ACS NSTEMI/UAP

השתלמות מתמחים בקרדיולוגיה 2010

Alex Blatt, MD

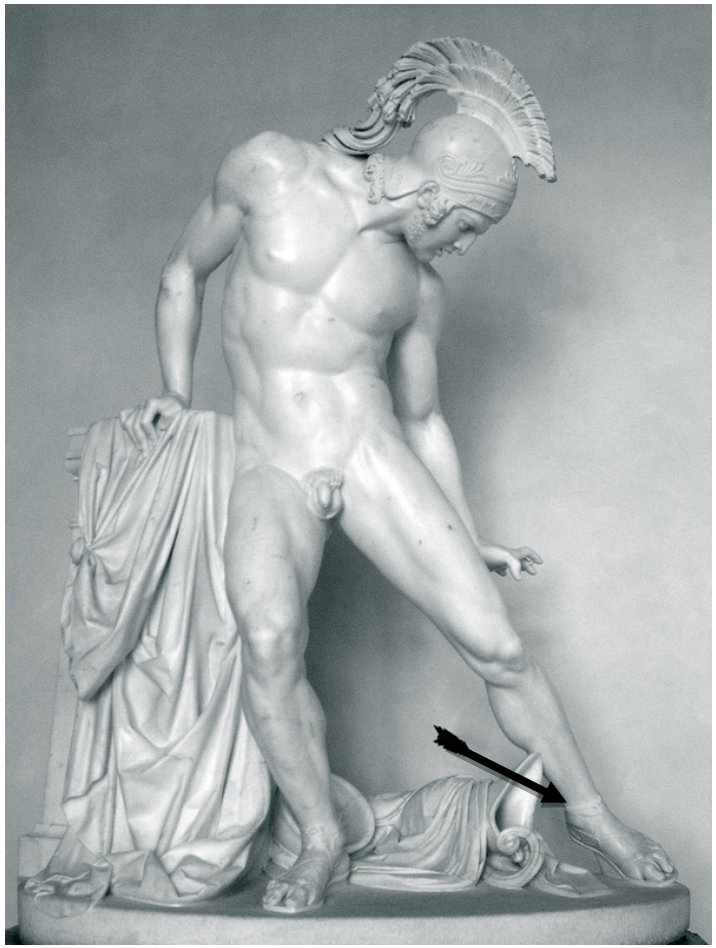
ICU Assaf Harofeh MC

Tel Aviv University

Learning Objetives

- ✓ Understand the linkage between pathophysiology and treatment
- ✓ Discussing the leading literature in a critisizing manner.
- ✓ Highlighting the landmark trials and review last year's articles
- ✓ Help u cross the Israeli certification exam successfully !

דגש



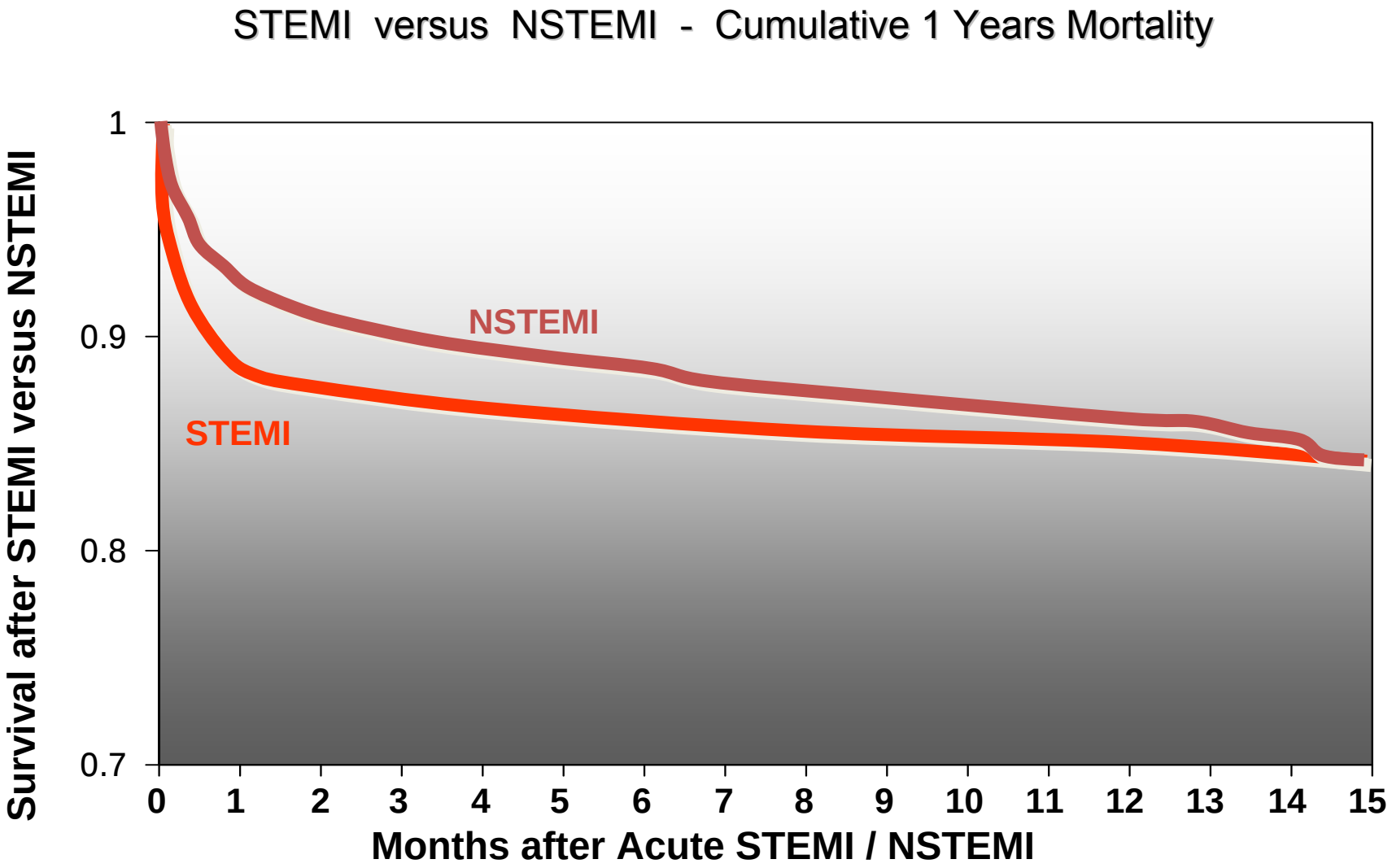
“Follow the Achilles arrow”

Agenda

1. Epidemiology
2. Pathphysiology
3. Diagnosis and Risk Assessment
4. Management:
    - 4.1 Medical therapy
    - 4.2 Invasive vs. Conservative approach
    - 4.3 Low risk patients
5. Complications

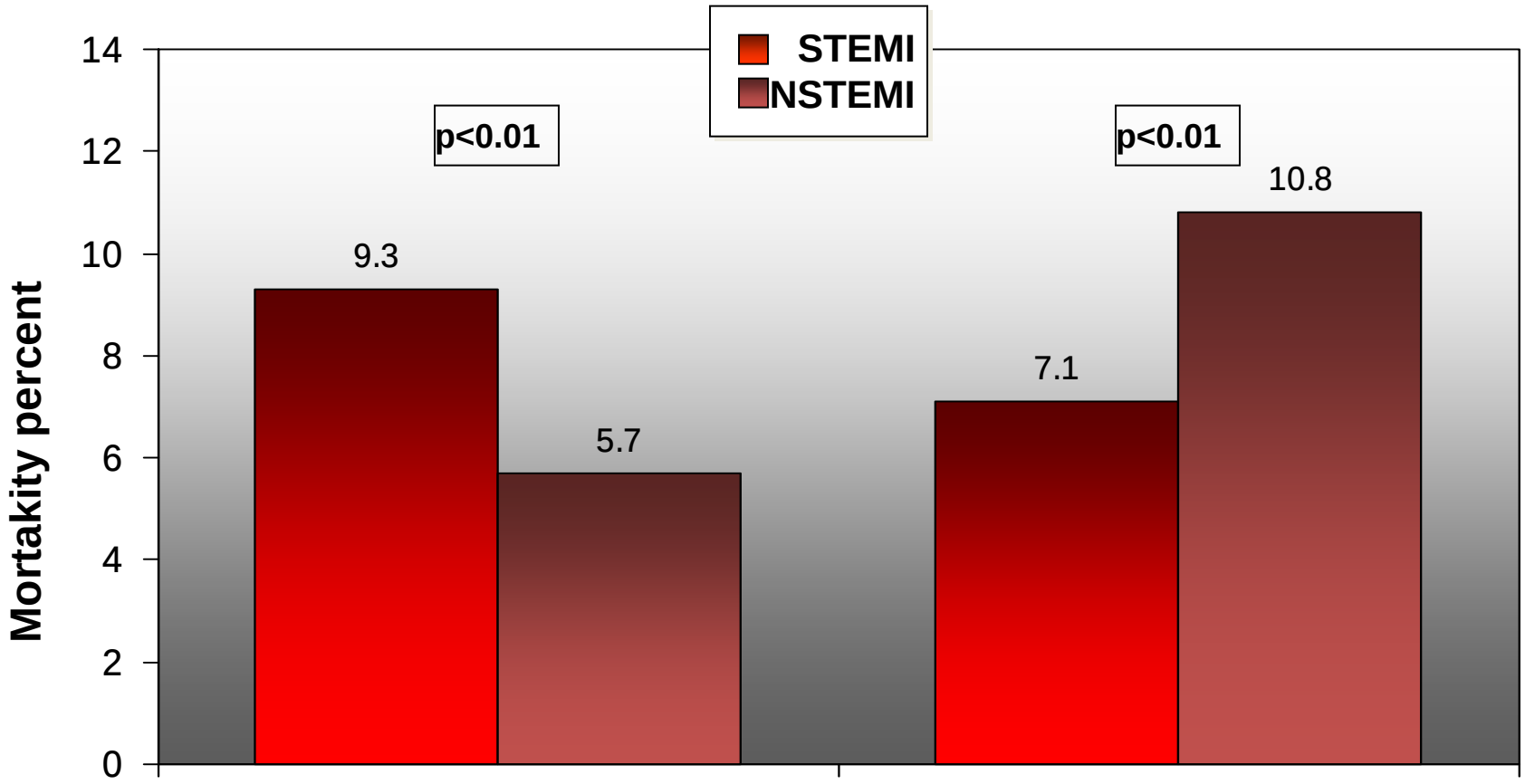
1. Epidemiology

Trends and prognosis in NSTE-ACS



STEMI versus NSTEMI

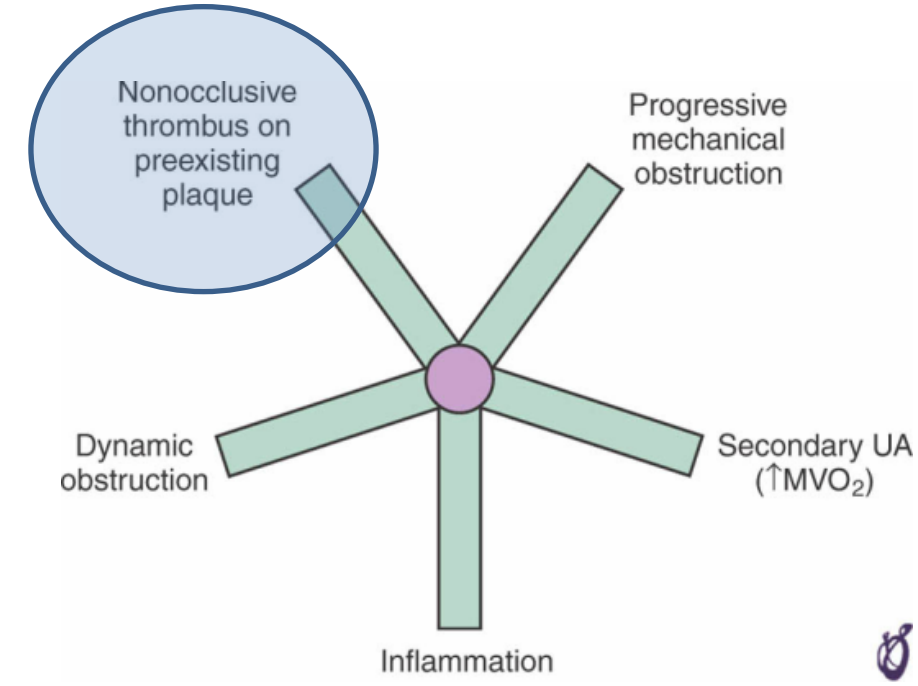
Hospital vs 1-Year-Mortality

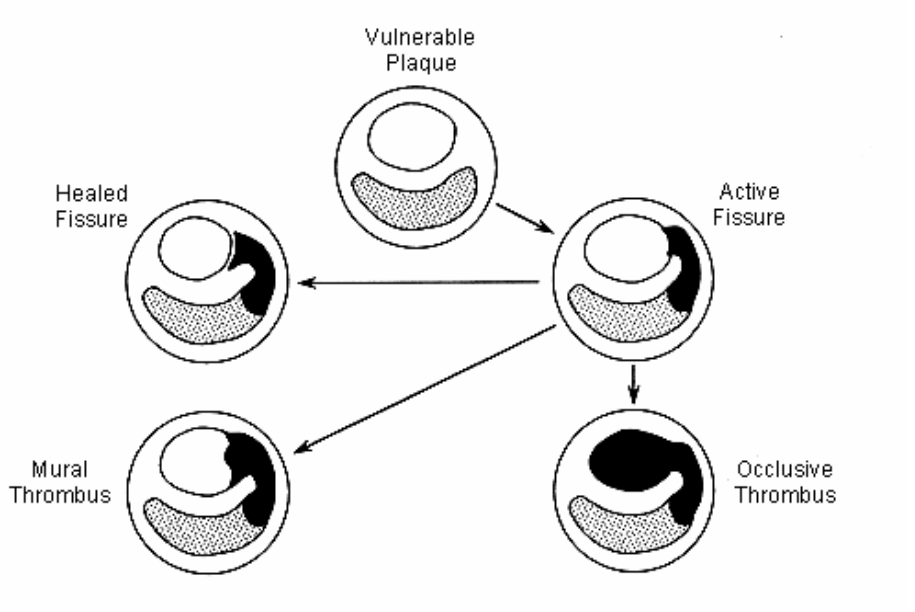


2. Phathophysiology

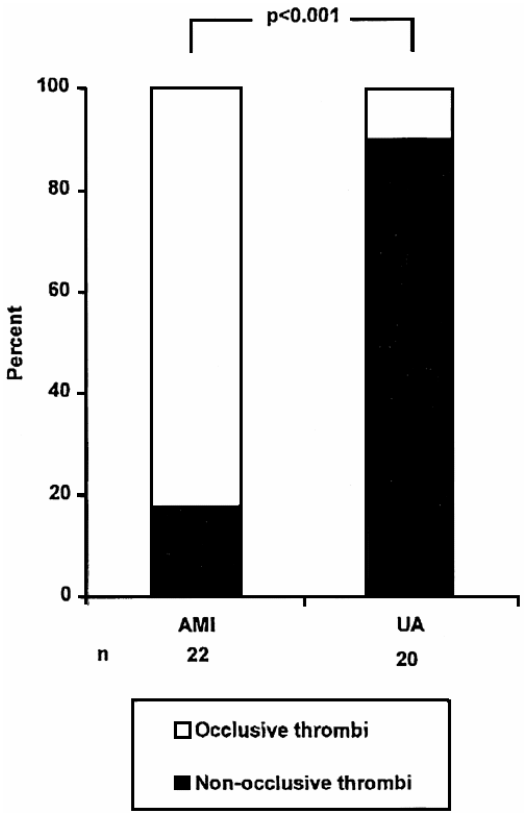
Phathophysiology

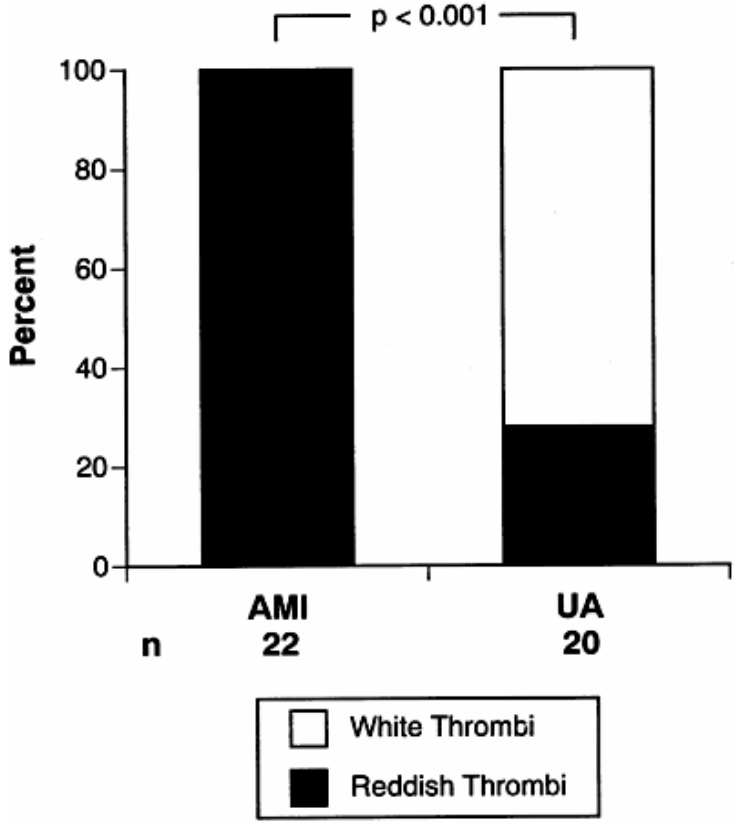
Atherothrombosis





Angioscopy Observation





Myocardial Infarction Pathogenesis II

Vulnerable Plaque

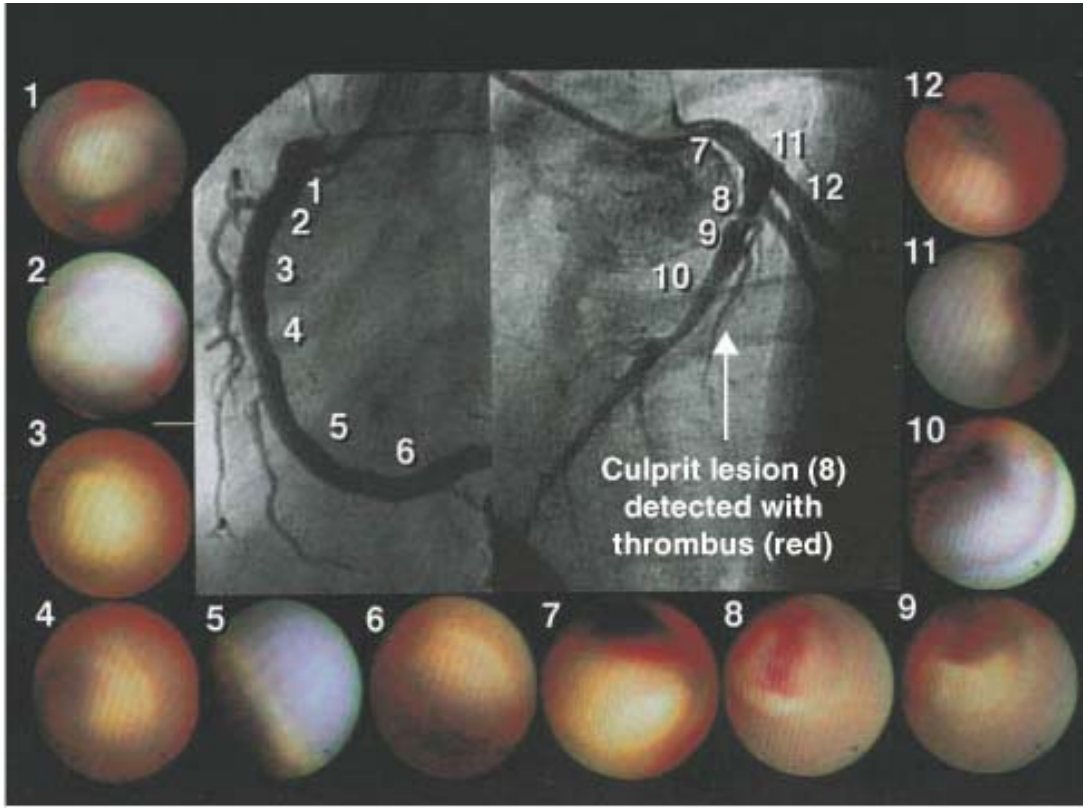
- ✓ Plaque contents: thin fibrous cap, lipid rich core
- ✓ Intraluminal mechanical forces
- ✓ Active matrix metalloproteinases

Vulnerable Patient

- ✓ Active smoking
- ✓ Inflammation
- ✓ Sympathetic tone
- ✓ Catecholamines

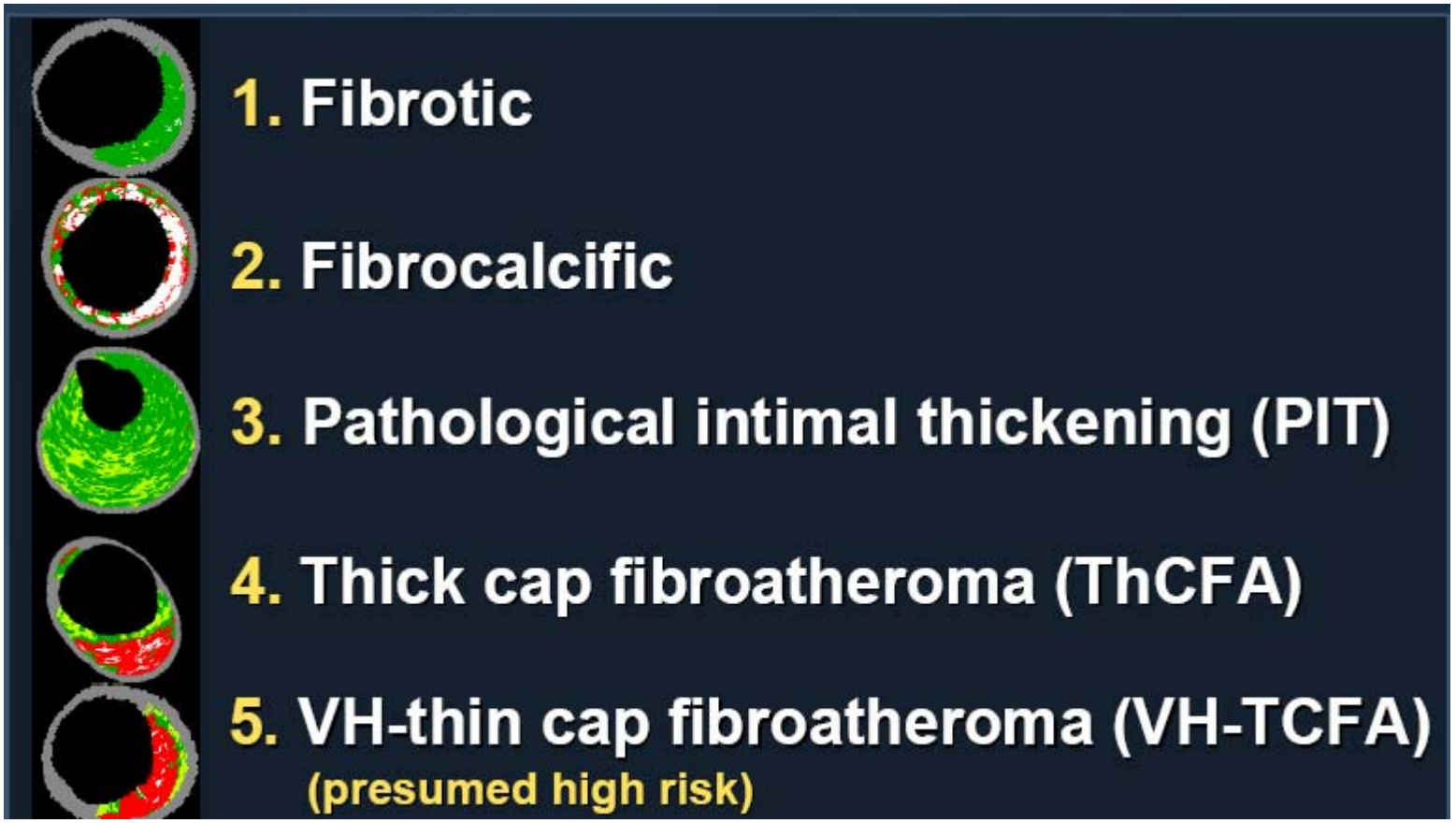
Atherothrombosis

Vulnerable Plaque



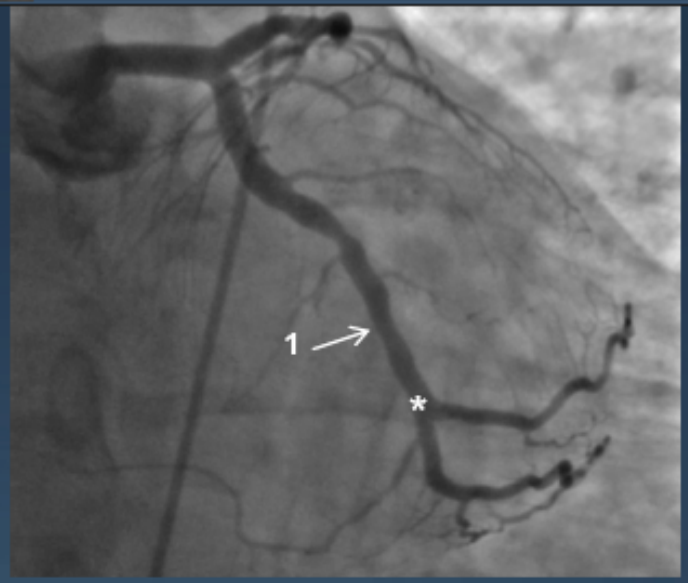
Multiple active plaque lesion coexisting with the culprit lesion

Virtual histology intravascular ultrasound analysis of non-culprit attenuated plaques detected by grayscale intravascular ultrasound in patients with acute coronary syndromes.



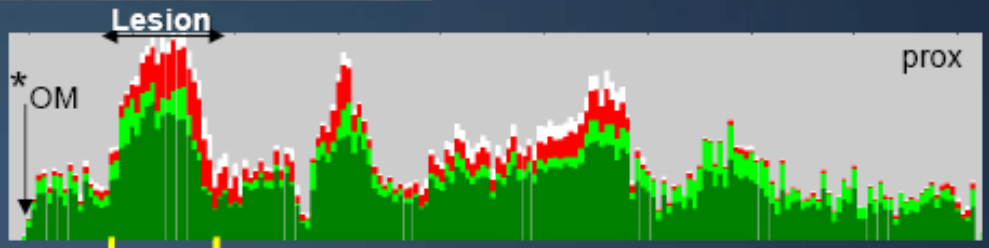
PROSPECT trial, Am J Cardiol. 2010 Jan 1;105(1):48-53.

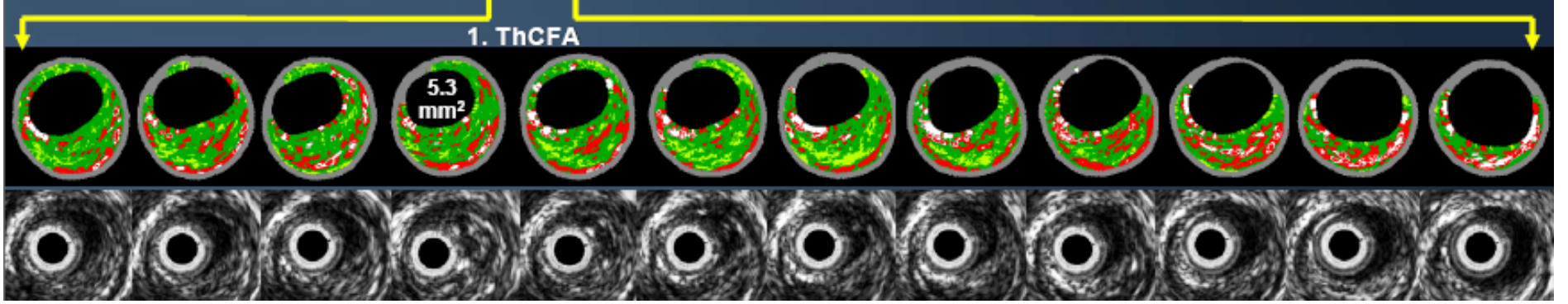
PROSPECT 82910-012: Index 2/13/06



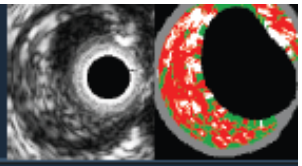
Baseline PLCX

QCA: RVD 2.82 mm,
DS 28.6%, length 6.8 mm
IVUS: MLA 5.3 mm²
VH: ThCFA





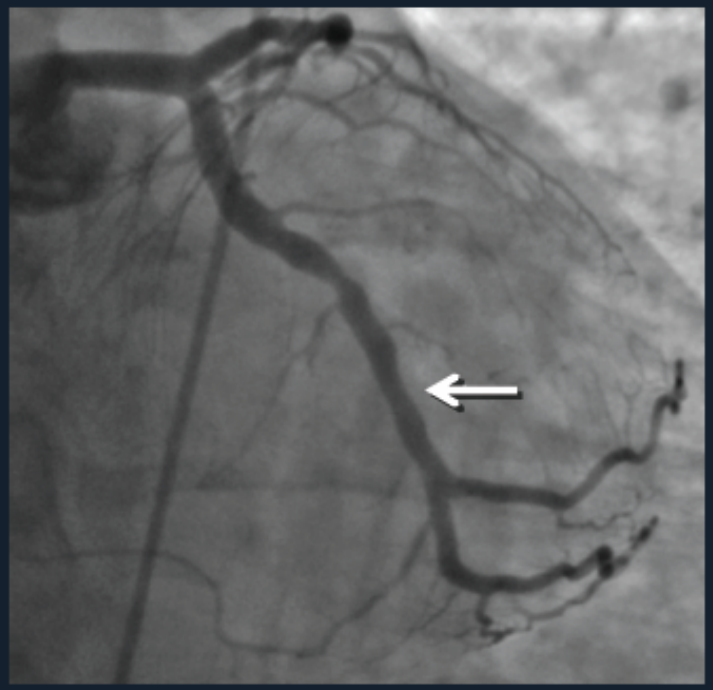
PROSPECT 82910-012: 52 yo♂



2/13/06: NSTEMI, PCI of MLAD

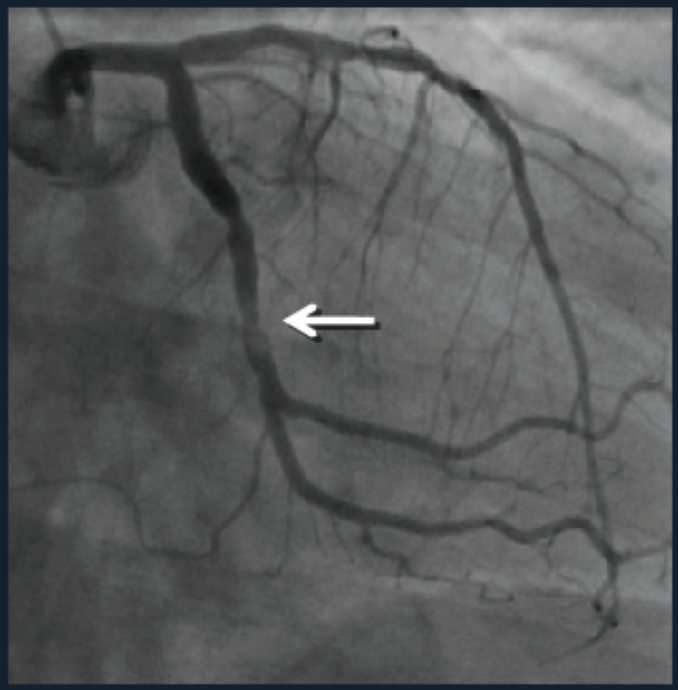
2/6/07 (51 weeks later): NSTEMI attributed to LCX

Index 2/13/06



QCA PLCX DS 28.6%

Event 2/6/07

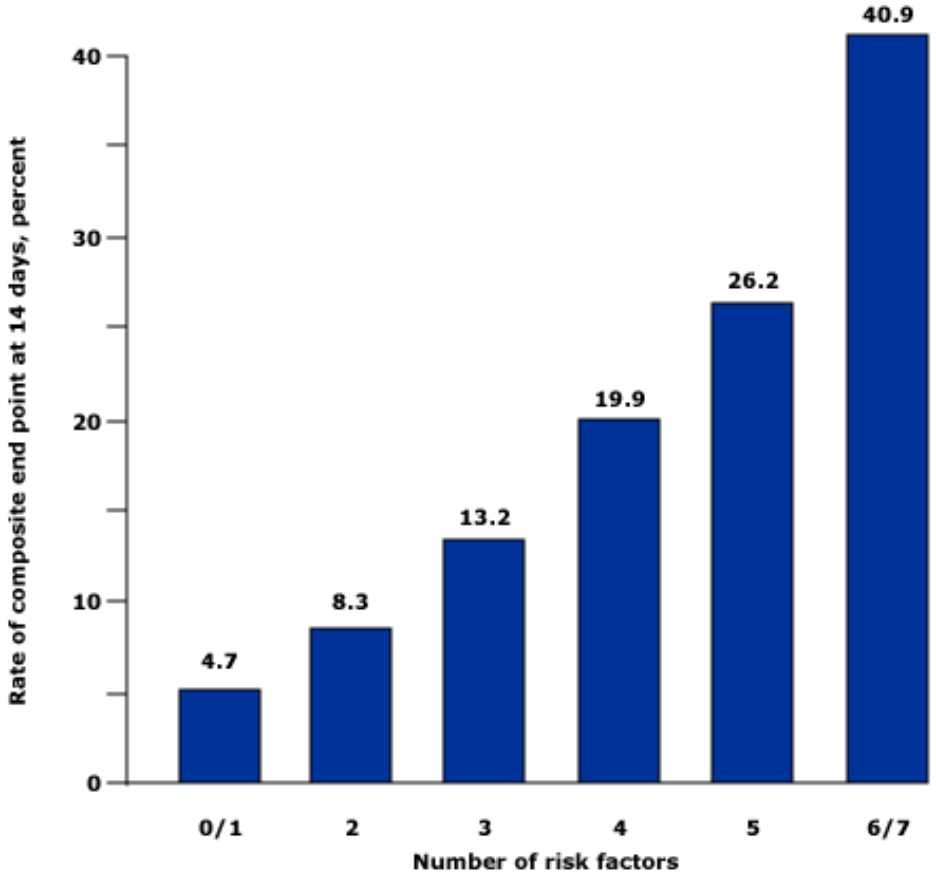


QCA PLCX DS 71.3%

3. Diagnosis and Risk Assessment

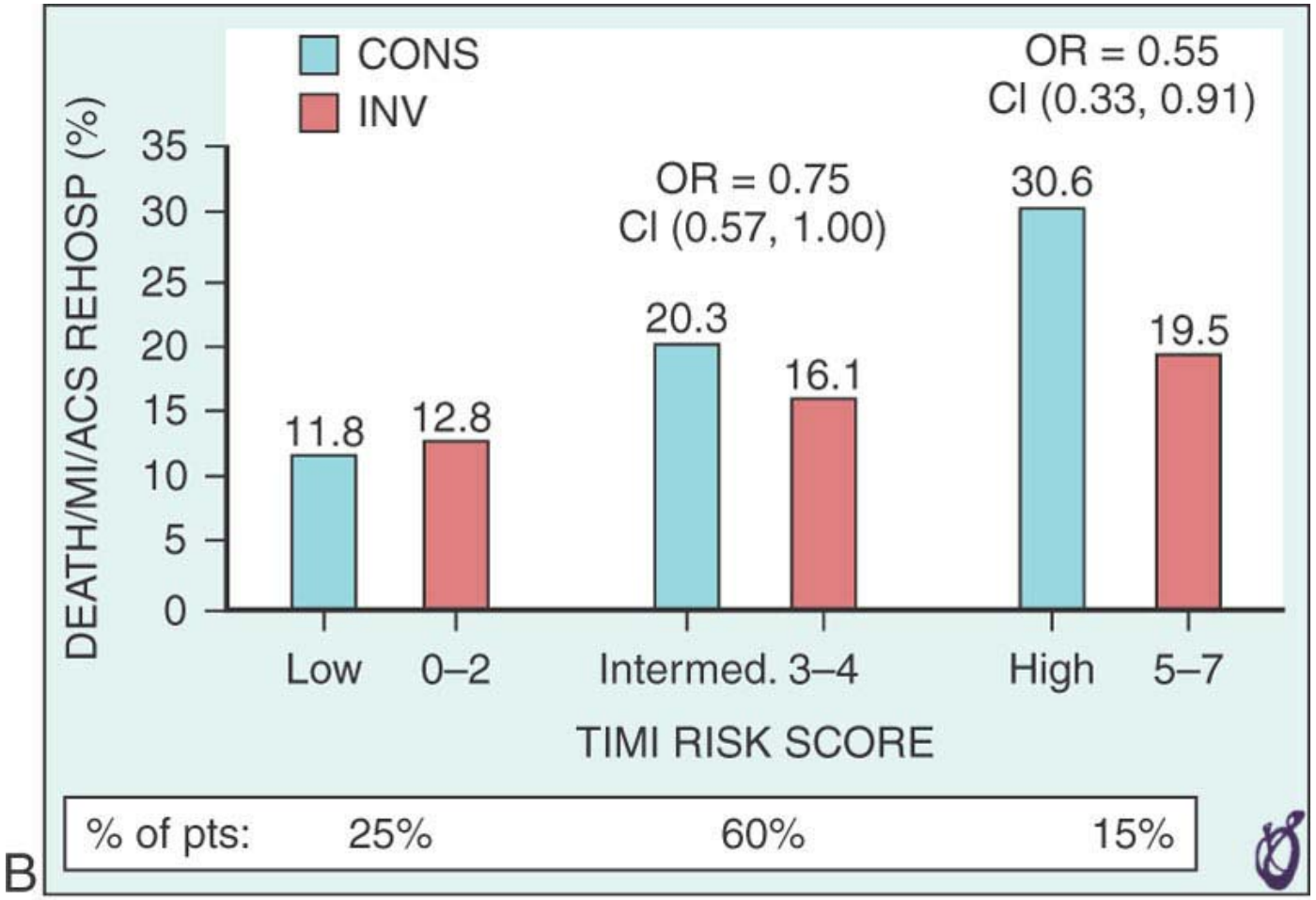
3.1 Risk Stratification

TIMI risk score for ACS-NSTE/UAP



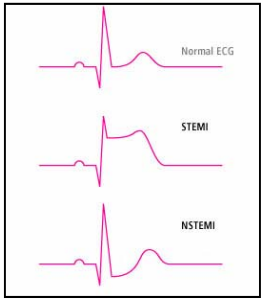
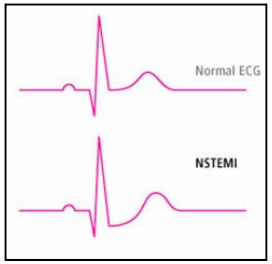
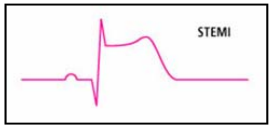
Test cohort						
Number (percent)	85 (4.3)	339 (17.3)	627 (32.0)	573 (29.3)	267 (13.6)	66 (3.4)

Risk Management Approach



(Data from Cannon CP, Weintraub WS, Demopoulos LA, et al: Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 344:1879, 2001.)

Scoring Comparison

GRACE		TIMI
	Population	
	ACS spectrum	 / 
	End points	
	Calculation	

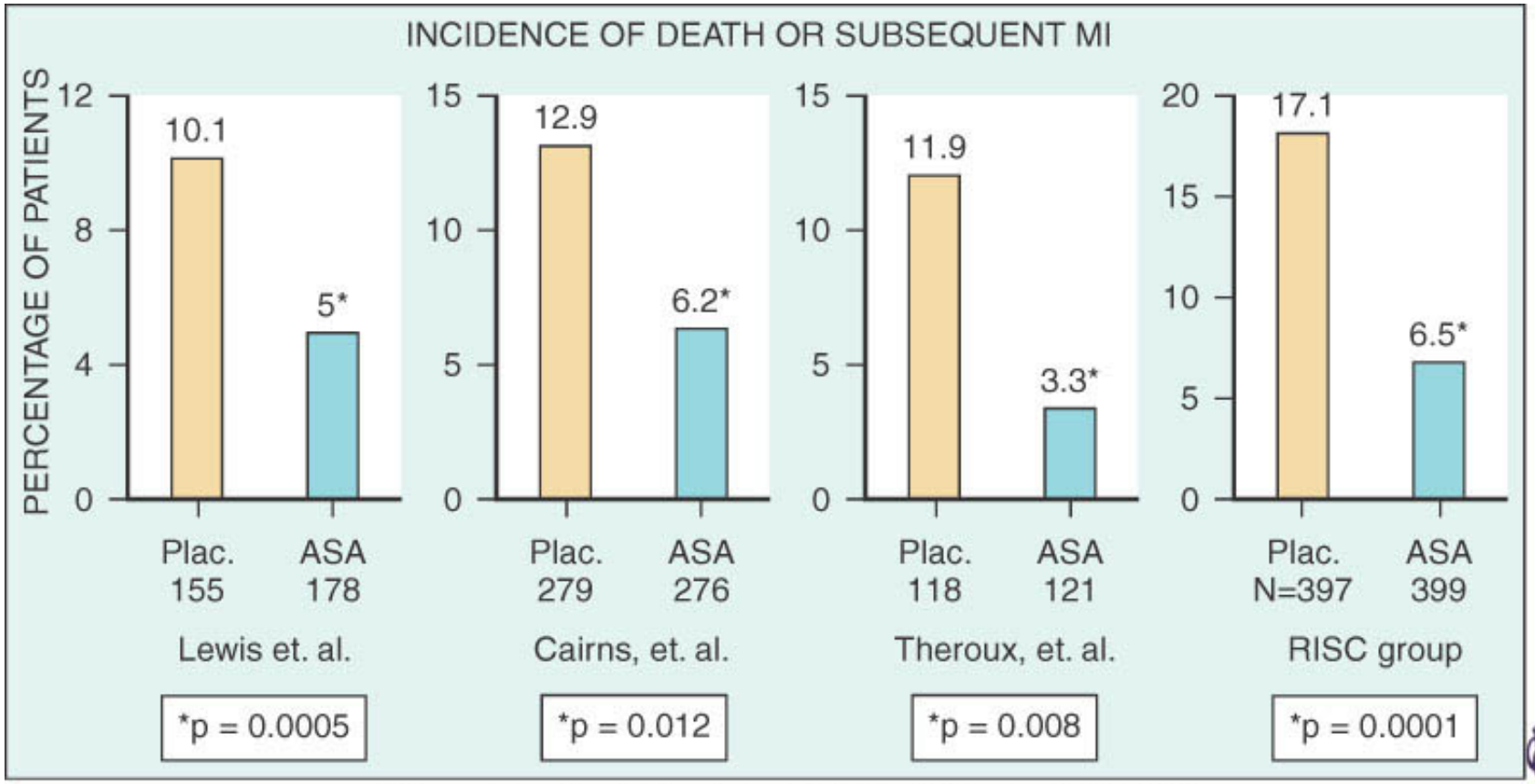
4. Management Medical therapy

4.1 Antiplatelets

4.2 Anticoagulants

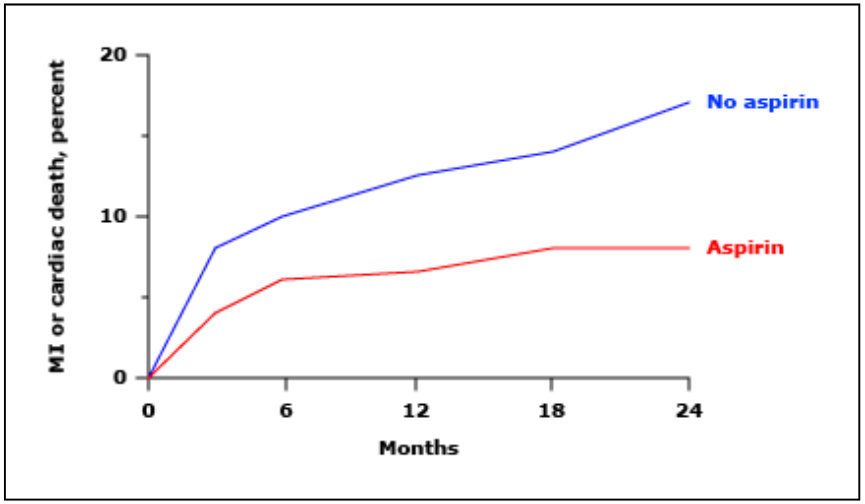
4.3 Lipid Lowering

4.1.1a Aspirin

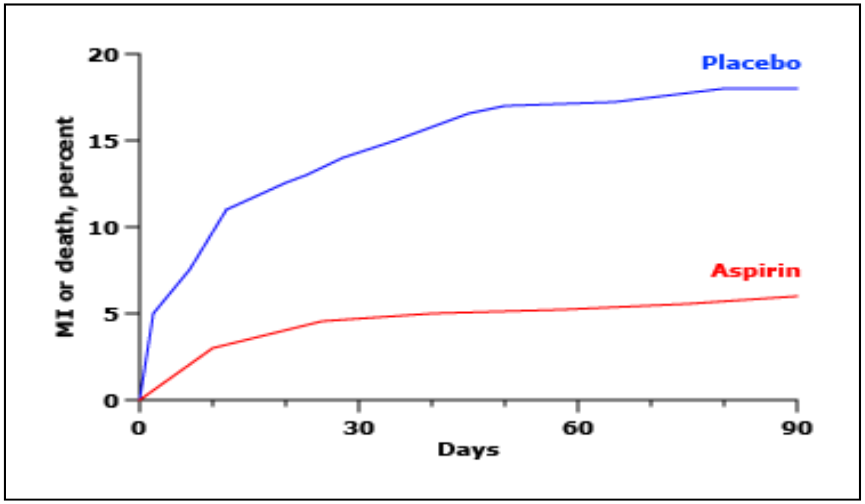


(Data from Lewis HD, et al: N Engl J Med 309:396-403, 1983; Cairns JA, et al: N Engl J Med 313:1369-75, 1985; Theroux P, et al: N Engl J Med 319:1105-11, 1988; RISC Group: Lancet 349:827-30, 1990.)

Aspirin is beneficial in UAP

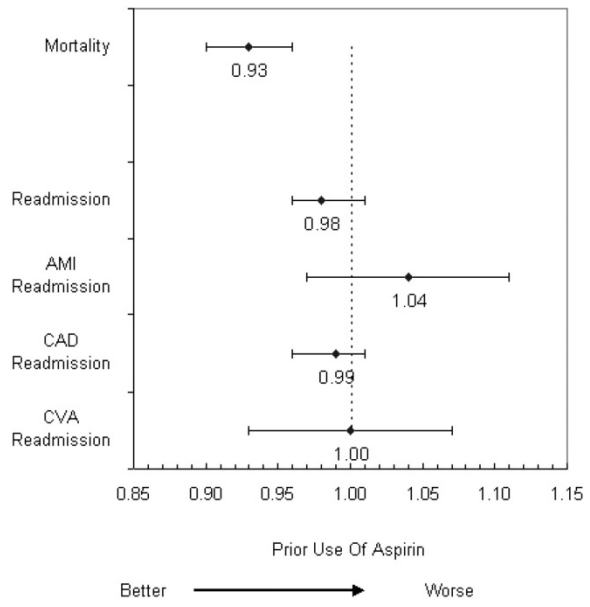


Canadian multic. trial,N Engl J Med 1985; 313:1369



The RISC Group, Lancet 1990; 336:827

ASA Failure, Nonresponse, Resistance and Paradox

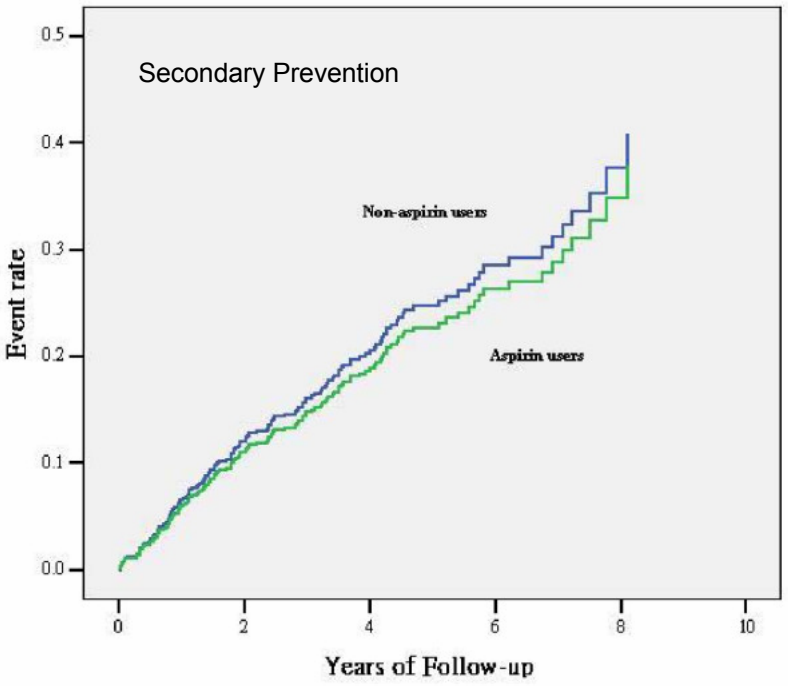


J Am Coll Cardiol, 2005; 46:967-974

Nonresponse and Resistance

Clinical Observation

Laboratory Finding

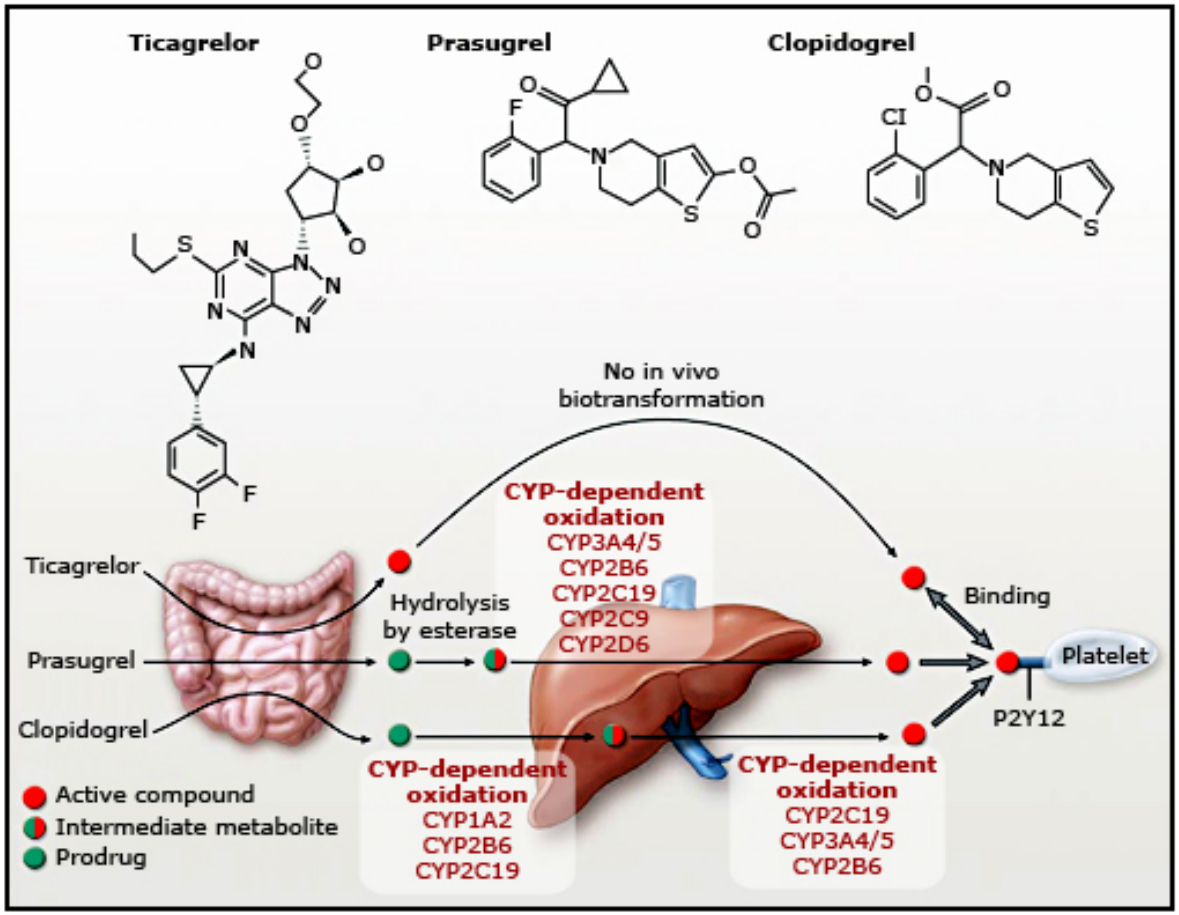


Leung *et al. Cardiovascular Diabetology* 2009 **8**:57

Range 60 to 1% (2-8%)

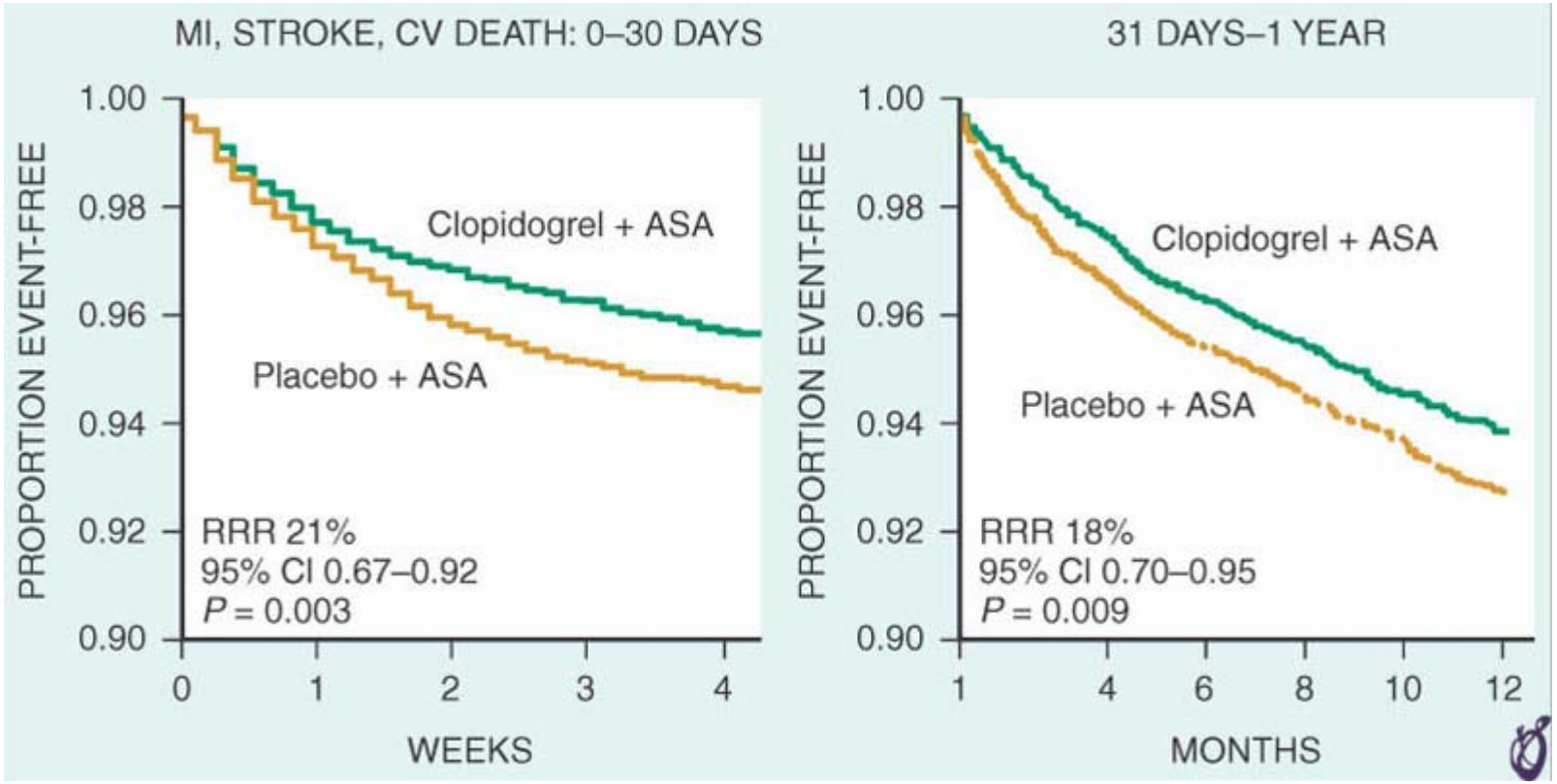
Failure of therapy reflects patients who have recurrent events on therapy

4.1.1b Platelet P2Y12 Receptor Blockers



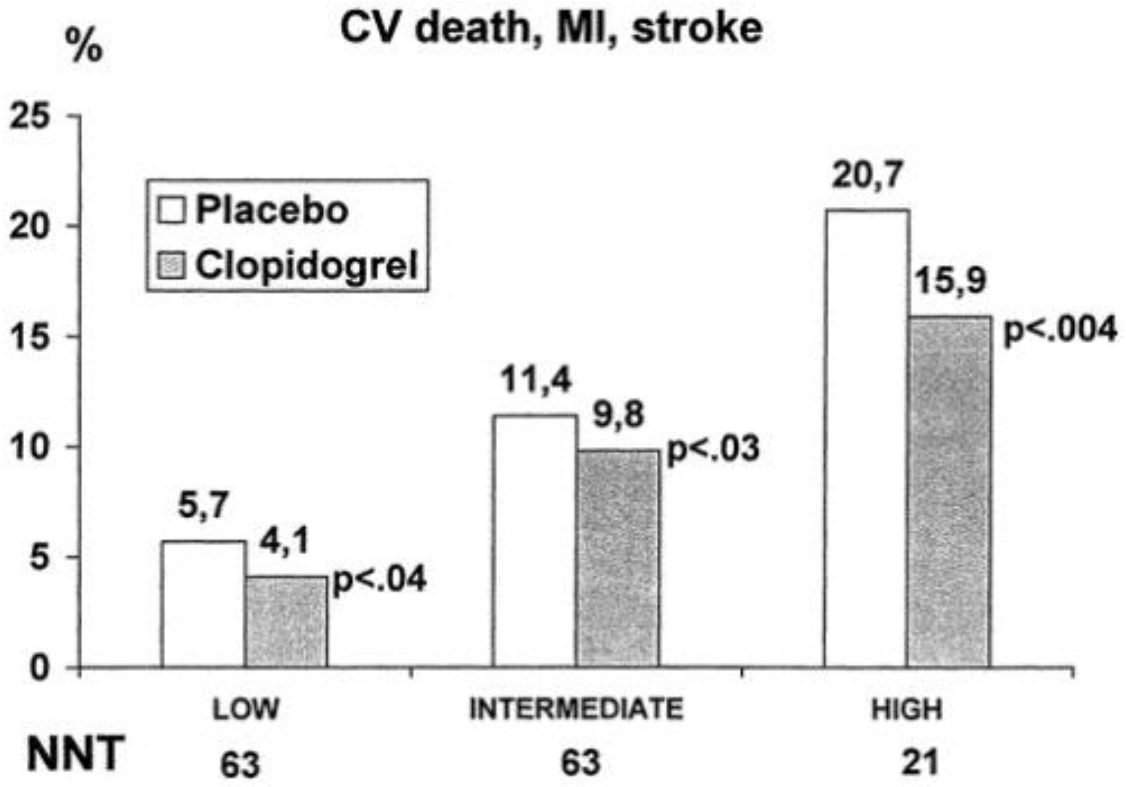
N Engl J Med 2009; 361:1108

CURE Trial



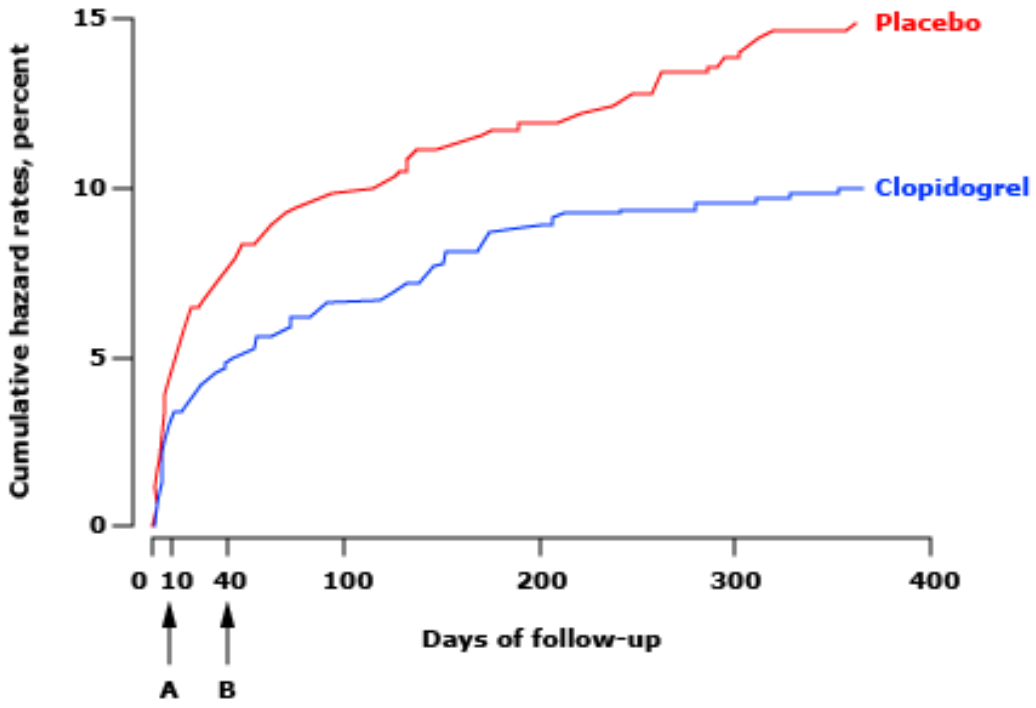
N Engl J Med 2001; 345:494
Circulation 2003; 107:966.

CURE: Risk Groups Benefit

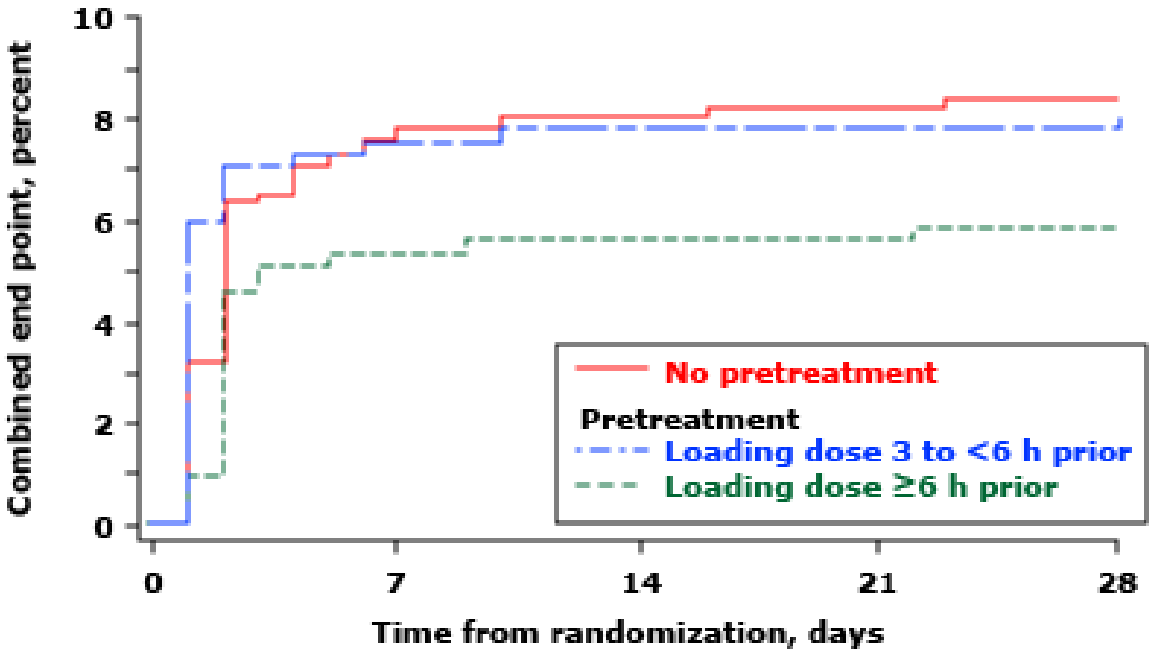


Circulation 2002;106:1622-26

PCI-CURE

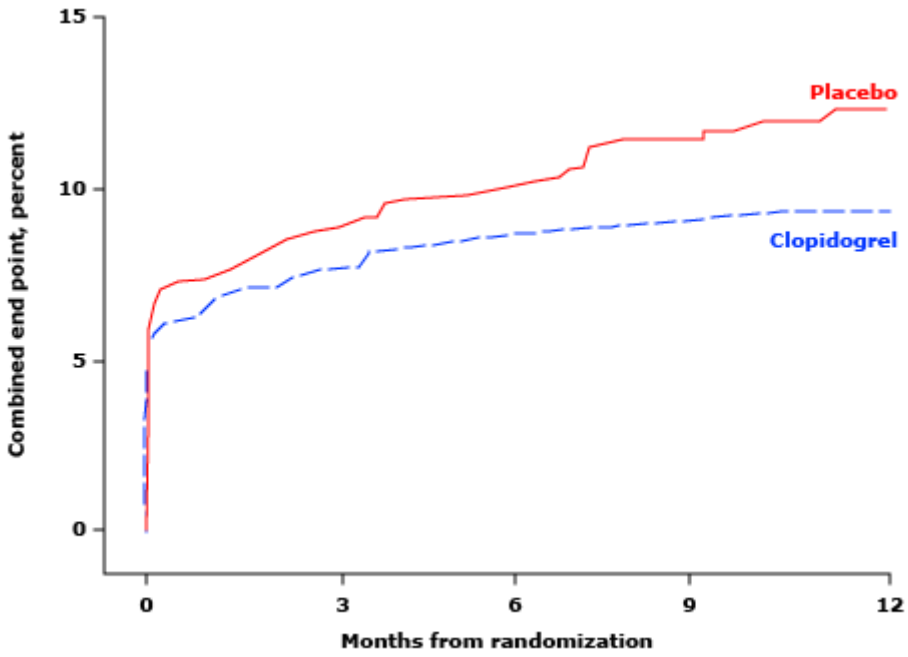

Cumulative hazard rates, percent
15
10
5
0
Placebo
Clopidogrel
0
10
40
100
200
300
400
Days of follow-up
A
B

Clopidogrel Pretreatment: CREDO Trial



JAMA 2002; 288:2411

Treatment Duration: 1 vs. 12 months

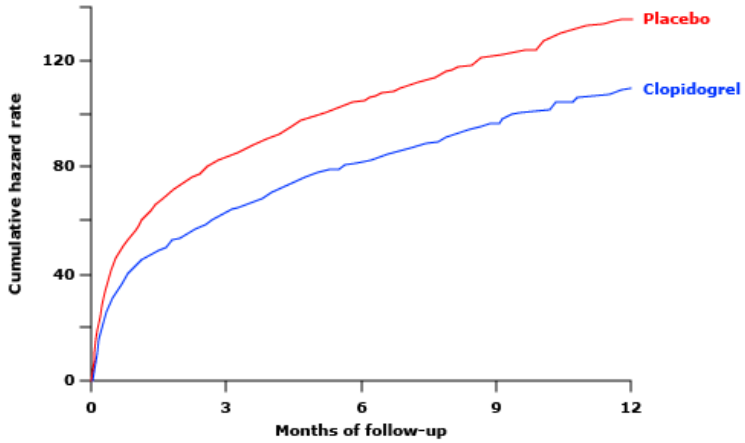


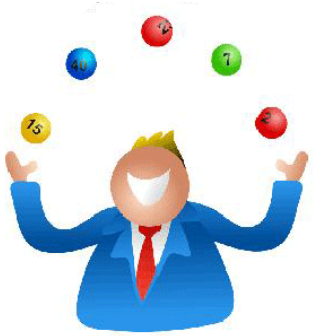
JAMA 2002; 288:2411

Clopidogrel Nonresponse and Resistance

Clinical Observation

Laboratory Finding



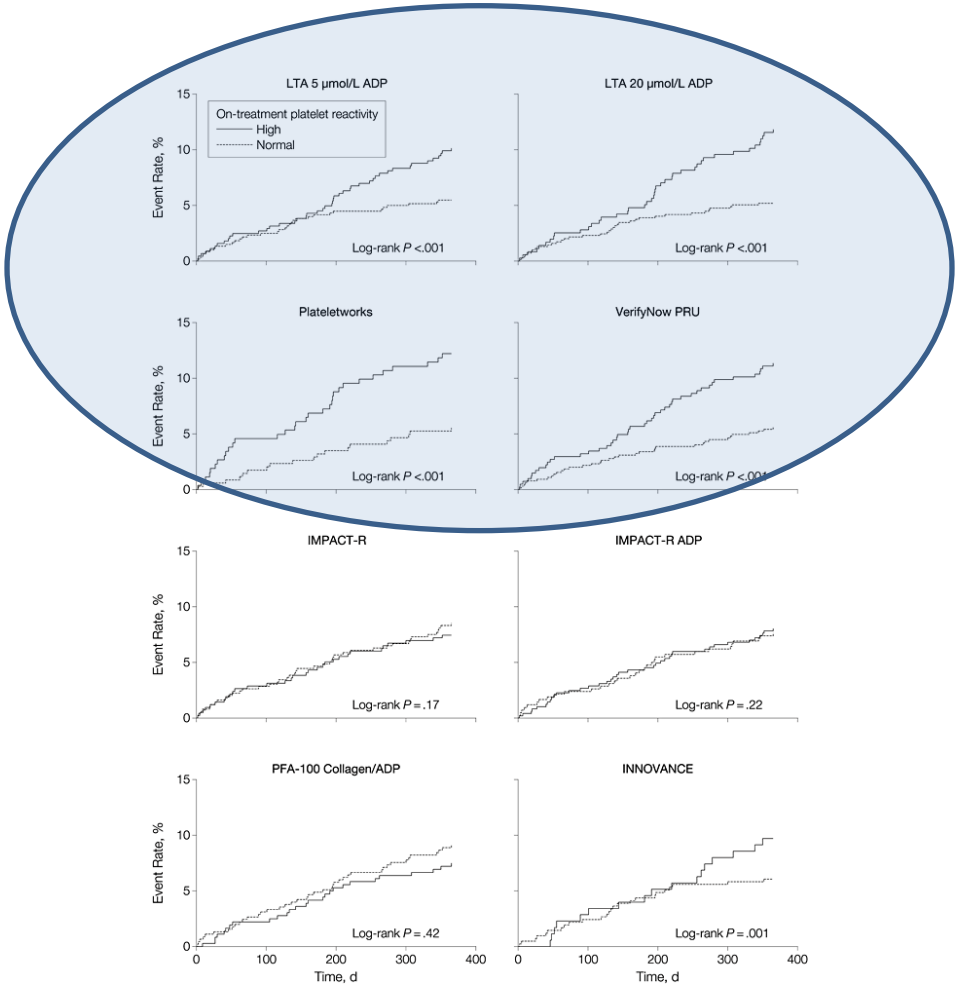


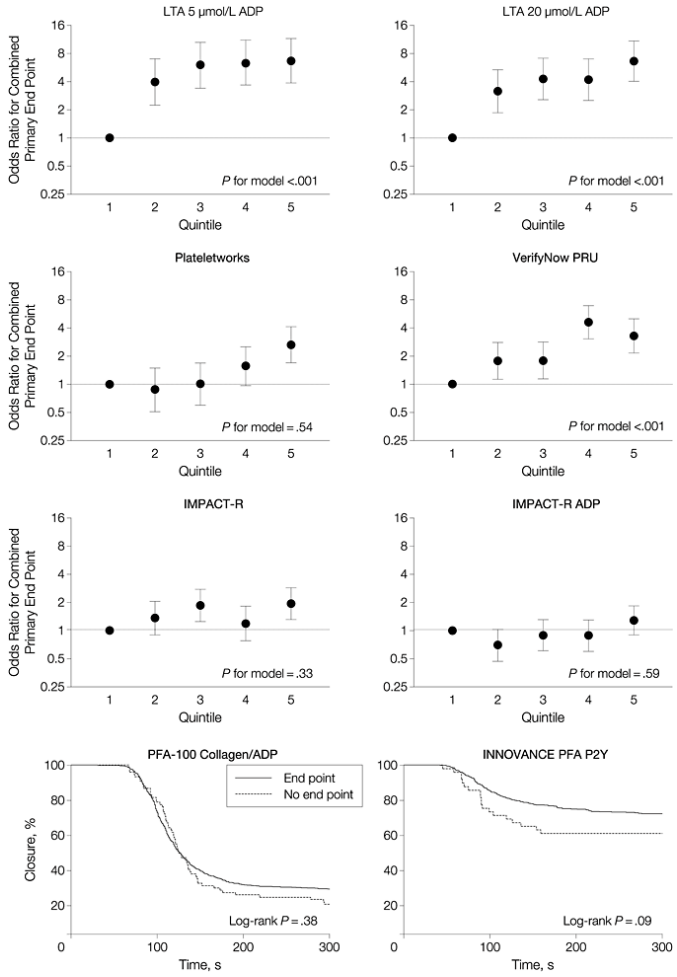
Range 4 to 30%

CURE Trial

Le J Am Coll Cardiol, 2005; 45:1157-1164

Predicting Clinical Outcomes

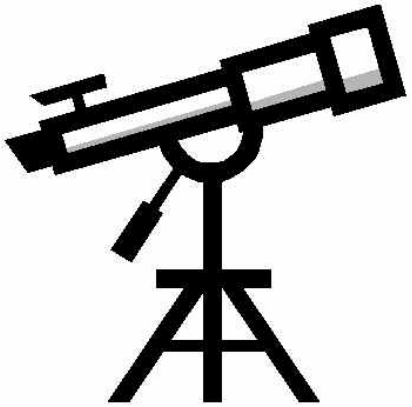




POPULAR study, JAMA. 2010 Feb 24;303(8):754-62.

Clopidogrel & PPI

Vs.



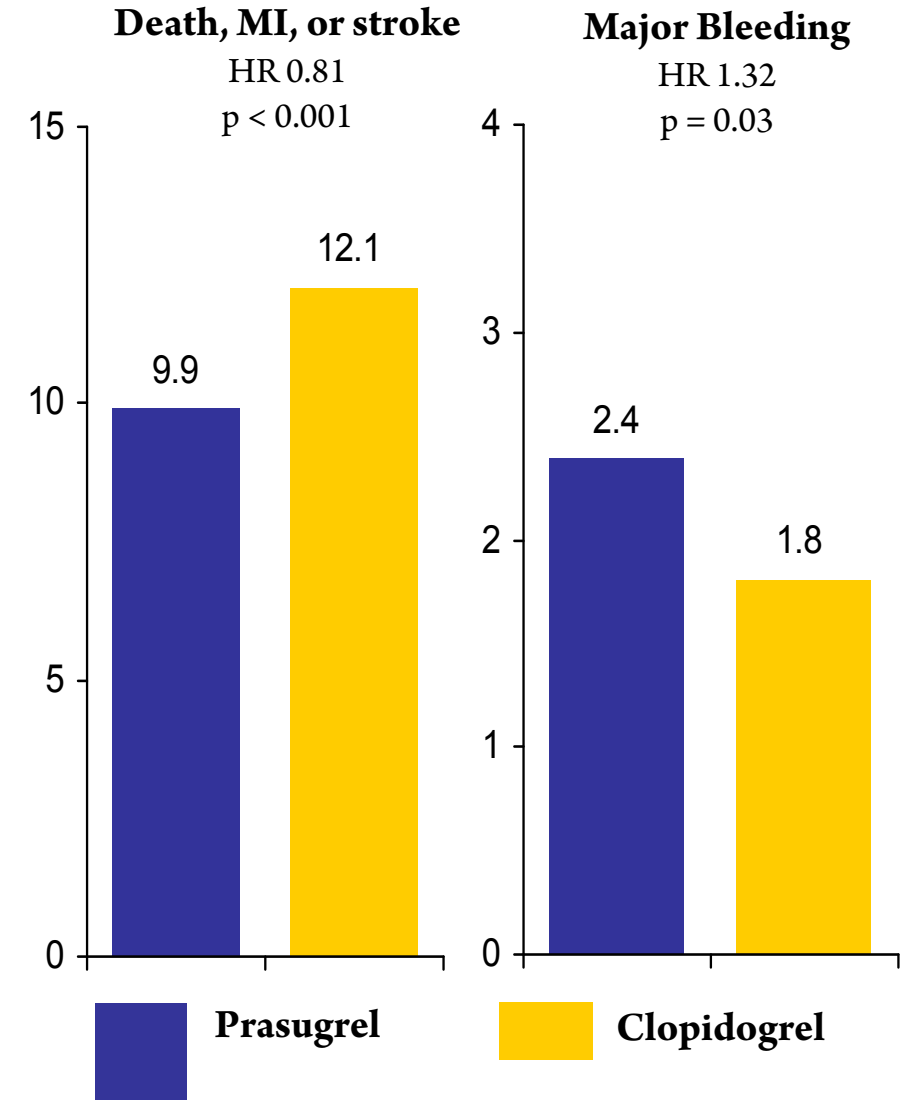
Vs.

Pharmacodynamic test

Observational Studies

RCT

TRITON –TIMI 18 Trial



→Post coronary angio loading

→Loading Clopidogrel 300 mg. vs 60 mg Prasugrel

→Duration Tx 14.5 months

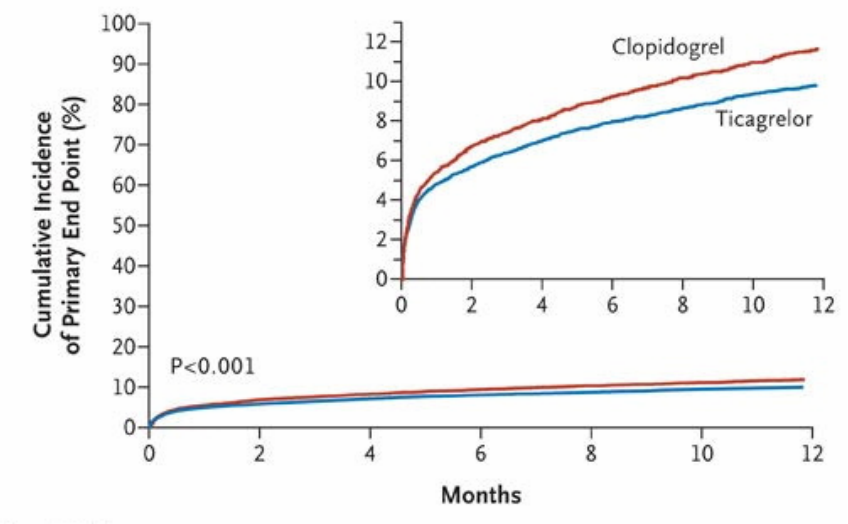
→Increase life-threatening bleeding with Prasugrel

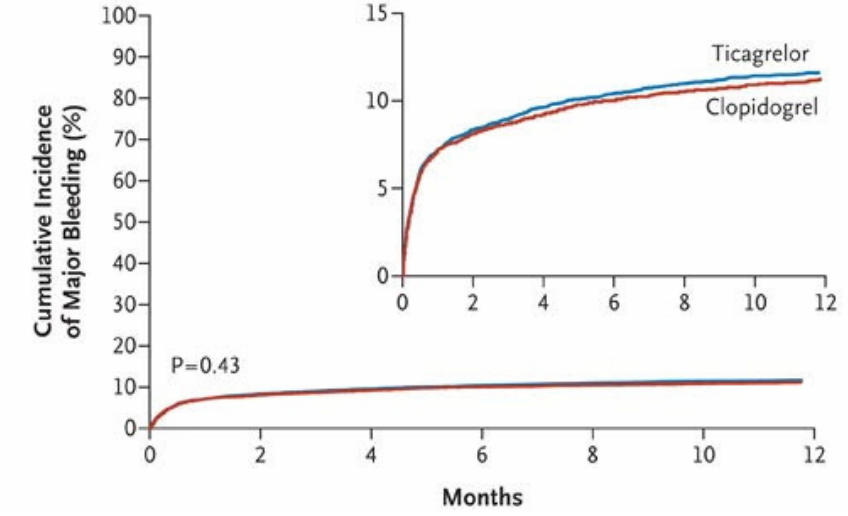
→Bleeding predictors: past CVA, body weight <60 kg, age >75.

→Prasugrel signif reduce ST

N Engl J Med 2007;357

PLATO Trial



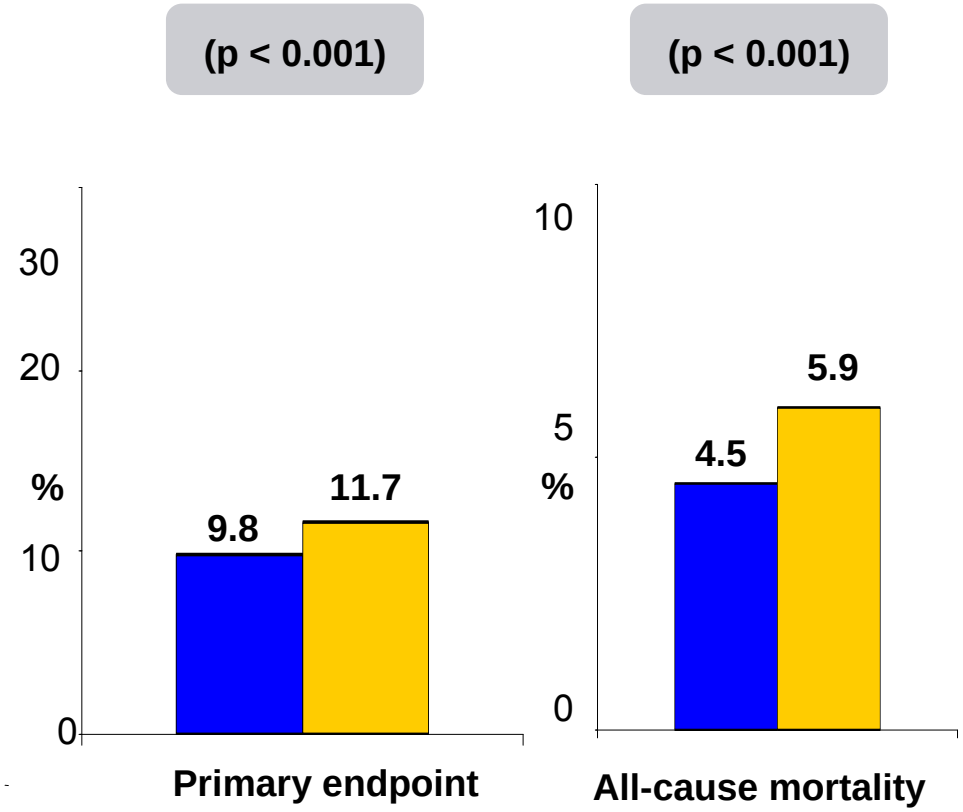


→1 EP and 2EP: Ticagrelor was superior to Clopidogrel

→Not significant in Major Bleeding rate, BUT Ticagrelor have significant increase risk of Major Bleeding not releted to CABG

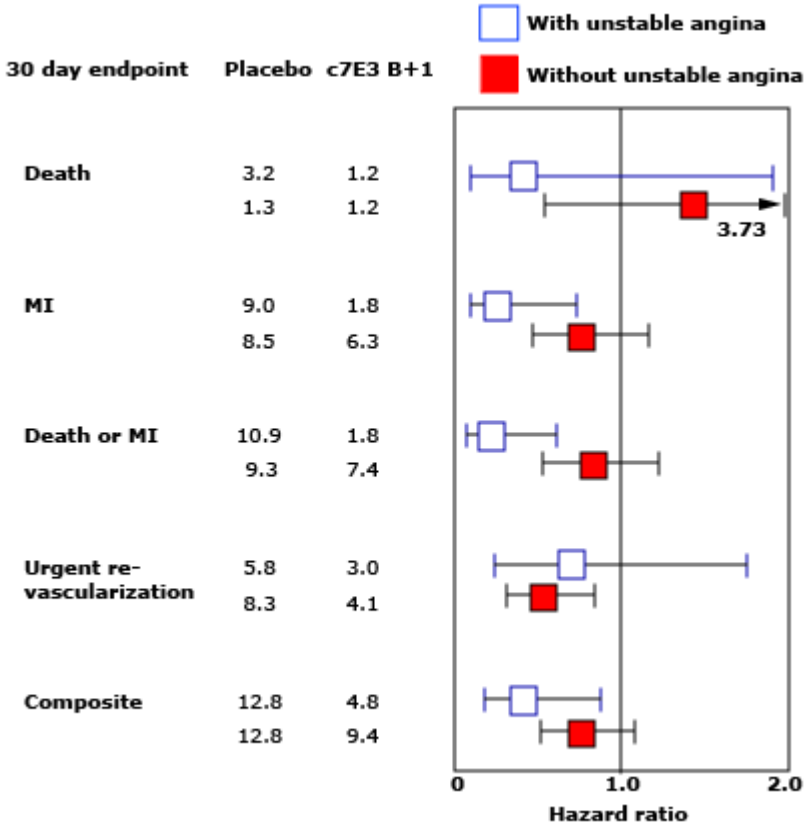
N Engl J Med 2009; 361:1045-1057

PLATO “PCI”

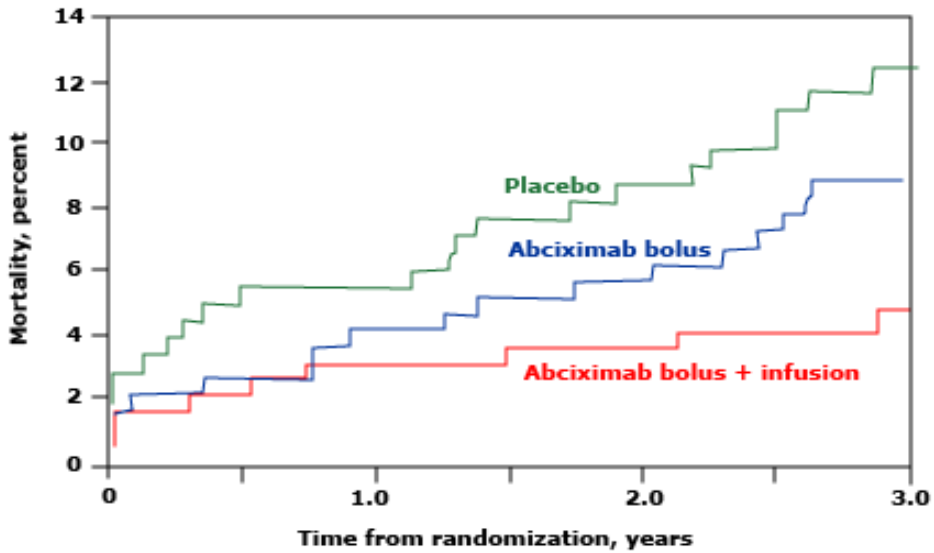


Cannon CP, et al. Lancet 2010;375:283-93

4.1.1c GP IIb/IIIa Inhibitors: Abciximab



J Am Coll Cardiol 1997; 30:149



JAMA 1997; 278:479

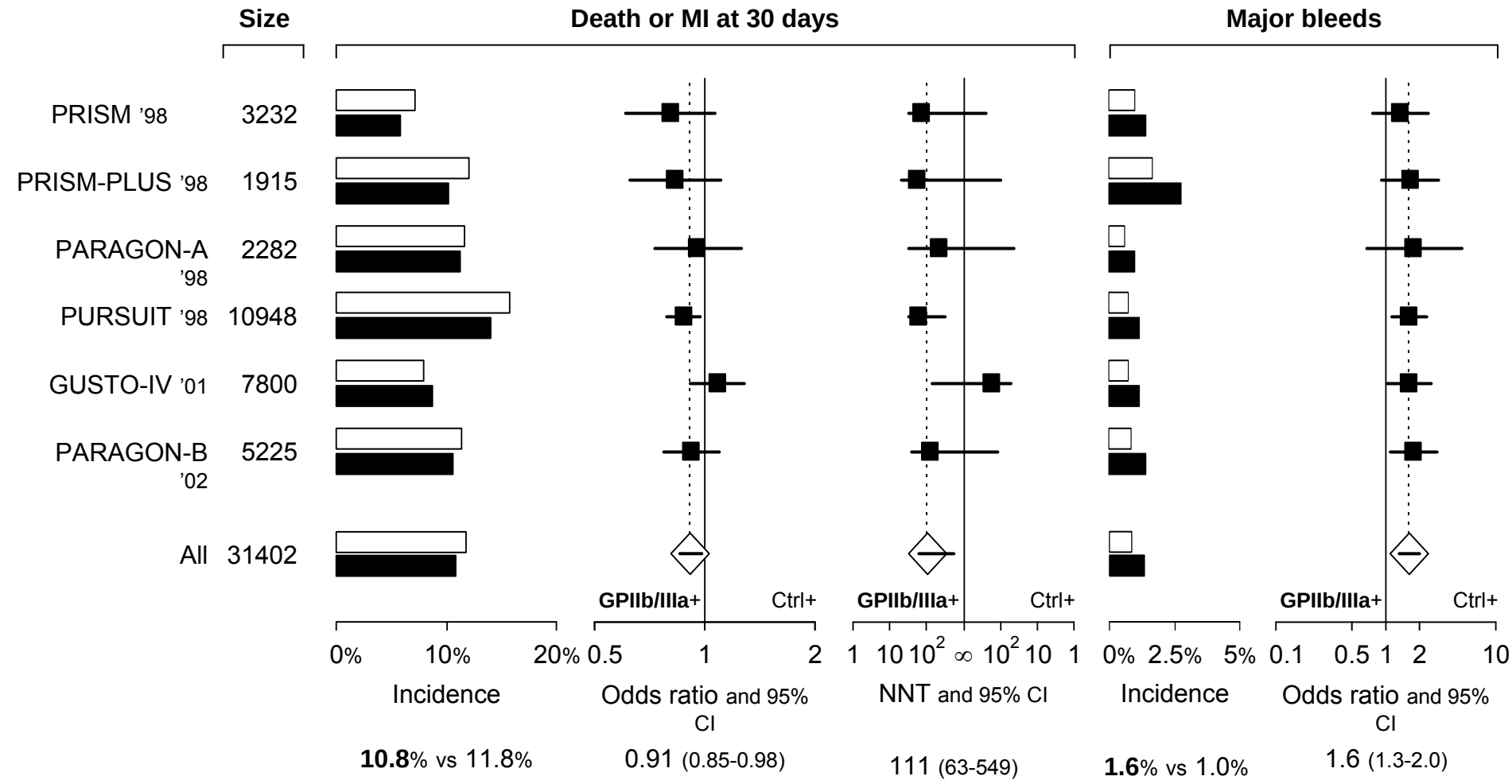
→ EPIC and CAPTURE Abciximab after balloon angioplasty without dual antiplatelet therapy

→Principally reduced MI

→GUSTO 4-ACS: (No PCI study), no benefit

RCT GP IIb/IIIa Inhibitors

Active drugs (dark bars) vs Control (open bars)



→These patients were not treded with P2Y12 receptor blockers !!!

RCT GP IIb/IIIa Inhibitors

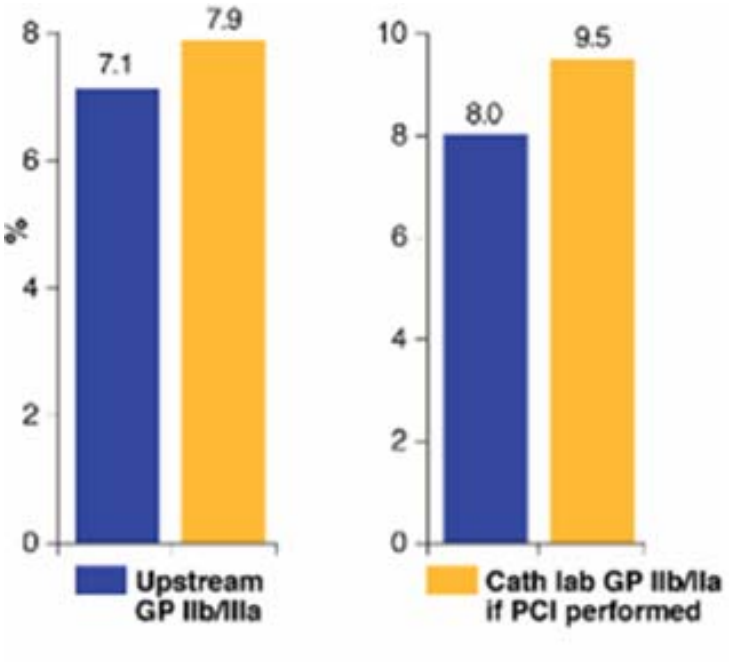
- → Effective with Medical Tx alone: PURUSIT, *PRISM, PRISM-PLUS, RESTORE* and PARAGON A (**Tirofiban*)
- → Effective with PCI: PURUSIT, *PRISM PLUS* and *ADVANCE* (**Tirofiban*)
- → Only improve mortality in diabetic patients (PURUSIT)
- → Tirofiban without heparin increase mortality (PRISM-PLUS)

GP IIb/IIIa upstream or provisional?

ACUITY Timing

p NS for inf. or sup.

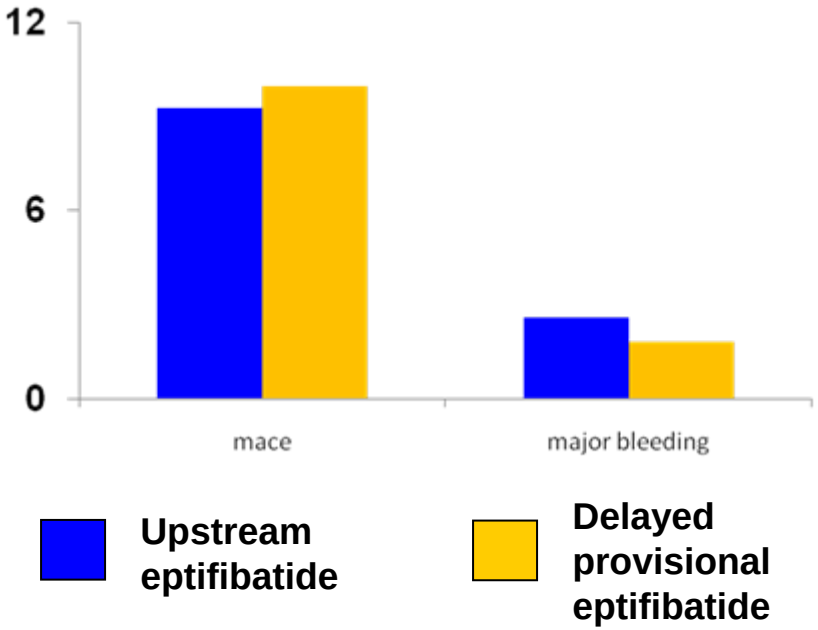
p 0.05 for superiority



JAMA. 2007;297:591-602

EARLY ACS

(*p* = 0.23) **(*p* = 0.015)**

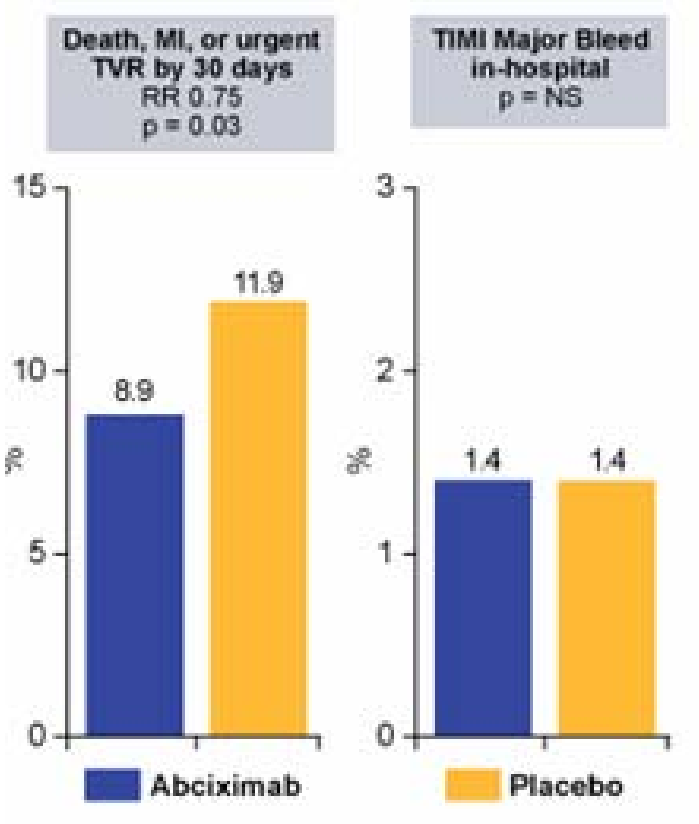


N Engl J Med 2009;360:2176-90

→GP IIb/IIIa inhibitor reserved to in high risk patients to early PCI

Does GP IIb/IIIa inhibitors any benefit effect on top Clopidogrel Tx?

ISAR-REACT 2 trial



→On subgroup analysis, the benefit was only seen in patients with an elevated serum troponin concentration

JAMA 2006;295:1531-1538

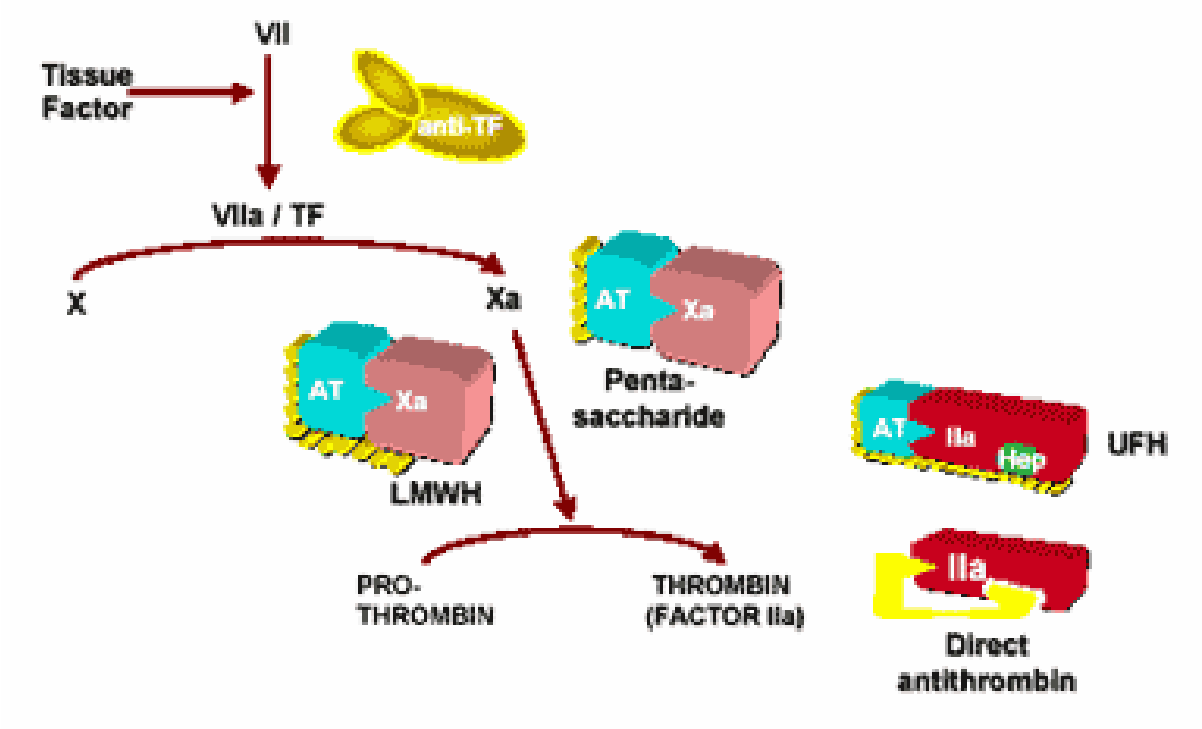
4. Management Medical therapy

4.1 Antiplatelets

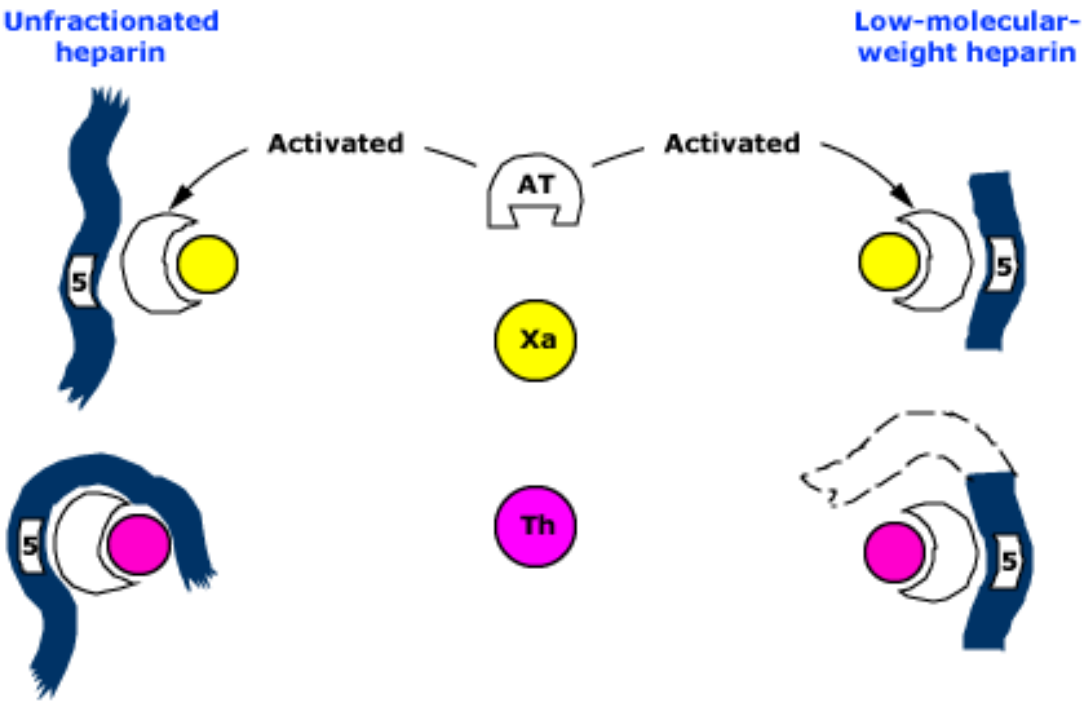
4.2 Anticoagulants

4.3 Lipid Lowering

4.1.2 Medical Therapy: Anticoagulation

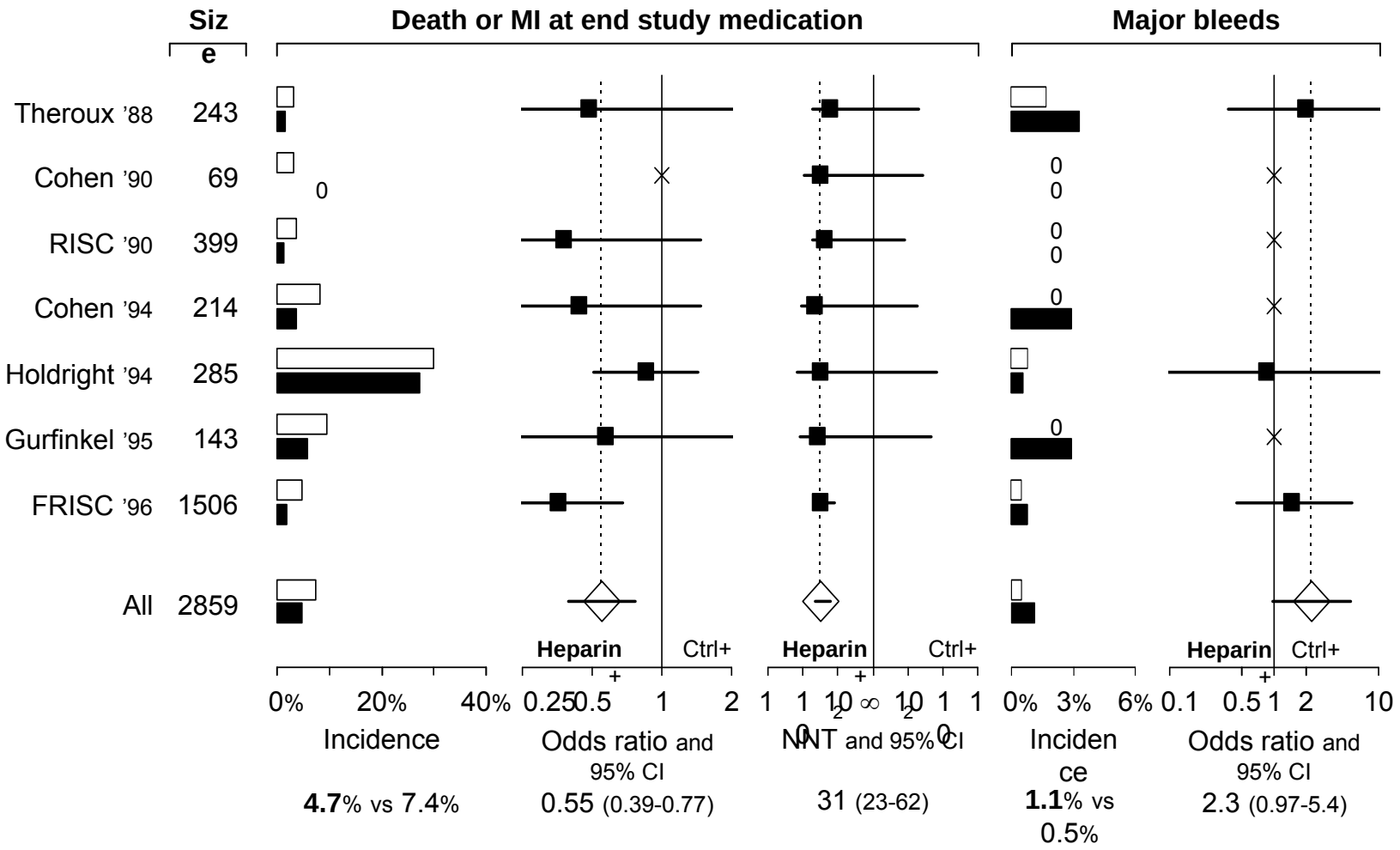


4.1.2a Heparins UFH and LMWH)



N Engl J Med 1996; 334:724

4.2a RCT of UFH/LMWH (Dark Bars) vs Control (open bars)



→ Performed before current modern Tx: clopidogrel, IIb/IIIa inhib and early PCI
→Compared with no-theraphy

UFH Limitations

PK

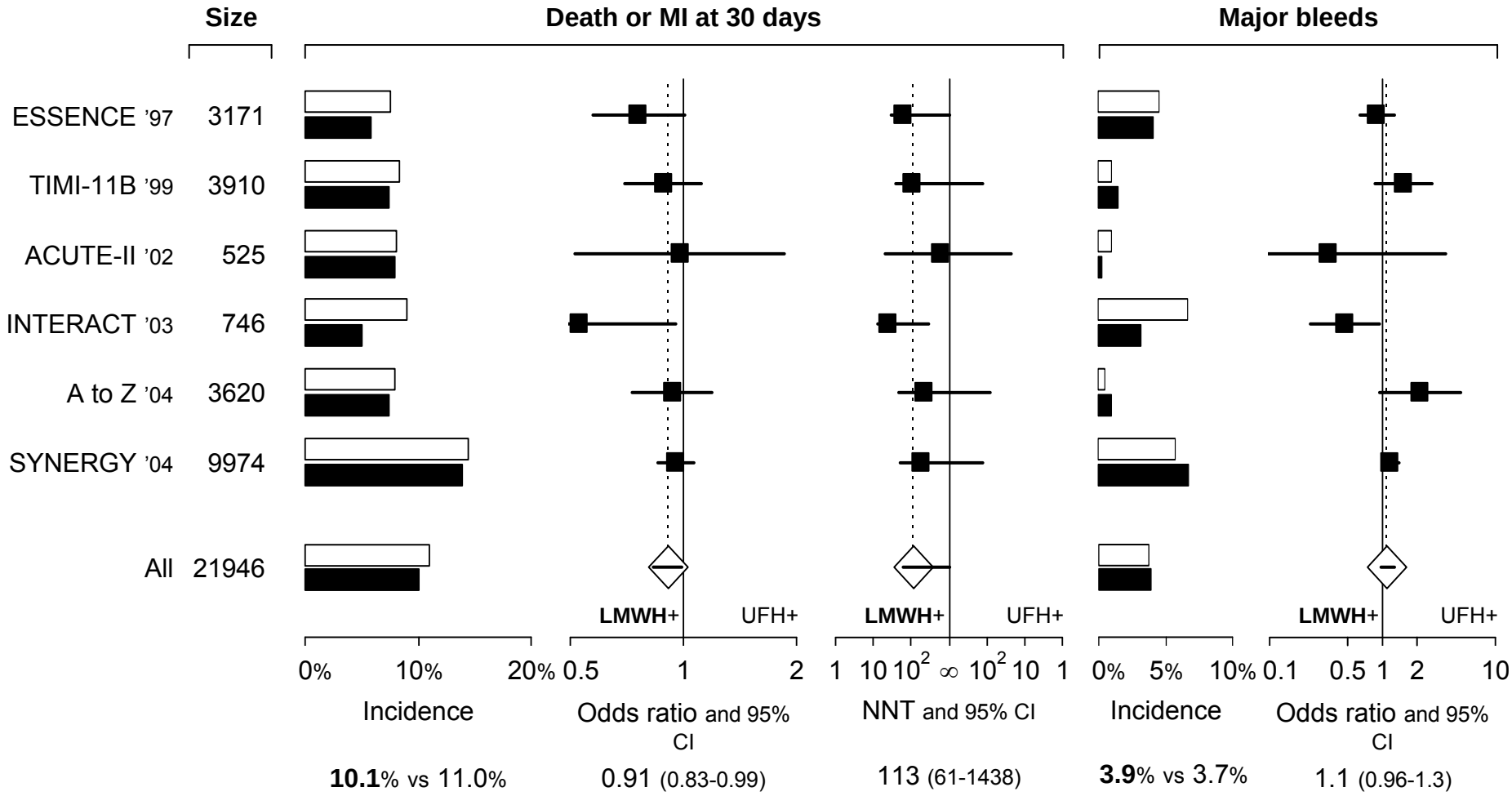
- Poor bioavailability at low dose
- Variable anticoagulant response

Biophysical

- Poor inactivator of platelet bound Xa
- Ineffective inactivator of fibrin-bound IIa
- Complicated with HIT

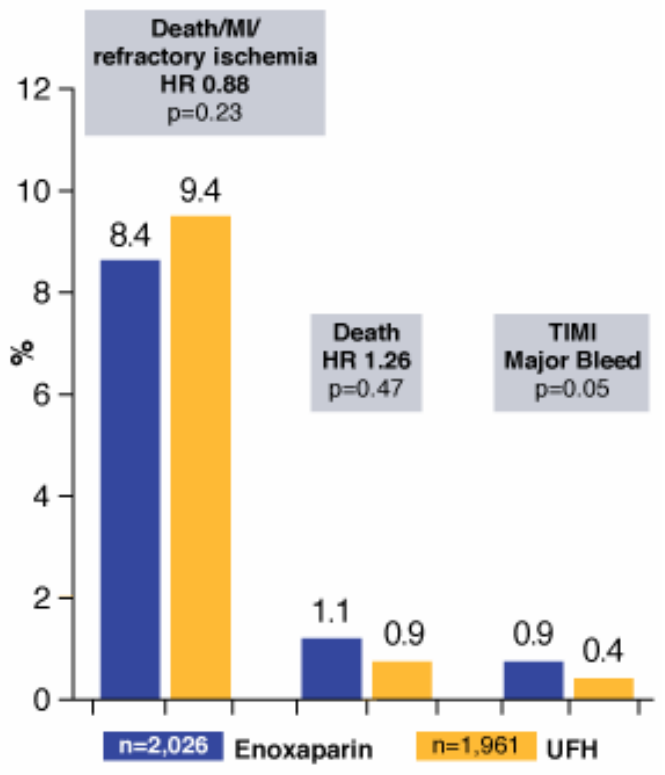
Antman EM, Circulation;103:2310-14

4.1.2b RCT Enoxaparin (Dark Bars) vs UFH (Open Bars)



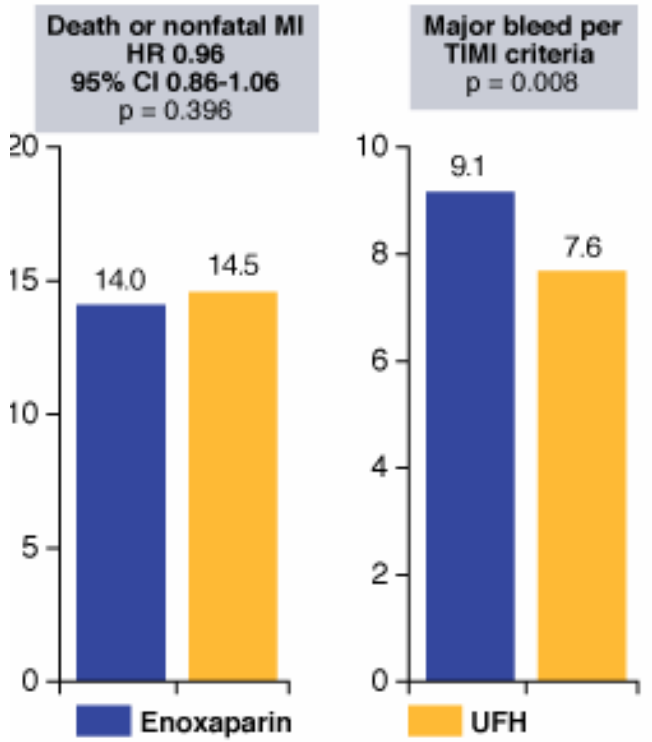
LMWH and GP IIb/IIIa

A to Z



JAMA 2004;292:55-64

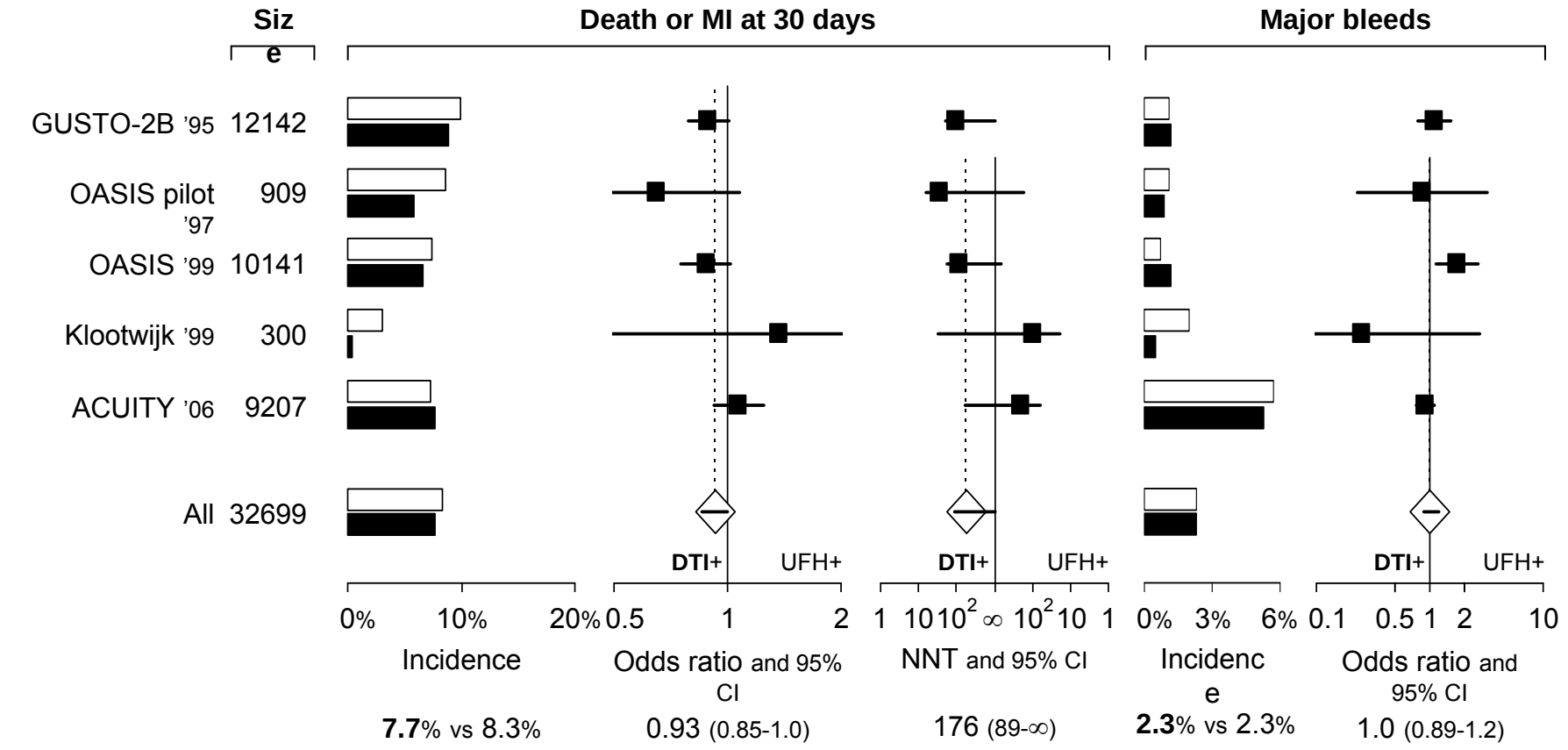
SYNERGY



JAMA 2004;292:45-54

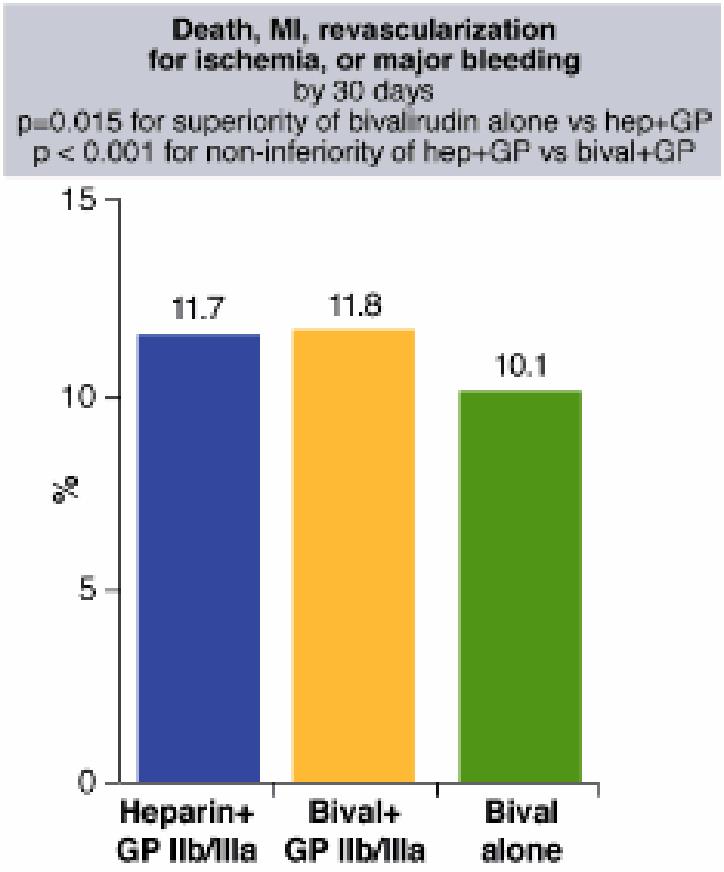
→New concept: switching therapy'
→CVS and bleeding outcomes were worse in 'switching therapy' pts

4.1.2c RCT Direct Thrombin Inhibitors (Dark Bars) vs UFH/LMWH (Open Bars)



Bivalirudin alone or with GP IIb/IIIa vs GP IIb/IIIa + UFH/LMWH on top Dual Tx

ACUITY Trial

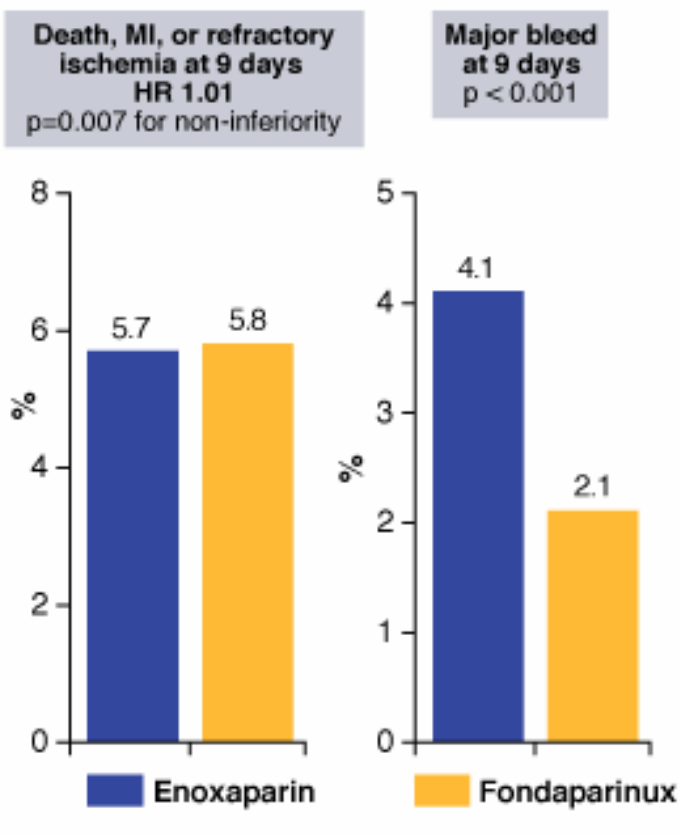


→Importance of clopidogrel pretreatment in patients given bivalirudin who are not treated with a GP IIb/IIIa inhibitor.

N Engl J Med. 2006;355:2203-16

4.1.2d Fondaparinux

OASIS 5 Trial



N Engl J Med 2006;354:1464-76

→In the PCI group, Fonda significantly reduced major bleeding at day nine

→Fonda associated with small but significant increase in catheter-related thrombi

→Fondap significantly reduced major bleeding in pts who received GP IIb/IIIa inhibitors and pts who received thienopyridines

4. Management Medical therapy

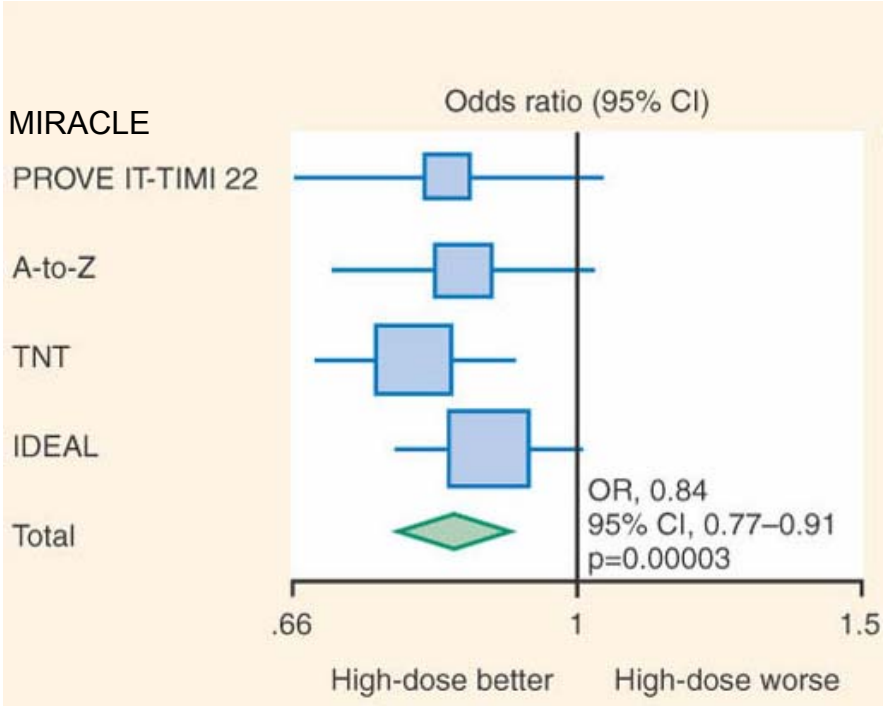
4.1 Antiplatelets

4.2 Anticoagulants

4.3 Lipid Lowering

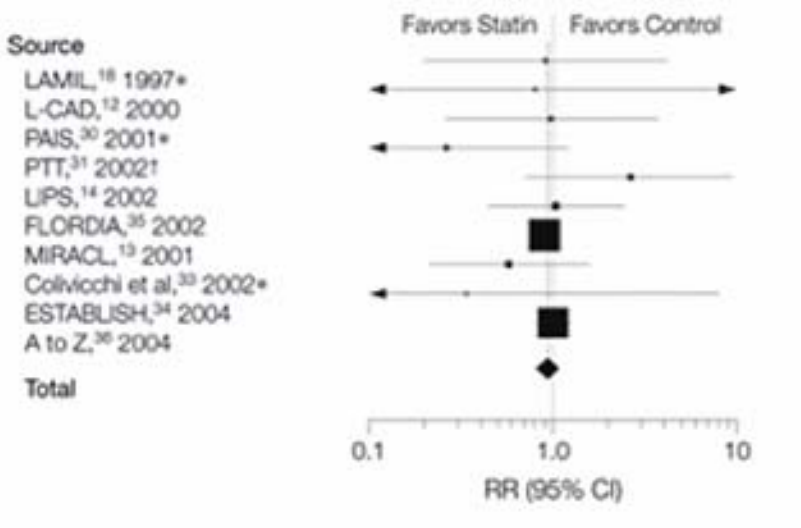
4.1.3 *Intensive* Statin Therapy

Meta-analysis 2006



Cannon CP, J Am Coll Cardiol 2006;48:438-45

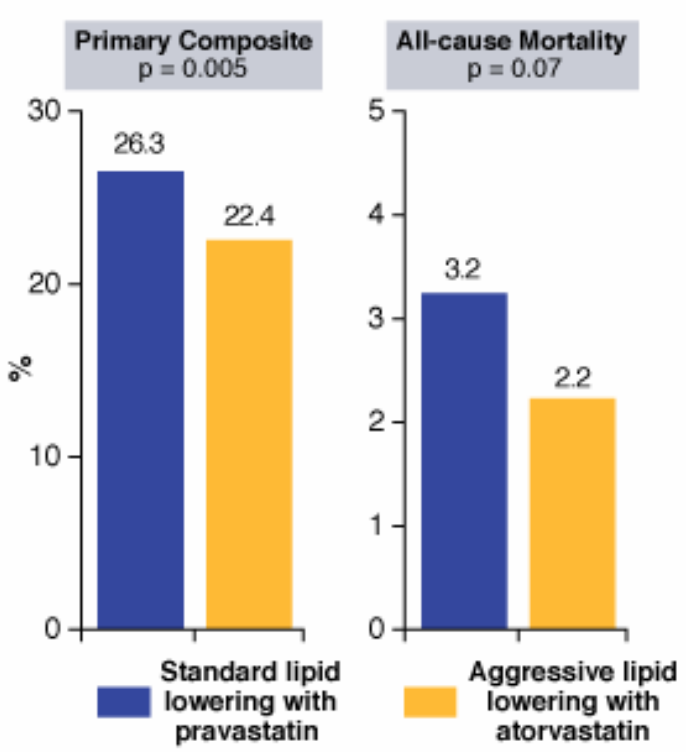
Meta-analysis 2006



Briel M, JAMA. 2006 May 3;295:2046-56

Early Initiation of *Intense* Statins Therapy

PROVE IT -TIMI 22



N Engl J Med 2004;350:1495-504

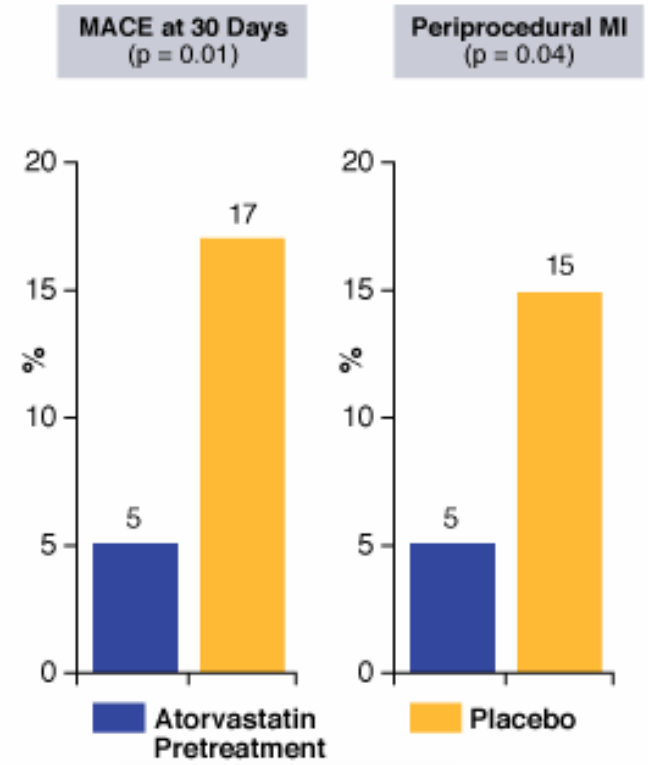
→The benefit of atorvastatin was apparent as early as 30d after and was persistent over time

→Trend toward lower all-cause mortality with atorvastatin

→Subset analysis, the benefit from atorvastatin was significant for patients with a baseline LDL-C ≥125 mg/dL, but not for those with a baseline LDL-C <125 mg/dL

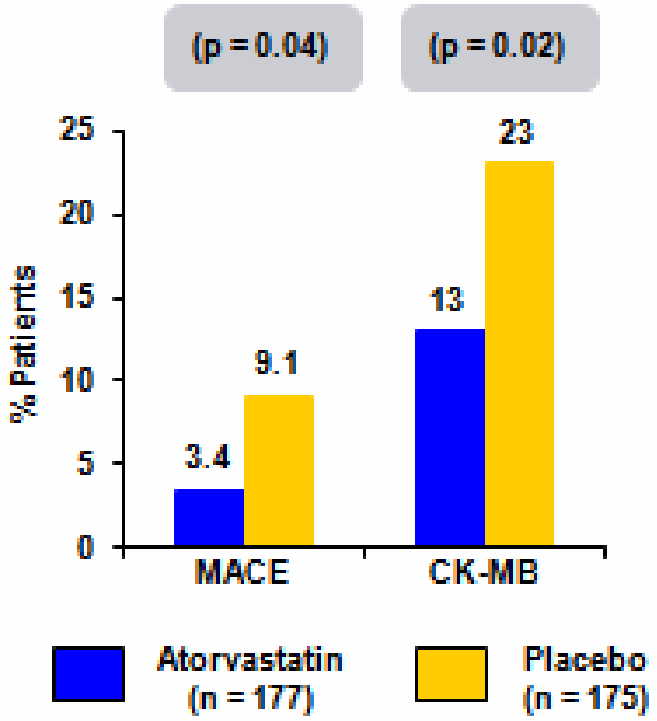
Pre-PCI Intense Statins Therapy

ARMYDIA ACS



J Am Coll Cardiol 2007;49:1272-8.

ARMYDIA -RECAPTURE

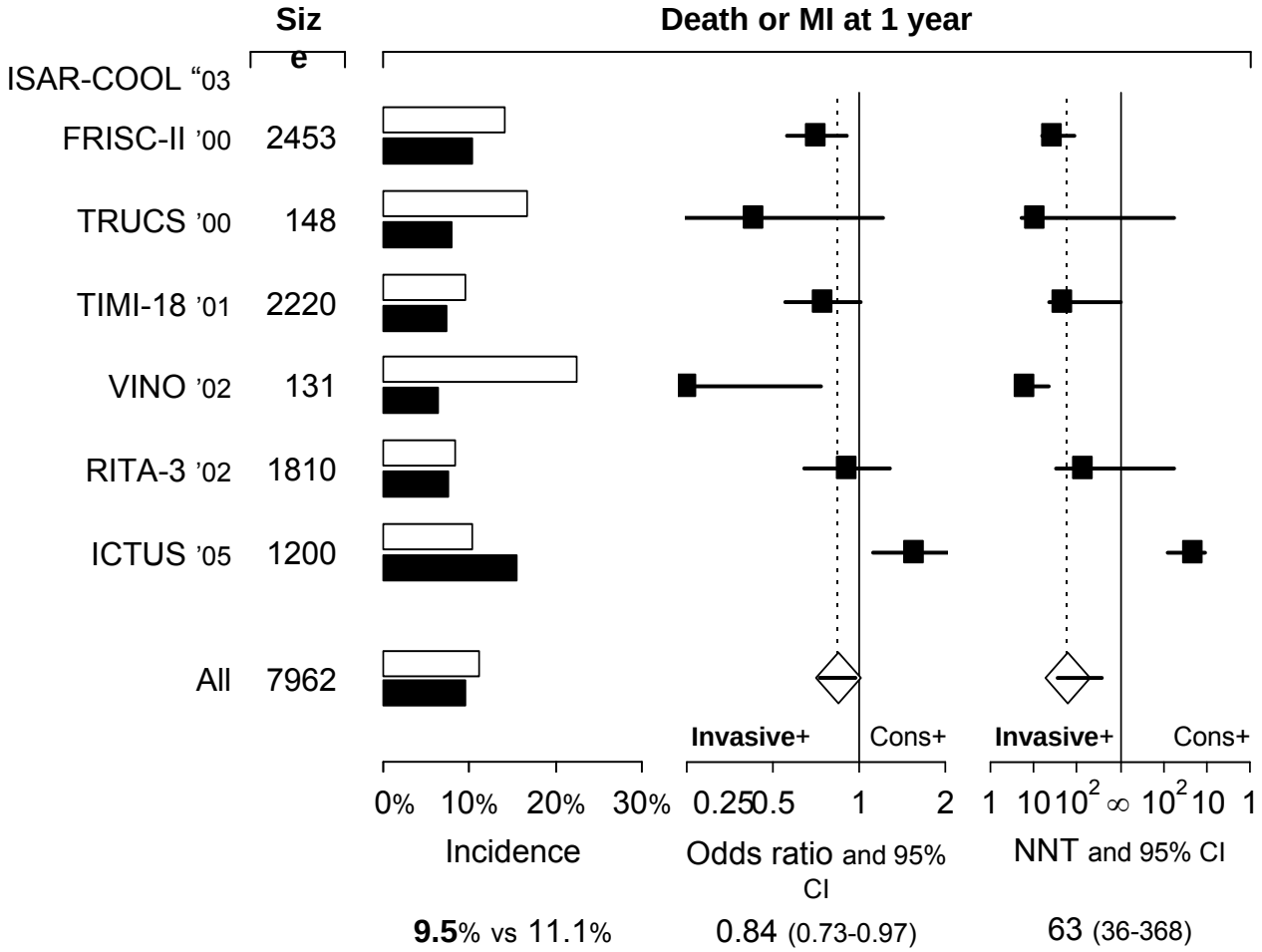


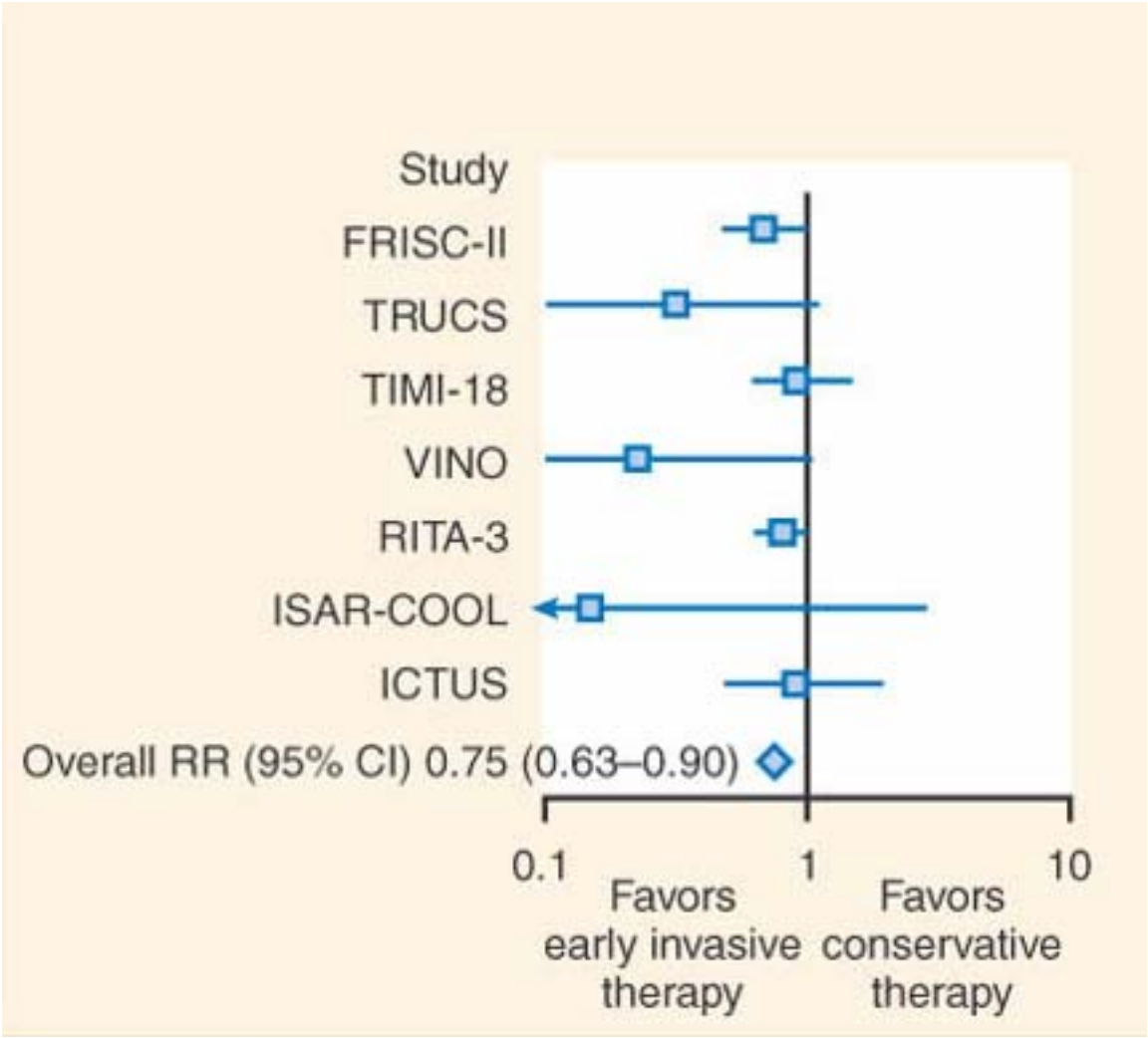
J Am Coll Cardiol. 2009 ;54:558-65

4.2 Management Strategies

Invasive vs. Conservative approach

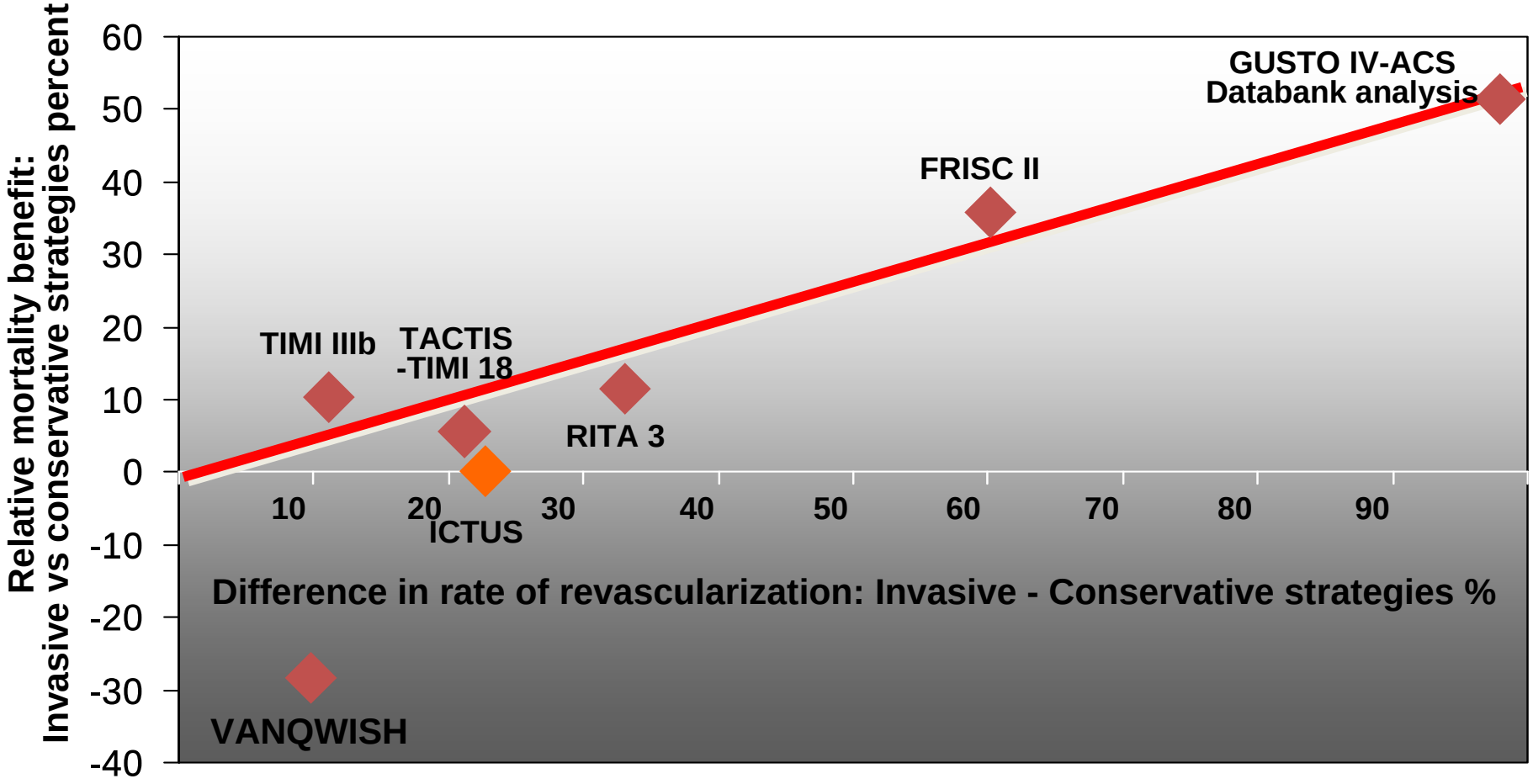
RCT Comparing Early Invasive (Dark Bars) vs Conservative Strategy (Open Bars)





J Am Coll Cardiol 48:1319-25, 2006

Relative Mortality Benefit with the Revascularisation vs Gradient in Rates of Revascularisation Between both Randomisation Arms



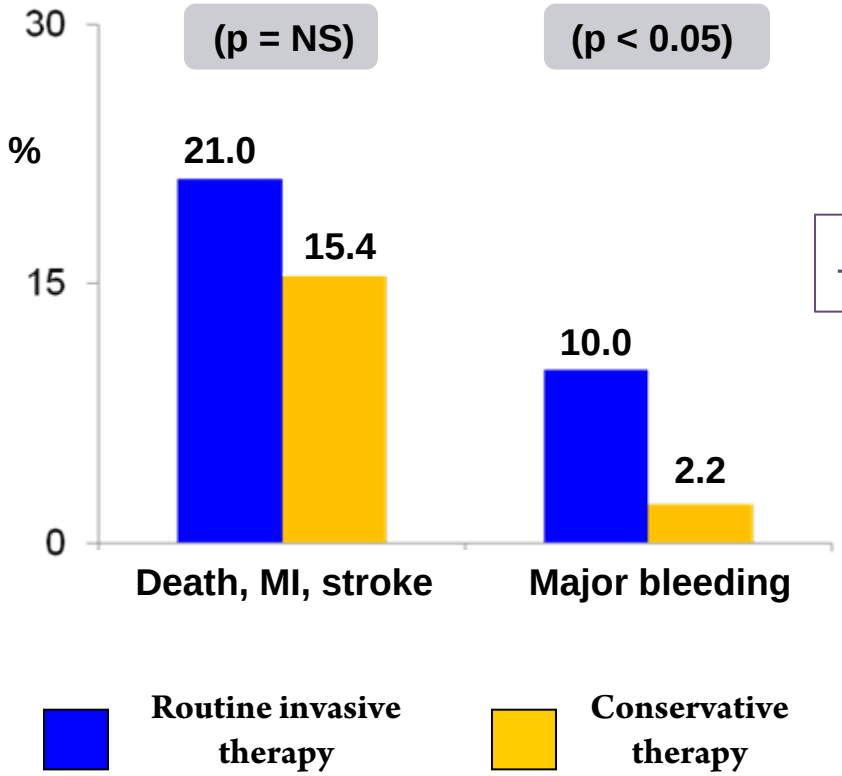
Eur Heart J 2004; 25: 1471-1472

Trials Pitfalls

- → TIMI IIIB: High crossover to the invasive therapy (64% angio 1 month and 58% revascularization by 1 year!)
- → VANQWISH: High CABG operative mortality (12%)
- → Both TIMI IIIB and VANQWISH performed before GP IIb/IIIa inhibitors and stenting era
- → FRISC II: the benefit restricted to men (1 and 5 years)
- → TACTIS-TIMI 18: equivalent benefit (m/f)

Invasive Strategy in Women With NSTE ACS

OASIS 5 Sub study

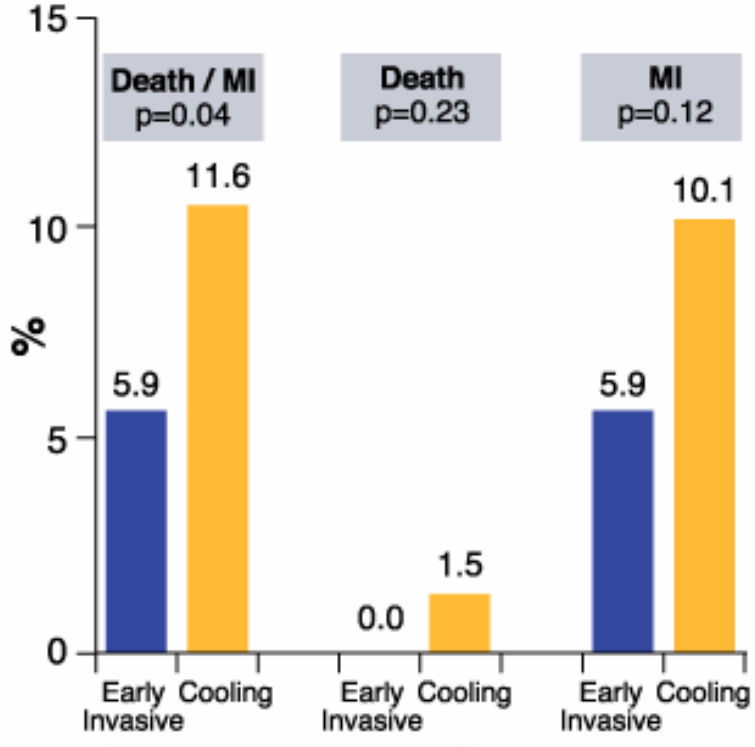


→Small sample size trial (184)

Eur Heart J 2009;Feb 7

PCI Timing: How Early is "Early"

ISAR-COOL trial



→The benefit was entirely due to a reduced incidence of events prior to Dx cath.

→There was no difference in the incidence of events after cath.

→BUT…

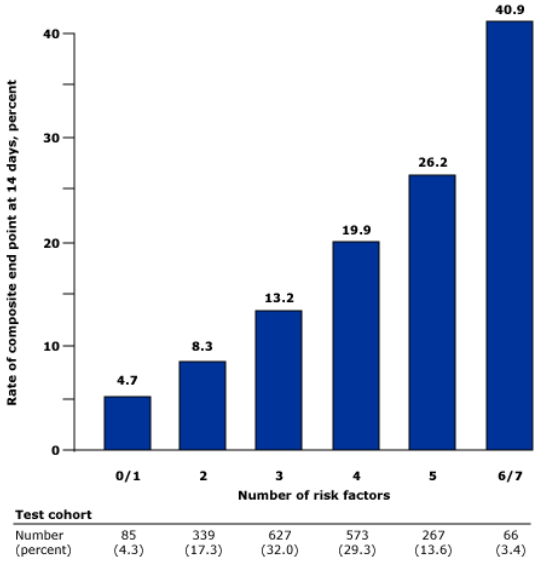
→Small sample size trial

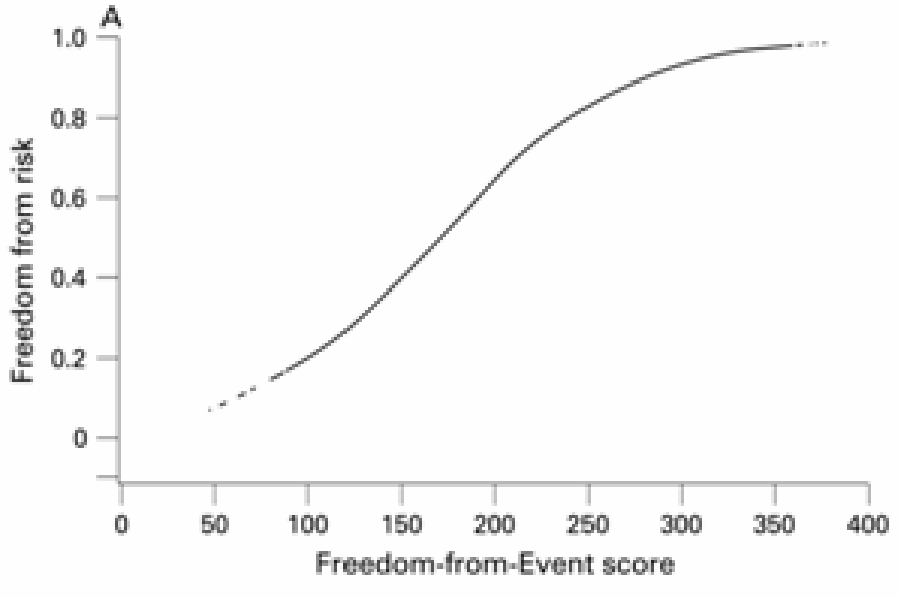
J Am Coll Cardiol, 2006; 48:1319-1325

4.3 Management Strategies

Low Risk Patient Approach

Low Risk ≠ No Risk



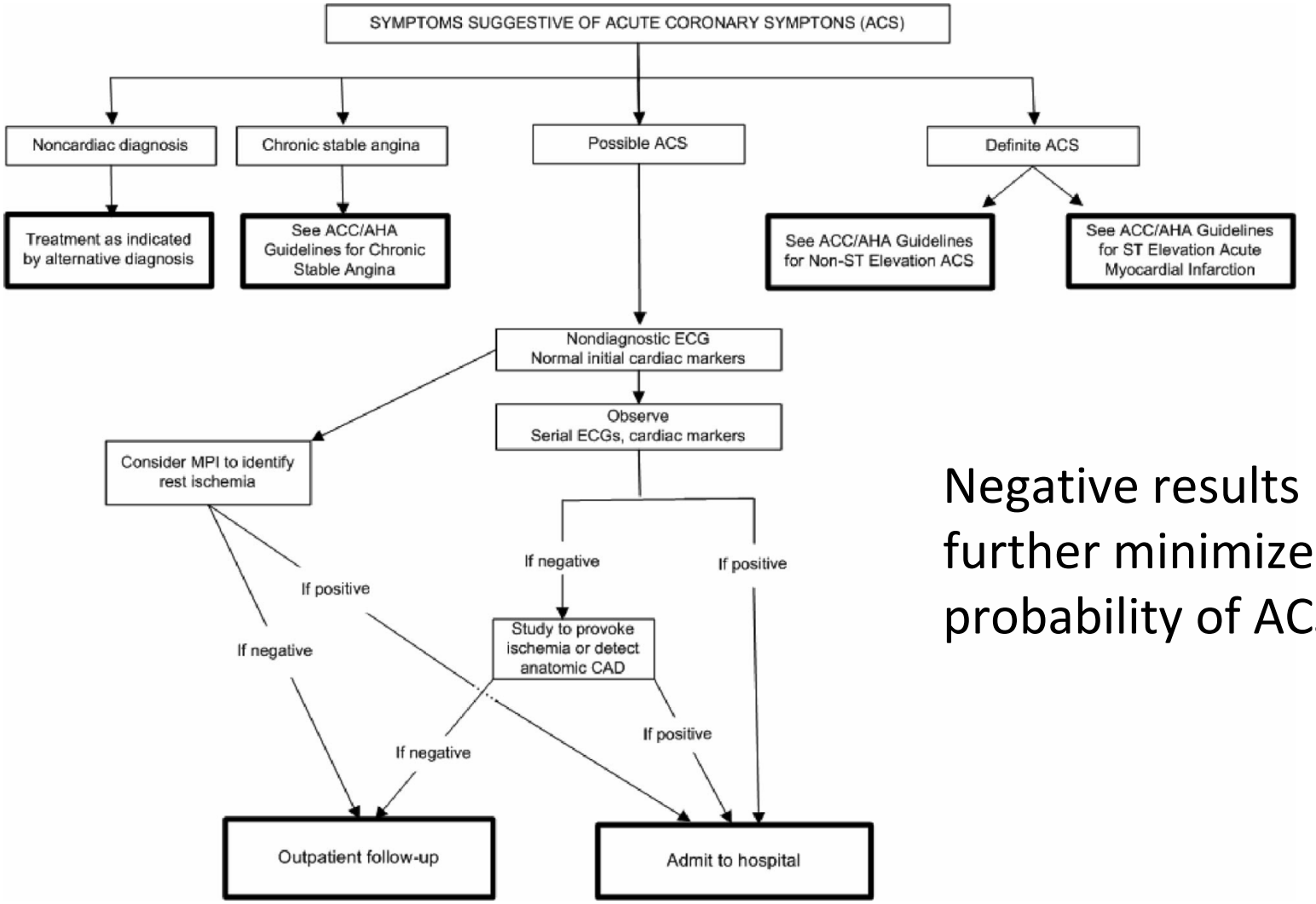


Remember…TIMI score 0: 2.1%, TIMI score1: 4.7%, TIMI score 2: 8.3% events

→"Freedom from events" score (GRACE database) Very low in-hospital mortality (<0.5%) and an uncomplicated clinical course (>93% event-free in hospital)

Heart. 2009 Jun;95(11):888-94

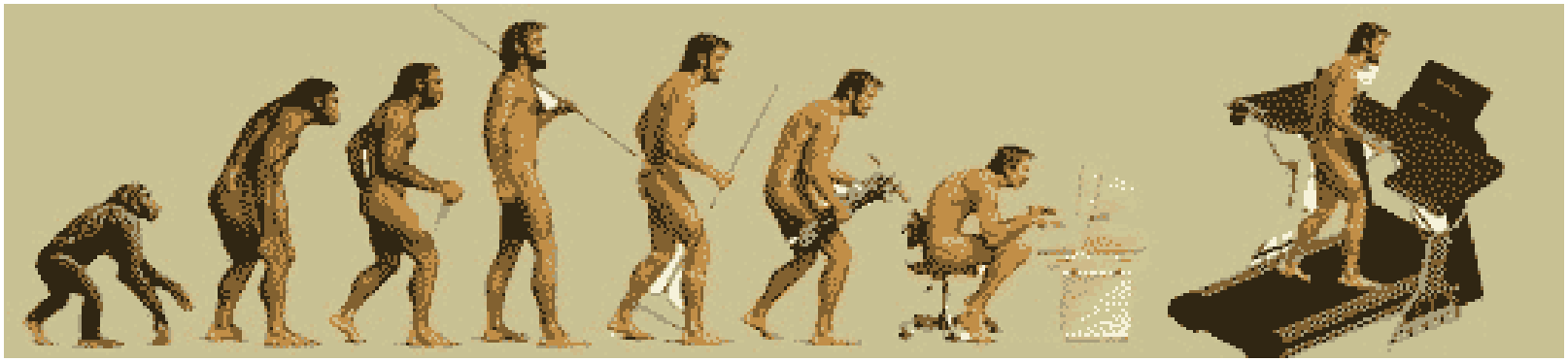
New Concept: Confirmatory Test



Negative results further minimize the probability of ACS.

Exercise Treadmill Testing

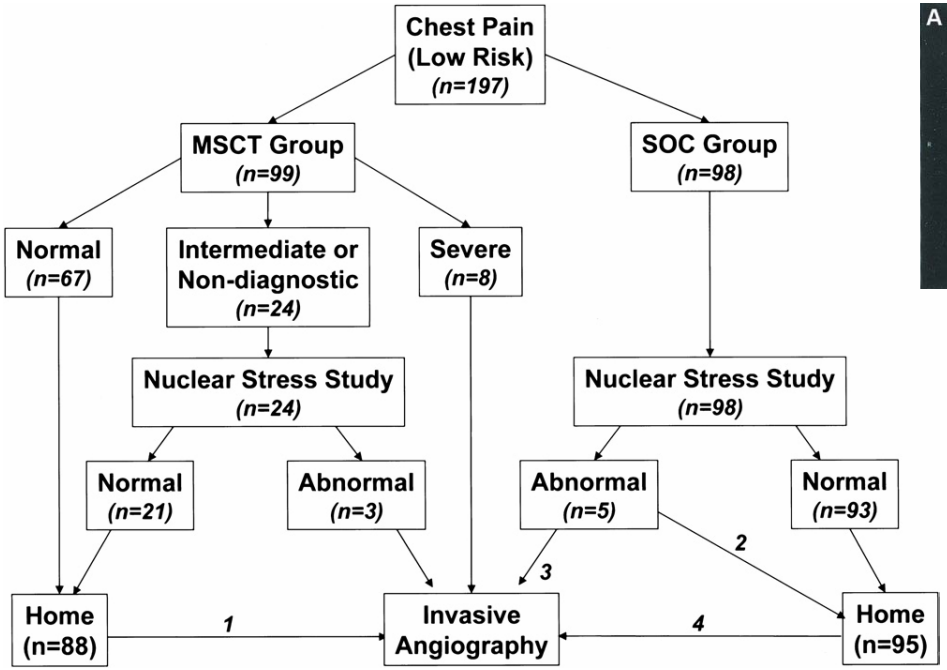
Concept evolution

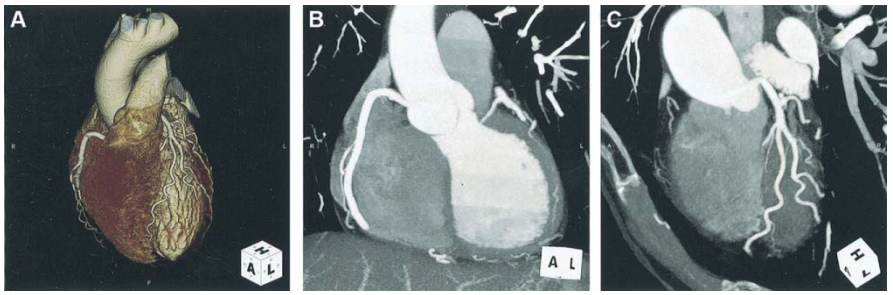


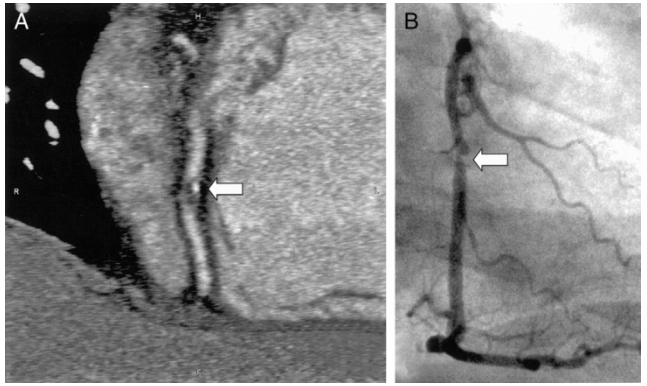
Advantages:

- ✓Low cost
- ✓Easy implementation
- ✓Low tech

64-slice CCTA



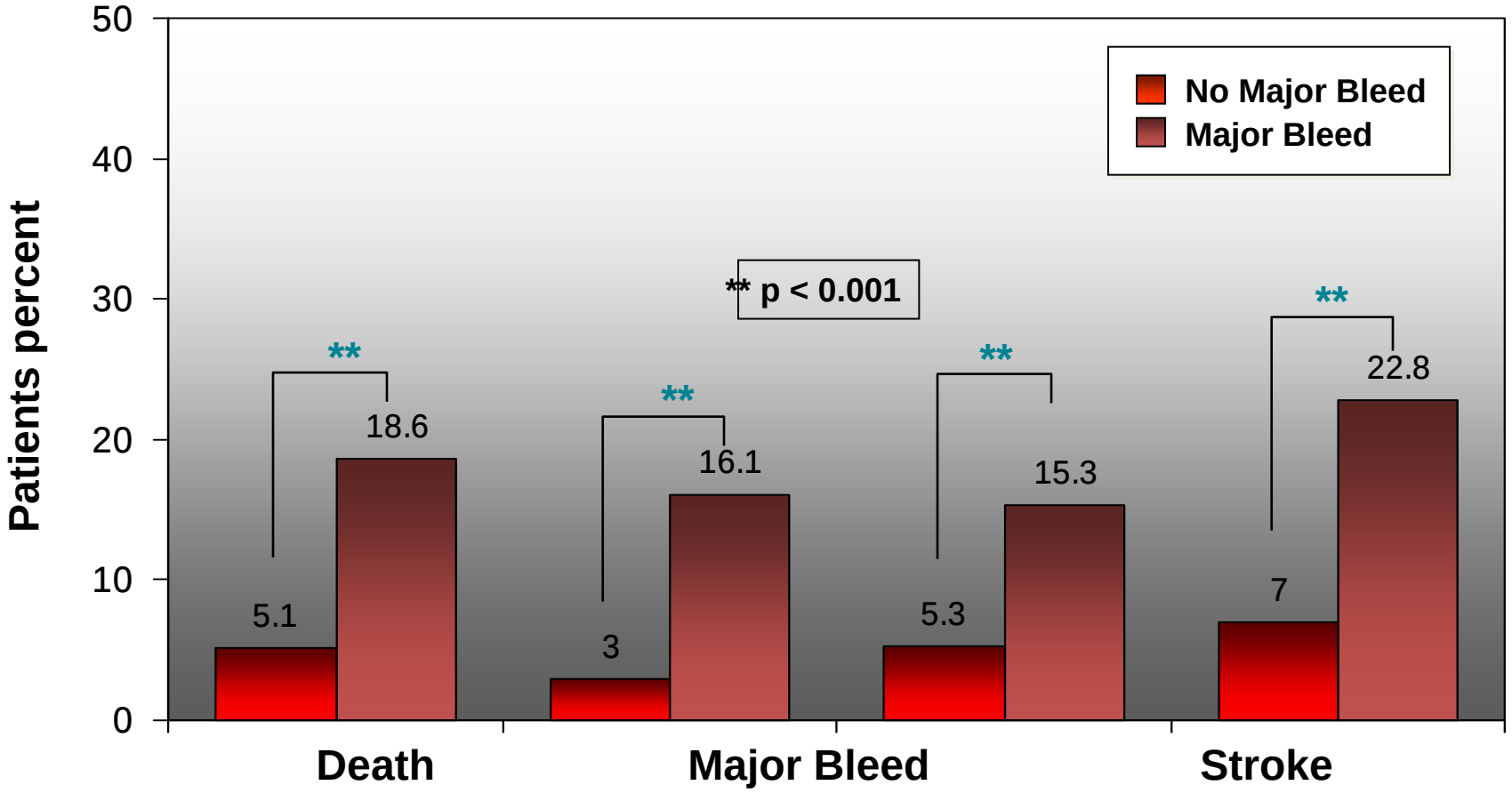




Goldstein JA et al, J Am Coll Cardiol. 2007 27;49(8):863-71

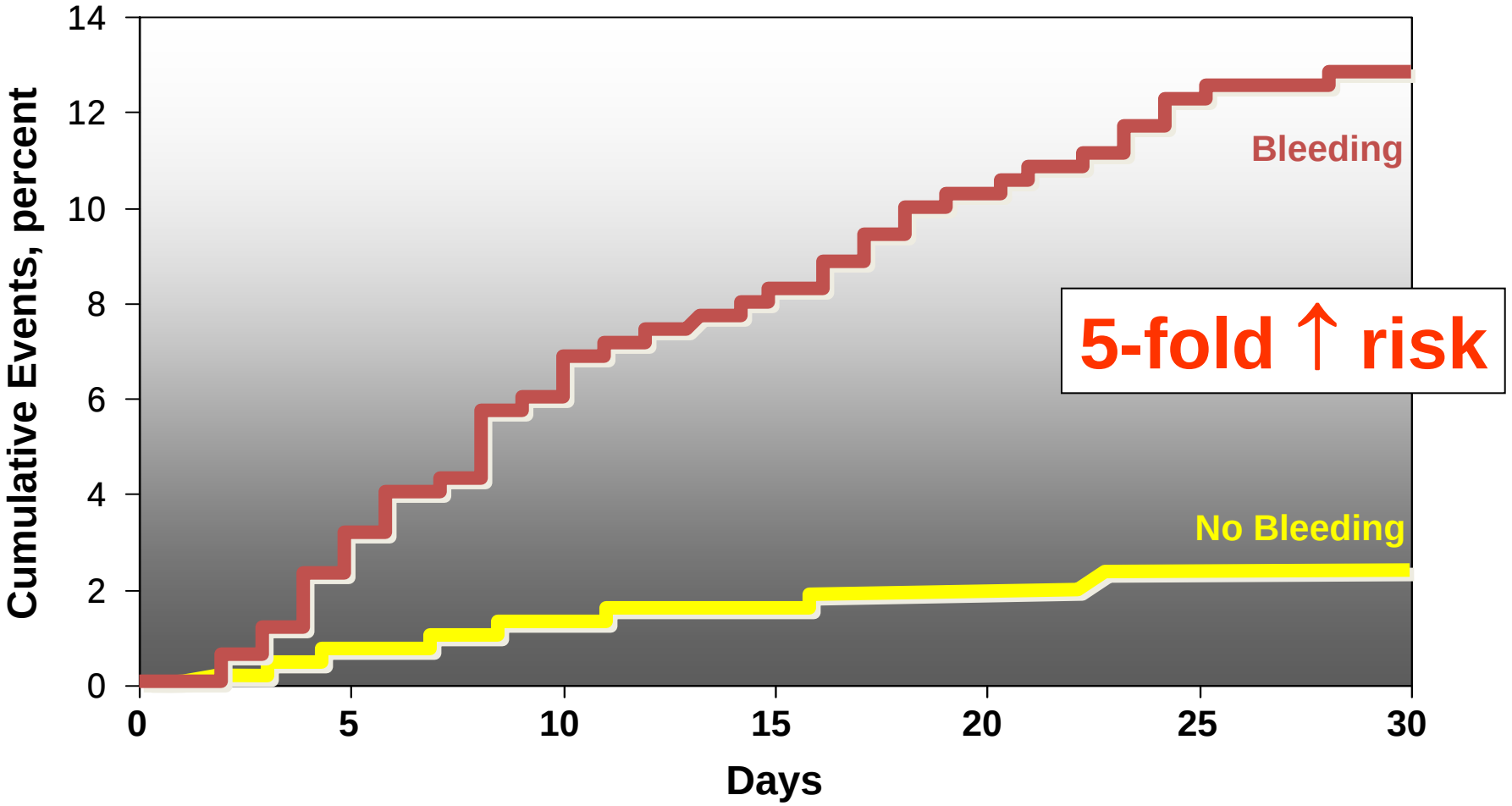
5. Complications

In-Hospital Death Rates in Patients According to Major Bleeding



Moscucci M et al. *Eur Heart J 2003;24:1815-23.*

30 Day Death According to Bleeding
OASIS Registry, OASIS-2, CURE

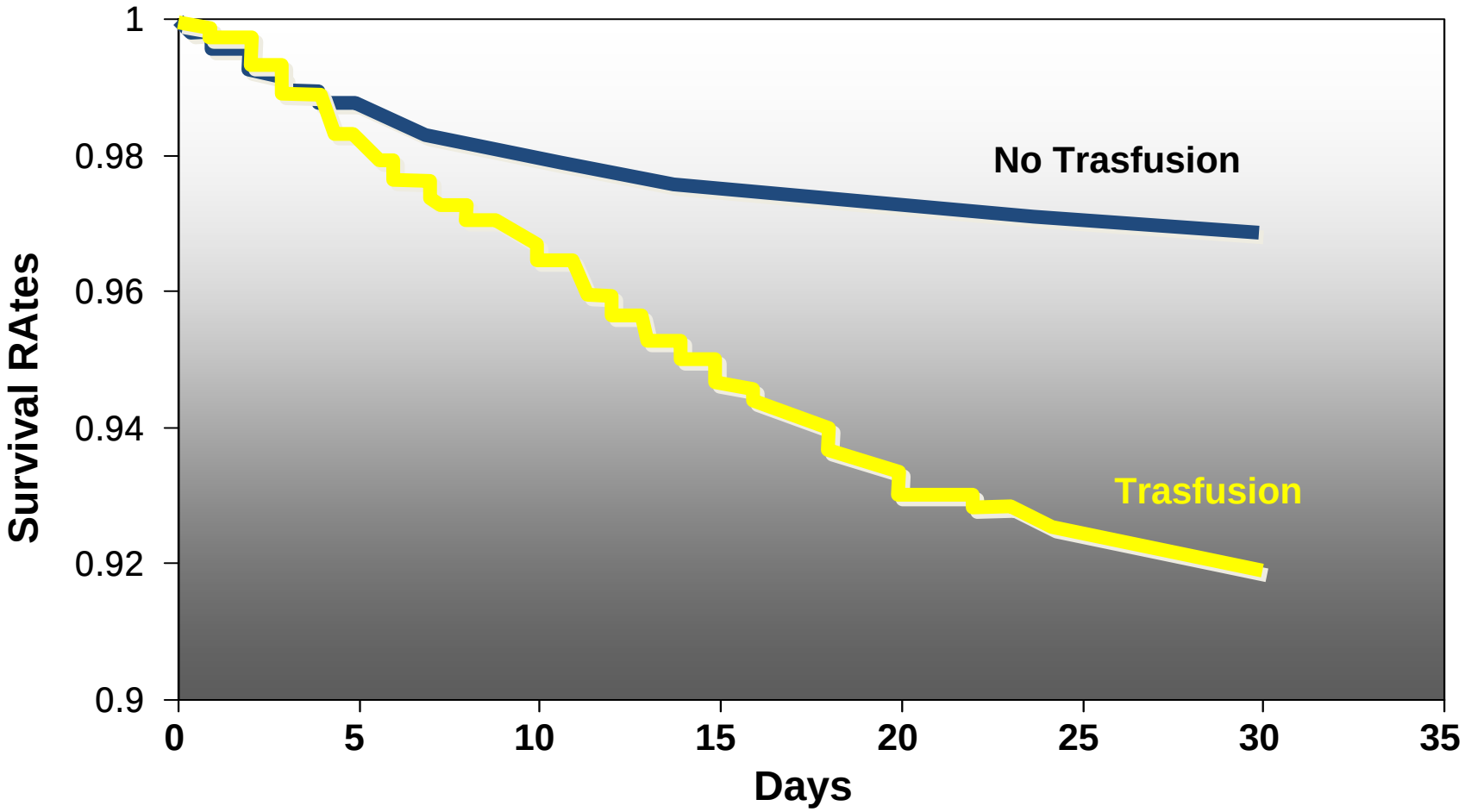


Eikelboom Circulation 2006;114: 774 - 782

30 Day Survival by Transfusion Group

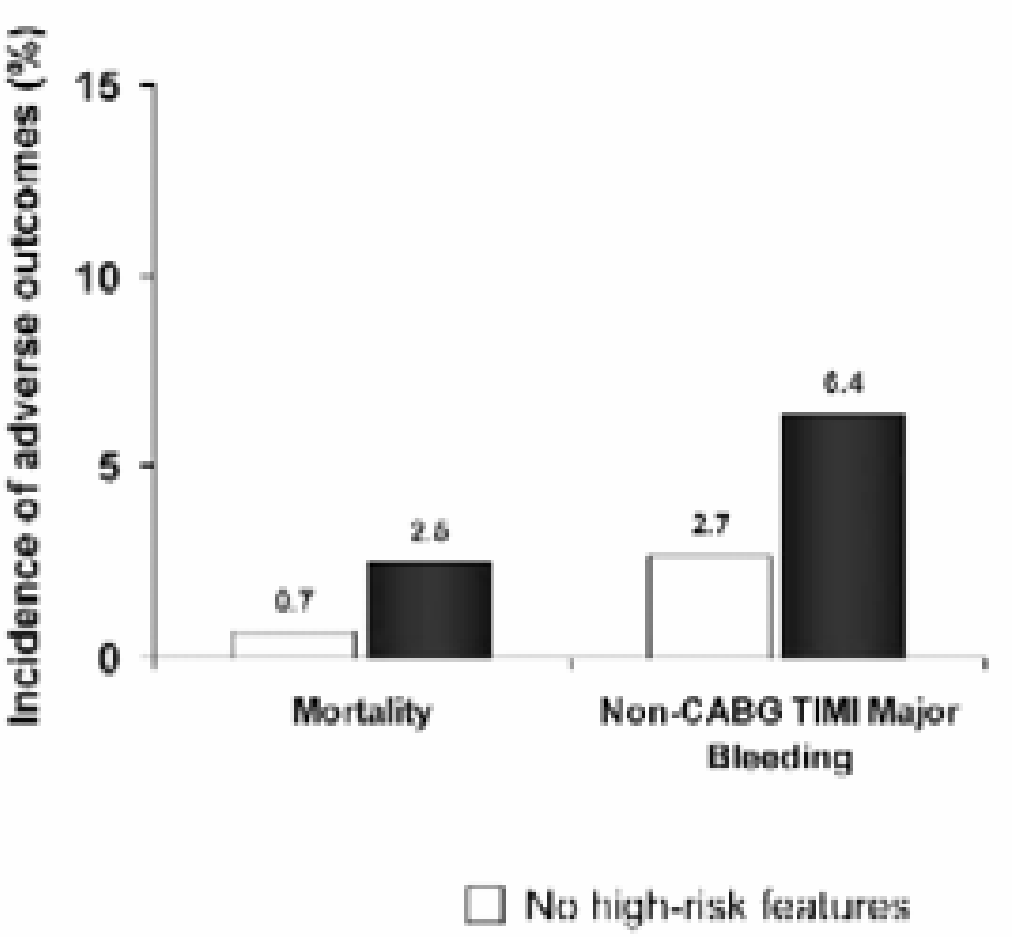
GUSTO IIb, PURSUIT, PARAGON B

(n=24,000 10% transfused)



Rao SV, JAMA 2004;292:1555

Bleeding Risk



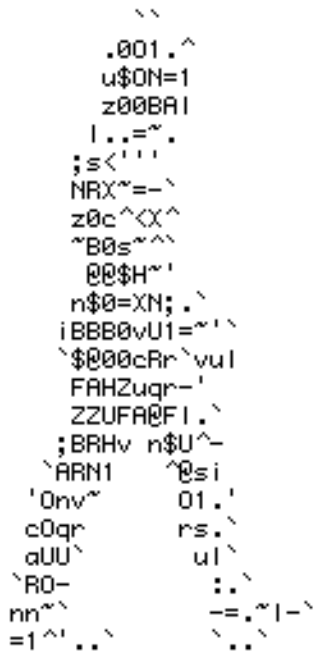
Circulation. 2008;118:S-916

A New Concept is Born

1. Bleeding carries a high risk of death, MI and stroke
2. Rate of major bleeding is as high as the rate of death at the acute phase of NSTE-ACS
3. Prevention of bleeding is equally as important as prevention of ischemic events and results in a significant risk reduction for death, MI and stroke
4. Risk stratification for bleeding should be part of the decision making process

Summery

- Epidemiology differences with STEMI pts
- Clinical implications of the pathophysiology
- Update and critical overview of the literature
- Emerging concepts: bleeding risk, confirmatory test for low risk pts,



Good Luck!

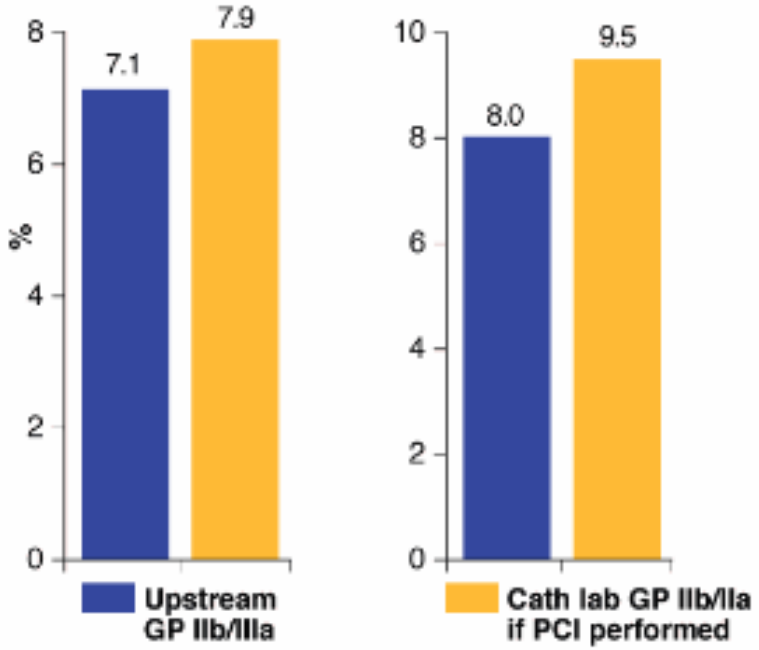
Apendix

ACUITY Timing

Trial Design: ACUITY Timing was a randomized trial within the main ACUITY trial of GP IIb/IIIa inhibitor administration upstream prior to angiography (n=4605) or during PCI as needed (n=4602) among patients with non-ST elevation acute coronary syndromes.

All patients:
Death, MI, revascularization for ischemia by 30 days
p = NS for non-inferiority
p = 0.13 for superiority

PCI treated Patients:
Death, MI, revasc for ischemia by 30 days
p = 0.05 for superiority



Results

- GP inhibitors used in 99% of early group and 56% of delayed group; mean time to from randomization to catheterization 6.2 hours
- Net clinical benefit non-inferior for upstream vs delayed administration (11.7% each, p<0.001 for non-inferiority)
- Triple ischemic endpoint did not meet criteria for non-inferiority (Figure)
- In cohort who received PCI (n=5,170), composite ischemic endpoint ↓ in upstream therapy group (Figure)
- Major bleeding ↓ in delayed group (4.9% vs 6.1%, p=0.009)

Conclusions

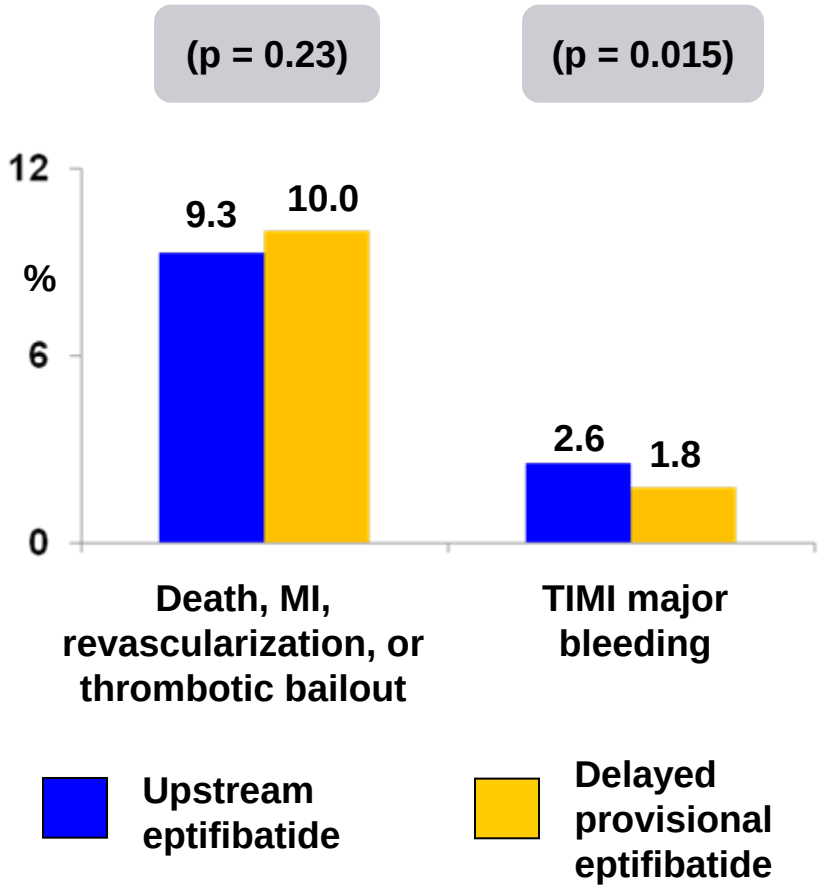
- Among patients with non-ST elevation ACS, upstream therapy with GP IIb/IIIa inhibitors was non-inferior for net-clinical benefit endpoint compared with delayed administration of GP IIb/IIIa inhibitor therapy, but did not meet criteria for non-inferiority for ischemic endpoint

www.cardiosource.com

JAMA. 2007;297:591-602

EARLY ACS

Trial design: Patients with NSTE ACS were randomized to upstream eptifibatide and 18- to 24-hour infusion (n = 4,722) versus upstream placebo and provisional eptifibatide immediately prior to PCI (n = 4,684).



Results

- Death, MI, revascularization, or thrombotic bailout at 96 hours: 9.3% with upstream eptifibatide vs. 10.0% with provisional eptifibatide (p = 0.23)
- Death or MI at 30 days: in 11.2% vs. 12.3% (p = 0.08), respectively
- TIMI major bleeding: 2.6% vs. 1.8% (p = 0.015), respectively

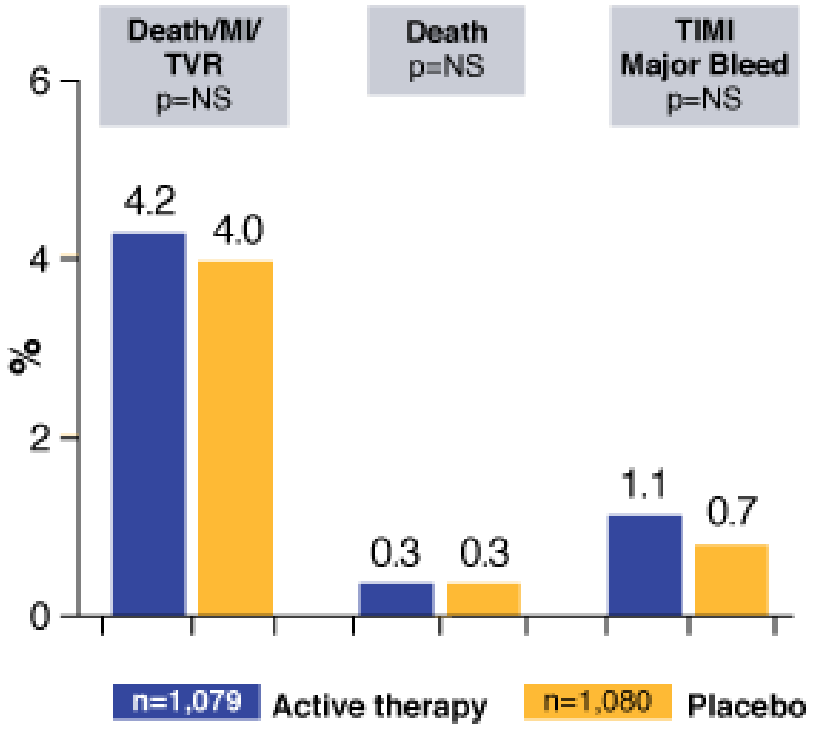
Conclusions

- Among patients with NSTE ACS treated with aspirin, clopidogrel, and heparin, there was no benefit to upstream eptifibatide compared with provisional use immediately prior to PCI
- Upstream use of eptifibatide increased major bleeding

Giugliano RP, et al. N Engl J Med 2009;360:2176-90

ISAR REACT

Trial Design: The ISAR REACT trial was a randomized, blinded trial of treatment with abciximab (n=1,079) compared with placebo (n=1,080) in low-risk patients pretreated with clopidogrel (600 mg loading dose, 2x75 mg/d through discharge, 75mg/d for 4 weeks) who undergo coronary stenting. The primary endpoint was composite of death, MI, and urgent target vessel revascularization within 30 days.



www.cardiosource.com

Results

- No difference in primary endpoint of death, MI or urgent TVR
- No difference in any components of composite
- No difference in TIMI major (Figure) or minor bleed (2.5% vs 1.9%, p=0.38) but more thrombocytopenia (0.9% vs 0%) and transfusions (2.4% vs 0.9%, p<0.05) in abciximab arm

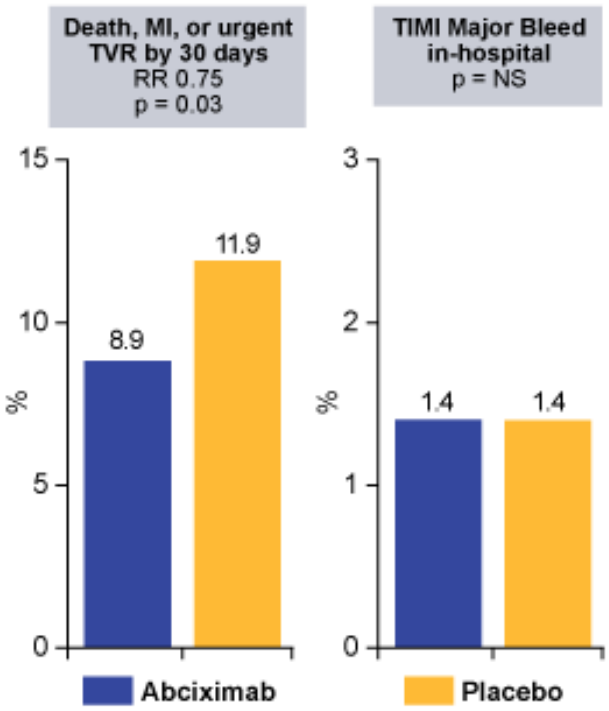
Conclusions

- Among low-risk patients with coronary disease pretreated with high-dose clopidogrel and undergoing elective coronary stenting, treatment with abciximab was not associated with a reduction in the primary composite endpoint of death, MI or urgent TVR at 30 days
- Patients were very low risk, excluding patients with insulin-dependent diabetes, ACS, and positive biomarkers
- Cannot extrapolate these data to higher risk patients such as ACS patients
- Clopidogrel loading dose was higher loading dose commonly used with stenting
- UFH dose ↑ in placebo arm (2 boluses of 70 U/kg)

N Engl J Med 2004;350:232-8

ISAR-REACT 2

Trial Design: ISAR-REACT 2 was a randomized, double-blind trial of treatment with abciximab (n=1012) or placebo (n=1010) among patients with non-ST elevation ACS undergoing PCI who were pre-treated with 600 mg loading dose of clopidogrel. Primary endpoint was composite of death, MI, or urgent target vessel revascularization due to myocardial ischemia by 30 days.



Results

- Patients relatively high-risk, with 74% having multivessel disease and 52% troponin positive
- Primary endpoint ↓ in abciximab group vs placebo (Figure), as was death or MI (8.6% vs 11.5%, RR 0.75, p<0.05)
- Abciximab most effective in troponin + patients (n=1049; 13.1% vs 18.3%, RR 0.71, p=0.02) with no difference in troponin - patients (n=973; 4.6% each, RR 0.99, p=0.98; interaction p=0.07)
- No difference in TIMI major bleeding

Conclusions

- Among patients undergoing PCI for non ST elevation ACS who were pre-treated with high-dose clopidogrel, treatment with abciximab was associated with reduction in death, MI or urgent TVR by 30 days compared with placebo
- Data show that even on background of 600 mg loading dose of clopidogrel, high-risk patients with ACS undergoing PCI benefit from administration of GP IIb/IIIa inhibitor

JAMA 2006;295 1531-1538

Potential Mechanisms of Clopidogrel Resistance

Extrinsic mechanisms

1. Patient non-compliance
2. Under-dosing or inappropriate dosing of clopidogrel
3. Drug-drug interactions involving CYP3A4

Intrinsic mechanisms

1. Genetic variables

a. Polymorphisms of $P2Y_{12}$ receptor

b. Polymorphisms of CYP3As

2. Increase release of ADP

3. Alternate pathways of platelet activation:

a. Failure to inhibit catecholamine-mediated platelet activation (epinephrine)

b. Greater extent of $P2Y_1$-dependent platelet aggregation

c. Up-regulation of $P2Y_{12}$-independent pathways (thrombin, thromboxane A_2, collagen)

ADP = adenosine diphosphate; CYP3As = cytochrome P450 3As

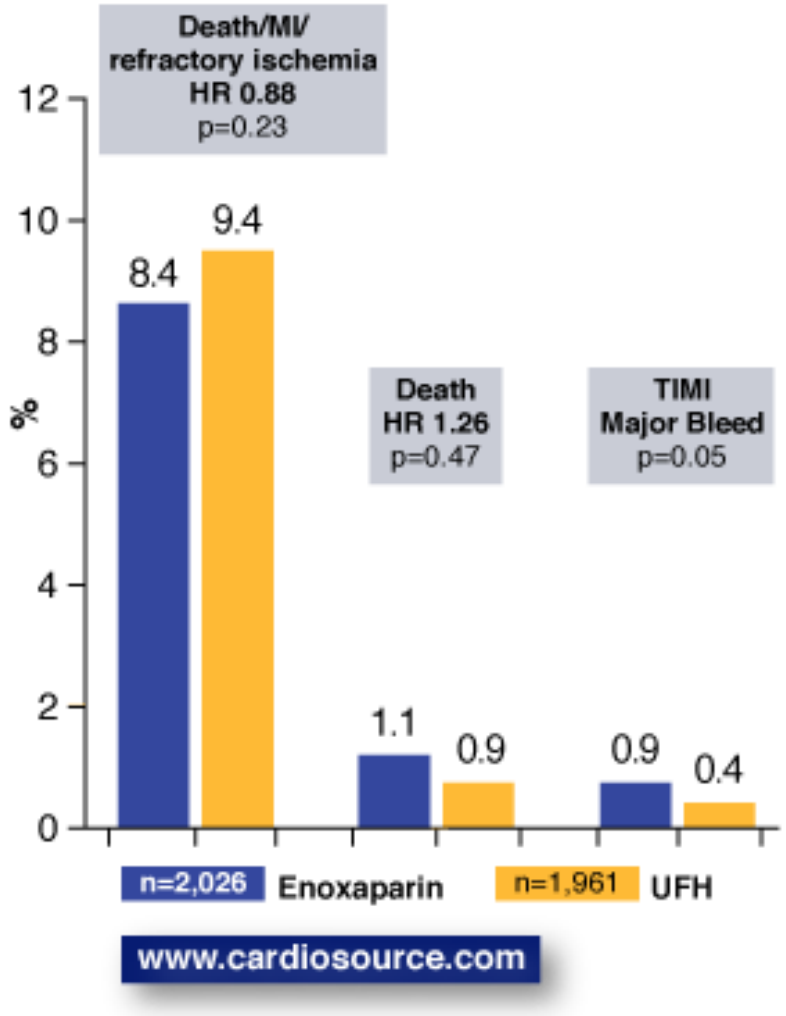
ACC/AHA guideline summary: Antiplatelet therapy in patients with unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI)

Class I - There is evidence and/or general agreement that antiplatelet and anticoagulation therapy in patients with UA or NSTEMI should be given in the following settings:
Antiplatelet therapy should be given as soon as possible after presentation.*
1. Aspirin (ASA) is the preferred first antiplatelet agent and is continued indefinitely.
2. Clopidogrel (loading dose followed by maintenance dose) is given to hospitalized patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance.
3. When an early noninterventional approach is planned, clopidogrel should be given in addition to aspirin and anticoagulant therapy to all hospitalized patients as soon as possible after presentation.
a. Clopidogrel is continued for at least one month and ideally for up to one year.
b. Clopidogrel should be withheld for five to seven days prior to planned coronary artery bypass graft surgery (CABG). Aspirin should be continued during this time.
4. In patients with a history of gastrointestinal bleeding, drugs to minimize the risk of recurrent bleeding should be given to patients taking ASA or clopidogrel.
5. In patients when an early invasive strategy is planned, clopidogrel OR a glycoprotein IIb/IIIa inhibitor should be given in addition to aspirin before angiography (invasive strategy).
6. For all patients, anticoagulation, in addition to antiplatelet therapy, with either subcutaneous low molecular weight heparin (LMWH), intravenous unfractionated heparin (UFH), or fondaparinux (or bivalirudin as a fourth choice for an invasive strategy) should be given as soon as possible after admission.•
Class IIa - The weight of evidence or opinion is in favor of benefit from antiplatelet therapy in patients with UA or NSTEMI in the following settings:
A glycoprotein IIb/IIIa inhibitor AND clopidogrel may be given, in addition to ASA, when the patient is scheduled for angiography (invasive strategy).
In addition to aspirin, heparin, and clopidogrel, a GP IIb/IIIa inhibitor may be added in patients who have recurrent ischemic discomfort and are then scheduled for diagnostic angiography (initial conservative strategy).
When bivalirudin is used as the anticoagulant before angiography, upstream glycoprotein IIb/IIIa inhibitor may be omitted as long as aspirin or clopidogrel (300 mg) were administered at least six hours before the procedure.
Class IIb - The evidence or opinion is less well established that antiplatelet and anticoagulation therapy is beneficial in patients with UA or NSTEMI in the following setting:
Eptifibatide or tirofiban, in addition to ASA, clopidogrel, and anticoagulant, in patients without continuing ischemia in whom PCI is not planned.
In addition to aspirin, heparin, and clopidogrel, a GP IIb/IIIa inhibitor may be added in patients who have recurrent ischemic discomfort and are then scheduled for diagnostic angiography (initial conservative strategy).
Class III - There is evidence that antiplatelet therapy in patients with UA or a NSTEMI is not useful and may be harmful in the following setting:
Abciximab administration in patients in whom PCI is not planned.

* Please see text for antiplatelet dosing.
• Please see text for the choice of anticoagulant and dosing.

A to Z: Phase A

Trial Design: The A to Z, Phase A trial was a randomized, open label trial of treatment with enoxaparin (n=2026) or UFH (n=1961) as adjunctive therapy to baseline treatment with tirofiban and aspirin in patients with non-ST elevation acute coronary syndromes. The primary endpoint was non-inferiority for the composite of all-cause mortality, recurrent MI, and refractory ischemia by 7 days.



Results

- Trial met pre-specified hypothesis of non-inferiority with enoxaparin for death, MI or refractory ischemia
- Upper 95% CI (HR 1.05) fell within the pre-specified non-inferiority boundary (HR 1.144)
- No difference in any component of composite
- Safety endpoints did not differ significantly: TIMI major bleed (Figure), TIMI major or minor bleed (3.0% vs 2.2%, p=0.13) or transfusion (1.0% vs 0.8%, p=NS)

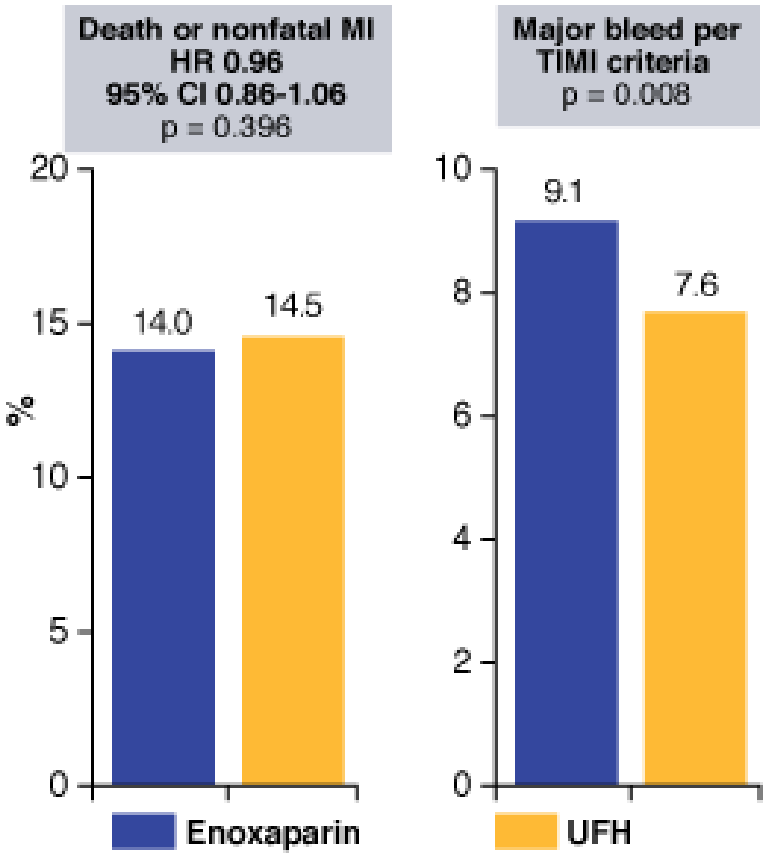
Conclusions

- Among patients with non-ST elevation acute coronary syndromes treated with aspirin and tirofiban, treatment with enoxaparin was non-inferior for death, MI or refractory ischemia at 7 days compared with UFH
- First randomized trial to look at enoxaparin vs UFH in patients who all received GP IIb/IIIa inhibitor
- SYNERGY trial addresses efficacy of enoxaparin vs UFH in patients who are all treated with an early invasive therapy (~60% of patients in A to Z treated early invasive)
- Results of "Z Phase" (simvastatin vs standard care) pending

JAMA. 2004;292:55-64

SYNERGY

Trial Design: SYNERGY was a multi-center, randomized, open-label trial of enoxaparin (n=4,993; s.c. 1 mg/kg every 12 hours) or UFH (n=4,985; bolus of 60 U/kg and initial infusion of 12 U/kg/h) in high-risk patients with non-ST-segment elevation acute coronary syndromes (ACS) treated with an early invasive strategy. Primary endpoint was death or nonfatal myocardial infarction at 30 days.



Results

- Primary endpoint of death or nonfatal MI at 30 days did not meet superiority criteria (Figure; p=0.396) but did meet pre-specified non-inferiority criteria (below HR upper bound 95% confidence interval of 1.1)
- No difference in mortality (3.2% vs 3.1%, p=0.71) or infarction (11.7% vs 12.7%, p=0.14)
- In subgroup analysis of patients not pre-treated with anti-coagulation therapy (n=2,440), primary endpoint ↓ in enoxaparin group (12.6% vs 14.8%%, HR 0.84, 95% CI 0.68-1.05)
- Major bleed per TIMI criteria ↑ in enoxaparin arm (Figure) but no significant difference when using GUSTO criteria (2.7% vs 2.2%, p=0.08)

Conclusions

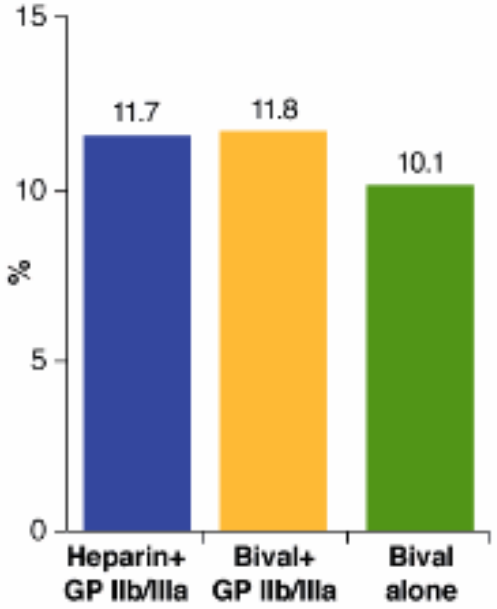
- Among high-risk patients with non-ST elevation MI ACS treated with an invasive management strategy, use of enoxaparin was non-inferior compared with use of UFH for death or MI at 30 days, but TIMI major bleeding was elevated with enoxaparin

JAMA. 2004;292:45-54

ACUITY

Trial Design: ACUITY was a randomized trial of UFH or enoxaparin plus a GP IIb/IIIa inhibitor (n=4603), bivalirudin plus a GP IIb/IIIa inhibitor (n=4604), or bivalirudin alone (n=4612) among patients with non-ST elevation acute coronary syndromes. Patients in the first two arms were sub-randomized to upstream or cath lab administration of the GP IIb/IIIa inhibitor for the ACUITY timing trial.

Death, MI, revascularization for ischemia, or major bleeding
by 30 days
p=0.015 for superiority of bivalirudin alone vs hep+GP
p < 0.001 for non-inferiority of hep+GP vs bival+GP



www.cardiosource.com

Results

- Management strategy PCI in 56% of patients, medical therapy in 33% and CABG in 11%
- Net clinical benefit significantly improved in bivalirudin alone group vs UFH / Enox plus GP IIb/IIIa group and non-inferior for UFH / Enox plus GP IIb/IIIa group vs bivalirudin plus GP IIb/IIIa group (Figure)
- Compared with heparin plus GP IIb/IIIa group (7.3%), composite ischemic endpoint non-inferior for bivalirudin alone group (7.8%) and bivalirudin plus GP IIb/IIIa group (7.7%)
- Major bleeding ↓ for bivalirudin alone group vs heparin plus GP IIb/IIIa group (3.0% vs 5.7%, p<0.001 for superiority), and non-inferior but not superior for bivalirudin plus GP IIb/IIIa inhibitor vs UFH / Enox plus GP IIb/IIIa (5.3% vs 5.7%)

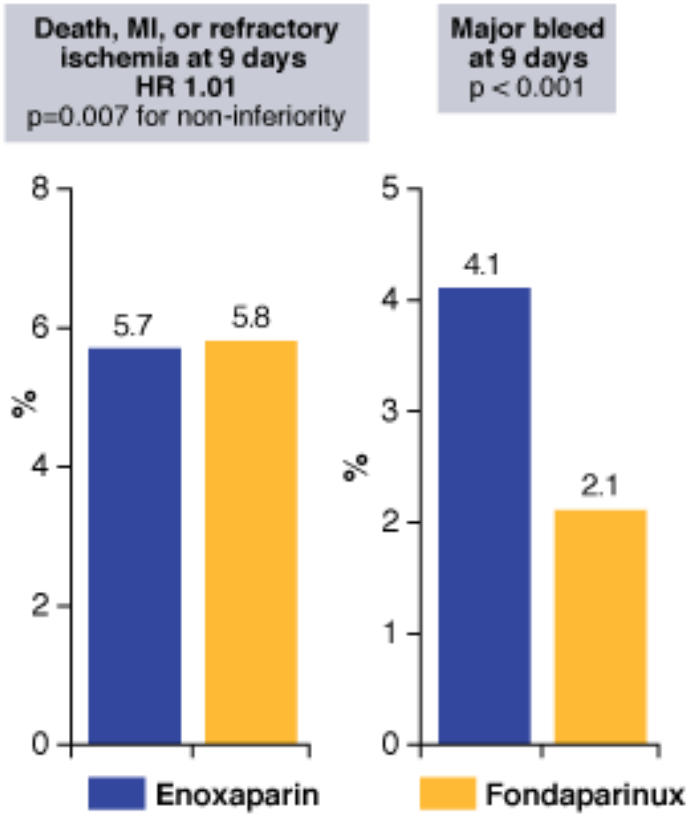
Conclusions

- Among patients with non-ST elevation ACS, treatment with bivalirudin alone was associated with improvement in net clinical benefit endpoint compared with UFH/Enox plus GP IIb/IIIa inhibitors, driven primarily by reduction in bleeding
- Additionally, bivalirudin plus GP IIb/IIIa inhibitor was shown to be non-inferior for net clinical benefit endpoint compared with UFH/Enox plus GP IIb/IIIa inhibitor

N Engl J Med. 2006;355:2203-16

OASIS-5

Trial Design: OASIS-5 was a randomized, open-label trial of fondaparinux (2.5 mg/day, n=10,057), a new anticoagulant, compared with enoxaparin (1.0 mg/kg twice daily, n=10,021) in patients with non-ST elevation acute coronary syndromes. Primary efficacy endpoint was death, MI, or refractory ischemia at 9 days assessed for non-inferiority (upper bound of CI 1.185) and primary safety endpoint was major bleed at 9 days.



www.cardiosource.com

Results

- Primary efficacy endpoint of death, MI, or refractory ischemia at day 9 met non-inferiority criteria
- Major bleed by day 9 ↓ in fondaparinux group, as was minor bleed (1.1% vs. 3.2%, p<0.001)
- No difference in composite of death, MI, or refractory ischemia at 30 days (8.0% for fondaparinux vs. 8.6% for enoxaparin)
- Mortality at 30 days ↓ in fondaparinux group (2.9% vs. 3.5%, p=0.02), as was 6 month mortality (5.8% vs. 6.5%, p=0.05) and stroke (1.3% vs. 1.7%, p=0.04, but no difference in MI (6.3% vs. 6.6%, p=NS)

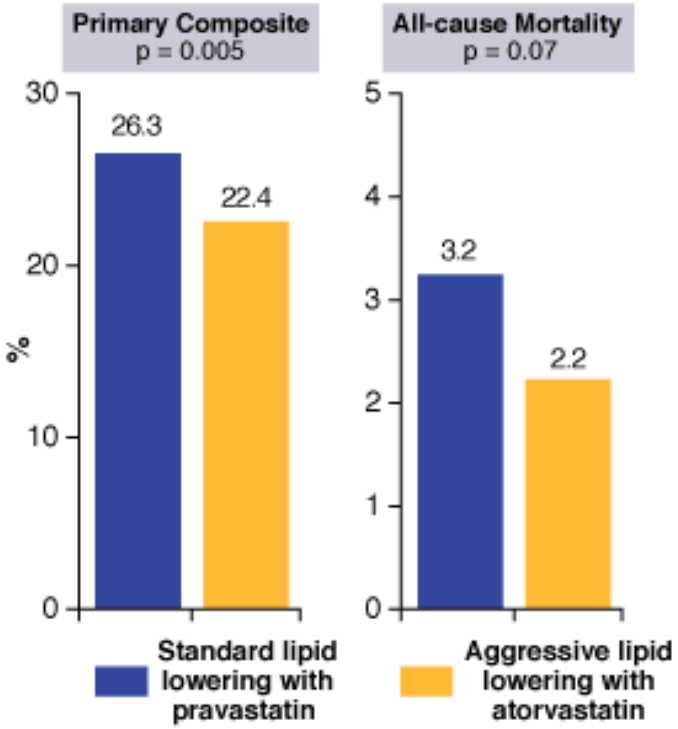
Conclusions

- Among patients with non-ST elevation acute coronary syndromes, fondaparinux was non-inferior for composite of death, MI, or refractory ischemia at day 9 vs enoxaparin
- Additionally, bleeding reduced in fondaparinux group, as was secondary endpoint of 6 month mortality
- Mortality reduction not driven by reduction in fatal coronary events, but rather by reduction in fatal bleeds
- Age subgroup analysis showed no benefit in younger patients but ↑ hazard with enoxaparin in those age >65 years, raising question of whether there was benefit with fondaparinux or whether dose of enoxaparin was too high, resulting in excess bleeding events among elderly patients

N Engl J Med 2006;354:1464-76

PROVE IT / TIMI 22 - Lipid Lowering Results

Trial Design: PROVE IT was a multi-center, randomized, blinded 2 x 2 factorial trial of standard lipid lowering with pravastatin (40 mg/day; n=2,063) or aggressive lipid lowering using atorvastatin (80 mg/day; n=2,099) in patients hospitalized for an acute coronary syndrome (ACS). Primary endpoint was composite of death, MI, unstable angina requiring rehospitalization, revascularization, and stroke at mean follow-up of 24 months.



www.cardiosource.com

Results

- LDL ↓ from 106 mg/dl at baseline in each group to 95 mg/dl in standard-dose pravastatin group and 62 mg/dl in high-dose atorvastatin group ($p<0.001$ for difference in change between treatment groups)
- Median CRP ↓ from 12.3 mg/l at baseline to 2.1 mg/l for pravastatin and 1.3 mg/l for atorvastatin ($p<0.001$)
- Primary composite endpoint ↓ in aggressive lipid lowering group (Figure)
- Mortality trended ↓ atorvastatin arm (Figure)
- ALT ≥3x ULN ↑ in atorvastatin arm (3.3% vs 1.1%, $p<0.001$)

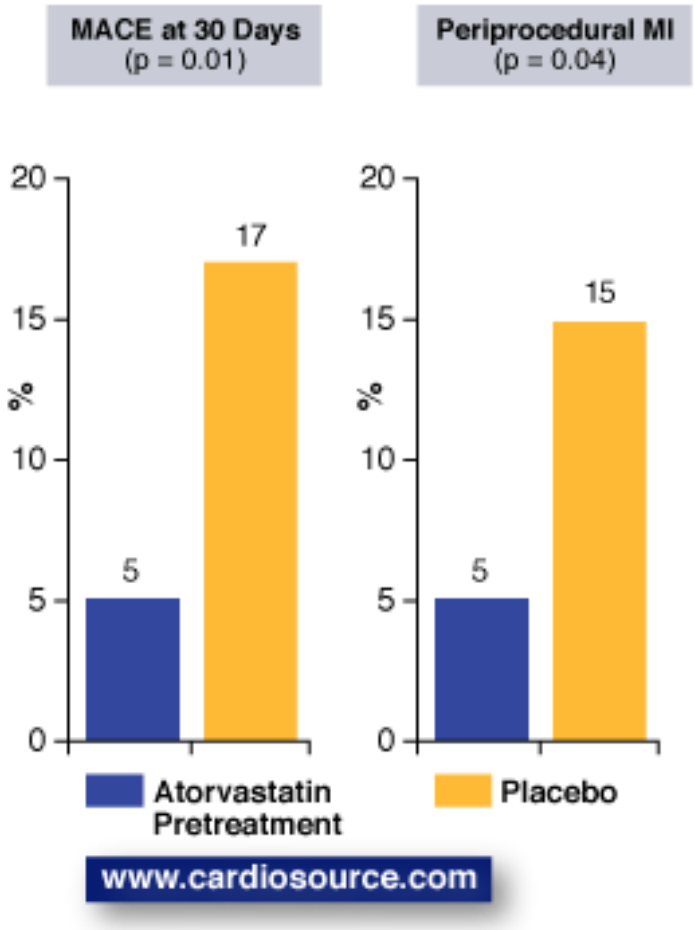
Conclusions

- Among patients hospitalized for an ACS, use of an aggressive lipid lowering strategy was associated with a reduction in the primary composite endpoint compared with standard lipid lowering strategy
- First large-scale trial to demonstrate an added clinical benefit of a more intensive lipid lowering therapy in post-ACS patients beyond current guidelines of LDL <100 mg/dL

N Engl J Med 2004;350:1495-504

ARMYDA-ACS

Trial Design: ARMYDA-ACS was a randomized, double-blind trial of pretreatment with atorvastatin (80 mg 12 hours prior to PCI and 40 mg immediately pre-PCI; n = 86) or matching placebo (n = 85) in patients with acute coronary syndromes (ACS) undergoing PCI. Primary endpoint was major adverse cardiac events (MACE; death, MI, or unplanned revascularization) at 30 days.



Results

- Index event unstable angina in 64% of patients and non-ST elevation MI in 36%
- Mean time to angiography was ~23 hours
- Primary endpoint of MACE at 30 days ↓ in atorvastatin pretreatment group vs. placebo group, driven by ↓ periprocedural MI (Figures)
- Percent increase in C-reactive protein from pre- to post-PCI ↓ in atorvastatin group (63% vs. 147%, p = 0.01)

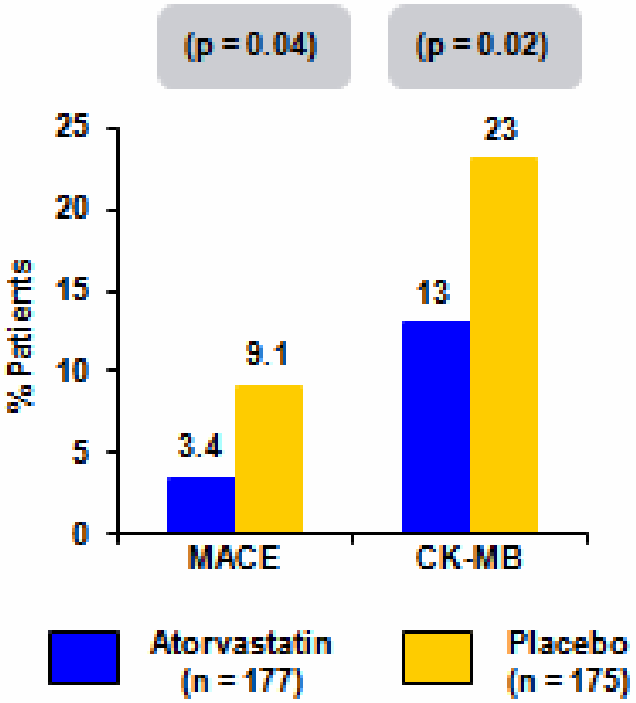
Conclusions

- Among patients with ACS undergoing PCI, pretreatment with atorvastatin 80 mg was associated with reduction in MACE at 30 days compared with placebo, driven exclusively by reduction in periprocedural MI
- Results are similar to original ARMYDA study, which also showed reduction in periprocedural MI with atorvastatin pretreatment but in low-risk, stable angina, elective PCI population

J Am Coll Cardiol 2007;49:1272-8

ARMYDA-RECAPTURE

Trial design: This study evaluated the efficacy of an atorvastatin reloading strategy in patients on chronic statin therapy undergoing PCI for stable angina or NSTEMI.



Results

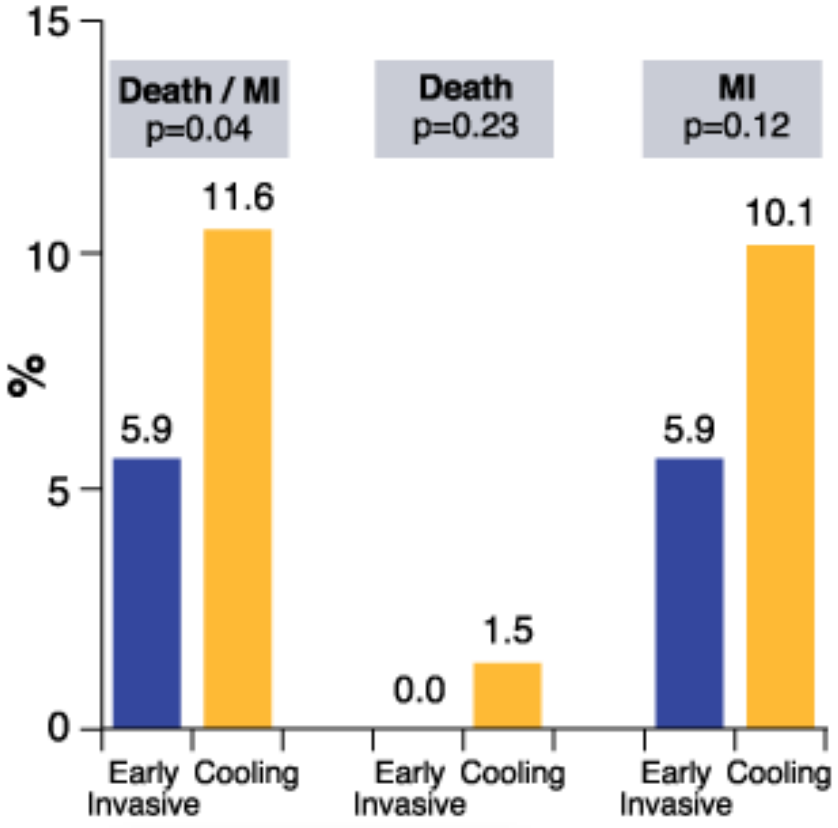
- 30-day MACE: 3.4% vs. 9.1%, p = 0.04
- CK-MB elevation: 13% vs. 23%, p = 0.02
- Troponin-I elevation: 36% vs. 47%, p = 0.03
- Peak CRP: 2.1± 6.7 vs. 3.0± 9.5, p = 0.12

Conclusions

- An 80 mg loading dose of atorvastatin followed by a 40 mg preprocedural dose may reduce the incidence of post-procedure MACE in patients on background statin therapy
- These data support a strategy of routine atorvastatin reloading prior to PCI in patients on background statin therapy

ISAR-COOL

Trial Design: ISAR-COOL was a multi-center randomized trial comparing an extended antithrombotic cooling off therapy for 72-120 hours (n=207) vs early intervention within 6 hours (n=203) in patients with unstable coronary syndromes. The primary endpoint was death or MI at 30 days.



www.cardiosource.com

Results

- ISAR-COOL based on hypothesis that an intensive antiplatelet therapy would "cool-off" the artery prior to PCI and would reduce procedure-related events
- Opposite results were seen: death/MI was higher during "cooling-off" period in the delayed arm

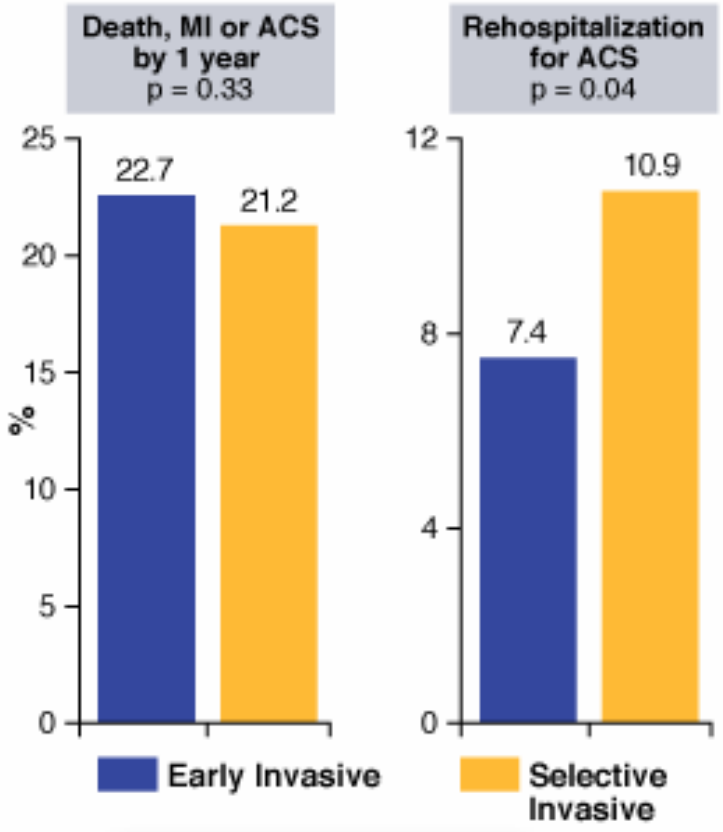
Conclusions

- As with TACTICS-TIMI 18 and FRISC II, an early intervention strategy had ↓ event rate vs delayed antithrombotic cooling strategy for ACS
- ISAR-COOL results support an early intervention strategy for ACS

JAMA. 2003;290:1593-1599

ICTUS

Trial Design: ICTUS was a randomized trial of an early invasive strategy (coronary angiography within 24-48 hours and PCI within 48 hours or CABG as soon as possible; n=604) or a selective invasive strategy (medical stabilization with angiography and revascularization only in case of refractory angina or ischemia on pre-discharge exercise testing; n=596) among patients with unstable angina who were troponin positive. Primary endpoint was composite of death, MI or rehospitalization for acute coronary syndrome (ACS) at one year.



www.cardiosource.com

Results

- Revascularization performed in 76% of early invasive group and 40% of selective invasive group
- No difference by treatment group in primary composite endpoint of death, MI, or rehospitalization for ACS at one year (Figure)
- Lack of difference in primary endpoint driven by divergent results for endpoint of MI (15.0% in early invasive vs 10.0% in selective invasive, RR 1.50, p=0.005) and rehospitalization for ACS (Figure)

Conclusions

- Among troponin positive patients with non-ST elevation ACS, treatment with an early invasive strategy was not associated with a difference in primary endpoint compared with a selective invasive strategy. However, two major components of primary endpoint, MI and rehospitalization for ACS, show treatment differences in opposite direction
- Rate of MI in present trial notably higher than other similar trials, likely reflecting peri-procedural MI given non-stringent definition of MI of CKMB>1 x ULN

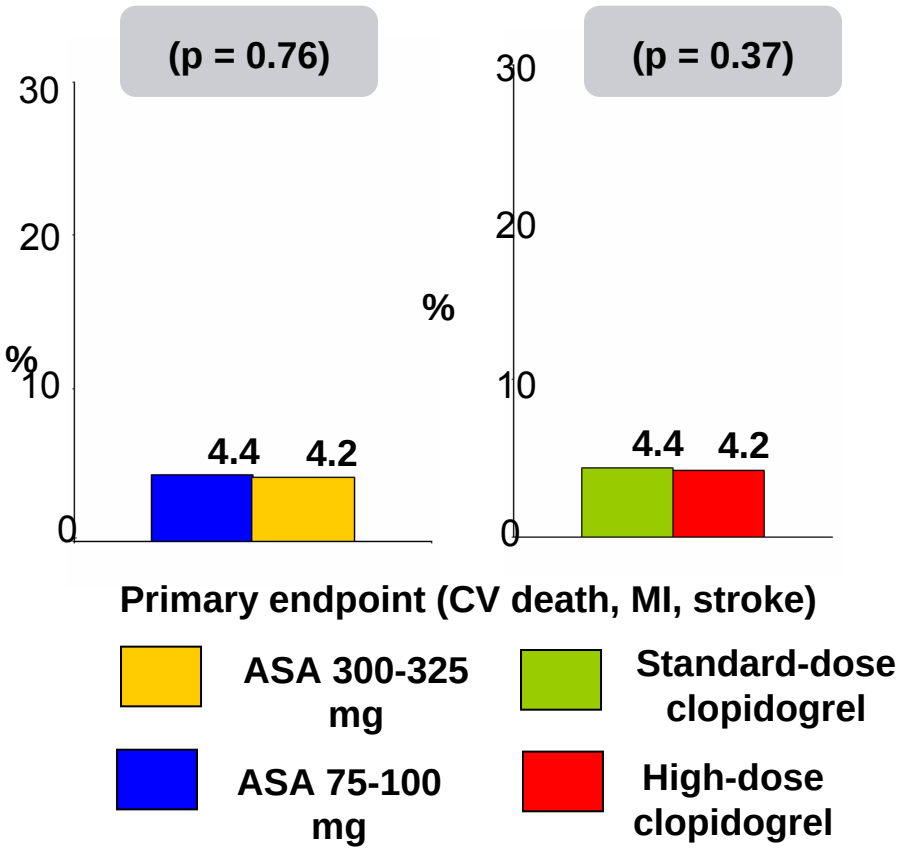
N Engl J Med 2005;353:1095-104

TIMI and GUSTO Bleeding Definitions

TIMI Bleeding Classification	
Major	Intracranial haemorrhage or clinically overt bleeding (including imaging) ≥ 5 g/dL decrease in the haemoglobin concentration
Minor	Clinically overt bleeding (including imaging) with 3 to < 5 g/dL decrease in the haemoglobin concentration
Minimal	Clinically overt bleeding (including imaging) with a < 3 g/dL decrease in the haemoglobin concentration
GUSTO Bleeding Classification	
Severe or life threatening	Either intracranial haemorrhage or bleeding that causes haemodynamic compromise and requires intervention
Moderate	Bleeding that requires blood transfusion but does not result in haemodynamic compromise
Mild	Bleeding that does not meet criteria for either severe or moderate bleeding

CURRENT OASIS 7

Trial design: Patients presenting with ACS were randomized in a 2 x 2 factorial design to either low-dose or high-dose aspirin, and standard-dose or high-dose clopidogrel. Patients were followed for 30 days.



Results

- No difference in primary endpoint between aspirin arms; benefit noted in high-dose arm on high-dose clopidogrel (p = 0.04)
- No difference in primary endpoint between clopidogrel arms, but significant interaction with aspirin dose; benefit noted in high-dose arm undergoing PCI (p < 0.05)
- Major bleeding similar in both aspirin arms, but higher in high-dose clopidogrel arm (p = 0.01)

Conclusions

- High-dose aspirin and high-dose clopidogrel associated with significant clinical benefit at 30 days in ACS patients; more in PCI subgroup
- Bleeding complications were higher with high-dose clopidogrel, but not with aspirin
- Important findings; likely to be in future guidelines

Presented by Dr. Shamir Mehta at ESC 2009