The Window for Fibrinolysis

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ESC STEMI Guidelines : December 2008

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ESC GUIDELINES

Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation

The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology:

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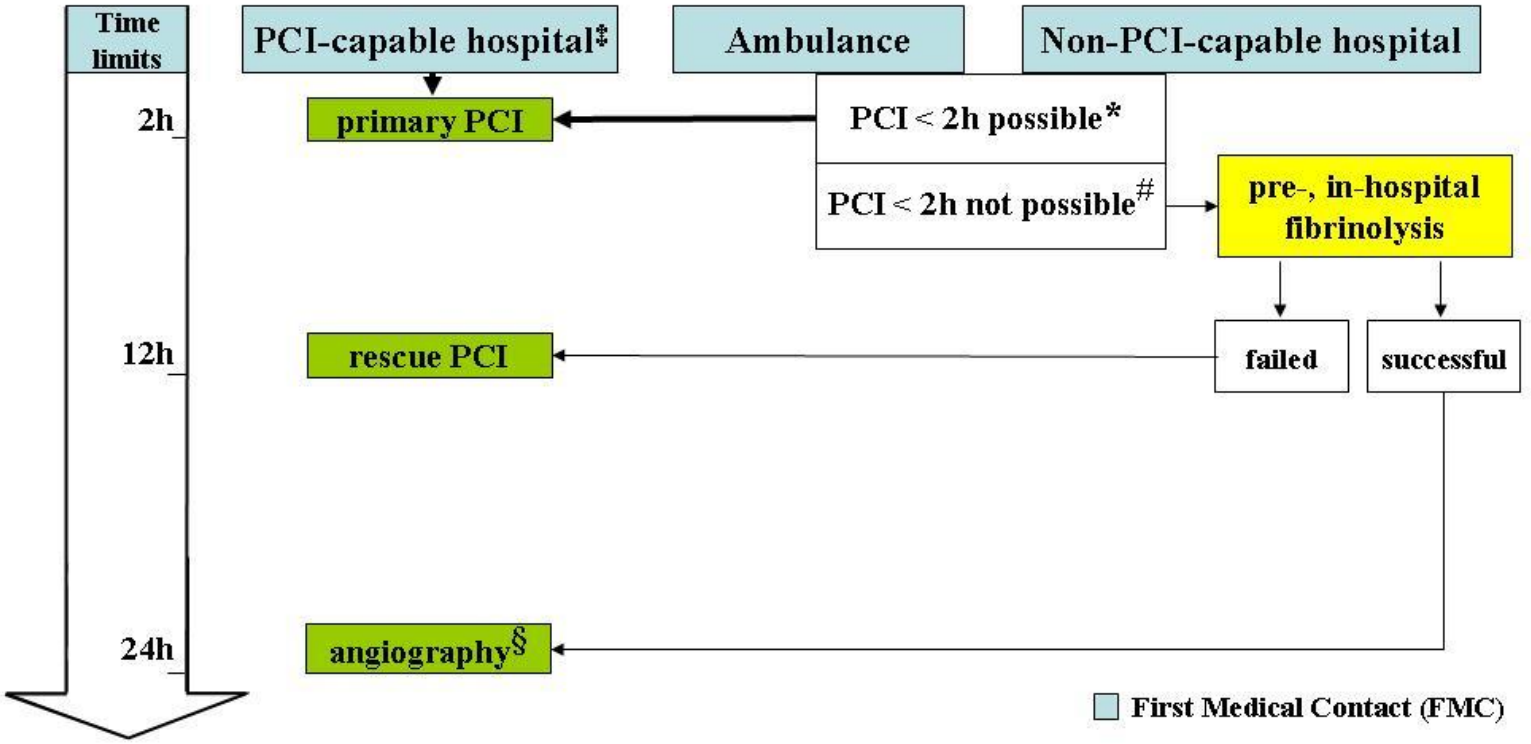
Reperfusion Therapy: Fibrinolytic Therapy

Recommendations	Class	LOE
▪ In the absence of contraindications and if primary PCI cannot be performed within the recommended time	I	A
▪ A fibrin-specific agent should be given	I	B
▪ Pre-hospital initiation of fibrinolytic therapy	IIa	B

Reperfusion Therapy

Recommendations	Class	LOE
▪ Indicated in all pts with chest pain/discomfort of < 12 h and with persistent ST-segment elevation or (presumed) new LBBB	I	A
▪ Should be considered if there is clinical and/or ECG evidence of ongoing ischaemia if symptoms started > 12 h before	IIa	C
▪ Reperfusion (PCI) in stable pts presenting > 12 h to 24 h after symptom onset	IIb	B
▪ PCI of totally occluded infarct artery in stable pts > 24 h after symptom onset without signs of ischaemia	III	B

ESC 2008 STEMI Guidelines
Reperfusion Strategies



* Time FMC to first balloon inflation must be shorter than 90 min in patients presenting early (< 2 h after symptom onset), with large amount of viable myocardium and low risk of bleeding.

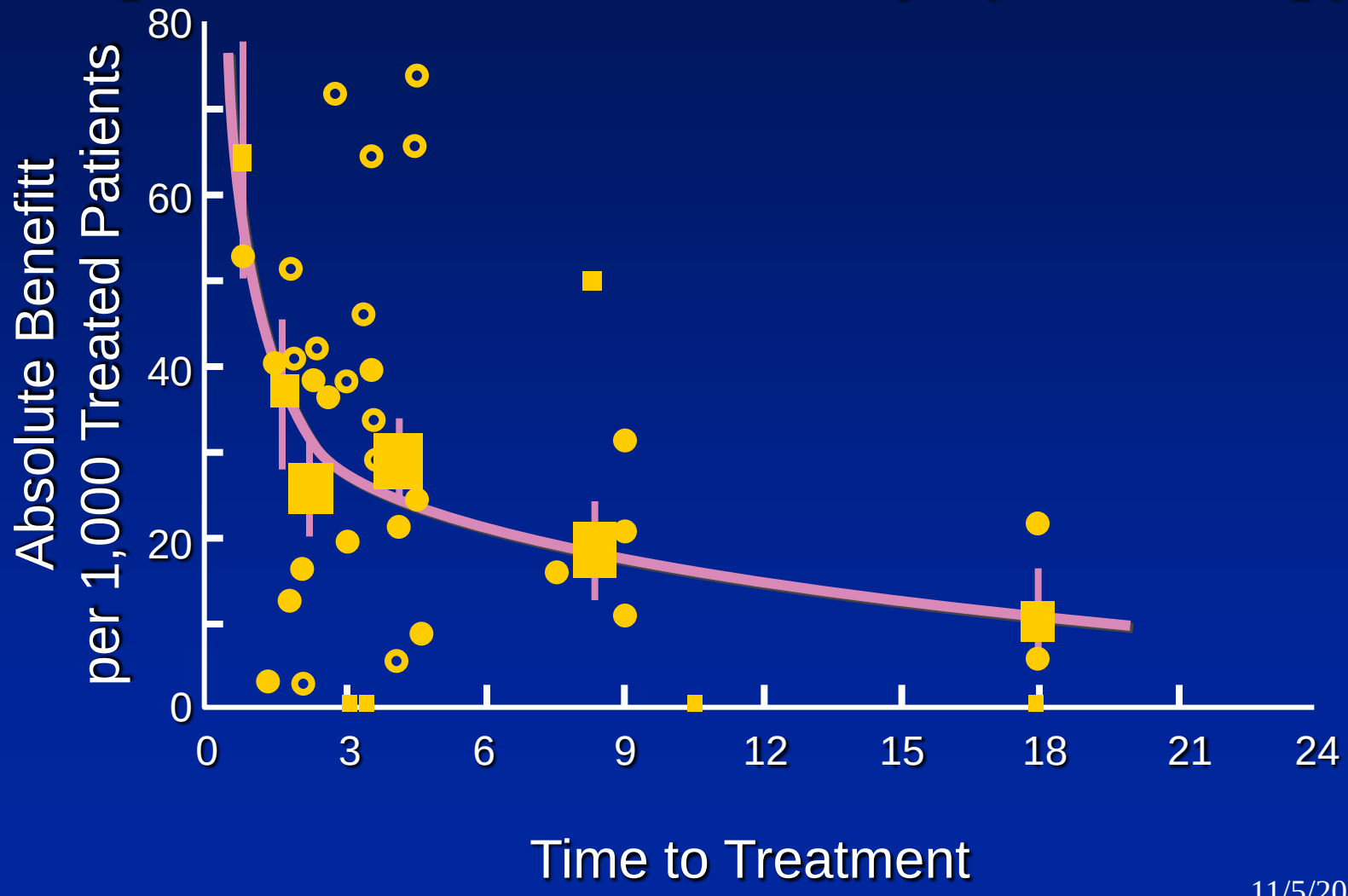
If PCI is not possible < 2 h of FMC, start fibrinolytic therapy as soon as possible.

§ Not earlier than 3 h after start fibrinolysis

‡ 24/7 service

The Importance of Time to Treatment

A Meta-analysis of 50,246 Pts in placebo controlled trials of Lytic Therapy

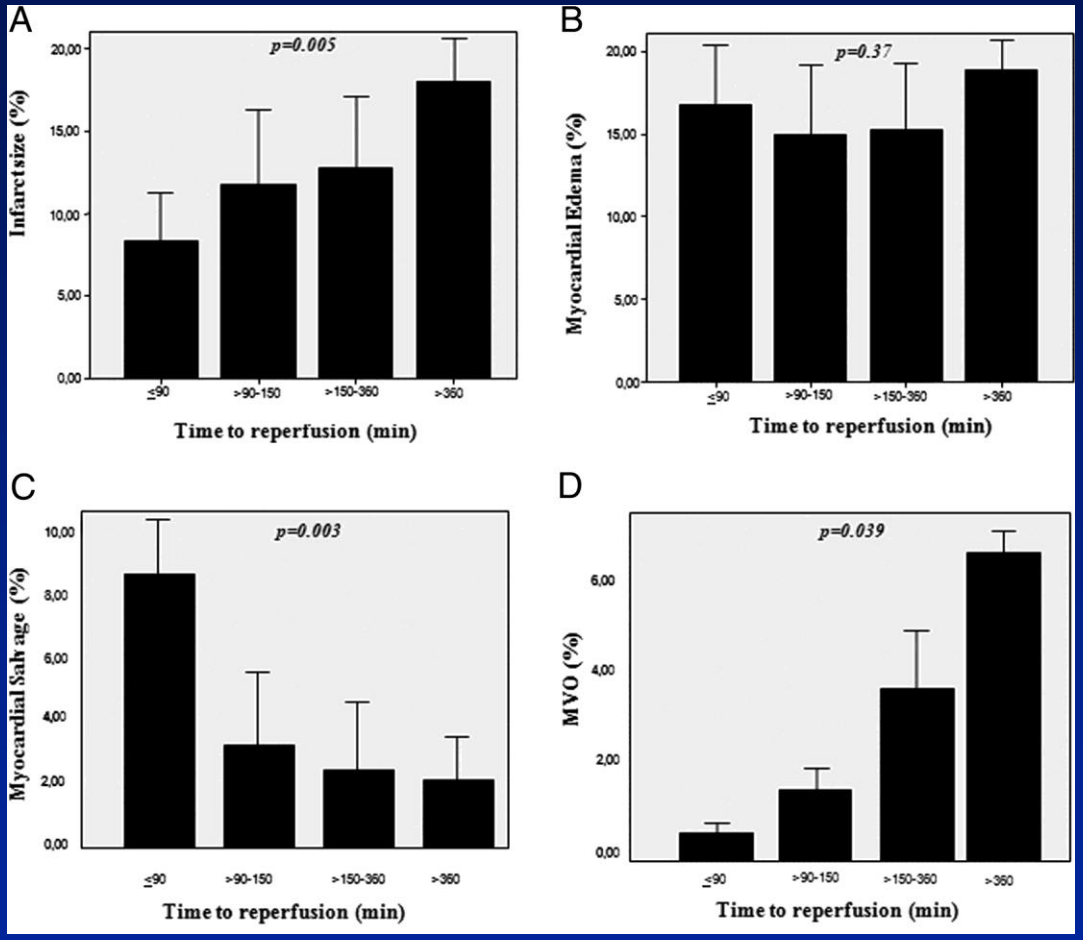


Boersma E, et al. *Lancet*. 1996; 348: 771- 5

11/5/2010

Myocardial Reperfusion by PPCI assessed by CMR

Infarct Size



Edema

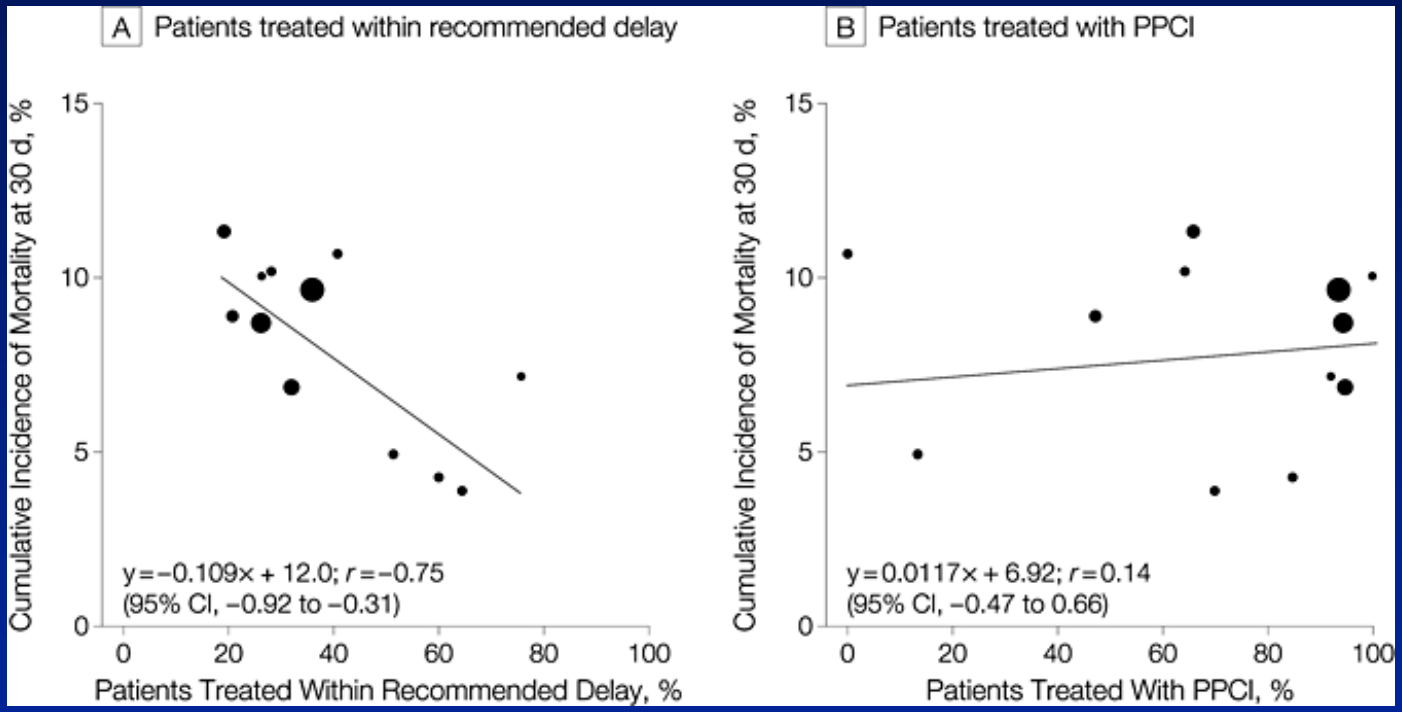
Myoc. Salvage

MVO

Time to reperfusion from sympton onset: ≤90 90-150 150-360 ≤360 min

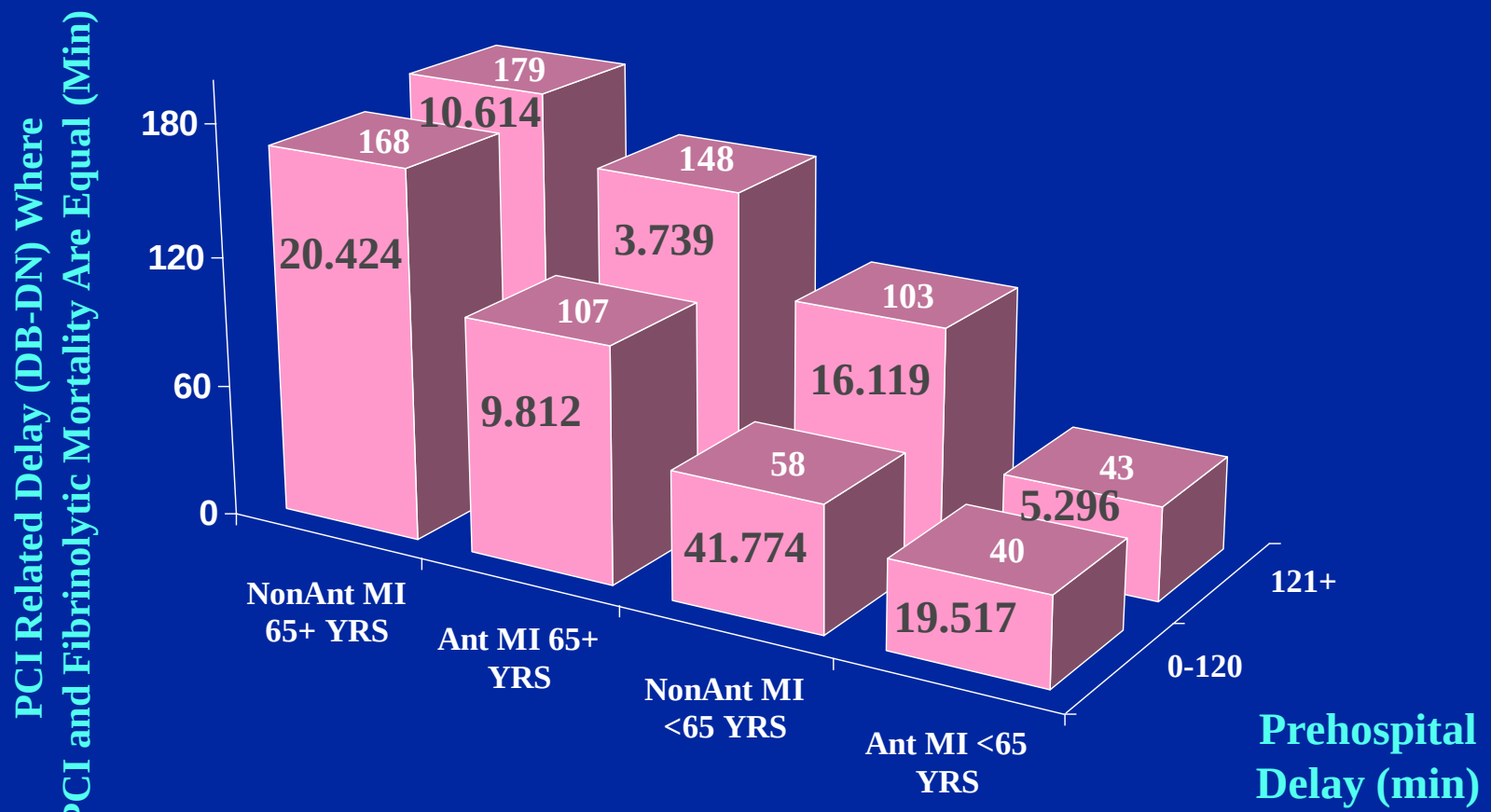
Francone et al.JACC 2009;54:2145

30-Day Mortality of STEMI Patients by % Treated Within Recommended Delays and % Receiving Reperfusion With PPCI



Lambert, L. et al. JAMA 2010;303:2148-2155.

PCI vs. Lysis: Importance of *Presentation Delay* and *Baseline Characteristics* Data from NRMI 2,3 and 4 Registries



Pinto et al. Circulation, 2006

ACC/AHA STEMI Guidelines : November 2009

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Frederick G. Kushner, Mary Hand, Sidney C. Smith, Jr, Spencer B. King, III, Jeffrey L. Anderson, Elliott M. Antman, Steven R. Bailey, Eric R. Bates, James C. Blankenship, Donald E. Casey, Jr, Lee A. Green, Judith S. Hochman, Alice K. Jacobs, Harlan M. Krumholz, Douglass A. Morrison, Joseph P. Ornato, David L. Pearle, Eric D. Peterson, Michael A. Sloan, Patrick L. Whitlow and David O. Williams

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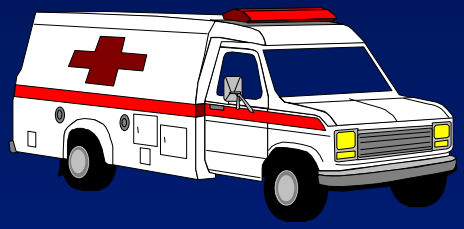
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Transport of Patients with STEMI and Initial Reperfusion Treatment

Call 9-1-1
Call fast



Onset of symptoms of STEMI

9-1-1 EMS dispatch

EMS on scene
- **Encourage 12-lead ECGs**
- **Consider pre-hospital fibrinolytic if capable and EMS–to–needle within 30 min**

EMS triage plan

Hospital fibrinolysis: Door–to–needle ≤ 30 min

Not PCI capable

Inter-hospital transfer

PCI capable

GOALS

5 min | **8 min** | **EMS Transport**

Patient | **EMS**

Dispatch 1 min

Pre-hospital fibrinolysis EMS–to–needle ≤ 30 min

EMS transport EMS-to-balloon ≤ 90 min

Patient self-transport Hospital door-to-balloon ≤ 90 min

"Golden Hour" = 1st 60 min

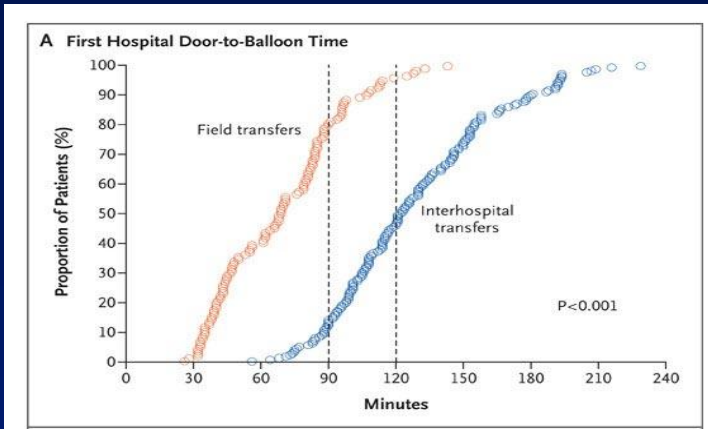
Total ischaemic time: within 120 min

Antman, et al. *J Am Coll Cardiol* 2004;44:671-719.

Antman, et al. *Circulation* 2004;110: 588-636.

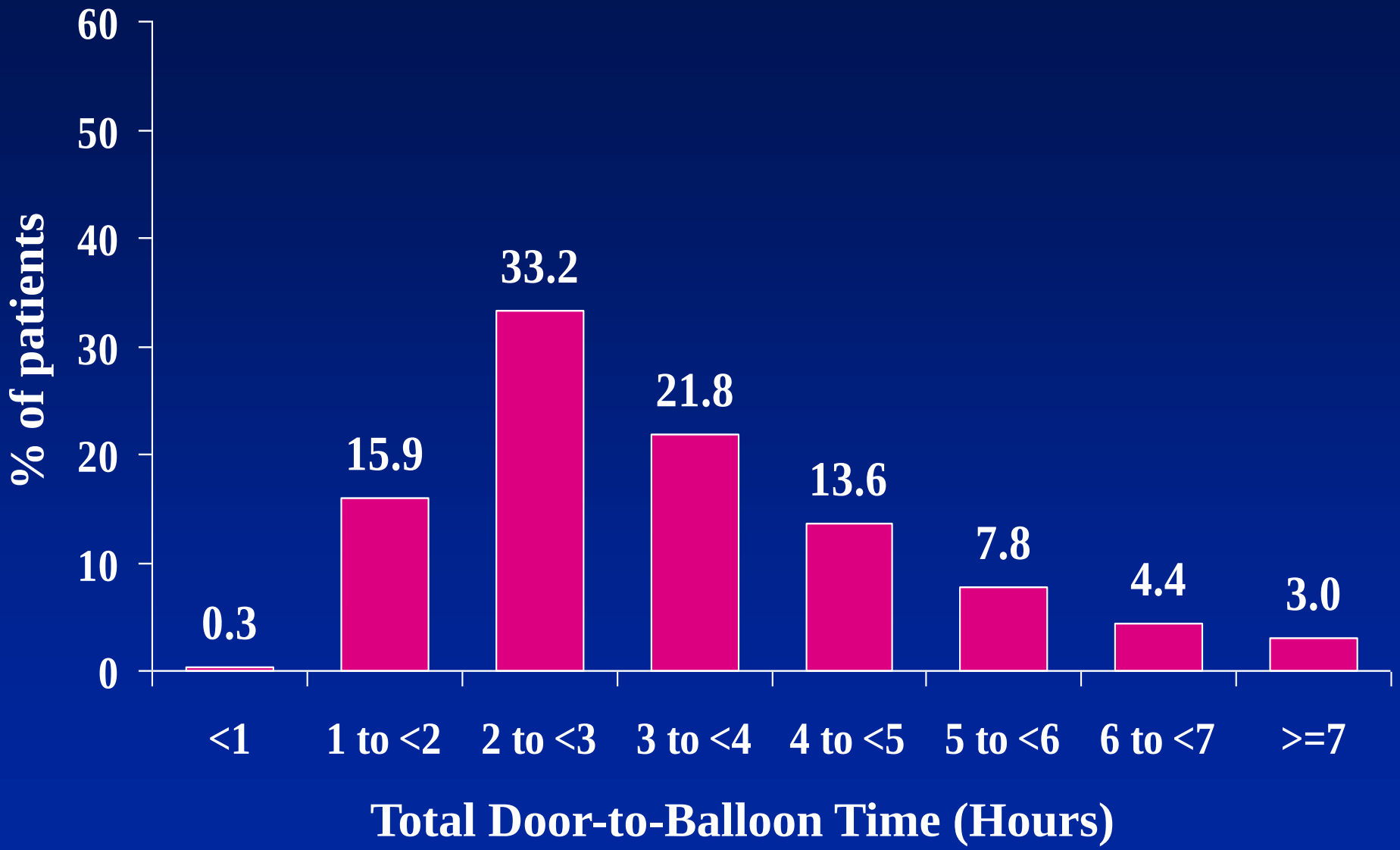
The Real World

Cumulative Time-to-Balloon Intervals in OTTAWA



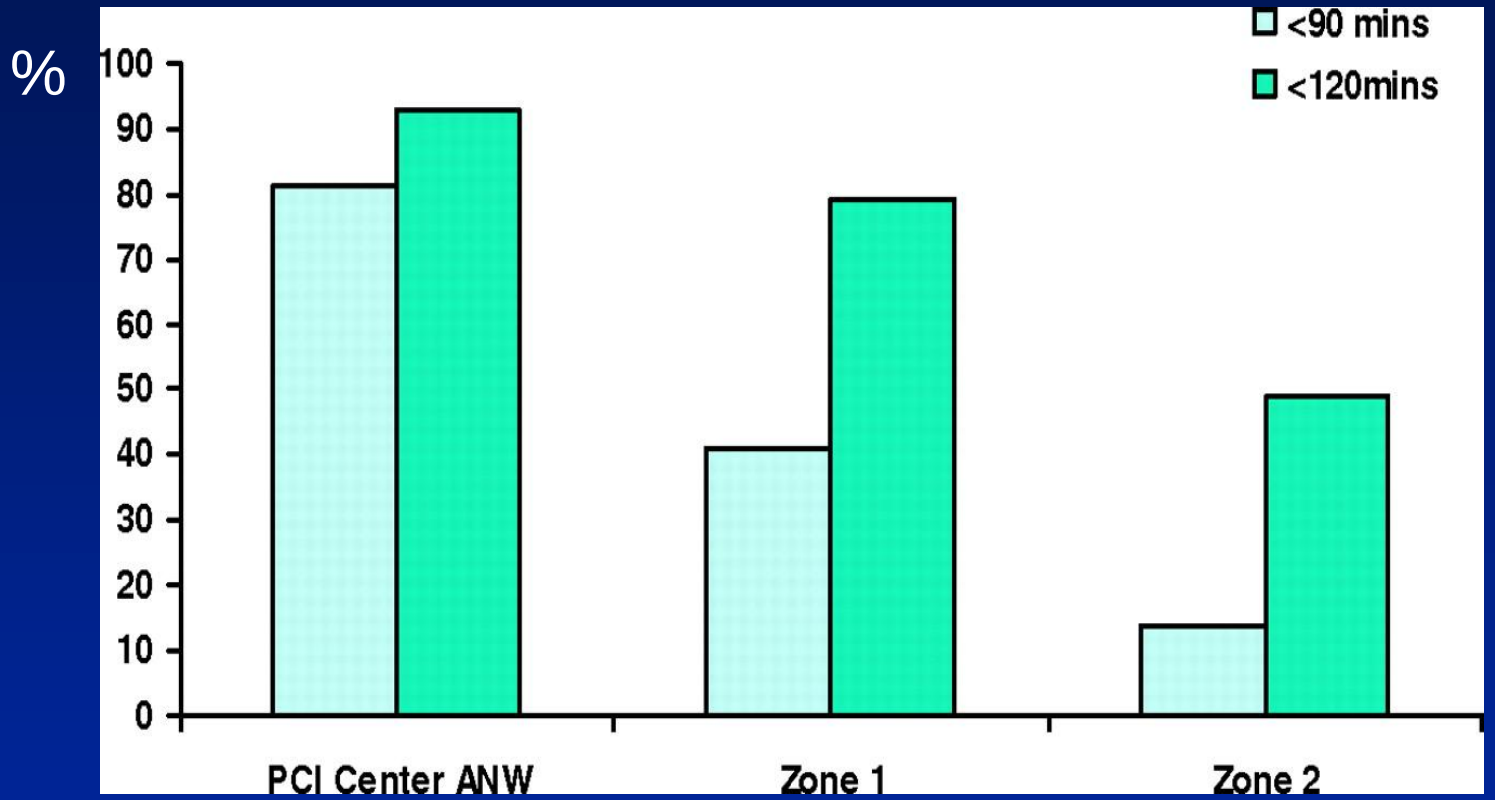
Le May M et al. N Engl J Med 2008;358:231-240

Time delays in Transfer Patients for Primary PCI



Nallamothu et al. Circulation, 2005

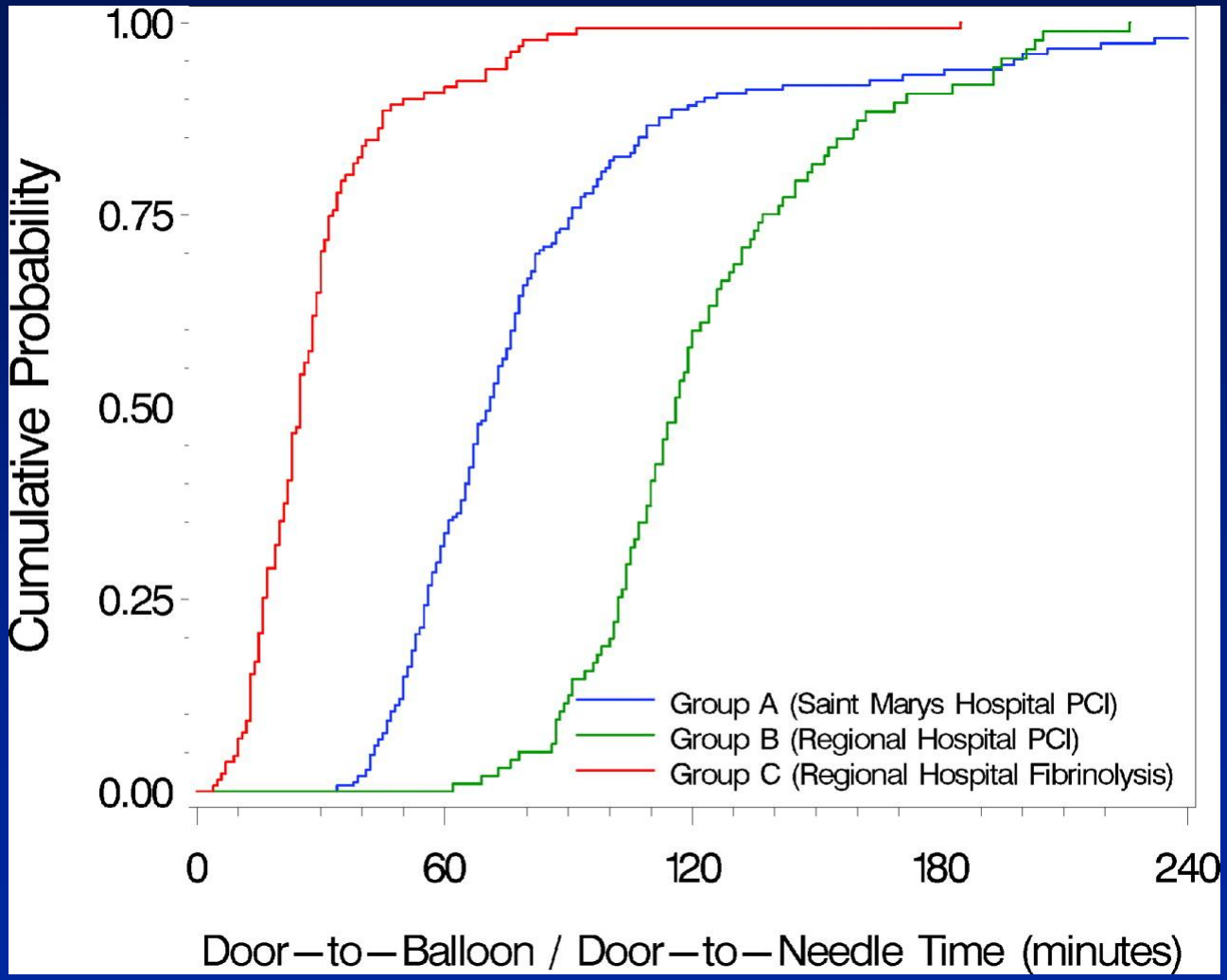
MINNESOTA Study: First Door-to-Balloon



Henry, T. D. et al. Circulation 2007;116:721-728

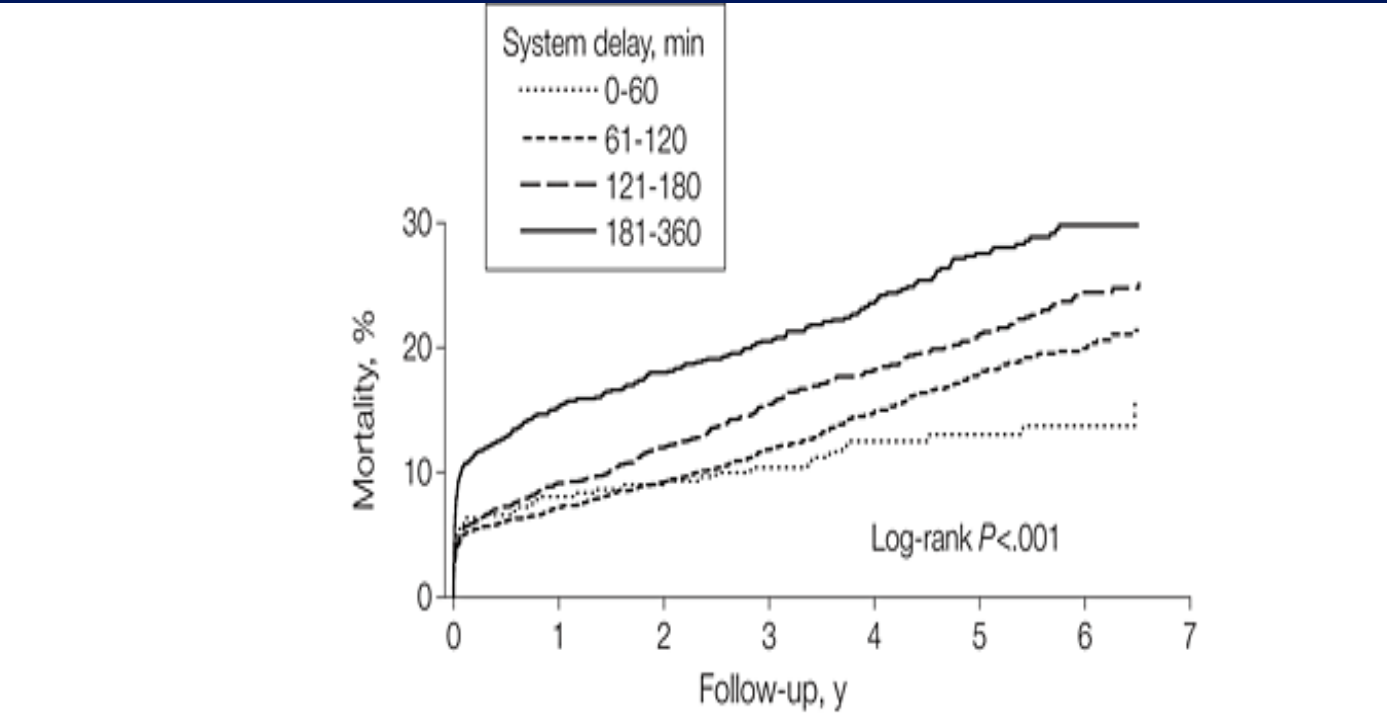
Zone 1 : < 60 miles
Zone 2 : 60-210 miles

MAYO STUDY : Door-to-balloon and door-to-needle times for group A (PCI-hospital), group B (regional hospital transfer for PCI), and group C (regional hospital fibrinolysis)



Ting, H. H. et al. Circulation 2007;116:729-736

Mortality Estimates for 6209 Danish Patients With STEMI Treated With Primary PCI



No. at risk

System delay, min							
0-60	347	311	278	230	192	138	87
61-120	2643	2339	1906	1420	1006	667	375
121-180	2092	1836	1503	1183	842	533	278
181-360	1127	923	765	647	491	332	172

Terkelsen, C. J. et al. JAMA 2010;304:763-771.

Two Different Strategies

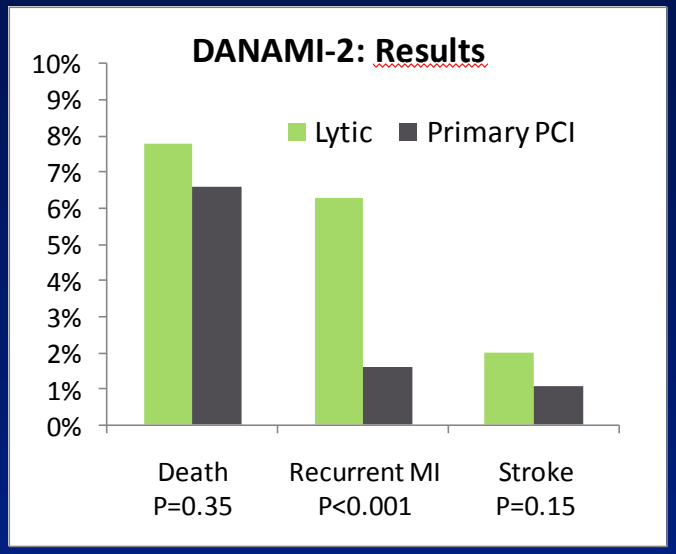
- **Facilitated PCI:** pharmacological reperfusion treatment delivered prior to a **planned PCI** in order to bridge the PCI-related time delay

- **Pharmacoinvasive strategy:** intravenous fibrinolytic treatment, followed by coronary angiography on an urgent basis if lytic therapy failed (rescue PCI) or later to determine long-term treatment (PCI, CABG, medical).

A Conservative vs Invasive Transfer Appraoch

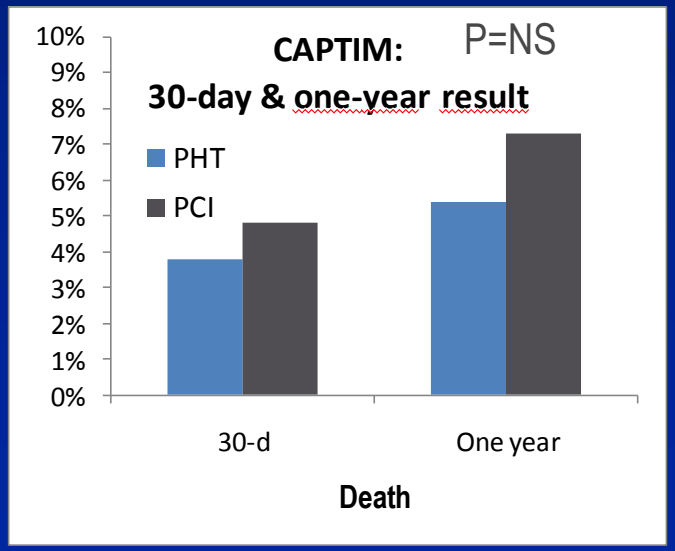
DANAMI-2:
benefits of PPCI even in transfer patients

Rescue PCI: 1.8%
Any Revasc: 17%



CAPTIM:
lower mortality with PHT up to 5 years

Rescue PCI: 26%
Any Revasc: 72%

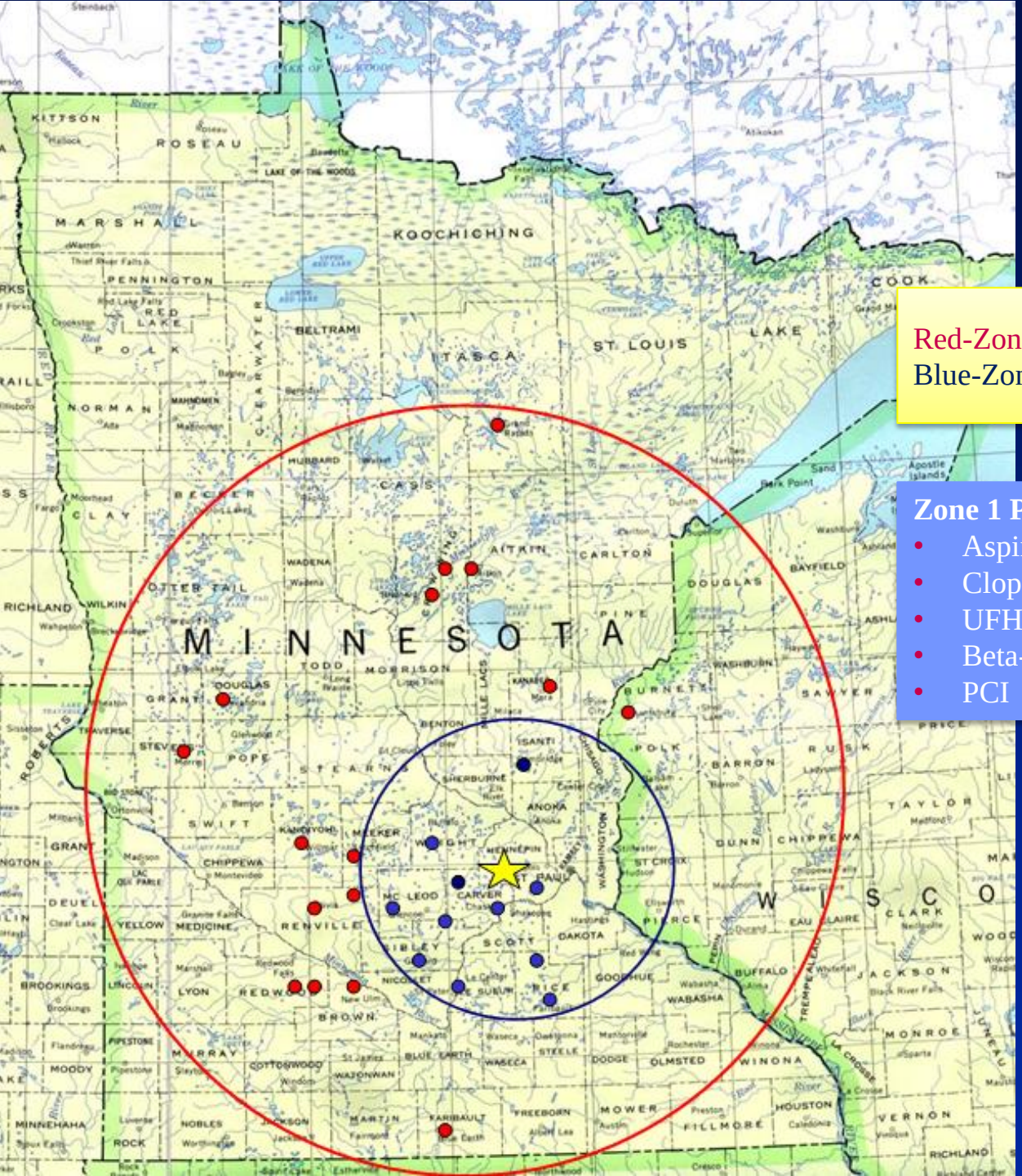


N Engl J Med 2003; 349: 733-42
Bonnefoy et al. Lancet 2002 & AHA 2002

Comparison of key results from DANAMI-2 and CAPTIM

Results	DANAMI-2 Trial		CAPTIM Trial	
	In-hospital fibrinolysis (*n* = 562)	Transfer to PPCI (*n* = 567)	Prehospital fibrinolysis (*n* = 419)	Transfer to PPCI (*n* = 419)
Median age (years)	64	62	58	58
Median time to fibrinolysis (min)	169		107	
Median time to PCI (min)		224		190
Rescue PCI (%)	1.8		26	
Reinfarction (%)	6.2	1.9	3.7	1.7
Elective revascularization‡ (%)	17		72	
30-day all-cause mortality (%)	8.5	6.5	3.8	4.8
All-cause mortality at follow-up* (%)	33.3	26.7	9.7	12.6
Cardiac mortality at follow-up* (%)	16.4	12.8		

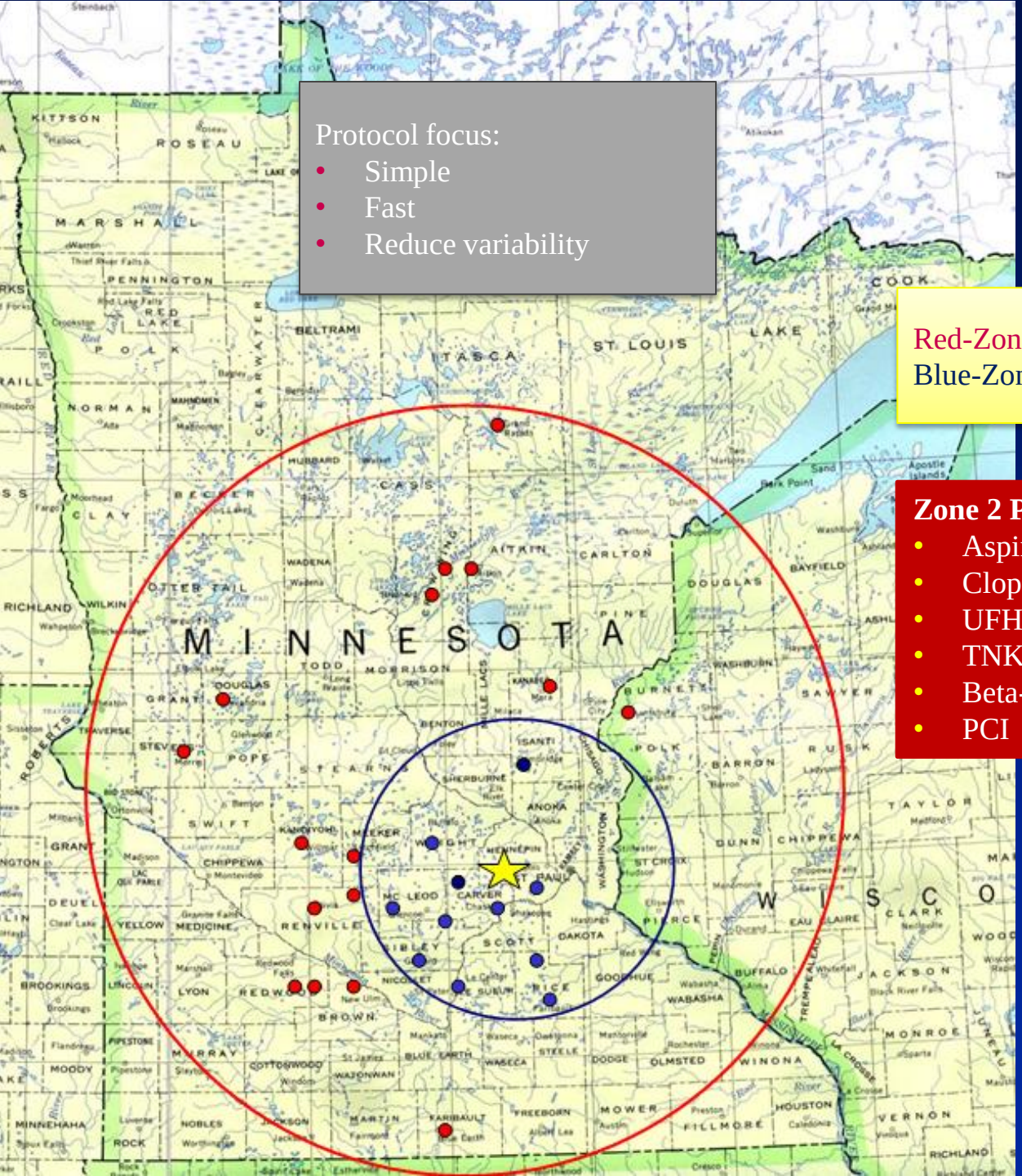
*In the first 30-days. ‡Follow-up was 5 years in the CAPTIM Trial and 7.8 years in the DANAMI-2 Trial. Abbreviations: CAPTIM, comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction; DANAMI, Danish Acute Myocardial Infarction; NA, not applicable; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention.



Red-Zone II (90-120mins)
Blue-Zone I (<90 mins)

Zone 1 Protocol

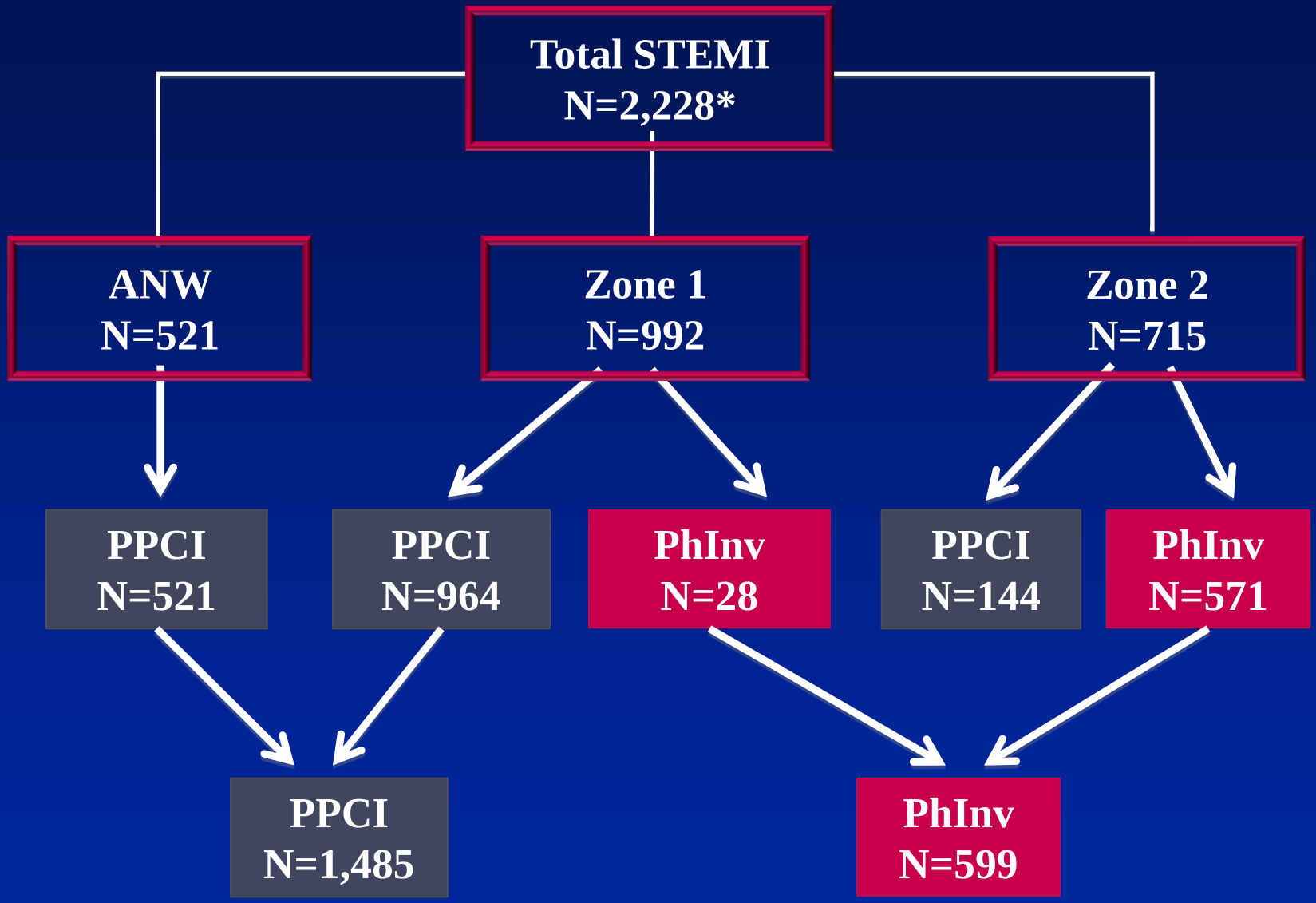
- Aspirin 325 mg
- Clopidogrel 600mg
- UFH
- Beta-blocker
- PCI


Protocol focus:
• Simple
• Fast
• Reduce variability
Red-Zone II (90-120mins)
Blue-Zone I (<90 mins)
Zone 2 Protocol
• Aspirin 325 mg
• Clopidogrel 600mg
• UFH
• TNK ½ dose
• Beta-blocker
• PCI
MINNESOTA

Time to reperfusion segments (min)

	PCI Hosp	Zone 1 (<60 miles)	Zone 2 (60-210 miles)	P value
Symptoms to hospital	103 (60, 232)	88 (47, 195)	88 (44,185)	0.008/ 0.002
In door – out door	NA	49 (36, 67)	61 (48, 83)	
Door to fibrinolytic	NA	NA	29	
Transport	NA	22 (16, 31)	35 (26, 48)	
Door to balloon	64 (44, 84)	95 (81, 117)	121 (101, 151)	<0.001/ <0.001
Total reperfusion	171 (118, 318)	195 (142, 305)	218 (165, 329)	<0.001/ <0.001

Patients presenting between 2003 and 2009



*Excluding no culprits. Patients presented between 2003 and 2009

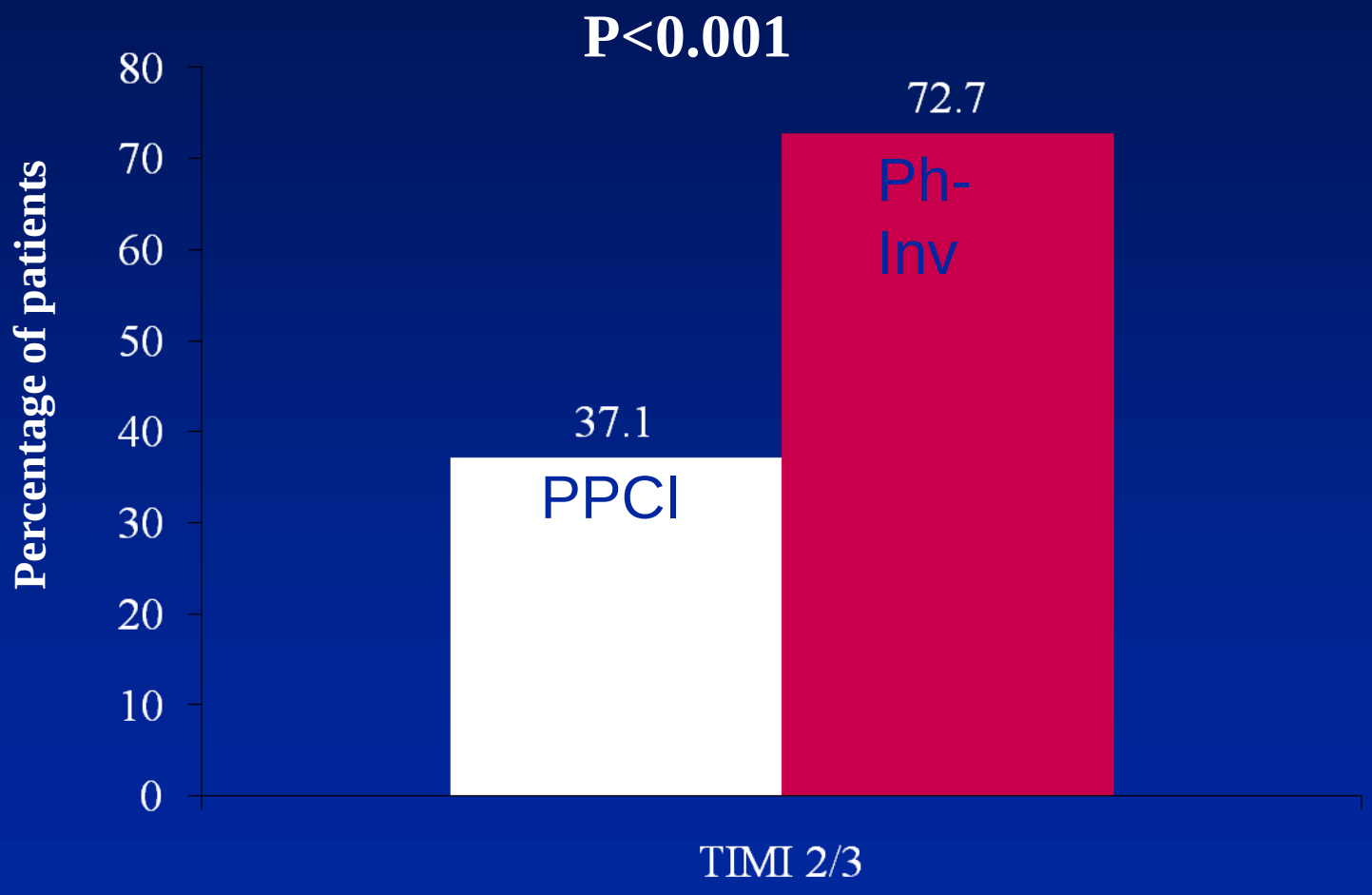
Baseline characteristics

	PPCI	Ph-Inv	P value
Age	62.4 ± 14.1	63.3 ± 13.2	0.18
Patients ≥ 75 yrs	343 (23.1)	138 (24.0)	0.98
Male	1088 (73.3)	452 (75.5)	0.30
Hyperlipidaemia	820 (57.1)	327 (56.8)	0.88
Hypertension	850 (57.6)	329 (55.1)	0.29
Diabetes	233 (15.8)	101 (16.9)	0.53
Current smoking	593 (40.3)	242 (40.7)	0.87
History of MI	276 (18.7)	114 (10.0)	0.84
History of CABG	91 (6.2)	33 (5.5)	0.58
History of PCI	297 (20.1)	107 (17.9)	0.24

Clinical characteristics

	PPCI	Ph-Inv	P value
Cardiogenic shock before PCI	155 (10.4)	49 (8.2)	0.12
Cardiac arrest before PCI	137 (9.2)	39 (6.5)	0.044
Out of hosp cardiac arrest	79 (5.3)	24 (4.0)	0.21
Anterior MI	499 (33.8)	211 (35.4)	0.48
Killip Class 2-4	223 (15.0)	86 (14.4)	0.70
LBBB	38 (2.6)	9 (1.5)	0.14

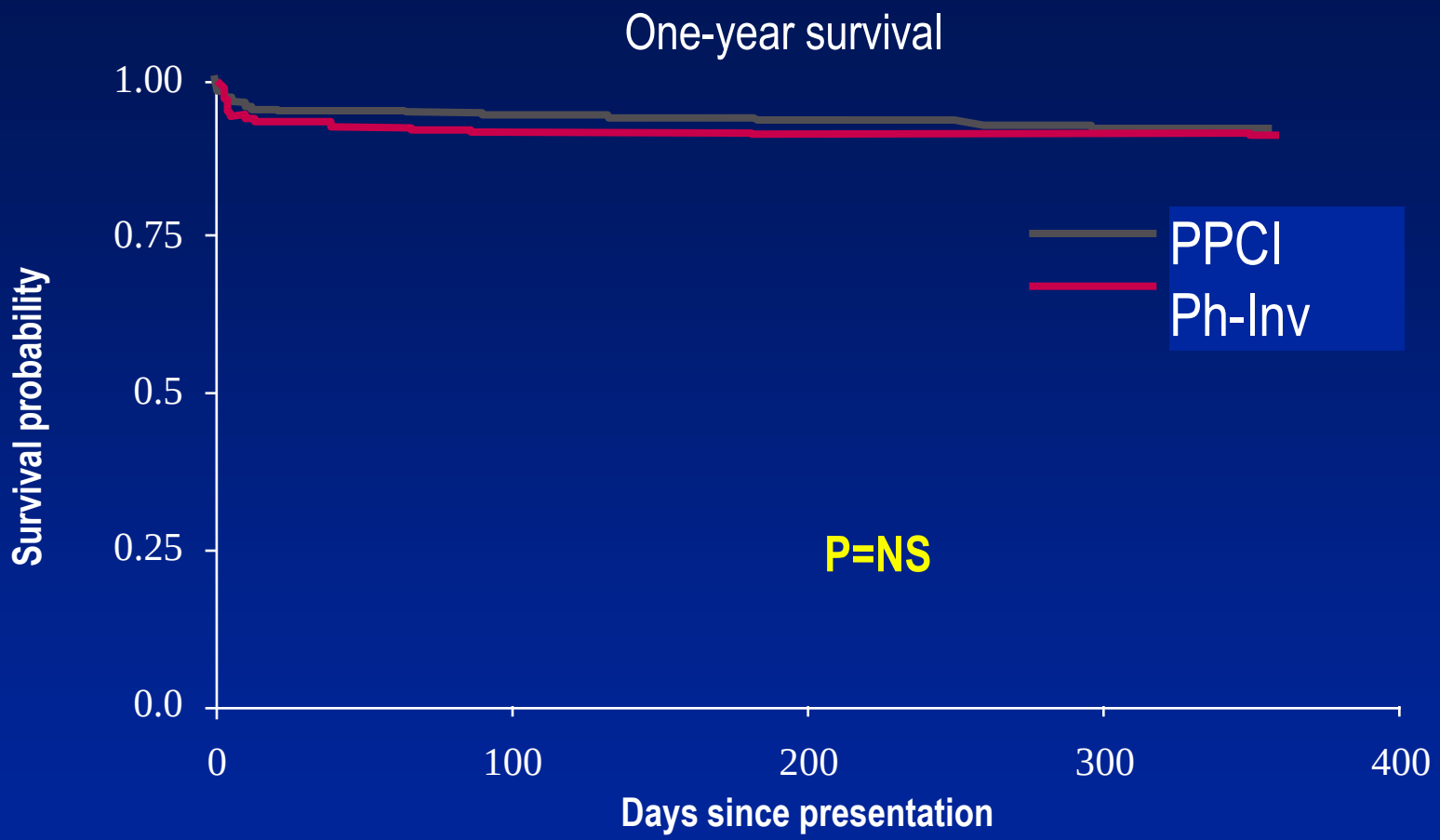
Pre-PCI patency



Results

	PCI Hosp PPCI N=496	Zone 1 (<60) PPCI N=1,005	Zone 2 (60-210) Ph-Inv N=606	P value PCI Hosp vs. Zone 2
D2B time	64 (44, 84)	95 (81, 117)	123 (102, 151)	<0.0001
Mortality hospital	5.0%	4.4%	5.5%	0.76
Mortality 30 day	5.7%	5.2%	5.8%	0.93
Re-ischaemia 30 days	3.0%	0.9%	1.0%	0.014
Major Bleeding	1.4%	0.7%	1.2%	0.71
Stroke 30 days	1.2%	0.5%	1.0%	0.73

Kaplan-Meier survival



STrategic Reperfusion Early After MI

Patients presenting with STEMI <3 hrs from onset of symptoms that cannot reliably undergo primary PCI <60 min

Group A

- **<75 years: TNK, Routine ASA**
  - **Clopidogrel: LD 300 mg + 75 mg QD**
  - **Enoxaparin: 30 mg IV + 1 mg/kg SC Q12h**
- **≥ 75 years: 1/2TNK, Routine ASA**
  - **Clopidogrel: 75 mg QD**
  - **Enoxaparin: 0.75mg/kg SC Q12h**

ECG at 90 min: ST resolution ≥ 50%

- **YES** → **Diagnostic angiography + PCI / stent, if indicated > 6 hrs / < 24 hrs**
- **NO** → **Rescue angiography + PCI / stent immediately**

Group B

- **ASA, No lytic**
- **Antiplatelet and anticoagulation treatment according to local standards**
- **Standard angiography + PCI / stent immediately**

Ambulance → cath lab

Cath lab ← hospital ← ambulance

2009 ACC/AHA New or Modified Recommendations for Triage and Transfer for PCI

- **Class IIa . It is reasonable for high-risk patients who receive fibrinolytic therapy as primary reperfusion therapy at a non–PCI-capable facility to be transferred as soon as possible to a PCI-capable facility where PCI can be performed either when needed or as a pharmacoinvasive strategy. Consideration should be given to initiating a preparatory antithrombotic (anticoagulant plus antiplatelet) regimen before and during patient transfer to the catheterization laboratory.(*Level of Evidence: B*)**

2009 ACC/AHA New or Modified Recommendations for Triage and Transfer for PCI

- **Class IIb . Patients who are not at high risk who receive fibrinolytic therapy as primary reperfusion therapy at a non–PCI-capable facility may be considered for transfer as soon as possible to a PCI-capable facility where PCI can be performed either when needed or as a pharmacoinvasive strategy. Consideration should be given to initiating a preparatory antithrombotic (anticoagulant plus antiplatelet) regimen before and during patient transfer to the catheterization laboratory. (*Level of Evidence: C*)**

Polls at the TCT Website (October 12,2010)

POLL

Which therapy for STEMI patients would to like to learn more about?

Pharmacologic therapy
20%

Aspiration thrombectomy
38%

Out-of-hospital reperfusion
12%

DES as standard of care
30%

POLL

Fibrinolytic therapy should be given to STEMI patients with:

Transfer delays up to 60 min
22%

Transfer delays up to 90 min
31%

Transfer delays up to 120 min
32%

Always
6%

Never
9%

POLL

Which strategies would you like to compare for STEMI patients?

Facilitated PCI (Y/N)
22%

Thrombolysis vs. primary PCI
20%

DES vs. BMS
39%

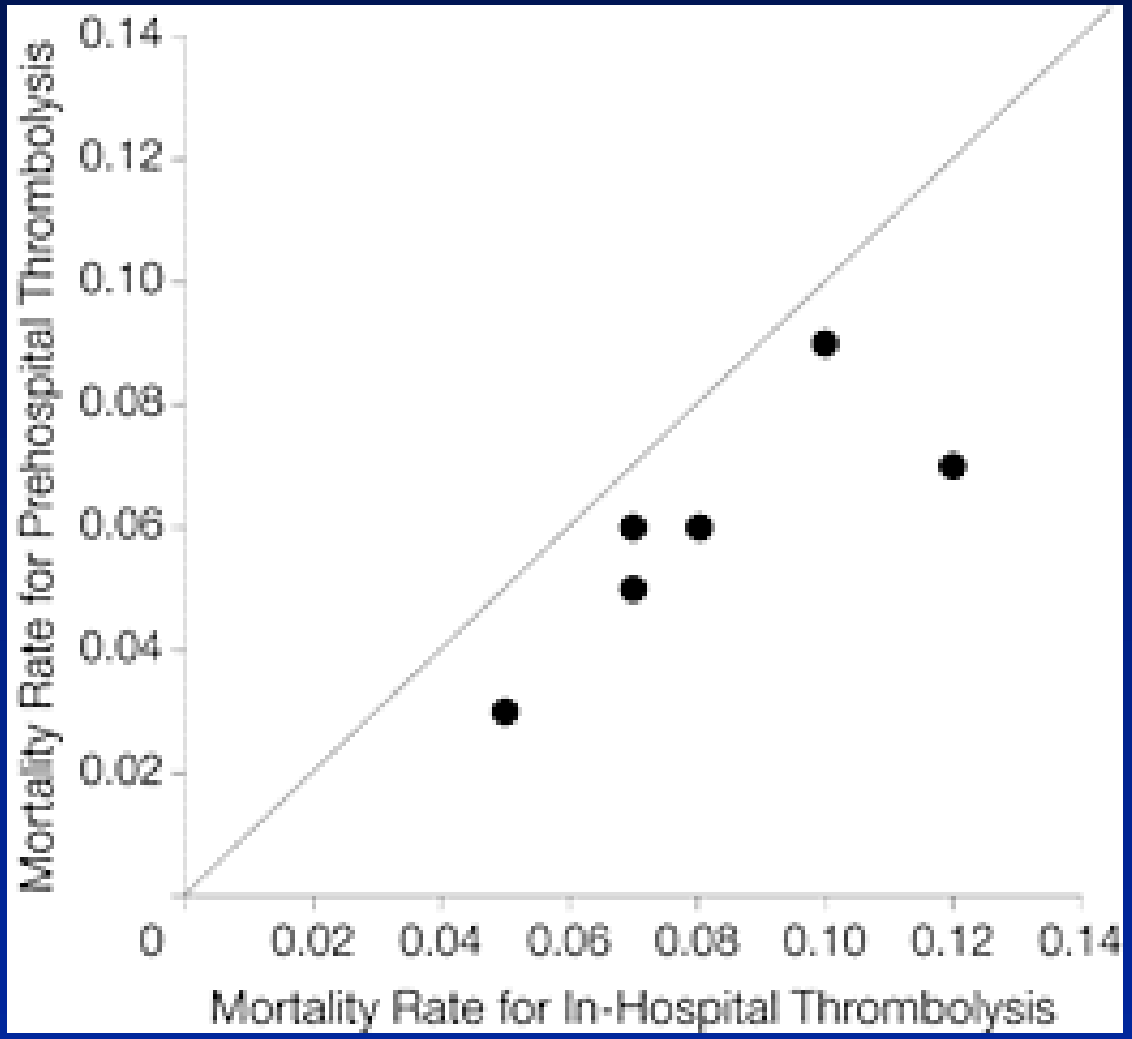
Heparin vs. Bivalirudin
19%

Conclusions
The Window forFibrinolysis

- **“Outside the window of primary PCI”**
- **Whether it should be given up to 12h after onset of infarction is debatable (if primay PCI is not available)**
- **Inter-hospital transport of STEMI patients for primary PCI remains major issue**

11/5/2010

Mortality Rates in Control and Treatment Groups for Each Prehospital Thrombolytic Trial

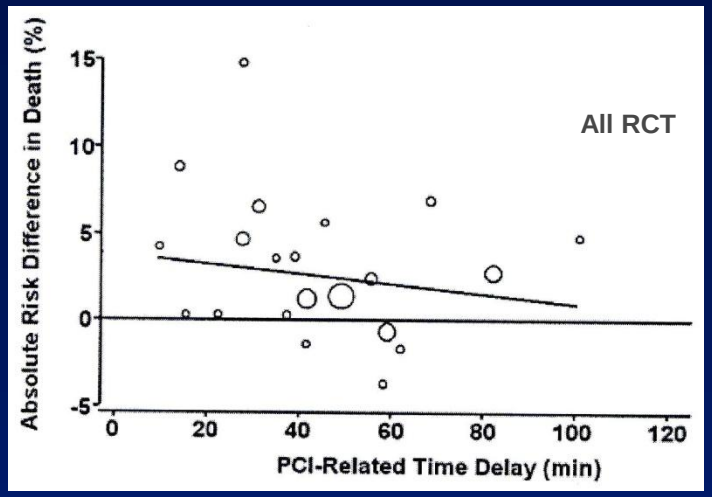


Morrison, L. J. et al. JAMA 2000;283:2686-2692.

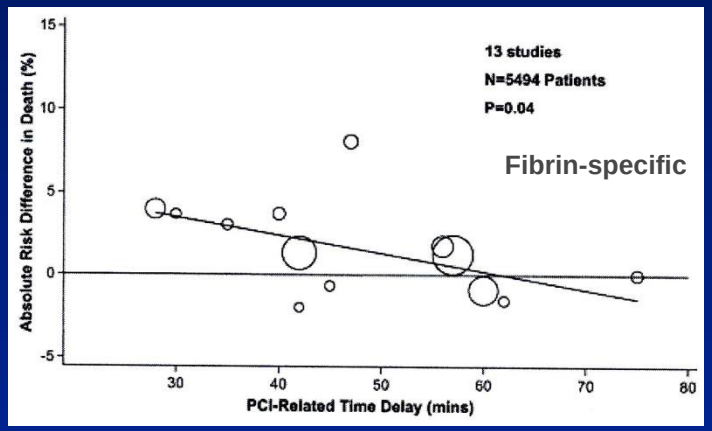
Recommended Logistics

- **Pre-hospital triage/care:**
  - **EMS**
    - **unique telephone number**
    - **tele-consultation**
  - **Ambulance**
    - **12-ECG recorder/defibrillator**
    - **staff able to provide basic and advanced life support**
- **Networks:**
  - **implementation of a network of hospitals with different levels of technology connected by an efficient ambulance service using the same protocol**
- **Targets:**
  - **< 10 min ECG transmission**
  - **< 5 min tele-consultation**
  - **< 120 min to first balloon inflation**
  - **< 30 min start fibrinolytic therapy**

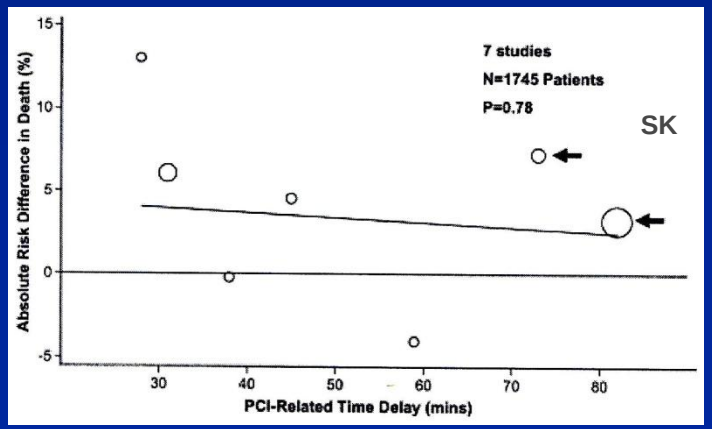
Importance of *PCI-related Delay* Data from Randomized Trials



Betriu and Masotti
Mortality equipose: 110 min
Am J Card 2005;95:100-101

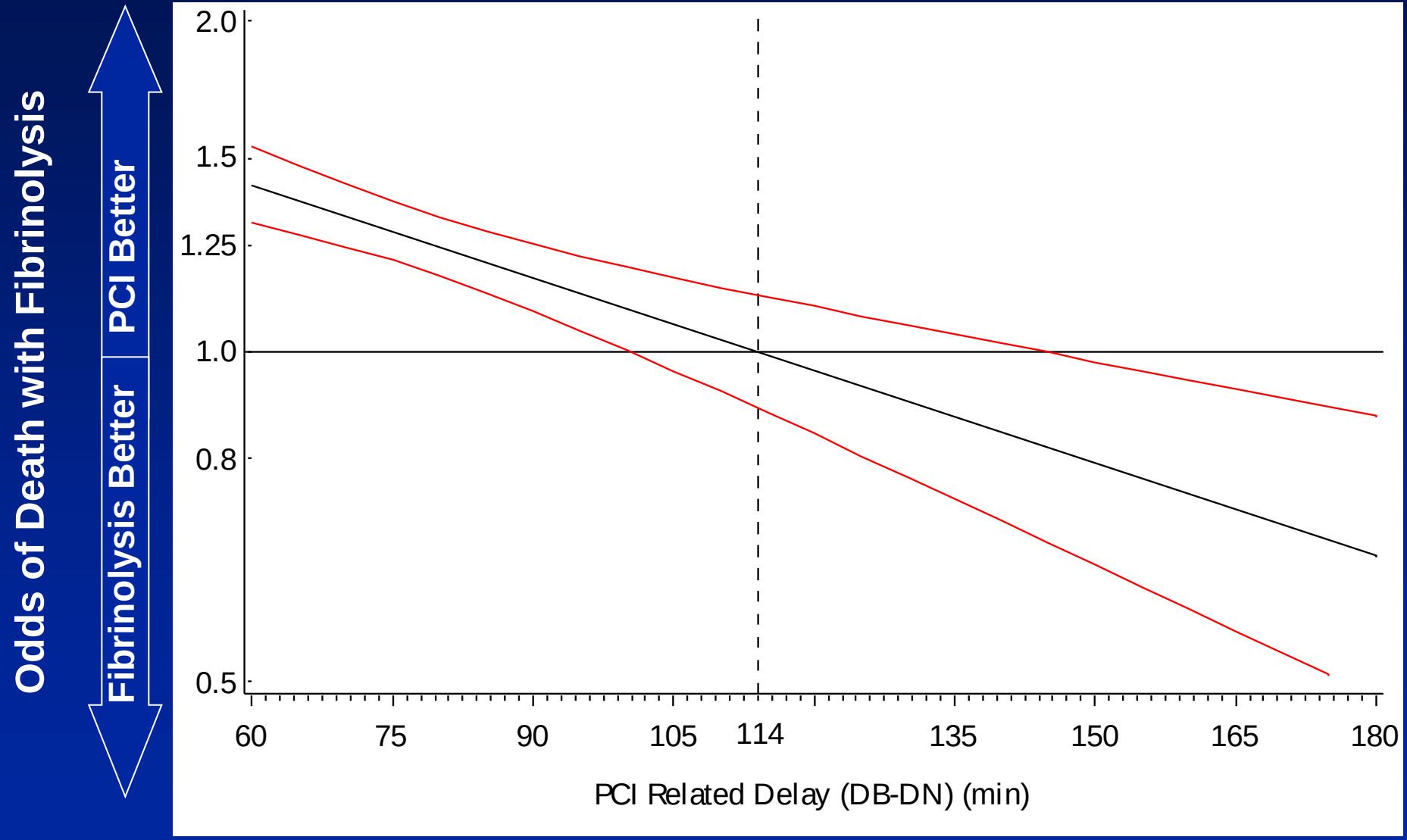


Nallomothu, Antman and Bates
Mortality equipose : 62 min
Am J Cardiol 2004;94:772-774



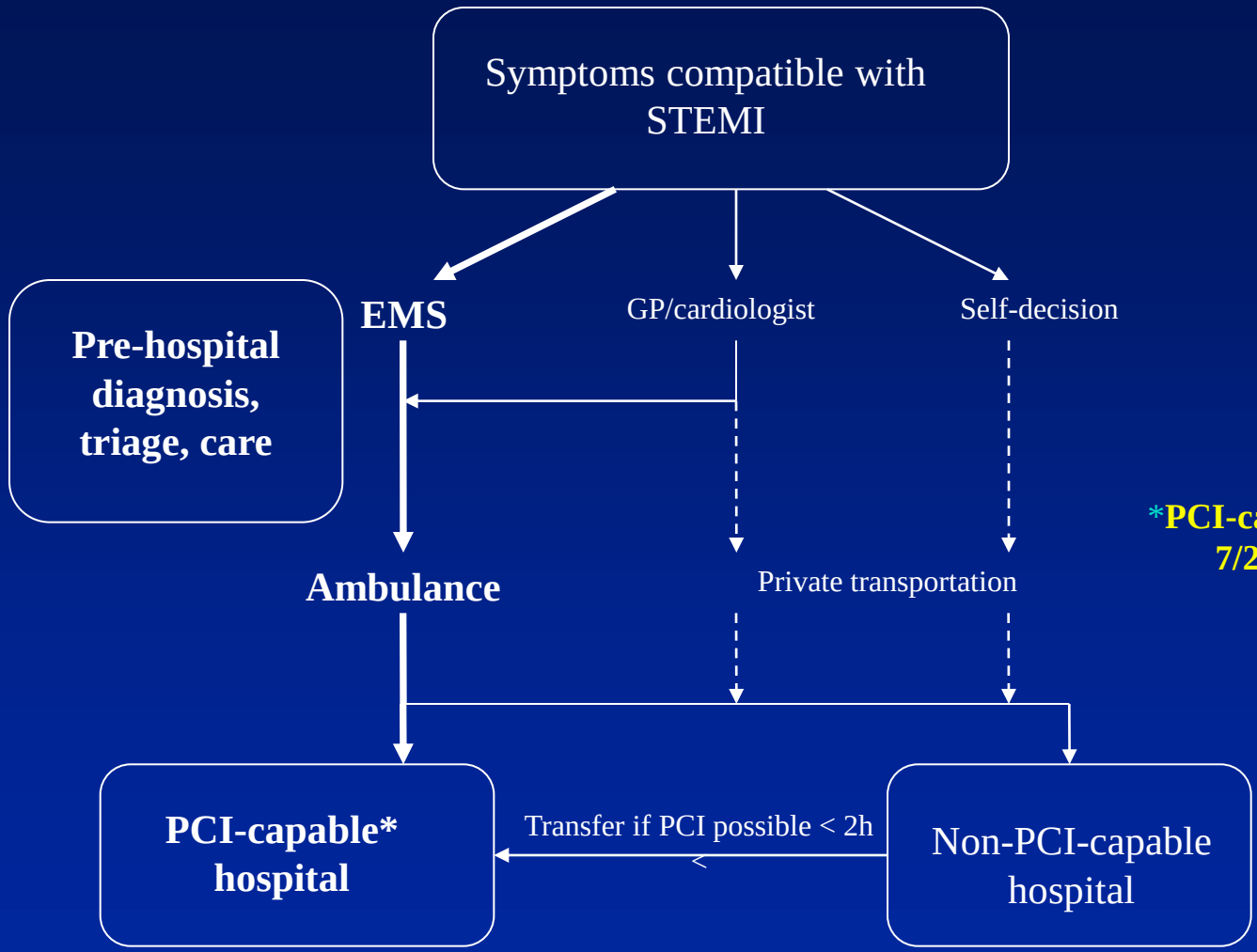
Nallomothu, Antman and Bates
Mortality equipose : >170 min
Am J Cardiol 2004;94:772-774

PCI vs. Lysis: Importance of *PCI-related Delay* in NRMI 2,3,4 Registries



Pinto et al. Circulation, 2006

Pre-hospital Management

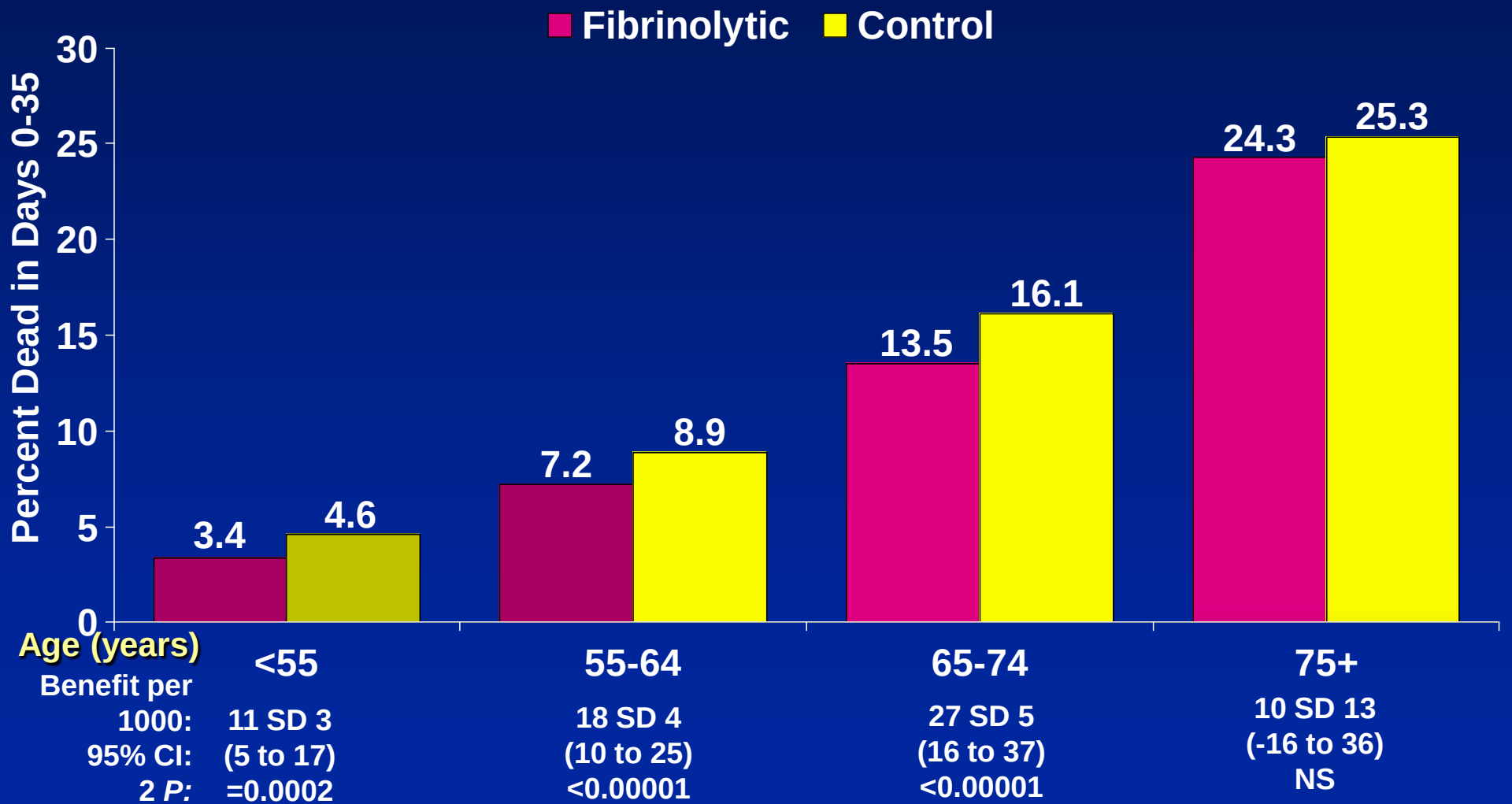


*PCI-capable-hospital = 7/24 service !

EMS: Emergency Medical System; STEMI: Acute ST-segment Elevation Myocardial Infarction; GP: General Practitioner; PCI: percutaneous coronary intervention

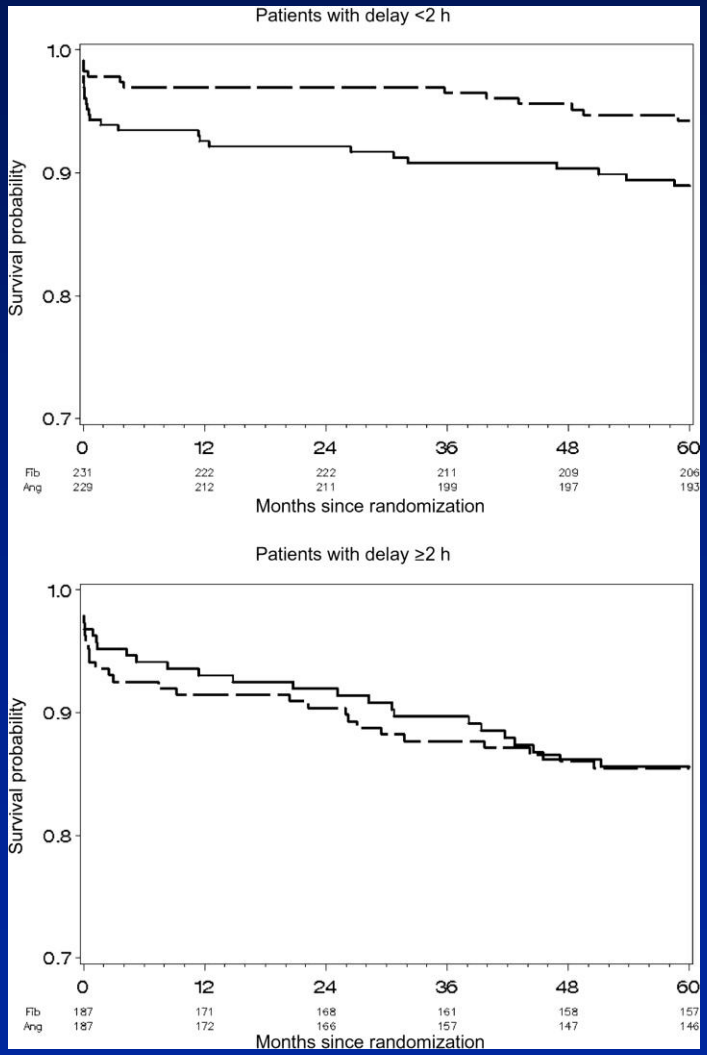
Thick arrows: preferred patient flow; dotted line: to be avoided

Mortality and the Use of Fibrinolytics According to Age



FTT Collaborative Group. *Lancet*. 1994;343:311-322.

CAPTIM: 5 Year Survival Prehospital Thrombolysis vs Primary PCI



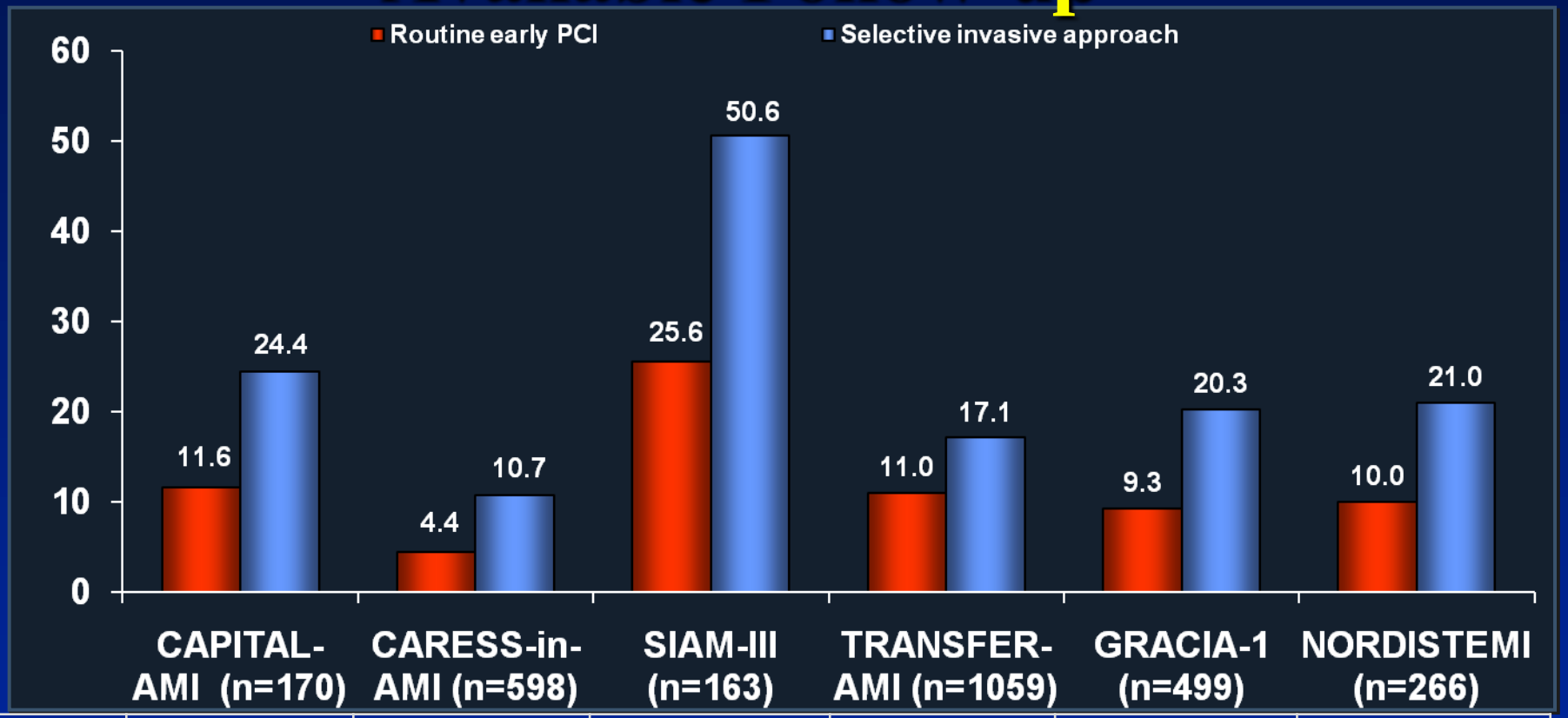
<2 hrs

HR 0.50 (95% CI, 0.25–0.97); *P* = 0.04

>2 hrs

Bonnefoy, E. et al. Eur Heart J 2009 30:1598-1606

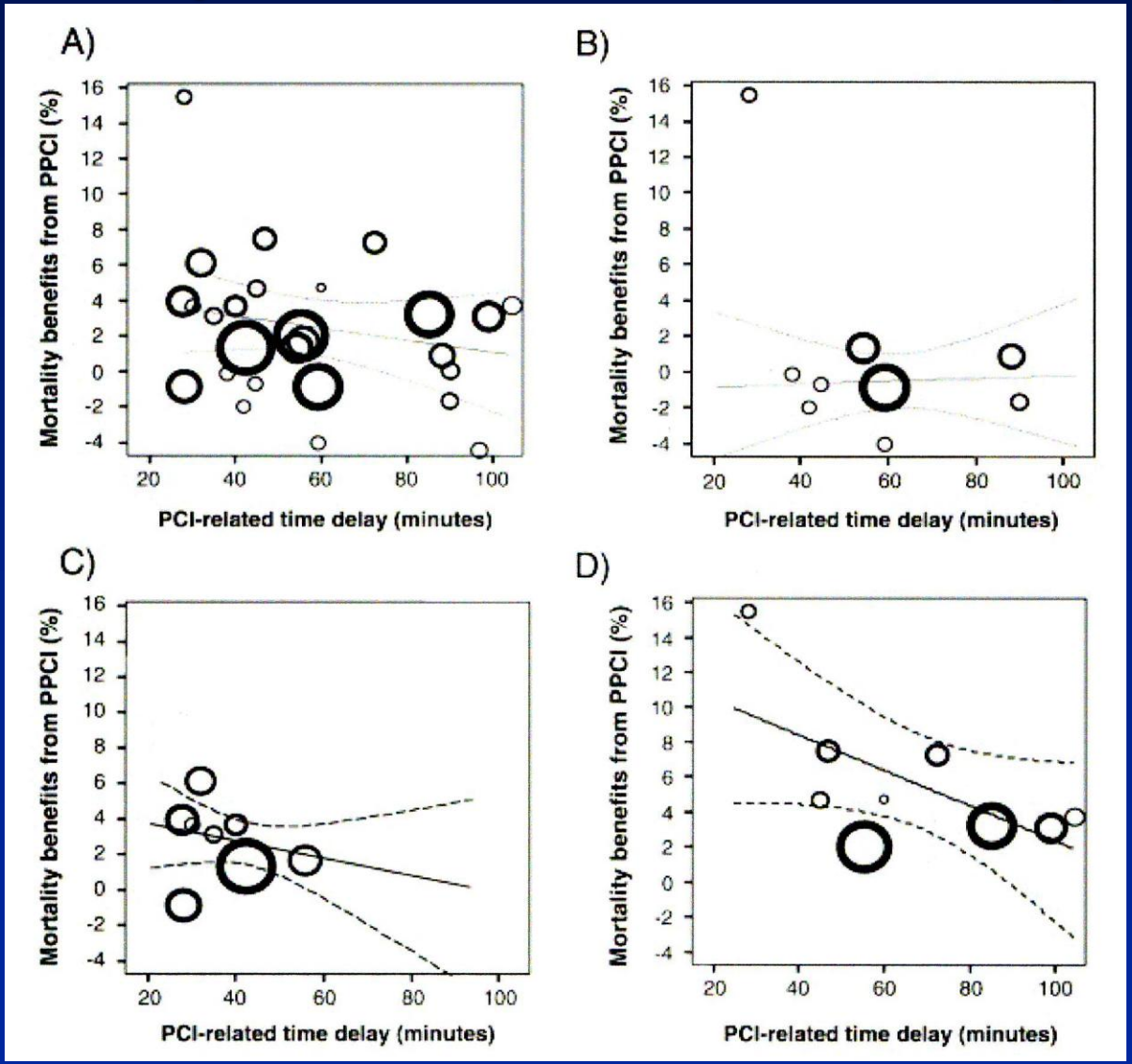
Rate of Ischemic Events at the Available Follow-up



Time from Fibrinolysis to Routine Early PCI (hr)	**1.6**	**2.3**	**3.7**	**3.9**	**16.7**	**2.7**

Impact of PCI-related delay on Mortality Benefit from Primary PCI

All patients
180 min



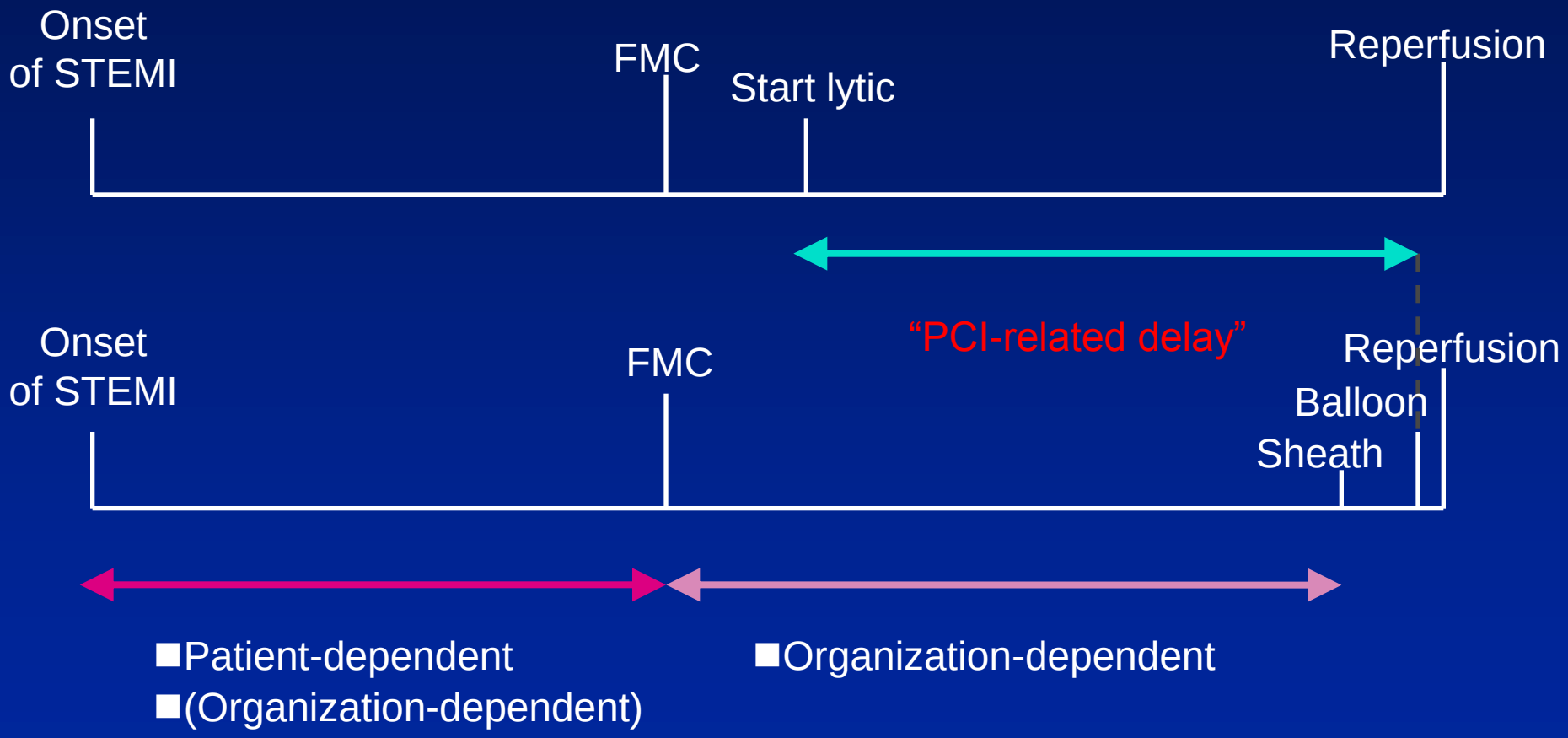
Low risk
no relationship

Medium risk
92 min

High risk
131 min

De Luca et al;Am J Em Med 2009;27:712-719

Reperfusion Therapy: Important Time Lines



FMC:First Medical Contact or
First Diagnostic ECG

Polls at the TCT Website

POLL

Which therapy for STEMI patients would to like to learn more about?

Pharmacologic therapy
20%

Aspiration thrombectomy
38%

Out-of-hospital reperfusion
12%

DES as standard of care
30%

POLL

Fibrinolytic therapy should be given to STEMI patients with:

Transfer delays up to 60 min
22%

Transfer delays up to 90 min
31%

Transfer delays up to 120 min
32%

Always
6%

Never
9%

POLL

Which strategies would you like to compare for STEMI patients?

Facilitated PCI (Y/N)
22%

Thrombolysis vs. primary PCI
20%

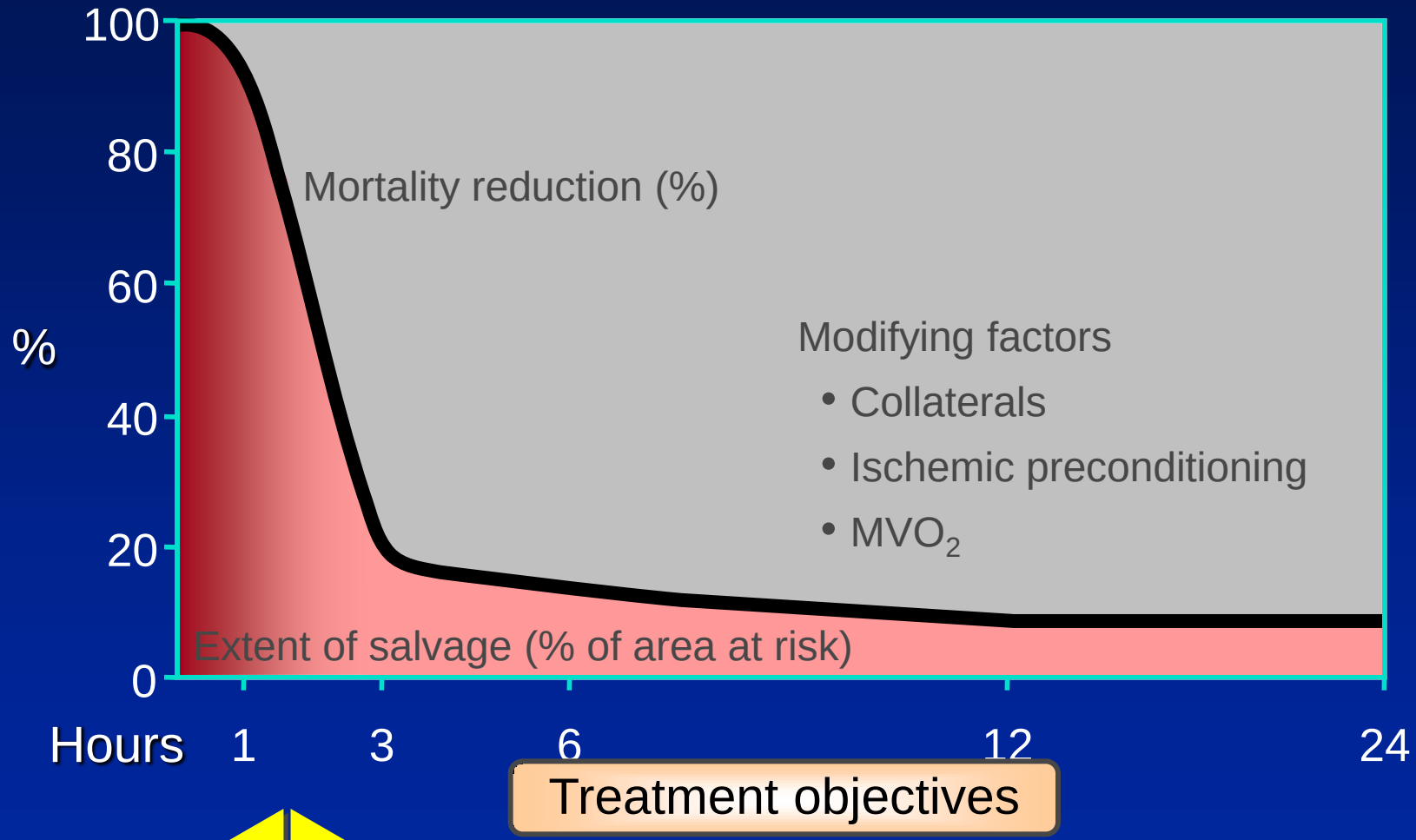
DES vs. BMS
39%

Heparin vs. Bivalirudin
19%

Absolute Reduction in 35-Day Mortality Versus Delay From Symptom Onset to Randomization in Patients With ST-Segment Elevation or LBBB

Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet.* 1994;343:311-322.

Relationship Between Myocardial Salvage and Survival



Gersh B. *JAMA* 2005