cardiol 1998;82:1173-7.

Ito et al, Circulation, 1996



Midventricular short-axis magnetic resonance image demonstrating acute transmural infarction of the lateral wall (arrowheads). A dense rim of subendocardial signal void (black arrow) corresponds to the region of no reflow or microvascular obstruction. Because gadolinium does not reach this portion of the myocardium, there is no T1 shortening. Therefore, no hyperenhancement can be visualized.

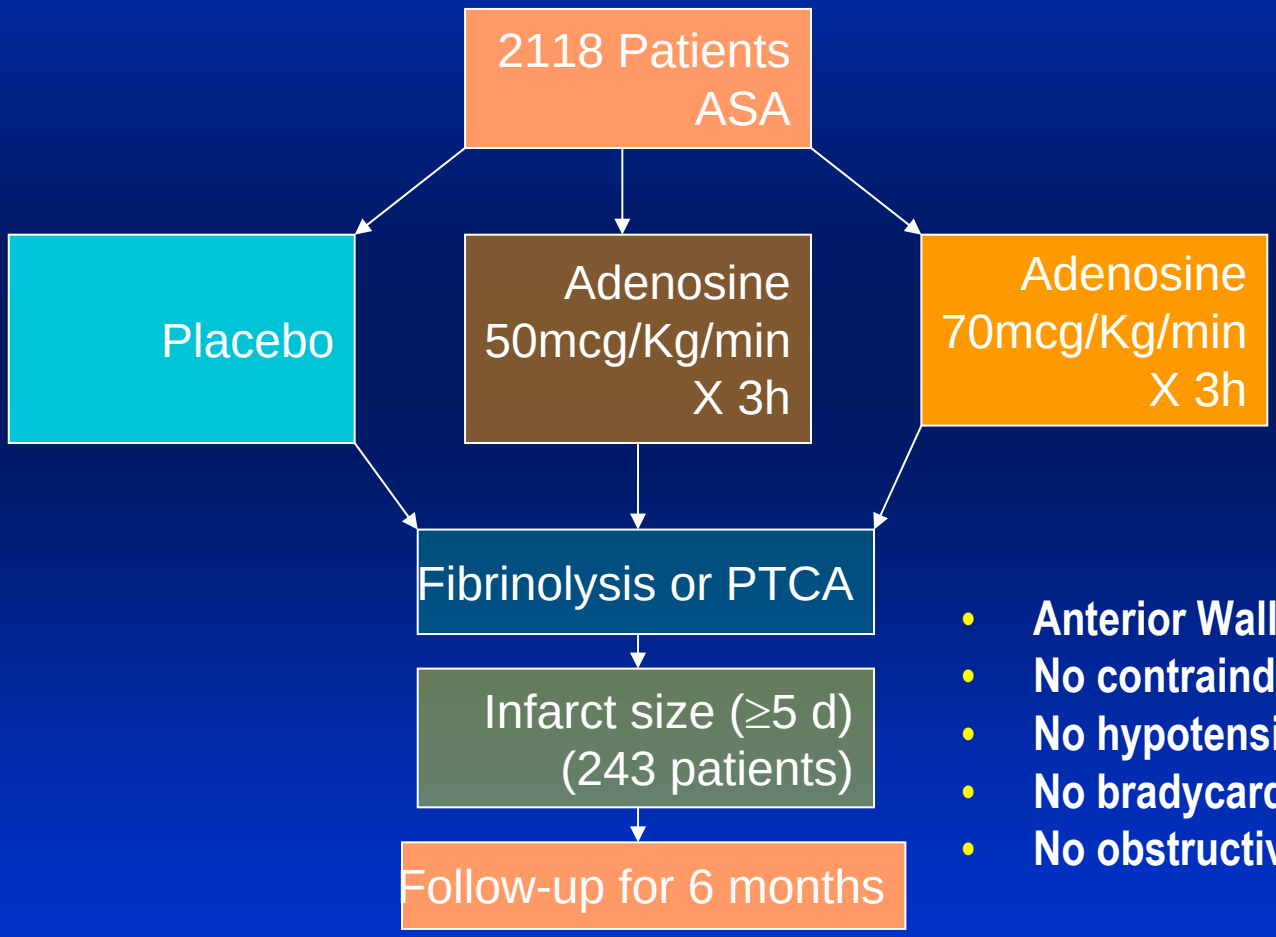
PHARMACOLOGICAL MANAGEMENT OF NO REFLOW

- ADENOSINE
- VERAPAMIL
- NITROPRUSSIDE

ADENOSINE :

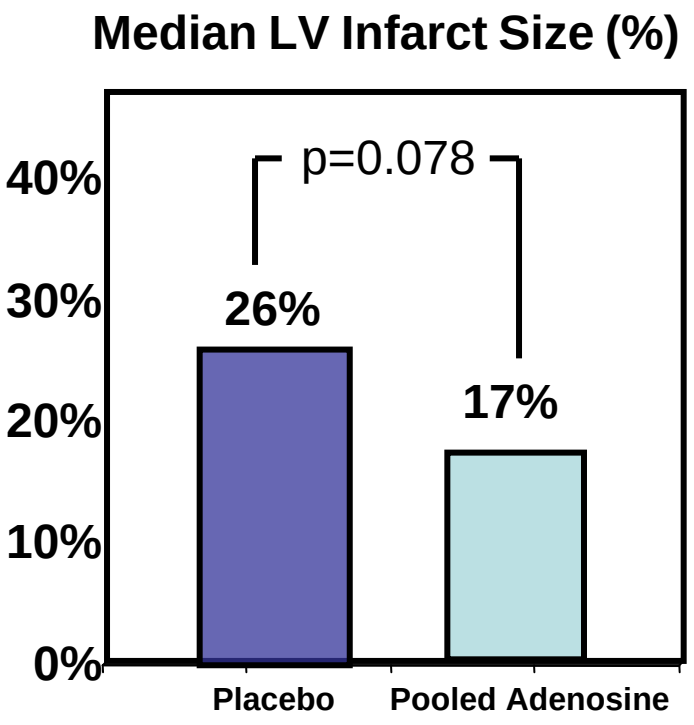
- Promotes preservation of microvascular blood flow
- Inhibits neutrophils
- Restores key metabolic substrates
- Inhibits production of oxygen-derived free radicals
- Restores calcium homeostasis
- Mediates pre-and post-conditioning

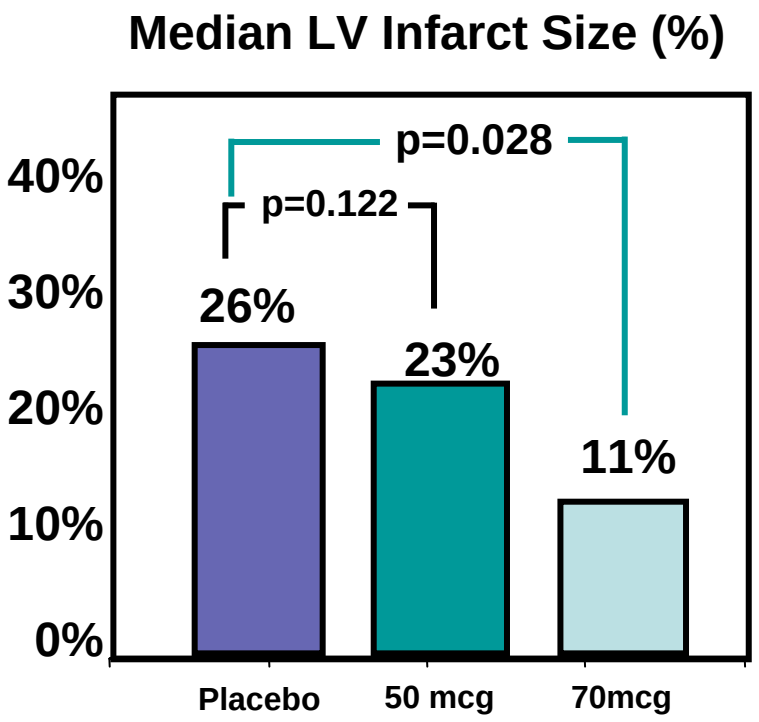
AMISTAD II



- **Anterior Wall MI (STE, LBBB) ≤6h**
- **No contraindication for lysis**
- **No hypotension**
- **No bradycardia**
- **No obstructive airway disease**

AMISTAD II Infarct Size

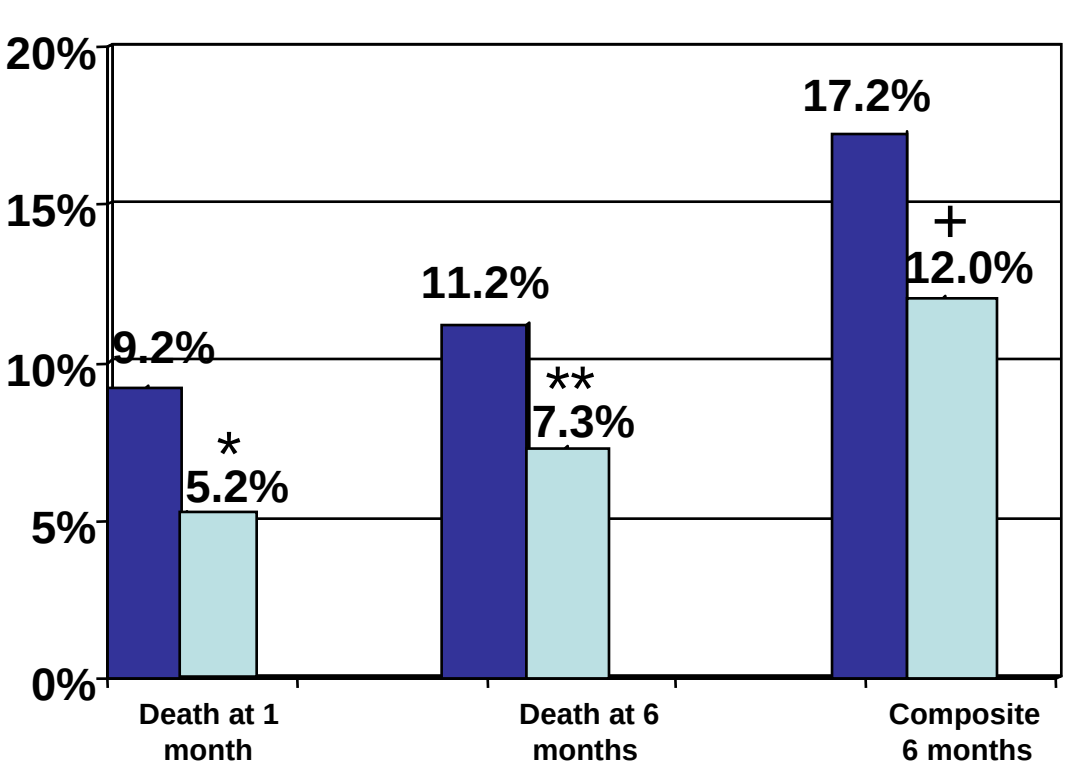




57% reduction in median infarct size with 70mcg/kg/min group relative to placebo

AMISTAD II- Post Hoc Analysis

Effect of early reperfusion treatment (3.1 hrs) on clinical outcomes



Placebo

Pooled Adenosine

* p=0.01

**p=0.03

\+ p=0.02

VERAPAMIL

- Relieves vessel spasm
- Improves calcium homeostasis in ischemic myocardial cells
- May inhibit platelet aggregation and thrombus formation in the microvasculature
- May reduce myocardial ischemia and infarct size by reducing heart rate and blood pressure

VERAPAMIL (2)

- Several small studies suggest that routine IC verapamil at the time of PCI prevents microvascular dysfunction and TIMI flow rates in STEMI and in SVG interventions

Nitroprusside

- A short acting potent vasodilator acting in the resistance arteriolar circulation
- Nitric oxide (NO) donor
- Intracoronary administration was found to be an effective and safe treatment for impaired blood flow and no-reflow during elective PCI [Hillegas at all.JACC-2001]

Intracoronary Nitroprusside for the Prevention of No-reflow Following Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction. A Randomized, Double Blind, Placebo-Controlled Clinical Trial.

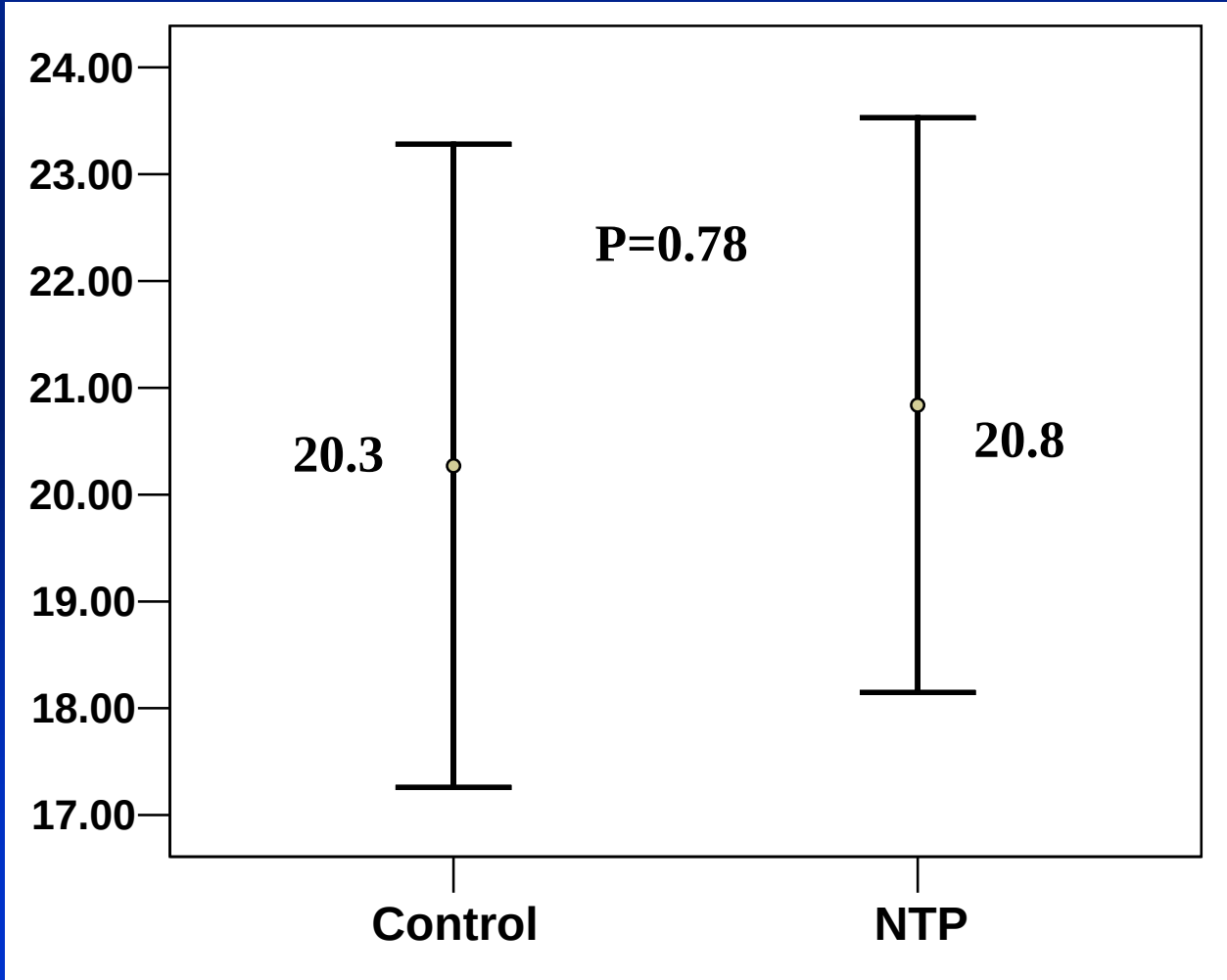
G. Amit, C. Cafri, S. Yeroslavtzev, A. Abu-Ful, J.M. Weinstein, A. Wolak, S. Fuchs, R. Ilia and D. Zahger

Dept. of Cardiology,
Soroka University Medical Center & Faculty of Health Sciences,Ben Gurion University of the Negev,
Beer-Sheva

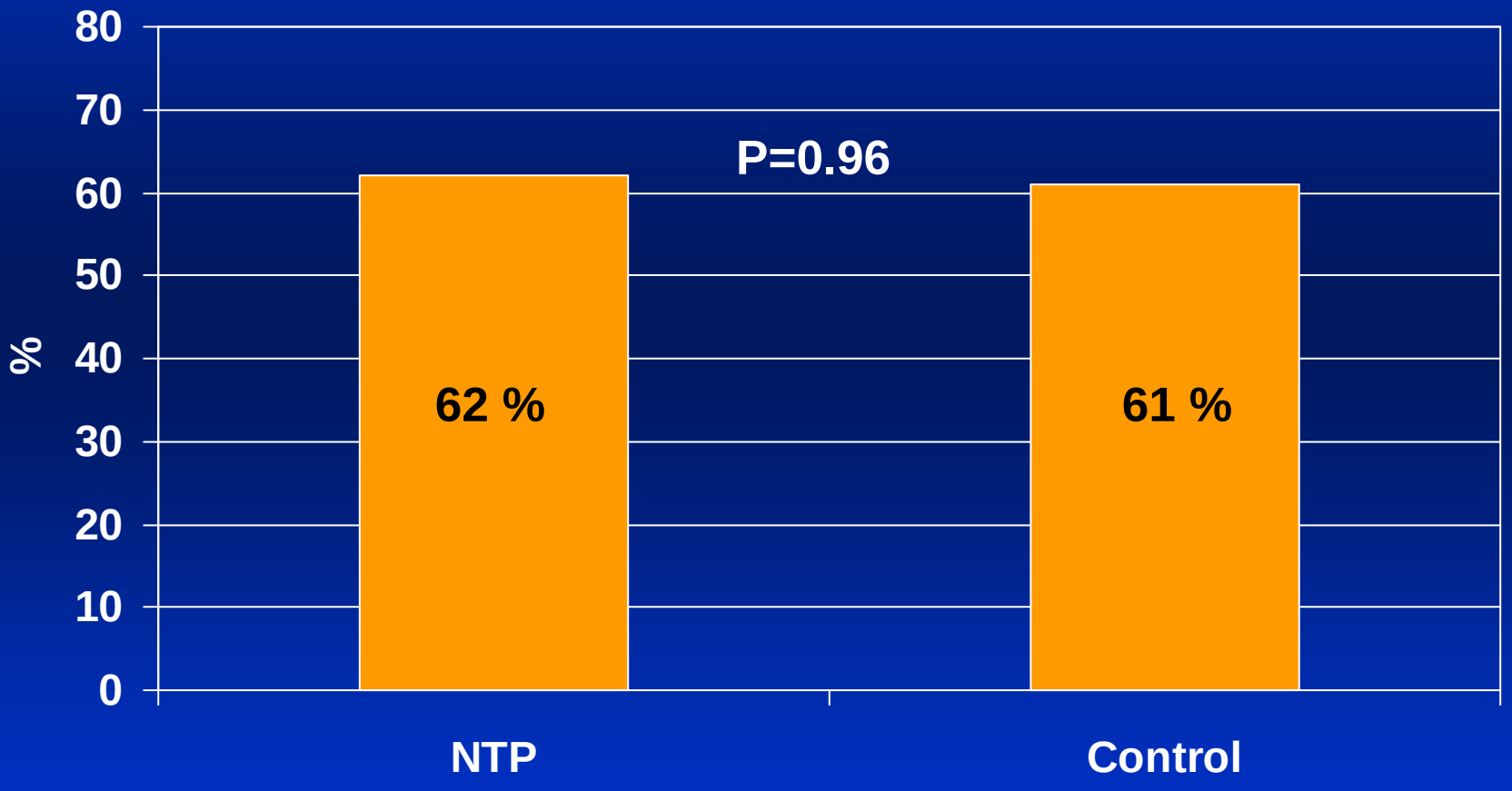
Am Heart J 2006;152:887.e9-14

Primary end point- Corrected TIMI Frame Count

CTFC Mean ± SEM



Primary end point- ST-segment elevation resolution



NICORANDIL

- A hybrid of a K ATP opener and a nitrate
- Intravenous nicorandil, started before PPCI, improves tissue perfusion, reduces infarct size, and improves patient outcome (Ishii H Circulation 2005)

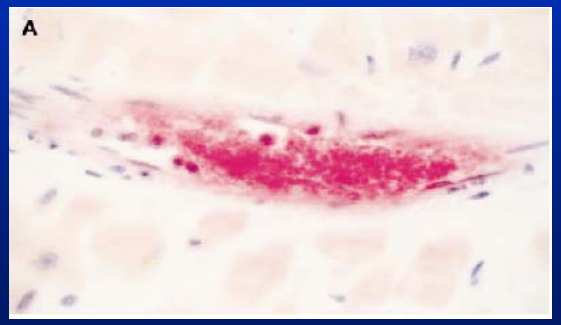
NICARDIPINE

- Highly potent microcirculatory vasodilator
- Longer duration of action
- Greater coronary vasoselectivity
- Minimal myocardial or AV nodal depression
- Prevention of no reflow especially in grafts (Huang RI et al. CCI-2006, Fischell T et al. J Invas Cardiol-2006,2008)

Background

PPCI

Large thrombotic burden *procedures with a large embolic risk!*

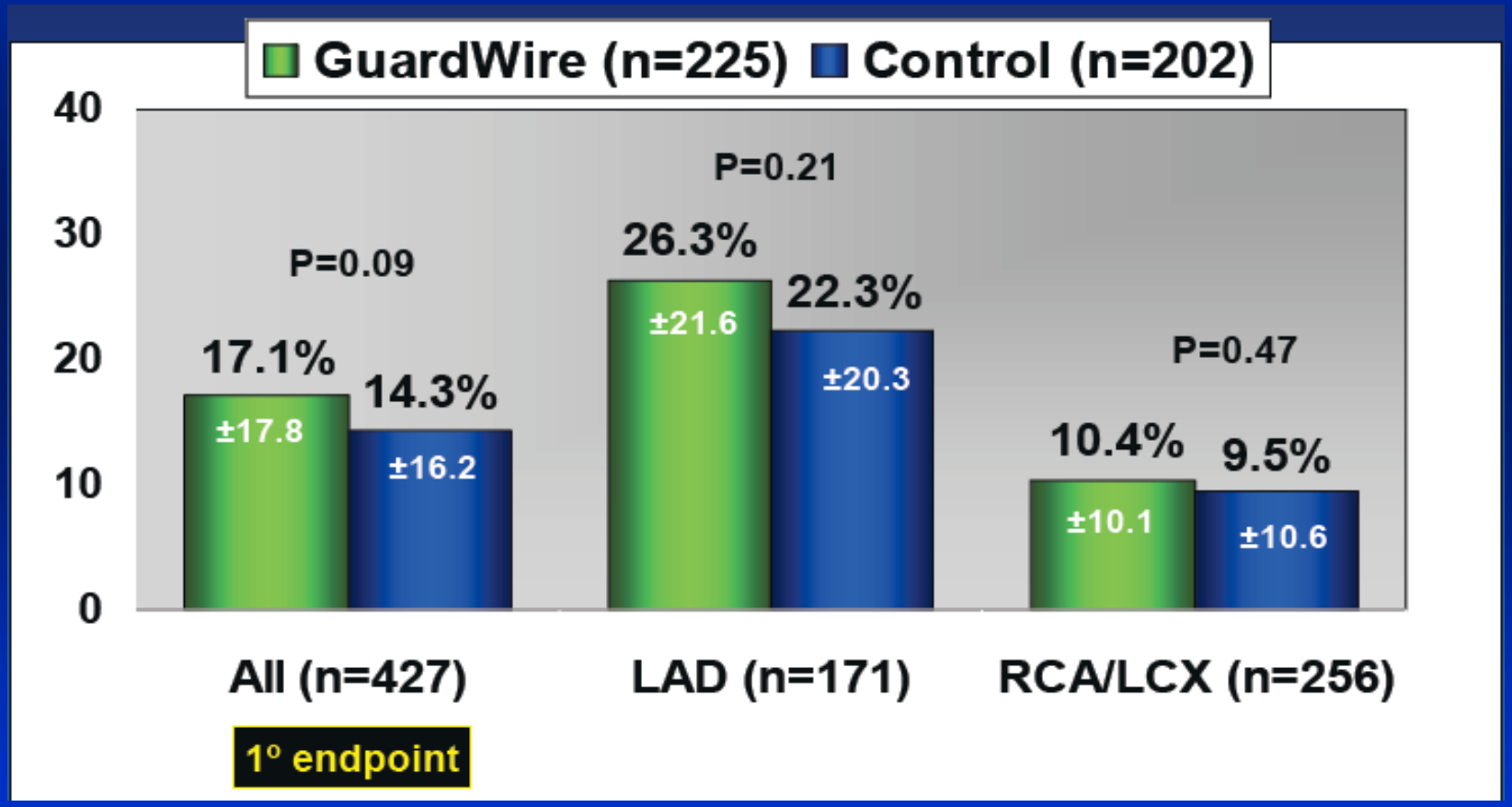


Distal **embolization** of particles during primary PCI may be a major contributing cause of the suboptimal myocardial perfusion

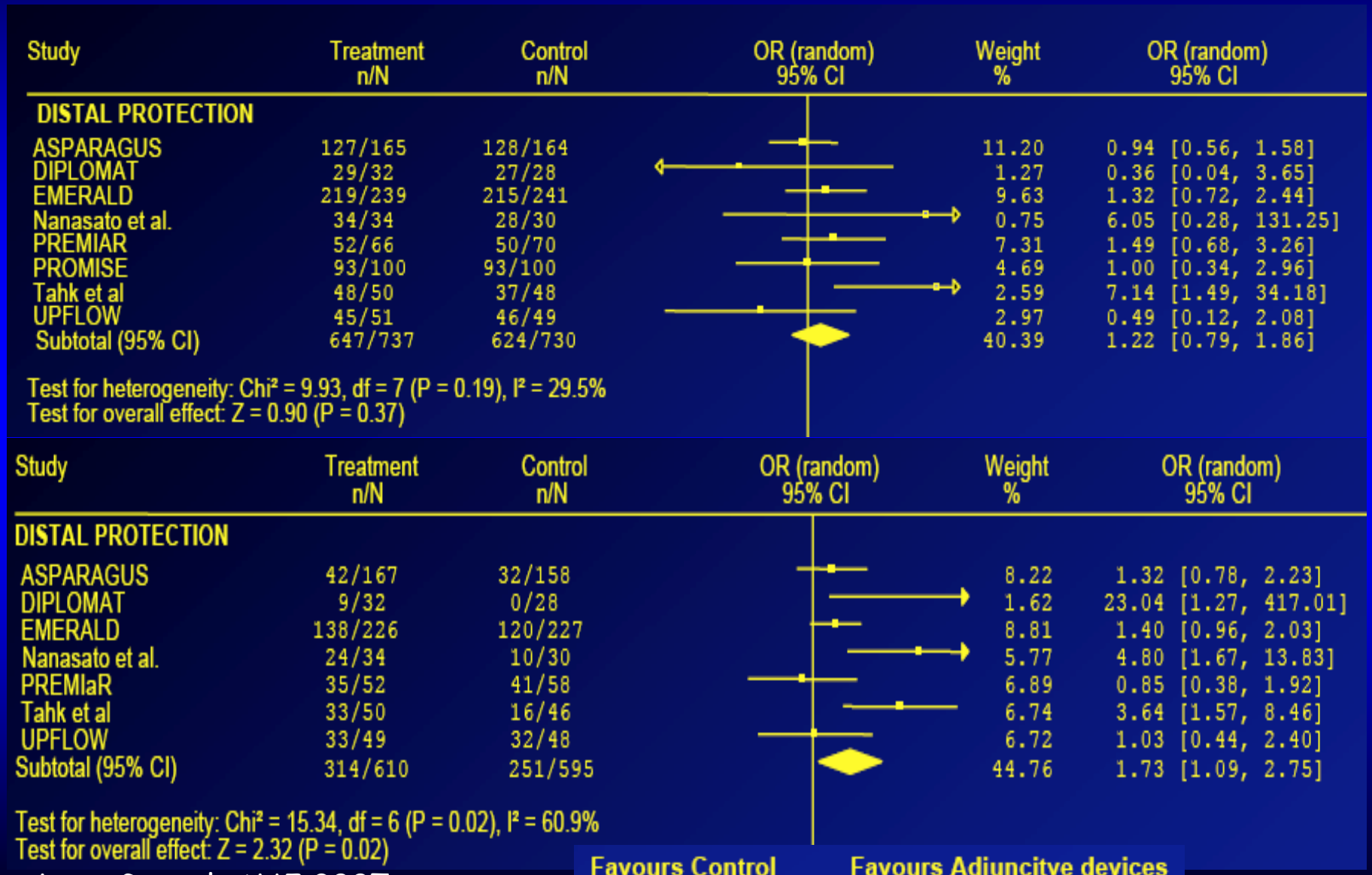
Thus a devices that could capture and remove thrombus or embolic particles before they reach the myocardium could improve myocardial perfusion

The EMERALD Study

Infarct size by Tc-99m-SPECT
Infarct size, %LV



PREVENTION OF DISTAL EMBOLIZATION IN AMI: A META-ANALYSIS TIMI 3 FLOW & MPG 3



De Luca G et al. AHJ 2007

Why did studies of distal protection in AMI PCI show no benefit?

- **Patient related issues?**
  - Distal protection may be beneficial in subgroups of patients (large size vessels with increased thrombotic load)
- **Device related issues?**
  - Crossing profile and wire manipulation
  - Sizing (especially small vessels)
  - Capturing (still sub-optimal in some cases)
  - Different device may be needed
  - Combination devices (i.e. sequential approach)
- **Misconception related issues?**
  - Myocardial preservation (i.e. pharmacologic) vs. mechanical protection approach or may be both

TAPAS Trial Design

1071 STEMI patients randomized

535 were assigned to thrombus aspiration

536 were assigned to conventional PCI

33 did not undergo PCI
502 underwent primary PCI
295 underwent TA followed by - direct stenting
153 underwent TA with additional - balloon dilation
54 had crossover to conventional - PCI

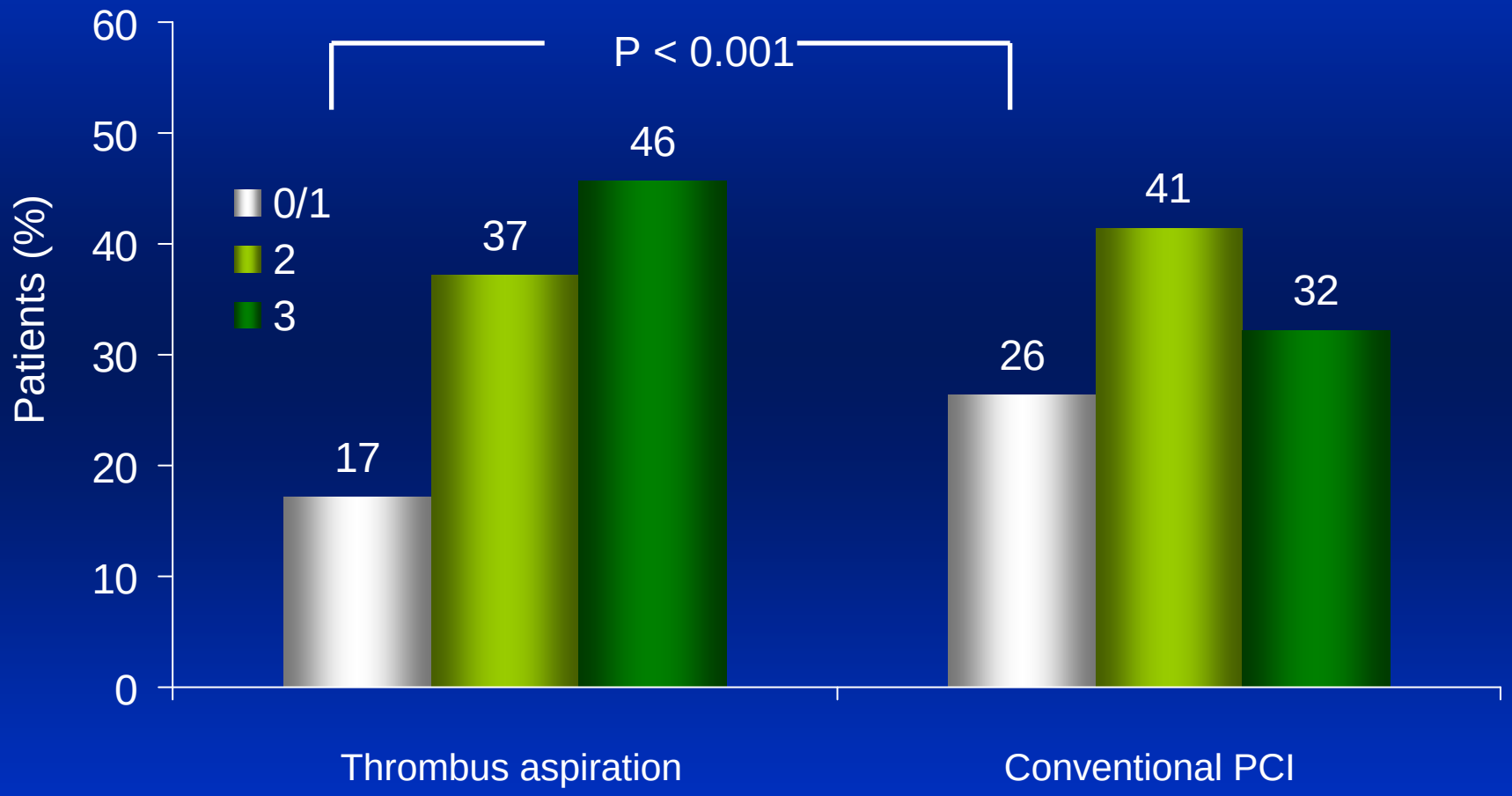
33 did not undergo PCI
503 underwent primary PCI
485 underwent balloon dilation - followed by stening
12 underwent conventional PCI - with additional TA
6 had crossover to TA-

530 complete follow-up at 1 year

530 complete follow-up at 1 year

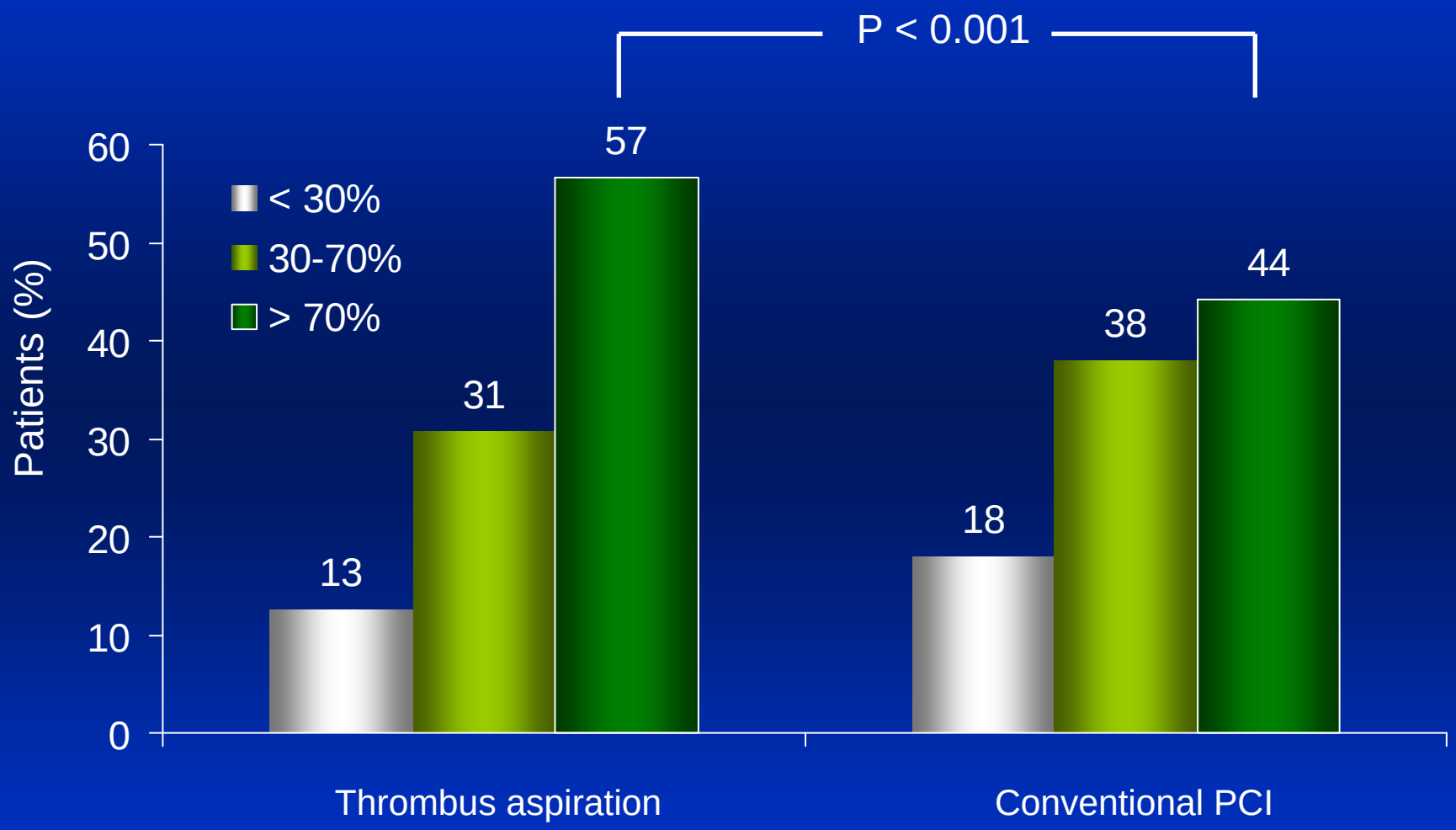
Vlaar PJ, et al. *Lancet*. 2008 Jun 7;371(9628):1915-20.

Primary endpoint: Myocardial blush grade



Svilaas T et al. NEJM 2008;358:557 - FZ 2008-8

ST-segment elevation resolution

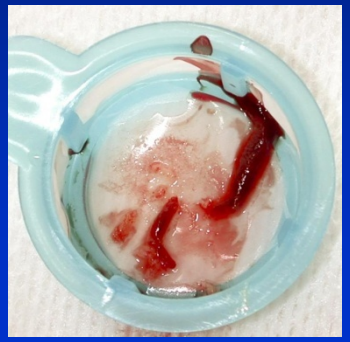


Svilaas T et al. NEJM 2008;358-557 - FZ 2008-9

TAPAS: Summary of findings at 30 days

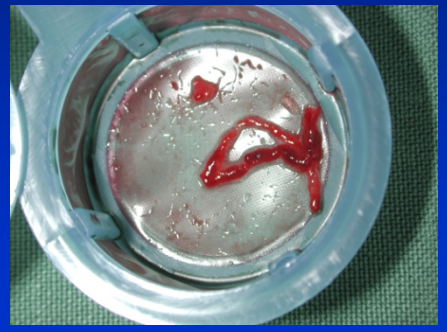
- Thrombus aspiration results in improved myocardial reperfusion
- Myocardial blush grade predicts 30-day rates of death and reinfarction

- Does improved myocardial reperfusion translate into clinical benefit at 1 year?

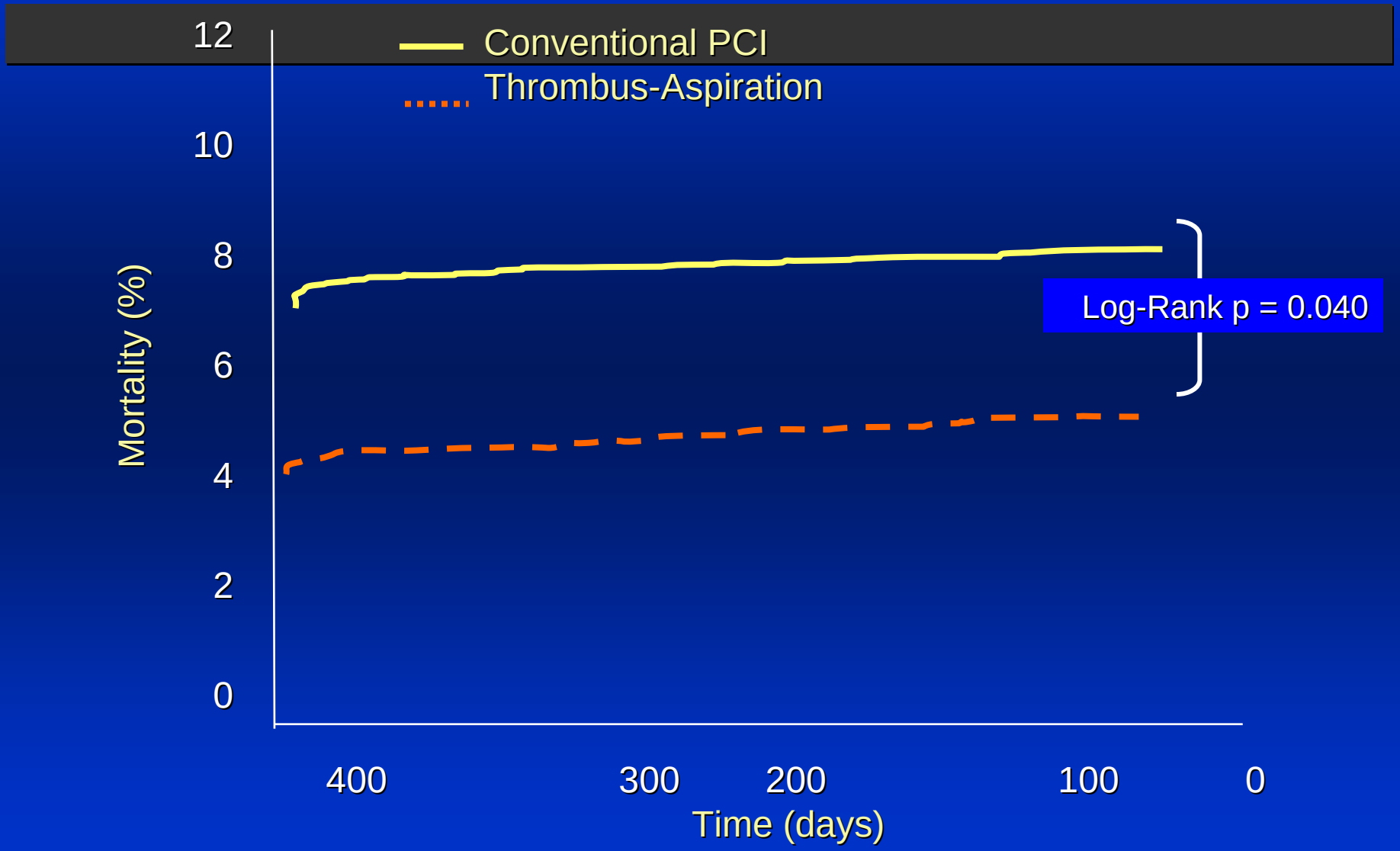


?

FZ 2008-11



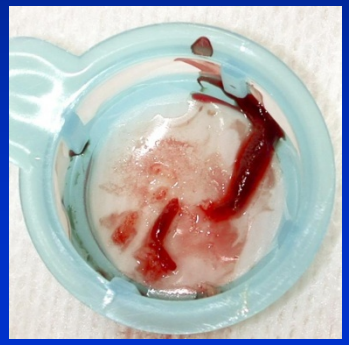
Mortality at 1 Year



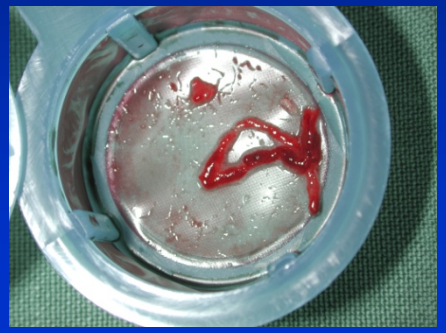
Vlaar PJ, et al. *Lancet*. 2008 Jun 7;371(9628):1915-20.

TAPAS: Mortality and reinfarction at 1 year

- **Myocardial blush grade predicts clinical outcome at 1 year**
- **Thrombus aspiration results in a lower mortality and combined mortality and non-fatal reinfarction at 1 year**



FZ 2008-15



CONCLUSIONS

- No reflow is a common and serious complication of reperfusion therapy
- No reflow can be predicted by grade 3 ischemia, longer time to treatment and anterior MI
- Diagnosis based on TIMI flow and blush, failure of ST resolution
- No medical intervention consistently beneficial
- Thrombus aspiration is the best available strategy

THANK YOU!!!