

The first 90 Minutes and beyond on Acute Coronary Syndrome

Friday, June 17, 2011
Madrid I ~ 10:55am - 11:40am

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Objectives

- Understand treatment strategies

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Acute Coronary Syndromes:
the first 90 minutes and beyond


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Director, Peripheral Interventions and Advanced Cardiac Imaging
INTEGRIS Baptist Medical Center
Clinical Associate Professor of Medicine
University of Oklahoma

The challenge in diagnosis of coronary heart disease

“The majority of people destined to die suddenly will not have a positive exercise test. The likely reason that they will die suddenly is that only a mild, non-flow - limiting coronary plaque will have been present before the sudden development of an occlusive thrombus.”

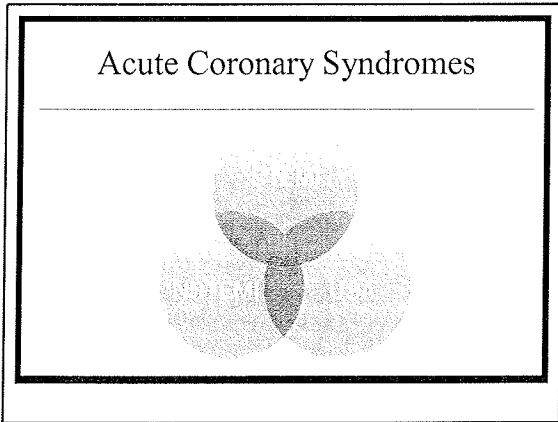
- Stephen Epstein
New England Medical Journal 1989

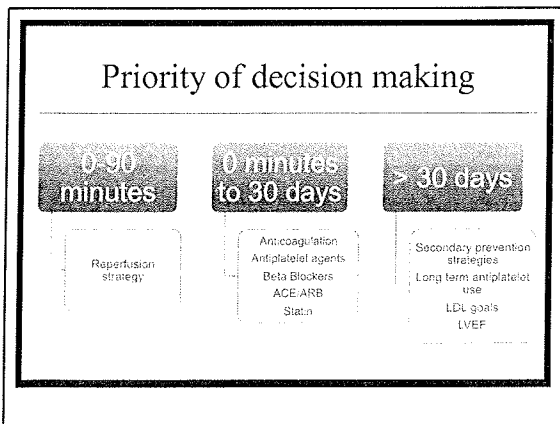
“If you die, it doesn't matter how.”

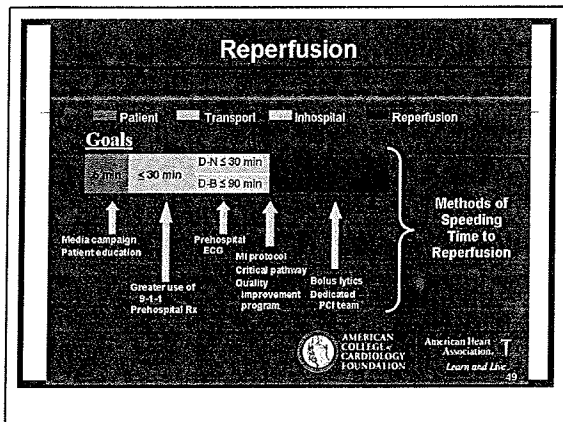


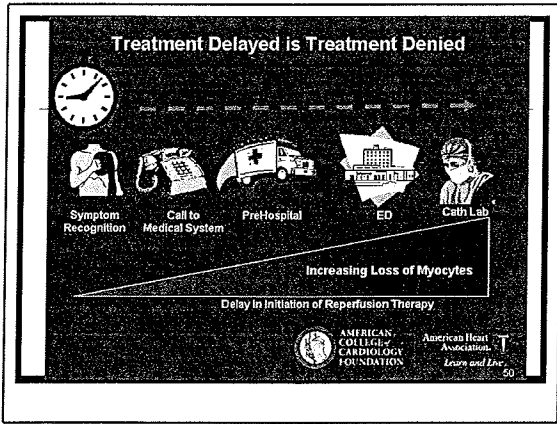
Eric Topol, M.D.

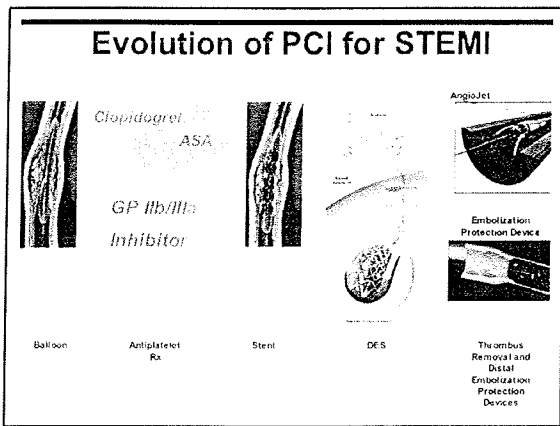
the heart.org









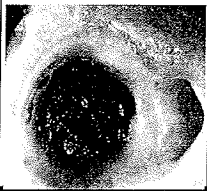


Question #1: Is the thrombus the same in STEMI as in NSTEMI?

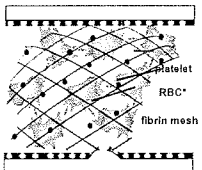
- A. True
- B. False

The Thrombus in STEMI

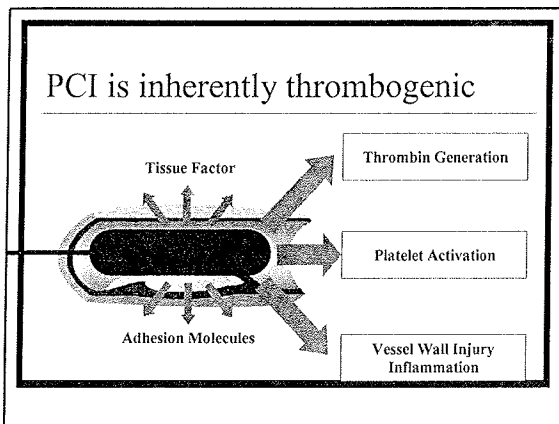
STEMI is generally caused by a completely occlusive fibrin-rich thrombus in a coronary artery

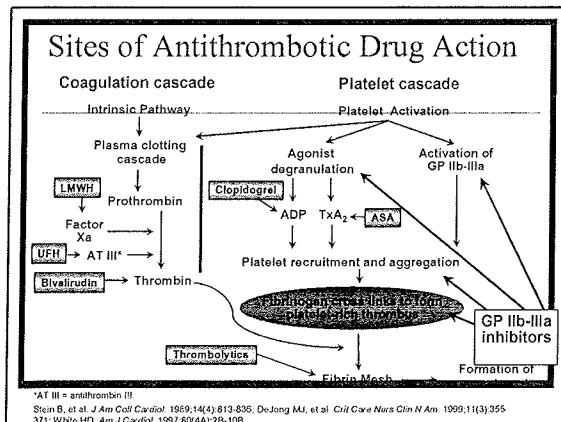


Results from stabilization by fibrin mesh of a platelet aggregate at site of plaque rupture



*RBC = red blood cell. GP IIb/IIIa inhibitors are not indicated for STEMI.
 White HD. Am J Cardiol. 1997;80(4A):28-108
 Van de Wief F. Thromb Haemostaz. 1997;76(1):210-215. Davies MJ. Heart. 2000;85(3):361-368

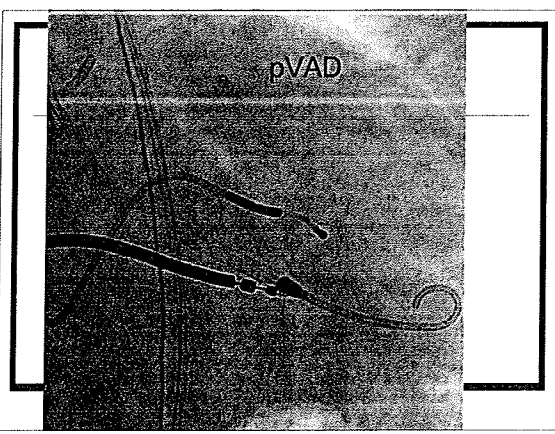




D2B Activity

Activity	Start Time	End Time	Count	Percentage
ED1 Quick Reg		11/13/2008 17:31		0
ED3 Triage Process	11/13/2008 17:31	11/13/2008 17:31	0	0
ED2 to Hospital EKG	11/13/2008 17:31	11/13/2008 17:32	1	1
ED4 Transfer to ED Room	11/13/2008 17:31	11/13/2008 17:35	4	4
ED6 EKG to Cath Crew				
ED6 EKG to Cath Crew	11/13/2008 17:32	11/13/2008 17:41	9	10
EM Set 1	11/13/2008 17:32	11/13/2008 17:46	14	15
CL1 Cath Crew Travel	11/13/2008 17:41	11/13/2008 17:50	9	10
CL2 Patient Pickup	11/13/2008 17:50	11/13/2008 17:53	3	3
CL3 Cardiology Prep		11/13/2008 18:07		30
CL5 PCI Sheath Insertion	11/13/2008 18:07	11/13/2008 18:11	4	4
CL6 PCI Balloon Inflation	11/13/2008 18:11	11/13/2008 18:21	10	50

- ### STEMI management
- Utility of thrombolytics
 - Utility of PCI
 - PCI vs lytics
 - Facilitated PCI
 - "Rescue" PCI
 - Transport to PCI centers
 - Case examples



Fibrinolytic Therapy

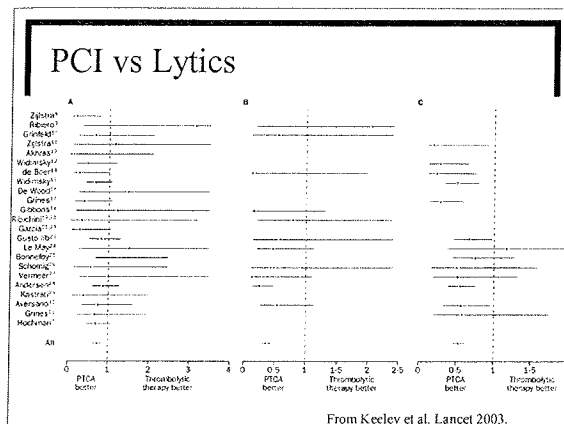
- Reperfusion within 12 hours of symptom onset
 - Increased myocardial salvage
 - Preservation of LV function
 - Improved survival

From the FTT Collaborative Group, Lancet, 1994.

Quantitative Review of PCI vs TL: 23 randomised trials

- 23 trials, 7739 pts eligible for TL with STE
- 76% received fibrin-specific TL
- Stents in 12 trials, IIb/IIIa inhibitors in 8
- D/MI/stroke
- Looked at short-term and long-term outcomes

From Keeley, et al. Lancet 2003.



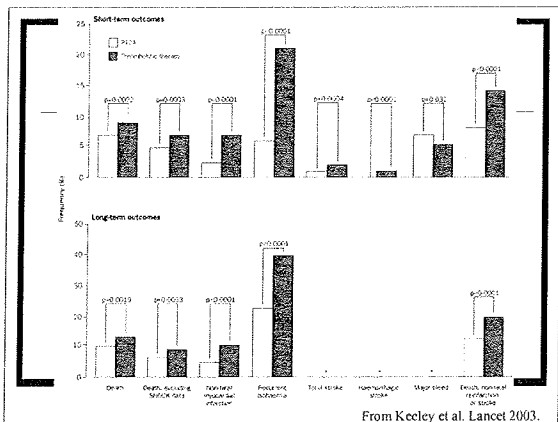


Table. Obstacles to Instituting Primary Percutaneous Coronary Intervention as the Universal Treatment for ST-Segment Elevation Myocardial Infarction

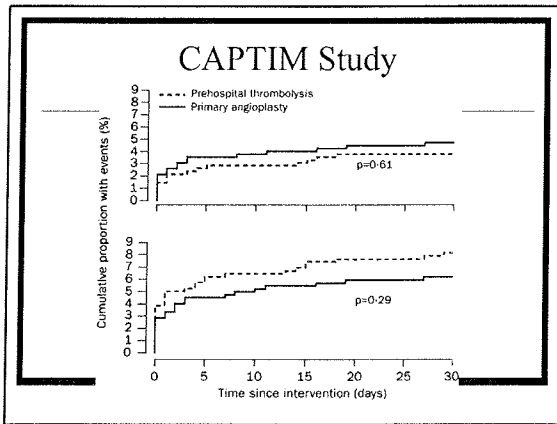
Availability Technical expertise of center and operator Patient subgroups that are not studied in randomized trials Comparisons of primary percutaneous coronary intervention to newer pharmacologic regimens
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From Keeley EC. Annals of Int Med 2004.

Prehospital Thrombolysis

- 840 patients presented within 6 hr of symptoms (STEMI)
- 419 to prehospital lytics
- 421 to PTCA
- All transferred to PCI center
- Composite endpoint (D/RI/Stroke at 30 days)

From the CAPTIM study group. Lancet, 2002.



CAPTIM Study

- 26% of thrombolysis group received rescue PTCA

Endpoint or event	Prehospital fibrinolysis (n=419)	Primary angioplasty (n=423)	p
Death and recurrent ischaemia	57 (13.5%)	41 (9.6%)	0.06
Cardiovascular death	16 (3.8%)	18 (4.3%)	0.88
Recurrent ischaemia	29 (7.2%)	16 (4.0%)	0.09
Severe haemorrhage	2 (0.5%)	8 (2.0%)	0.06
Haemorrhagic stroke	2 (0.5%)	0	0.50
Ischaemic stroke	2 (0.5%)	0	0.50
Cardiogenic shock from randomisation to hospital discharge	10 (2.5%)	20 (4.9%)	0.09
Cardiogenic shock from randomisation to hospital admission	0	9 (2.1%)	0.004

Percentages are calculated as in table 1.

Facilitated PCI

- Low dose TL +/- IIb/IIIa inhibitor before PCI
- Provide pharmacologic reperfusion prior to mechanical revascularization

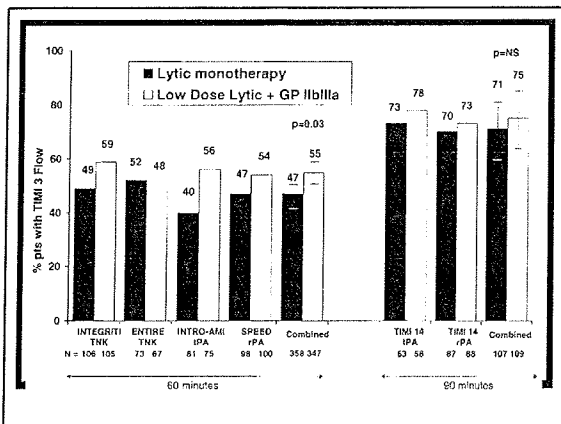
Question #2: Does Facilitated PCI provide clinical benefit over Thrombolytics alone?

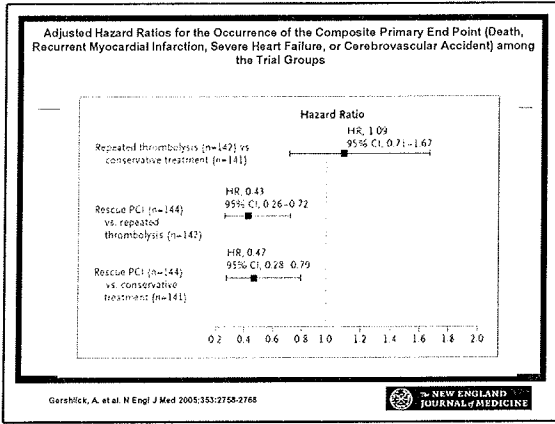
- A. Yes
- B. No

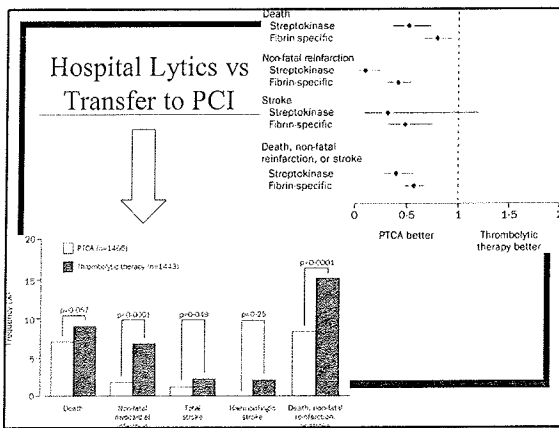
Facilitated PCI: Review of Current Trials

Author	Year	Design	Intervention	Control	Sample Size	Primary End Point	Relative Risk (95% CI)	Number of Events
Wang et al. (2006)	2006	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2007)	2007	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2008)	2008	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2009)	2009	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2010)	2010	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2011)	2011	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2012)	2012	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2013)	2013	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2014)	2014	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2015)	2015	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2016)	2016	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2017)	2017	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2018)	2018	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2019)	2019	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2020)	2020	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2021)	2021	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2022)	2022	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2023)	2023	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2024)	2024	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100
Wang et al. (2025)	2025	Randomized	Facilitated PCI	Thrombolysis	1000	30-day mortality	0.85 (0.72-1.00)	100

From Keeley et al. Lancet 2006







Transport to PCI vs Lytics

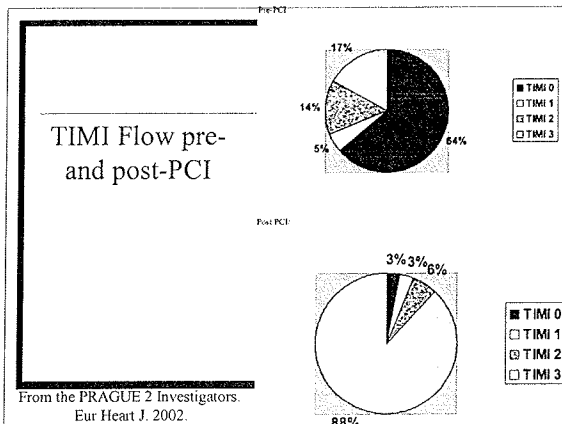
- PRAGUE-2
- DANAMI-2
- Air-PAMI

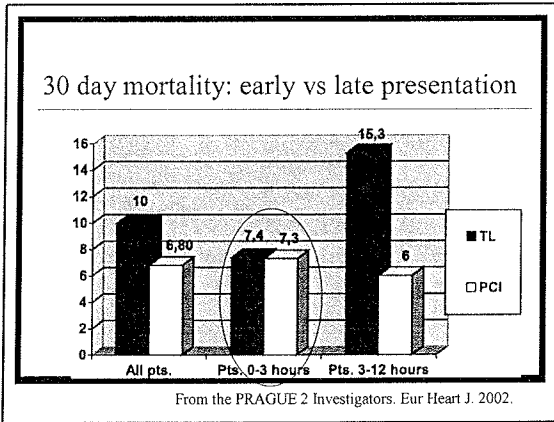
Question #3: If a patient presents to an ER 1-2 hours away and > 3 hours after symptoms started with STEMI, the best strategy is?

- 1. Give thrombolytics and transfer
- 2. Give thrombolytics and wait to see if reperfusion occurs, then transfer
- 3. Transfer to PCI center on heparin and IIB/ IIIA
- 4. Give ½ dose lytics and IIB/IIIA and transfer to PCI center

PRAGUE 2

- 850 pts w/ STEMI
- Presentation <12 hr from symptom onset
- 421-TL; 429-PCI
- Primary endpoint-30 day mortality
- Secondary endpoints: D/MI/stroke





DANAMI II

- 1572 pts w/ STEMI
- Primary endpoint-D/MI/Stroke at 30 days
- 95% of pts were transferred to PCI center within 2 hours

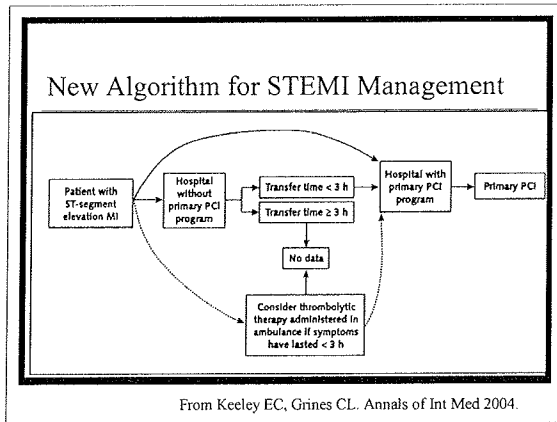
Andersen, H. et al. N Engl J Med 2003;349:733-742

Clinical Outcome at 30 Days

Table 3. Clinical Outcome at 30 Days.

Outcome	Referral Hospitals			Invasive-Treatment Centers			All Hospitals		
	Fibrinolytic Group (N=567)	Angioplasty Group (N=567)	p Value	Fibrinolytic Group (N=270)	Angioplasty Group (N=273)	p Value	Fibrinolytic Group (N=742)	Angioplasty Group (N=790)	p Value
Dead	41 (8.1)	37 (6.5)	0.20	13 (4.9)	15 (6.7)	0.72	41 (7.8)	52 (6.6)	0.35
Reinfarction	35 (6.2)	11 (1.9)	<0.001	14 (6.4)	2 (0.9)	0.002	49 (6.3)	13 (1.6)	<0.001
Disabling stroke	11 (2.0)	9 (1.6)	0.64	5 (2.3)	0	0.02	16 (2.0)	9 (1.1)	0.15
Composite end point	30 (14.7)	48 (8.3)	0.032	27 (12.3)	15 (6.7)	0.05	107 (13.7)	63 (8.0)	<0.001

Andersen, H. et al. N Engl J Med 2003;349:733-742



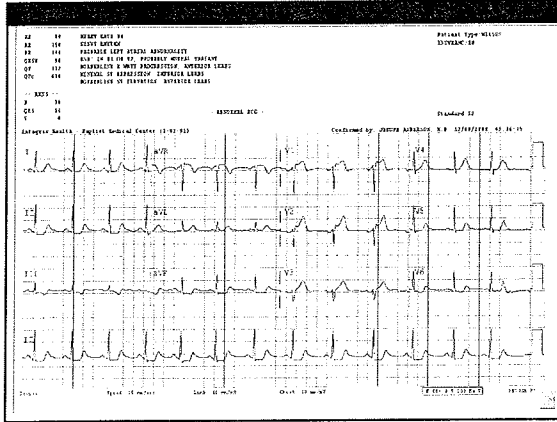
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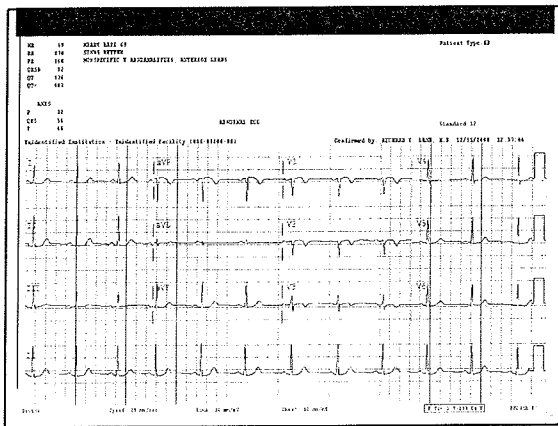
- 1. Give thrombolytics and transfer
- 2. Give thrombolytics and wait to see if reperfusion occurs, then transfer
- 3. Transfer to PCI center on heparin and IIB/ IIIA
- 4. Give ½ dose lytics and IIB/IIIA and transfer to PCI center

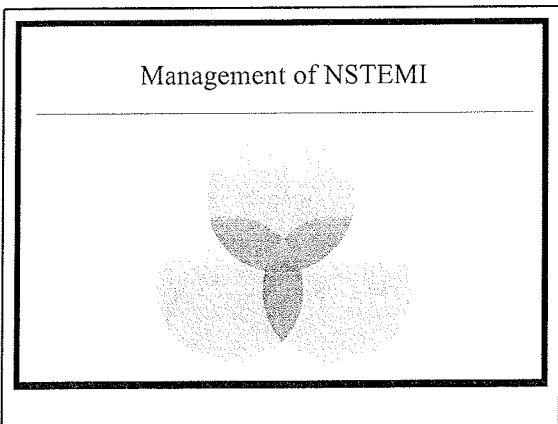
Adjunctive Therapy

- Meta-analysis of 6 trials of 931 STEMI pts
- TIMI III flow demonstrated more with early administration of GP IIb/IIIa
- 28% reduction in mortality from 4.7% to 3.4% with early administration (p=NS)

JAMA
Montalescot et al. JAMA 2004







ACC/AHA Treatment Recommendations for the Long-term Management of ACS

ACS (UA/NSTEMI) patients

Medical Management **Cath lab**

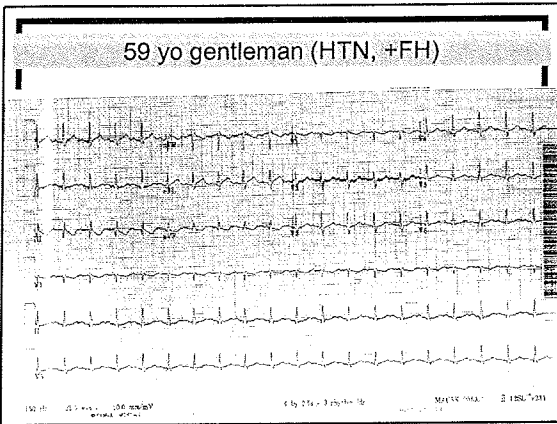
Medical Management **PCI (with or without stent)** **CABG†**

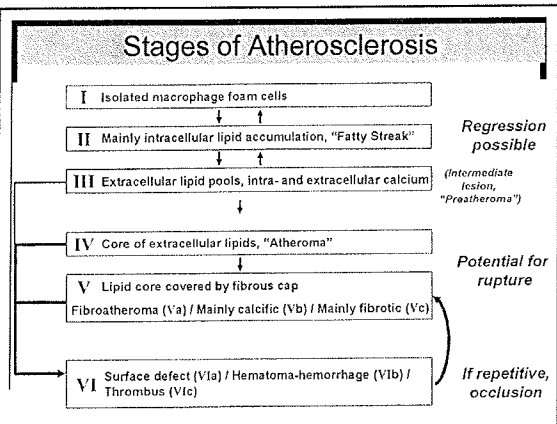
Long-term management

1. Clopidogrel
2. ASA
3. Beta-blocker
4. ACE inhibitor
5. Statin

*UA/NSTEMI: aspirin 81 mg daily; clopidogrel 75 mg once daily; aspirin 81 mg once daily + clopidogrel 75 mg once daily (if not on aspirin)
 †PCI: aspirin 81 mg daily; clopidogrel 75 mg once daily; aspirin 81 mg once daily + clopidogrel 75 mg once daily (if not on aspirin)
 ‡ASA: aspirin 81 mg daily; clopidogrel 75 mg once daily; aspirin 81 mg once daily + clopidogrel 75 mg once daily (if not on aspirin)
 §Statin: atorvastatin 40 mg daily or simvastatin 40 mg daily


18





Antiplatelet and Anticoagulant Agents in the Setting of NSTEMI ACS

Therapeutic Goal: Inhibit platelet aggregation to prevent distal embolization with microvascular occlusion



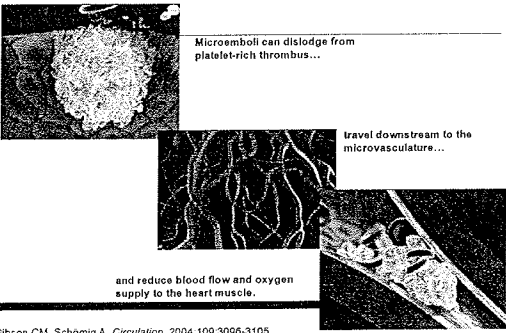
Aspirin
Thrombolytics and anticoagulants each block a single pathway (thromboxane A2, ADP, and thrombin respectively) to inhibit platelet activation.

GP IIb/IIIa inhibitors
Inhibitors prevent platelet aggregation and improve perfusion to the microvasculature.

Aspirin
Aspirin blocks inflammatory activities that could further destabilize plaque.

White HD. Am J Cardiol. 1997;80(4A):2B-10B; DeJong MJ, et al. Crit Care Nurs Clin North Am. 1999;11(5):355-371

Mechanism of Microembolization



Microemboli can dislodge from platelet-rich thrombus...

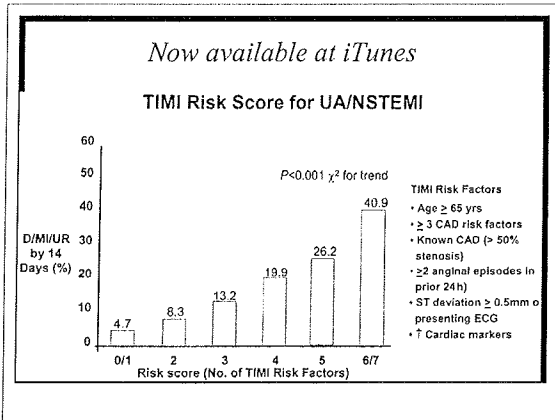
travel downstream to the microvasculature...

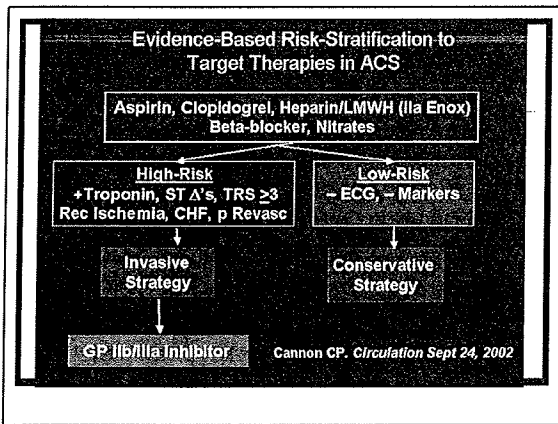
and reduce blood flow and oxygen supply to the heart muscle.

Gibson CM, Schömig A. Circulation. 2004;109:3096-3105

Treatment strategies

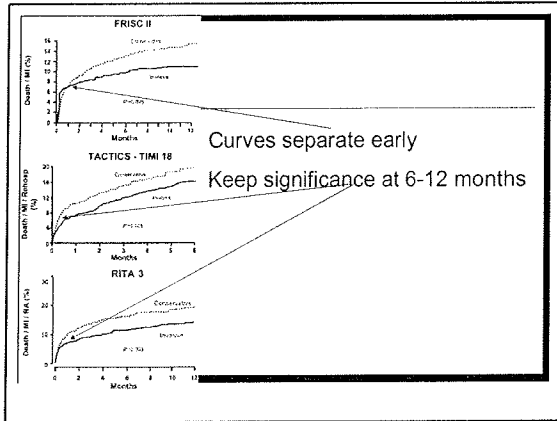
- Plasminogen activators lyse fibrin-rich areas (red clot). They do not eliminate the platelet core
- Paradoxically, fibrinolysis exposes thrombin, which is a potent platelet activator
- GP IIb/IIIa antagonists attack white clot

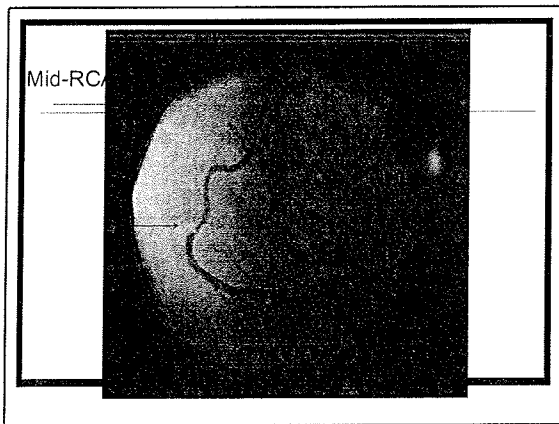


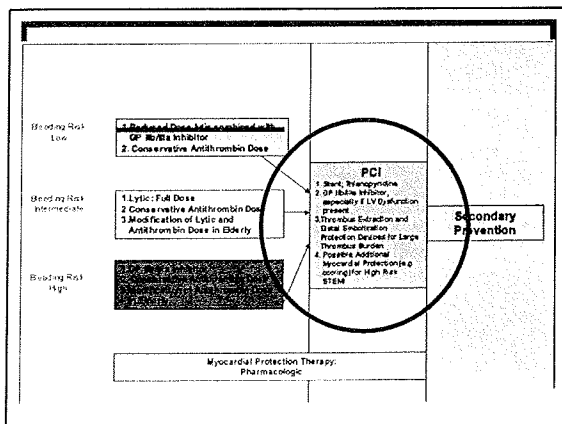


Why an early invasive strategy?

- Disease process better understood
- Safety of cardiac catheterization
- Shorter hospital stays
- Definition of anatomy...plavix use
- Better data from the latest trials







Question #4: Do IIB/IIIA inhibitors show clinical benefit in all patients with ACS?

- Yes
- No

The Contenders: GP IIb/IIIa inhibition

	Abciximab	Tirofiban	Eptifibatid	Lamifiban
Structure	Monoclonal antibody	Synthetic non-peptide	Synthetic cyclic peptide	Peptidomimetic
Molecular weight (Dalton)	47,615	495	832	468
Integrin specificity				
α _v β ₃	++	Specific	Specific	Specific
α _{IIb} β ₃	+	-	-	-
α _{IIb} β ₁	+	-	-	-
Inhibition	Noncompetitive	Competitive	Competitive	Competitive
Binding	Permanent	Reversible	Reversible	Reversible
Availability for receptor	High	Low	Low	Low
Plasma t _{1/2}	Very short	2 hours	2.5 hours	2.5 hours
Recovery of platelet function	24-48 hours	4-8 hours	>4 hours	4-8 hours
Antigenicity	Present	Absent	Absent	Absent
Recommended dosage				
Bolus	0.25 µg/kg	25 µg/kg	180 µg/kg × 2	500 µg
Infusion	0.125 µg/kg/min	0.2 µg/kg/min	2 µg/kg/min	1-2 µg/min

The Facts

- 31,402 UA/ NSTEMI pts
- 5847 underwent early invasive strategy (all of the benefit of IIb/IIIa confined to this group)
- + troponin 16,000 (-11% death/MI)
- - troponin (no benefit)
- "Busto IV"

**2007 ACC/AHA UA/NSTEMI Guidelines
 Antiplatelets and Anticoagulants: PCI**

	I	IIa	IIb	III
A				
A				
A				
B				
B				

Continue aspirin

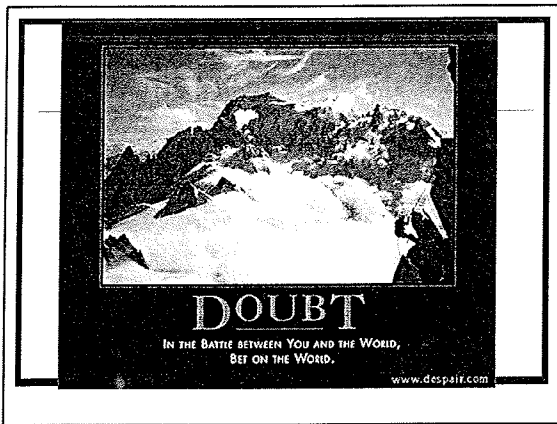
Clopidogrel if not started before diagnostic cath

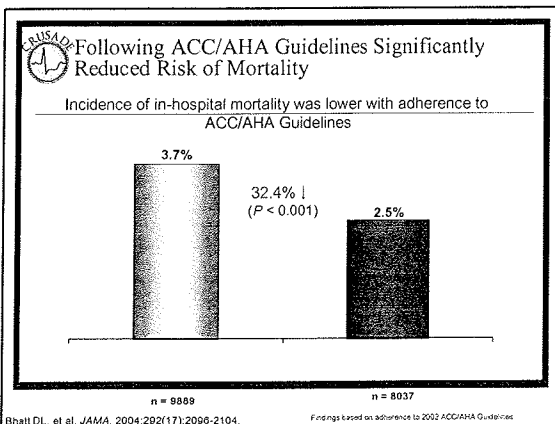
GP IIb-IIIa inhibitor if not started before diagnostic angiography for troponin-positive and other high-risk patients

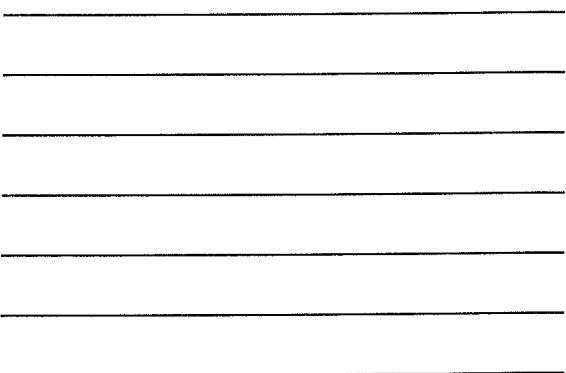
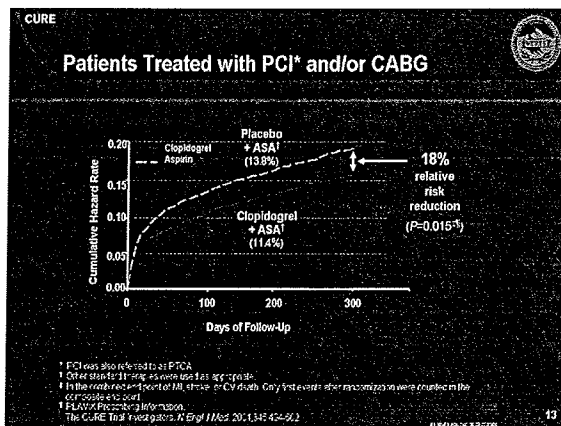
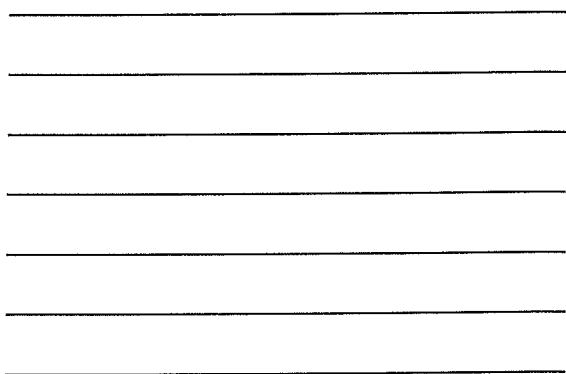
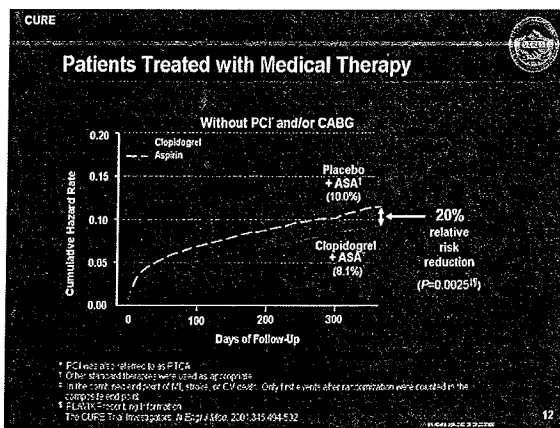
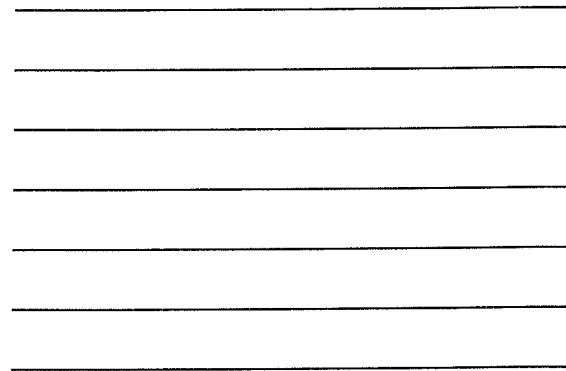
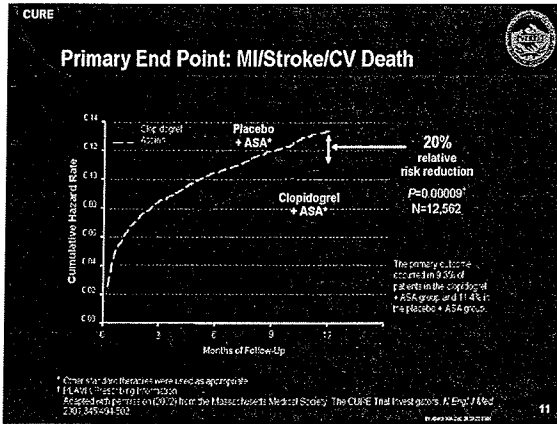
At least 300 mg of clopidogrel administered at least 6 hours prior to PCI if bivalirudin is selected as the anticoagulant and GP IIb-IIIa is omitted

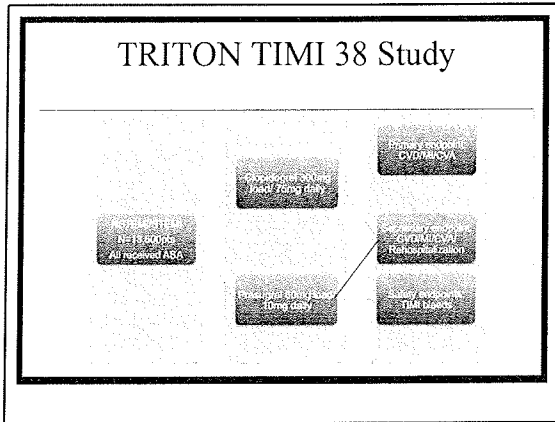
Discontinue anticoagulant therapy after PCI for uncomplicated cases

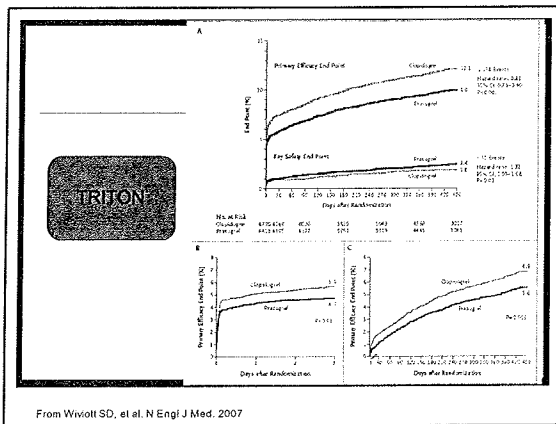
Anderson JL, et al. Circulation 2007;116:e148-e304











From Wiviott SD, et al. N Engl J Med. 2007

TRITON Safety Endpoints

End Point	Prasugrel n = 10,135	Clopidogrel n = 10,135	Hazard Ratio for Prasugrel (95% CI)	P Value	P Value for Interaction
History of stroke or TIA					
Death from cardiovascular causes, nonfatal MI, or vascular stroke (primary efficacy end point)	47/262 (19.1)	35/256 (14.4)	1.37 (0.89-2.13)	0.15	
Non-CABG-related TIMI major bleeding	14/257 (5.0)	6/252 (2.9)	2.46 (0.94-6.42)	0.06	
Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related vascular TIMI major bleeding	37/262 (27.0)	30/256 (16.0)	1.54 (1.02-2.32)	0.04	

From Wiviott SD, et al. N Engl J Med. 2007

2011 UA/NSTEMI Guideline Focused Update

ASA + Clopidogrel or Prasugrel + DAPT therapy with or without PCI

Ticagrelor was not FDA approved at the time of update

From the 2011 ACCF/AHA focused update of the guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. J Am Coll Cardiol. 2011

Ticagrelor

- Cyclopentyltriazolopyrimidine: not a prodrug
- Binds reversibly to P2Y12 receptor
- Releases RBC adenosine
- Onset of action and platelet inhibition similar to prasugrel
- Platelet function 48hr after D/C
- BID dosing; no resistance

PLATO Study

NSTEMI/STEMI
N= 18,624 pts

Clopidogrel 300mg load 75mg daily	Ticagrelor 180mg load 90mg bid
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6-12 month exposure

Primary endpoint: CV death/MI/CVA
Primary safety endpoint: total major bleeding
