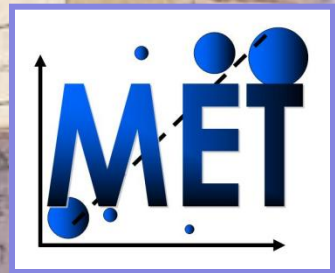


European Society of Cardiology Annual Session 2009

**Management of ST-elevation
myocardial infarction - Update 2009**
Late comers: which options?

Antonio Abbate, MD

Assistant Professor of Medicine
Virginia Commonwealth University
Division of Cardiology
Department of Internal Medicine
Richmond, VA, USA



VCU Pauley Heart Center
Virginia Commonwealth University

Conflict of interests

**NO POTENTIAL CONFLICTS OF
INTERESTS TO BE DISCLOSED**

Definition

"Late comers":

The current reperfusion paradigm in STEMI is that prompt reperfusion should be attempted within 12 hours of symptoms onset* → hence "late comers" are patients presenting >12 hours after symptom onset

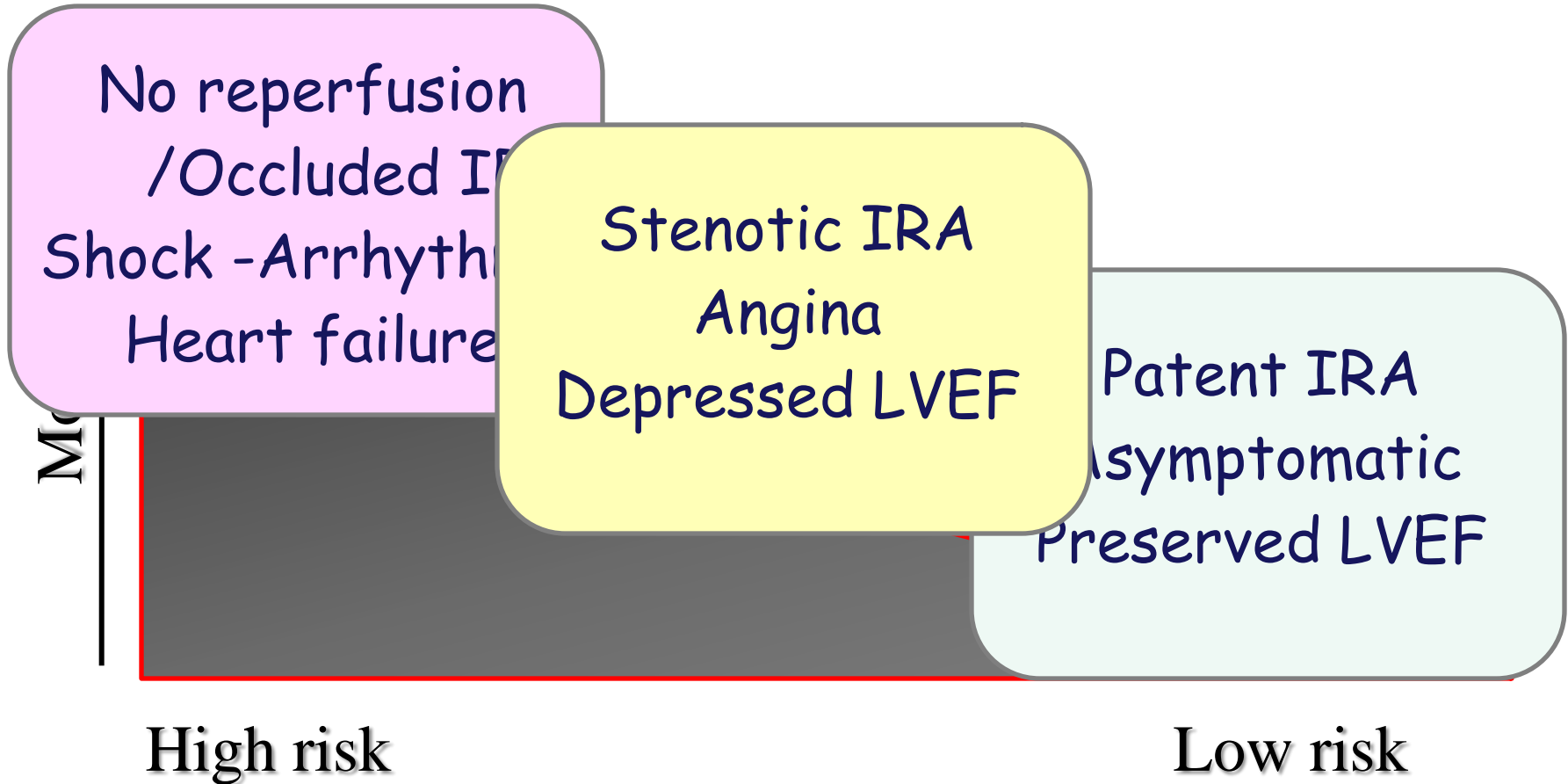
* Exceptions include stuttering chest pain, or shock.

Who are the Late Comers?

- Timing 12-72 h vs >72 h
- Hemodynamics stable vs unstable
- Symptoms angina/heart failure/none
- Reperfusion complete/incomplete/none
- IRA obstruction 100% vs 70-99%

Who are the Late Comers?

A heterogenous group



High risk STEMI Cardiogenic shock

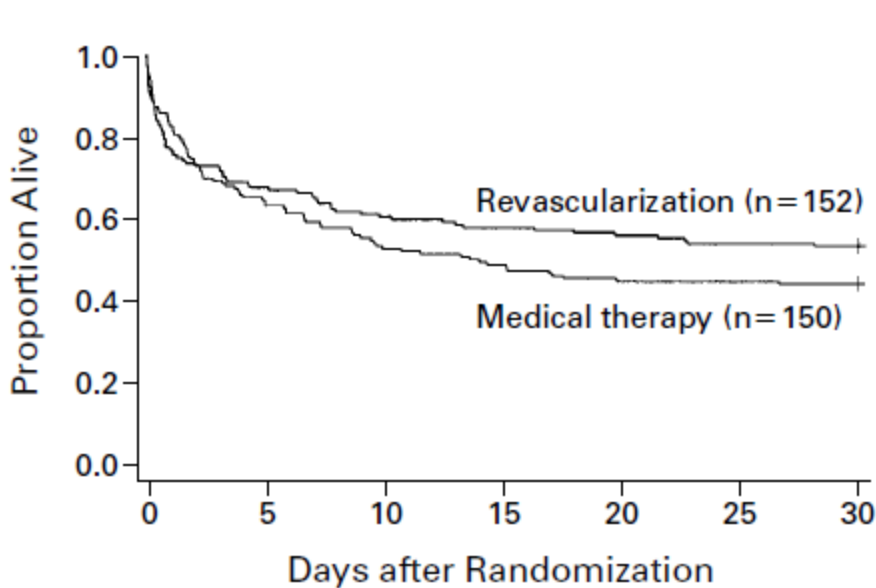
Case #1: 45 yo F presenting with hypotension, requiring vasopressor/inotropes, chest discomfort ongoing for 14-16 hours, ECG shows ST elevation V1-V4

Question:

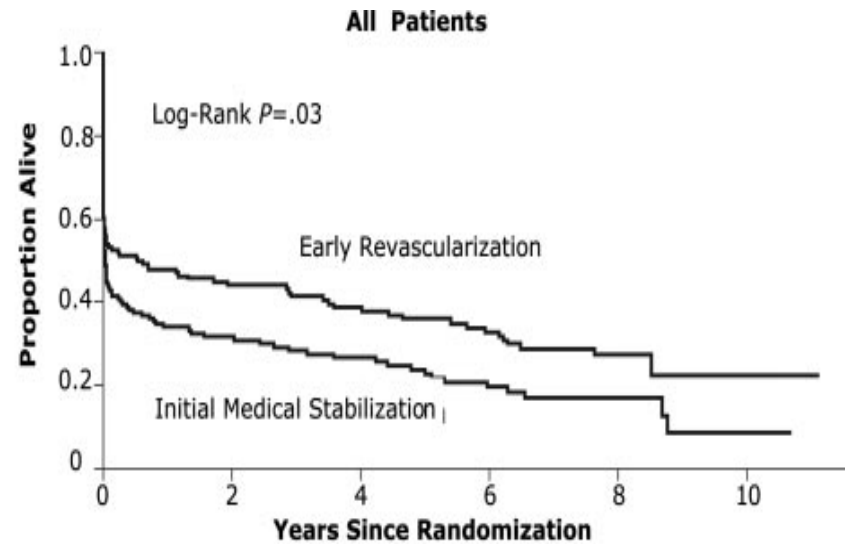
→ Should this patient be offered emergent angiogram and PCI/CABG ?

High risk STEMI Cardiogenic shock

The SHOCK trial (Hochman et al. NEJM 1999) included patients with STEMI and shock within 54 hours of presentation (median 11.5 hours)



Hochman et al. NEJM 1999



Reynold and Hochman. Circulation 2008

High risk STEMI Cardiogenic shock

Case #1: 45 yo F presenting with hypotension, requiring vasopressor/inotropes, chest discomfort ongoing for 14-16 hours, ECG shows ST elevation V1-V4

Question:

→ Should this patient be offered emergent angiogram and PCI/CABG ?

Definitely yes

The "not so late" late-comers

12 to 72 hours

Case #2: 65 yo M presenting with chest pain ongoing for 16 hours, ST elevation V1-V4

Options:

→ Fibrinolysis?

Fibrinolysis 12 to 24 hours

→ Fibrinolysis? → not a viable option

Data from >2 RCT and a meta-analysis (FTT collaborative review - Lancet 1994) suggest that the benefit of fibrinolysis for pts presenting between 12-24 hours is minimal (35-day mortality 10.0% vs 10.5%, p=NS)

The "not so late" late-comers

12 to 72 hours

Case #2: 65 yo M presenting with chest pain ongoing for 16 hours, ST elevation V1-V4

Options:

- Fibrinolysis? NO
- Mechanical reperfusion ?

Mechanical reperfusion

12 to 72 hours

→ PCI ? → conflicting results

The BRAVE-2 study (Schoemig et al. JAMA 2005)

- 365 pts (57% TIMI 0/1 flow, 23% TIMI 2 flow)

- 12-48 h (median 23 hours)

- invasive (PCI 95%) vs conservative strategy

→ 6.8% mean reduction in infarct size

→ 45% RRR for 4-year mortality (11 vs 20%)

(Ndrepepa et al. JAMA 2009)

Mechanical reperfusion

12 to 72 hours

→ PCI ? → conflicting results

A substudy of the OAT study (Menon et al. EHJ 2009)

- 331 pts (approx 15% of all OAT pts)

- 24-72 h (median 66 hours)

- PCI of occluded IRA vs conservative strategy (approx 20% had failed thrombolysis)

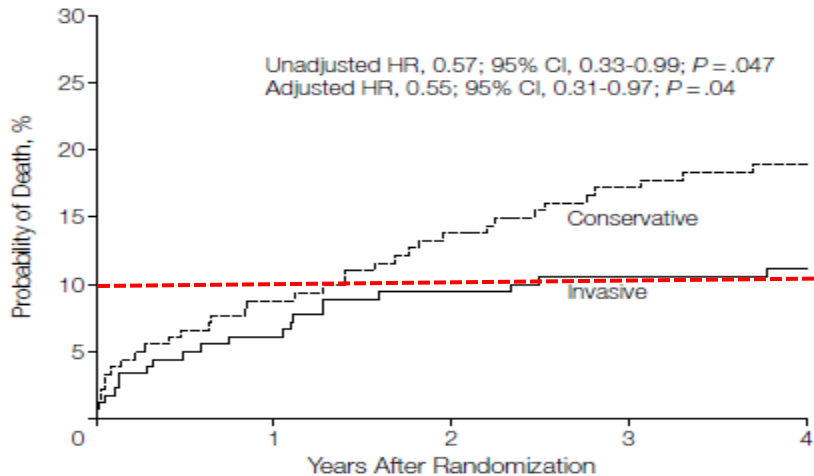
→ No difference in the Kaplan-Meier 4-year mortality (8 vs 8%)

Mechanical reperfusion

12 to 72 hours

BRAVE-2

23 hours (12-48 hours)



	0	1	2	3	4
Conservative	183	166	153	146	125
Invasive	182	170	162	159	142

11% vs 20%, p=0.04

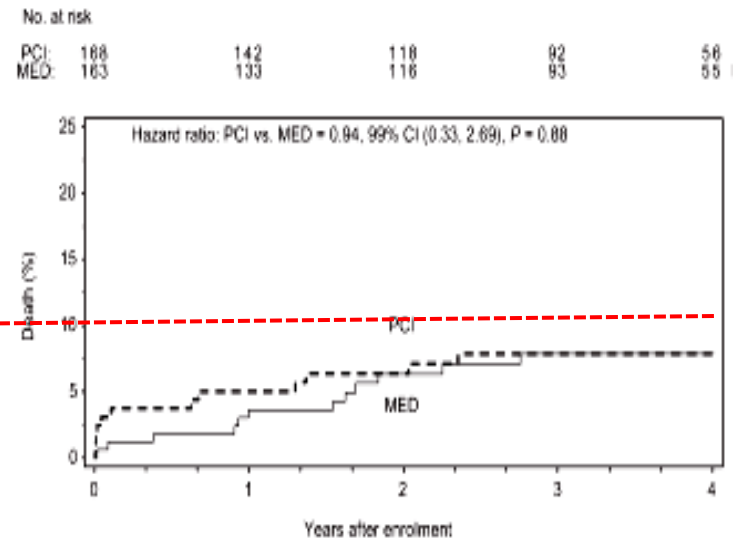
57%

4-year mortality

TIMI 0/1 flow

OAT substudy

66 hours (24-72 hours)



10%

8% vs 8%, p=0.84

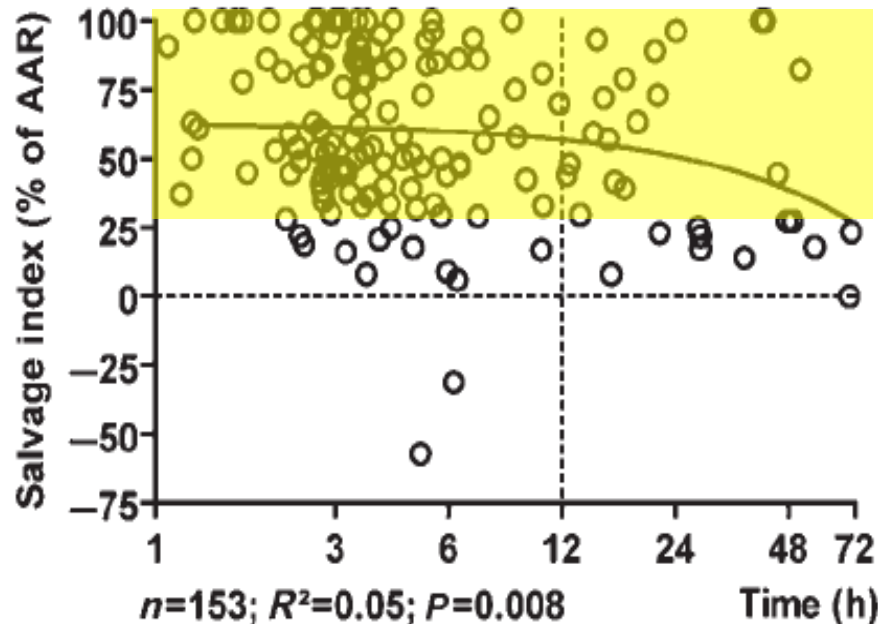
99%

Mechanical reperfusion

12 to 72 hours

→ Which is the time frame for infarct salvage?

Busk et al (Eur Heart J 2009) looked at 247 pts with total occlusion undergoing PCI within 72 hours



The "not so late" late-comers

12 to 72 hours

Case #2: 65 yo M presenting with chest pain ongoing for 16 hours, ST elevation V1-V4

Options:

- | | |
|----------------------------|----------|
| → Fibrinolysis? | NO |
| → Mechanical reperfusion ? | Possibly |
| → Within 24 hours | Yes |
| → 24-72 hours | Yes/No |

The "very late" late-comers

>72 hours

Case #3: 55 yo M on day 7 after non-reperfused anterior STEMI, asymptomatic (at rest)

Question:

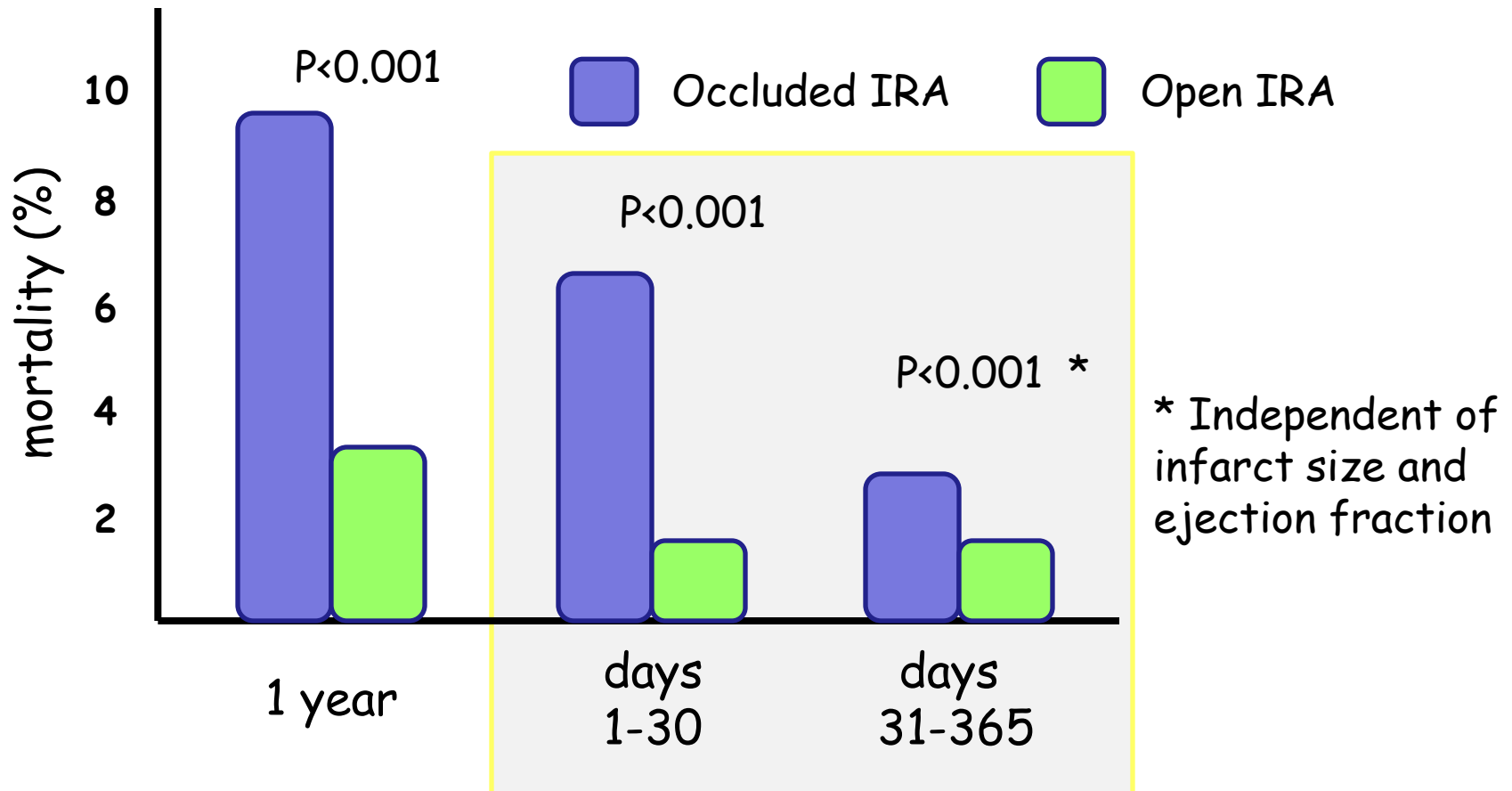
→ Should he be offered a coronary angiogram and late revascularization?

The "very late" late-comers

>72 hours

GUSTO - I angiographic substudy

Modified from Puma et al. Am J Cardiol 1999



The "very late" late-comers

>72 hours

TOSCA-2 trial

- OAT substudy (Dzavik et al. Circulation 2006)
- paired angiograms at baseline and 12 months

→ Irrespective of randomization arm,
-54% had a patent IRA and 46% did not

→ **patients with a patent IRA at follow-up had a greater increase in LVEF than those with an occluded artery (absolute difference of 3.0%; $p=0.003$).** "

supporting *Braunwald's Open Artery Hypothesis*

The "very late" late-comers

>72 hours

ALKK study (Zeymer et al. Circulation 2003)

- 300 patients
 - 8-42 days after STEMI (median 23 days)
 - 1-vessel CAD (30% had total occlusion)
- 34% RRR in the composite endpoint (p=0.020)

SWISSI II study (Erne et al. JAMA 2007)

- 201 patients
 - 3-58 days after STEMI (median 32 days)
 - all with silent ischemia (30% had total occlusion)
- 80% RRR in mortality at 10 years (p<0.001)

The "very late" late-comers

>72 hours

DECOPI study (Steg et al. Eur Heart J 2004)

- 212 patients
 - >48 hours after STEMI (median 5 days)
 - all with total (100%) IRA occlusion
- No differences in outcome (but > LVEF increase with PCI)

OAT study (Hochman et al. N Engl J Med 2006)

- 2,166 patients
 - 3-28 days after STEMI (median 8 days)
 - all with total (100%) IRA occlusion (88% collaterals)
- No differences in outcome (but ↓ angina with PCI and a trend in more favorable remodeling [TOSCA-2 substudy])

The "very late" late-comers

>72 hours

Case #3: 55 yo M on day 7 after non-reperfused anterior STEMI, asymptomatic (at rest).

Question:

→ Should he be offered a coronary angiogram and late revascularization?

CONFLICTING DATA FROM RCT

The "very late" late-comers

>72 hours

Better late than never ?

Modified from Abbate et al. J Am Coll Cardiol 2008

- A meta-analysis of 10 studies → 3,560 patients
- late PCI of the infarct-related artery >12h of AMI
- median 12 days (range 1-26 days) after AMI
- 10 studies → over more than 15 years
- variable inclusion and exclusion criteria
- variable interventional and non-interventional tx

The "very late" late-comers

>72 hours

Better late than never ?

Modified from Abbate et al. J Am Coll Cardiol 2008

Death

Study

OR (random)
95% CI

ALKK
BRAVE-2
DECOPI
Horie et al
OAT
Silva et al
SWISSI II
TOAT
TOMIIS
TOPS

3 studies showed a mortality benefit

Median F/U
2.8 years

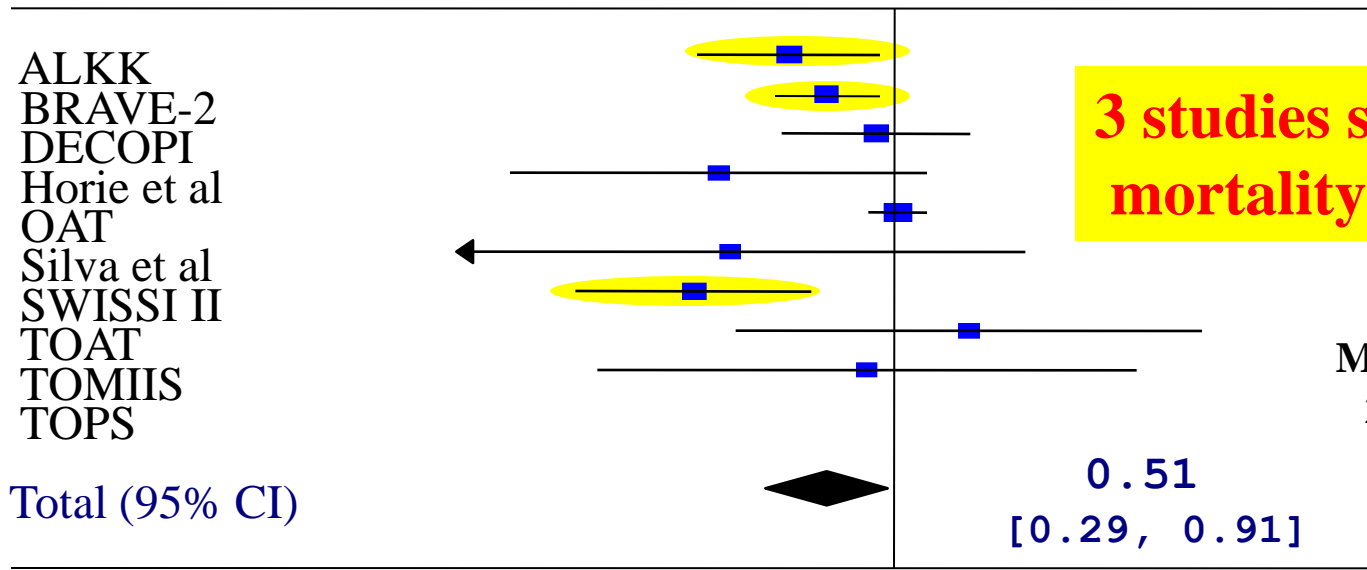
Total (95% CI)

0.51
[0.29, 0.91]

P=0.03
6.3% vs 8.4%

0.01 0.1 1 10 100
Favours PCI

Favours medical Rx



The "very late" late-comers

>72 hours

Better late than never ?

Modified from Abbate et al. J Am Coll Cardiol 2008

Late PCI lead also to:

- A greater increase in LVEF (+4.4%, p=0.009)
- A smaller increase in EDVi (-7.0 ml/m², p=0.008)
- A smaller increase in ESVi (-7.5 ml/m² , p=0.004)

Even if analyzing the study with 100% IRA occlusion alone (Appleton et al. Cath Cardiovasc Int 2008):
LVEF (+3.0%, p<0.001), EDVi (-5.1 ml/m², p=0.02),
ESVi (-5.2 ml/m², p<0.001)

The "very late" late-comers

>72 hours

Better late than never ?

Modified from Abbate et al. J Am Coll Cardiol 2008

A meta-regression analysis showed:

- Greater length of follow up predicted survival benefit and change in LVEF with PCI
- Studies enrolling also IRA 70-99% obstruction (representing 4 of the 10 studies, 16% of patients) more likely to be positive
- Studies that did not exclude patient with > moderate ischemia were also more likely to be positive

The "very late" late-comers

>72 hours

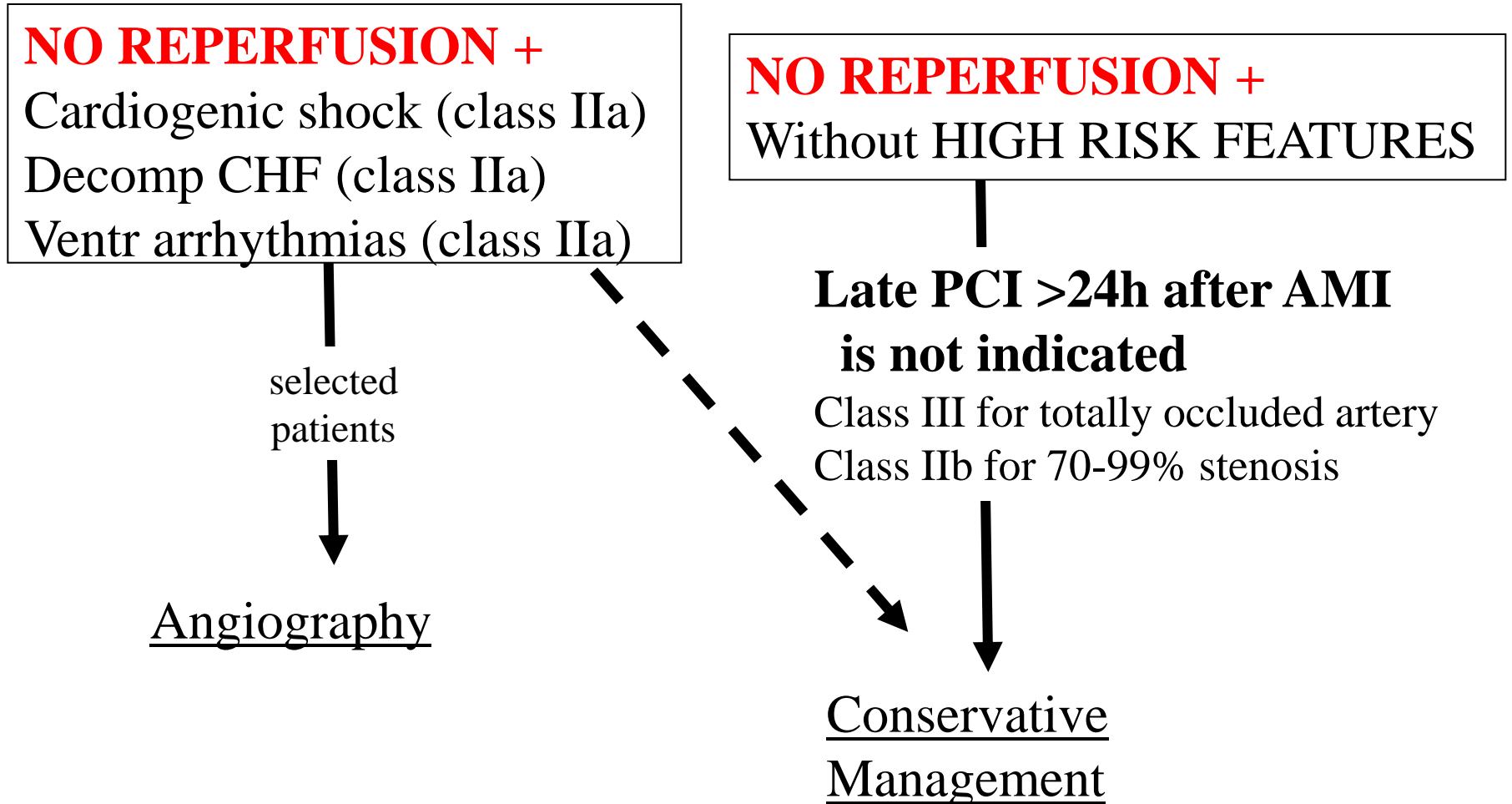
Case #3: 55 yo M on day 7 after non-reperfused anterior STEMI, asymptomatic (at rest).

Question:

- Should he be offered a coronary angiogram and late revascularization?
 - If the IRA 70-99% stenosed → Yes
 - If angina/ischemia present → Yes
 - If no angina/IRA 100% → Yes/No

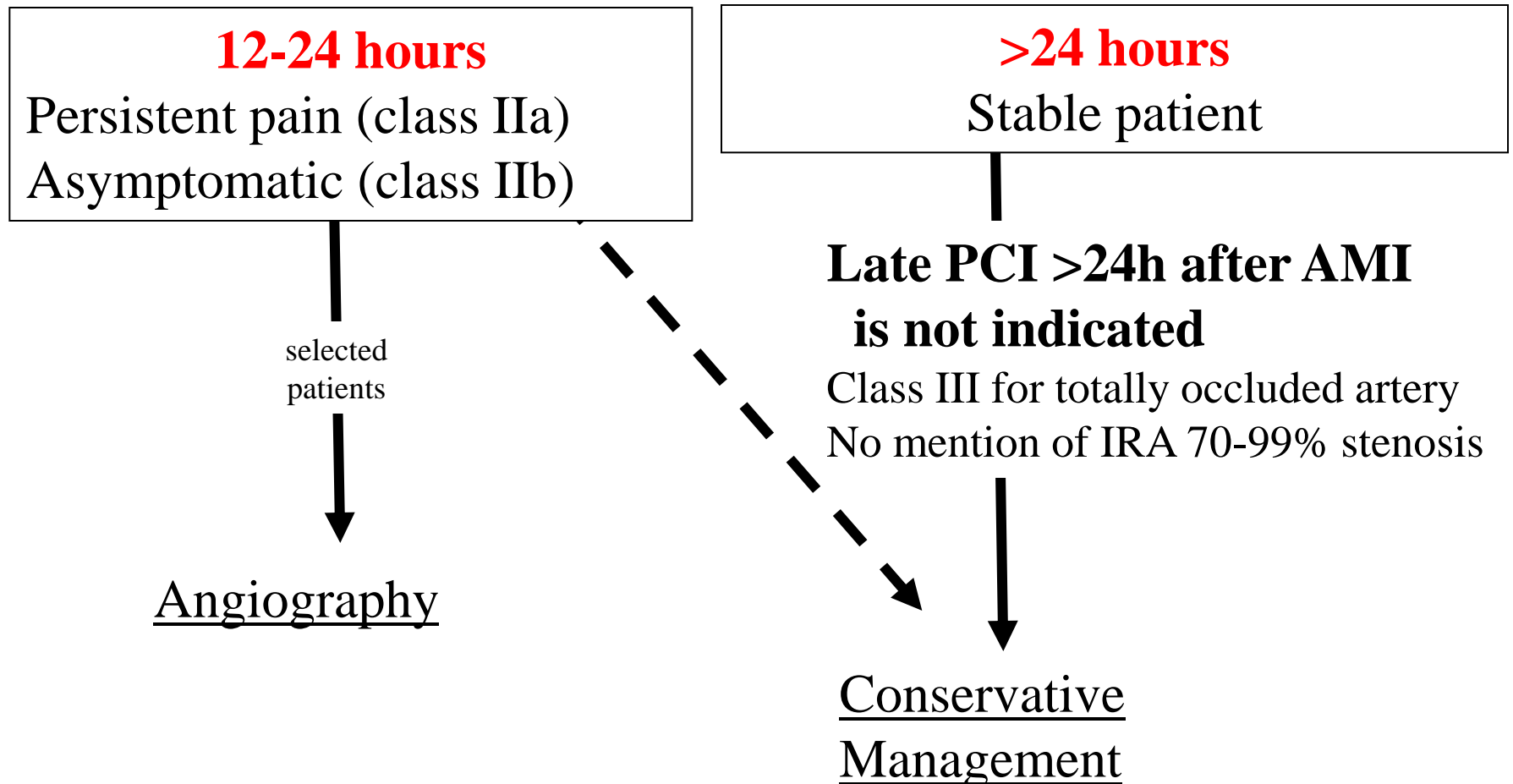
What do the ACC/AHA guidelines recommend?

Beyond 24 hours



What do the ESC guidelines recommend?

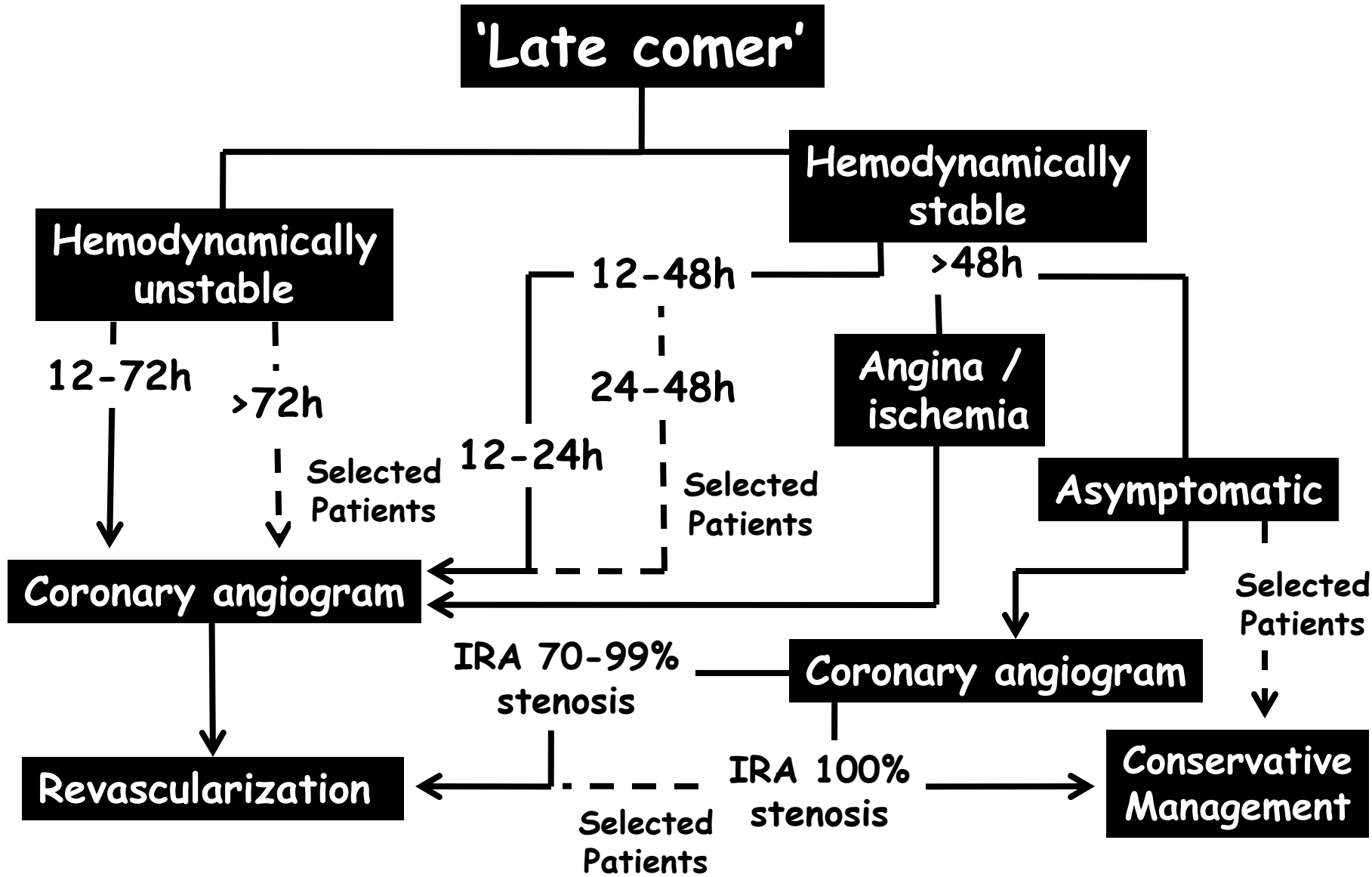
Beyond 12 hours



Conclusions

- 1) STEMI 'late comers' represents a heterogeneous group of patients
- 2) The benefits of late reperfusion are largely variable
- 3) A patient-tailored approach is preferable weighing risk/benefits, patients' preference, and physician judgment
- 4) To date <4,000 pts have been studied → calling for more RCT to address these questions

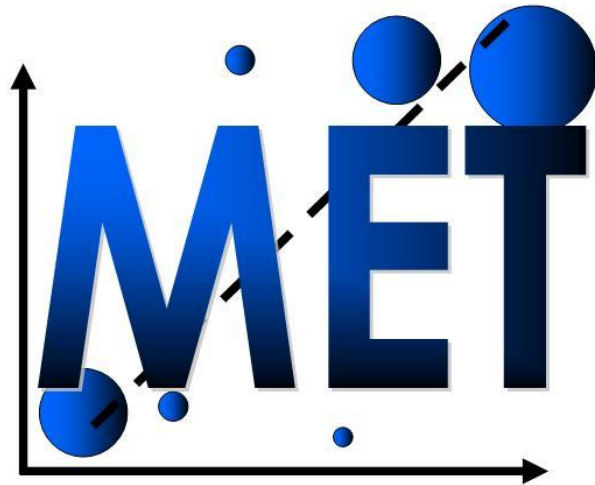
My approach *



* This proposed approach may be in disagreement with current AHA/ACC or ESC guidelines

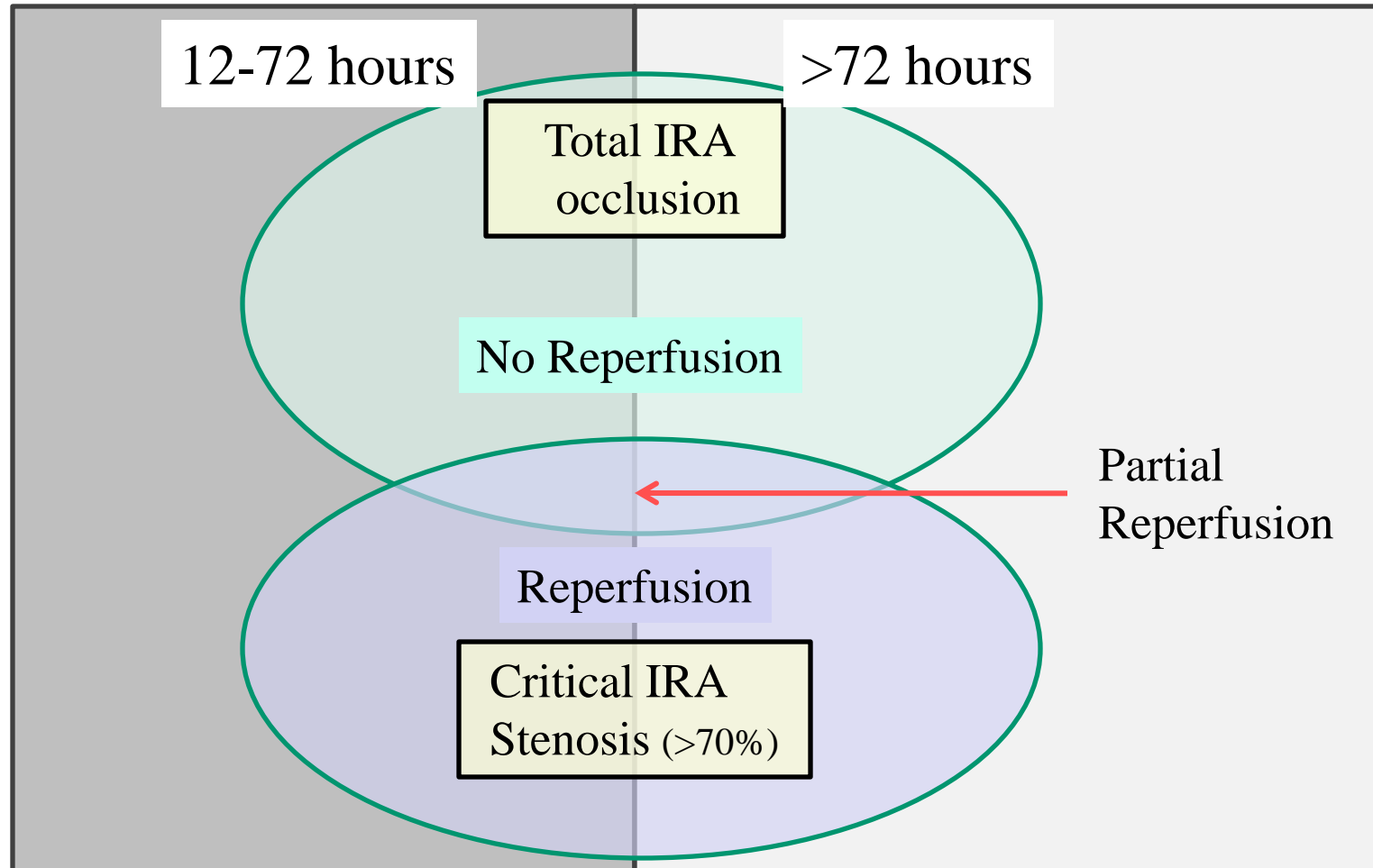
**For further slides on these topics
please feel free to visit the
metcardio.org website:**

<http://www.metcardio.org/slides.html>



THE END

Who are the Late Comers?



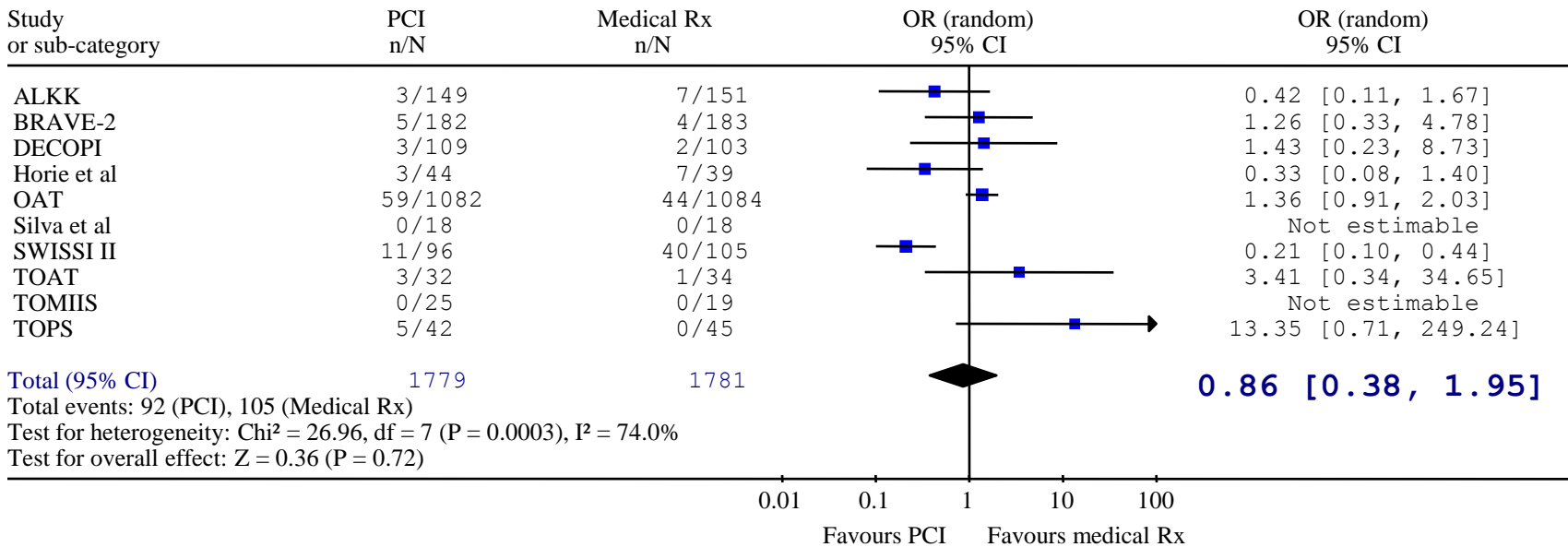
The "very late" late-comers

>72 hours

What about the risk of recurrent AMI

Modified from Abbate et al. J Am Coll Cardiol 2008

Review: Late percutaneous coronary intervention for infarct-related artery occlusion
Comparison: Late percutaneous coronary intervention vs best medical therapy for infarct-related artery occlusion
Outcome: Non-fatal Myocardial infarction



The OAT in perspective

***“We opened those patients
that we thought should be
opened and any patient left
went to OAT”***

Anonymous Investigator Quote

OAT: Who Were They?

Age	58
Class I	83%
Throm. Therapy	20%
Time from MI to Randomization	8 days
Stress test	27%
Ischemia mild/none	90%
SVD	82% (50% RCA)

Stable, untreated, non-ischemic, young,
single vessel, 1 week out.....
Who sees these???????

Coronary Intervention for Persistent Occlusion After Myocardial Infarction (OAT Trial)

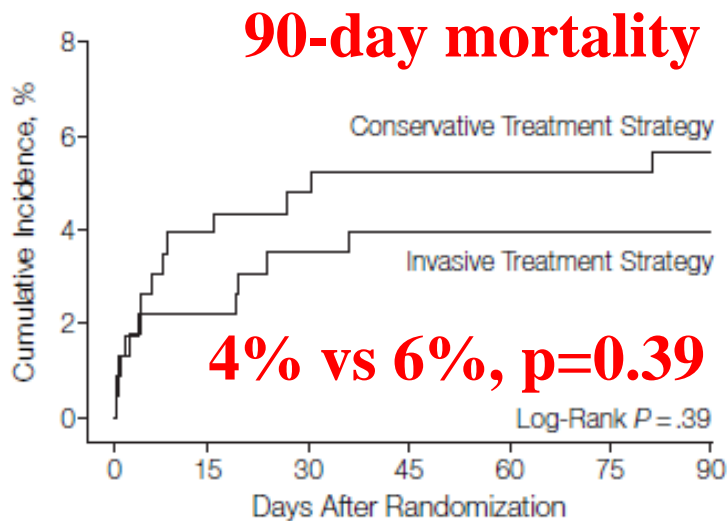
Critical Review

- ② **Extraordinary amount of time to recruit**
- ② **Study underpowered for endpoints**
- ② **Represents a very small % of post-MI pts**
- ② **Most had no viability in distribution of IRA**
- ② **Only 8% had DES**
- ② **No statistically significant difference in primary or secondary endpoints**
- ② **89% of stented pts had patent artery at 1 year**
- ② **Long term F/U incomplete – only 44% to 3 years**
- ② **Data meaningless in treating most post-MI pts**

Mechanical reperfusion

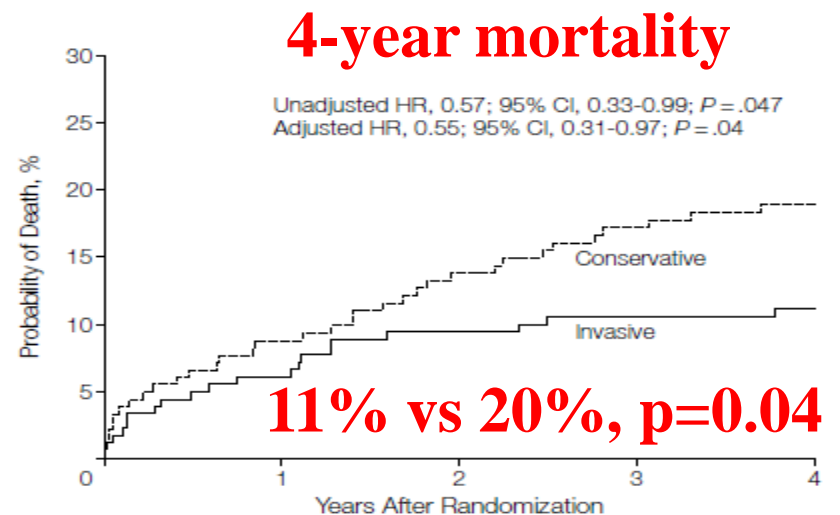
12 to 72 hours

→ PCI ? → clinical benefit? → BRAVE-2 study



Treatment Strategy	0	15	30	45	60	75	90
Conservative	183	173	171	171	170	167	166
Invasive	182	177	174	170	166	162	162

Schoemig et al. JAMA 2005



No. at risk	0	1	2	3	4
Conservative	183	166	153	146	125
Invasive	182	170	162	159	142

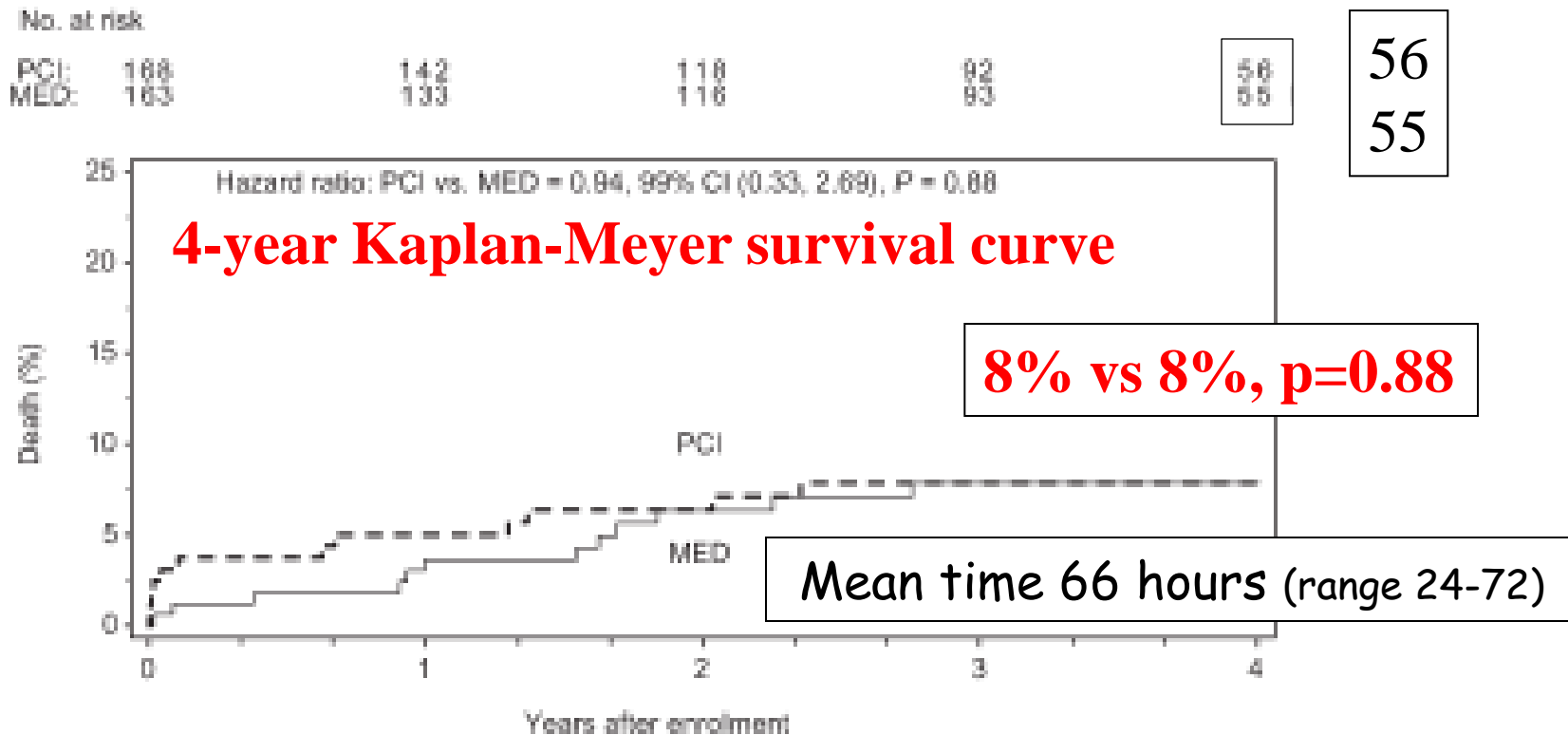
Ndrepepa et al. JAMA 2009

Median time to randomization 23 hours (absolute range 12-48 hours)

Mechanical reperfusion

12 to 72 hours

→ PCI ? → clinical benefit? → OAT substudy



Menon et al. Eur Heart J 2009

Mechanical reperfusion

12 to 72 hours

→ Is there a Role for an Early Viability Study ?

The VIAMI study (abstract presentation- Gruberg - 2006)

- 291 pts (approx 50% post-lytics)

- Low-dose dobutamine 48-72 h after MI

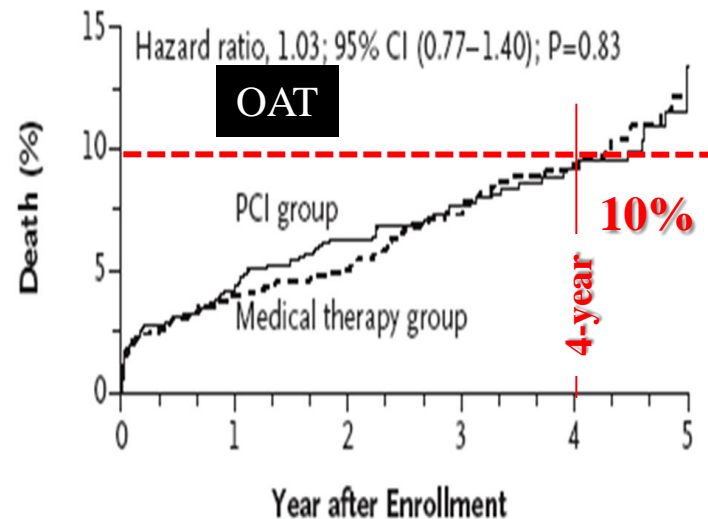
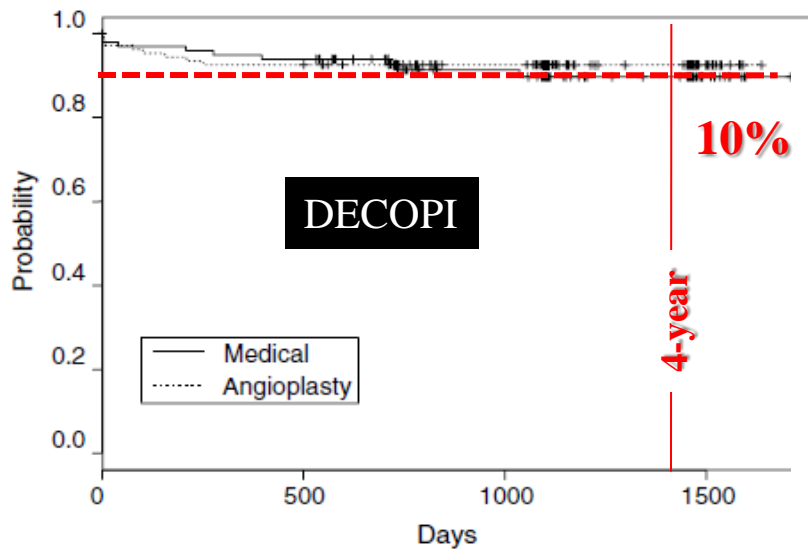
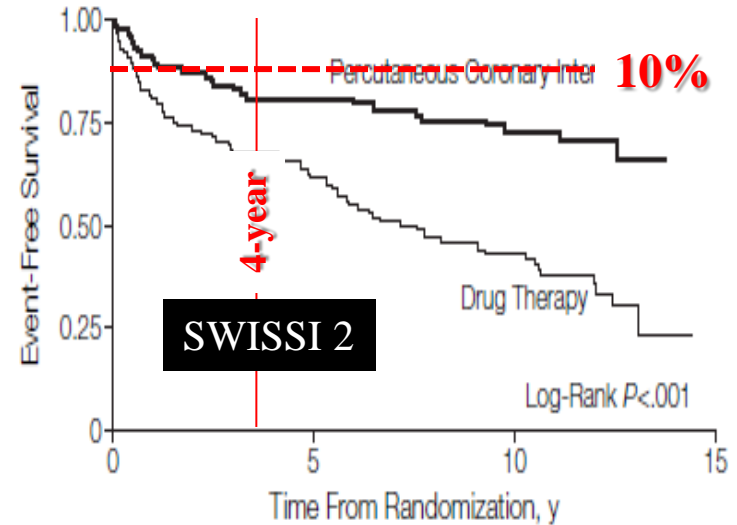
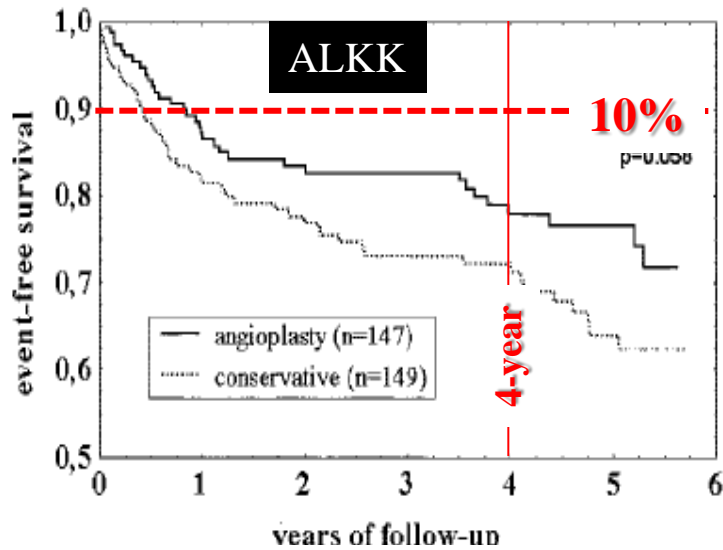
→ viability → randomized to PCI or cons tx

→ no viability → registry

→ In 'viable' pts, PCI lead to a reduction in events (D/MI/UA) (16% vs 7%, p=0.04)

→ The 'non-viable' pts had lowest rate (5%)

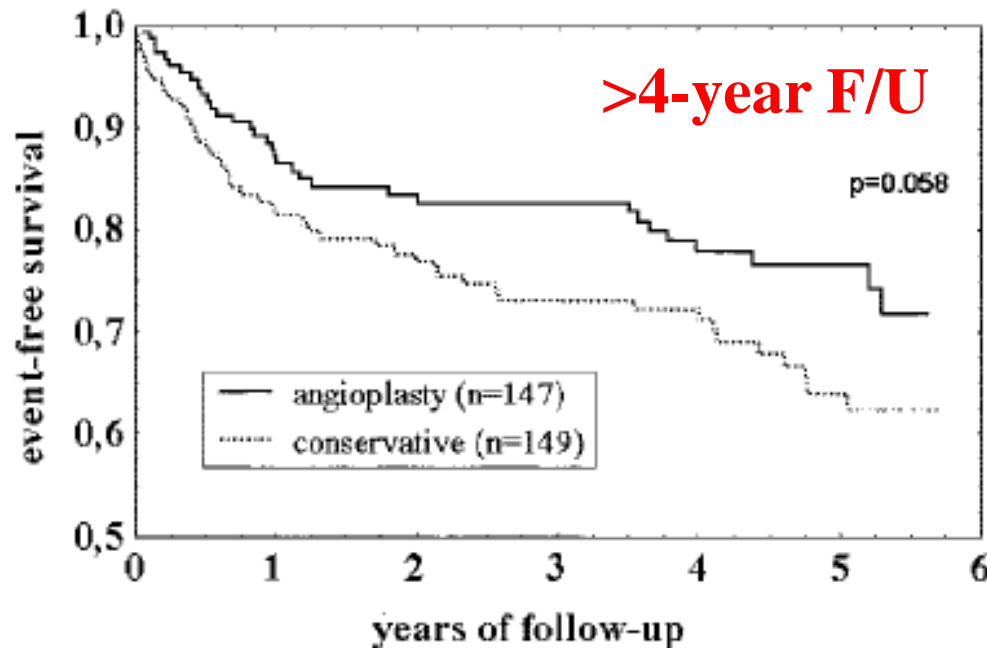
Variable risk / variable benefit



The "very late" late-comers

>72 hours

The ALKK study (Zeymer et al. Circulation 2003) randomized patients with 1-vessel CAD, 8-42 days after STEMI, to PCI vs conservative



**Event rates 38% vs 25%,
p=0.02 favoring PCI**

Of note:

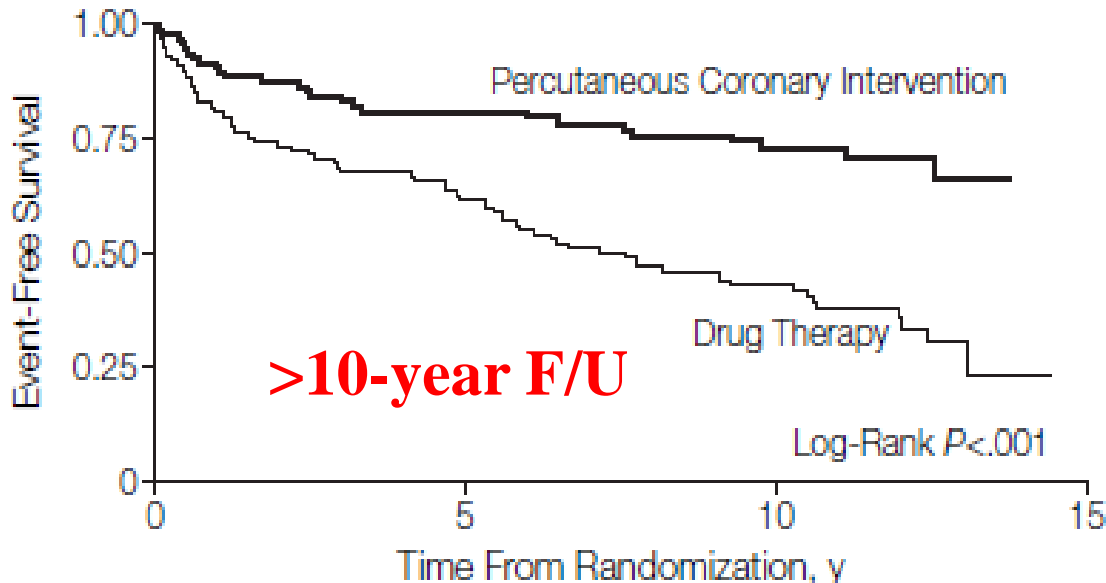
>70% pts had IRA stenosis
<100%,

Pts with 100% IRA
occlusion had less
benefit

The "very late" late-comers

>72 hours

The SWISSI-2 study (Erne et al. JAMA 2007) randomized patients with 3-58 days after STEMI to PCI vs conservative therapy



**Death rate 3% vs 21%,
p=0.01 favoring PCI**

Of note:

**>70% pts had IRA stenosis
<100%,**

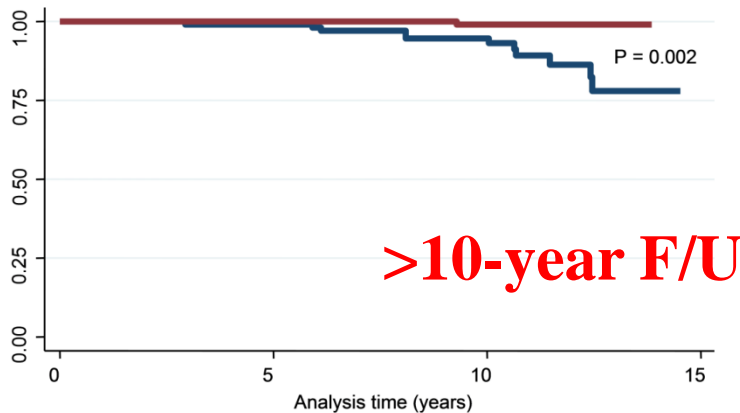
**All pts had inducible
silent ischemia**

The "very late" late-comers

>72 hours

A substudy of the SWISSI-2 study (Schoenenberger et al. Am J Cardiol 2009) looked at sudden death in PCI vs conservative therapy

Survival free of sudden cardiac death
By treatment group



Number at risk		0	5	10	15
MED group	105	97	59	0	
PCI group	96	93	70	0	

— MED group — PCI group

**Sudden Death 1% vs 11%,
p=0.002 favoring PCI**

Of note:

**>70% pts had IRA stenosis
<100%,**

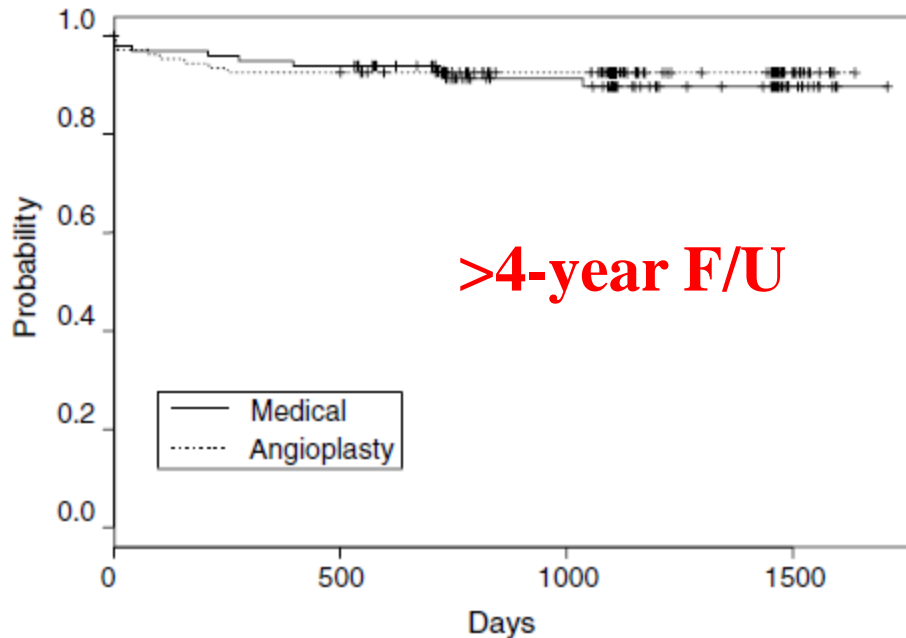
All pts had silent ischemia

**The risk of sudden death was
related to LVEF decline**

The "very late" late-comers

>72 hours

The DECOPI study (Steg et al. Eur Heart J 2004) randomized patients with >48 hours after STEMI to PCI vs conservative therapy



No differences in outcome

Of note:

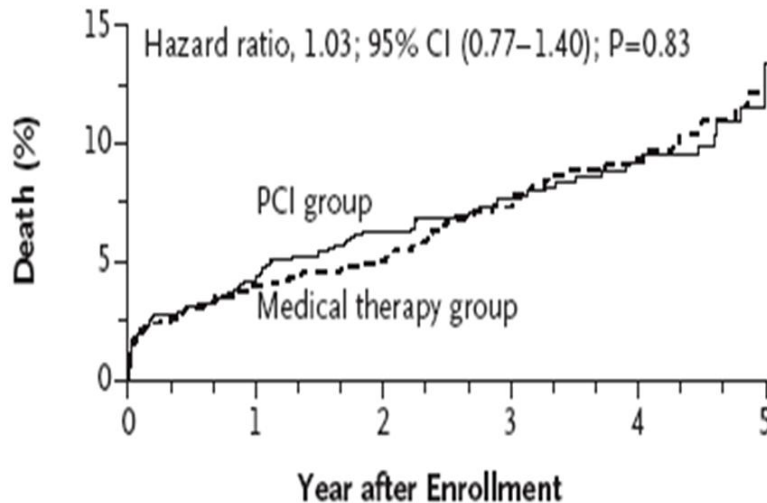
All pts had 100% IRA stenosis

**PCI was associated with
greater LVEF increase**

The "very late" late-comers

>72 hours

The OAT study (Hochman et al. N Engl J Med 2006) is the largest (>2,000 pts) randomized trial of late PCI vs conservative therapy



No differences in outcome

Of note:

All pts had 100% IRA stenosis

Median follow up <3 yrs

No. at Risk	0	1	2	3	4	5
PCI group	1082	959	777	528	296	95
Medical therapy	1084	965	770	517	298	84

The "very late" late-comers

>72 hours

The OAT study (Hochman et al. N Engl J Med 2006) is the largest (>2,000 pts) randomized trial of late PCI vs conservative therapy

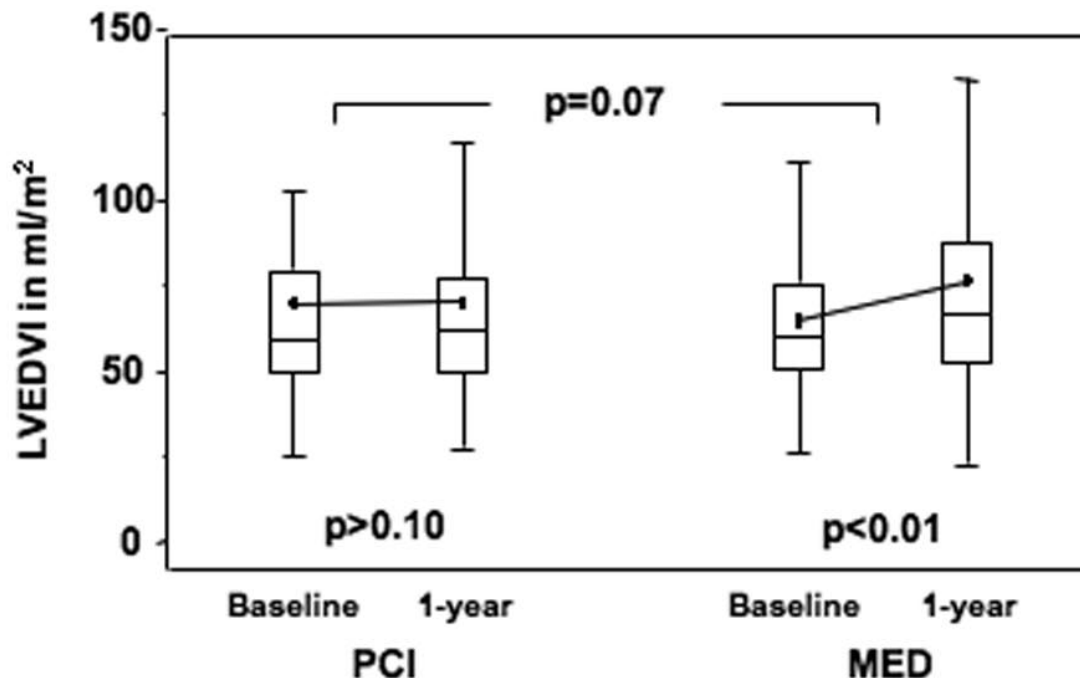
Fewer patients had angina w/ PCI up to 24 months

	PCI <i>Num (%)</i>	MED <i>Num (%)</i>	P-value
Angina Pectoris			
4-Month	190/1015 (18.7)	256/1026 (25.0)	<0.001
12-Month	158/964 (16.4)	211/958 (22.0)	0.002
24-Month	101/735 (13.7)	128/728 (17.6)	0.04

The "very late" late-comers

>72 hours

The TOSCA-2 trial is a substudy of the OAT (Dzavik et al. Circulation 2006) in which patients had paired angiograms at baseline and 12 months.



Patients in the PCI group tended to have a more favorable remodeling

17% of PCI group had late IRA occlusion

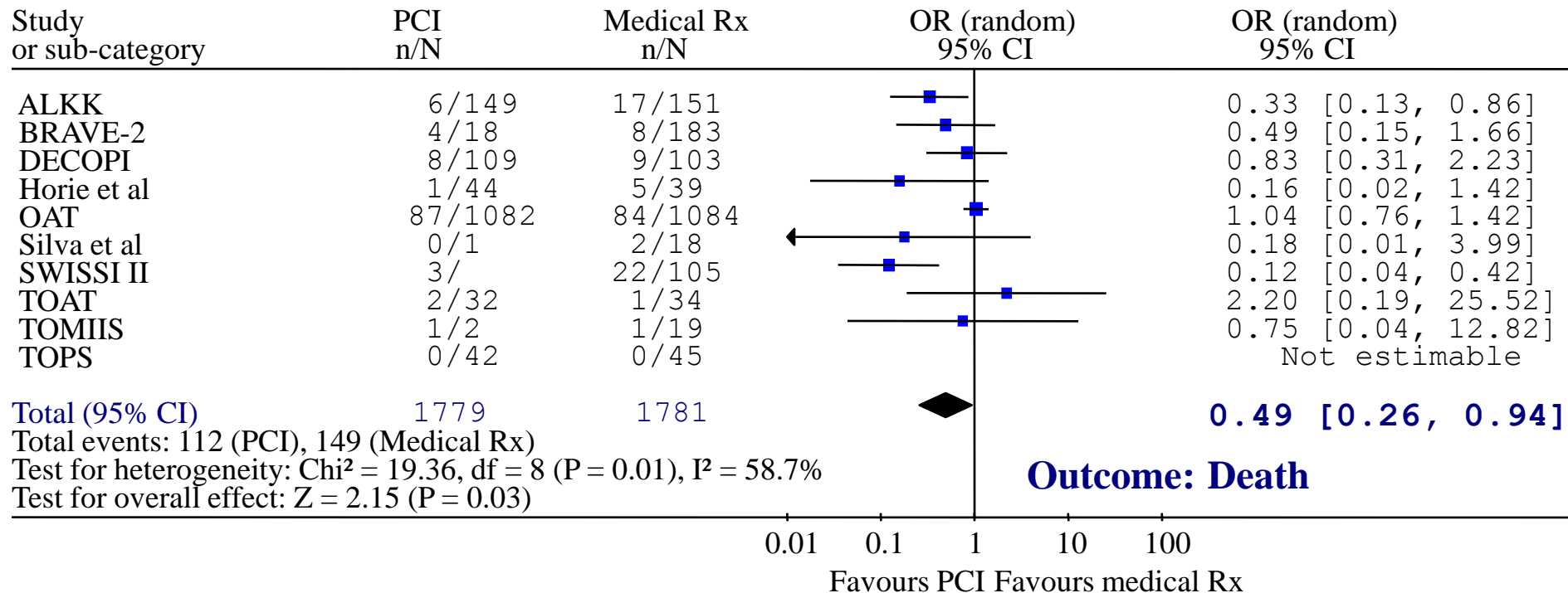
25% of MED had late IRA patency

The "very late" late-comers

>72 hours

Better late than never ?

Modified from Abbate et al. J Am Coll Cardiol 2008

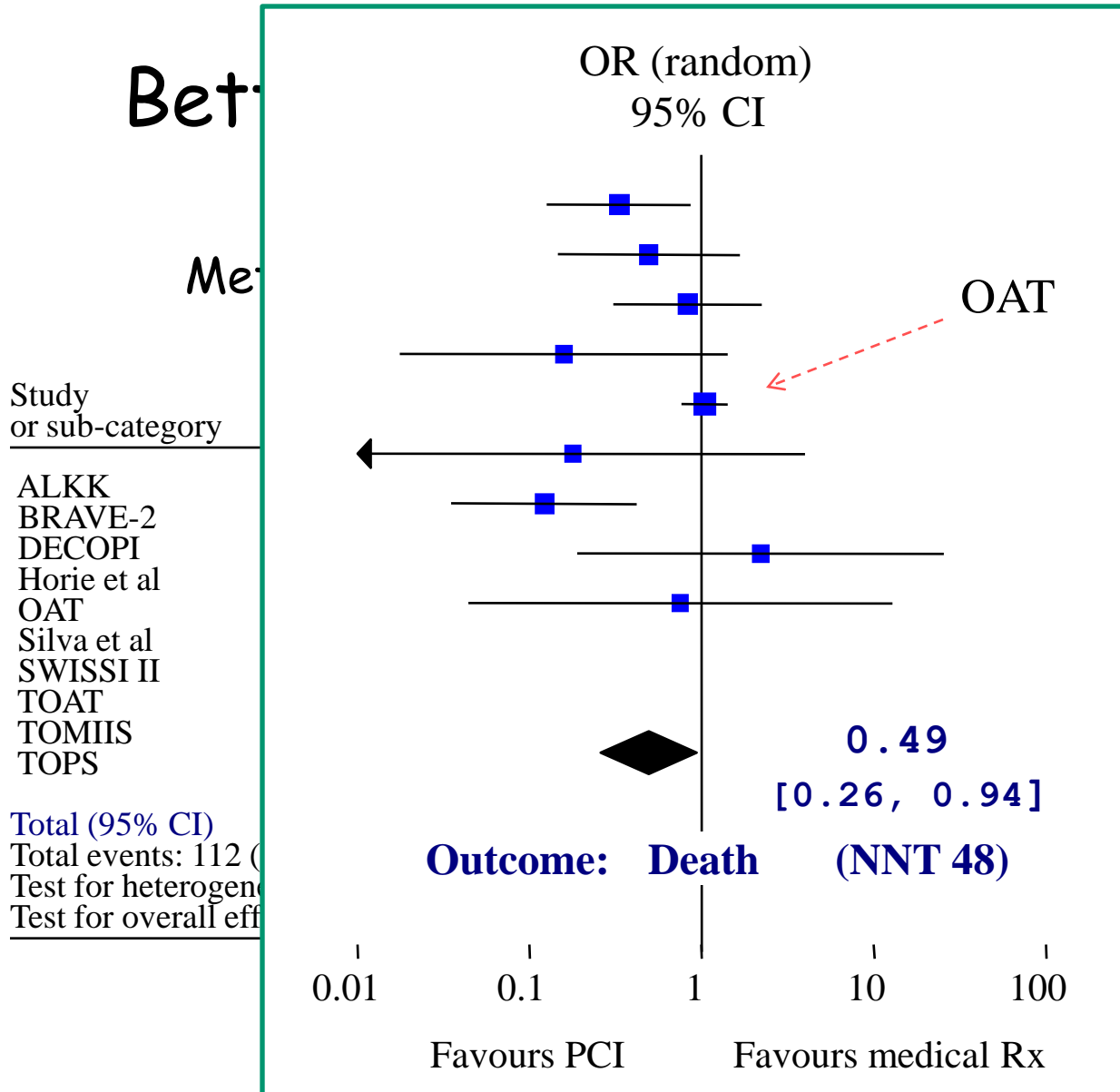


Late presentation / No reperfusion

is it better?

Cardiol 2008

different RCTs



OAT

m)

OR (random)
95% CI

0.33	[0.13, 0.86]
0.49	[0.15, 1.66]
0.83	[0.31, 2.23]
0.16	[0.02, 1.42]
1.04	[0.76, 1.42]
0.18	[0.01, 3.99]
0.12	[0.04, 0.42]
2.20	[0.19, 25.52]
0.75	[0.04, 12.82]
Not estimable	

0.49 [0.26, 0.94]

Outcome: Death

10 100
hours medical Rx

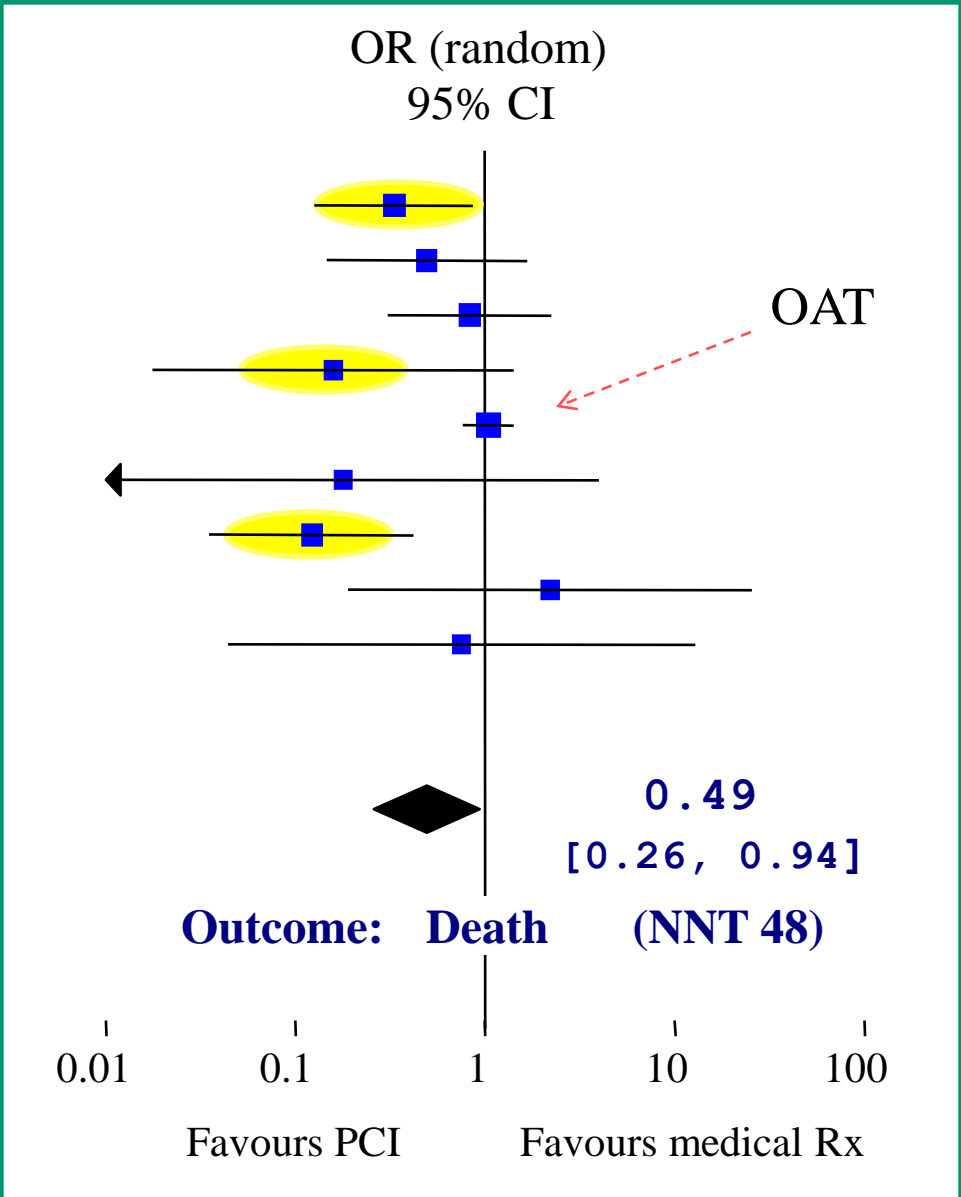
Why such a difference in outcome?

Longer follow-up

Review: Late percutaneous coronary intervention
 Comparison: Late percutaneous coronary intervention vs medical treatment
 Outcome: Death

Study or sub-category	PCI n/N
<u>ALKK</u>	6/149
BRAVE-2	4/18
DECOPI	8/109
<u>Horie et al</u>	1/44
OAT	87/1
Silva et al	0/1
<u>SWISSI II</u>	3/
TOAT	2/32
TOMIIS	1/2
TOPS	0/42

Total (95% CI) 1779
 Total events: 112 (PCI), 149 (Medical Rx)
 Test for heterogeneity: $\text{Chi}^2 = 19.36$, $\text{df} = 8$
 Test for overall effect: $Z = 2.15$ ($P = 0.03$)



ery occlusion
 om)
 3, 0.86]
 5, 1.66]
 81, 2.23]
 02, 1.42]
 76, 1.42]
 01, 3.99]
 04, 0.42]
 19, 25.52]
 04, 12.82]
 stimable
 26, 0.94]

Data from the recent BRAVE-

Why such a difference in outcome?

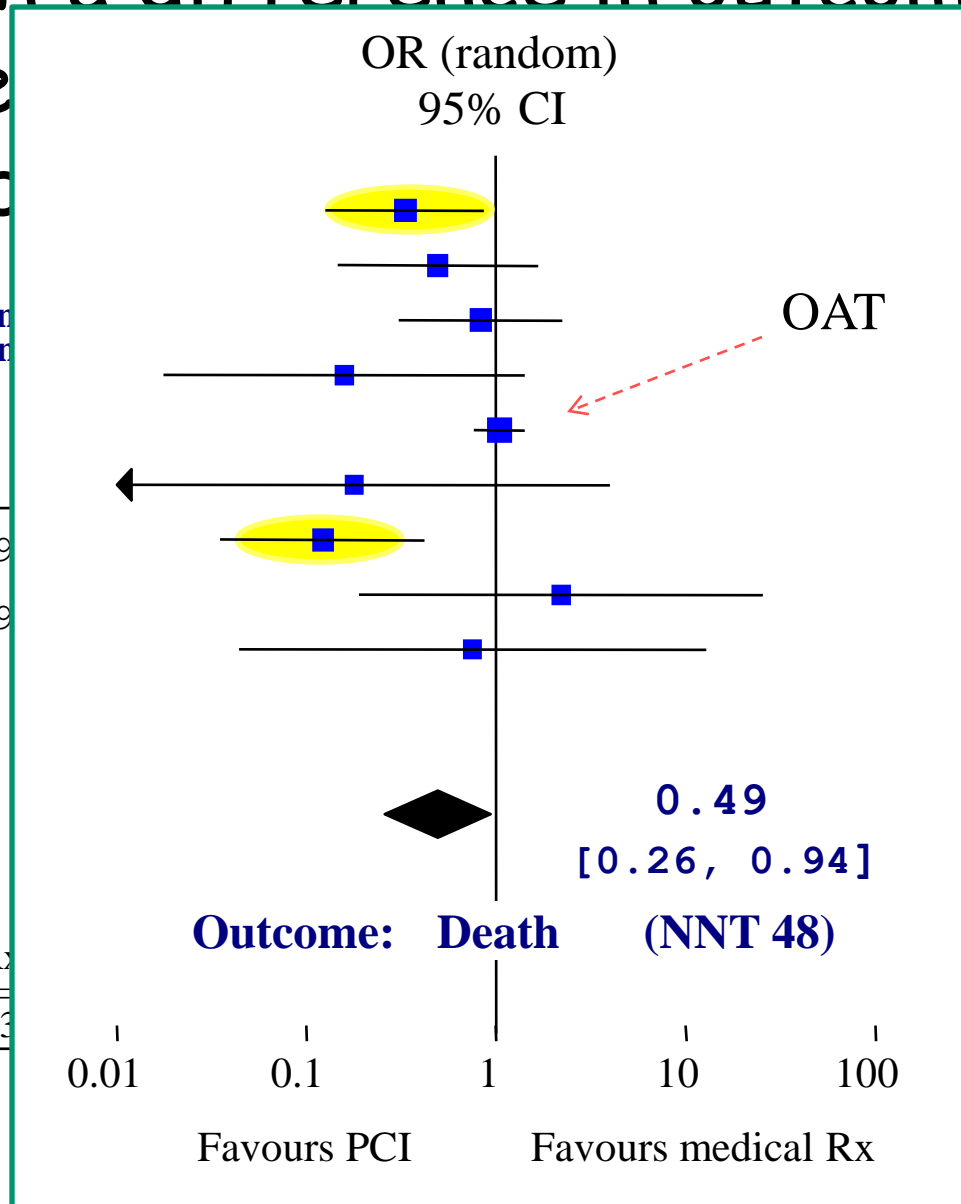
Presented at ESC 2014

Subocclusion

Review: Late percutaneous coronary intervention
 Comparison: Late percutaneous coronary intervention vs. optimal medical therapy
 Outcome: Death

Study or sub-category	PCI n/N
<u>ALKK</u>	6/149
BRAVE-2	4/18
DECOPI	8/109
Horie et al	1/44
OAT	87/1
Silva et al	0/1
<u>SWISSI II</u>	3/
TOAT	2/32
TOMIIS	1/2
TOPS	0/42

Total (95% CI) 1779
 Total events: 112 (PCI), 149 (Medical Rx)
 Test for heterogeneity: $\text{Chi}^2 = 19.36$, $\text{df} = 10$, $\text{I}^2 = 65\%$
 Test for overall effect: $Z = 2.15$ ($P = 0.03$)



fit

artery occlusion

random)
CI

0.13, 0.86]

0.15, 1.66]

0.31, 2.23]

0.02, 1.42]

0.76, 1.42]

0.01, 3.99]

0.04, 0.42]

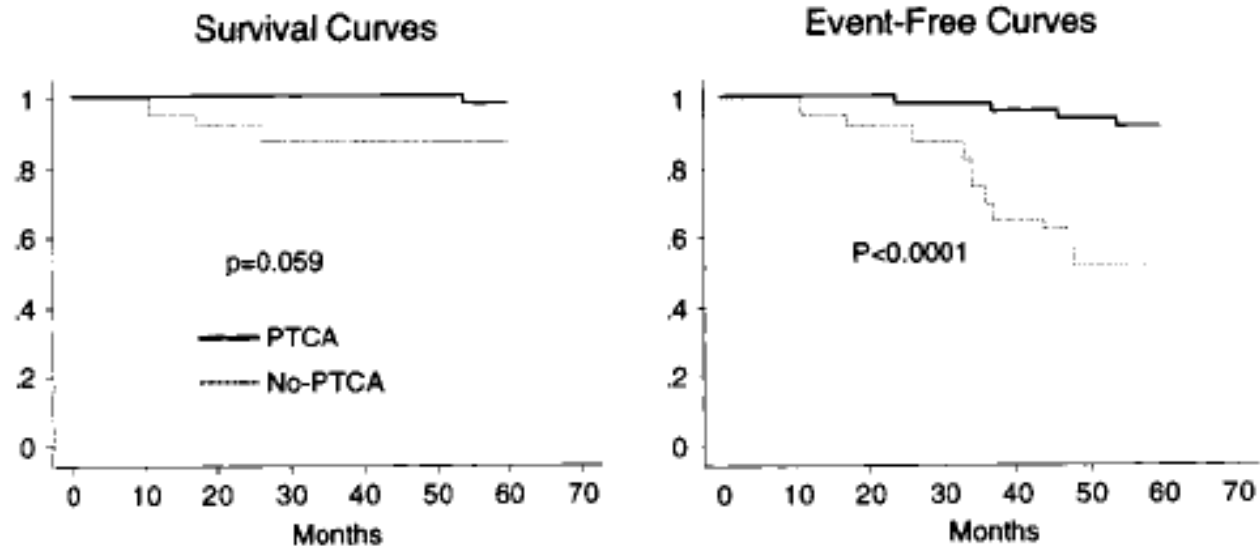
0.19, 25.52]

0.04, 12.82]

estimable

0.26, 0.94]

Horie et al. Circulation 1998



Five-year Kaplan-Meier actuarial cardiac survival and event-free curves for the PTCA (n=44) and no-PTCA (n=39) groups. With regard to cardiac survival, no significant difference was observed between the 2 groups. However, the no-PTCA group had worse prognosis. With regard to cardiac events (including cardiac death, nonfatal recurrence of MI, and development of CHF), the PTCA group had better prognosis than the no-PTCA group during the 5-year period.

Mechanical reperfusion

12 to 72 hours

→ Is there a Role for an Early Viability Study ?

The VIAMI study (abstract presentation- Gruberg - 2006)

- 291 pts (approx 50% post-lytics) 48-72 h after MI

- Low-dose dobutamine

→ viability → randomized to PCI or cons tx

→ no viability → registry

→ In 'viable' pts, PCI lead to a reduction in events (D/MI/UA) (16% vs 7%, p=0.04)

→ The 'non-viable' pts had lowest event rate