ACUTE CORONARY SYNDROME

ACS

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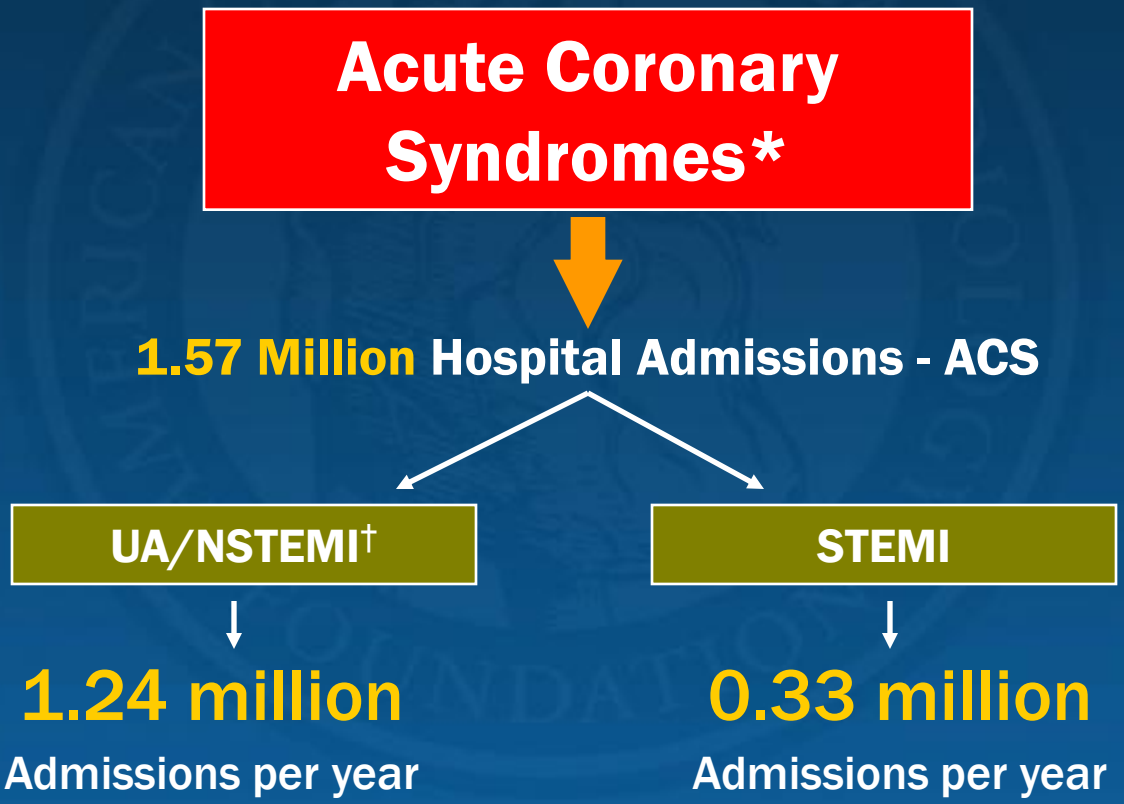
Patient Presentation:

- 66 Y/O male, 10 Kg, referred from another city
- He recently was admitted with NSEMI and received DES.
- Takes ASA, Plavix, and not sure of his other medication
- Other active problems:
  - GERD
  - HTN
  - HLP
- SH: Prior smoker, 1-2 oz alcohol / week

Patient Presentation:

- BP 148/88 with a heart rate 72
- Exam:
  - HEENT negative, no carotid bruit
  - Chest: CTA
  - Heart: S4, no murmurs
- Additional information's:
  - Hbg A1C
  - Fasting Blood Sugar
  - LVEF

Hospitalizations in the U.S. Due to ACS



*Primary and secondary diagnoses. †About 0.57 million NSTEMI and 0.67 million UA.
Heart Disease and Stroke Statistics – 2007 Update. Circulation 2007; 115:69–171.

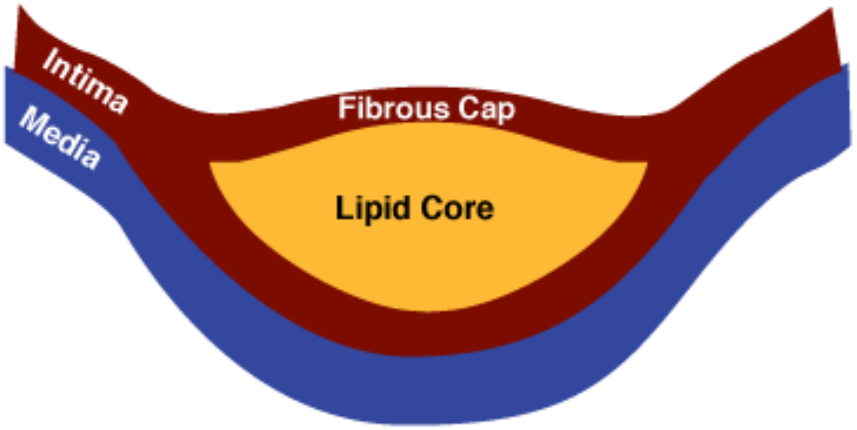
ACS: Unstable Atheroma

Factors Increasing Stress

- Thin Fibrous Cap
- Large Lipid Pool
- Less Stenotic Lesions
- ↑ (Ester/Free) Cholesterol

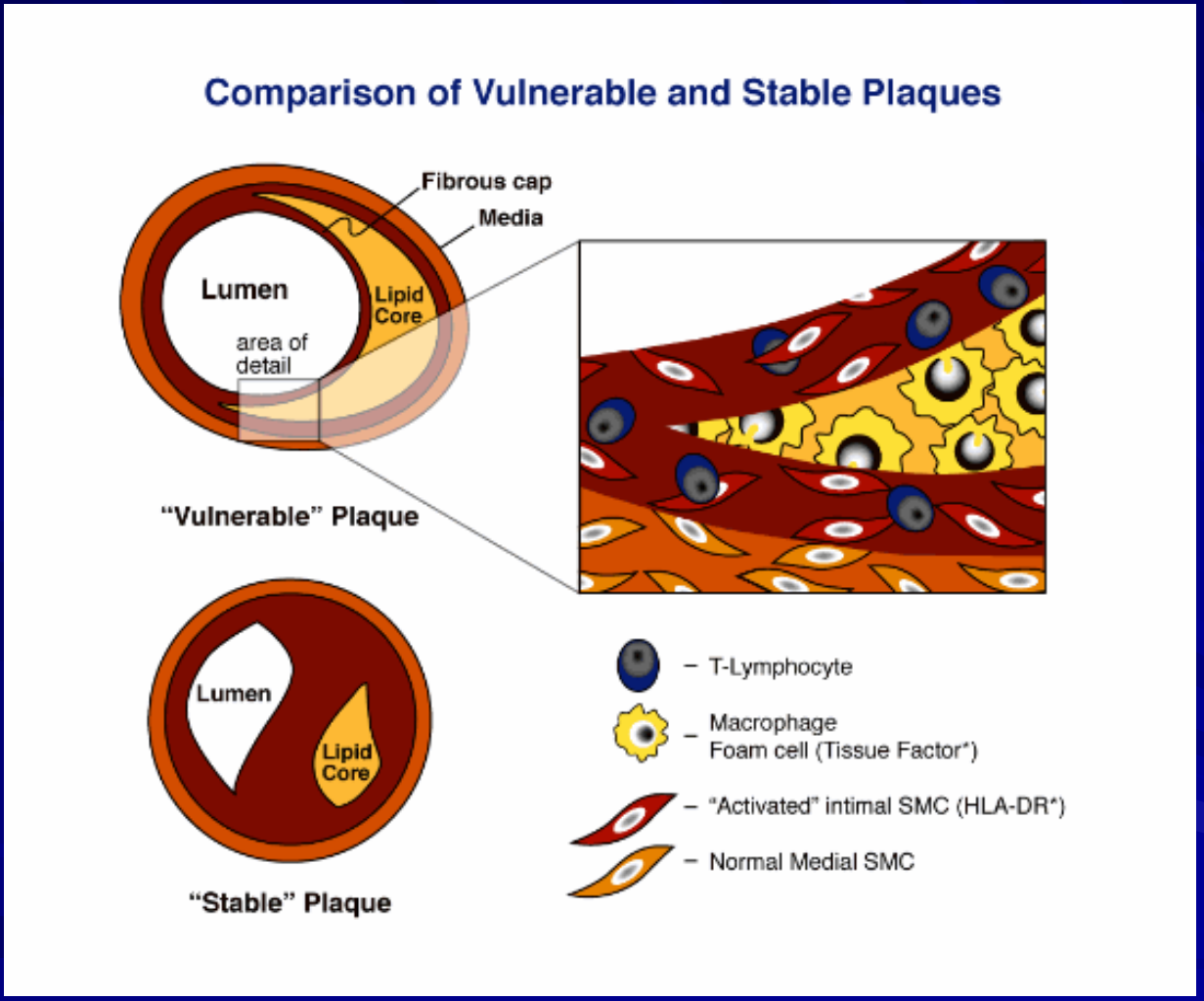
Factors Weakening the Cap

- ↓ Collagen Synthesis
- ↑ Collagen Degradation
- ↑ Macrophages, T-Cells
- ↓ Smooth Muscle Cells



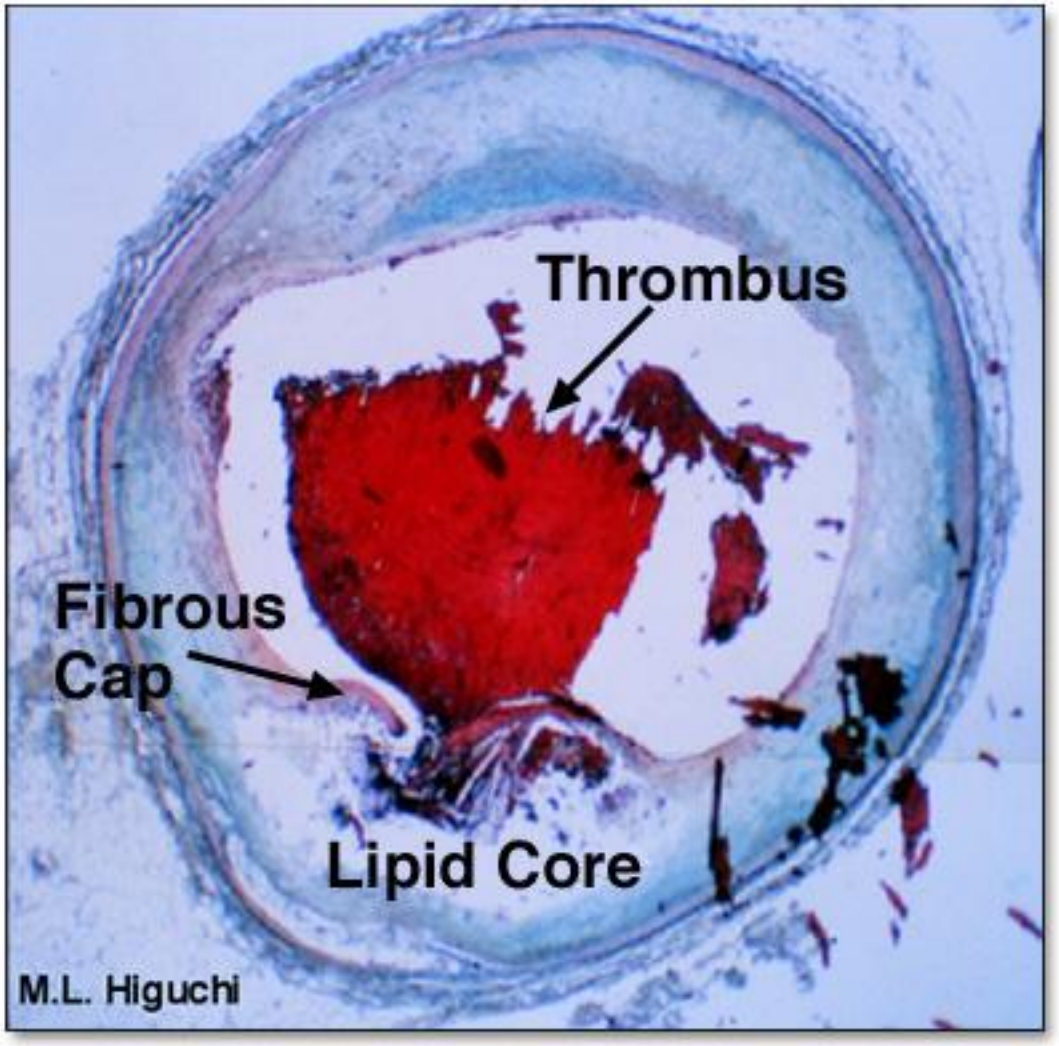
Arterioscler Thromb Vasc Biol 1997;17:1859

ACS: Unstable Atheroma



Circulation 1995;91:2844-50

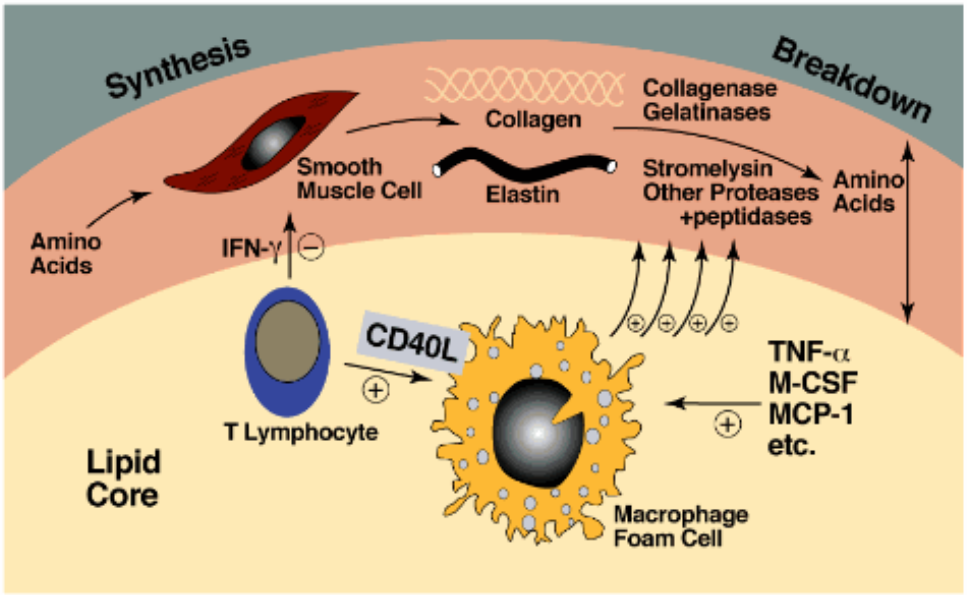
Human Coronary Plaque Rupture



Cardiovasc Pathol 2001;10:189-96.

Plaque Fibrous Cap Metabolism

- Reduced Collagen synthesis by SMC
- Increased Collagen Catabolis by:
  - T. Lymphcyte
  - Macrophage secretion of proteinases



Circulation 1995;91:2844-50

Ischemic Discomfort

Acute Coronary Syndrome

Presentation

↓

Working Dx

↓

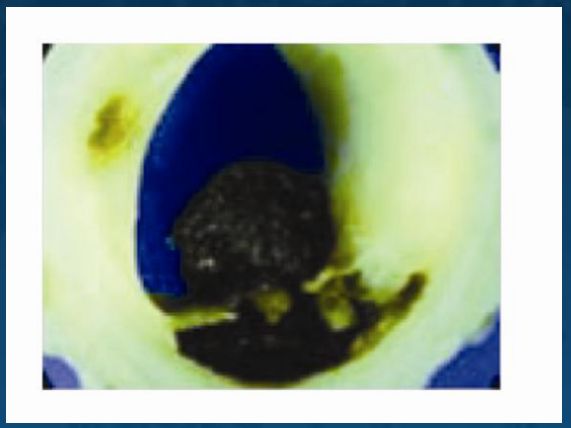
ECG

↓

Cardiac Biomarker

↓

Final Dx



← No ST Elevation →

ST Elevation

[← Non-ST ACS →]

UA

NSTEMI

Unstable Angina

Myocardial Infarction

NQMI

Qw MI

Libby P. Circulation 2001;104:365, Hamm CW, Bertrand M, Braunwald E, Lancet 2001; 358:1533-1538; Davies MJ. Heart 2000; 83:361-366. Anderson JL, et al. *J Am Coll Cardiol.* 2007;50:e1-e157, Figure 1. Reprinted with permission.

Factors Affecting Plaque Rupture

Hemodynamic Paradigm → Biologic Paradigm

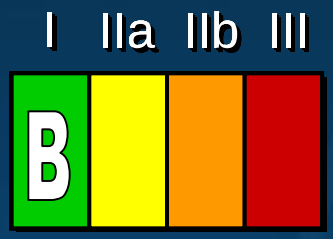
- Severity (%) of Plaque Stenosis
- Local Vasospasm
- Changes in Intraluminal Pressure or Tone
- Mechanical Injury
- Bending and Twisting of Coronary Artery During Each Contraction

- Plaque Inflammatory Cell Content & Activity
- Plaque Lipid Content and Oxidation
- Thickness of Fibrous Cap
- Collagen Metabolism & Metallproteinase Activity
- Positive Coronary Artery Remodeling
- Apoptosis

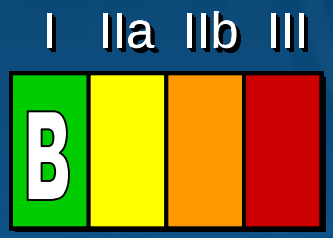
Management Before UA/NSTEMI and Onset of UA/NSTEMI

Management Before UA/NSTEMI and Onset of UA/NSTEMI

Early Risk Stratification

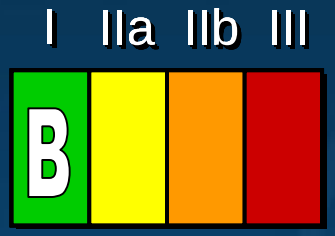


Cardiac biomarkers should be measured in all patients who present with chest discomfort consistent with ACS.

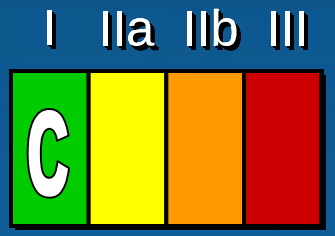


A cardiac-specific troponin is the preferred marker, and if available, it should be measured in all patients who present with chest discomfort consistent with ACS.

Early Risk Stratification

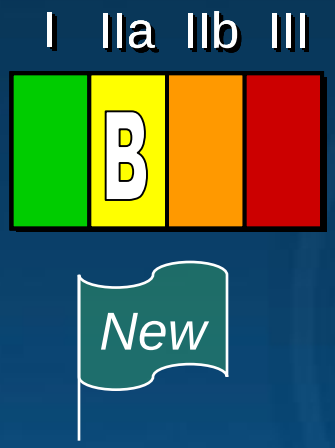


Patients with negative cardiac biomarkers within 6 h of the onset of symptoms consistent with ACS should have biomarkers remeasured in the time frame of 8 to 12 h after symptom onset. (The exact timing of serum marker measurement should take into account the uncertainties often present with the exact timing of onset of pain and the sensitivity, precision, and institutional norms of the assay being utilized as well as the release kinetics of the marker being measured.)

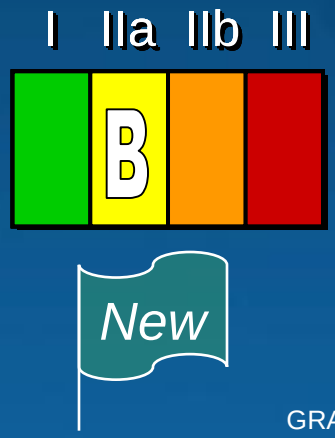


The initial evaluation of the patient with suspected ACS should include the consideration of noncoronary causes for the development of unexplained symptoms.

Early Risk Stratification



Use of risk-stratification models, such as the TIMI or GRACE risk score or PURSUIT risk model, can be useful to assist in decision making with regard to treatment options in patients with suspected ACS.



It is reasonable to remeasure positive biomarkers at 6- to 8-h intervals 2 to 3 times or until levels have peaked, as an index of infarct size and dynamics of necrosis.

GRACE = Global Registry of Acute Coronary Events; PURSUIT = Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; TIMI = Thrombolysis In Myocardial Infarction.

Variables Used in the TIMI Risk Score

- Age ≥ 65 years
- At least 3 risk factors for CAD
- Prior coronary stenosis of ≥ 50%
- ST-segment deviation on ECG presentation
- At least 2 anginal events in prior 24 hours
- Use of aspirin in prior 7 days
- Elevated serum cardiac biomarkers

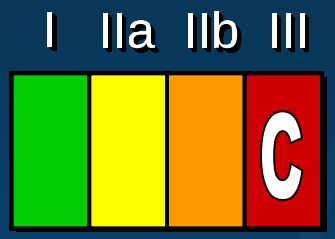
The TIMI risk score is determined by the sum of the presence of the above 7 variables at admission. 1 point is given for each variable. Primary coronary stenosis of 50% or more remained relatively insensitive to missing information and remained a significant predictor of events. Antman EM, et al. *JAMA* 2000;284:835–42.
TIMI = Thrombolysis in Myocardial Infarction.

TIMI Risk Score

TIMI Risk Score	All-Cause Mortality, New or Recurrent MI, or Severe Recurrent Ischemia Requiring Urgent Revascularization Through 14 Days After Randomization %
0-1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6-7	40.9

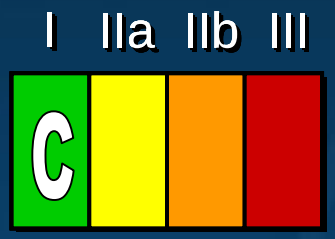
The TIMI risk calculator is available at www.timi.org.
Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157, Table 8.
TIMI = Thrombolysis in Myocardial Infarction.

Early Risk Stratification



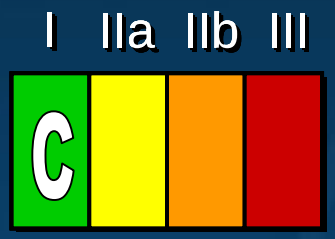
Total CK (without MB), aspartate aminotransferase (AST, SGOT), alanine transaminase, beta-hydroxybutyric dehydrogenase, and/or lactate dehydrogenase should not be utilized as primary tests for the detection of myocardial injury in patients with chest discomfort suggestive of ACS.

Immediate Management

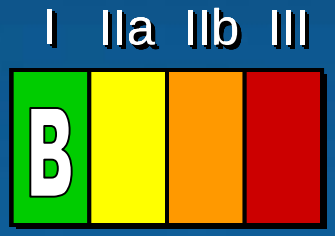


In patients with suspected ACS in whom ischemic heart disease is present or suspected, if the follow-up 12-lead ECG and cardiac biomarkers measurements are normal, a stress test (exercise or pharmacological) to provoke ischemia should be performed in the ED, in a chest pain unit, or on an outpatient basis in a timely fashion (within 72 h) as an alternative to inpatient admission. Low-risk patients with a negative diagnostic test can be managed as outpatients.

Immediate Management

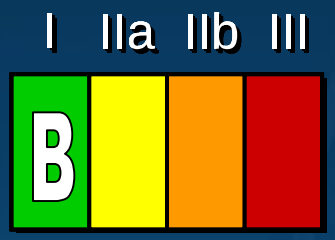


Patients with definite ACS and ongoing ischemic symptoms, positive cardiac biomarkers, new ST-segment deviations, new deep T-wave inversions, hemodynamic abnormalities, or a positive stress test should be admitted to the hospital for further management. Admission to the critical care unit is recommended for those with active, ongoing ischemia/injury or hemodynamic or electrical instability. Otherwise, a telemetry step-down unit is reasonable.



Patients with possible ACS and negative cardiac biomarkers who are unable to exercise or who have an abnormal resting ECG should undergo a pharmacological stress test.

Anti-Ischemic Therapy



Oral beta-blocker therapy should be initiated within the first 24 h for patients who do not have 1 or more of the following: 1) signs of HF, 2) evidence of a low-output state, 3) increased risk* for cardiogenic shock, or 4) other relative contraindications to beta blockade (PR interval greater than 0.24 s, second or third degree heart block, active asthma, or reactive airway disease).

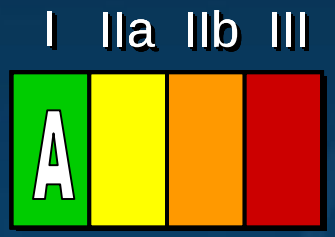
*Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk of developing cardiogenic shock): age greater than 70 years, systolic blood pressure less than 120 mmHg, sinus tachycardia greater than 110 or heart rate less than 60, increased time since onset of symptoms of UA/NSTEMI. Chen ZM, et al. *Lancet* 2005;366:1622–32.

ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)

- 45,852 patients within 24 h acute MI
  - 93% STEMI or LBBB
- Up to 15 mg IV → 200 mg po metoprolol daily vs placebo
- Co-primary outcomes
  - death, reinfarction, or cardiac arrest
  - death from any cause to discharge or up to 4 wk in hospital
- Neither co-primary outcome ↓ by metoprolol
  - 5 fewer reinfarctions, 5 fewer VF
  - 11 more/1000 → cardiogenic shock
- ↑ Risk cardiogenic shock especially with initial hemodynamic instability
  - moderate late benefit with relative stability
- Recommend: start β-blocker po when hemodynamically stable

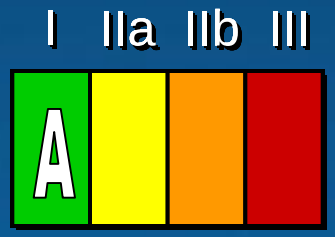
Chen ZM, et al. *Lancet* 2005;366:1622–32.

Anti-Ischemic Therapy



Major Change

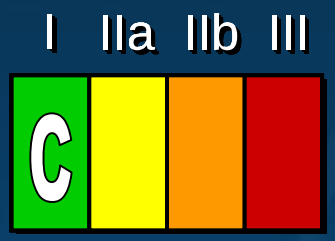
An ACE inhibitor should be administered orally within the first 24 h to UA/NSTEMI patients with pulmonary congestion or LV ejection fraction (LVEF) ≤ 40%, in the absence of hypotension (systolic blood pressure < 100 mm Hg or < 30 mm Hg below baseline) or known contraindications to that class of medications.



New

An angiotensin receptor blocker should be administered to UA/NSTEMI patients who are intolerant of ACE inhibitors and have either clinical or radiological signs of HF or LVEF ≤ 40%.

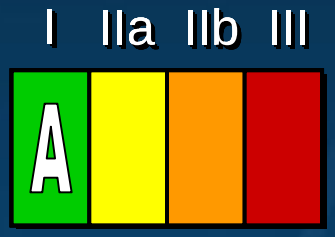
Anti-Ischemic Therapy



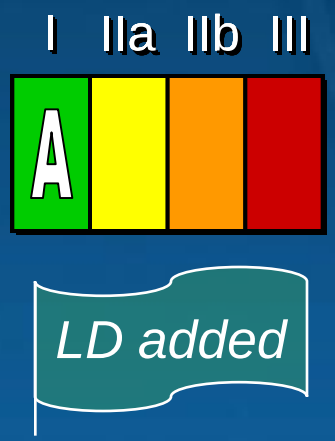
Because of the increased risks of mortality, reinfarction, hypertension, HF, and myocardial rupture associated with their use, nonsteroidal anti-inflammatory drugs (NSAIDs), except for ASA, whether nonselective or cyclooxygenase (COX)-2–selective agents, should be discontinued at the time a patient presents with UA/NSTEMI.

The selective COX-2 inhibitors and other nonselective NSAIDs have been associated with increased cardiovascular risk. An AHA scientific statement on the use of NSAIDs concluded that the risk of cardiovascular events is proportional to COX-2 selectivity and the underlying risk to the patient (Antman EM, et al. Use of nonsteroidal antiinflammatory drugs. An update for clinicians. A scientific statement from the American Heart Association. *Circulation* 2007;115:1634–42. Further discussion can be found in Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157 and in the Secondary Prevention Section of this slide set.

Antiplatelet Therapy



Aspirin should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients not known to be intolerant of that medication. (Box A)



Clopidogrel (loading dose [LD] followed by daily maintenance dose)* should be administered to UA/NSTEMI patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance. (Box A)

*Some uncertainty exists about optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral maintenance dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but the additive clinical efficacy and the safety of higher oral loading doses have not been rigorously established.

Selection of Initial Treatment Strategy: Initial Invasive Versus Conservative Strategy

Invasive	Recurrent angina/ischemia at rest with low-level activities despite intensive medical therapy
	Elevated cardiac biomarkers (TnT or TnI)
	New/presumably new ST-segment depression
	Signs/symptoms of heart failure or new/worsening mitral regurgitation
	High-risk findings from noninvasive testing
	Hemodynamic instability
	Sustained ventricular tachycardia
	PCI within 6 months
	Prior CABG
	High risk score (e.g., TIMI, GRACE)
	Reduced left ventricular function (LVEF < 40%)
Conservative	Low risk score (e.g., TIMI, GRACE)
	Patient/physician presence in the absence of high-risk features

Fragmin during Instability in Coronary Artery Disease (FRISC-2)

- Patients within 48 h UA/NSTEMI
- Early inv vs conserv & dalteparin vs placebo
- 3048 patients → dalteparin for 5–7 d → 2457 continued dalteparin/placebo & received either inv or conserv rx strategy
- Meds: ASA, β-blockers unless contraindicated
- No ↓ death/MI @ 3 mo by dalteparin
- ↓ Death/MI @ 6 mo, 1 y & 5 y for inv strategy
  - Benefit confined to men, nonsmokers, and patients with ≥ 2 risk factors

Wallentin L, et al. *Lancet* 2000;356:9–16 (1-year results). Lagerqvist B, et al. *J Am Coll Cardiol* 2001;38:41–8 (women vs men). Lagerqvist B, et al. *Lancet* 2006;368:998–1004 (5-yr follow-up).

Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI-18)

- 2,220 patients within 24 h UA/NSTEMI
- Early inv or conserv (selective invasive) strategy
- Meds: ASA, heparin and tirofiban
- ↓ Death, MI, and rehosp for an ACS @ 6 mo for inv strategy
  - Benefit in medium and high-risk patients (TnT ↑ of > 0.01 ng/mL, ST-segment deviation, TIMI risk score > 3)
  - No high-risk features, outcomes ↔
  - ↓ Death/MI @ 6 mo for older adults with early inv strategy
  - Benefit of early inv strategy for high-risk women (↑ TnT); low-risk women tended to have worse outcomes, incl ↑ risk of major bleeding

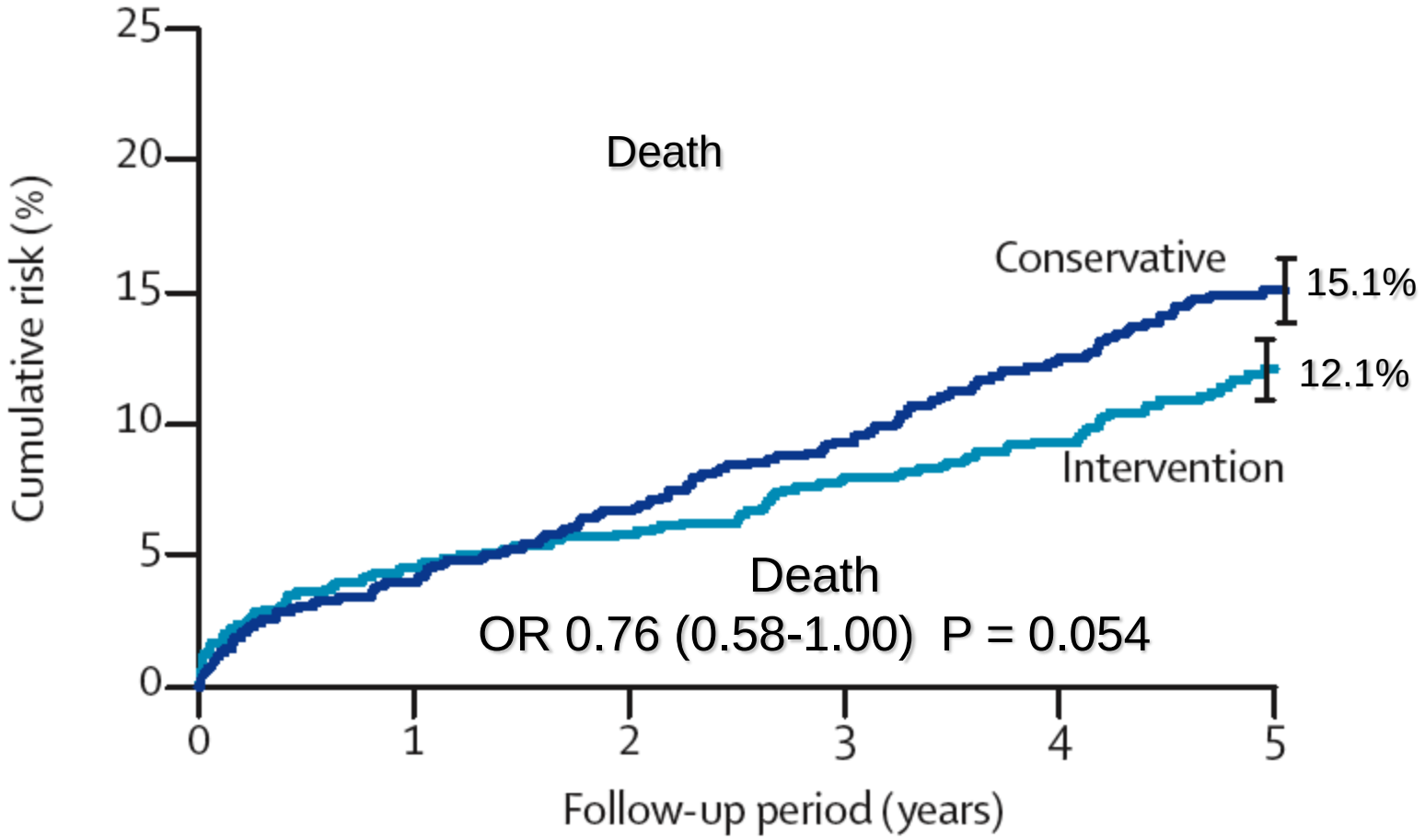
Cannon CP, et al. *N Engl J Med* 2001;344:1879–87.

Third Randomized Intervention Treatment of Angina (RITA-3)

- 1,810 moderate-risk ACS patients
- Early inv or conserv (ischemia-driven) strategy
- Exclusions: CK-MB > 2X ULN @ randomization, new Q-waves, MI w/in 1 mo, PCI w/in 1 y, any prior CABG
- ↓ Death, MI, & refractory angina for inv strategy
  - Benefit driven primarily by ↓ in refractory angina
- ↓ Death/MI @ 5 y for early inv arm
- No benefit of early inv strategy in women

Fox KA, et al. *Lancet* 2002;360:743–51. Fox KA, et al. *Lancet* 2005;366:914–20 (5-y results).

RITA-3 --- 5 Year Follow-up

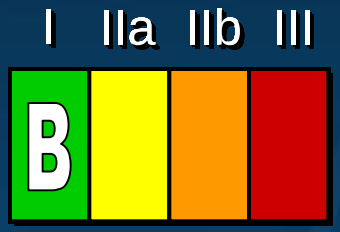


Numbers at risk

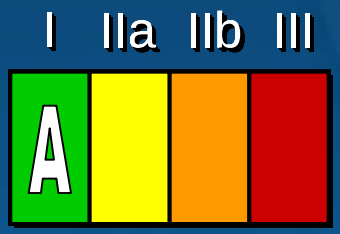
Intervention	895	854	842	822	743	470
Conservative	915	878	853	828	729	463

Fox KA, et al. *Lancet* 2005;366:914–20. Reprinted with permission from Elsevier.

Initial Conservative Versus Initial Invasive Strategies



An early invasive strategy* is indicated in UA/NSTEMI patients who have refractory angina or hemodynamic or electrical instability (without serious comorbidities or contraindications to such procedures).



An early invasive strategy* is indicated in initially stabilized UA/NSTEMI patients (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events.

*Diagnostic angiography with intent to perform revascularization.

Intracoronary Stenting with Antithrombotic Regimen Cooling-off Study (ISAR-COOL)

- 410 patients within 24 h intermediate-high risk UA/NSTEMI
- Very early angio (cath median time 2.4 h) + revasc or delayed inv/"cooling off" (cath median time 86 h) strategy
- Meds: ASA, heparin, clopidogrel (600-mg LD) and tirofiban
- ↓ Death/MI @ 30 d for early angio group
- Diff in outcome attributed to events that occurred before cath in the "cooling off" group, which supports rationale for intensive medical rx & very early angio

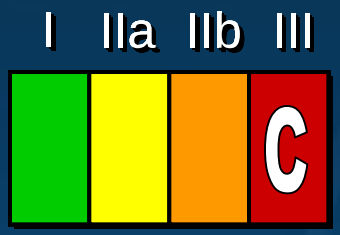
Neumann FJ, et al. *JAMA* 2003;290:1593–9. LD = loading dose.

Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS)

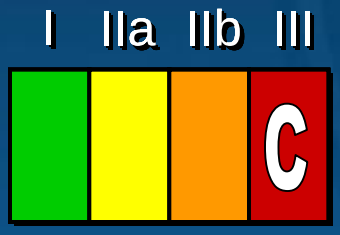
- 1,200 high-risk ACS patients
- Routine inv vs selective inv strategy
- Meds: ASA, clopidogrel, LMWH, and lipid-lowering rx; abciximab for revasc patients
- No ↓ death, MI, and ischemic rehosp @ 1 y and longer-term follow-up by routine inv strategy
- Relatively high (47%) rate revasc actually performed in selective inv arm and lower-risk pop than in other studies
- Recommendation: Initially conserv (i.e., selectively inv) strategy may be considered in initially stabilized patients who have ↑ risk for events, incl troponin + (*Class IIb, LOE:B*)

de Winter RJ, et al. *N Engl J Med* 2005;353:1095–104. Hirsch A, et al. *Lancet* 2007;369:827–35 (follow-up study).
LOE = level of evidence.

Initial Conservative Versus Initial Invasive Strategies



An early invasive strategy* is not recommended in patients with extensive comorbidities (e.g., liver or pulmonary failure, cancer), in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization.

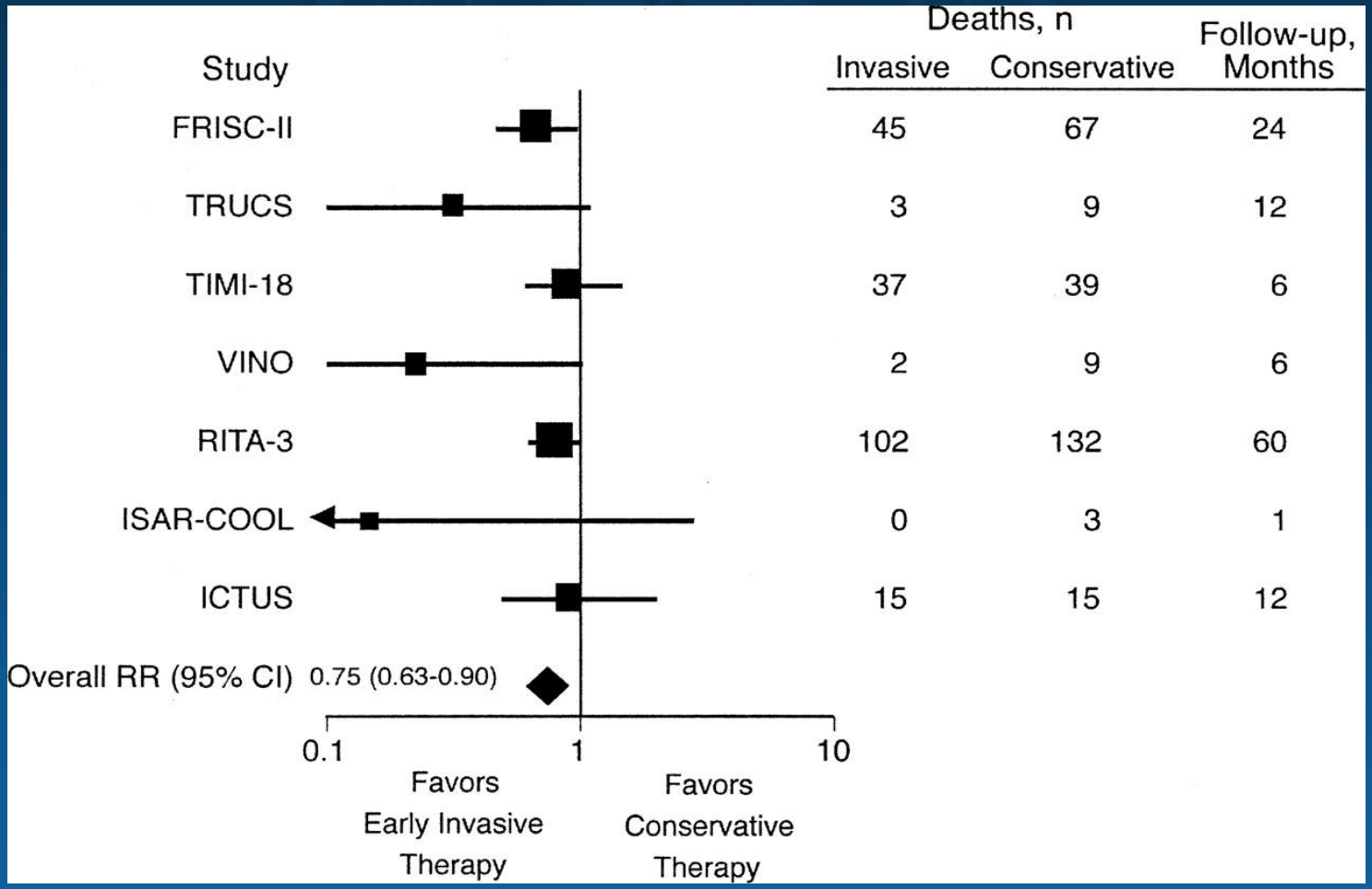


An early invasive strategy* is not recommended in patients with acute chest pain and a low likelihood of ACS.

An early invasive strategy* should not be performed in patients who will not consent to revascularization regardless of the findings.

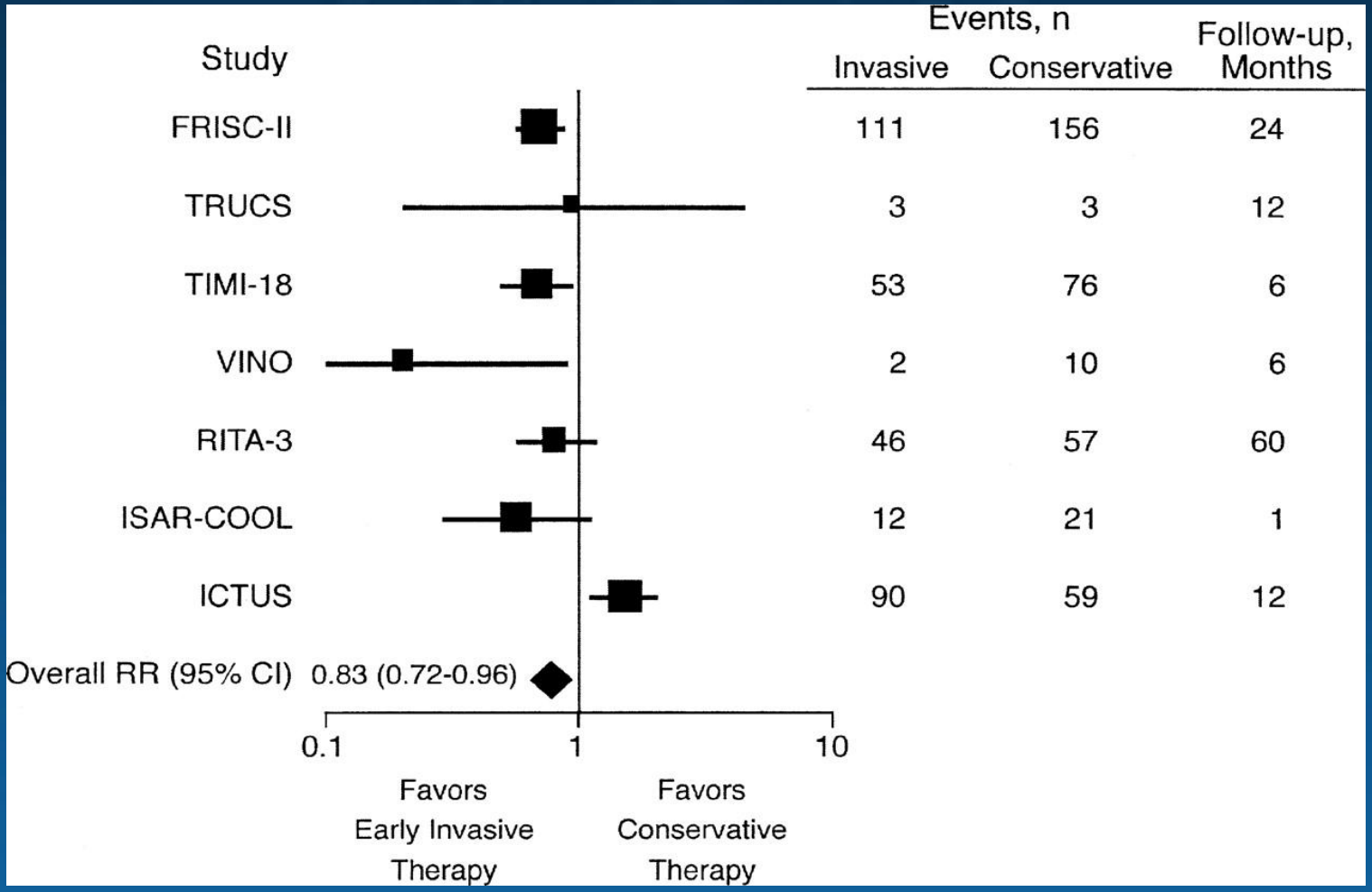
*Diagnostic angiography with intent to perform revascularization.

Relative Risk of All-Cause Mortality for Early Invasive Therapy Compared With Conservative Therapy at a Mean Follow-Up of 2 y



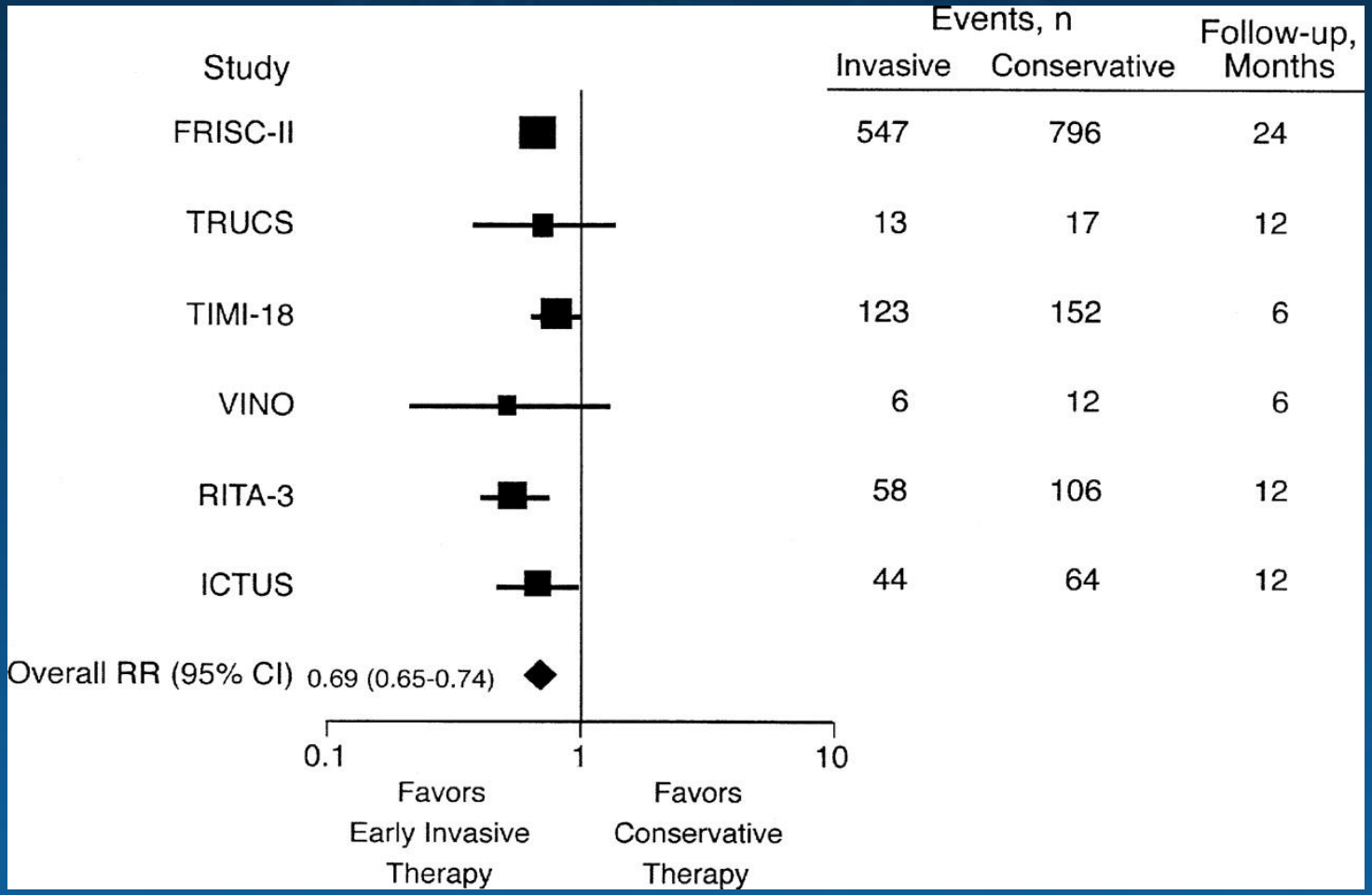
Bavry AA, et al. *J Am Coll Cardiol* 2006;48:1319–1325. Reprinted with permission from Elsevier. CI = confidence interval; RR = relative risk.

Relative Risk of Recurrent Nonfatal MI for Early Invasive Therapy Compared With Conservative Therapy at a Mean Follow-Up of 2 y



Bavry AA, et al. *J Am Coll Cardiol* 2006; 48:1319–1325. CI = confidence interval; RR = relative risk. Reprinted with permission from Elsevier.

Relative Risk of Recurrent UA Resulting in Rehosp for Early Invasive Therapy Compared With Conservative Therapy at a Mean Follow-Up of 13 Months



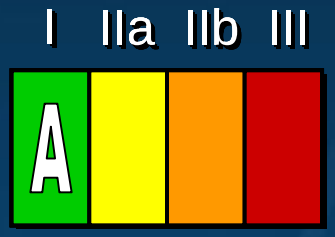
Bavry AA, et al. *J Am Coll Cardiol* 2006; 48:1319–1325. Reprinted with permission from Elsevier. CI = confidence interval; RR = relative risk; UA = unstable angina.

Initial Invasive Strategy

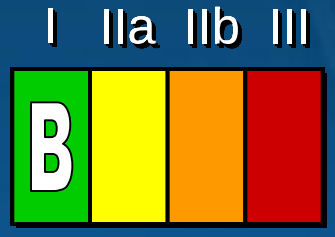
Major Changes

- *New Drugs*
- *Longer Duration of Rx*
- *Revised Algorithm*

Initial Invasive Strategy: Antiplatelet Therapy



For UA/NSTEMI patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to ASA should be initiated before diagnostic angiography (upstream) with either clopidogrel (loading dose followed by daily maintenance dose)* or an IV GP IIb/IIIa inhibitor. (Box B2)



Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor.†

*Some uncertainty exists about optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral maintenance dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but the additive clinical efficacy and the safety of higher oral loading doses have not been rigorously established; †Factors favoring administration of both clopidogrel and a GP IIb/IIIa inhibitor include: delay to angiography, high-risk features, and early ischemic discomfort.

Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE)

- 12,562 patients within 24 h UA/NSTEMI
- Placebo vs clopidogrel (LD 300 mg → 75 mg qd)
- Other meds: ASA
- ↓ CV death, MI, or stroke, rate of recurrent ischemia & revasc with clopidogrel
- ↑ Major (non–life-threatening) bleeding with clopidogrel
- No routine inv strategy, 23% revasc during initial admission
- Although well tolerated, < 10% GP IIb/IIIa + ASA + clopidogrel + heparin use in study patients

Yusuf S, et al. *N Engl J Med* 2001;345:494–502.

Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using InTegrilin (PURSUIT)

- 10,948 patients within 24 h UA/NSTEMI
- Low-dose eptifibatide (n=1,487) vs high-dose eptifibatide (n=4,722) vs placebo (n=4,739)
- Other meds: ASA, heparin
- ↓ Death/MI @ 96 hours, 7 d, 30 d with eptifibatide
  - 1.5% ARR 4–30 d
  - ↑ major bleeding
  - no diff stroke
- ↑ Event rate in 11% of patients not treated with concomitant heparin

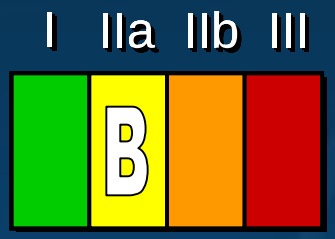
The PURSUIT Trial Investigators. *N Engl J Med* 1998;339:436–43. Boersma E, et al. *Circulation* 2000;101:2557–67.
ARR= absolute risk reduction.

Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS)

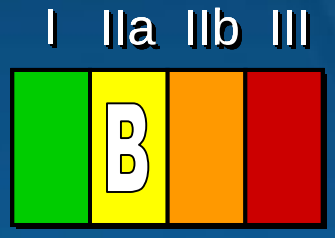
- 1,915 patients within 12 h UA/NSTEMI
- Tirofiban alone, UFH alone, or both for 48–108 h.
- Tirofiban-alone arm discontinued d/t ↑ mortality rate.
- ↓ Death, MI, or refractory ischemia at 7 d, 30 d & 6 mo by tirofiban + heparin
- High rate of angio could have contributed to important ↓ in event rates
- Recommend: Tirofiban + heparin for medical rx or during PCI

PRISM-PLUS Study Investigators. *N Engl J Med* 1998;338:1488–97.

Initial Invasive Strategy: Antiplatelet Therapy



For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to initiate antiplatelet therapy with both clopidogrel (loading dose followed by daily maintenance dose)* and an intravenous GP IIb/IIIa inhibitor. (Box B2)

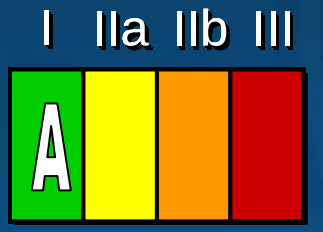


Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor.†

*Some uncertainty exists about optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral maintenance dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but the additive clinical efficacy and the safety of higher oral loading doses have not been rigorously established; †Factors favoring administration of both clopidogrel and a GP IIb/IIIa inhibitor include: delay to angiography, high-risk features, and early ischemic discomfort.

Initial Invasive Strategy: Anticoagulant Therapy

Anticoagulant therapy should be added to antiplatelet therapy in UA/NSTEMI patients as soon as possible after presentation.



- For patients in whom an invasive strategy is selected, regimens with established efficacy at a *Level of Evidence: A* include enoxaparin and unfractionated heparin (UFH) (Box B1), and those with established efficacy at a *Level of Evidence: B* include bivalirudin and fondaparinux (Box B1).

New Drugs

Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) trial

- 3,171 patients within 24 h UA/NSTEMI
- Enoxaparin vs UFH
- Other meds: ASA
- ↓ Death, MI or recurrent angina for enox @ 14 d, 30d and 1 y
  - minor bleeding ↑
  - major bleeding ↔

Cohen M, et al. *N Engl J Med* 1997;337:447–52. Cohen M, et al. *Am J Cardiol* 1998;82:19L–24L (bleeding). Goodman SG, et al. *J Am Coll Cardiol* 2000;36:6934–8 (1-y results).

Thrombolysis In Myocardial Ischemia trial, phase 11B (TIMI 11B)

- 3,910 patients within 24 h UA/NSTEMI
- Enoxaparin vs UFH
- Other meds: ASA
- ↓ Death, MI or urgent revasc for enox @ 48 h, 8 d, 14 d, & 43 d
- ↑ major & minor bleeding (inhosp) with enox

Antman EM, et al. *Circulation* 1999;100:1593–601.

Superior Yield of the New strategy of Enoxaparin, Revascularization and GlYcoprotein IIb/IIIa Inhibitors (SYNERGY)

- 9,978 patients within 24 h high-risk UA/NSTEMI
- Enoxaparin vs UFH → early inv strategy
- Other meds: ASA, GP IIb/IIIa @ physician discretion
- Enox noninferior for death/MI @ 30 d, 6 mo 1 y
- ↑ Major bleeding with enox
  - ? due to crossover to UFH @ time of PCI

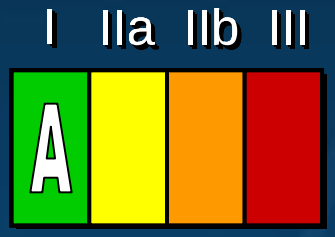
Ferguson JJ, et al. *JAMA* 2004;292:45–54. Mahaffey KW, et al. *Am Heart J* 2005;149:S81–S90 (6 mo & 1-y results).

Initial Conservative Strategy

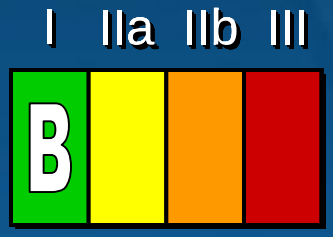
Major Changes

- *New Drugs*
- *Longer Duration of Rx*
- *Revised Algorithm*

Initial Conservative Strategy: Antiplatelet Therapy



For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected, clopidogrel (loading dose followed by daily maintenance dose)* should be added to ASA and anticoagulant therapy as soon as possible after admission and administered for at least 1 month *(Level of Evidence: A)* and ideally up to 1 year. *(Level of Evidence: B)* (Box C2)



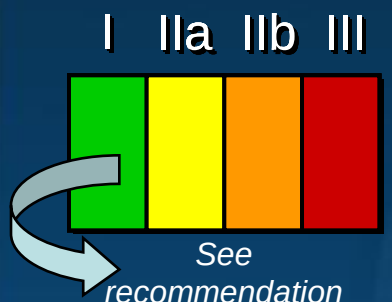
*Some uncertainty exists about optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral maintenance dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but the additive clinical efficacy and the safety of higher oral loading doses have not been rigorously established.

Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty (ARMYDA-2)

- Patients with stable angina or UA/NSTEMI
- Clopidogrel 600 mg LD (n=126) vs clopidogrel 300 mg LD (n=129) 4 to 8 h before PCI
- ↓ Death, MI or TVR up to 30 days by 600 mg LD
  - Benefit d/t ↓ periprocedural MI
- Small study of relatively low-risk patients, low use of GP IIb/IIIa

Patti G, et al. *Circulation* 2005;111:2099 –106. LD = loading dose.

Initial Conservative Strategy: Antiplatelet Therapy



- For UA/NSTEMI patients in whom an initial conservative strategy is selected, if recurrent symptoms/ischemia, HF, or serious arrhythmias subsequently appear, then diagnostic angiography should be performed. *(Level of Evidence: A)* (Box D)
- Either an IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban; *Level of Evidence: A*) or clopidogrel (loading dose followed by daily maintenance dose; *Level of Evidence: A)** should be added to ASA and anticoagulant therapy before diagnostic angiography (upstream). *(Level of Evidence: C)*

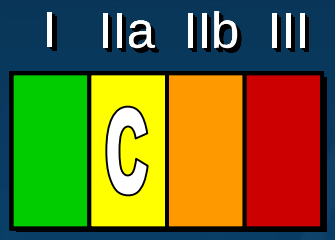
*Some uncertainty exists about optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral maintenance dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but the additive clinical efficacy and the safety of higher oral loading doses have not been rigorously established.

Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM)

- 3,232 patients within 24 h UA/NSTEMI
- Tirofiban vs UFH over 48 h
- Other meds: ASA
- ↓ Death, MI, or refractory ischemia at 48 h & 7 d by tirofiban
  - ↓ Death/MI @ 30 d
  - No ↑ bleeding; thrombocytopenia ↑

PRISM Study Investigators. *N Engl J Med* 1998;338:1498–505.

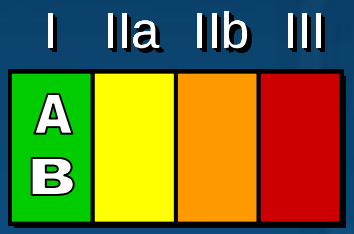
Initial Conservative Strategy: Antiplatelet Therapy



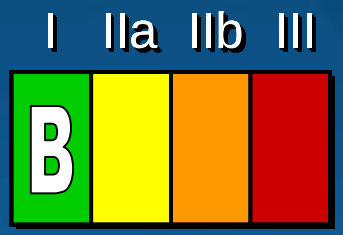
For UA/NSTEMI patients in whom an initial conservative strategy is selected and who have recurrent ischemic discomfort with clopidogrel, ASA, and anticoagulant therapy, it is reasonable to add a GP IIb/IIIa antagonist before diagnostic angiography.

Initial Conservative Strategy: Anticoagulant Therapy

Anticoagulant therapy should be added to antiplatelet therapy in UA/NSTEMI patients as soon as possible after presentation.



- For patients in whom a conservative strategy is selected, regimens using either enoxaparin* or UFH *(Level of Evidence: A)* or fondaparinux *(Level of Evidence: B)* have established efficacy. (Box C1)

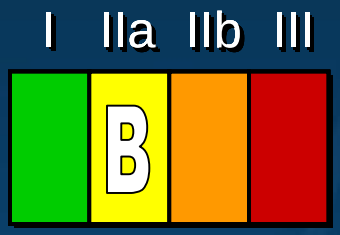


- In patients in whom a conservative strategy is selected and who have an increased risk of bleeding, fondaparinux is preferable. (Box C1)

New Drugs

*Limited data are available for the use of other low-molecular-weight heparins (LMWHs), e.g., dalteparin.

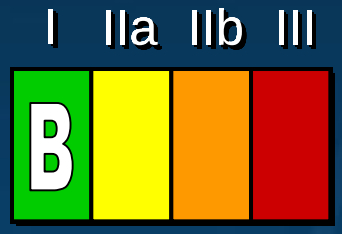
Initial Conservative Strategy: Anticoagulant Therapy



For UA/NSTEMI patients in whom an initial conservative strategy is selected, enoxaparin* or fondaparinux is preferable to UFH as anticoagulant therapy, unless CABG is planned within 24 h.

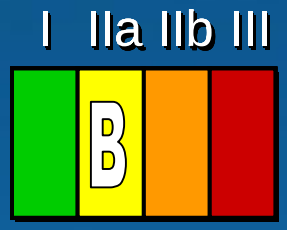
*Limited data are available for the use of other low-molecular-weight heparins (LMWHs), e.g., dalteparin.

Initial Conservative Strategy: Additional Management Considerations



For UA/NSTEMI patients in whom an initial conservative strategy is selected and in whom no subsequent features appear that would necessitate diagnostic angiography (recurrent symptoms/ischemia, HF, or serious arrhythmias), LVEF should be measured. (Box L)

If LVEF is ≤ 40%, it is reasonable to perform diagnostic angiography. (Box M)



If LVEF is > 40%, it is reasonable to perform a stress test. (Box N)

Noninvasive Test Results That Predict High Risk for Adverse Outcomes

Stress Radionuclide Ventriculography	Stress Echocardiography	Stress Radionuclide Myocardial Perfusion Imaging
Exercise EF ≤ 50 %	Rest EF ≤ 35%	Abnormal myocardial tracer distribution in > 1 coronary artery region
Rest EF ≤ 35%	Wall-motion score > 1	Abnormal myocardial distribution with ↑ lung intake
Fall in EF ≥ 10%		Cardiac enlargement

Adapted from O'Rourke RA, et al. *J Am Coll Cardiol* 1986;8:1471–83 and Cheitlin MD, et al. *Circulation* 1997;95:1686–744.
EF = ejection fraction.

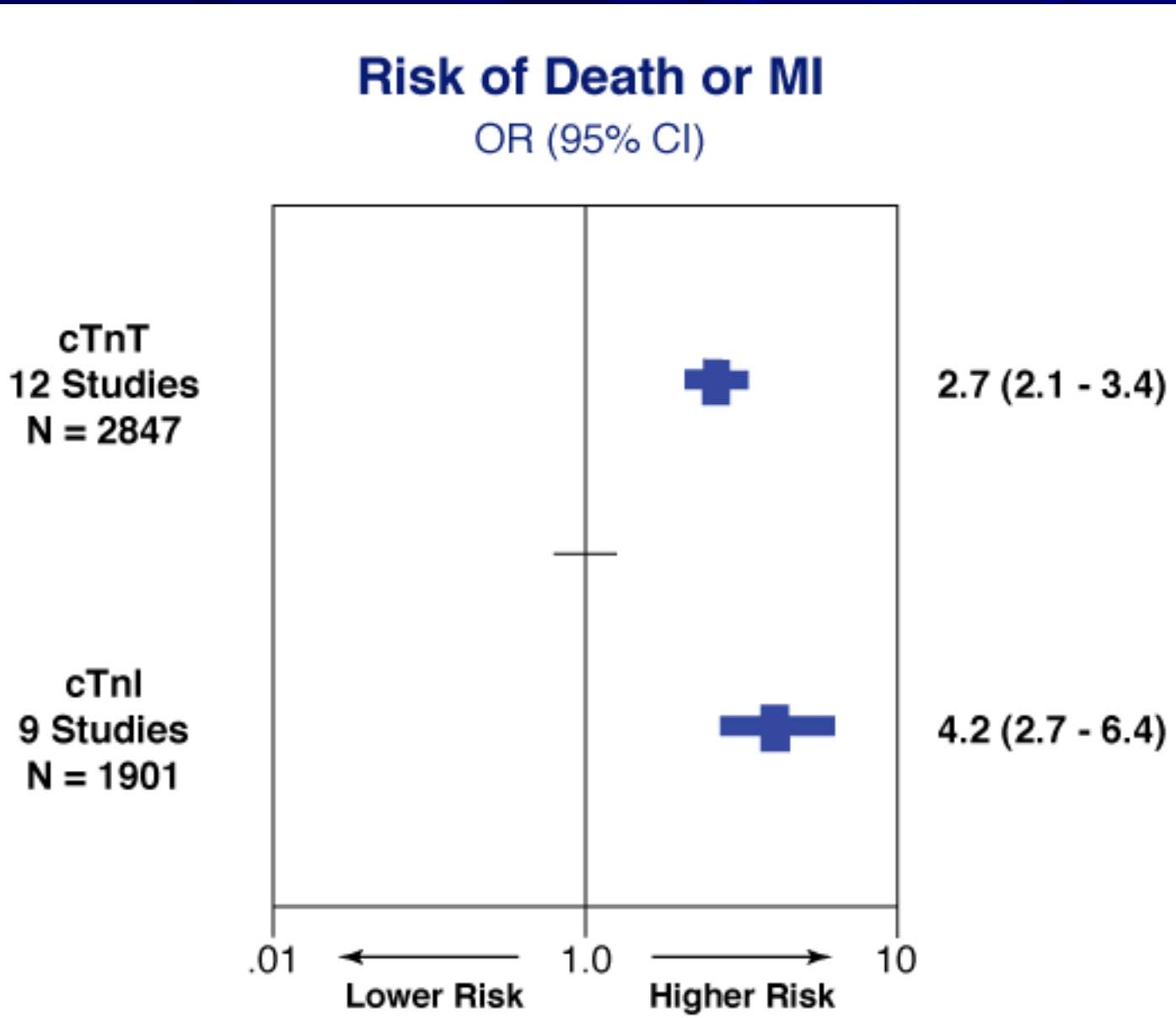
Release Patterns of Biomarkers of Myocardial Necrosis

Marker	Molecular Mass (kD)	Time to Initial Elevation (hr)	Mean Time to Peak Elevation	Time to Return to Normal Range
Myoglobin	17.8	1-4	6-7 hr	12-24 hr
MLC Myosin light chain	19-27	6-12	2-4 d	6-12 d
cTnI	23.5	3-12	24 hr	5-10 d
cTnT	33.0	3-12	24 hr	5-14 d
CK-MB	86.0	3-12	24 hr	48-72 h
LD	135.0	10	24-28 hr	10-14 d
MHC Myosin heavy chain	400.0	48	5-6 d	14 d

Advantages and Disadvantages of Cardiac Biomarkers of Necrosis (Selected) for the Evaluation and Management of Patients With Suspected Non-ST-Elevation Acute Coronary Syndrome

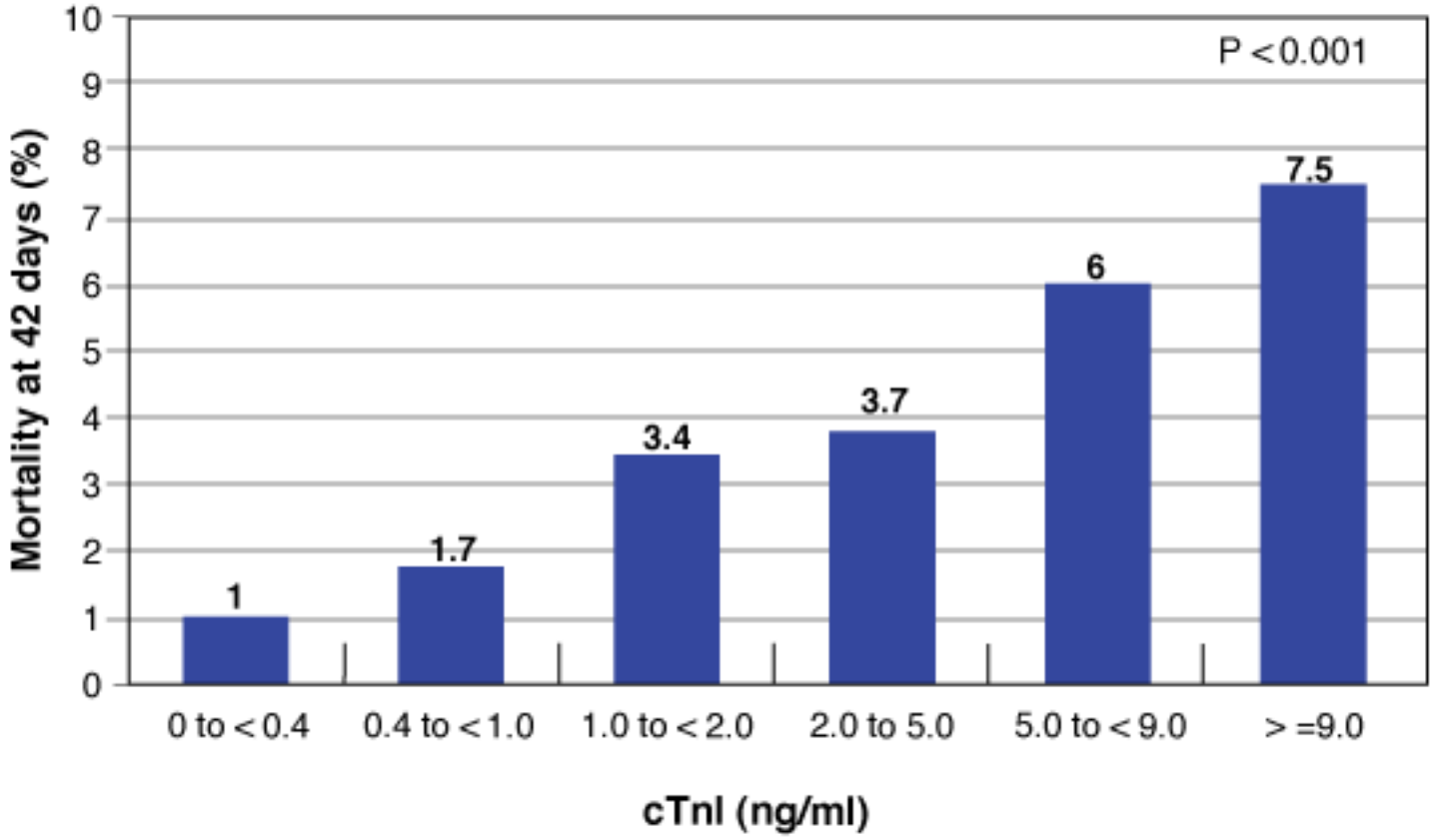
Marker	Advantages	Disadvantages	Comment
CK-MB	1) Rapid, cost efficient, accurate assays 2) Ability to detect early reinfarction	1) Loss of specificity in setting of skeletal muscle disease or injury 2) Low sensitivity for MI early (<6 hr) or late (>36 hr) after symptom onset	Does not detect "minor myocardial damage" identifiable with troponins
Myoglobin	1) Early detection of MI 2) Useful for detection of reperfusion of STEMI	1) Very low specificity in setting of skeletal muscle injury or disease 2) Rapid return to normal range limits sensitivity late after symptom onset	Has diminished usefulness with availability of more sensitive troponin assays
Cardiac Troponins	1) Powerful tools for risk stratification 2) Improved sensitivity compared with CK-MB 3) Improved specificity compared with CK-MB in setting of skeletal muscle disease or injury 4) Detection of recent MI up to 2 weeks after onset 5) Useful for selection of therapy	1) Lower sensitivity early after symptom onset (<6 hr) compared with after 6 hr 2) May have more limited ability to detect late minor reinfarction	Clinicians should familiarize themselves with clinical cut-points for the assay used in their laboratory

J Am Coll Cardiol 2000;36:970-1062.



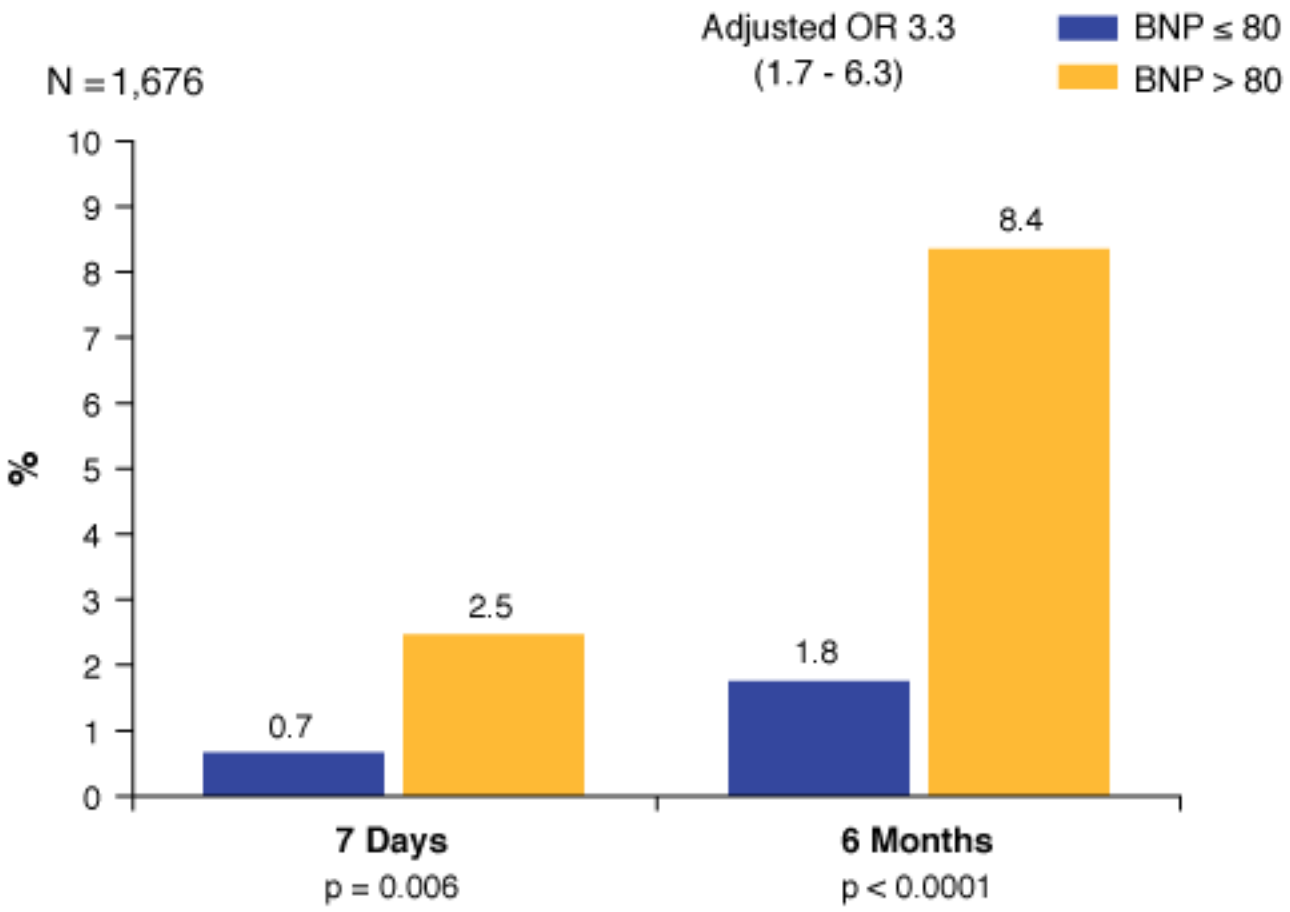
Am J Cardiol 1998;81:1405-10.

Panel A. Risk of Death in TIMI 3B

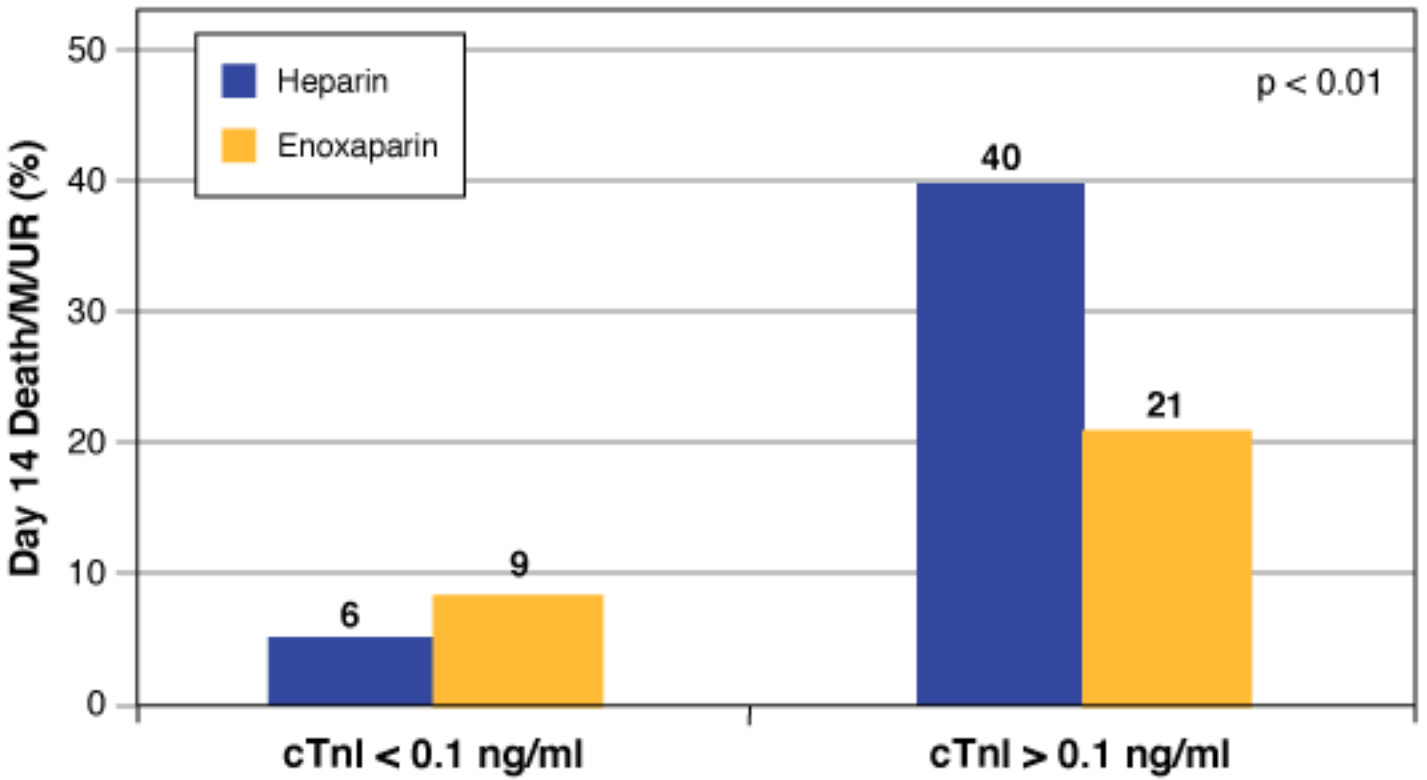


N Eng J Med 1996;335:1342-9

BNP & Risk of Death in UA/NSTEMI

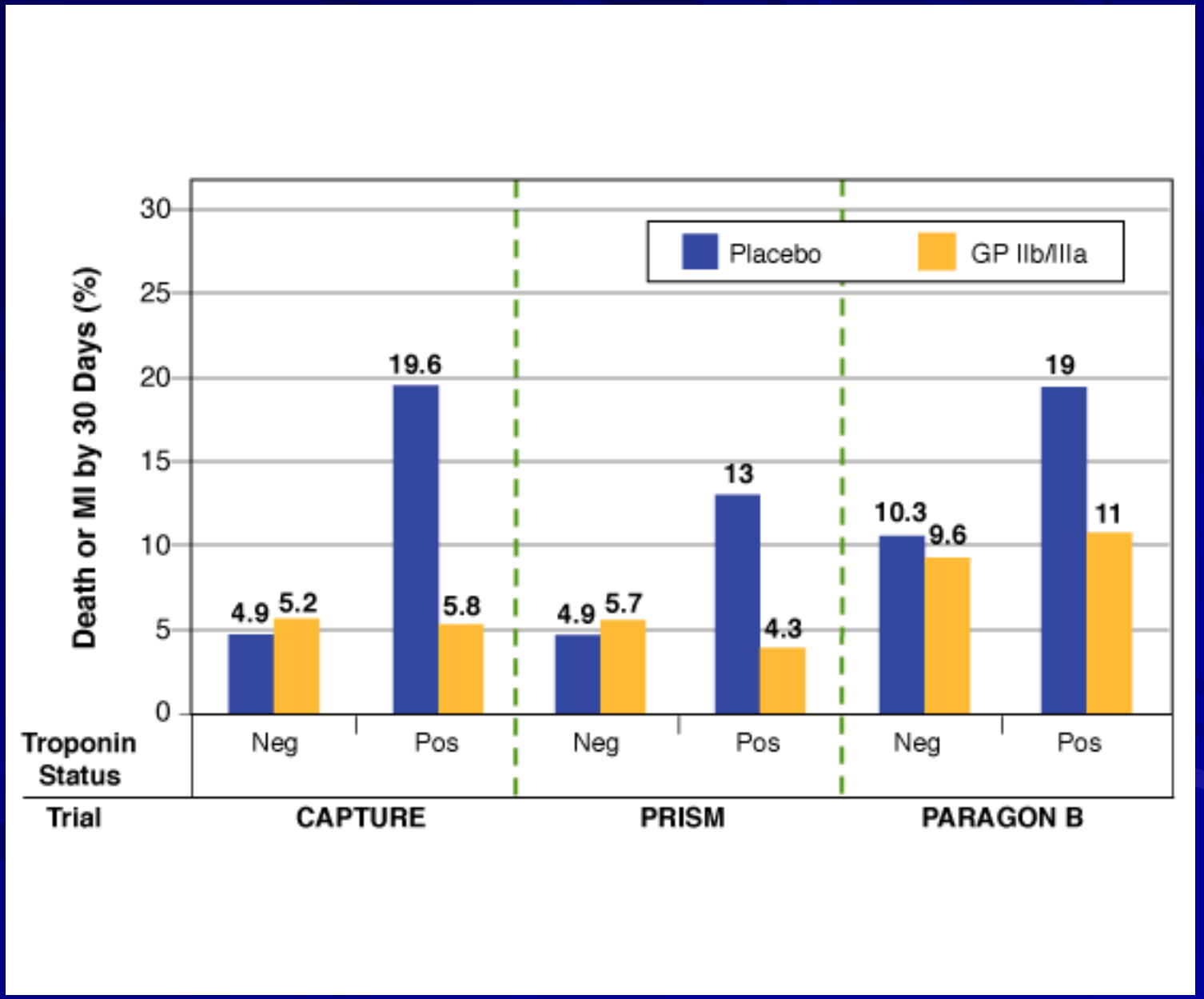


TACTICS-TIMI 18

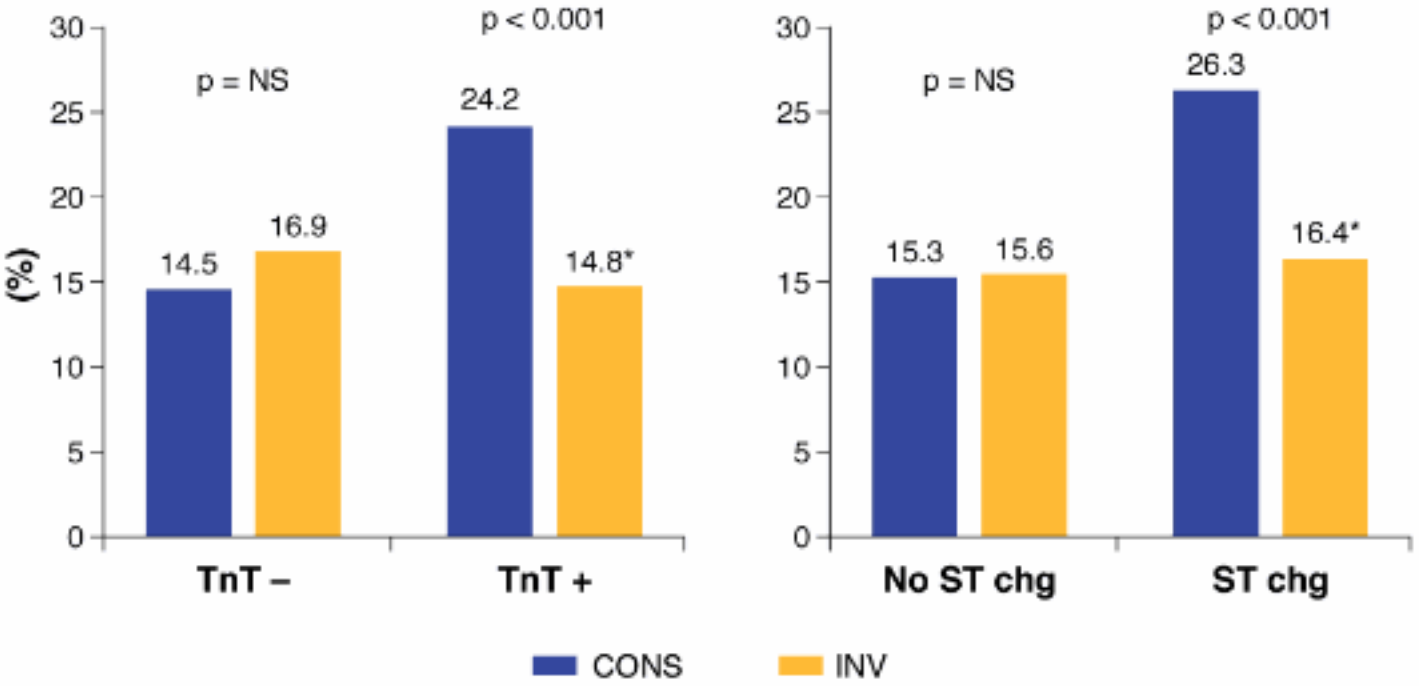


J Am Coll Cardiol 2000;36:1812-7

Outcomes with glycoprotein IIB-IIIa Inhibitors



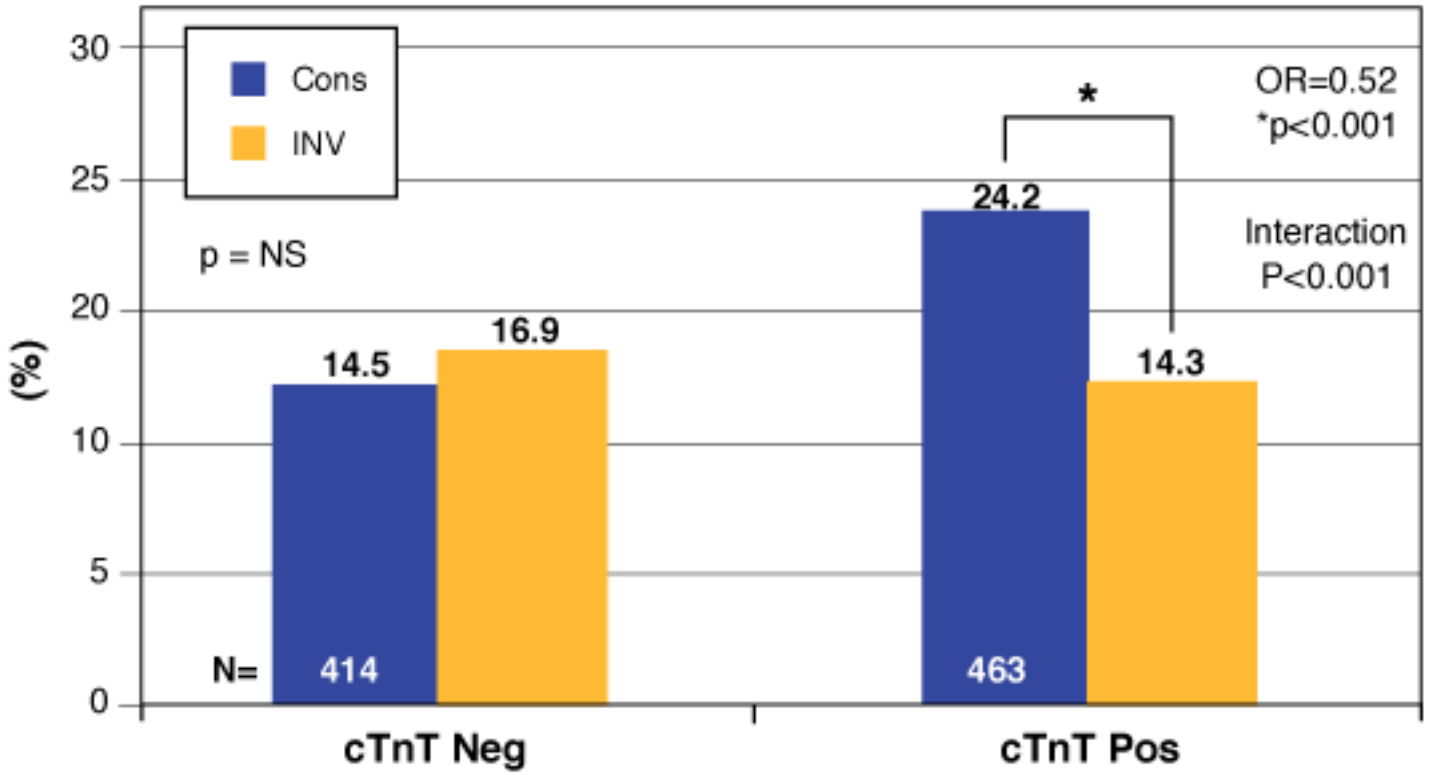
Incidence of Death, Myocardial Infarction, or Rehospitalization for Acute Coronary Syndrome at 6 Months in TACTICS-TIMI 18 According to Troponin and ST-Segment Deviation



TACTICS-TIMI 18

N Engl J Med 2001;344:1879-87

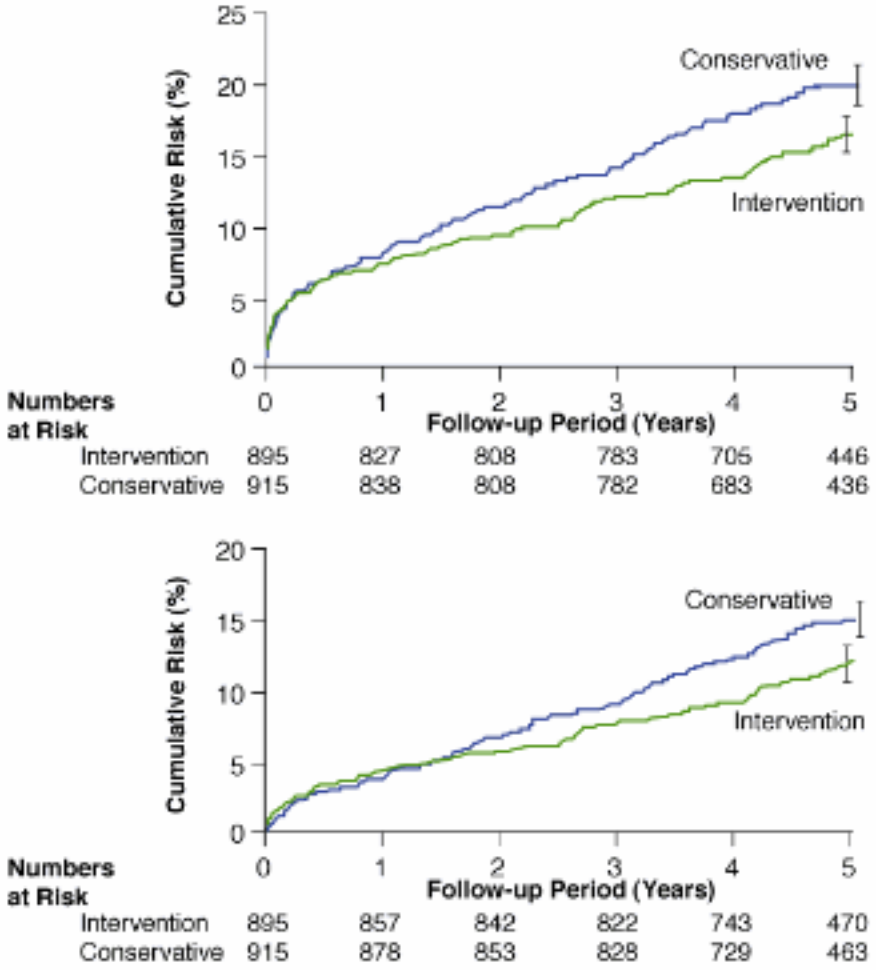
Death, MI, Rehospitalization for ACS at 6 Months



TACTICS-TIMI 18

N Engl J Med 2001;344:1879-87.

Cumulative Risk of Death or MI (top) or of Death (bottom) in the RITA 3 Trial of Patients With Non-ST-Elevation Acute Coronary Syndromes



Lancet 2005;366:914-20.

Noninvasive Risk Stratification

High Risk (greater than 3% annual mortality rate)

- Severe resting LV dysfunction (LVEF less than 0.35)
- High-risk treadmill score (score –11 or less)
- Severe exercise LV dysfunction (exercise LVEF less than 0.35)
- Stress-induced large perfusion defect (particularly if anterior)
- Stress-induced multiple perfusion defects of moderate size
- Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201)
- Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (thallium-201)
- Echocardiographic wall motion abnormality (involving more than two segments) developing at low dose of dobutamine (10 mcg/kg/min or less) or at a low heart rate (less than 120 bpm)
- Stress echocardiographic evidence of extensive ischemia

Intermediate Risk (1% to 3% annual mortality rate)

- Mild/moderate resting LV dysfunction (LVEF 0.35-0.49)
- Intermediate-risk treadmill score (—11 to 5)
- Stress-induced moderate perfusion defect without LV dilation or increased lung intake (thallium-201)
- Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving ≤2 segments

Low Risk (less than 1% annual mortality rate)

- Low-risk treadmill score (score 5 or greater)
- Normal or small myocardial perfusion defect at rest or with stress*
- Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress*

*Although the published data are limited, patients with these findings will probably not be at low risk in the presence of either a high-risk treadmill score or severe resting LV dysfunction (LVEF less than 0.35).

J Am Coll Cardiol 2007;50:2264-74.

Thrombogenic subendothelial matrix

Platelet activation

Tissue factor

Thrombin generation

Lipid core

Platelet agregation

Platelet-rich clot

Recruits additional platelets

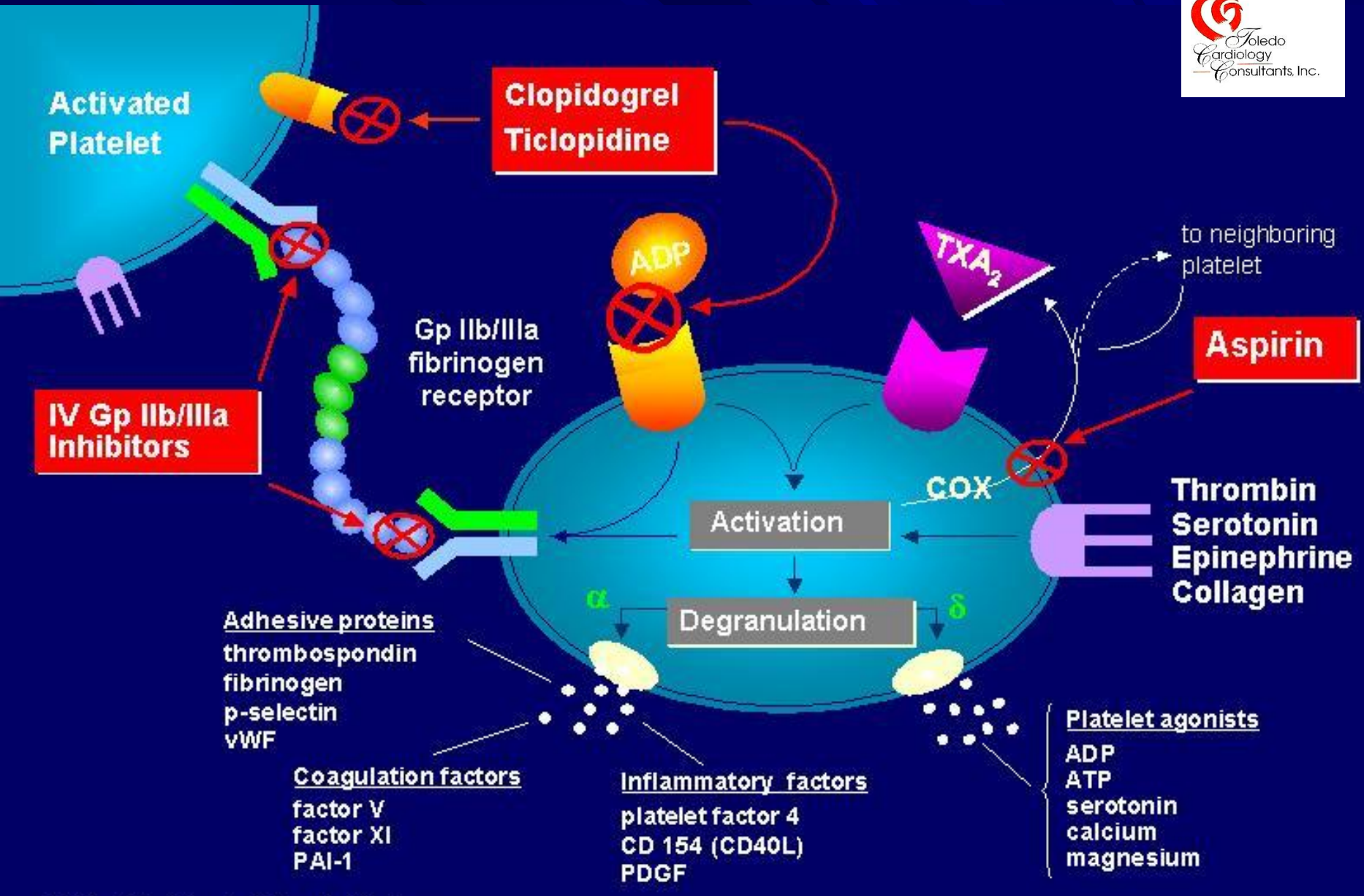
Thrombin

Stabilization of Platelet-rich clot

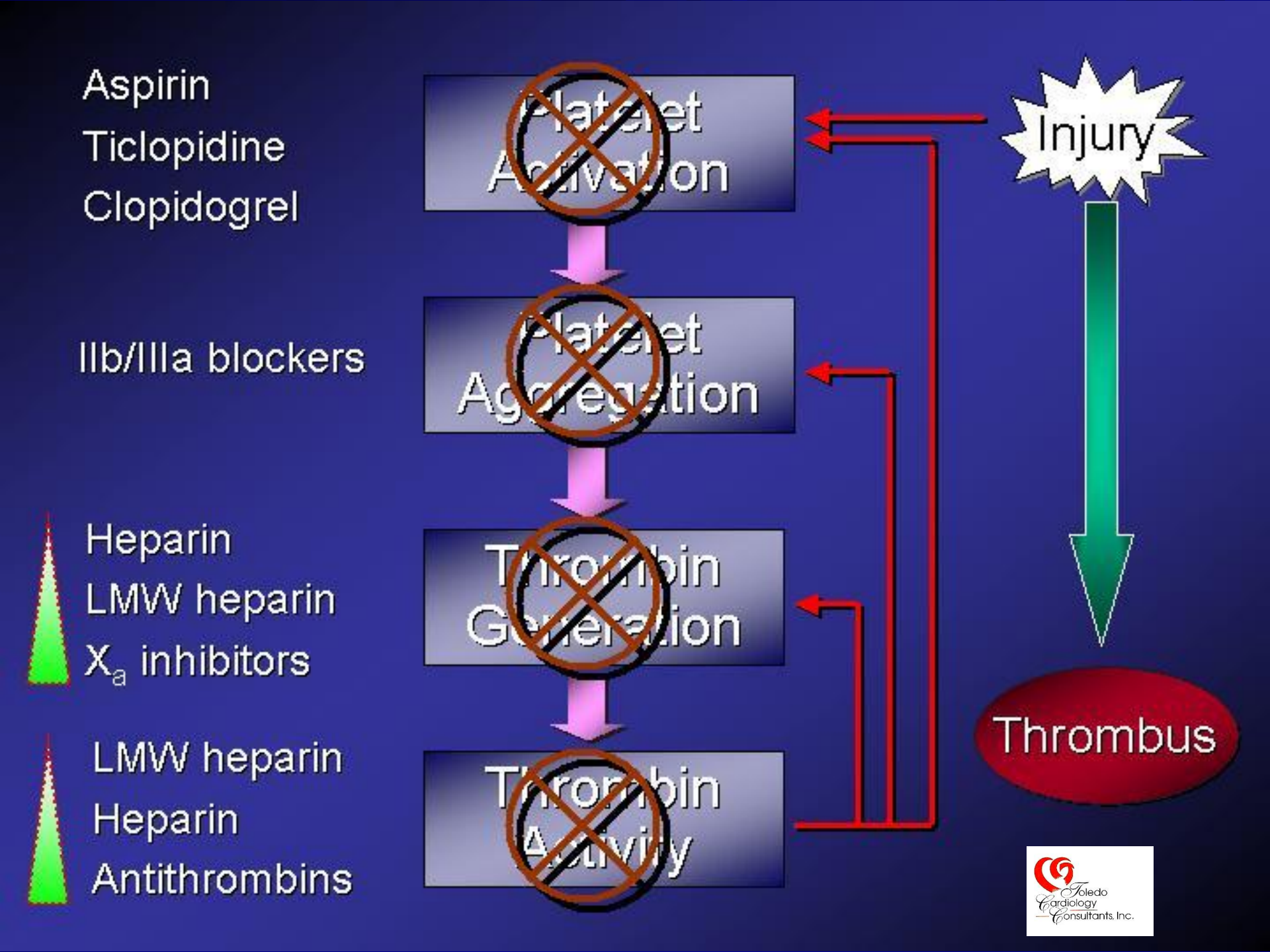
Fibrin

Fibrinogen

Toledo Cardiology Consultants, Inc.



Mehta SR. *J Am Coll Cardiol.* In Press.


Aspirin
Ticlopidine
Clopidogrel
IIb/IIIa blockers
Heparin
LMW heparin
X_a inhibitors
LMW heparin
Heparin
Antithrombins
Injury
Thrombus
Toledo Cardiology Consultants, Inc.

Recommendations for Antithrombotic Therapy from ACC/AHA Guidelines

Possible ACS	Likely / Definite ACS	Definite ACS With Cath and PCI or High-risk
Aspirin	Aspirin + SQ LMWH or IV heparin + *clopidogrel*	Aspirin + SQ LMWH or IV heparin + IV platelet GP IIb/IIIa antagonist + *clopidogrel*

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