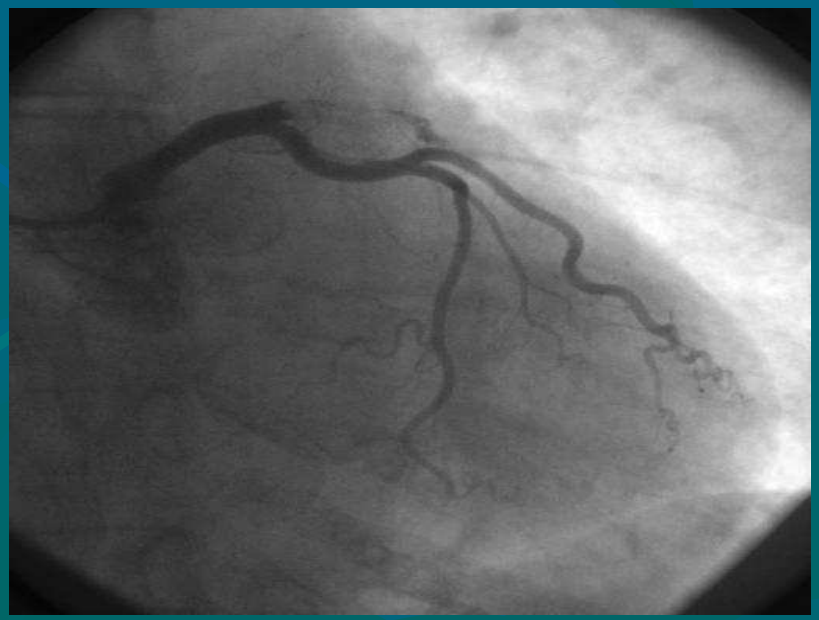
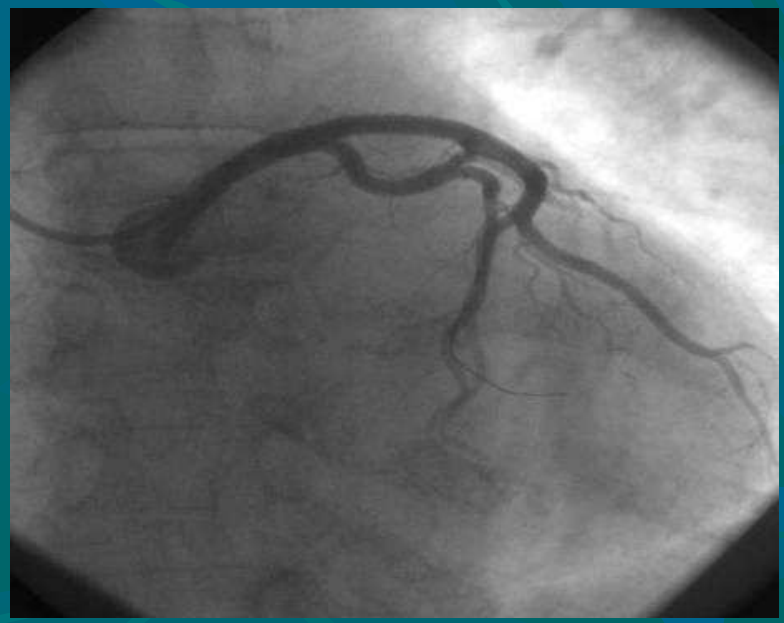
Diagnostic et Prise en Charge des Echecs De Thrombolyse

Antoine Sarkis, MD





Jeudi 24 Novembre 2005

Diagnostic et Prise en Charge des Echecs De Thrombolyse

- Modalités de traitement de l'infarctus aigu du myocarde (AMI)
  - Thrombolyse
  - Variétés d'angioplastie (PCI) dans AMI
- Critères d'échec de thrombolyse
- Angioplastie après échec de thrombolyse

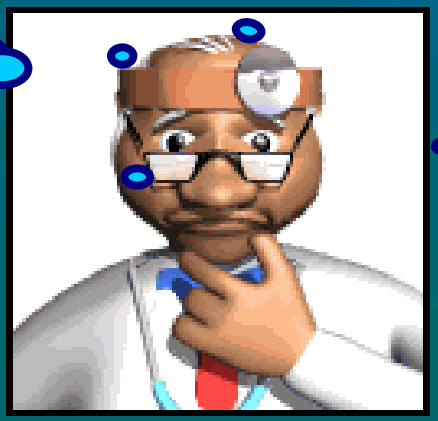
r-PTCA

d-PTCA

t-PTCA

f-PTCA

p-PTCA



a-PTCA

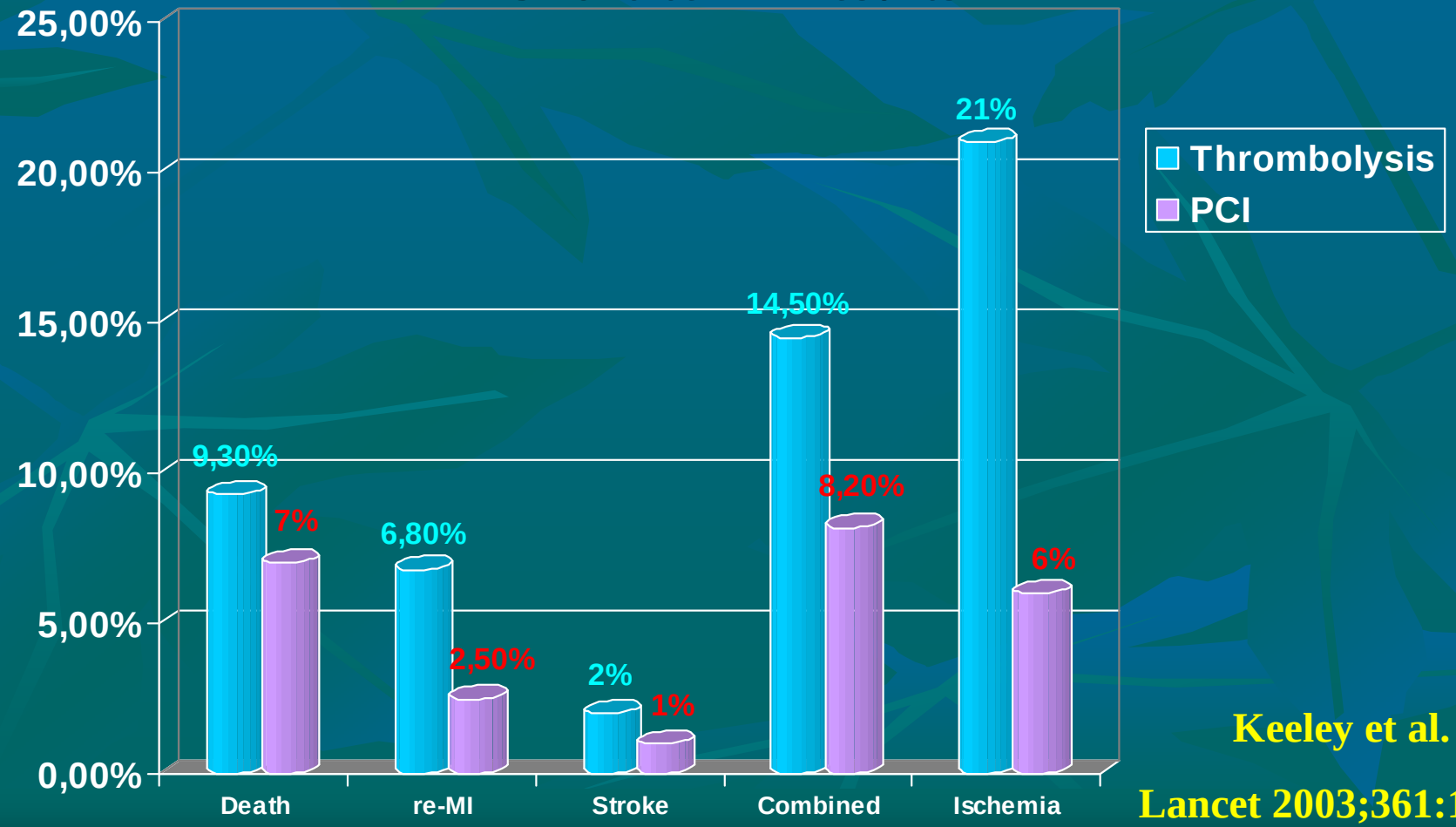
PCI in AMI

Variétés de PTCA in AMI

- Primary (P-PTCA)
- Transfer (T-PTCA)
- Facilitated PCI––after reduced dose lytics alone, or with IIb/IIIa inhibitors (F-PTCA)
- PCI early after thrombolytic therapy
  - Routine-immediately after- (Adjunctive) (A-PTCA)
  - Rescue – in pts with persistent occlusion or reduced flow in the infarct artery (R-PTCA)
- Delayed— hours to days later (D-PTCA)

P-PTCA=Primary PTCA

PCI v/s Thrombolysis in STEMI :
« A quantitative review of 23 randomized trials »
Short-term Results



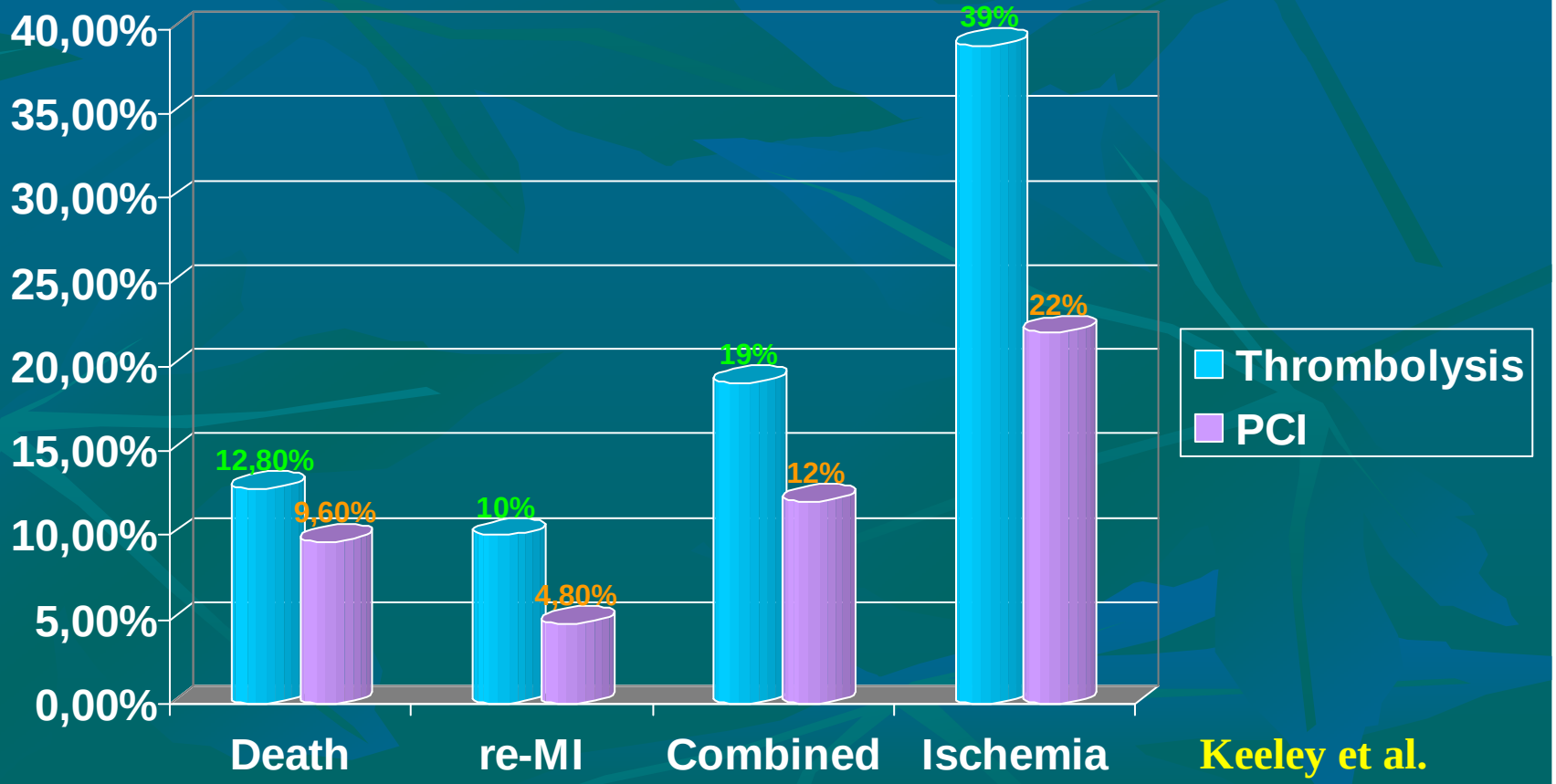
Keeley et al.

Lancet 2003;361:13-20

P-PTCA=Primary PTCA

PCI v/s Thrombolysis in STEMI :

Long-term Results



Keeley et al.

Lancet 2003;361:13-20

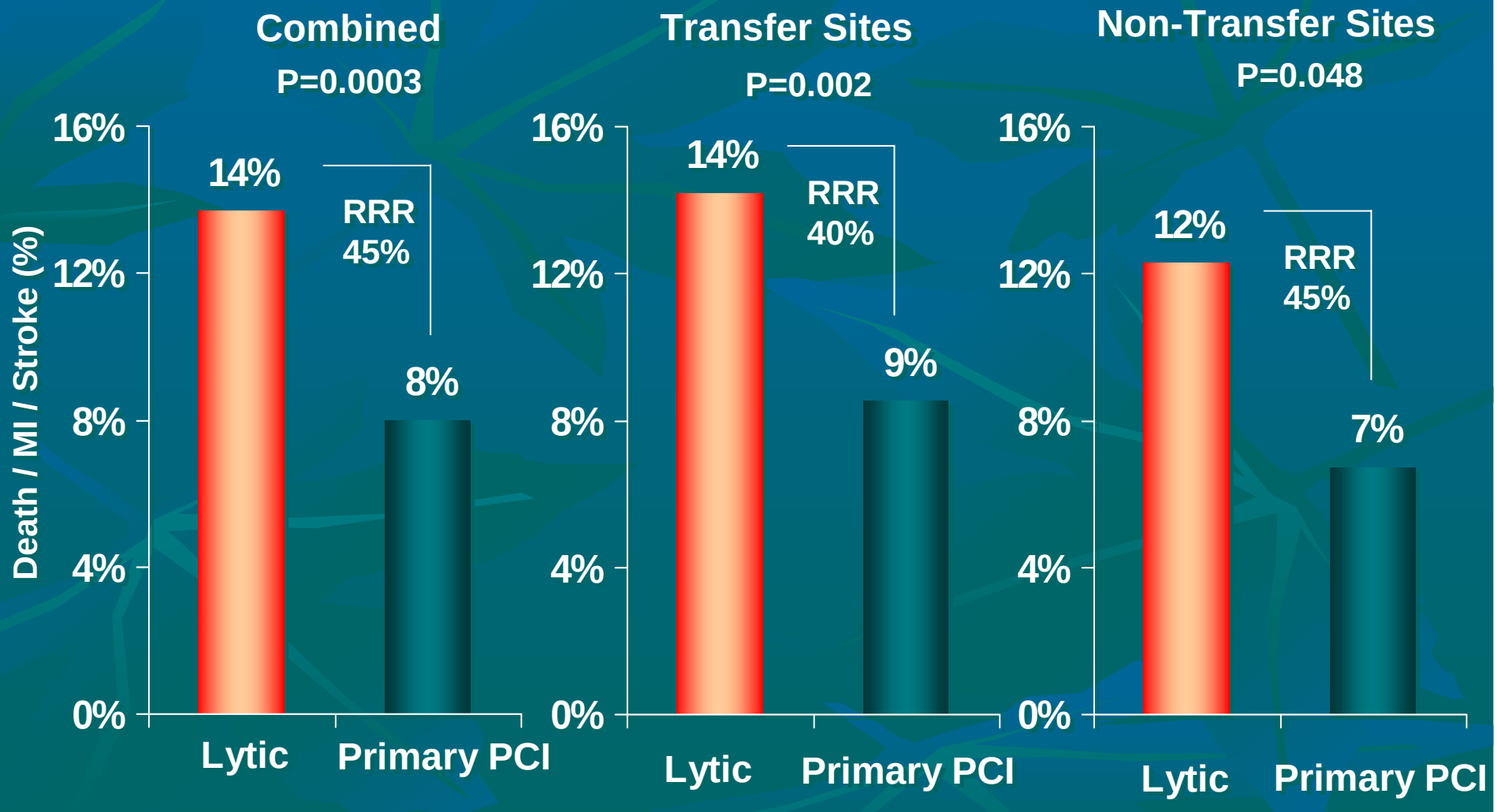
Transfer PCI
The DANAMI-2 Trial

Danish Trial in Acute Myocardial Infarction-2

Dr. Henning Rud Andersen
for the DANAMI-2 investigators

NEJM 2003, 349:733-742

DANAMI-2: Primary Results



Captim trial:

Outcomes in patients randomized within first two hours of symptom onset

End point	Prehospital lysis <2 hours (%)	Primary PCI <2 hours (%)	p
30-day death, reinfarction, or stroke	7.4	6.6	0.855
30-day death	2.2	5.7	0.058
30-day reinfarction	4.0	1.4	0.141
30-day stroke	1.3	0.0	0.249
Cardiogenic shock (between randomization and discharge)	1.3	5.3	0.032
Cardiogenic shock (between randomization and admission)	0.0	3.6	0.007

Steg et al, Circulation 2003,108:2851

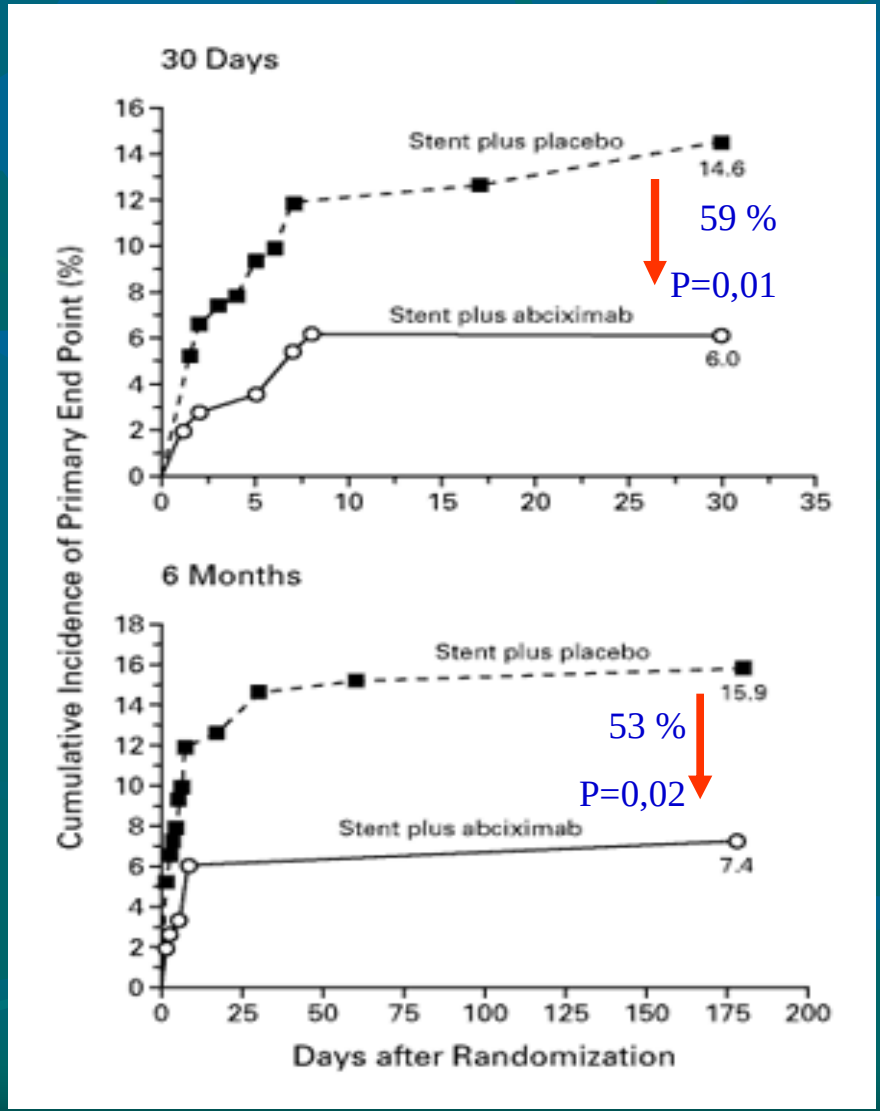
Peut-on encore améliorer les résultats de l'angioplastie coronaire ?

F-PTCA=Facilitated PCI

- PCI could be facilitated with :
  - Thrombolysis (PACT, BRAVE, ASSENT 4, FINESSE…)
  - GIIb/IIIa inhibitors (ADMIRAL, ON-TIME, TIGER-PA, BRIDGING…)

Anti GP IIb-IIIa F-PTCA

- ADMIRAL
- 300 pts
- Abciximab + stent vs stent alone
- Combined end-point (mortality, reinfarction, revascularisation) lower in abciximab group at 30 days: (6 vs 14.6%), and at six months (7.4 vs 15.9%)
- TIMI 3 flow before angiogram : 16.8 vs 5.4%



NEJM 2001; 341:1895-1903

Thrombolysis F-PTCA

Large AMI < 6hrs
Planned PCI
Cath lab delay of 1-3 hr

Randomize

ASA
UFH (bolus)
TNK

n = 2,000

ASA
UFH (bolus)
No lytic

n = 2,000

Cath lab

Angiography / PCI (immediate)

Stent / clopidogrel (optional)

Heparin as routinely used

NO GP IIb/IIIa inhibitors

Angiography / PCI (immediate)

Stent / clopidogrel (optional)

Heparin as routinely used

GP IIb/IIIa inhibitors at investigators discretion

ASSENT 4
Pharmaco-Mechanical Reperfusion

- **The study was prematurely stopped because of a significant increase of death in the TNK group.**

Outcome	TNK+PCI (n=828)	PCI alone (n=838)	p
Number (%) of deaths	50 (6.0)	32 (3.8)	0.04

ASSENT-4: 30-day mortality results

van de Werf F. European Society of Cardiology Congress 2005; September 4-7, 2005; Stockholm, Sweden.

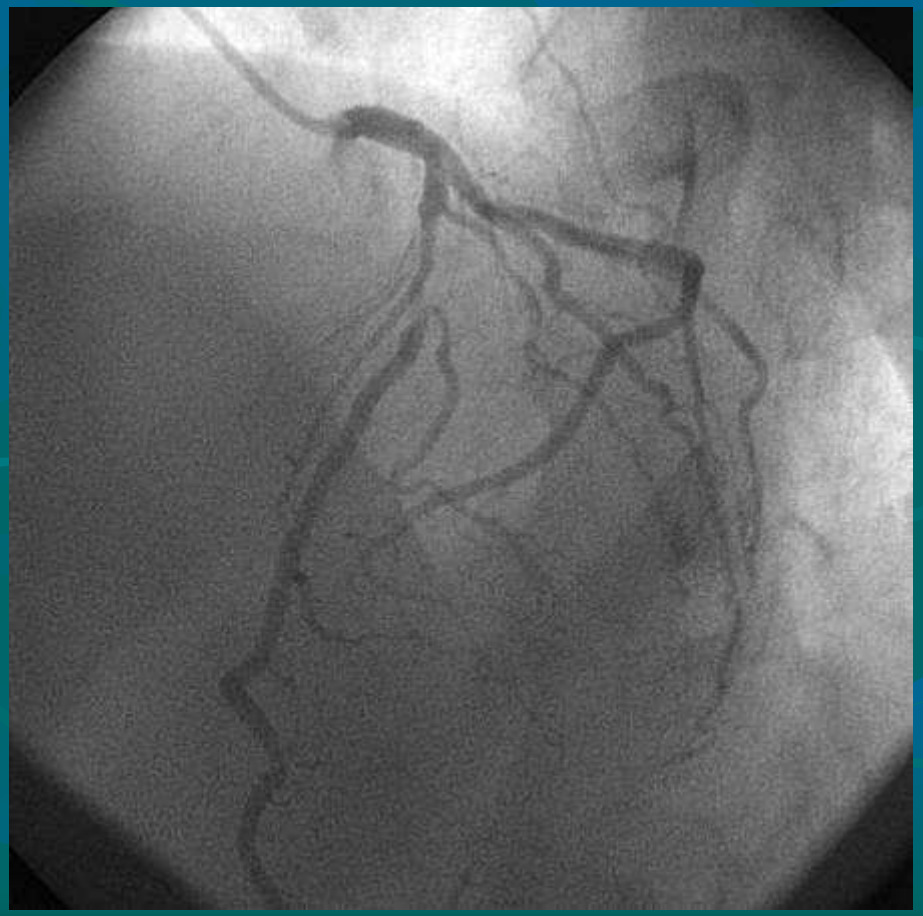
AMI : ESC recommendations

- PTCA is the preferred therapy if :
  - Artery can be opened in less than 90 minutes after first medical contact
  - Contra-indications to thrombolytic therapy
  - Cardiogenic shock
- Thrombolytic therapy in all other cases

Questions raised by thrombolytic therapy: The Gray Areas

- Major difficulties in clinical practice to assess the success of thrombolytic therapy based on clinical and ECG data
- What should be done if a coronary angiogram is performed immediately after thrombolytic therapy ?

Angiographie de routine et angioplastie après Thrombolyse (Adjunctive PTCA)



Adjunctive PTCA after Thrombolytic Therapy

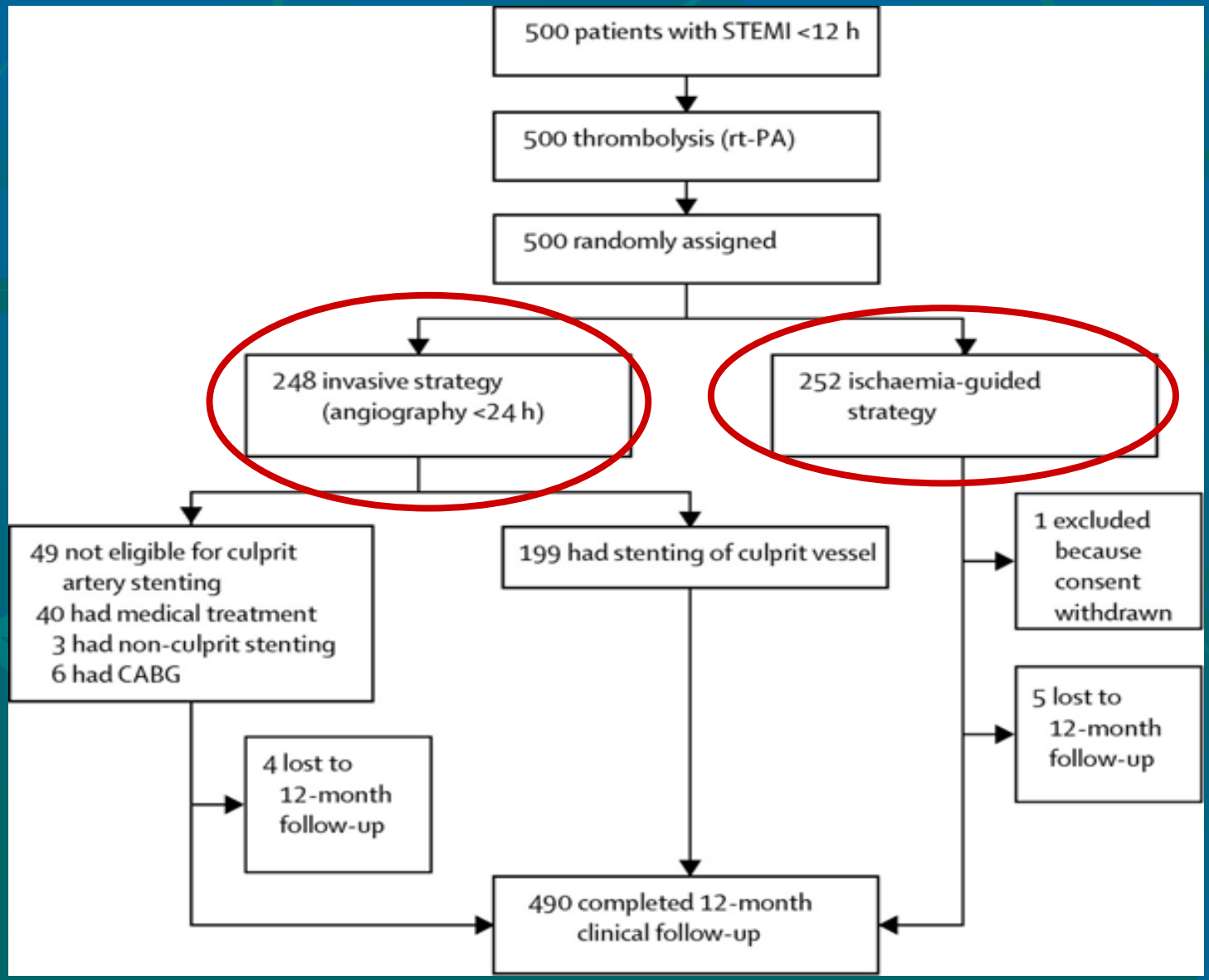
- 3 trials performed in the 80's
  - Topol et al (TAMI I), N Engl J Med 1987, 371; 581-8
  - Simoons et al Lancet 1988, 1; 197-203
  - TIMI IIA study, Circulation 1990; 81, 1457-1476

- Routine immediate angiography and PTCA did not improve clinical outcomes and was associated with increased bleeding and a trend towards increased mortality

Adjunctive PTCA after Thrombolytic Therapy

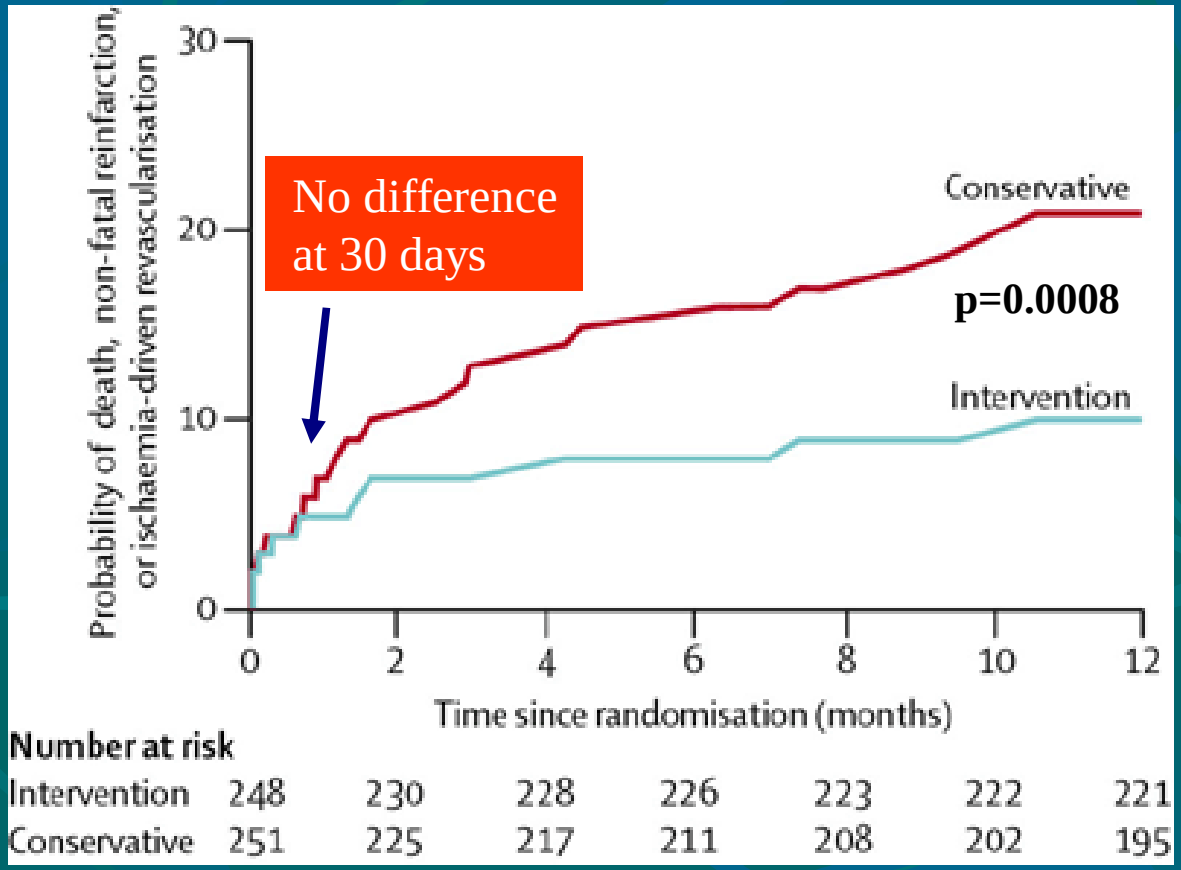
- Patients treated with thrombolytic therapy have increased levels of platelet activation and aggregation
- These trials are old
- Would GP IIb-IIIa antagonists help?
- Would stenting help?

GRACIA TRIAL



Fernandes-Aviles et al, Lancet 2004;364 : 1045-53

GRACIA Trial:

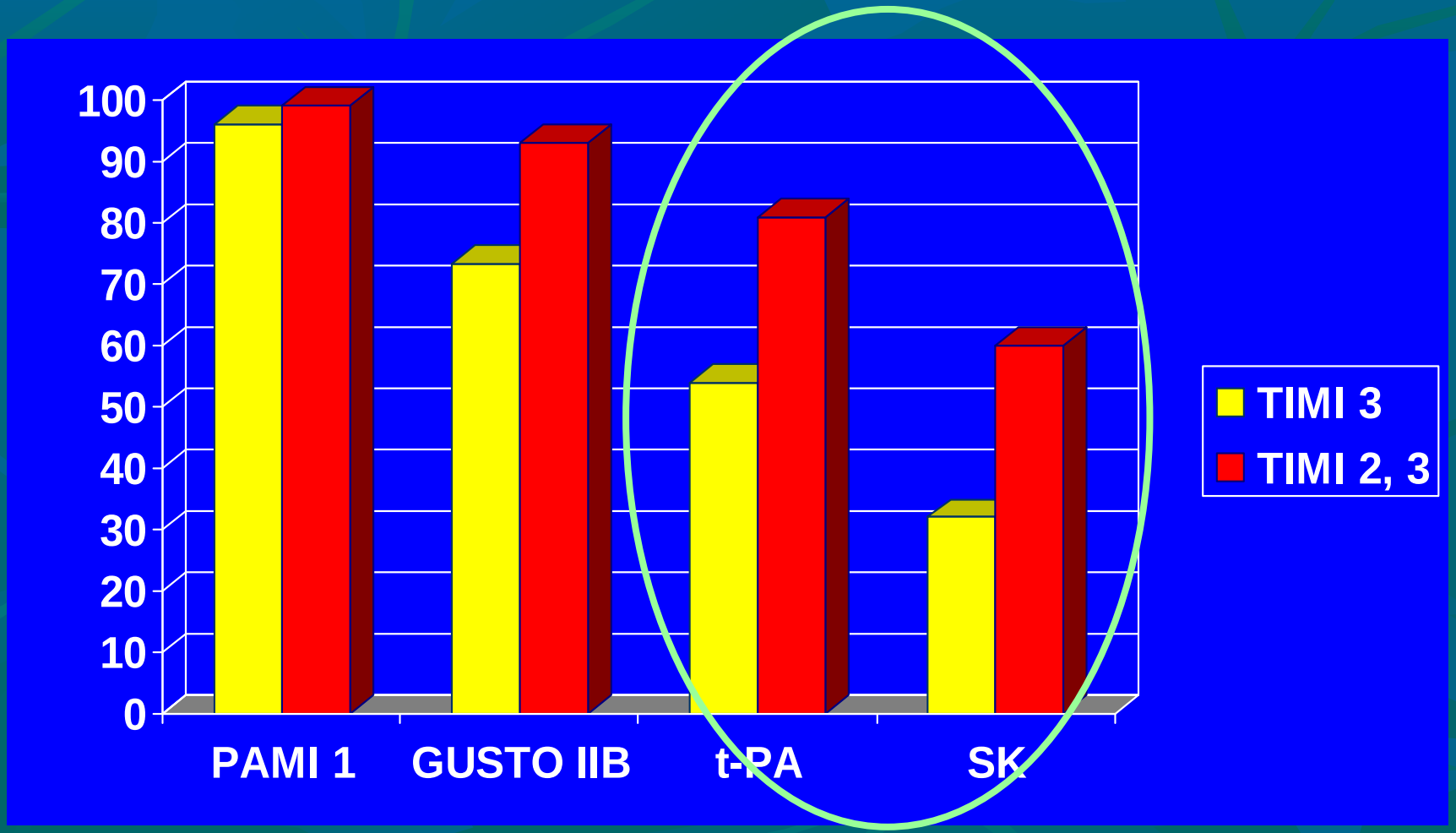


Fernandes-Aviles et al, Lancet 2004;364 : 1045-53

Angioplasty after failure of thrombolysis (RESCUE)

- Definition of failure of thrombolysis
- Detection of failure
- Therapeutic options
  - Re thrombolysis
  - Gp IIB IIIA
  - Rescue Angioplasty
  - Ballon de contrepulsion

TIMI Flow After Thrombolytic Therapy



60 to 90 min after administration !!!!!

TIMI Flow After Thrombolytic Therapy

- TIMI grade III patency is obtained in less than 60% of patients
- We have probably reached the plateau
- Adjunctive (antiplatelet) medication provides little extra benefit, with excess adverse effects due to the narrow therapeutic window of clot lysis versus bleeding risk

Diagnostic d'échec de thrombolyse

- Douleur: difficile à quantifier
- Seule la sédation totale de la douleur est un bon signe prédictif mais elle est trouvée seulement dans 29 % des artères ouvertes
- Les analgésiques peuvent masquer ce signe

Electrocardiogramme

- Très spécifique pour prédire la perméabilité de l'artère responsable de infarctus quand il y a une résolution complète (>70 %) du sus décalage du segment ST, mais ceci survient chez seulement une minorité de patients.
- Chez la plupart des patients, il y a une résolution partielle ou absence de résolution du sus décalage du segment ST, et l'état de perméabilité de l'artère responsable de l'infarctus est alors incertain.
- Un chiffre seuil (cut off) de 50 % de résolution du segment ST est un bon compromis
- Rythme Idioventriculaire Accéléré

Enzymes et Marqueurs Biochimiques

- Cinétique des enzymes :
- En faveur d'un échec de thrombolyse: un rapport Troponin T, ou CK-MB mass, ou myoglobin, par rapport au chiffre de base
  - < 5 à 60 mn
  - < 10 à 90 mn
- Sont surtout réservés pour une confirmation post hoc, plutôt que comme aide au diagnostic immédiat

Autres outils diagnostiques de non reperfusion ?

- Scintigraphie: Mais besoin d'obtenir des images avant la thrombolyse
- Echographie myocardiaque avec contraste pour évaluer la perfusion microvasculaire

Manque de méthodes non invasives fiables pour détecter la reperfusion après traitement thrombolytique

- En Conséquence, une coronarographie en urgence est souvent nécessaire pour déterminer la perméabilité de l'artère coupable, en particulier en cas d'infarctus antérieur ou étendu avec
  - Douleur thoracique persistante
  - Absence de résolution du sus décalage du segment ST
  - Ou atteinte hémodynamique
  - Persistant plus de 90 min après traitement thrombolytique.

Que faire après échec de thrombolyse?

- Angioplastie
  Evidemment ?

Rescue Coronary Angioplasty

Meta-Analysis (small number of pts, non randomized studies)

	Pt (no.)	Success (%)	Reocclusion (%)	Mortality (%)
Topol	86	73	29	10.4
Califf	52	87	5	NR
Belenkie	16	81	NR	6.7
Fung	13	92	16	7.6
Topol	22	86	3	0.0
Grines	12	100	8	NR
Holmes	34	71	NR	11.0
Grines	10	90	12	10.0
O'Connor	90	89	14	17.0
Balm	37	92	26	5.4
Whitlow	44	84	28	NR
Ellis	173	78	20	10.0
Total	560	451/560 (80%)	69/380 (18%)	10.6

Ellis SG et al: JACC 19:681-6, 1992

RESCUE Trial

Anterior MI ≥2 mm ST ↑

↓

IV thrombolytic therapy; Ongoing chest pain

↓

Coronary angiography 90 min – 8 hours from onset

↓

TIMI flow grade 0-1

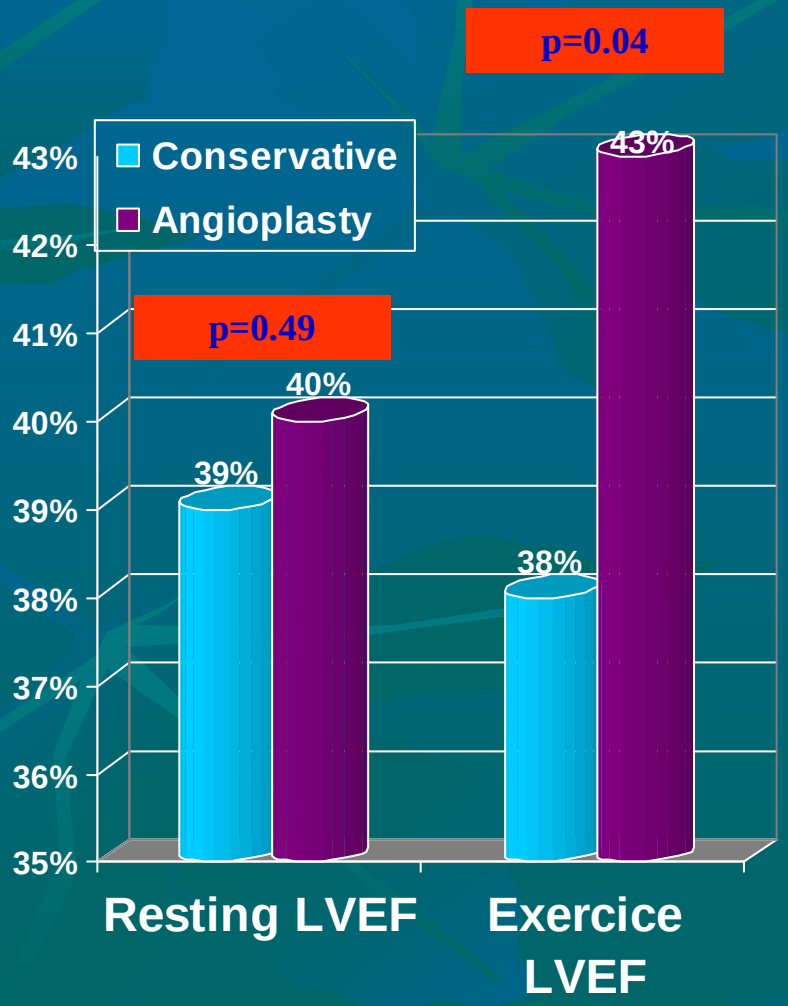
Excluded:
- **Shock**
- **Prior MI**
- **Left main ≥50%**

PTCA n=78	Conservative strategy n=73

Lytics to angiography 4.5±1.9 hr (mean)

Ellis SG et al: Circulation, 1994; 90:2280-84

RESCUE : 30 days Results



Rescue Angioplasty in the setting of failed thrombolysis seems to improve exercise but not rest ejection fraction

Ellis et al, Circulation 1994;90:2280-4

MERLIN Trial

(The Middlesbrough Early Revascularization to Limit Infarction)

ST ↑ MI
Lytic Tx ≤10 hr
n=307

<50% reduction in ST ↑ at 60 min
Or, absence of accelerated idioventricular rythm

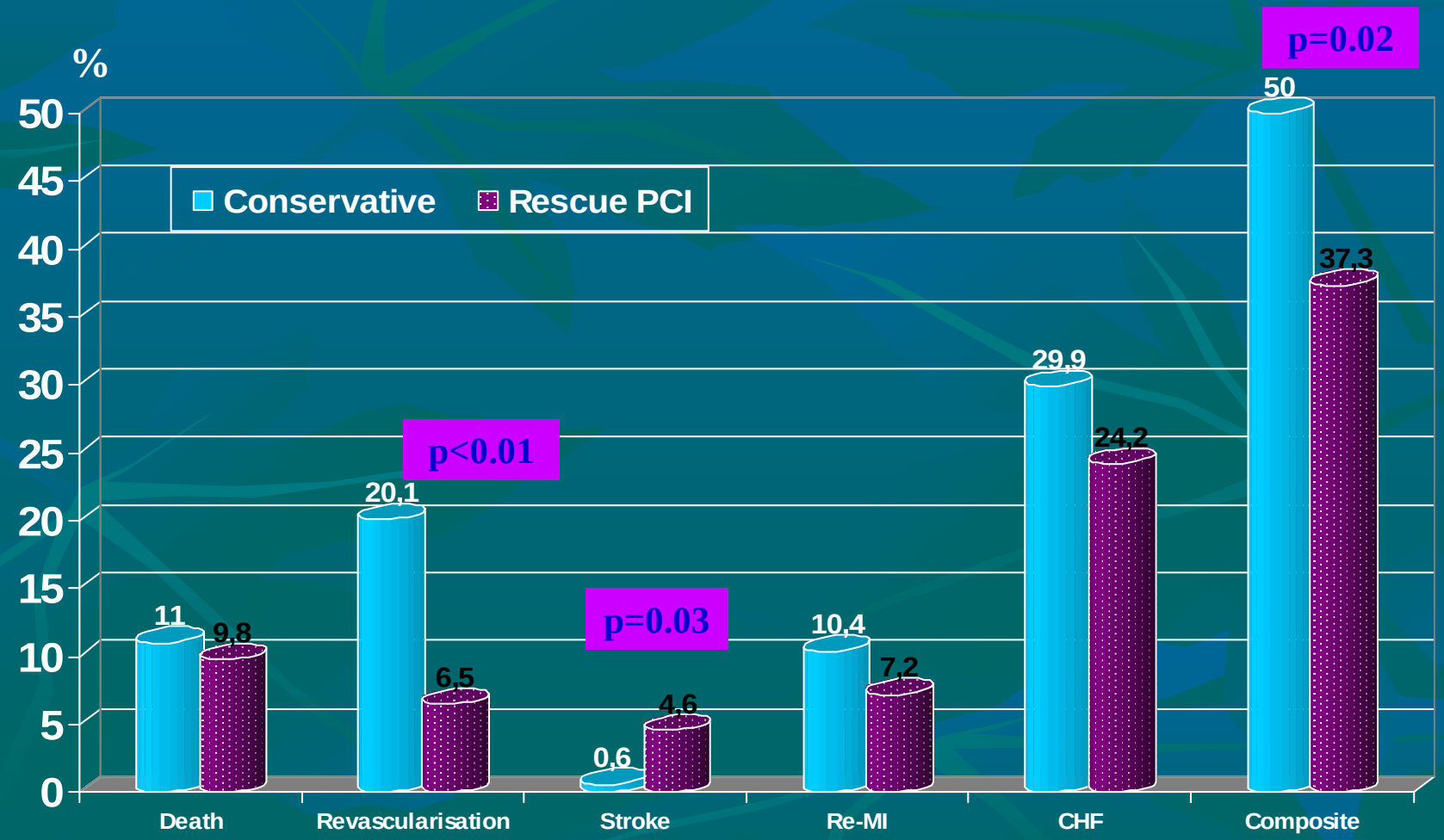
Continued Medical Tx (n=154)

Rescue PCI (n=153)

1° endpoint: Death@30 days

Sutton AG et al, J Am Coll Cardiol 2004 Jul 21;44(2):287-96

MERLIN : 30 Days results

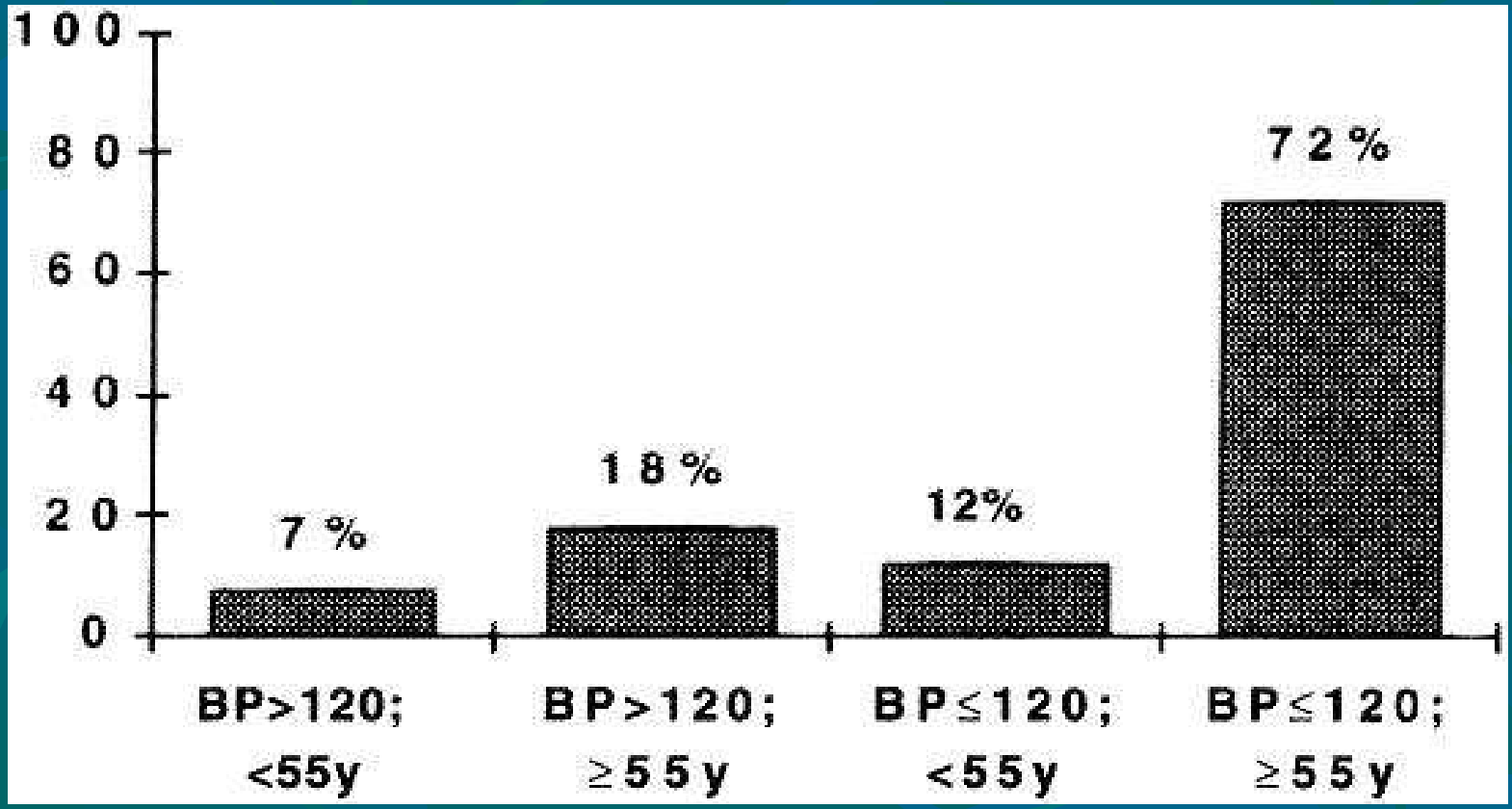


Sutton AG et al, J Am Coll Cardiol 2004 Jul 21;44(2):287-96

Raisons des résultats moins favorables de l'angioplastie après échec de thrombolyse

- Délais de diagnostic et de prise en charge
- La thrombolyse entraîne une activation plaquettaire.
- Les échecs de thrombolyse sont probablement associés à des plaques athéroscléreuses plus complexes.
- Dans un papier de Steffenino (Ital Heart J 2004;5:739-745), seulement 62% des « rescue » avaient un flux final TIMI grade 3.
- Même après reperfusion épicardique réussie (TIMI 3), la perfusion myocardique peut être déficiente (Embolisation distale de microthrombi plaquettaires, vasospasme, inflammation, lésions de reperfusion). Au maximum, No reflow
- En plus, une angioplastie de sauvetage qui échoue comporte une mortalité particulièrement élevée.

Impaired microvascular reperfusion (ST >or=to50%) despite successful mechanical recanalization



- according to age and systolic blood pressure (BP) on admission.

Claeys: Circulation, Volume 1999, 99(15); 1972-1977

Comment améliorer les résultats de l'angioplastie de sauvetage ?

- Inhibiteurs de la Glycoprotéine II B-IIIA
(améliorer la perfusion tissulaire)
- Stenting
(Stabiliser la lumière coronaire)

REACT Trial

Gershlick A et al, AHA 2004

ST ↑ MI
Lytic tx ≤ 6 hr
n=427

>50% ST ↑ on 90-min ECG (w/ or w/o CP)
PCI <12 hrs of sx onset

Continued Medical Tx n=200

Repeat Lytic Tx* n=200

Rescue PCI n=200

1° endpoint: Death, re-MI, CVA, severe CHF, 6, 12 mo

Study terminated due to poor enrollment

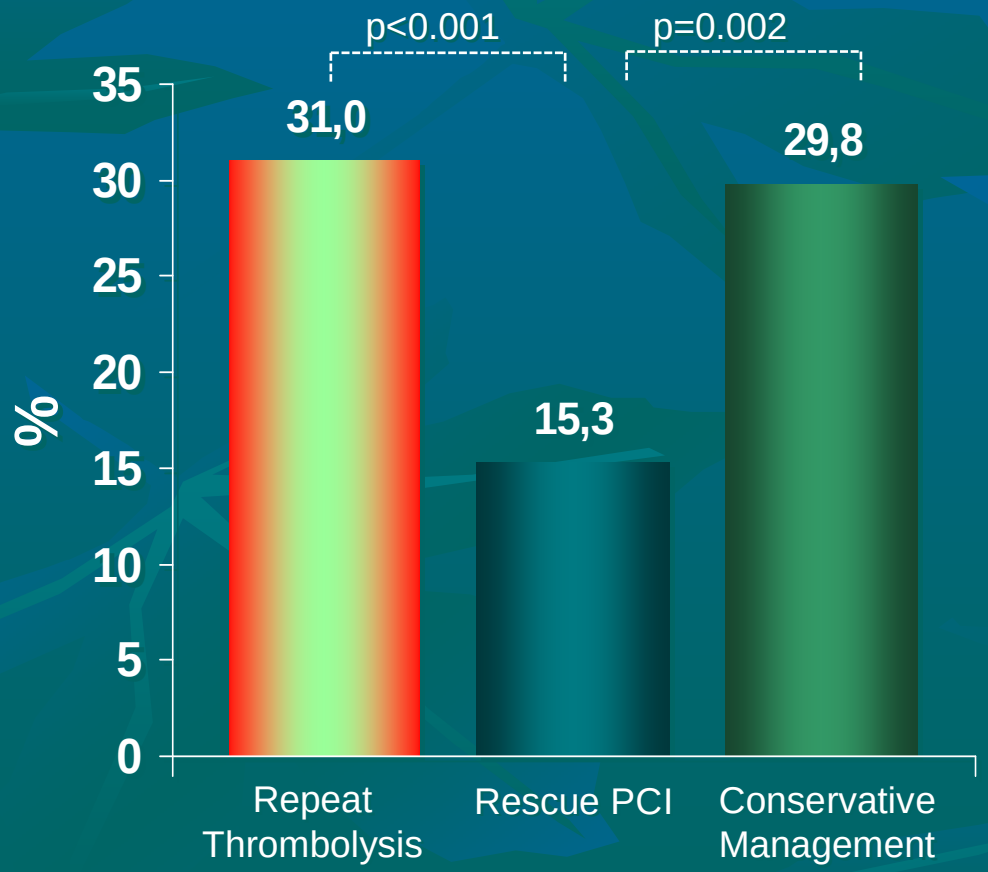
*Fibrin specific;

SK in 60%, RPA 27%, others 12%; Stents 88%, GP IIb/IIIa 55%

REACT: 6 month results

Primary Composite Endpoint at 6 Months

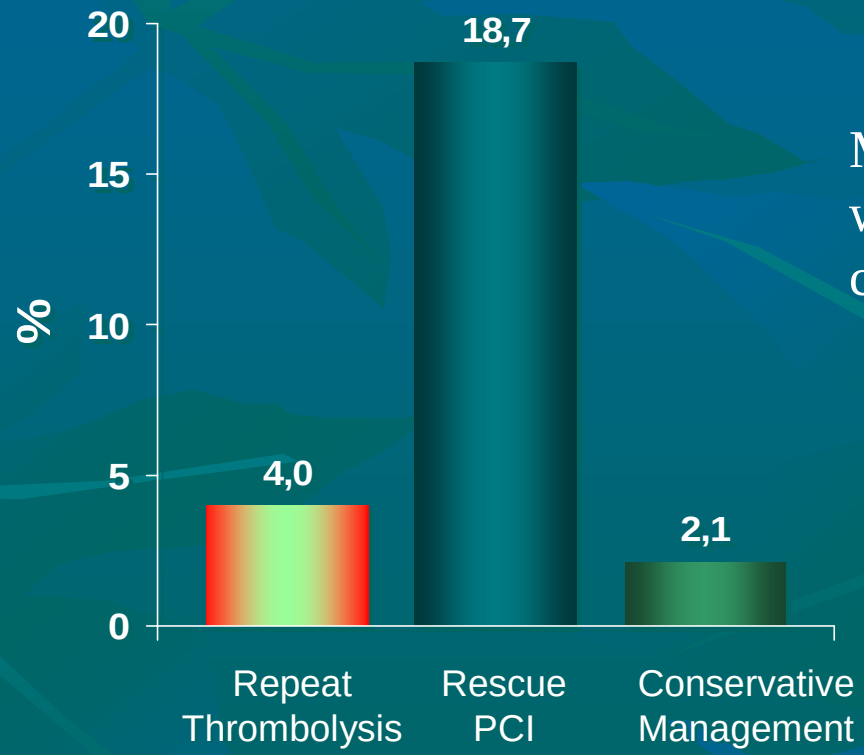
(Death, MI, CVA, or severe heart failure)



- The primary composite endpoint of death, MI, CVA or severe heart failure at 6 months was significantly lower in the rescue PCI group compared with either the repeat thrombolysis group or the conservative management group

Gershlick A et al, AHA 2004

Major Overt Bleeding



Majority of bleeding was sheath complications

Gershlick A et al, AHA 2004

REACT: Summary

- The REACT results disagree with those of MERLIN trial, which showed no difference between rescue angiography and conservative treatment strategies at 30 days.
- Hypotheses offered to explain the opposing outcomes of MERLIN and REACT include :
  - differences in initial thrombolysis (↑ streptokinase in MERLIN),
  - concomitant medications (↑ GP IIb/IIIa inhibitors in REACT),
  - and inclusion criteria (↑ time to rescue PCI in MERLIN)

New technologies and strategies

- Distal protection during PCI
- Mechanical thrombectomy
- Endovascular cooling system
- Inhibition of the complement
- Supersarturated Oxygen (Aqueous Oxygen)

PTCA after Thrombolytic Therapy: Conclusions

- Successfull reperfusion after thrombolytic therapy
  - 50-60%
  - Non-invasive methods to assess reperfusion are lacking
  - Systematic angiography after thrombolytic therapy ?
- If the coronary artery is occluded : RESCUE PTCA is justified
- If the coronary artery is open : Adjunctive or Deferred PTCA?
- The data are in apparent conflict with widespread practice patterns !!