# UA/NSTEMI Guidelines Slide Set

## 2011 ACCF/AHA Focused Update Incorporated Into the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction

***Developed In Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons***

***Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine***

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# Applying Classification of Recommendations and Level of Evidence, 2011 COR/LOE Table

Modified 2011

Note: The COR/LOE table shown was drafted in 2011. Both the new and modified recommendations from the 2011 UA/NSTEMI Focused Update were graded based on the latest version of the COR/LOE table. All of the unmodified recommendations were graded on the previous COR/LOE table, listed below.

SIZE OF TREATMENT EFFECT

| ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT | CLASS I<br>*Benefit >>> Risk*<br>Procedure/Treatment **SHOULD** be performed/ administered | CLASS IIa<br>*Benefit >> Risk*<br>*Additional studies with focused objectives needed*<br>**IT IS REASONABLE** to perform procedure/administer treatment | CLASS IIb<br>*Benefit ≥ Risk*<br>*Additional studies with broad objectives needed; additional registry data would be helpful*<br>Procedure/Treatment **MAY BE CONSIDERED** | CLASS III *No Benefit* or CLASS III *Harm*<br>Procedure/ Test / Treatment<br>COR III: No benefit — Not Helpful — No Proven Benefit<br>COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients |
|---|---|---|---|---|
| **LEVEL A**<br>Multiple populations evaluated*<br>Data derived from multiple randomized clinical trials or meta-analyses | ■ Recommendation that procedure or treatment is useful/effective<br>■ Sufficient evidence from multiple randomized trials or meta-analyses | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Some conflicting evidence from multiple randomized trials or meta-analyses | ■ Recommendation's usefulness/efficacy less well established<br>■ Greater conflicting evidence from multiple randomized trials or meta-analyses | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Sufficient evidence from multiple randomized trials or meta-analyses |
| **LEVEL B**<br>Limited populations evaluated*<br>Data derived from a single randomized trial or nonrandomized studies | ■ Recommendation that procedure or treatment is useful/effective<br>■ Evidence from single randomized trial or nonrandomized studies | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Some conflicting evidence from single randomized trial or nonrandomized studies | ■ Recommendation's usefulness/efficacy less well established<br>■ Greater conflicting evidence from single randomized trial or nonrandomized studies | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Evidence from single randomized trial or nonrandomized studies |
| **LEVEL C**<br>Very limited populations evaluated*<br>Only consensus opinion of experts, case studies, or standard of care | ■ Recommendation that procedure or treatment is useful/effective<br>■ Only expert opinion, case studies, or standard of care | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Only diverging expert opinion, case studies, or standard of care | ■ Recommendation's usefulness/efficacy less well established<br>■ Only diverging expert opinion, case studies, or standard of care | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Only expert opinion, case studies, or standard of care |
| Suggested phrases for writing recommendations | should<br>is recommended<br>is indicated<br>is useful/effective/beneficial | is reasonable<br>can be useful/effective/beneficial<br>is probably recommended or indicated | may/might be considered<br>may/might be reasonable<br>usefulness/effectiveness is unknown/unclear/uncertain or not well established | COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective<br>COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other |
| Comparative effectiveness phrases† | treatment/strategy A is recommended/indicated in preference to treatment B<br>treatment A should be chosen over treatment B | treatment/strategy A is probably recommended/indicated in preference to treatment B<br>it is reasonable to choose treatment A over treatment B | | |

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/ efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

# Applying Classification of Recommendations and Level of Evidence, Previous COR/LOE Table

| **Class I** | **Class IIa** | **Class IIb** | **Class III** |
|---|---|---|---|
| *Benefit >>> Risk*<br><br>Procedure/ Treatment **SHOULD** be performed/ administered | *Benefit >> Risk*<br>*Additional studies with focused objectives needed*<br><br>**IT IS REASONABLE** to perform procedure/administer treatment | *Benefit ≥ Risk*<br>*Additional studies with broad objectives needed; Additional registry data would be helpful*<br><br>Procedure/Treatment **MAY BE CONSIDERED** | *Risk ≥ Benefit*<br>*No additional studies needed*<br><br>Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL** |
| -should<br>-is recommended<br>-is indicated<br>-is useful/effective/ beneficial | -is reasonable<br>-can be useful/effective/ beneficial<br>-is probably recommended or indicated | -may/might be considered<br>-may/might be reasonable<br>-usefulness/effectiveness is unknown/unclear/uncertain or not well established | -is not recommended<br>-is not indicated<br>should not be done<br>-is not useful/effective/ beneficial<br>-potentially harmful |

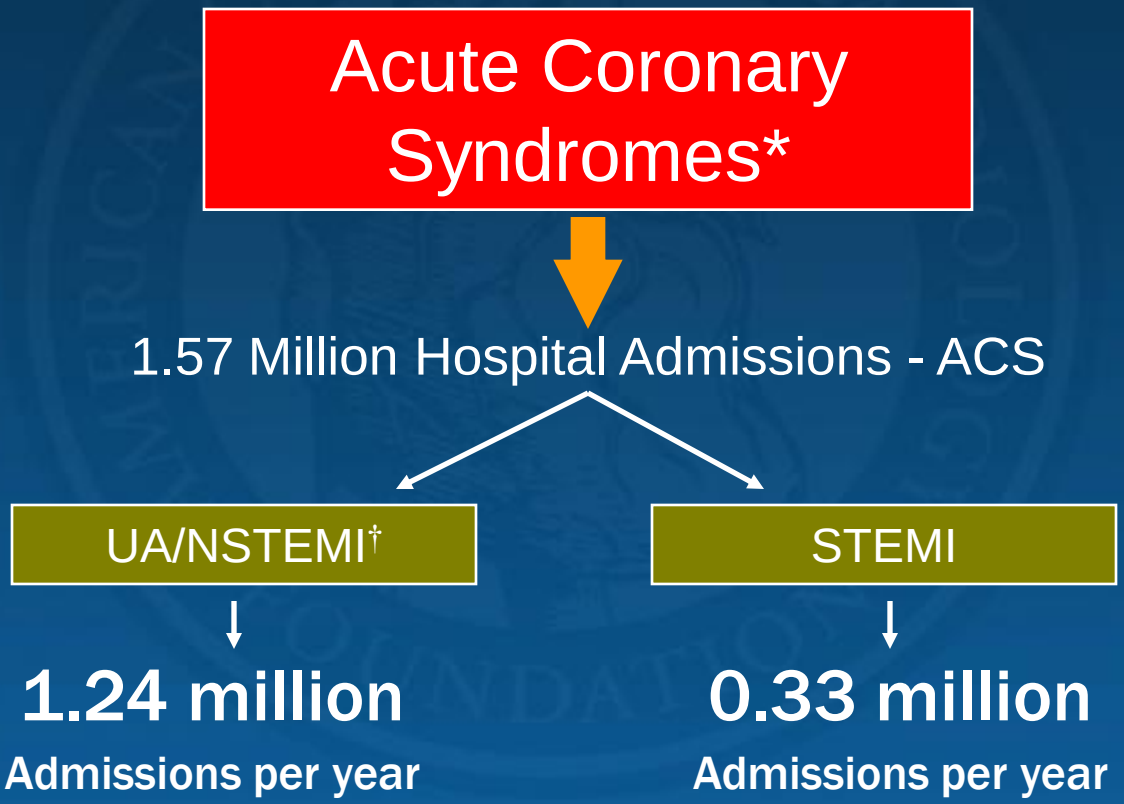
# Applying Classification of Recommendations and Level of Evidence, Previous COR/LOE Table

| Class I | Class IIa | Class IIb | Class III |
|---|---|---|---|
| *Benefit >>> Risk*<br><br>Procedure/ Treatment **SHOULD** be performed/ administered | *Benefit >> Risk*<br>*Additional studies with focused objectives needed*<br><br>**IT IS REASONABLE** to perform procedure/administer treatment | *Benefit ≥ Risk*<br>*Additional studies with broad objectives needed; Additional registry data would be helpful*<br><br>Procedure/Treatment **MAY BE CONSIDERED** | *Risk ≥ Benefit*<br>*No additional studies needed*<br><br>Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL** |

| | |
|---|---|
| **Level A:** | Recommendation based on evidence from multiple randomized trials or meta-analyses<br>Multiple (3-5) population risk strata evaluated; General consistency of direction and magnitude of effect |
| **Level B:** | Recommendation based on evidence from a single randomized trial or non-randomized studies<br>Limited (2-3) population risk strata evaluated |
| **Level C:** | Recommendation based on expert opinion, case studies, or standard-of-care<br>Very limited (1-2) population risk strata evaluated |

# Overview of Acute Coronary Syndromes (ACS)

# 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.

## Ischemic Discomfort

### Acute Coronary Syndrome

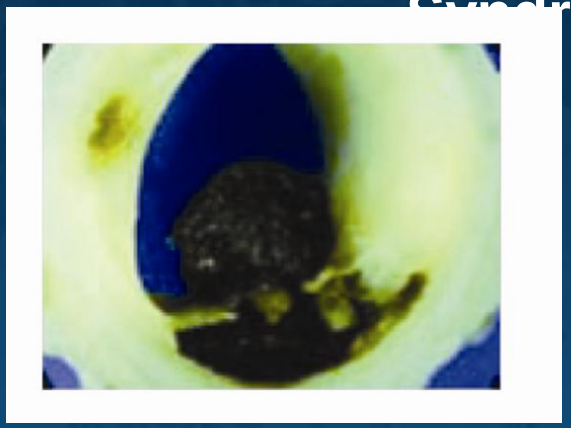
*Presentation*

*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.

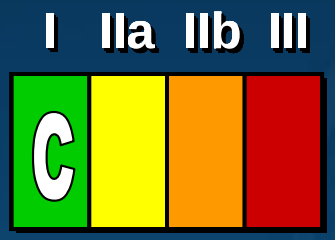
# Causes of UA/NSTEMI*

- Thrombus or thromboembolism, usually arising on disrupted or eroded plaque
  - Occlusive thrombus, usually with collateral vessels†
  - Subtotally occlusive thrombus on pre-existing plaque
  - Distal microvascular thromboembolism from plaque-associated thrombus
  - Thromboembolism from plaque erosion
- Non–plaque-associated coronary thromboembolism
- Dynamic obstruction (coronary spasm‡ or vascoconstriction) of epicardial and/or microvascular vessels
- Progressive mechanical obstruction to coronary flow
- Coronary arterial inflammation
- Secondary UA
- Coronary artery dissection§

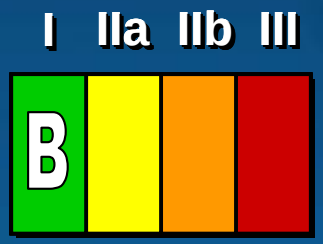
*These causes are not mutually exclusive; some patients have 2 or more causes. †DeWood MA, et al. *N Engl J Med* 1986;315:417–23. ‡May occur on top of an atherosclerotic plaque, producing missed-etiology angina or UA/NSTEMI. §Rare. Modified with permission from Braunwald E. *Circulation* 1998;98:2219–22. Anderson JL, et al. *J Am Coll Cardiol.* 2007;50:e1-e157, Table 3.

# Management Before UA/NSTEMI and Onset of UA/NSTEMI

# Identification of Patients at Risk of UA/NSTEMI



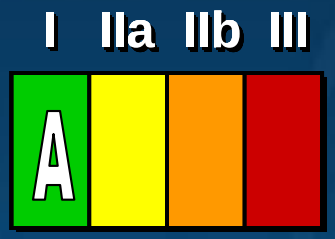

Primary care providers should evaluate the presence and status of control of major risk factors for coronary heart disease (CHD) for all patients at regular intervals (approximately every 3 to 5 years).




Ten-year risk (National Cholesterol Education Program [NCEP] global risk) of developing symptomatic CHD should be calculated for all patients who have 2 or more major risk factors to assess the need for primary prevention strategies.

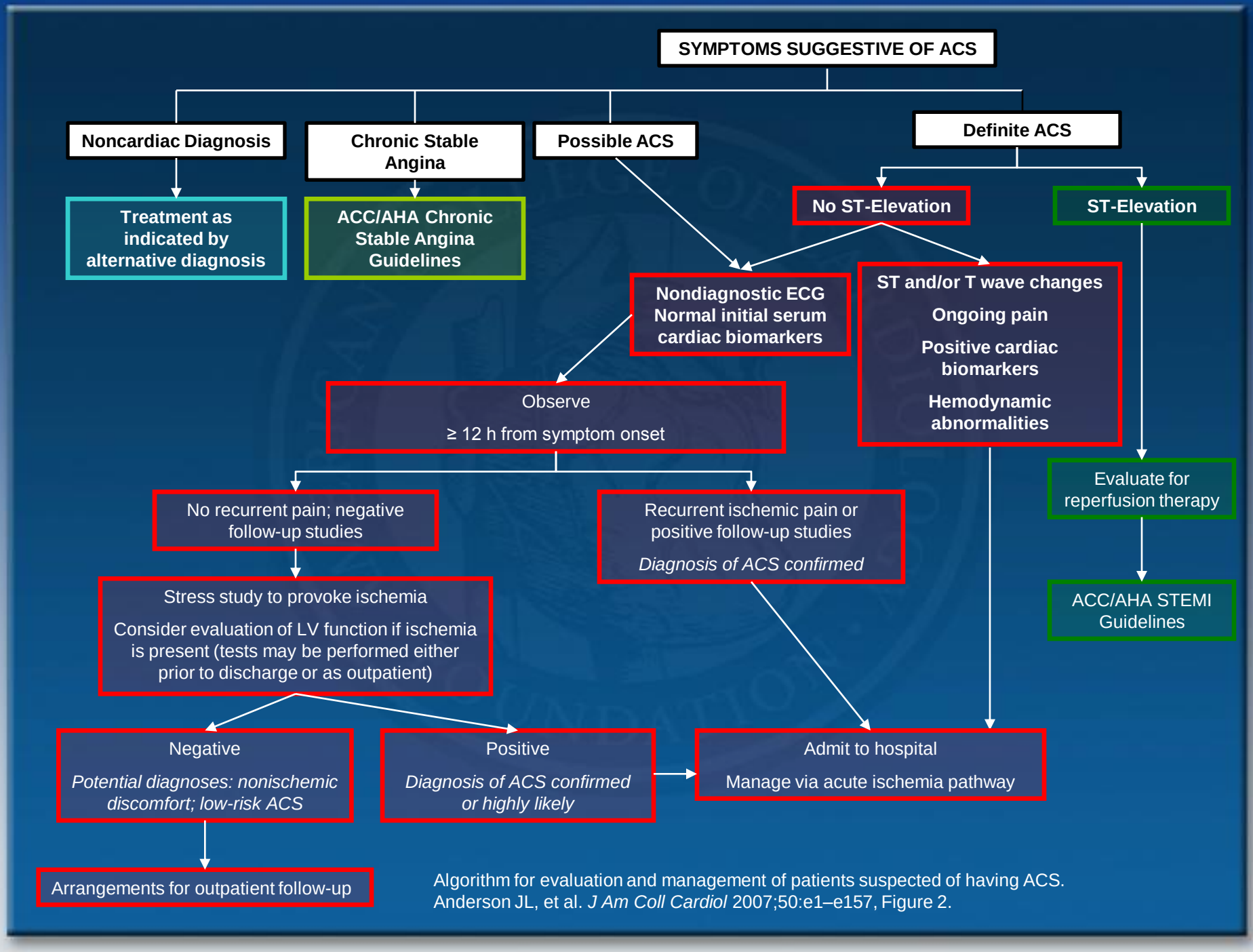
1. Grundy SM, et al. *Circulation* 2004;110:227–39.
2. NCEP ATP III Final Report. *Circulation* 2002;106:3143–421.

# Identification of Patients at Risk of UA/NSTEMI



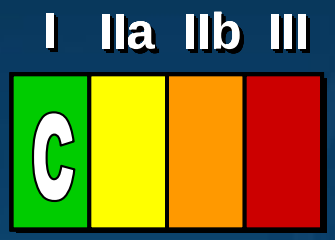

Patients with established CHD should be identified for secondary prevention efforts, and patients with a CHD risk equivalent (e.g., atherosclerosis in other vascular beds, diabetes mellitus, chronic kidney disease, or 10-year risk > 20% as calculated by Framingham equations) should receive equally intensive risk factor intervention as those with clinically apparent CHD.

# Initial Evaluation and Management of UA/NSTEMI



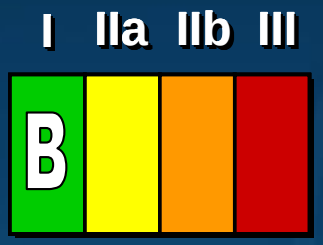

Algorithm for evaluation and management of patients suspected of having ACS.
Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157, Figure 2.

# Clinical Assessment




Patients with symptoms that may represent ACS should not be evaluated over the telephone, but should be referred to a facility that allows evaluation by a physician and the recording of a 12-lead ECG and biomarker determination (e.g., an emergency department [ED] or other acute care facility).

# Clinical Assessment




Patients with symptoms of ACS (chest discomfort with or without radiation to the arm[s], back, neck, jaw, or epigastrium; shortness of breath; weakness; diaphoresis; nausea; lightheadedness) should be instructed to call 9-1-1 and should be transported to the hospital by ambulance rather than by friends or relatives

# Identification of ACS Patients in the ED

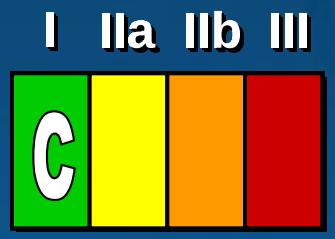
Patients with the following symptoms and signs require immediate assessment by the triage nurse for the initiation of the ACS protocol:

- Chest pain or severe epigastric pain, nontraumatic in origin, with components typical of myocardial ischemia or MI:
  - Central/substernal compression or crushing chest pain
  - Pressure, tightness, heaviness, cramping, burning, aching sensation
  - Unexplained indigestion, belching, epigastric pain
  - Radiating pain in neck, jaw, shoulders, back, or 1 or both arms
- Associated dyspnea
- Associated nausea/vomiting
- Associated diaphoresis

**If these symptoms are present, obtain stat ECG**

Adapted from the National Heart Attack Alert Program. Emergency Department: rapid identification and treatment of patients with acute myocardial infarction. US Department of Health and Human Services. US Public Health Service. National Institutes of Health. National Heart, Lung and Blood Institute; September 1993; NIH Publication No. 93-3278. Also see Table 2 of Anderson JL, et al. *J Am Coll Cardiol.* 2007;50:e1-e157.

# Clinical Assessment

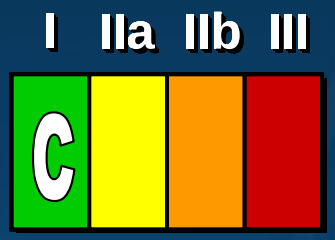



Health care providers should actively address the following issues regarding ACS with patients with or at risk for CHD and their families or other responsible caregivers:

a. The patient's heart attack risk;
b. How to recognize symptoms of ACS;
c. The advisability of calling 9-1-1 if symptoms are unimproved or worsening after 5 min, despite feelings of uncertainty about the symptoms and fear of embarrassment;
d. A plan for appropriate recognition and response to a potential acute cardiac event, including the phone number to access EMS, generally 9-1-1 (1).

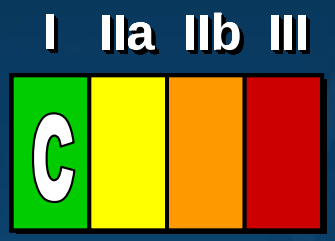
1. Dracup K, et al. *Ann Intern Med* 1997;126:645–51.

# Clinical Assessment

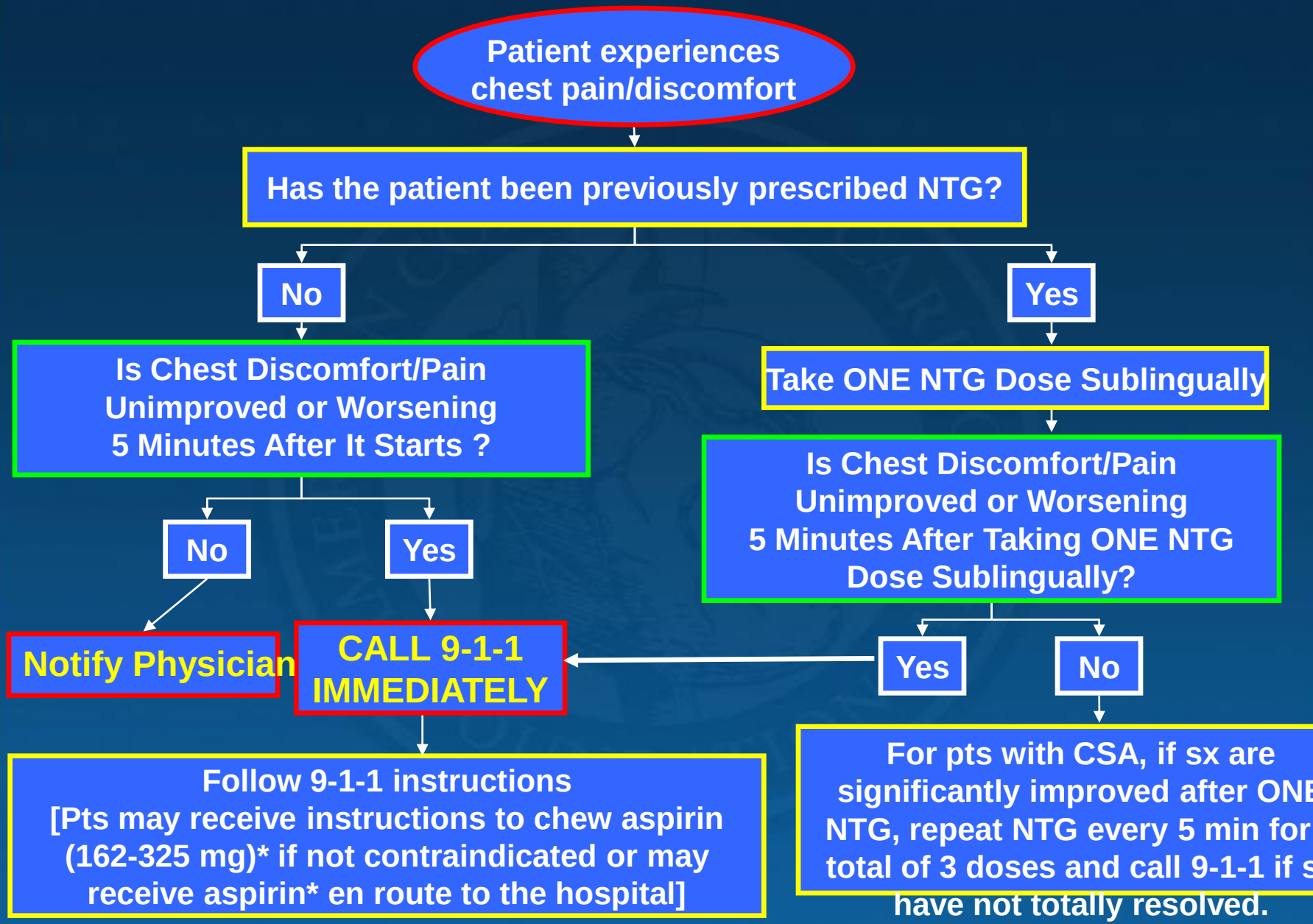



Prehospital emergency medical system (EMS) providers should administer 162 to 325 mg of aspirin (chewed) to chest pain patients suspected of having ACS unless contraindicated or already taken by the patient. Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non–enteric-coated formulations.

# Clinical Assessment

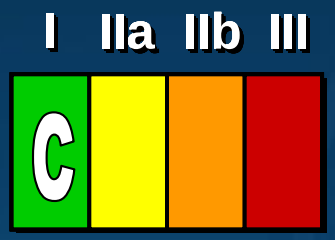



Health care providers should instruct patients with suspected ACS for whom nitroglycerin [NTG] has been prescribed previously to take not more than 1 dose of NTG sublingually in response to chest discomfort/pain. If chest discomfort/pain is unimproved or is worsening 5 min after 1 NTG dose has been taken, it is recommended that the patient or family member/friend/caregiver call 9-1-1 immediately to access EMS before taking additional NTG. In patients with chronic stable angina, if symptoms are significantly improved by 1 dose of NTG, it is appropriate to instruct the patient or family member/friend/caregiver to repeat NTG every 5 min for a maximum of 3 doses and call 9-1-1 if symptoms have not resolved completely.



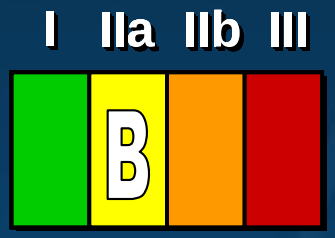

*Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non–enteric-coated formulations. Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157, Figure 3. CSA = chronic stable angina.

# Clinical Assessment

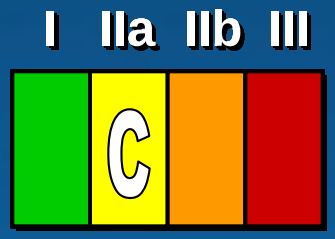



Patients with a suspected ACS with chest discomfort or other ischemic symptoms at rest for > 20 min, hemodynamic instability, or recent syncope or presyncope should be referred immediately to an ED. Other patients with suspected ACS who are experiencing less severe symptoms and who have none of the above high-risk features, including those who respond to an NTG dose, may be seen initially in an ED or an outpatient facility able to provide an acute evaluation.

# Clinical Assessment

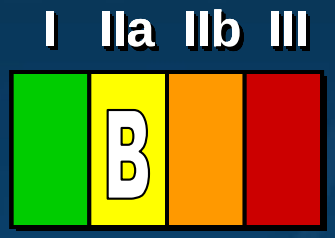



It is reasonable for health care providers and 9-1-1 dispatchers to advise patients without a history of aspirin allergy who have symptoms of ACS to chew aspirin (162 to 325 mg) while awaiting arrival of prehospital EMS providers. Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non–enteric-coated formulations.

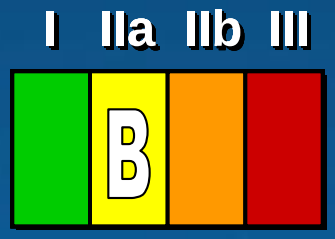



It is reasonable for health care providers and 9-1-1 dispatchers to advise patients who tolerate NTG to repeat NTG every 5 min for a maximum of 3 doses while awaiting ambulance arrival.

# Clinical Assessment

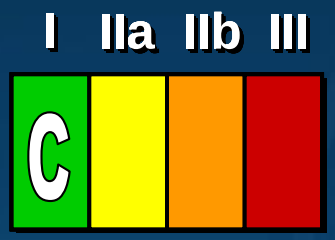



It is reasonable that all prehospital EMS providers perform and evaluate 12-lead ECGs in the field (if available) on chest pain patients suspected of ACS to assist in triage decisions. Electrocardiographs with validated computer-generated interpretation algorithms are recommended for this purpose.

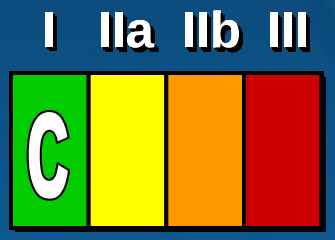



If the 12-lead ECG shows evidence of acute injury or ischemia, it is reasonable that prehospital ACLS providers relay the ECG to a predetermined medical control facility and/or receiving hospital.

# Early Risk Stratification

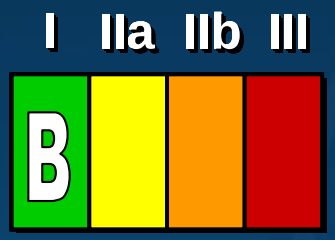



A rapid clinical determination of the likelihood risk of obstructive CAD (i.e., high, intermediate, or low) should be made in all patients with chest discomfort or other symptoms suggestive of an ACS and considered in patient management.

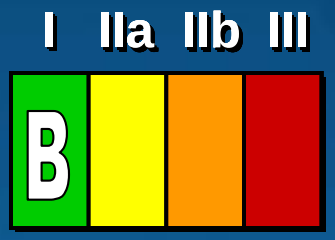



Patients who present with chest discomfort or other ischemic symptoms should undergo early risk stratification for the risk of cardiovascular events (e.g., death or [re]MI) that focuses on history, including anginal symptoms, physical findings, ECG findings, and biomarkers of cardiac injury, and results should be considered in patient management.

# Early Risk Stratification

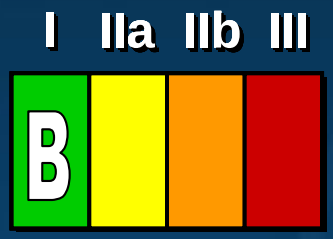



A 12-lead ECG should be performed and shown to an experienced emergency physician as soon as possible after ED arrival, with a goal of within 10 min of ED arrival for all patients with chest discomfort (or anginal equivalent) or other symptoms suggestive of ACS.

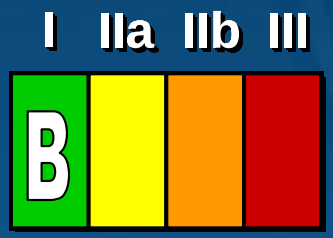



If the initial ECG is not diagnostic but the patient remains symptomatic and there is high clinical suspicion for ACS, serial ECGs, initially at 15- to 30-min intervals, should be performed to detect the potential for development of ST-segment elevation or depression.

# Early Risk Stratification

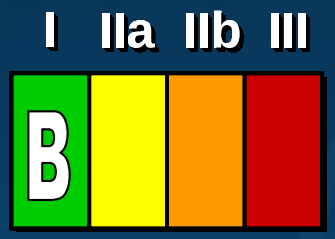



Cardiac biomarkers should be measured in all patients who present with chest discomfort consistent with ACS.

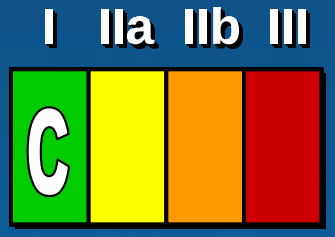



A cardiac-specific troponin is the preferred marker, and if available, it should be measured in all patients who present with chest discomfort consistent with ACS.

# Early Risk Stratification

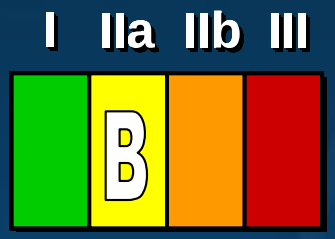



Patients with negative cardiac biomarkers within 6 h of the onset of symptoms consistent with ACS should have biomarkers remeasured in the time frame of 8 to 12 h after symptom onset. (The exact timing of serum marker measurement should take into account the uncertainties often present with the exact 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.)

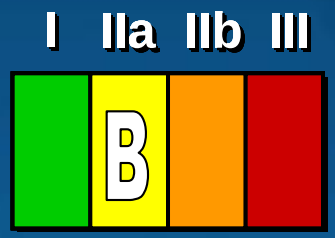



The initial evaluation of the patient with suspected ACS should include the consideration of noncoronary causes for the development of unexplained symptoms.

# 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 |

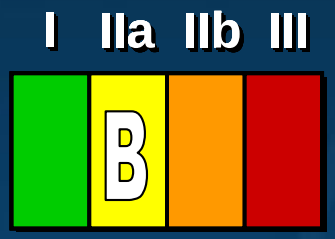

Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157, Table 8. TIMI = Thrombolysis in Myocardial Infarction.

# GRACE Risk Score

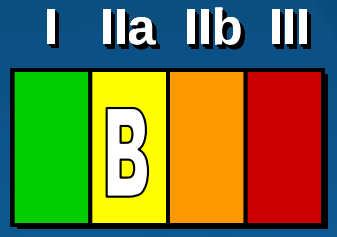
| Variable | Odds ratio |
|---|---|
| Older age | 1.7 per 10 y |
| Killip class | 2.0 per class |
| Systolic BP | 1.4 per 20 mm Hg ↑ |
| ST-segment deviation | 2.4 |
| Cardiac arrest during presentation | 4.3 |
| Serum creatinine level | 1.2 per 1-mg/dL ↑ |
| Positive initial cardiac biomarkers | 1.6 |
| Heart rate | 1.3 per 30-beat/min ↑ |

The sum of scores is applied to a reference monogram to determine the corresponding all-cause mortality from hospital discharge to 6 months. Eagle KA, et al. *JAMA* 2004;291:2727–33. The GRACE clinical application tool can be found at www.outcomes-umassmed.org/grace. Also see Figure 4 in Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157.
GRACE = Global Registry of Acute Coronary Events.

# Early Risk Stratification

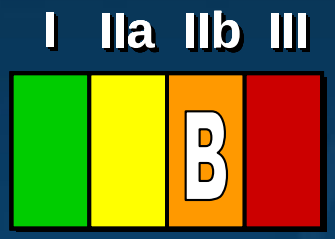



It is reasonable to obtain supplemental ECG leads $V_7$ through $V_9$ in patients whose initial ECG is nondiagnostic to rule out MI due to left circumflex occlusion.

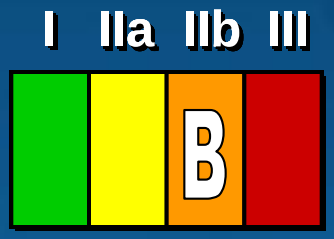



Continuous 12-lead ECG monitoring is a reasonable alternative to serial 12-lead recordings in patients whose initial ECG is nondiagnostic.

# Early Risk Stratification

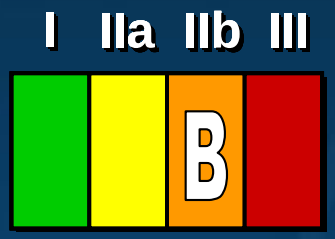



For patients who present within 6 h of the onset of symptoms consistent with ACS, assessment of an early marker of cardiac injury (e.g., myoglobin) in conjunction with a late marker (e.g., troponin) may be considered.

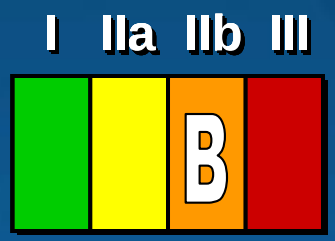



For patients who present within 6 h of symptoms suggestive of ACS, a 2-h delta CK-MB mass in conjunction with 2-h delta troponin may be considered.

# Early Risk Stratification




For patients who present within 6 h of symptoms suggestive of ACS, myoglobin in conjunction with CK-MB mass or troponin when measured at baseline and 90 min may be considered.



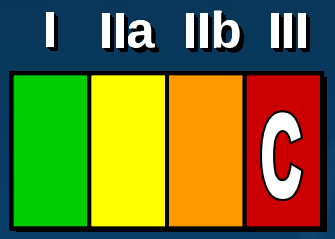

Measurement of B-type natriuretic peptide (BNP) or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS.

# B-Type Natriuretic Peptide

- B-type natriuretic peptide (BNP): new biomarker of considerable interest
- BNP is a cardiac neurohormone released on ventricular myocyte stretch as proBNP, which is enzymatically cleaved to the N-terminal proBNP (NT-pro-BNP) and, subsequently, to BNP
- Natriuretic peptides are strong predictors of both short- and long-term mortality in patients with STEMI and UA/NSTEMI
- Recommend: Measurement of BNP or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS (*Class IIb, LOE: B*)

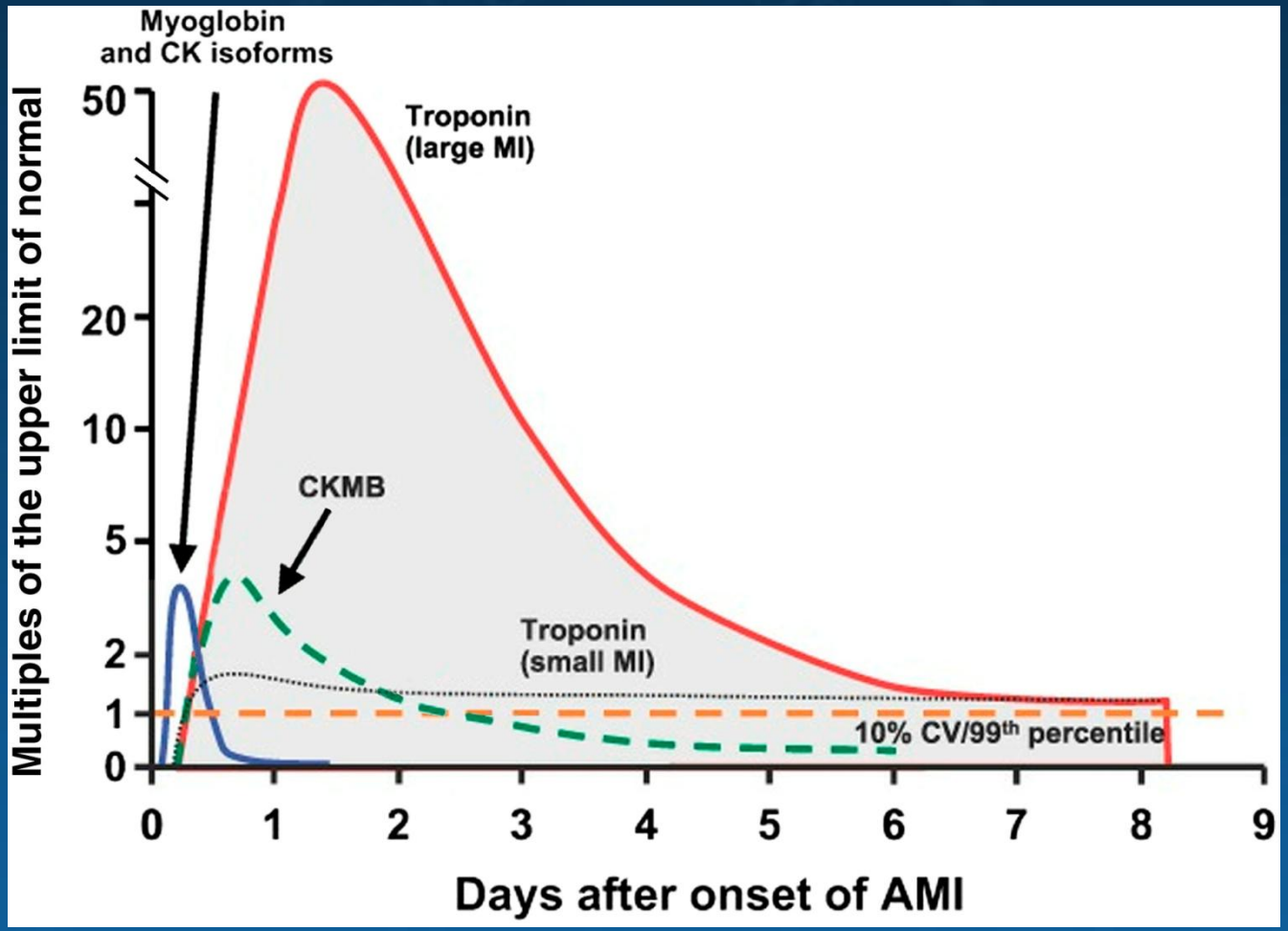
Galvani M, et al. *Circulation* 2004;110:128–34. LOE = level of evidence.

# Early Risk Stratification



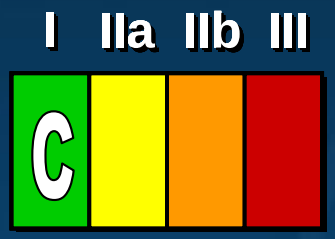

Total CK (without MB), aspartate aminotransferase (AST, SGOT), alanine transaminase, beta-hydroxybutyric dehydrogenase, and/or lactate dehydrogenase should not be utilized as primary tests for the detection of myocardial injury in patients with chest discomfort suggestive of ACS.

# Timing of Release of Various Biomarkers After Acute Myocardial Infarction



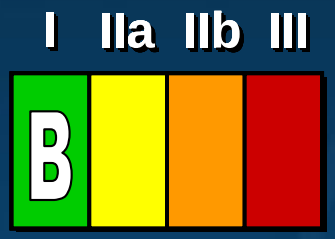

Shapiro BP, Jaffe AS. Cardiac biomarkers. In: Murphy JG, Lloyd MA, editors. Mayo Clinic Cardiology: Concise Textbook. 3rd ed. Rochester, MN: Mayo Clinic Scientific Press and New York: Informa Healthcare USA, 2007:773–80. Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157, Figure 5.

# Immediate Management




The history, physical examination, 12-lead ECG, and initial cardiac biomarker tests should be integrated to assign patients with chest pain into 1 of 4 categories: a noncardiac diagnosis, chronic stable angina, possible ACS, and definite ACS.

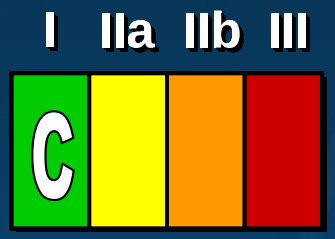
# Immediate Management




Patients with probable or possible ACS but whose initial 12-lead ECG and cardiac biomarker levels are normal should be observed in a facility with cardiac monitoring (e.g., chest pain unit or hospital telemetry ward), and repeat ECG (or continuous 12-lead ECG monitoring) and repeat cardiac biomarker measurement(s) should be obtained at predetermined, specified time intervals*.

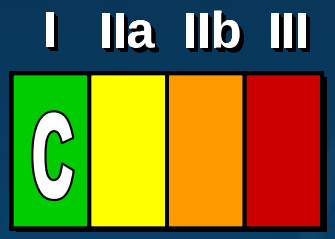
*See Section 2.2.8 in Anderson JA, et al. *J Am Coll Cardiol* 2007:50:e1-e157.

# Immediate Management



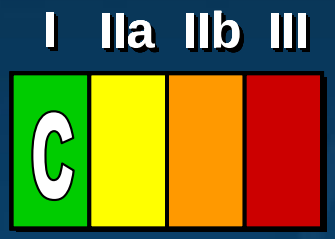

In patients with suspected ACS in whom ischemic heart disease is present or suspected, if the follow-up 12-lead ECG and cardiac biomarkers measurements are normal, a stress test (exercise or pharmacological) to provoke ischemia should be performed in the ED, in a chest pain unit, or on an outpatient 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

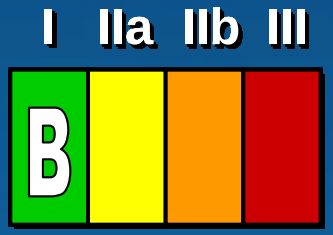



In low-risk patients who are referred for outpatient stress testing (see previous slide), precautionary appropriate pharmacotherapy (e.g., aspirin, sublingual NTG, and/or beta blockers) should be given while awaiting results of the stress test.

# Immediate Management

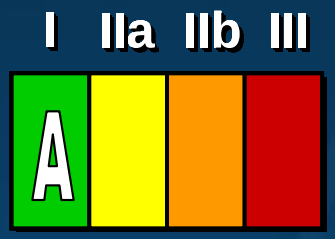



Patients with definite ACS and ongoing ischemic symptoms, positive cardiac biomarkers, new ST-segment deviations, new deep T-wave inversions, hemodynamic abnormalities, or a positive stress test should be admitted to the hospital for further management. Admission to the critical care unit is recommended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

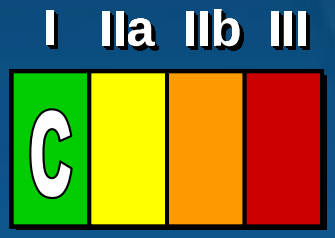



Patients with possible ACS and negative cardiac biomarkers who are unable to exercise or who have an abnormal resting ECG should undergo a pharmacological stress test.

# Immediate Management

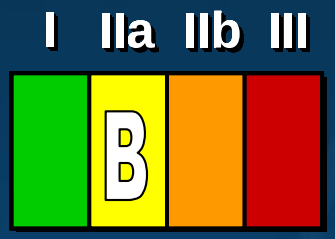



Patients with definite ACS and ST-segment elevation in leads $V_7$ to $V_9$ due to left circumflex occlusion should be evaluated for immediate reperfusion therapy.




Patients discharged from the ED or chest pain unit should be given specific instructions for activity, medications, additional testing, and follow-up with a personal physician.

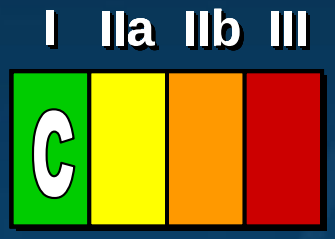
# Immediate Management



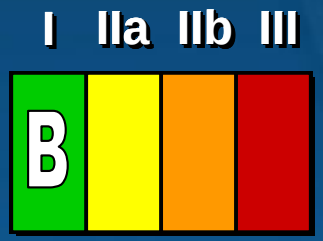

In patients with suspected ACS with a low or intermediate probability of CAD, in whom the follow-up 12-lead ECG and cardiac biomarkers measurements are normal, performance of a noninvasive coronary imaging test (i.e., coronary CT angiography) is reasonable as an alternative to stress testing.

# Early Hospital Care

# Anti-Ischemic Therapy

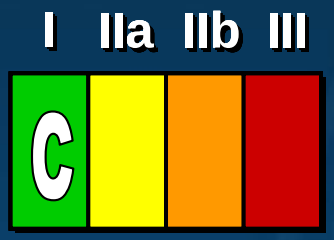



Bed/chair rest with continuous ECG monitoring is recommended for all UA/NSTEMI patients during the early hospital phase.

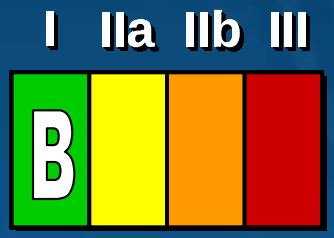



Supplemental oxygen should be administered to patients with UA/NSTEMI with an arterial saturation <90%, respiratory distress, or other high-risk features for hypoxemia. (Pulse oximetry is useful for continuous measurement of $SaO_2$.)

# Anti-Ischemic Therapy

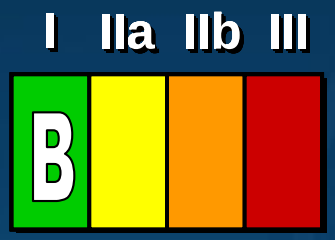



Patients with UA/NSTEMI with ongoing ischemic discomfort should receive sublingual NTG (0.4 mg) every 5 min for a total of 3 doses, after which assessment should be made about the need for intravenous NTG, if not contraindicated.




Intravenous NTG is indicated in the first 48 h after UA/NSTEMI for treatment of persistent ischemia, heart failure (HF), or hypertension. The decision to administer intravenous NTG and the dose used should not preclude therapy with other proven mortality-reducing interventions such as beta blockers or angiotensin-converting enzyme (ACE) inhibitors.

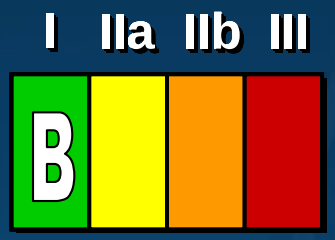
# Anti-Ischemic Therapy




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).

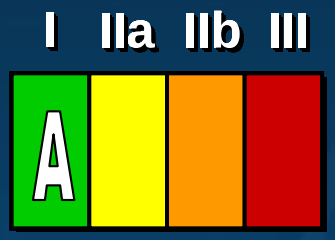
*Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk of developing cardiogenic shock): age greater than 70 years, systolic blood pressure less than 120 mmHg, sinus tachycardia greater than 110 or heart rate less than 60, increased time since onset of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

# Anti-Ischemic Therapy

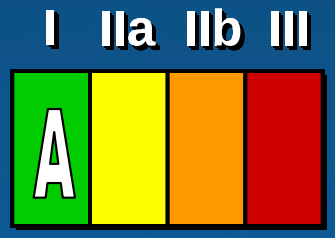



In UA/NSTEMI patients with continuing or frequently recurring ischemia and in whom beta blockers are contraindicated, a nondihydropyridine calcium channel blocker (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction or other contraindications.

# Anti-Ischemic Therapy

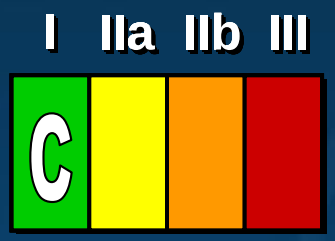



An ACE inhibitor should be administered orally within the first 24 h to UA/NSTEMI patients with pulmonary congestion or LV ejection fraction (LVEF) ≤40%, in the absence of hypotension (systolic blood pressure <100 mm Hg or <30 mm Hg below baseline) or known contraindications to that class of medications.




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%.

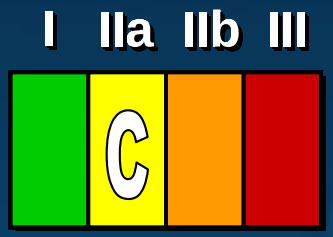
# Anti-Ischemic Therapy



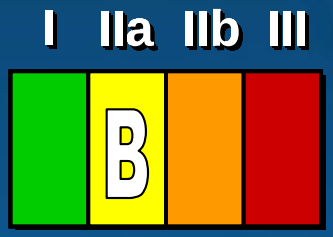

Because of the increased risks of mortality, reinfarction, hypertension, HF, and myocardial rupture associated with their use, nonsteroidal anti-inflammatory drugs (NSAIDs), except for aspirin, whether nonselective or cyclooxygenase (COX)-2–selective agents, should be discontinued at the time a patient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

# Anti-Ischemic Therapy

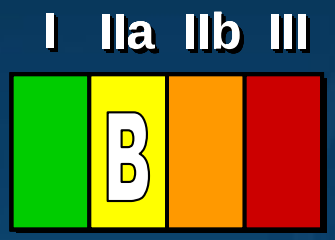



It is reasonable to administer supplemental oxygen to all patients with UA/NSTEMI during the first 6 h after presentation.




In the absence of contradictions to its use, it is reasonable to administer morphine sulfate intravenously to UA/NSTEMI patients if there is uncontrolled ischemic chest discomfort despite NTG, provided that additional therapy is used to manage the underlying ischemia.

# Anti-Ischemic Therapy




It is reasonable to administer intravenous beta blockers at the time of presentation for hypertension to UA/NSTEMI 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).

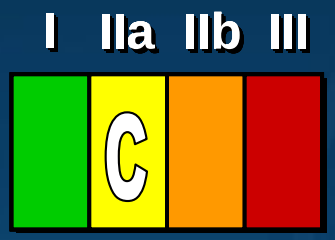
*Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk of developing cardiogenic shock): age greater than 70 years, systolic blood pressure less than 120 mmHg, sinus tachycardia greater than 110 or heart rate less than 60, increased time since onset of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

# ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)

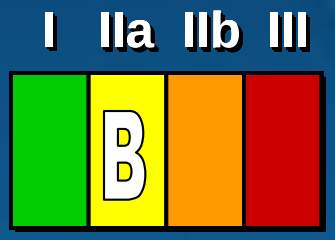
- 45,852 patients within 24 h acute MI
  - 93% STEMI or LBBB
- Up to 15 mg IV → 200 mg po metoprolol daily vs placebo
- Co-primary outcomes
  - death, reinfarction, or cardiac arrest
  - death from any cause to discharge or up to 4 wk in hospital
- Neither co-primary outcome ↓ by metoprolol
  - 5 fewer 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

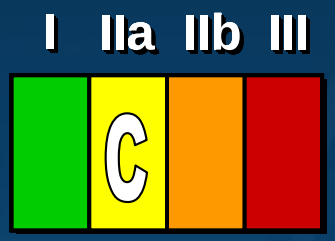



Oral long-acting nondihydropyridine calcium antagonists are reasonable for use in UA/NSTEMI patients for recurrent ischemia in the absence of contraindications after beta blockers and nitrates have been fully used.



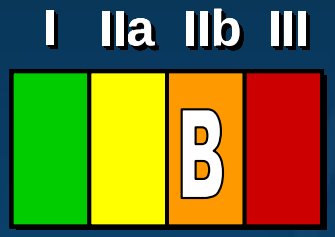

An ACE inhibitor administered orally within the first 24 h of UA/NSTEMI can be useful in patients without pulmonary congestion or LVEF ≤40% in the absence of hypotension (systolic blood pressure <100 mm Hg or <30 mm Hg below baseline) or known contraindications to that class of medications.

# Anti-Ischemic Therapy

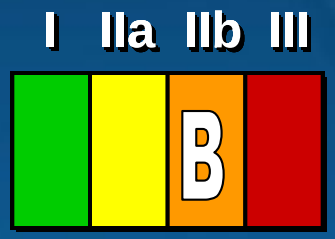



Intra-aortic balloon pump (IABP) counterpulsation is reasonable in UA/NSTEMI patients for severe ischemia that is continuing or recurs frequently despite intensive medical therapy, for hemodynamic instability in patients before or after coronary angiography, and for mechanical complications of MI.

# Anti-Ischemic Therapy

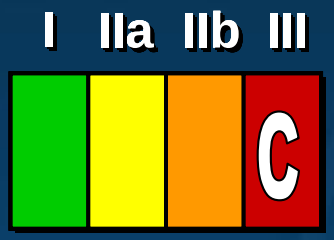



The use of extended-release forms of nondihydropyridine calcium antagonists instead of a beta blocker may be considered in patients with UA/NSTEMI.

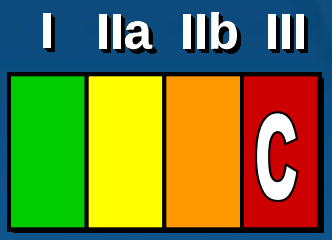



Immediate-release dihydropyridine calcium antagonists in the presence of adequate beta blockade may be considered in patients with UA/NSTEMI with ongoing ischemic symptoms or hypertension.

# Anti-Ischemic Therapy

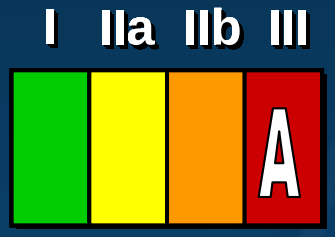



Nitrates should not be administered to UA/NSTEMI patients with systolic blood pressure <90 mm Hg or ≥30 mm Hg below baseline, severe bradycardia (<50 beats per minute), tachycardia (>100 beats per minute) in the absence of symptomatic HF, or right ventricular infarction.

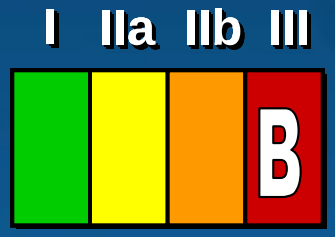



Nitroglycerin or other nitrates should not be administered to patients with UA/NSTEMI who had received a phosphodiesterase inhibitor for erectile dysfunction within 24 h of sildenafil or 48 h of tadalafil use. The suitable time for the administration of nitrates after vardenafil has not been determined.

# Anti-Ischemic Therapy




Immediate-release dihydropyridine calcium antagonists should not be administered to patients with UA/NSTEMI in the absence of a beta blocker.



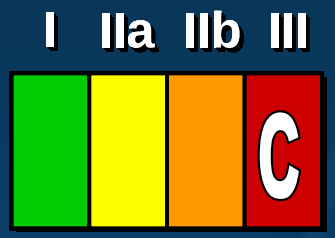

An intravenous ACE inhibitor should not be given to patients within the first 24 h of UA/NSTEMI because of the increased risk of hypotension. (A possible exception may be patients with refractory hypertension.)

# Anti-Ischemic Therapy


It may be harmful to administer intravenous beta blockers to UA/NSTEMI patients who have contraindications to beta blockade, signs of HF or low-output state, or other risk factors* for cardiogenic shock.

*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.

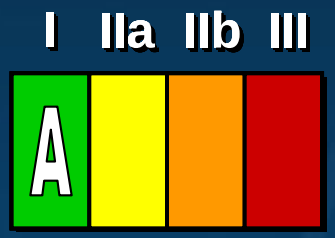
# Anti-Ischemic Therapy




Nonsteroidal anti-inflammatory drugs (except for aspirin), whether nonselective or COX-2–selective agents, should not be administered during hospitalization for UA/NSTEMI because of the increased risks of mortality, reinfarction, hypertension, HF, and myocardial rupture associated with their use.

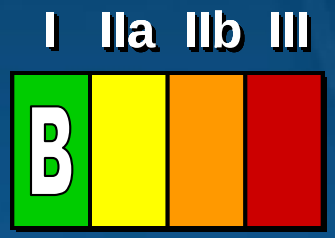
The selective COX-2 inhibitors and other nonselective NSAIDs have been associated with increased cardiovascular risk. An AHA scientific statement on the use of NSAIDs concluded that the risk of cardiovascular events is proportional to COX-2 selectivity and the underlying risk to the patient (Antman EM, 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




Modified 2011

Aspirin should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients who tolerate it.




Modified 2011

Clopidogrel (loading dose followed by daily maintenance dose) should be administered to UA/NSTEMI patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance.

*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.

# Meta-analysis Comparing Use of Long-term ASA vs. Control

- Primary prevention trials (pts at low average risk):
  - Serious vascular events – RR: 0.88; p=0.0001
  - CHD Death – RR: 0.95; p=0.5
  - Any stroke – RR: 0.95; p=0.4
  - Bleeds – RR: 1.54; p<0.0001
- Secondary prevention trials (pts at high average risk):
  - Serious vascular events – RR: 0.81; p<0.0001
  - CHD Death – RR: 0.87; p=0.02
  - Any stroke – RR: 0.81; p=0.002
  - Bleeds – RR: 2.69; p=0.01
- ASA use in primary prevention is uncertain, as reduction in occlusive events must be weighed against ↑ in major bleeds

Revised 2011

Antithrombotic Trialists (ATT) Collaboration, Lancet 2009;373:1849–60.

# Select Management Strategy:

# Initial Invasive Versus Initial Conservative Strategy

# Selection of Initial Treatment Strategy: Initial Invasive Versus Conservative Strategy

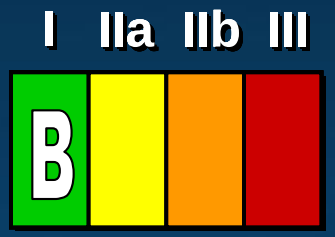
| | |
|---|---|
| **Invasive** | Recurrent angina/ischemia at rest with low-level activities despite intensive medical therapy |
| | Elevated cardiac biomarkers (TnT or TnI) |
| | New/presumably new ST-segment depression |
| | Signs/symptoms of heart failure or new/worsening mitral regurgitation |
| | 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 preference in the absence of high-risk features |

# Risk Scores

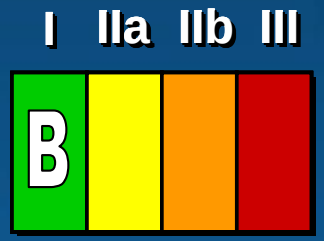
| | TIMI | GRACE |
|---|---|---|
| History | Age<br>Hypertension<br>Diabetes<br>Smoking<br>↑ Cholesterol<br>Family history<br>History of CAD | Age |
| Presentation | Severe angina<br>Aspirin within 7 days<br>Elevated markers<br>ST-segment deviation | Heart rate<br>Systolic BP<br>Elevated creatinine<br>Heart failure<br>Cardiac arrest<br>Elevated markers<br>ST-segment deviation |

Antman EM, et al. *JAMA* 2000;284:835–42. Eagle KA, et al. *JAMA* 2004;291:2727–33.
GRACE = Global Registry of Acute Coronary Events; TIMI = Thrombolysis in Myocardial Infarction.

# Initial Conservative Versus Initial Invasive Strategies




For women with high-risk features, recommendations for invasive strategy are similar to those of men.




In women with low-risk features, a conservative strategy is recommended.

These recommendations are also found in the Section Special Groups, Women.

# 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: aspirin, 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: aspirin, 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

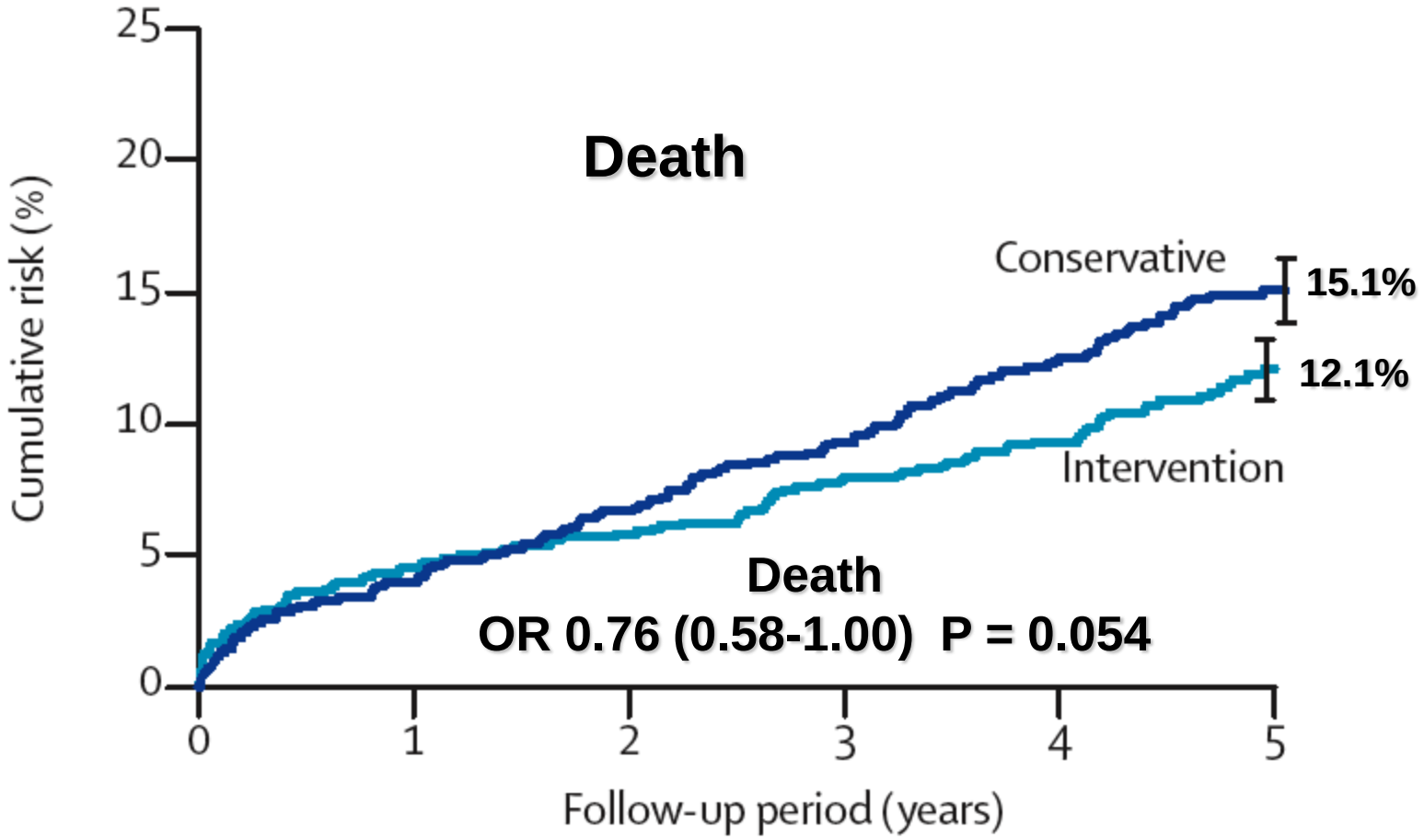
Cannon CP, et al. *N Engl J Med* 2001;344:1879–87.

# 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

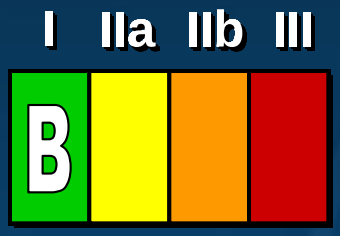



**Numbers at risk**

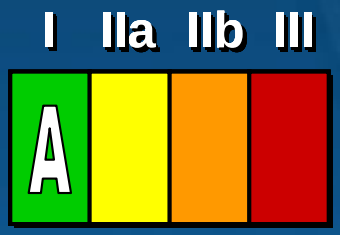
| | | | | | | |
|---|---|---|---|---|---|---|
| Intervention | 895 | 854 | 842 | 822 | 743 | 470 |
| Conservative | 915 | 878 | 853 | 828 | 729 | 463 |

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: aspirin, 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.

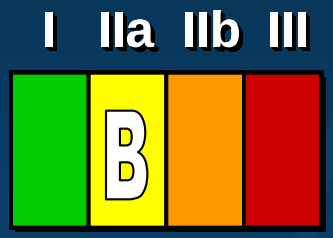
# Global Registry of Acute Coronary Events (GRACE)

- 24,165 ACS patients in 102 hospitals in 14 countries stratified by age
- ~ 2/3 men, but proportion ↓ with age
- ↑ Hx angina, TIA/stroke, MI, CHF, CABG, hypertension or AF in elderly (≥ 65y)
  - Delay in seeking medical attention and NSTEMI significantly ↑ in elderly
- ↓ Use in elderly aspirin, β-blockers, lytic therapy, statins and GP IIb/IIIa inhibitors;↑ calcium antagonists and ACE inhibitors
- UFH ↑ young patients; LMWHs ↔ across all age groups
- Angio and PCI rates significantly ↓ with ↑ age

*Elderly patients a high-risk population for whom physicians and healthcare systems should provide evidence-based ACS therapies, such as aggressive, early invasive strategy and key pharmacotherapies (e.g., anticoagulants, β-blockers, clopidogrel and GP IIb/IIIa inhibitors)*

Avezum A, et al. *Am Heart J* 2005;149:67–73.

# Initial Conservative Versus Initial Invasive Strategies




New 2011

It is reasonable to choose an early invasive strategy (within 12 to 24 hours of admission) over a delayed invasive strategy for initially stabilized high-risk patients with UA/NSTEMI.* For patients not at high risk, a delayed invasive approach is also reasonable.

*Immediate catheterization/angiography is recommended for unstable patients.

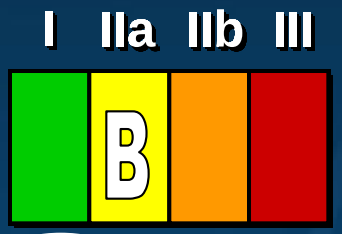
# TIMACS

- Routine early (angiography ≤24 h) vs. delayed intervention in ACS pts
- Death, MI, or stroke at 6 months: 9.6% routine early vs. 11.3% delayed (HR: 0.85; p=0.15)
- Death, MI, or refractory ischemia at 6 months (secondary outcome): 9.5% routine early vs. 12.9% delayed (HR: 0.72; p=0.003)
- Primary outcome did not differ greatly between early and delayed intervention, however, secondary outcome was superior in routine early to delayed intervention in high-risk patients

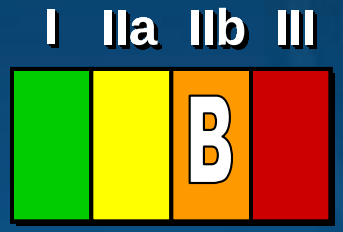
Revised 2011

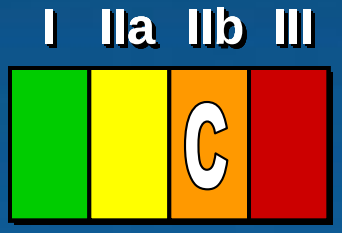
Mehta SR, et al. NEJM 2009;360:2165–75.

# Initial Conservative Versus Initial Invasive Strategies




Modified 2011




An invasive strategy may be reasonable in patients with chronic renal insufficiency.

In initially stabilized patients, an initially conservative (i.e., a selectively invasive) strategy may be considered as a treatment strategy for UA/ NSTEMI patients (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events including those who are troponin positive.

The decision to implement an initial conservative (vs. initial invasive) strategy in these patients may be made by considering physician and patient preference.

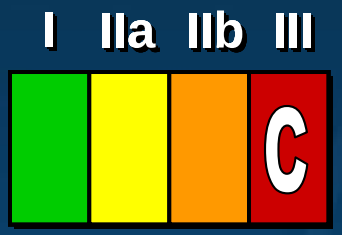
These recommendations are also found in the Chronic Kidney Disease Section.

# Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS)

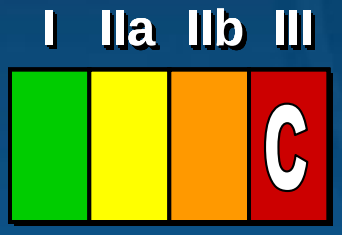
- 1,200 high-risk ACS patients
- Routine inv vs selective inv strategy
- Meds: aspirin, clopidogrel, LMWH, and lipid-lowering rx; abciximab for revasc patients
- No ↓ death, MI, and ischemic rehosp @ 1 y and longer-term follow-up by routine inv strategy
- Relatively high (47%) rate revasc actually performed 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.

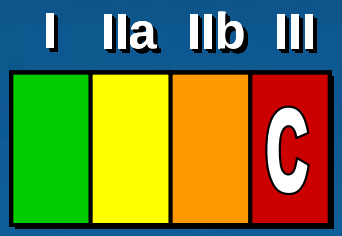
# Initial Conservative Versus Initial Invasive Strategies




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.



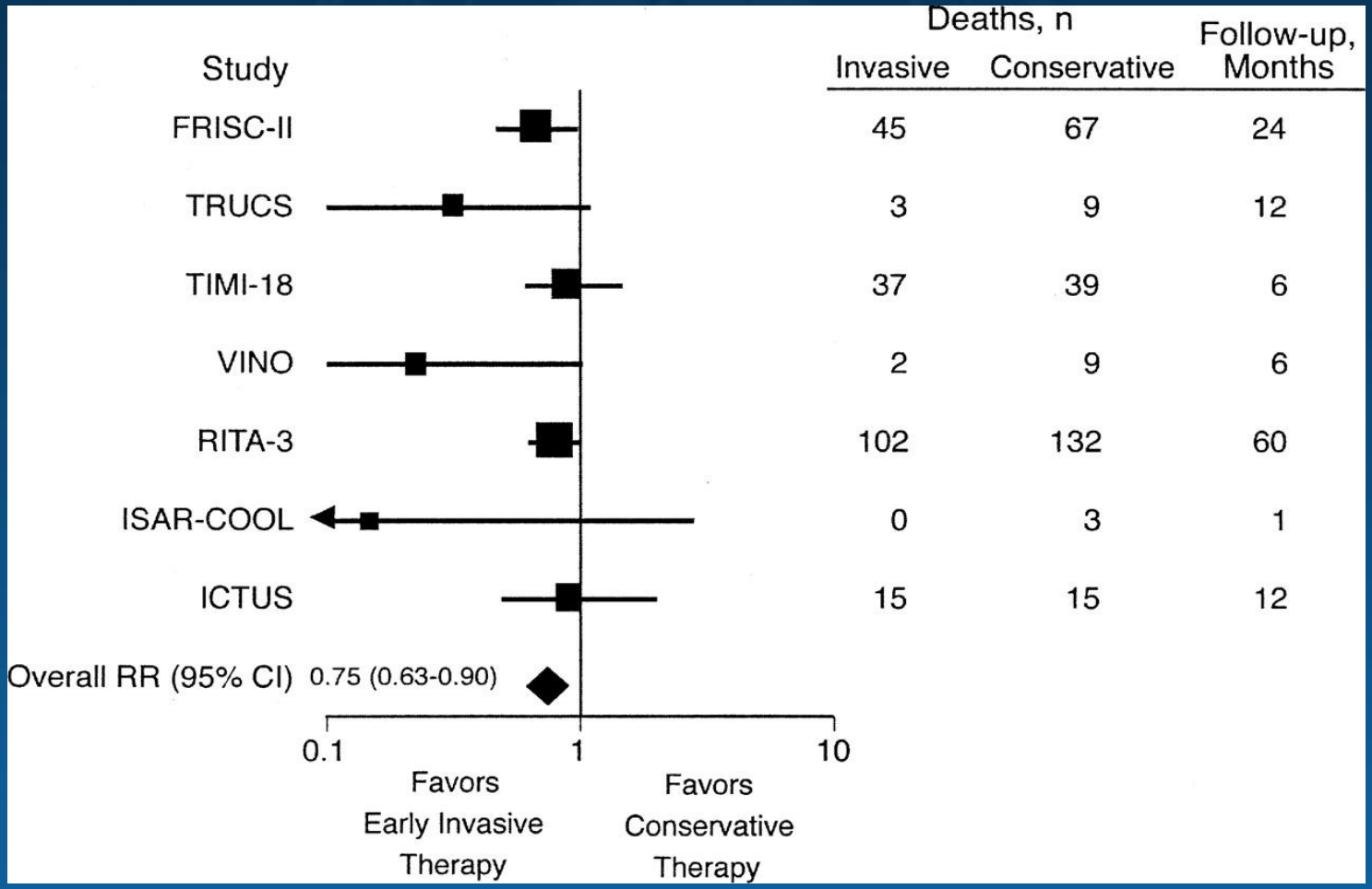

An early invasive strategy* is not recommended in patients with acute chest pain and a low likelihood of ACS.




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

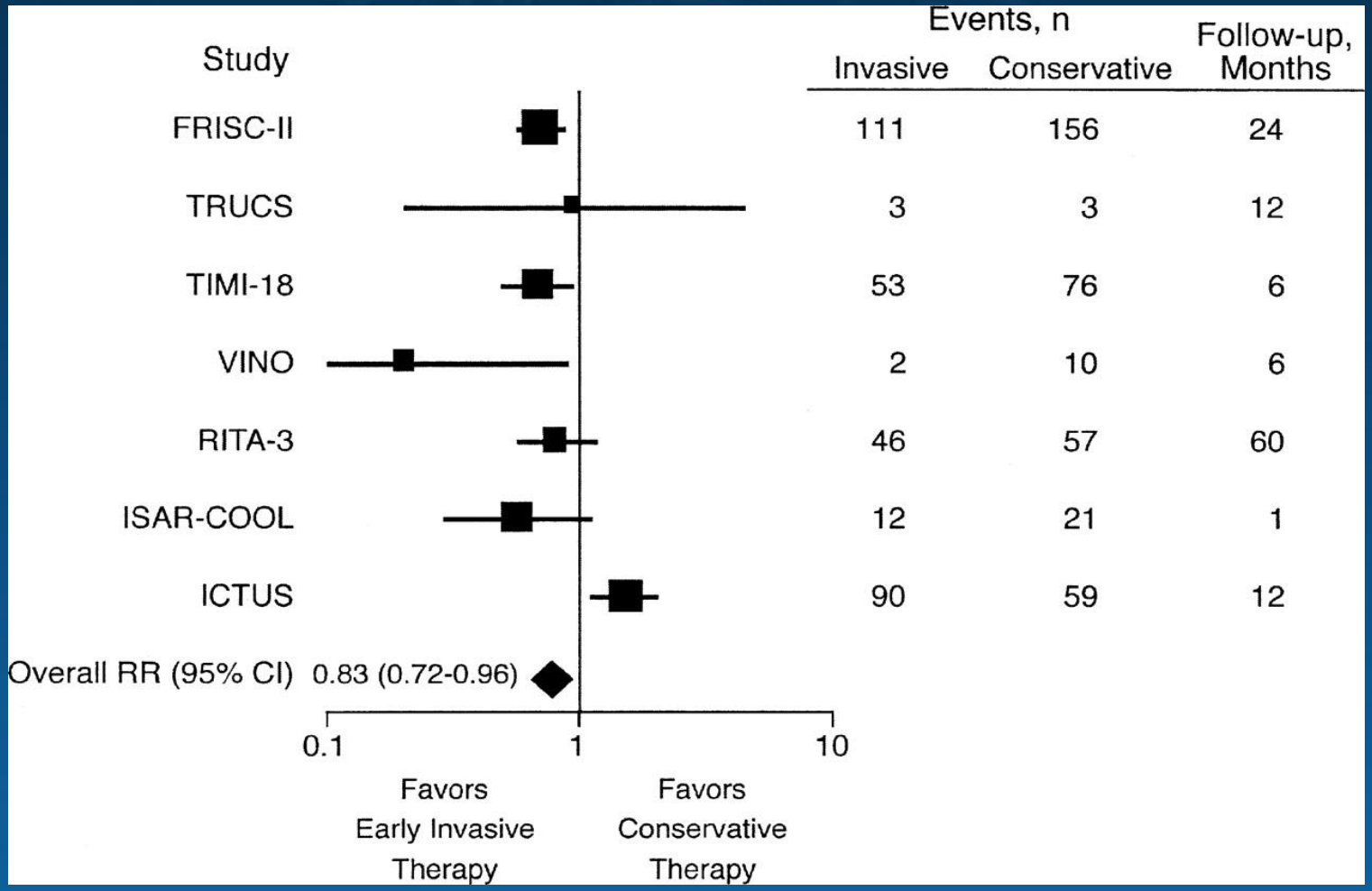
*Diagnostic angiography with intent to perform revascularization.

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



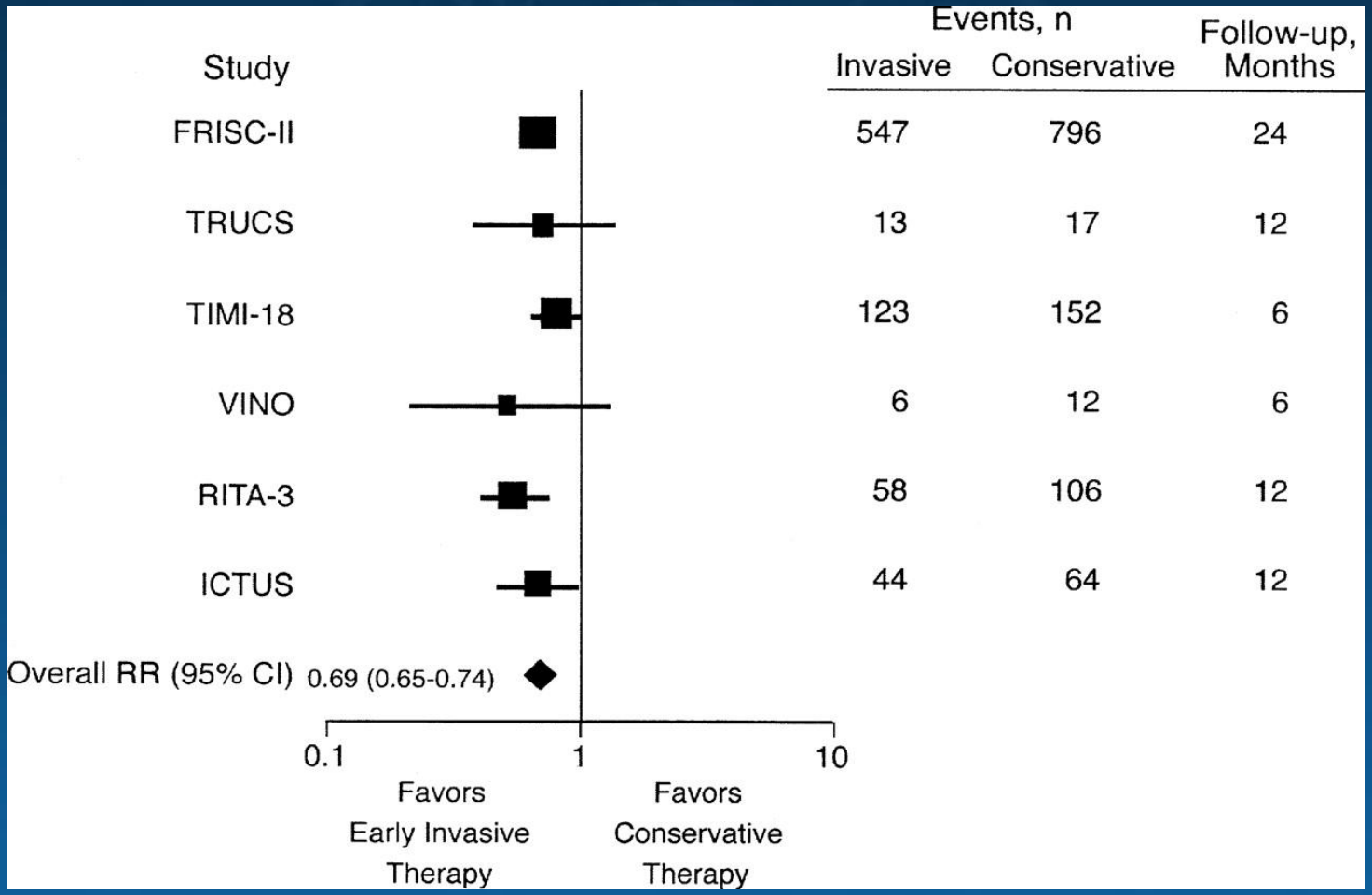

Bavry AA, et al. *J Am Coll Cardiol* 2006;48:1319–1325. Reprinted with permission from Elsevier. CI = confidence interval; RR = relative risk.

# 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.

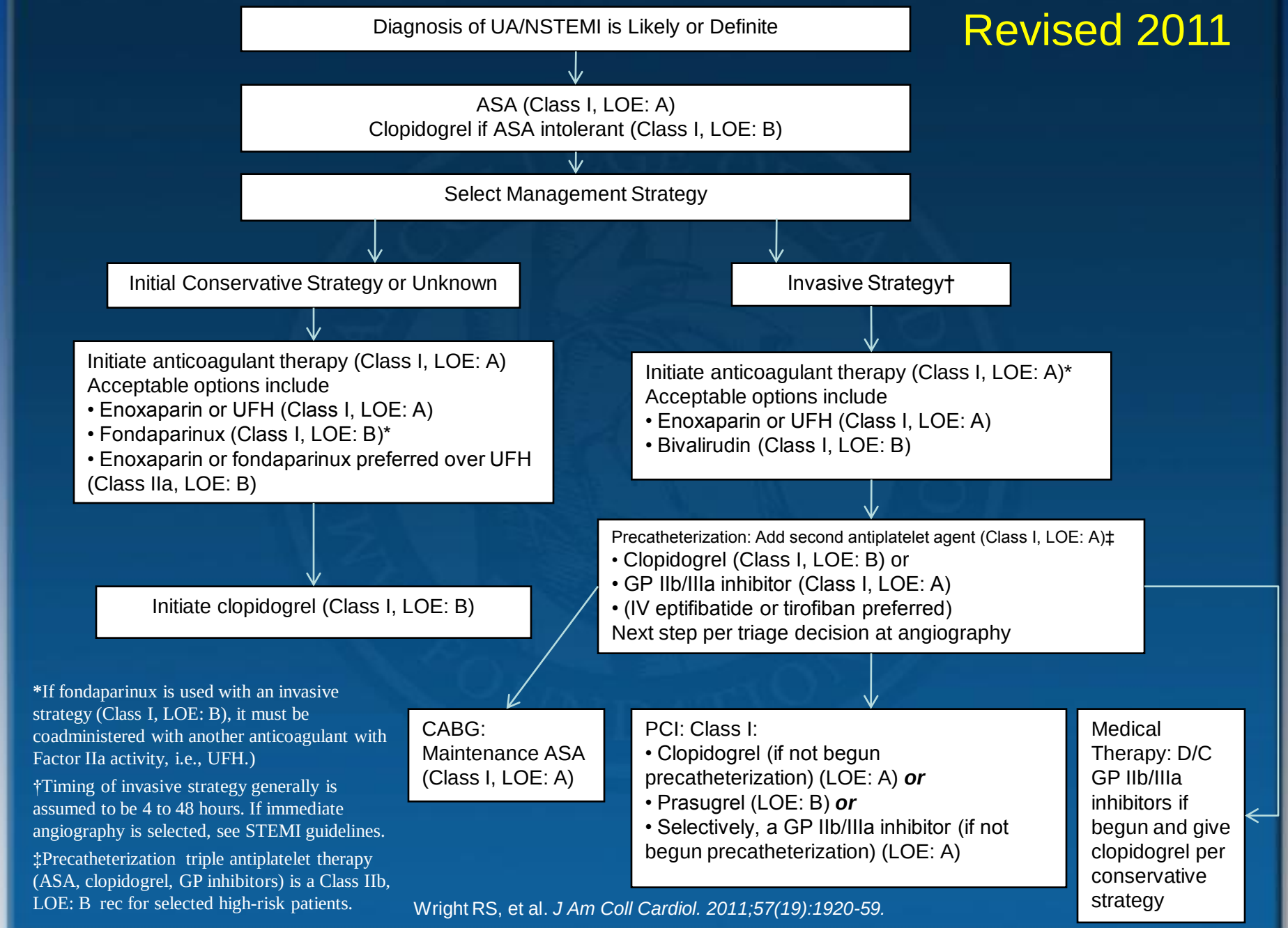
# Relative Risk of Recurrent UA Resulting in Rehosp for Early Invasive Therapy Compared With Conservative Therapy at a Mean Follow-Up of 13 Months




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

# Revised 2011



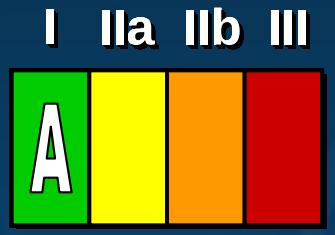

*If fondaparinux is used with an invasive strategy (Class I, LOE: B), it must be coadministered with another anticoagulant with Factor IIa activity, i.e., UFH.)

†Timing of invasive strategy generally is assumed to be 4 to 48 hours. If immediate angiography is selected, see STEMI guidelines.

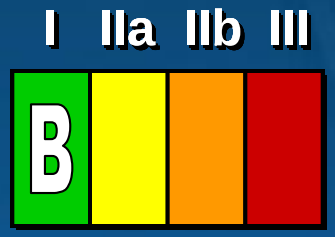
‡Precatheterization triple antiplatelet therapy (ASA, clopidogrel, GP inhibitors) is a Class IIb, LOE: B rec for selected high-risk patients.

Wright RS, et al. *J Am Coll Cardiol. 2011;57(19):1920-59.*

# Initial Invasive Strategy: Antiplatelet Therapy




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




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: aspirin
- ↓ 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 + aspirin + 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: aspirin, 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

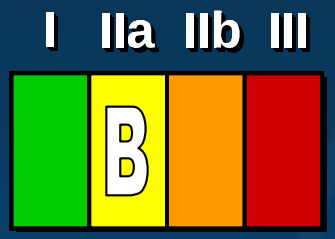
The PURSUIT Trial Investigators. *N Engl J Med* 1998;339:436–43. Boersma E, et al. *Circulation* 2000;101:2557–67.
ARR= absolute risk reduction.

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

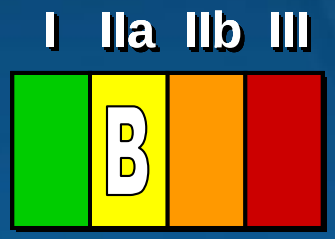
- 1,915 patients within 12 h UA/NSTEMI
- Tirofiban alone, UFH alone, or both for 48–108 h.
- Tirofiban-alone arm discontinued d/t ↑ mortality rate.
- ↓ Death, MI, or refractory ischemia at 7 d, 30 d & 6 mo by tirofiban + heparin
- High rate of angio could have contributed to important ↓ in event rates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




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.†

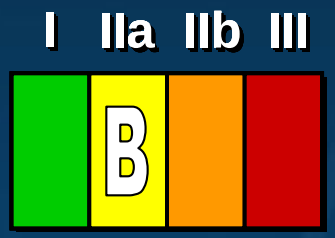
*Some uncertainty exists about optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral maintenance dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel more rapidly 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.

# Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment (ISAR-REACT)-2

- 2,022 patients within 48 h high-risk UA/NSTEMI
- aspirin + clopidogrel + abciximab vs aspirin + clopidogrel
- 600 mg LD clopidogrel ≥2 h before PCI → abciximab or placebo
- ↓ Death, MI, or urgent TVR by 30 d with abciximab
  - ↓ If cTnT +; no diff if cTnT –
- No diff major/minor bleeding
- Recommend: GP IIb/IIIa + clopidogrel if inv strategy used and high risk (*Class IIa, LOE: B*)

Kastrati A, et al. *JAMA* 2006;295:1531–8.
LD = loading dose; LOE = level of evidence.

# Initial Invasive Strategy: Antiplatelet Therapy




*Modified 2011*

For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to omit administration of an IV GP IIb/IIIa inhibitor if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 hours earlier than planned catheterization or PCI.

# ACUITY Timing Trial

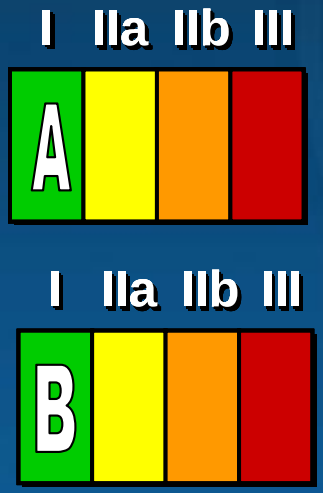
- Routine upstream Gp IIb/IIIa inhibitors vs. deferred selective Gp IIb/IIIa use in pts with moderate and high-risk ACS undergoing early, invasive treatment.
- Composite ischemia at 30 days: 7.1% in upstream vs. 7.9% in deferred (RR: 1.12; p=0.044 for noninferiority; p=0.13 for superiority)
- 30-day rates of major bleeding: 6.1% in upstream vs. 4.9% in deferred ($p<0.001$ for noninferiority; p=0.009 for superiority)
- Net clinical outcomes similar: 11.7% in upstream vs. 11.7% in deferred ($p<0.001$ for noninferiority; $p\leq0.93$ for superiority)
- Deferred routine upstream Gp IIb/IIIa inhibitors for selective administration in cath lab only to patients undergoing PCI resulted in ↑ composite ischemia (while not statistically significant) that did not meet criterion for noninferiority

Revised 2011

Stone GW, et al. JAMA. 2007;297:591–602.

# 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), and those with established efficacy at a *Level of Evidence: B* include bivalirudin and fondaparinux.

# 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: aspirin
- ↓ 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: aspirin
- ↓ Death, MI or urgent revasc for enox @ 48 h, 8 d, 14 d, & 43 d
- ↑ major & minor bleeding (inhosp) with enox

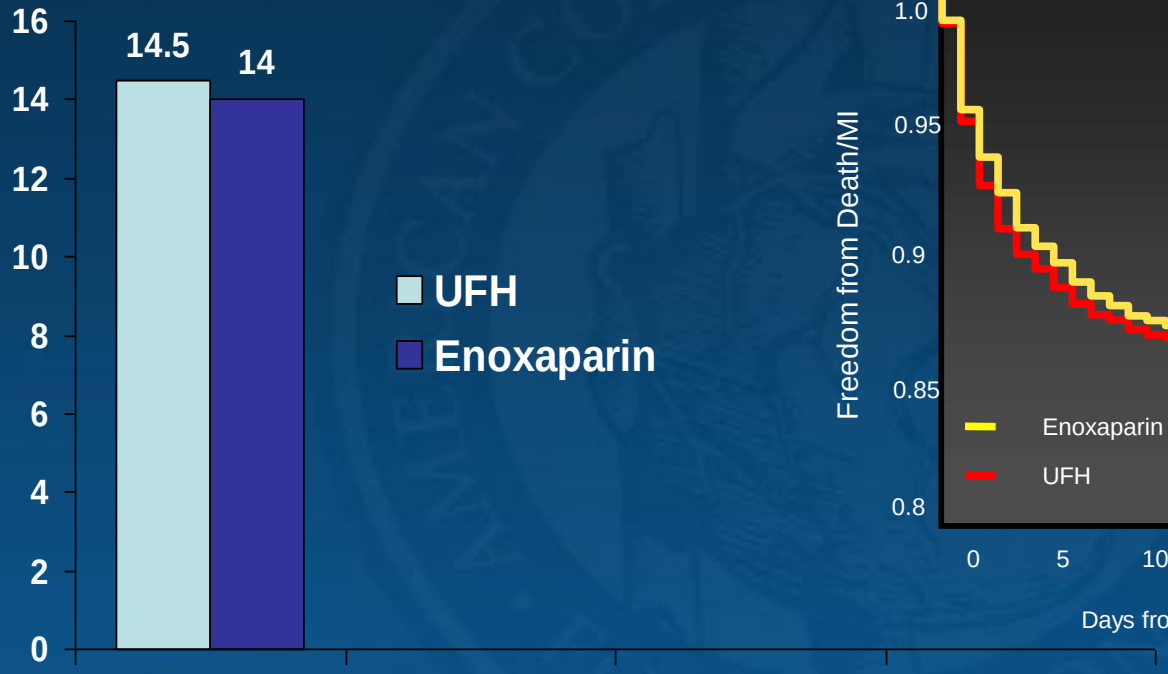
Antman EM, et al. *Circulation* 1999;100:1593–601.

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

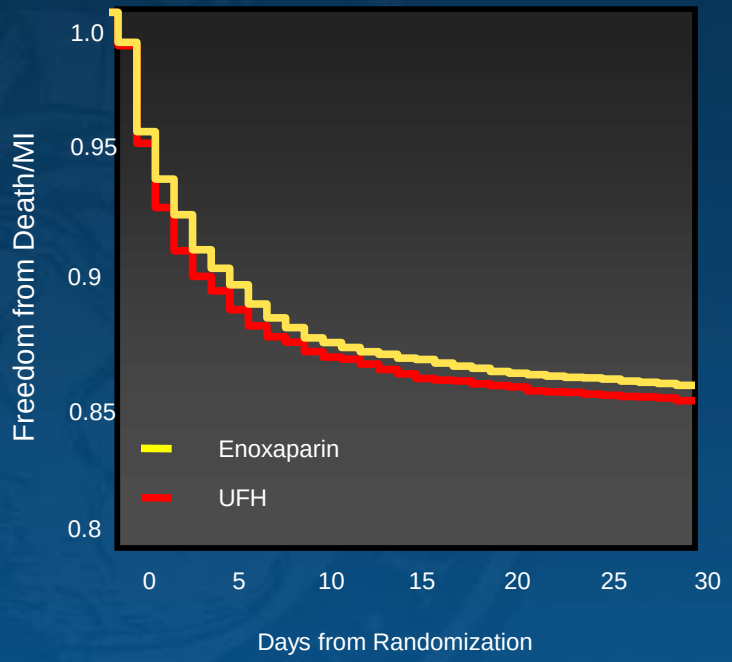
- 9,978 patients within 24 h high-risk UA/NSTEMI
- Enoxaparin vs UFH → early inv strategy
- Other meds: aspirin, GP IIb/IIIa @ physician discretion
- Enox noninferior for death/MI @ 30 d, 6 mo 1 y
- ↑ Major bleeding with enox
  - ? due to crossover to UFH @ time of PCI

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).

# SYNERGY Primary Outcomes




Death or MI at 30 d




Kaplan Meier Curve

| | |
|---|---|
| Absolute Risk Reduction | 0.5 |
| Hazard Ratio | 0.96 |
| 95% CI | 0.86–1.06 |
| p | 0.40 |

# Antithrombotic Combination Using Tirofiban and Enoxaparin (ACUTE II)

- 525 patients within 24 h UA/NSTEMI
- Enoxaparin vs UFH
- Other meds: aspirin, tirofiban LD 0.4 mcg/kg over 30 min → 0.1 mcg/kg/min
- No ↓ death/MI during first 30 d
  - Trend to lower event rates with enox
- No ↓ major/minor bleeding

Cohen M, et al. *Am Heart J* 2002;144:470–7. LD = loading dose.

# INTegrilin and Enoxaparin Randomized Assessment of Acute Coronary syndrome Treatment (INTERACT)

- 746 patients within 24 h high-risk UA/NSTEMI
- Enoxaparin vs UFH
- Other meds: aspirin, eptifibatide 180 mcg/kg IV bolus → 2.0 mcg/kg/min infusion for 48 hours
- ↓ Death/MI for enox @ 30 d
- Minor bleeding - ↑ for enox @ 96 h, no diff by 30 d
- Major bleeding - ↓ for enox @ 96 h ($1^{o}$ safety endpoint)

Goodman SG, et al. *Circulation* 2003;107:238–44.

# Aggrastat to Zocor (A to Z)

- 3,987 patients within 24 h UA/NSTEMI on aspirin & tirofiban
- Enoxaparin vs UFH
- Coronary angio in 60% of pts
- No ↓ all-cause mortality, MI or refractory ischemia w/in 7 d by enox
  - Nonsig trend to ↓ ischemic events with enox
- ↑ Major bleeding with enox

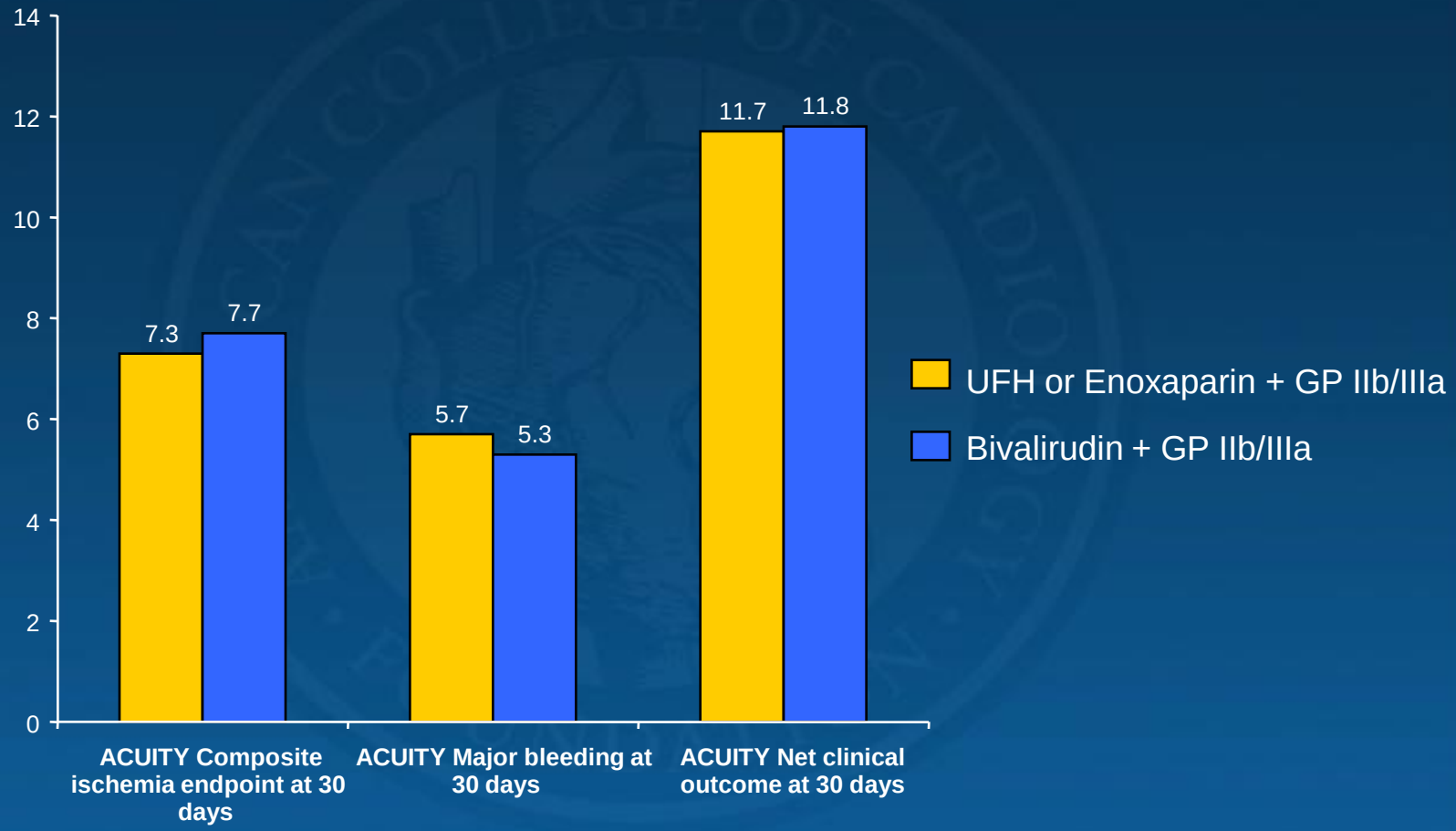
Blazing MA, et al. *JAMA* 2004;292:55–64.

# Acute Catheterization and Urgent Intervention Triage strategY (ACUITY)

- Within 24 h UA/NSTEMI → heparin (enox/UFH) ± upstream GP IIb/IIIa (n=4603) vs bivalirudin (bival) ± upstream GP IIb/IIIa (n=4604) vs bival alone + provisional GP IIb/IIIa (n=4612)
- Compared to heparin + GP IIb/IIa:
  - Bival + GP IIb/IIIa noninferior for composite ischemia, major bleeding & net clinical outcomes @ 30 d
  - Bival alone noninferior for composite ischemia; ↓ major bleeding;
    ↓ net clinical outcomes @ 30 d
- Caution using bival alone, esp with delay to angio and high-risk features, or if early ischemic discomfort occurs after initial antithrombotic strategy implemented
- Recommend: Concomitant use of GP IIb/IIIa or thienopyridine before angio whether bival-based or heparin-based strategy used

Stone GW, et al. *N Engl J Med* 2006;355:2203–16.

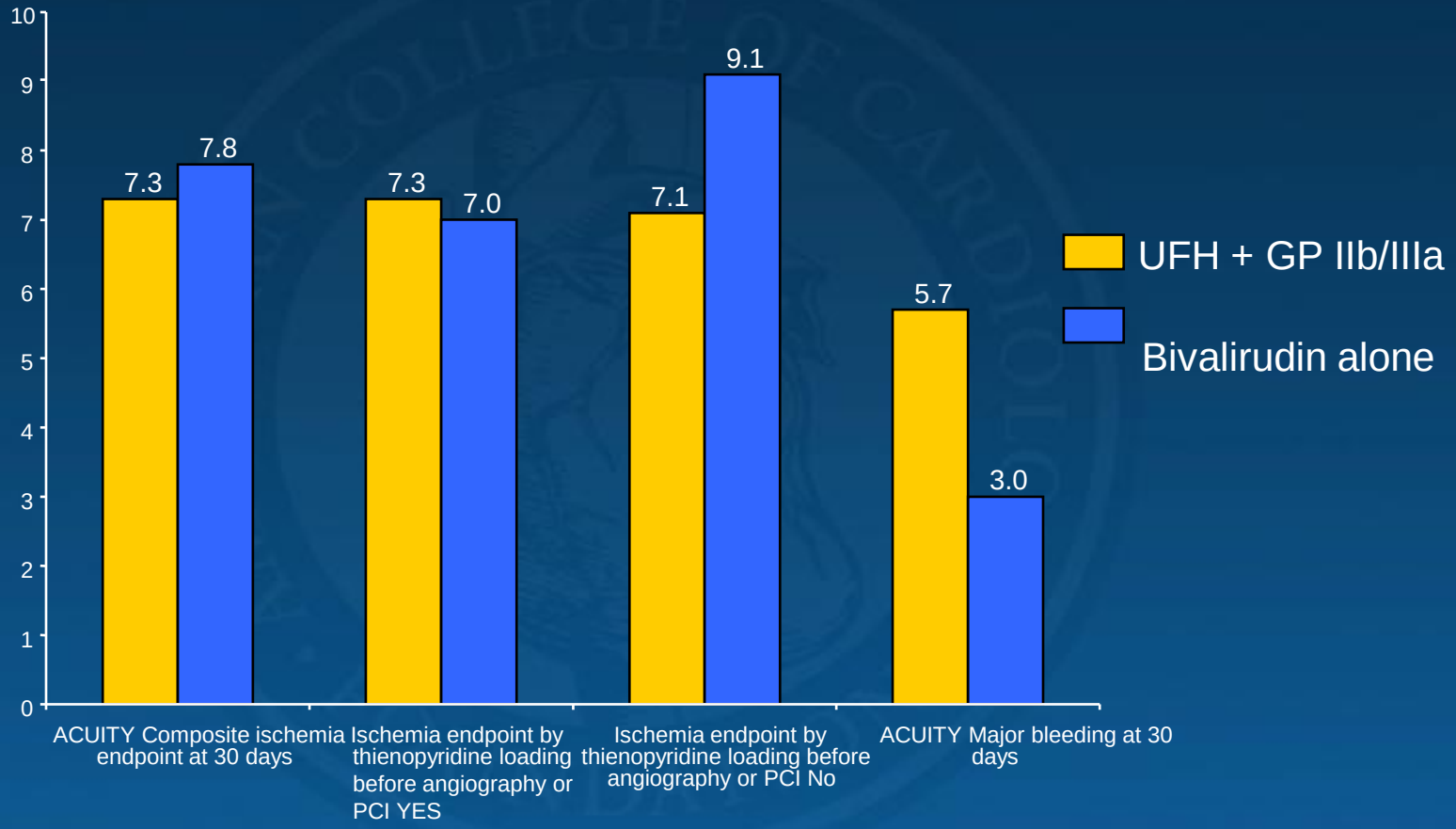
# ACUITY Clinical Outcomes at 30 d




| | | | |
|---|---|---|---|
| Absolute Risk Reduction | -0.4 | 0.4 | -0.1 |
| Hazard Ratio | 1.07 | 0.93 | 1.01 |
| 95% CI | 0.92–1.23 | 0.78–1.10 | 0.90–1.12 |
| p | 0.007* | < 0.001* | < 0.001* |

*p for noninferiority. Stone GW, et al. *N Engl J Med* 2006;355:2203–16.

# ACUITY Composite Ischemia & Bleeding Outcomes




| | | | | |
|---|---|---|---|---|
| Absolute Risk Reduction | -0.5 | 0.3 | -2.0 | 2.7 |
| Hazard Ratio | 1.08 | 0.97 | 1.29 | 0.53 |
| 95% CI | 0.93–1.24 | 0.80–1.17 | 1.03–1.63 | 0.43–0.65 |
| p | 0.32 | 0.054 (for interaction) | | < 0.001 |

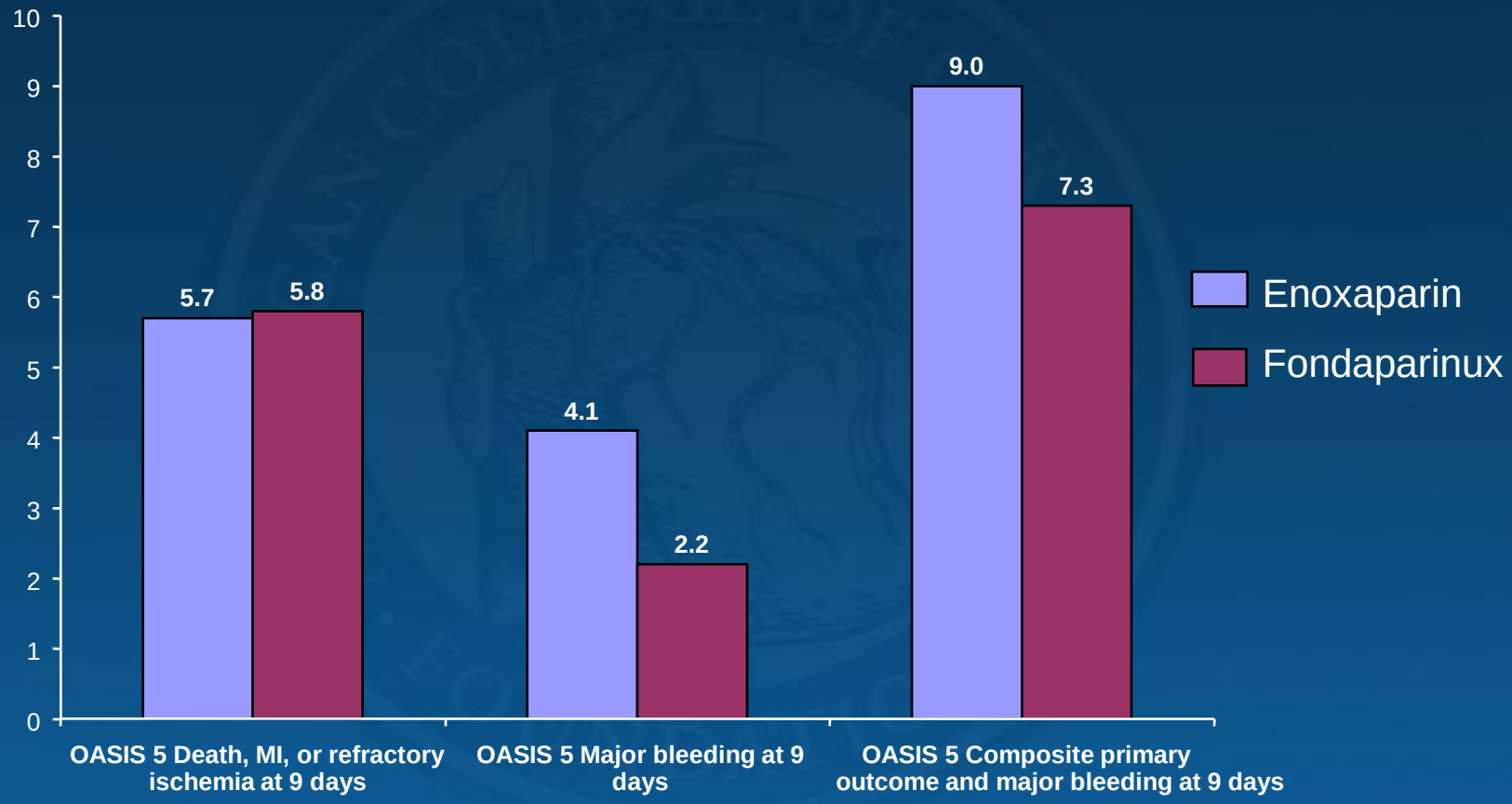
Stone GW, et al. *N Engl J Med* 2006;355:2203–16.

# Organization to Assess Strategies for Ischaemic Syndromes (OASIS-5)

- Fondaparinux (fonda) (2.5 mg/day, n=10,057) vs enox (1.0 mg/kg BID, n=10,021) in UA/NSTEMI patients
  - Enox patients undergoing PCI → UFH if last dose of enox > 6 h before PCI
- Other meds: aspirin, clopidogrel, GP IIb/IIIa @ investigator discretion
- No ↓ death, MI or refractory ischemia @ 9 d by fonda
  - Noninferiority criteria met
- ↓ Major bleeding with fonda
- ↓ Death @ 30 d and 180 d and ↓ death, MI and stroke @ 180 d with fonda
- ↑ Catheter-assoc thrombus with fonda

Yusuf S, et al. *N Engl J Med* 2006;354:1464–76.
Also see Section 3.2.5.5 in Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1-e157 for detailed discussion of trial results and dosing protocol.

# OASIS 5 Cumulative Risk of Death, MI, or Refractory Ischemia

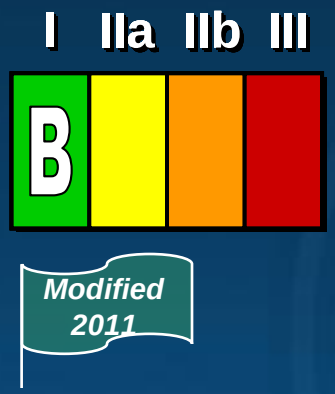



| | | | |
|---|---|---|---|
| Absolute Risk Reduction | -0.1 | 1.9 | 1.7 |
| Hazard Ratio | 1.01 | 0.52 | 0.81 |
| Confidence Interval | 0.90–1.13 | 0.44–0.61 | 0.73–0.89 |
| p | 0.007* | < 0.001† | < 0.001† |

*p for noninferiority; †p for superiority. Yusuf S, et al. *N Engl J Med* 2006;354:1464–76.

# Initial Conservative Strategy

# 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 aspirin and anticoagulant therapy as soon as possible after admission and administered for at least 1 month and ideally up to 1 year.

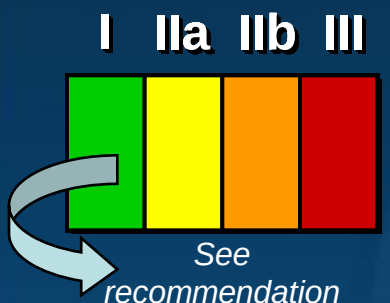
*Some uncertainty exists about optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral maintenance dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel more rapidly 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




Modified 2011

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). 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: B]) should be added to aspirin and anticoagulant therapy before diagnostic angiography (upstream). (Level of Evidence: C)

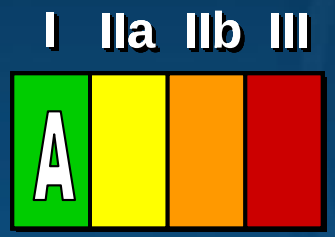
*Some uncertainty exists about optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral maintenance dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel more rapidly 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)

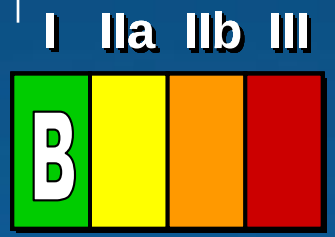
- 3,232 patients within 24 h UA/NSTEMI
- Tirofiban vs UFH over 48 h
- Other meds: aspirin
- ↓ Death, MI, or refractory ischemia at 48 h & 7 d by tirofiban
  - ↓ Death/MI @ 30 d
  - No ↑ bleeding; thrombocytopenia ↑

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

# Initial Conservative Strategy: Antiplatelet Therapy




New 2011




New 2011

A loading dose of thienopyridine is recommended for UA/NSTEMI patients for whom PCI is planned. Regimens should be 1 of the following:

a. Clopidogrel 300 to 600 mg should be given as early as possible before or at the time of PCI or

b. Prasugrel† 60 mg should be given promptly and no later than 1 hour after PCI once coronary anatomy is defined and a decision is made to proceed with PCI.

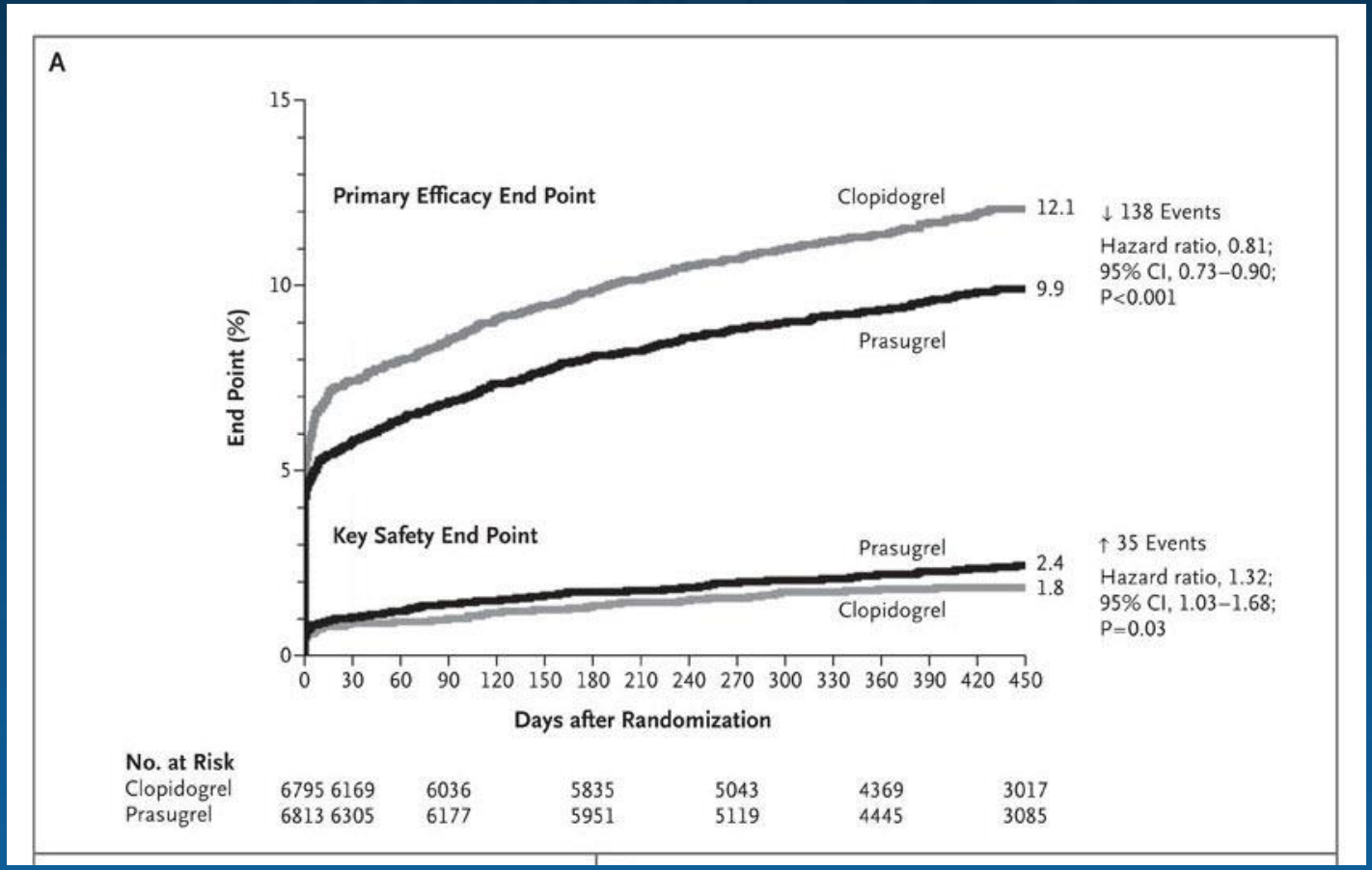
# TRITON-TIMI 38

- Moderate / high-risk ACS pts (n=13,608) scheduled for PCI randomized to:
  - Prasugrel (60 mg LD and 10 mg daily MD) or
  - Clopidogrel (300 mg LD and 75 mg daily MD) for 6 to 15 months
- Primary end point (CV death, nonfatal MI, nonfatal stroke), 9.9% prasugrel vs 12.1% clopidogrel (HR: 0.81; p<0.001)
- Prasugrel significant ↓ MI (7.4% vs. 9.7%; p<0.001), urgent TVR (2.5% vs. 3.7%), stent thrombosis (1.1% vs. 2.4%)
- Prasugrel significantly ↓ ischemic events, including stent thrombosis, but ↑ risk major bleeding, including fatal bleeding
- Overall mortality did not differ significantly between groups

Revised 2011

Wiviott SD, et al. for TRITON-TIMI 38 Investigators. NEJM 2007;357:2001–15.

# Cumulative Kaplan–Meier Estimates of the Rates of Key Study End Points during the Follow-up Period




Wiviott SD et al. N Engl J Med 2007;357:2001-2015.

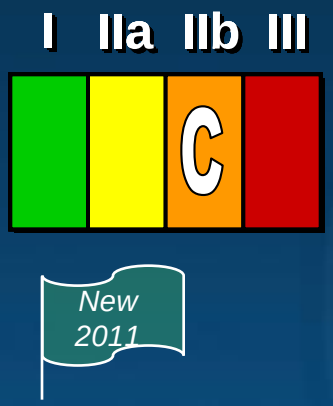
# Initial Conservative Strategy: Antiplatelet Therapy


The duration and maintenance dose of thienopyridine therapy should be as follows:

a. In UA/NSTEMI patients undergoing PCI, clopidogrel 75 mg daily or prasugrel† 10 mg daily should be given for at least 12 months.


b. If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by thienopyridine therapy, earlier discontinuation should be considered.

# Initial Conservative Strategy: Antiplatelet Therapy




Prasugrel† 60 mg may be considered for administration promptly upon presentation in patients with UA/NSTEMI for whom PCI is planned, before definition of coronary anatomy if both the risk for bleeding is low and the need for CABG is considered unlikely.

# Initial Conservative Strategy: Antiplatelet Therapy


The use of upstream GP IIb/IIIa inhibitors may be considered in high-risk UA/NSTEMI patients already receiving aspirin and a thienopyridine who are selected for an invasive strategy, such as those with elevated troponin levels, diabetes, or significant ST-segment depression, and who are not otherwise at high risk for bleeding.

# Early versus Delayed Provisional Eptifibatide in Acute Myocardial Infarction

## EARLY ACS

- 9492 patients with NSTEMI ACS
- Early routine vs. delayed, provisional eptifibatide
- Primary end point: death, MI, recurrent ischemia requiring urgent revascularization, or thrombotic complication during PCI that required bolus therapy opposite to initial study-group assignment ("thrombotic bailout") at 96 h
  - 9.3% early eptifibatide vs. 10.0% delayed eptifibatide
- Secondary end point: death or MI within first 30 d
  - 11.2% early eptifibatide vs. 12.3% delayed eptifibatide
- Eptifibatide 12 h or more before angiography not superior to provisional use after angiography
  - associated ↑ risk non-life-threatening bleeding, need for transfusion

Revised 2011

Giugliano RP, et al. N Engl J Med 2009; 360:2176-2190.

# Initial Conservative Strategy: Antiplatelet Therapy


In patients with definite UA/NSTEMI undergoing PCI as part of an early invasive strategy, the use of a loading dose of clopidogrel of 600 mg, *followed by a higher maintenance dose of 150 mg daily for 6 days*, then 75 mg daily may be reasonable in patients not considered at high risk for bleeding.

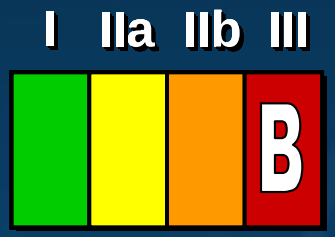
# CURRENT-OASIS 7

- 25,086 pts with ACS, intended PCI, double-dose (600 mg d1, 150 mg d2 to 7, then 75 mg daily) vs. standard-dose (300 mg d1, then 75 mg daily) clopidogrel, high-dose (300 to 325 mg daily) vs. low-dose (75 to 100 mg daily) ASA
- Primary outcome: CV death, MI, or stroke at 30 days – No significant difference in overall trial
  - ↑ major bleeding with double-dose clopidogrel vs. standard dose (2.5% vs. 2.0%, HR: 1.24; p=0.012)
- Primary outcome: CV death, MI, or stroke at 30 days (PCI subgroup)
  - ↓ double-dose clopidogrel vs. standard dose, 3.9% vs. 4.5%, p=0.035
  - High-dose and low-dose aspirin did not differ
- Definite stent thrombosis ↓ with double-dose vs standard dose clopidogrel, 0.7% vs. 1.3%, Adj HR: 0.54; p=0.0001 (PCI subgroup)

Revised 2011

Mehta SR et al. Lancet 2010;376:1233–43

# Initial Conservative Strategy: Antiplatelet Therapy




**No Benefit**

*New 2011*

In UA/NSTEMI patients who are at low risk for ischemic events (e.g., TIMI risk score ≤2) or at high risk of bleeding and who are already receiving aspirin and clopidogrel, upstream GP IIb/IIIa inhibitors are not recommended.

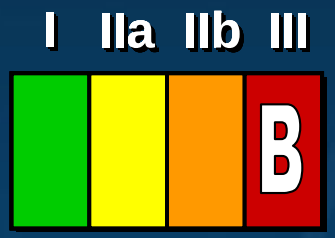
# CRUSADE Bleeding Score in NSTEMI

- (8) predictors in-hospital major bleeding in CRUSADE Quality Improvement Initiative: baseline Hct, CrCl, HR, sex, CHF at presentation, prior vascular disease, DM, systolic BP
- ↑ rate major bleeding by bleeding risk score quintiles:
  - 3.1% very low risk (score ≤20)
  - 5.5% low risk (score 21-30)
  - 8.6% moderate risk (score 31-40)
  - 11.9% high risk (score 41-50)
  - 19.5% very high risk (score >50)
- CRUSADE bleeding score quantifies risk for in-hospital major bleeding; enhances risk assessment in NSTEMI care

Revised 2011

Subherwal S, et al. Circulation 2009;119:1873–82.

# Initial Conservative Strategy: Antiplatelet Therapy

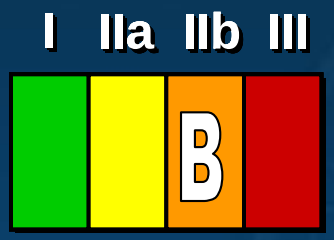



Harm

*New 2011*

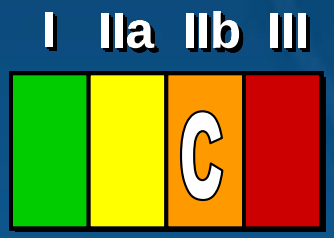
In UA/NSTEMI patients with a prior history of stroke and/or TIA for whom PCI is planned, prasugrel is potentially harmful as part of a dual-antiplatelet therapy regimen.

# Initial Conservative Strategy: Antiplatelet Therapy





Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACS and PCI) on thienopyridine therapy may be considered if results of testing may alter management.





Genotyping for a CYP2C19 loss of function variant in patients with UA/NSTEMI (or, after ACS and with PCI) on clopidogrel therapy might be considered if results of testing may alter management.

# Tailored Clopidogrel LD According to Platelet Reactivity Monitoring

- Investigated ↓ stent thrombosis with tailored clopidogrel LD (by platelet reactivity) investigated
- 429 PCI pts with low clopidogrel response after 600 mg LD
- VASP guided pts (up to 3 additional clopidogrel 600 mg LDs) → VASP index <50%
- Stent thrombosis at 1 m significantly ↓ in VASP group vs. control (0.5% vs. 4.2%; $p<0.01$)
- MACE higher in control group (8.9% vs. 0.5%; $p<0.001$)
- No difference in bleeding rate (2.8% vs 3.7%; $p=0.8$)
- Tailored clopidogrel LD according to platelet reactivity monitoring ↓ early stent thrombosis after PCI without ↑ bleeding

Revised 2011

Bonello L, et al. Am J Cardiol. 2009;103:5–10.

# Platelet Function Testing – Predicting Clinical Outcome (Taking Clopidogrel and Undergoing PCI with Stent)

- High compared to normal on-treatment platelet reactivity and atherothrombotic events following PCI/Stent
- Results:
  - Light transmittance aggregometry – OR: 2.09 (11.7% vs. 6.0%); p<0.001 (AUC 0.63)
  - VerifyNow P2Y12 – OR: 2.53 (13.3 vs. 5.7%); p<0.001 (AUC 0.62)
  - Plateletworks – OR: 2.22 (12.6 vs. 6.1%); p=0.005 (AUC 0.61)
  - Innovance PFA P2Y – OR: 2.06 (12.2 vs. 6.3%); p=0.02 (AUC 0.56)
- Predictive accuracy of tests only modest.
  - No test identified ↑ bleeding risk.
- Conclusion: Platelet function tests significantly associated with ↑ all-cause death, nonfatal MI, stent thrombosis, and ischemic stroke at 12 m.

Breet NJ, et al. JAMA. 2010;303:754–62. Erratum in: JAMA. 2011;305:2174.

Revised 2011

# Point-of-care Assay: Residual Platelet Reactivity (RPR) to ADP for ACS Patients on DAPT Undergoing PCI/stent

- RPR measured with VerifyNow P2Y12 assay: clopidogrel non-responsiveness
- Single 600 mg clopidogrel LD followed by 75 mg of clopidogrel daily (100 to 325 mg ASA daily)
- 12 m follow-up: 51 ischemic events
- RPR values ≥240 were significant / independent predictor of:
  - CV death (HR: 2.55; p=0.034)
  - Nonfatal MI (HR: 3.36; p=0.004)
  - No significant association high RPR and TVR
- RPR to ADP point-of-care assay can detect ACS pts at ↑ risk of CV death and nonfatal MI at 12 m (optimal cutoff value 240 P2Y12 reaction units)

Revised 2011

Marcucci R, et al. Circulation. 2009;119:237–42.

# Meta-analysis: Clopidogrel Non-responsiveness and CV Mortality Post PCI

- 14 studies, 4,564 CAD pts
- Residual platelet reactivity (despite clopidogrel treatment) significantly associated with ↑ risk of death and/or thrombotic recurrence (OR: 5.67; $p<0.00001$)
- Significant association between residual platelet reactivity and recurrent CV events (clopidogrel non – responsiveness)

Revised 2011

Sofi F, et al. Thromb Haemost. 2010;103:841–8.

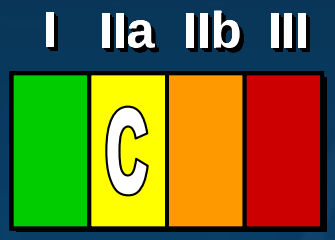
# ACCF/AHA Clopidogrel Clinical Alert: Approaches to the FDA "Boxed Warning"

- Pharmacogenomic testing to identify pts with altered clopidogrel metabolism / risk for suboptimal clinical response to plavix
- Plavix conversion to active form due to low CYP 2C19 activity active form may not occur due to low CYP 2C19 activity
- Tests available to identify CYP2C19 genotype
- Consider other antiplatelet medications or alternative plavix dosing strategies in pts who are poor metabolizers
- Consider plavix higher dose regimen (600 mg LD followed by 150 mg daily) in poor metabolizers; however, appropriate dose regimen for poor metabolizers not established
- Insufficient evidence to recommend routine genetic or platelet function testing
- Additional information available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm

Revised 2011

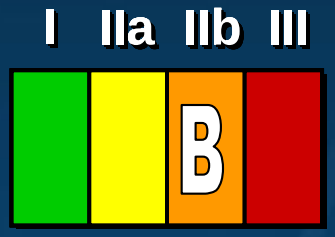
ACCF/AHA Clopidogrel Clinical Alert. JACC 2010;56:321–41.

# 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, aspirin, and anticoagulant therapy, it is reasonable to add a GP IIb/IIIa antagonist before diagnostic angiography.

# Initial Conservative Strategy: Antiplatelet Therapy

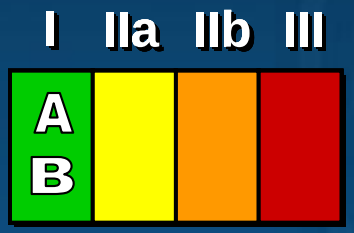



For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected, it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy.

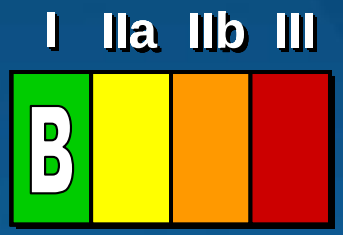

Abciximab should not be administered to patients in whom PCI is not planned.

# Initial Conservative Strategy: Anticoagulant Therapy

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



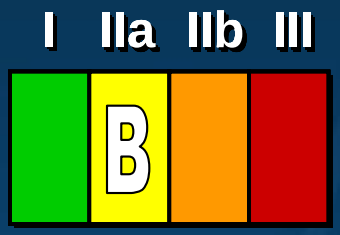

- For patients in whom a conservative strategy is selected, regimens using either enoxaparin* or UFH *(Level of Evidence: A)* or fondaparinux *(Level of Evidence: B)* have established efficacy.




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

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

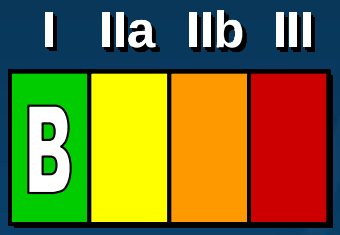
# Initial Conservative Strategy: Anticoagulant Therapy



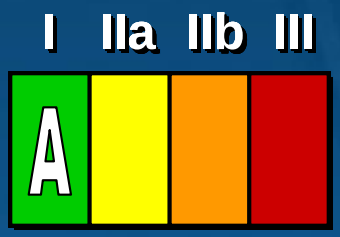

For UA/NSTEMI patients in whom an initial conservative strategy is selected, enoxaparin* or fondaparinux is preferable to UFH as anticoagulant therapy, unless CABG is planned within 24 h.

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

# Initial Conservative Strategy: Additional Management Considerations



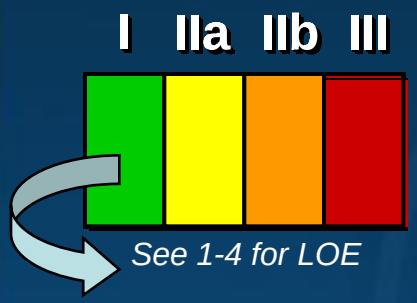

For UA/NSTEMI patients in whom an initial conservative strategy is selected and no subsequent features appear that would necessitate diagnostic angiography (recurrent symptoms/ischemia, HF, or serious arrhythmias), a stress test should be performed.




a. If, after stress testing, the patient is classified as not at low risk, diagnostic angiography should be performed.

*This recommendation continues on the next slide.*

# Initial Conservative Strategy: Additional Management Considerations




b. If, after stress testing, the patient is classified as being at low risk, the instructions noted below should be followed in preparation for discharge:

1. Continue aspirin indefinitely. *(Level of Evidence: A)*

Modified 2011

2. Continue clopidogrel for at least 1 month and ideally up to 1 year. *(Level of Evidence: B)*

3. Discontinue IV GP IIb/IIIa inhibitor if started previously. *(Level of Evidence: A)*

Modified 2011

4. Continue UFH for 48 hours (Level of Evidence: A) or administer enoxaparin (Level of Evidence: A) or fondaparinux (Level of Evidence: B) for the duration of hospitalization, up to 8 days, and then discontinue anticoagulant therapy.

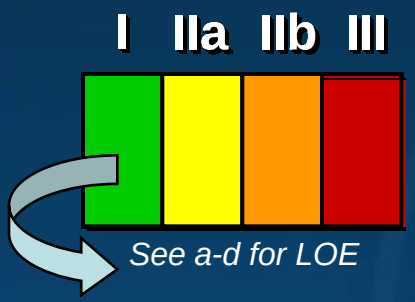
# OASIS-5: PCI Substudy

- ACS pts with cath or PCI during hospitalization (n=20,078)
- Fondaparinux vs enoxaparin (if PCI <6 h from last SC dose, no additional anticoagulant; if PCI >6 h, additional IV UFH)
- Fondaparinux ↓ major bleeding at day 9 vs. enoxaparin (2.4% vs. 5.1%; p<0.00001); similar ischemic events
- Superior net clinical benefit (death, MI, stroke, major bleeding) fondaparinux vs enoxaparin (8.2% vs. 10.4%; p=0.004)
- Catheter thrombus ↑ with fondaparinux vs. enoxaparin (0.9% vs. 0.4%)
  - Largely prevented by UFH at time of PCI (without ↑ in bleeding)

Mehta SR, et al. JACC 2007;50:1742–51.

Revised 2011

# Initial Conservative Strategy: Additional Management Considerations




For UA/NSTEMI patients in whom a conservative strategy is selected and who do not undergo angiography or stress testing, the instructions noted below should be followed:

a. Continue aspirin indefinitely. *(Level of Evidence: A)*

Modified 2011

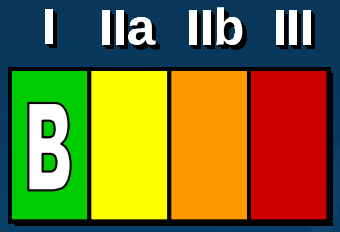
b. Continue clopidogrel for at least 1 month and ideally up to 1 year. (Level of Evidence: B)

c. Discontinue IV GP IIb/IIIa inhibitor if started previously. *(Level of Evidence: A)*

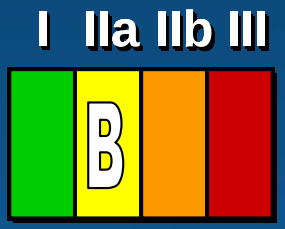
Modified 2011

d. Continue UFH for 48 hours (Level of Evidence: A) or administer enoxaparin (Level of Evidence: A) or fondaparinux (Level of Evidence: B) for the duration of hospitalization, up to 8 days, and then discontinue anticoagulant therapy.

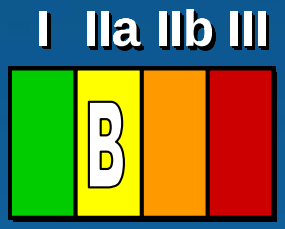
# Initial Conservative Strategy: Additional Management Considerations




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.




If LVEF is ≤40%, it is reasonable to perform diagnostic angiography.



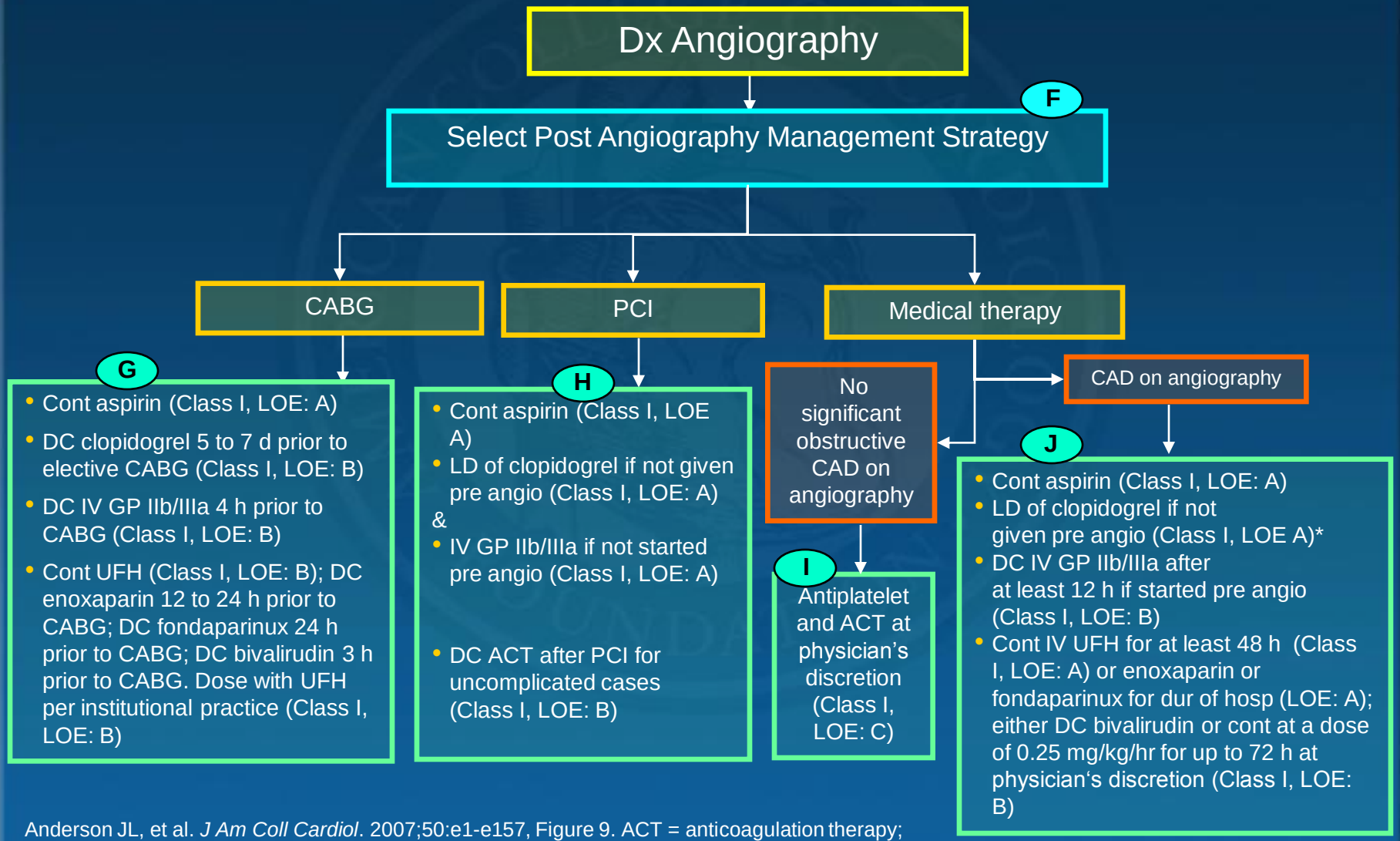

If LVEF is >40%, it is reasonable to perform a stress test.

# Additional Management Considerations for Antiplatelet and Anticoagulant Therapy


Intravenous fibrinolytic therapy is not indicated in patients without acute ST-segment elevation, a true posterior MI, or a presumed new left bundle-branch block.

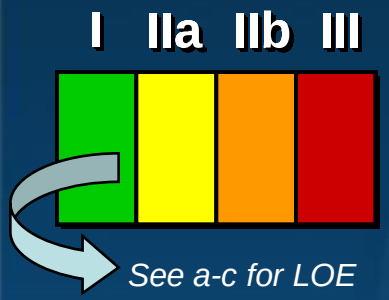
# Revascularization and Late Hospital Care

# Management after Diagnostic Angiography in Patients with UA/NSTEMI




Anderson JL, et al. *J Am Coll Cardiol*. 2007;50:e1-e157, Figure 9. ACT = anticoagulation therapy; LOE = level of evidence.

# CABG as Postangiography Management Strategy




For UA/NSTEMI patients in whom **CABG** is selected as a postangiography management strategy, the instructions noted below should be followed.

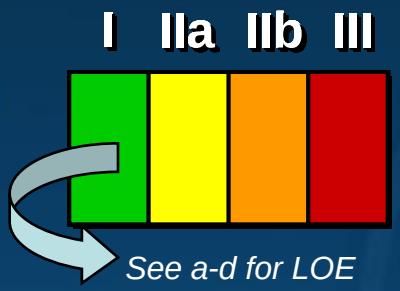
a. Continue aspirin. *(Level of Evidence: A)*

b. See Class I, #3, in this section.

c. Discontinue intravenous GP IIb/IIIa inhibitor (eptifibatide or tirofiban) 4 h before CABG. *(Level of Evidence: B)*

CABG = coronary artery bypass graft surgery

# CABG as Postangiography Management Strategy




For UA/NSTEMI patients in whom **CABG** is selected as a postangiography management strategy, anticoagulant therapy should be managed as follows:

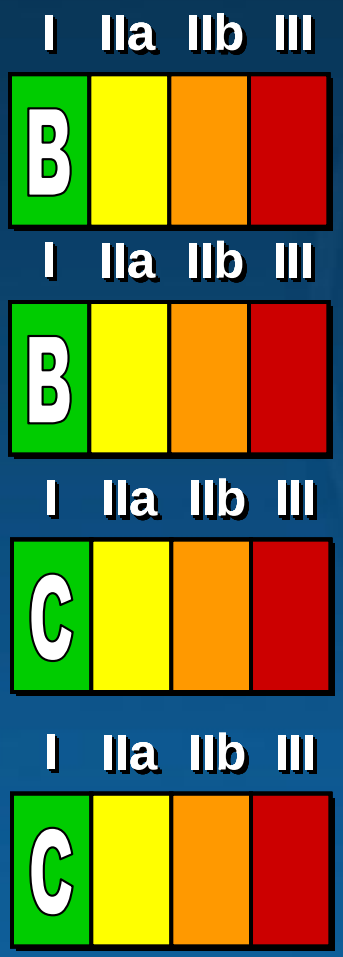
a. Continue UFH. *(Level of Evidence: B)*

b. Discontinue enoxaparin 12 to 24 h before CABG and dose with UFH per institutional practice. *(Level of Evidence: B)*

c. Discontinue fondaparinux 24 h before CABG and dose with UFH per institutional practice. *(Level of Evidence: B)*

d. Discontinue bivalirudin 3 h before CABG and dose with UFH per institutional practice. *(Level of Evidence: B)*

# CABG as Postangiography Management Strategy




In patients taking a thienopyridine in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect (Level of Evidence: B) The period of withdrawal should be at least 5 days in patients receiving clopidogrel (Level of Evidence: B) and at least 7 days in patients receiving prasugrel* (Level of Evidence: C) unless the need for revascularization and/or the net benefit of the thienopyridine outweighs the potential risks of excess bleeding. (Level of Evidence: C)

*Modified 2011*

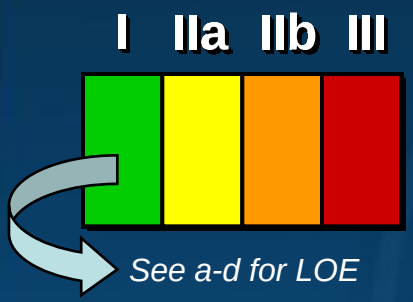
# Prasugrel Package Insert

- "Do not start prasugrel in pts likely to undergo urgent CABG."
- When possible, discontinue prasugrel at least 7 d prior to any surgery
- Do not use prasugrel in pts with active pathological bleeding or history of TIA or stroke
- Post hoc analysis TRITON-TIMI 38 identified subgroups who did not have favorable net clinical benefit: patients with previous stroke or TIA (net harm from prasugrel; HR: 1.54; p=0.04)

Revised 2011

Prasugrel package insert. 2009 (http://pi.lilly.com/us/effient.pdf)

# PCI as Postangiography Management Strategy




Modified 2011

For UA/NSTEMI patients in whom **PCI** has been selected as a postangiography management strategy, the instructions noted below should be followed:

a. Continue aspirin. *(Level of Evidence: A)*

b. Administer a loading dose of a thienopyridine if not started before diagnostic angiography. (Level of Evidence: A)

c. See Class IIa, #1, in this section.

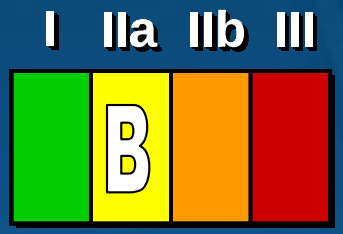
d. Discontinue anticoagulant therapy after PCI for uncomplicated cases. *(Level of Evidence: B)*

Recommendation was modified to include language to allow for prasugrel as a choice of thienopyridine.

*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; †See Class IIa recommendation on subsequent slide if bivalirudin was selected as the anticoagulant. PCI = percutaneous coronary intervention.

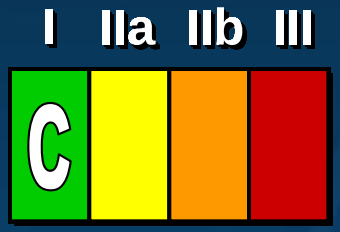
# PCI as Postangiography Management Strategy


For UA/NSTEMI patients in whom PCI has been selected as a postangiography management strategy, it is reasonable to administer an IV GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban) if not started before diagnostic angiography, particularly for troponin-positive and/or other high-risk patients.

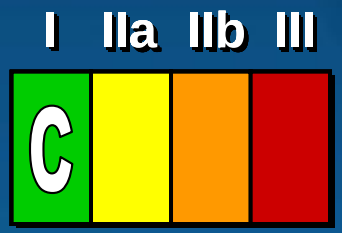



For UA/NSTEMI patients in whom **PCI** is selected as a postangiography management strategy, it is reasonable to omit administration of an intravenous GP IIb/IIIa antagonist if bivalirudin was selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 h earlier.

# Medical Therapy as Postangiography Management Strategy

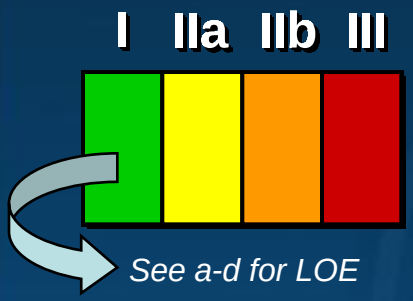



For UA/NSTEMI patients in whom **medical therapy** is selected as a postangiography management strategy and in whom no significant obstructive CAD on angiography was found, antiplatelet and anticoagulant therapy should be administered at the discretion of the clinician.




For patients in whom evidence of coronary atherosclerosis is present (e.g., luminal irregularities or intravascular ultrasound-demonstrated lesions), albeit without flow-limiting stenoses, long-term treatment with aspirin and other secondary prevention measures should be prescribed.

# Medical Therapy as Postangiography Management Strategy




For UA/NSTEMI patients in whom **medical therapy** is selected as a management strategy and in whom CAD was found on angiography, the following approach is recommended:

a. Continue aspirin. *(Level of Evidence: A)*

Modified 2011

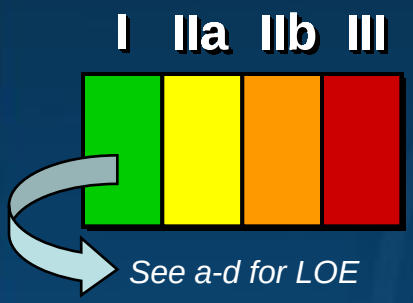
b. Administer a loading dose of clopidogrel* if not given before diagnostic angiography. *(Level of Evidence: B)*

c. Discontinue intravenous GP IIb/IIIa inhibitor if started previously. *(Level of Evidence: B)*

Recommendation was modified, LOE changed from A to B for clopidogrel loading dose.

*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

# Medical Therapy as Postangiography Management Strategy




For UA/NSTEMI patients in whom **medical therapy** is selected as a management strategy and in whom CAD was found on angiography, anticoagulant therapy should be managed as follows:

a. Continue intravenous UFH for at least 48 h

or until discharge if given before diagnostic angiography. *(Level of Evidence: A)*

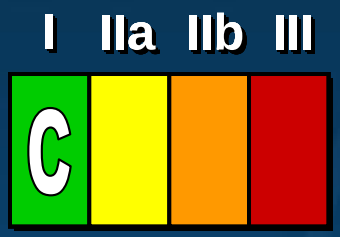
b. Continue enoxaparin for duration of hospitalization, up to 8 d, if given before diagnostic angiography. *(Level of Evidence: A)*

c. Continue fondaparinux for duration of hospitalization, up to 8 d, if given before diagnostic angiography. *(Level of Evidence: B)*

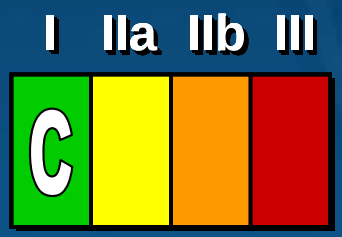
d. Either discontinue bivalirudin or continue at

a dose of 0.25 mg per kg per h for up to 72 h at the physician's discretion, if given before diagnostic angiography. *(Level of Evidence: B)*

# Risk Stratification Before Discharge




Noninvasive stress testing is recommended in low-risk patients who have been free of ischemia at rest or with low-level activity and of HF for a minimum of 12 to 24 h.




Noninvasive stress testing is recommended in patients at intermediate risk who have been free of ischemia at rest or with low-level activity and of HF for a minimum of 12 to 24 h.

# Short-Term Risk of Death/Nonfatal MI in Patients With UA/NSTEMI

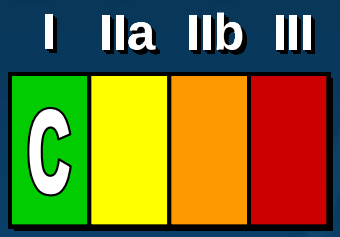
| Feature | High Risk<br>*≥1 of the features below must be present:* | Intermediate Risk<br>*No high-risk features, but must have 1 of the following:* | Low Risk<br>*No high- or intermediate-risk features but may have any features below:* |
|---|---|---|---|
| **History** | Accelerating tempo of ischemic sx in preceding 48 h | Prior MI, peripheral or cerebrovascular disease, or CABG; prior aspirin use | |
| **Character of pain** | Prolonged ongoing (>20 min) rest pain | • Prolonged (>20 min) rest angina, now resolved, w/ moderate/high likelihood of CAD<br>• Rest angina (>20 min) or relieved with rest or sublingual NTG<br>• Nocturnal angina<br>• New-onset or progressive CCS class III/IV angina in past 2 wks w/o prolonged (>20 min) rest pain but with intermediate/high likelihood of CAD | • ↑ Angina frequency, severity or duration<br>• Angina provoked at lower threshold<br>• New onset angina with onset 2 wks to 2 mos prior to presentation |

# Short-Term Risk of Death/Nonfatal MI in Patients With UA/NSTEMI, Continued

| Feature | High risk | Intermediate risk | Low risk |
|---|---|---|---|
| **Clinical findings** | • Pulmonary edema, most likely due to ischemia<br>• New/worsening MR murmur<br>• $S_3$ or new/worsening rales<br>• Hypotension, bradycardia, tachycardia<br>• Age >75 y | Age > 70 y | |
| **ECG** | • Angina @ rest with transient ST-segment changes >0.5 mm<br>• BBB, new/presumed new<br>• Sustained VT | • T-wave changes<br>• Pathological Q-waves/resting ST-depression <1 mm in multiple lead groups (anterior, inferior, lateral) | Normal or unchanged ECG |
| **Cardiac markers** | ↑ Cardiac TnT, TnI, or CK-MB (e.g., TnT/TnI >0.1 ng/mL) | Slightly ↑ cardiac TnT, TnI, or CK-MB (e.g., TnT >0.01, but <0.1 ng/mL) | Normal |

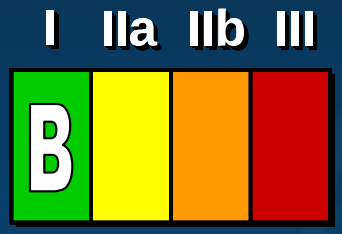
Estimation of the short-term risk of death and nonfatal cardiac ischemic events in UA/NSTEMI is a complex multivariable problem that cannot be fully specified in a table such as this; this table is mean to offer general guidance & illustration rather than rigid algorithms. Braunwald E, et al. AHCPR Publication No. 94-0602:1–154. Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157, Table 7.

# Risk Stratification Before Discharge

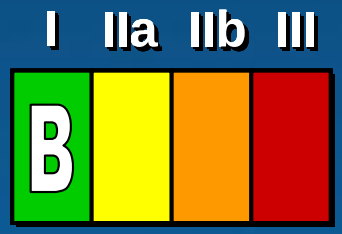



The choice of stress test is based on the resting ECG, ability to perform exercise, local expertise, and technologies available. Treadmill exercise is useful in patients able to exercise in whom the ECG is free of baseline ST-segment abnormalities, bundle-branch block, LV hypertrophy, intraventricular conduction defect, paced rhythm, preexcitation, and digoxin effect.

# Risk Stratification Before Discharge

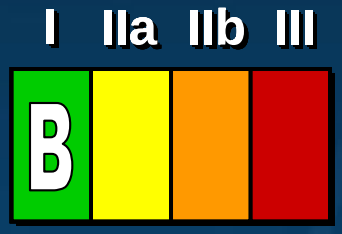



An imaging modality should be added in patients with resting ST-segment depression (≥0.10 mV), LV hypertrophy, bundle-branch block, intraventricular conduction defect, preexcitation, or digoxin who are able to exercise. In patients undergoing a low-level exercise test, an imaging modality can add sensitivity.

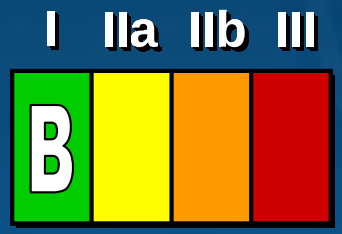



Pharmacological stress testing with imaging is recommended when physical limitations (e.g., arthritis, amputation, severe peripheral vascular disease, severe chronic obstructive pulmonary disease, or general debility) preclude adequate exercise stress.

# Risk Stratification Before Discharge




Prompt angiography without noninvasive risk stratification should be performed for failure of stabilization with intensive medical treatment.




A noninvasive test (echocardiogram or radionuclide angiogram) is recommended to evaluate LV function in patients with definite ACS who are not scheduled for coronary angiography and left ventriculography.

# Noninvasive Risk Stratification: High Risk

High risk (>3% annual mortality rate)

- Severe resting LV dysfunction (LVEF <35%)
- High-risk treadmill score (score ≤11)
- Severe exercise LV dysfunction (exercise LVEF <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 >2 segments) developing at low dose of dobutamine (≤10 mcg per kg per min) or at a low heart rate (<120 beats per min)
- Stress echocardiographic evidence of extensive ischemia

# Noninvasive Risk Stratification: Intermediate Risk

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

- Mild/moderate resting LV dysfunction (LVEF = 0.35 to 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

# Noninvasive Risk Stratification: Low Risk

Low risk (<1% annual mortality rate)

- Low-risk treadmill score (score ≥5)
- 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 < 35%). Noninvasive risk stratification: high-, intermediate- and low-risk reproduced from Table 23 in Gibbons RJ, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina. Available at: www.acc.org/qualityandscience/clinical/statements.htm

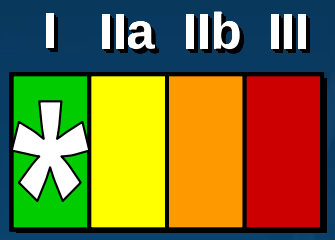
# Noninvasive Test Results That Predict High Risk for Adverse Outcomes

| 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 |

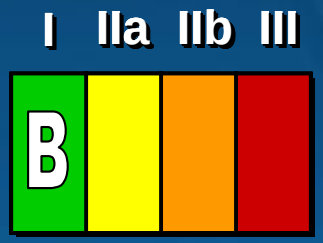
Adapted from O'Rourke RA, et al. *J Am Coll Cardiol* 1986;8:1471–83 and Cheitlin MD, et al. *Circulation* 1997;95:1686–744.
EF = ejection fraction.

# Coronary Revascularization

# Recommendations for PCI in Patients With UA/NSTEMI



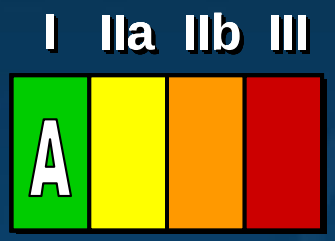

An early invasive PCI strategy is indicated for patients with UA/NSTEMI who have no serious comorbidity and who have coronary lesions amenable to PCI and any of the high-risk features listed in the previous section.



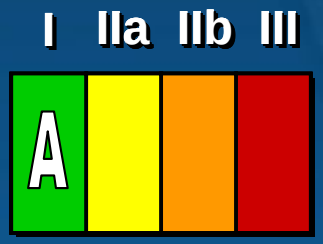

PCI (or CABG) is recommended for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal left anterior descending (LAD) CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing.

*Specific recommendations and their level of evidence can be found in the previous section on Initial Conservative Versus Initial Invasive Strategies.

# Recommendations for PCI in Patients With UA/NSTEMI



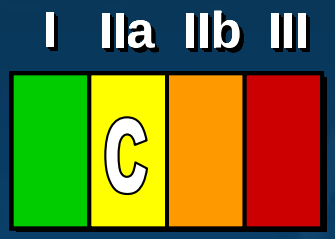

PCI (or CABG) is recommended for UA/NSTEMI patients with multivessel coronary disease with suitable coronary anatomy, with normal LV function, and without diabetes mellitus.



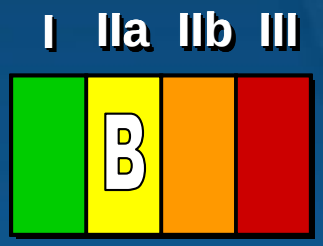

An intravenous platelet GP IIb/IIIa inhibitor is generally recommended in UA/NSTEMI patients undergoing PCI.*

*See the previous section on antiplatelet/anticoagulant therapy for details on timing and dosing recommendations.

# Recommendations for PCI in Patients With UA/NSTEMI

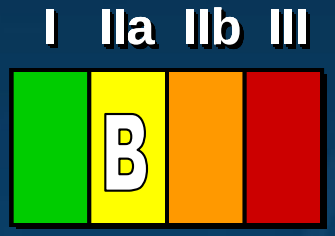



PCI is reasonable for focal saphenous vein graft (SVG) lesions or multiple stenoses in UA/NSTEMI patients who are undergoing medical therapy and who are poor candidates for reoperative surgery.

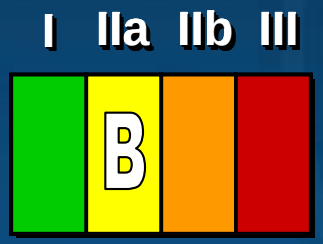



PCI (or CABG) is reasonable for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal LAD CAD but with a moderate area of viable myocardium and ischemia on noninvasive testing.

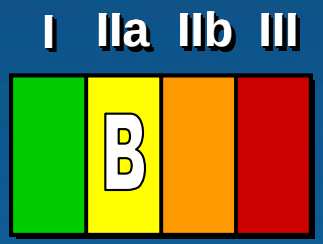
# Recommendations for PCI in Patients With UA/NSTEMI




PCI (or CABG) can be beneficial compared with medical therapy for UA/NSTEMI patients with 1-vessel disease with significant proximal LAD CAD.



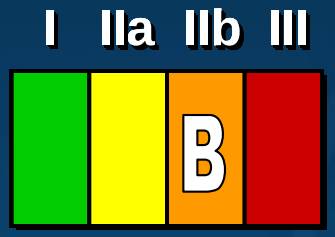

Use of PCI is reasonable in patients with UA/NSTEMI with significant left main CAD (>50% diameter stenosis) who are candidates for revascularization but are not eligible for CABG or who require emergent intervention at angiography for hemodynamic instability.



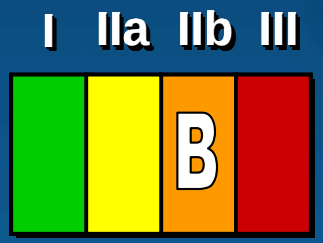

PCI is reasonable for UA/NSTEMI patients with diabetes mellitus with single-vessel disease and inducible ischemia.*

*This recommendation also appears in the Section Special Groups, Diabetes Mellitus.

# Recommendations for PCI in Patients With UA/NSTEMI

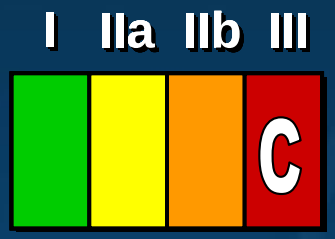



In the absence of high-risk features associated with UA/NSTEMI, PCI may be considered in patients with single-vessel or multivessel CAD who are undergoing medical therapy and who have 1 or more lesions to be dilated with a reduced likelihood of success.

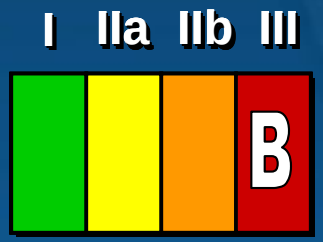



PCI may be considered for UA/NSTEMI patients who are undergoing medical therapy who have 2- or 3-vessel disease, significant proximal LAD CAD, and treated diabetes or abnormal LV function, with anatomy suitable for catheter-based therapy.

# Recommendations for PCI in Patients With UA/NSTEMI

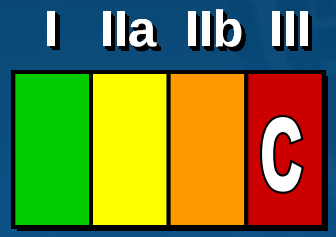


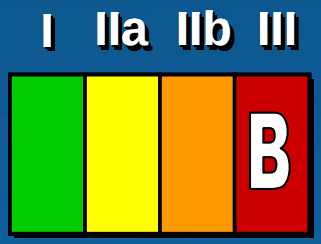

PCI (or CABG) is not recommended for patients with 1- or 2-vessel CAD without significant proximal LAD CAD with no current symptoms or symptoms that are unlikely to be due to myocardial ischemia and who have no ischemia on noninvasive testing.




A PCI strategy in stable patients with persistently occluded infarct-related coronary arteries after NSTEMI is not indicated.

# Recommendations for PCI in Patients With UA/NSTEMI




In the absence of high-risk features associated with UA/NSTEMI, PCI is not recommended for patients with UA/NSTEMI who have single-vessel or multivessel CAD and no trial of medical therapy, or who have 1 or more of the following:

a. Only a small area of myocardium at risk.

b. All lesions or the culprit lesion to be dilated with morphology that conveys a low likelihood of success.

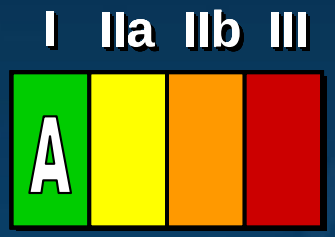
c. A high risk of procedure-related morbidity or mortality.

d. Insignificant disease (<50% coronary stenosis).

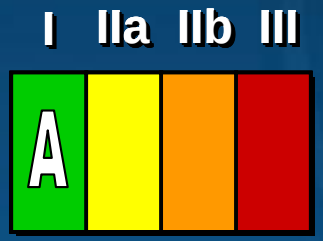
e. Significant left main CAD and candidacy for CABG.

Recommendations a-d are level of evidence: C; d is level of evidence: B.

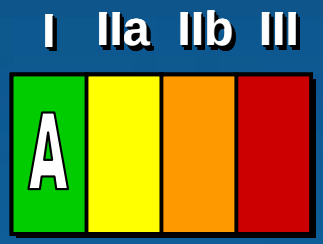
# Recommendations for CABG in Patients With UA/NSTEMI




CABG is recommended for UA/NSTEMI patients with significant left main CAD (>50% stenosis).

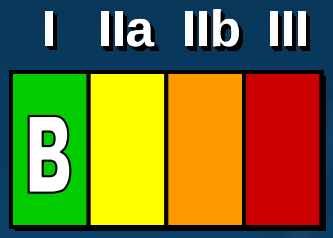



CABG is recommended for UA/NSTEMI patients with 3-vessel disease; the survival benefit is greater in patients with abnormal LV function (LVEF <50%).

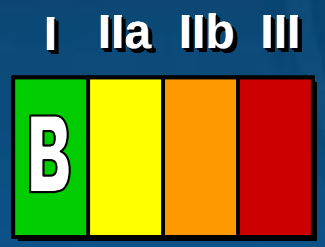



CABG is recommended for UA/NSTEMI patients with 2-vessel disease with significant proximal LAD CAD and either abnormal LV function (LVEF <50%) or ischemia on noninvasive testing.

# Recommendations for CABG in Patients With UA/NSTEMI



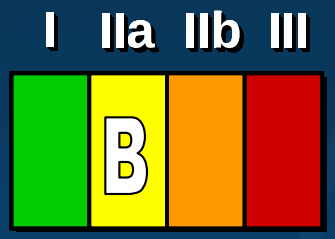

CABG is recommended for UA/NSTEMI patients in whom percutaneous revascularization is not optimal or possible and who have ongoing ischemia not responsive to maximal nonsurgical therapy.



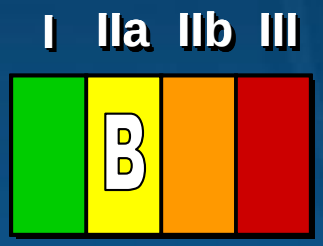

CABG (or PCI) is recommended for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal LAD CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing.


CABG (or PCI) is recommended for UA/NSTEMI patients with multivessel coronary disease with suitable coronary anatomy, with normal LV function, and without diabetes mellitus.

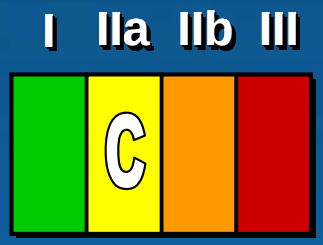
# Recommendations for CABG in Patients With UA/NSTEMI




For patients with UA/NSTEMI and multivessel disease, CABG with use of the internal mammary arteries can be beneficial over PCI in patients being treated for diabetes.



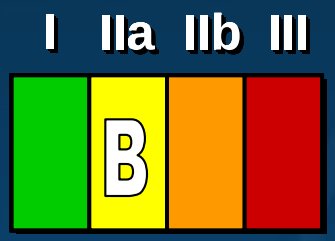

It is reasonable to perform CABG with the internal mammary artery for UA/NSTEMI patients with multivessel disease and treated diabetes
mellitus.



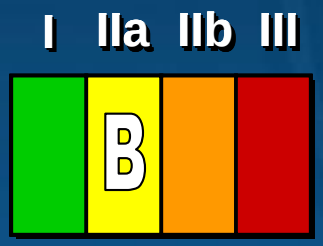

Repeat CABG is reasonable for UA/NSTEMI patients with multiple SVG stenoses, especially when there is significant stenosis of a graft that supplies the LAD.

*These recommendations also appear in the Section Special Groups, Diabetes Mellitus.

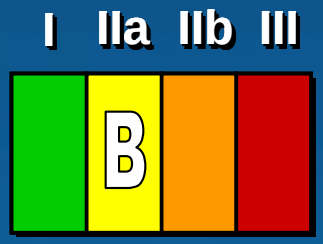
# Recommendations for CABG in Patients With UA/NSTEMI




CABG (or PCI) is reasonable for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal LAD CAD but with a moderate
area of viable myocardium and ischemia on noninvasive testing.

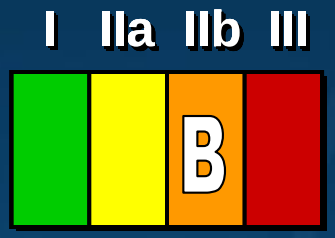



CABG (or PCI) can be beneficial compared with medical therapy for UA/NSTEMI patients with 1-vessel disease with significant proximal LAD CAD.



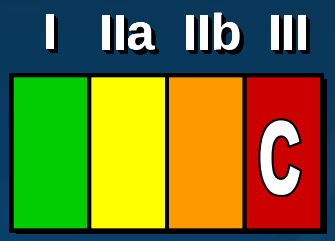

CABG (or PCI with stenting) is reasonable for patients with multivessel disease and symptomatic myocardial ischemia.

# Recommendations for CABG in Patients With UA/NSTEMI



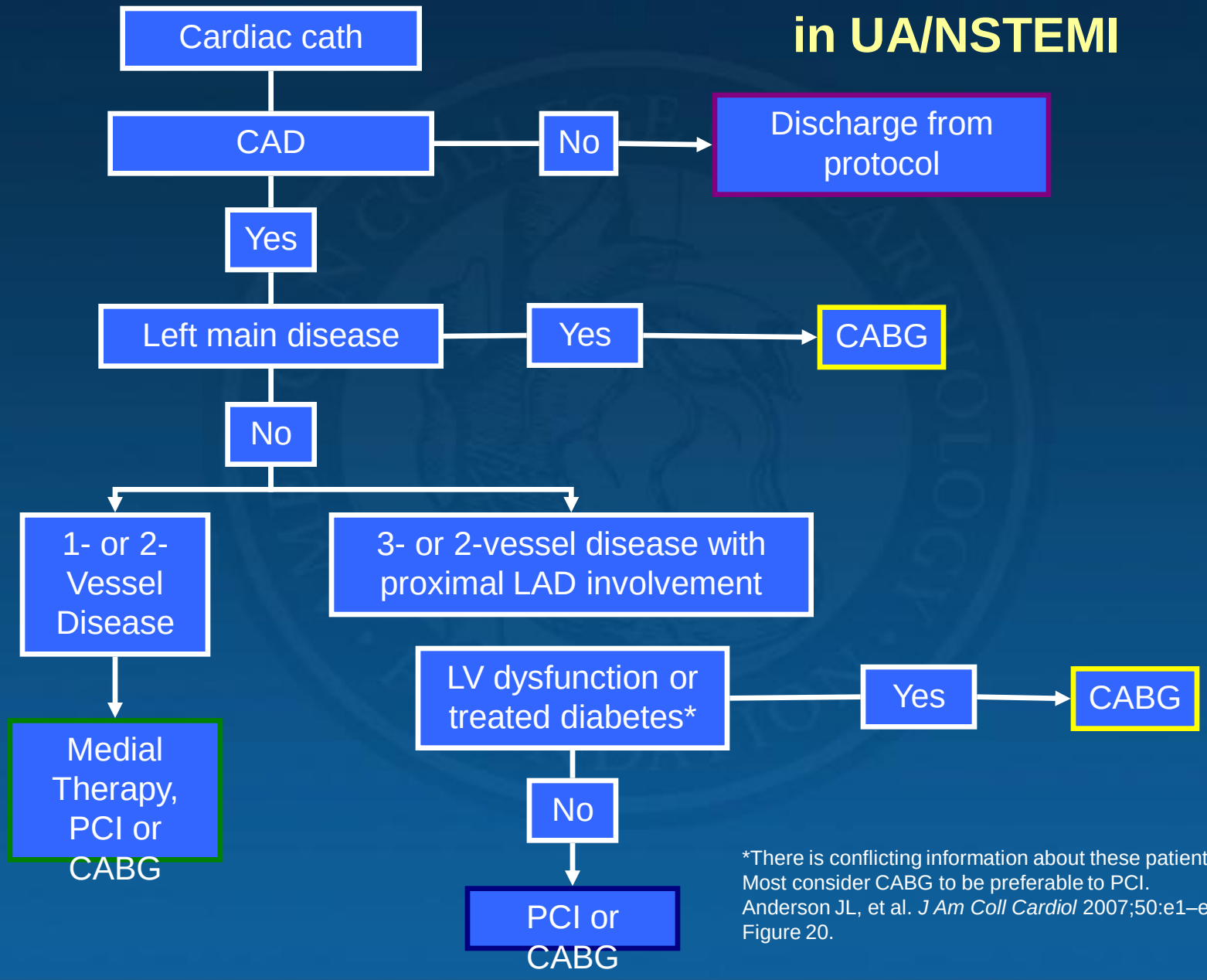

CABG may be considered in patients with UA/NSTEMI who have 1- or 2-vessel disease not involving the proximal LAD with a modest area of ischemic myocardium when percutaneous revascularization is not optimal or possible. (If there is a large area of viable myocardium and high-risk criteria on noninvasive testing, this recommendation becomes a Class I recommendation.)

# Recommendations for CABG in Patients With UA/NSTEMI




CABG (or PCI) is not recommended for patients with 1- or 2-vessel CAD without significant proximal LAD CAD with no current symptoms or symptoms that are unlikely to be due to myocardial ischemia and who have no ischemia on noninvasive testing.

# Revascularization Strategy in UA/NSTEMI

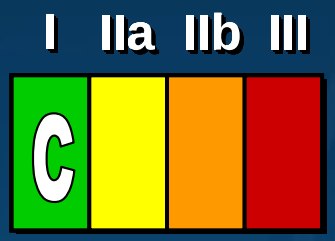



*There is conflicting information about these patients. Most consider CABG to be preferable to PCI.

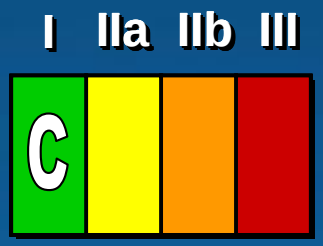
Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157, Figure 20.

# Late Hospital Care, Hospital Discharge and Post-Hospital Discharge Care

# Medical Regimen and Use of Medications

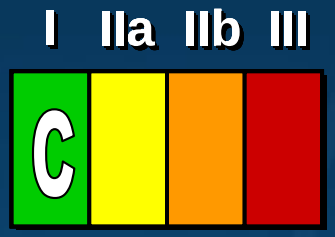



Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with UA/NSTEMI who do not undergo coronary revascularization, patients with unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Upward or downward titration of the doses may be required.

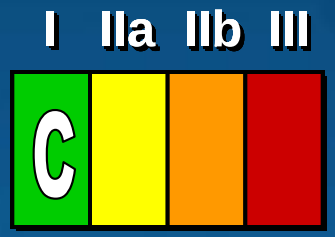



All post-UA/NSTEMI patients should be given sublingual or spray NTG and instructed in its use.

# Medical Regimen and Use of Medications

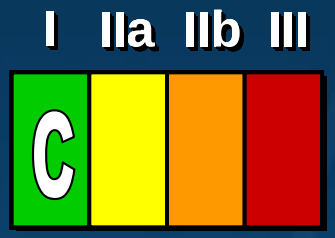



Before hospital discharge, patients with UA/NSTEMI should be informed about symptoms of worsening myocardial ischemia and MI and should be instructed in how and when to seek emergency care and assistance if such symptoms occur.



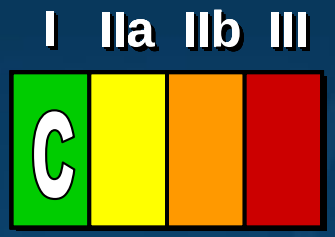

Before hospital discharge, post-UA/NSTEMI patients and/or designated responsible caregivers should be provided with supportable, easily understood, and culturally sensitive instructions with respect to medication type, purpose, dose, frequency, and pertinent side effects.

# Medical Regimen and Use of Medications




In post-UA/NSTEMI patients, anginal discomfort lasting more than 2 or 3 min should prompt the patient to discontinue physical activity or remove himself or herself from any stressful event. If pain does not subside immediately, the patient should be instructed to take 1 dose of NTG sublingually. If the chest discomfort/pain is unimproved or worsening 5 min after 1 NTG dose has been taken, it is recommended that the patient or a family member/friend call 9-1-1 immediately to access EMS. While activating EMS access, additional NTG (at 5-min intervals 2 times) may be taken while lying down or sitting.

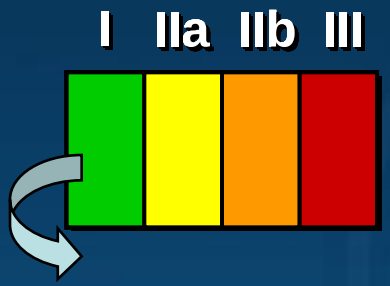
# Medical Regimen and Use of Medications




If the pattern or severity of anginal symptoms changes, which suggests worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or now occurs at rest), the patient should contact his or her physician without delay to assess the need for additional treatment or testing.

# Long-Term Medical Therapy and Secondary Prevention

# Antiplatelet Therapy




See recommendation for LOE

*Modified 2011*

For UA/NSTEMI patients treated medically without stenting, aspirin* (75 to 162 mg per day) should be prescribed indefinitely (Level of Evidence: A); clopidogrel† (75 mg per day) should be prescribed for at least 1 month and ideally up to 1 year. (Level of Evidence: B)

Recommendation was modified, LOE changed from A to B for 1-month duration of clopidogrel.

*For aspirin-allergic patients, use clopidogrel alone (indefinitely), or try aspirin desensitization.

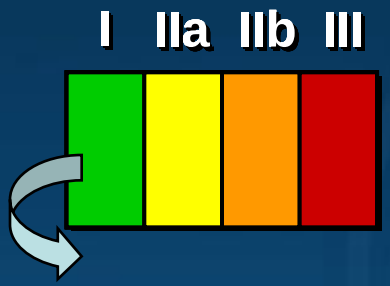
†For clopidogrel-allergic patients, use ticlopidine 250 mg by mouth twice daily.

# Antiplatelet Trialists' Collaboration

- Meta-analysis of randomized trials of antiplatelet therapy for prevention of death, MI, and stroke in high-risk patients
- 195 trials and > 143,000 pts
- 22% ↓ in odds of vascular death, MI, or stroke with antiplatelet therapy across broad spectrum of clinical presentations that included UA/NSTEMI
- Similar ↓ in odds of vascular events with aspirin doses of 75-1500 mg daily; <75 mg benefit ↓; dose-dependent ↑ bleeding*

* Yusuf S, et al. *N Engl J Med* 2001;345:494–502 (bleeding analysis from CURE trial).
Antiplatelet Trialists' Collaboration. *BMJ* 1994;308:81–106. Antithrombotics Trialists' Collaboration. *BMJ* 2002; 324:71– 86.

# Antiplatelet Therapy




See recommendation for LOE

*Modified 2011*

For UA/NSTEMI patients treated with bare-metal stents, aspirin* 162 to 325 mg per day should be prescribed for at least 1 month (Level of Evidence: B), then continued indefinitely at a dose of 75 to 162 mg per day. (Level of Evidence: A) The duration and maintenance dose of thienopyridine therapy should be as follows:

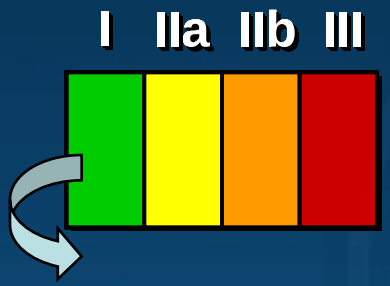
a. Clopidogrel 75 mg daily or prasugrel† 10 mg daily should be given for at least 12 months. (Level of Evidence: B)

b. If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by thienopyridine therapy, earlier discontinuation should be considered. (Level of Evidence: C)

Recommendation was modified to be concordant with 2009 STEMI and PCI Focused Update.

*For aspirin-allergic patients, use clopidogrel alone (indefinitely), or try aspirin desensitization.

# Antiplatelet Therapy




See recommendation for LOE

*Modified 2011*

For UA/NSTEMI patients treated with drug-eluting stents, aspirin* 162 to 325 mg per day should be prescribed for at least 3 months after sirolimus-eluting stent implantation and 6 months after paclitaxel-eluting stent implantation (Level of Evidence: B), then continued indefinitely at a dose of 75 to 162 mg per day. (Level of Evidence: A). The duration and maintenance dose of thienopyridine therapy should be as follows:

a. Clopidogrel 75 mg daily or prasugrel† 10 mg daily should be given for at least 12 months. (Level of Evidence: B)

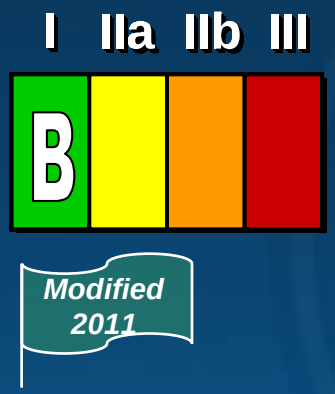
b. If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by thienopyridine therapy, earlier discontinuation should be considered. (Level of Evidence: C)

Recommendation was modified to be concordant with 2008 STEMI and PCI Focused Update

*For aspirin-allergic patients, use clopidogrel alone (indefinitely), or try aspirin desensitization.

†For clopidogrel-allergic patients, use ticlopidine 250 mg by mouth twice daily.

# Antiplatelet Therapy




Clopidogrel 75 mg daily (preferred) or ticlopidine (in the absence of contraindications) should be given to patients recovering from UA/NSTEMI when aspirin is contraindicated or not tolerated because of hypersensitivity or gastrointestinal intolerance (despite use of gastroprotective agents such as PPIs).

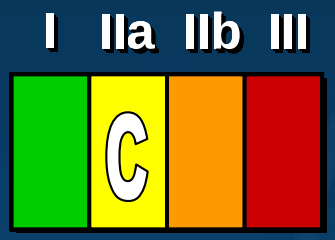
Changed wording for clarity. LOE changed from A to B, because trials do not address the specific subgroups in this recommendation.

# Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE)

- 19,185 patients w/ atherosclerotic vascular disease manifest as recent ischemic stroke, recent MI (≤35 d), or symptomatic PAD
- Clopidogrel vs aspirin
- ↓ Ischemic stroke, MI, or vascular death by clopidogrel (5.3% vs 5.8%, p=0.04)
- Benefit greatest for PAD

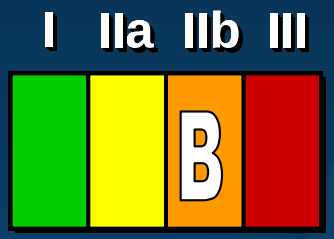
CAPRIE Steering Committee. *Lancet* 1996;348:1329–39. PAD = peripheral arterial disease.

# Antiplatelet Therapy

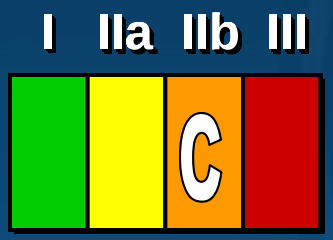



For UA/NSTEMI patients in whom the physician is concerned about the risk of bleeding, a lower initial aspirin dose after PCI of 75 to 162 mg per day is reasonable.

# Antiplatelet Therapy

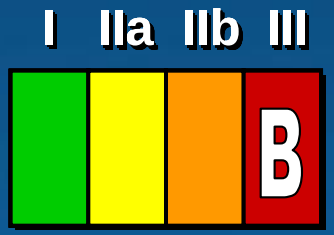



For UA/NSTEMI patients who have an indication for anticoagulation, the addition of warfarin‡ may be reasonable to maintain an INR of 2.0 to 3.0.§




Continuation of clopidogrel or prasugrel beyond 15 months may be considered in patients following DES placement.

New 2011



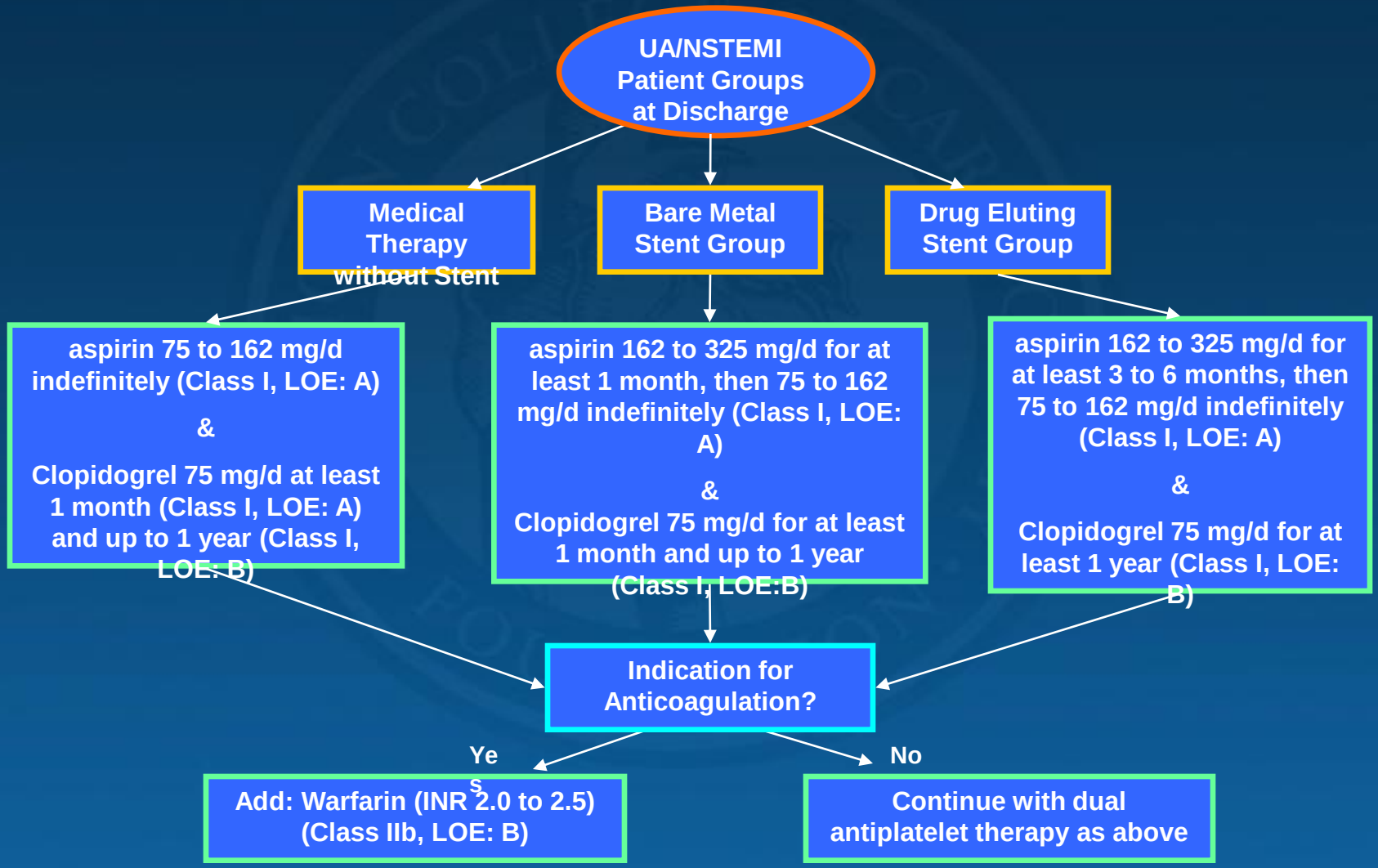

No Benefit

Dipyridamole is not recommended as an antiplatelet agent in post-UA/NSTEMI patients because it has not been shown to be effective.

Modified 2011

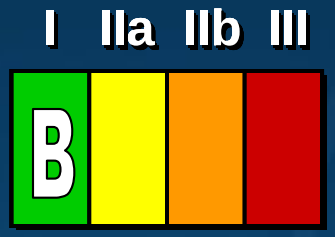
‡Continue aspirin indefinitely and warfarin long term as indicated for specific conditions such as atrial fibrillation; LV thrombus; or cerebral, venous, or pulmonary emboli.
§An INR of 2.0 to 2.5 is preferable while given with aspirin and clopidogrel, especially in older patients and those with other risk factors for bleeding. For UA/NSTEMI patients who have mechanical heart valves, the INR should be at least 2.5 (based on type of prosthesis).

# Long-Term Antithrombotic Therapy at Hospital Discharge after UA/NSTEMI

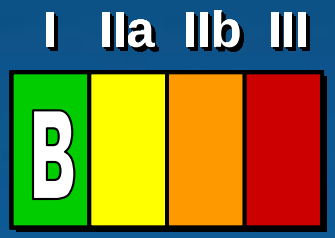



Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157, Figure 11. INR = international normalized ratio; LOE = level of evidence.

# Beta Blockers

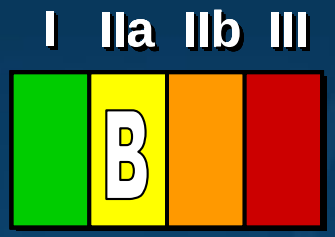



Beta blockers are indicated for all patients recovering from UA/NSTEMI unless contraindicated. (For those at low risk, see Class IIa on the next slide). Treatment should begin within a few days of the event, if not initiated acutely, and should be continued indefinitely.



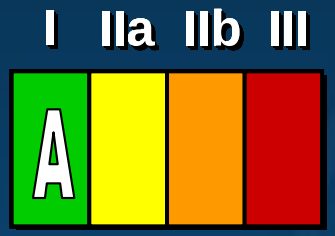

Patients recovering from UA/NSTEMI with moderate or severe LV failure should receive beta-blocker therapy with a gradual titration scheme.

# Beta Blockers

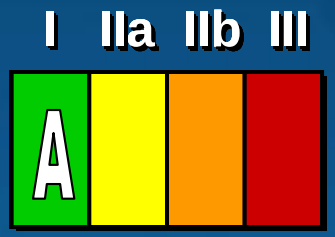



It is reasonable to prescribe beta blockers to low-risk patients (i.e., normal LV function, revascularized, no high-risk features) recovering from UA/NSTEMI in the absence of absolute contraindications.

# Inhibition of the Renin-Angiotensin-Aldosterone System

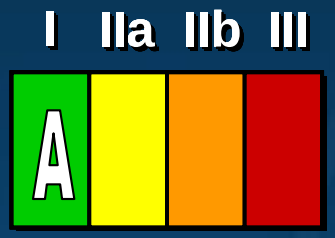



ACE inhibitors should be given and continued indefinitely for patients recovering from UA/NSTEMI with HF, LV dysfunction (LVEF <40%), hypertension, or diabetes mellitus, unless contraindicated.



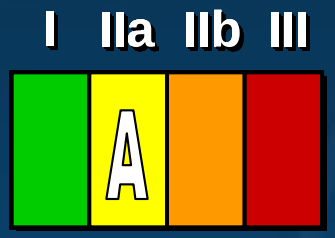

An ARB should be prescribed at discharge to those UA/NSTEMI patients who are intolerant of an ACE inhibitor and who have either clinical or radiological signs of HF and LVEF <40%.

# Inhibition of the Renin-Angiotensin-Aldosterone System

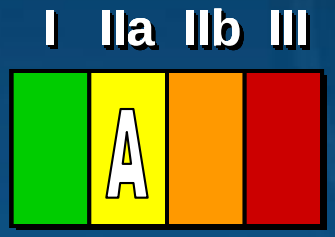



Long-term aldosterone receptor blockade should be prescribed for UA/NSTEMI patients without significant renal dysfunction (estimated creatinine clearance should be >30 mL per min) or hyperkalemia (potassium should be ≤5 mEq per liter) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF ≤40%, and have either symptomatic HF or diabetes mellitus.

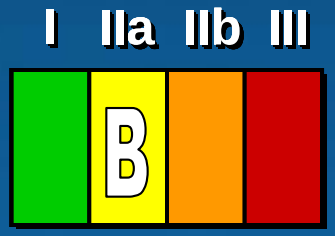
# Inhibition of the Renin-Angiotensin-Aldosterone System




ACE inhibitors are reasonable for patients recovering from UA/NSTEMI in the absence of LV dysfunction, hypertension, or diabetes mellitus unless contraindicated.

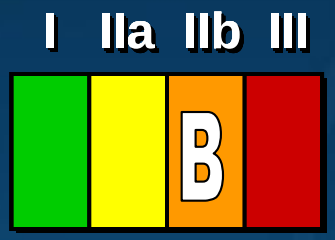



ACE inhibitors are reasonable for patients with HF and LVEF >0.40.




In UA/NSTEMI patients who do not tolerate ACE inhibitors, an ARB can be useful as an alternative to ACE inhibitors in long-term management provided there are either clinical or radiological signs of HF and LVEF <40%.

# Inhibition of the Renin-Angiotensin-Aldosterone System




The combination of an ACE inhibitor and an ARB may be considered in the long-term management of patients recovering from UA/NSTEMI with persistent symptomatic HF and LVEF <40%* despite conventional therapy including an ACE inhibitor or an ARB alone.

*The safety of this combination has not been proven in patients also on aldosterone antagonist and is not recommended.

# Heart Outcomes Prevention Evaluation (HOPE)

- 9,297 moderate-risk CAD patients, many w/ preserved LV function + patients @ high risk of developing CAD
  - 52% prior MI, 25% UA
- Ramipril (10 mg/day) or placebo
- ↓ CV death, MI, or stroke, or each of indiv endpoints by ramipril

Yusuf S, et al. *N Engl J Med* 2000;342:145–53.

# EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA)

- 12,218 moderate-risk CAD patients without apparent HF
- Perindopril (8 mg/day) or placebo
- ↓ CV mortality, MI, and cardiac arrest by perindopril
- Largest trial to show such benefit in stable, moderate-risk CAD patients

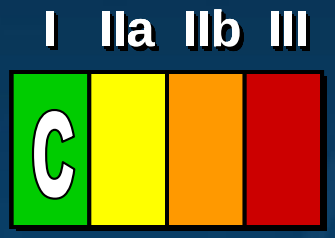
Fox KM. *Lancet* 2003;362:782–8.

# Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE)

- 8,290 low-risk stable CAD patients without HF
- Trandolapril (target dose of 4 mg/day) or placebo
- No ↓ cardiovascular death, MI, or revasc by trandolapril

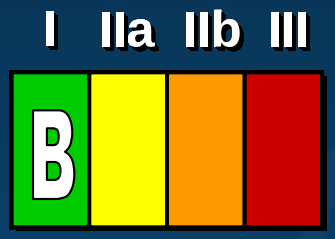
Braunwald E, et al. *N Engl J Med* 2004;351:2058–68.

# Nitroglycerin

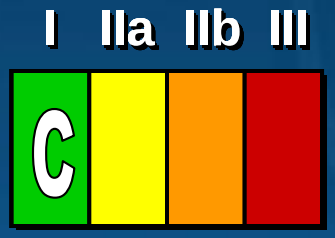



Nitroglycerin to treat ischemic symptoms is recommended.

# Calcium Channel Blockers




Calcium channel blockers* are recommended for ischemic symptoms when beta blockers are not successful.




Calcium channel blockers* are recommended for ischemic symptoms when beta blockers are contraindicated or cause unacceptable side effects.

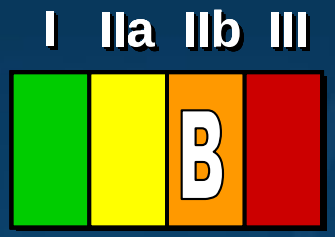
*Short-acting dihydropyridine calcium channel antagonists should be avoided.

# Warfarin Therapy


Use of warfarin in conjunction with aspirin and/or a thienopyridine agent is associated with an increased risk of bleeding, and patients and clinicians should watch for bleeding, especially gastrointestinal, and seek medical evaluation for evidence of bleeding.

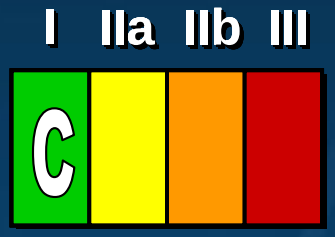
Recommendation was modified, updated to include a choice of thienopyridine.

# Warfarin Therapy

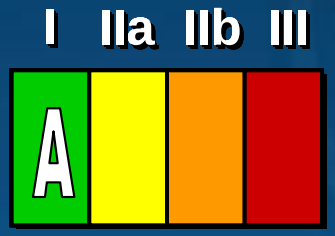



Warfarin either without (INR 2.5 to 3.5) or with low-dose aspirin (75 to 81 mg per day; INR 2.0 to 2.5) may be reasonable for patients at high CAD risk and low bleeding risk who do not require or are intolerant of clopidogrel.

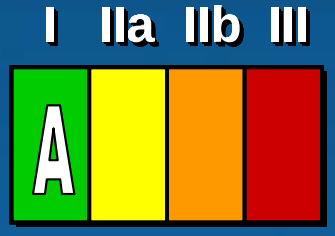
# Lipid Management




Lipid management should include assessment of a fasting lipid profile for all patients, within 24 h of hospitalization.




Hydroxymethyl glutaryl-coenzyme A reductase inhibitors (statins), in the absence of contraindications, regardless of baseline LDL-C and diet modification, should be given to post-UA/
NSTEMI patients, including postrevascularization patients.



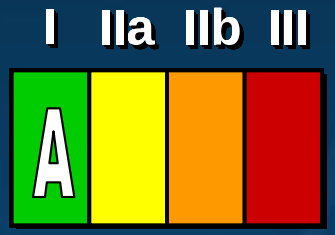

For hospitalized patients, lipid-lowering medications should be initiated before discharge.

# Heart Protection Study (HPS)

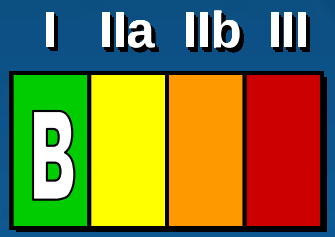
- 20,536 patients with CHD
- Simvastatin (40 mg qd) vs placebo
- ↓ Total mortality by simvastatin
  - ↓ Total CHD, total stroke, revascularization
  - ↑ Benefit over time, irrespective of initial cholesterol level and in broad spectrum of patients (e.g., women, elderly & patients with diabetes)
- Recommend: Statin in all patients at discharge regardless of baseline LDL-C (*Class I, LOE: A*)

Heart Protection Collaborative Group. *Lancet* 2002;360:7–22.

# Lipid Management




For UA/NSTEMI patients with elevated LDL-C (≥100 mg per dL), cholesterol-lowering therapy should be initiated or intensified to achieve an LDL-C <100 mg per dL.
Further titration to less than 70 mg per dL is reasonable. (*Class IIa, Level of Evidence: A*)




Therapeutic options to reduce non–HDL-C* are recommended, including more intense LDL-C–lowering therapy.

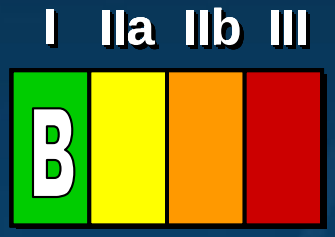
*Non-HDL-C = total cholesterol minus HDL-C

# PRavastatin Or atorVastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 (PROVE-IT TIMI 22)

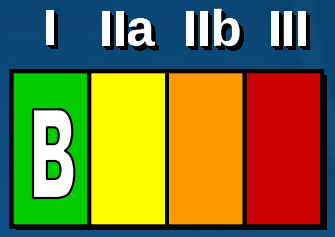
- 4,162 patients within 10 d of ACS
- 40 mg pravastatin vs 80 mg atorvastatin daily
- ↓ All-cause death, MI, UA requiring hosp, revasc & stroke @ 2 y by atorvastatin
  - Median LDL-C ↓ (62 vs 95 mg/dL)

Cannon CP, et al. *N Engl J Med* 2004;350:1495–504.

# Lipid Management

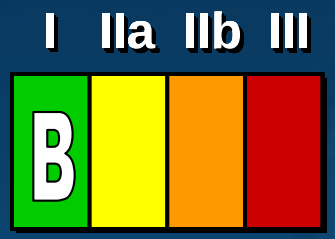


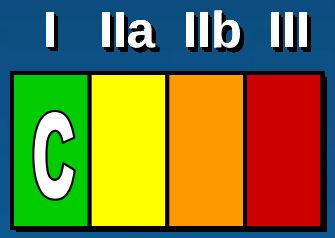

Dietary therapy for all patients should include reduced intake of saturated fats (to <7% of total calories), cholesterol (to <200 mg per day), and trans fat (to <1% of energy).




Promoting daily physical activity and weight management are recommended.

# Lipid Management



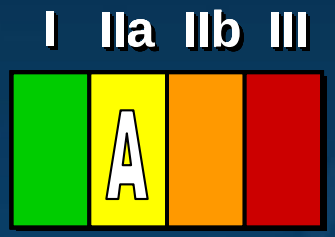




Treatment of triglycerides (TG) and non-HDL-C is useful, including the following:

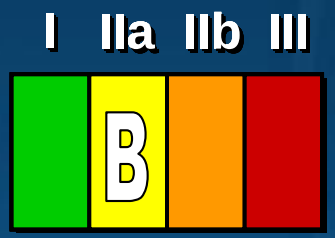
a. If TG are 200 to 499 mg per dL, non-HDL-C* should be <130 mg per dL.
b. If TG are ≥500 mg per dL†, therapeutic options to prevent pancreatitis are fibrate‡ or niacin‡ before LDL-lowering therapy is recommended. It is also recommended that LDL-C be treated to goal after TG-lowering therapy. Achievement of a non-HDL-C* <130 mg per dL (i.e., 30 mg per dL >LDL-C target) if possible is recommended.

*Non-HDL-C = total cholesterol minus HDL-C.
†Patients with very high TG should not consume alcohol. The use of bile acid sequestrants are relatively contraindicated when TG are > 200 mg/dL
‡The combination of high-dose statin plus fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination. Dietary supplement niacin must not be used as a substitute for prescription niacin.

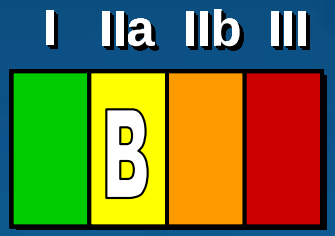
# Lipid Management




Further reduction of LDL-C to <70 mg per dL is reasonable.



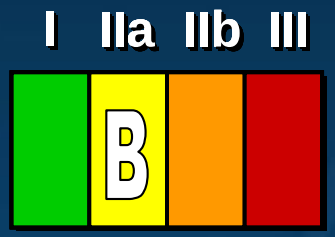

If baseline LDL cholesterol is 70 to 100 mg per dL, it is reasonable to treat LDL-C to <70 mg per dL.



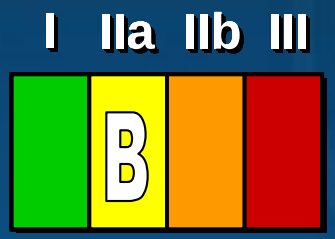

Further reduction of non-HDL-C* to <100 mg per dL is reasonable; if TG are 200 to 499 mg per dL, non- HDL-C target is <130 mg per dL. Therapeutic options to reduce non-HDL-C* (after LDL-C lowering) include niacin† or fibrate‡ therapy.

*Non-HDL-C = total cholesterol minus HDL-C.
†The combination of high-dose statin plus fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination. Dietary supplement niacin must not be used as a substitute for prescription niacin.
‡Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrants is relatively contraindicated when triglycerides are greater than 200 mg per dL.

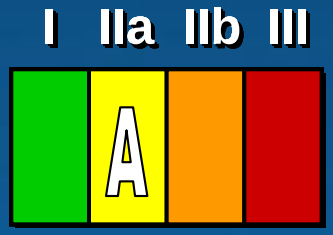
# Lipid Management




Nicotinic acid (niacin)* and fibric acid derivatives (fenofibrate, gemfibrozil)† can be useful as therapeutic options (after LDL-C–lowering therapy) for HDL-C <40 mg per dL.



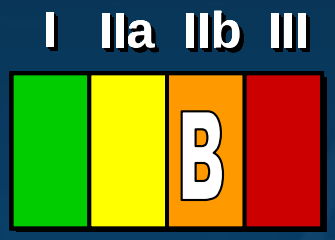

Nicotinic acid (niacin)* and fibric acid derivatives (fenofibrate, gemfibrozil)† can be useful as therapeutic options (after LDL-C–lowering therapy) for TG >200 mg per dL.




The addition of plant stanol/sterols (2 g per day) and/or viscous fiber (>10 g per day) is reasonable to further lower LDL-C.

*The combination of high-dose statin plus fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination. Dietary supplement niacin must not be used as a substitute for prescription niacin.
†Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrants is relatively contraindicated when triglycerides are greater than 200 mg per dL.

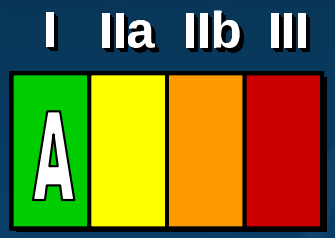
# Lipid Management




Encouraging consumption of omega-3 fatty acids in the form of fish* or in capsule form (1 g per d) for risk reduction may be reasonable in post-UA/NSTEMI patients. For treatment of elevated TG, higher doses (2 to 4 g per day) may be used for risk reduction.

*Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.

# Blood Pressure Control




Blood pressure control according to JNC 7 guidelines* is recommended (i.e., BP <140/90 mm Hg or <130/80 mm Hg if the patient has diabetes mellitus or chronic kidney disease).

*Chobanian AV, et al. JAMA 2003;289:2560-2572.
JNC 7 = 7th report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.

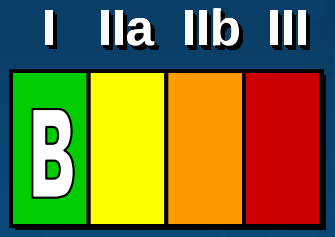
# Seventh Joint National Committee on High Blood Pressure (JNC 7)

- Guidelines for 1º prevention in pts with high BP*
- Specific rx recommendations based on level of hypertension and patient's other risk factors
- Systolic hypertension a powerful predictor of adverse outcome, particularly among elderly
- Recommended BP <140/90 mm Hg ; <130/80 mm Hg if patient has diabetes or chronic kidney disease
- Hypertension guidelines have adapted for patients with ischemic heart disease†

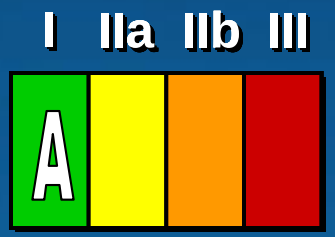
*Chobanian AV, et al. JAMA 2003;289:2560–72. †Rosendorff C, et al. *Circulation* 2007;115:2761–88.

# Blood Pressure Control

Additional measures recommended to treat and control BP include the following:

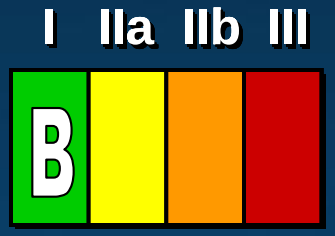



a. Patients should initiate and/or maintain lifestyle modifications, including weight control, ↑ physical activity, alcohol moderation, sodium ↓, and emphasis on ↑ consumption of fresh fruits, vegetables, and low-fat dairy products.

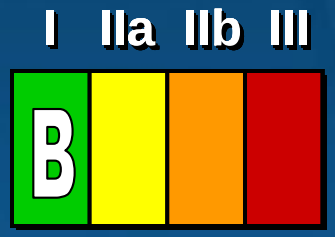



b. For patients with BP ≥140/90 mm Hg (or ≥130/80 mm Hg for individuals with chronic kidney disease or diabetes mellitus), it is useful to add BP medication as tolerated, treating initially with beta blockers and/or ACE inhibitors, with addition of other drugs such as thiazides as needed to achieve target BP.

# Diabetes Mellitus

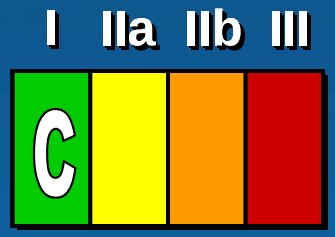



Diabetes management should include lifestyle and pharmacotherapy measures to achieve a near-normal
HbA1c level of <7%.



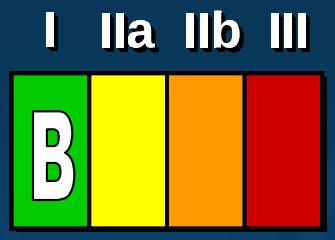

Diabetes management should also include the following:

a. Vigorous modification of other risk factors (e.g., physical activity, weight management, BP control, and cholesterol management) as recommended should be initiated and maintained.



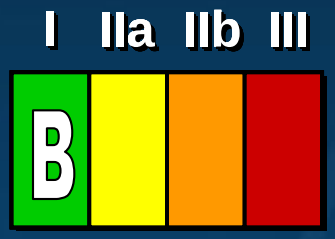

b. It is useful to coordinate the patient's diabetic care with the patient's primary care physician or endocrinologist

# Smoking Cessation



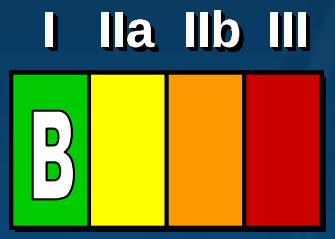

Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home are recommended. Follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement) is useful, as is adopting a stepwise strategy aimed at smoking cessation (the 5 As are: Ask, Advise, Assess, Assist, and Arrange).

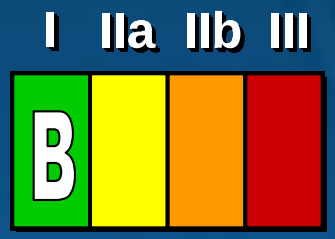
# Weight Management

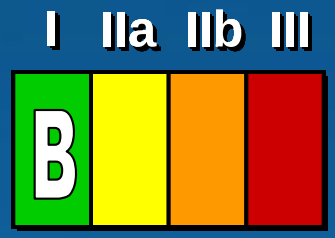



Weight management, as measured by body mass index (BMI) and/or waist circumference, should be assessed on each visit. A BMI of 18.5 to 24.9 kg per $m^2$ and a waist circumference (measured horizontally at the iliac crest) of <40 inches for men and <35 inches for women is recommended.

# Weight Management



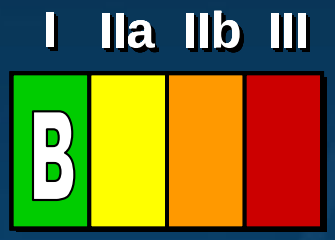

Additional weight management practices recommended include the following:

a. On each patient visit, it is useful to consistently encourage weight maintenance/reduction through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve a BMI between 18.5 and 24.9 kg per $m^2$.

b. If waist circumference is ≥35 inches in women or ≥40 inches in men, it is beneficial to initiate lifestyle changes and consider treatment strategies for metabolic syndrome as indicated.

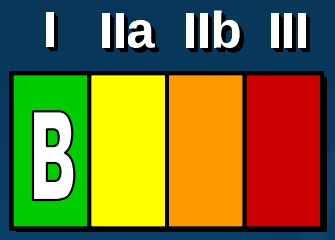
c. The initial goal of weight loss therapy should be to ↓ body weight by ~10% from baseline. With success, further weight loss can be

# Physical Activity



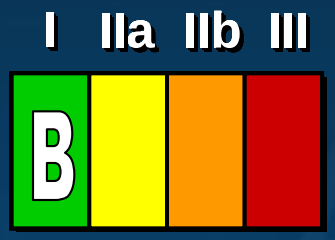

The patient's risk after UA/NSTEMI should be assessed on the basis of an in-hospital determination of risk. A physical activity history or an exercise test to guide initial prescription is beneficial.

# Physical Activity



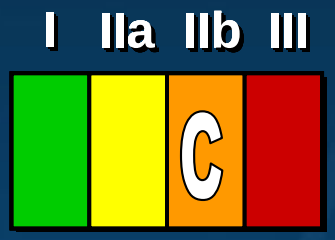

Guided/modified by an individualized exercise prescription, patients recovering from UA/NSTEMI generally should be encouraged to achieve physical activity duration of 30 to 60 min per day, preferably 7 (but at least 5) days per week of moderate aerobic activity, such as brisk walking, supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, and household work).

# Physical Activity



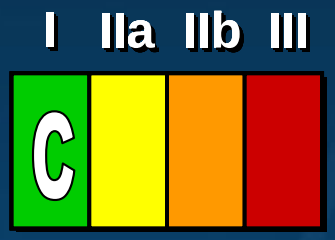

Cardiac rehabilitation/secondary prevention programs are recommended for patients with UA/NSTEMI, particularly those with multiple modifiable risk factors and/or those moderate- to high-risk patients in whom supervised exercise training is particularly warranted.

# Physical Activity




The expansion of physical activity to include resistance training on 2 days per week may be reasonable.

# Patient Education



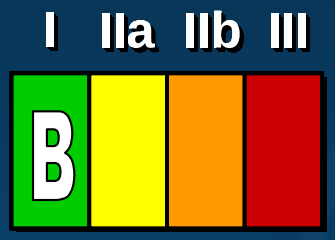

Beyond the detailed instructions for daily exercise, patients should be given specific instruction on activities (e.g., heavy lifting, climbing stairs, yard work, and household activities) that are permissible and those that should be avoided. Specific mention should be made regarding resumption of driving, return to work, and sexual activity.

# Energy Levels Required to Perform Some Common Activities

| < 3 METS | 3–5 METS | 5–7 METS | 7–9 METS | > 9 METS |
|---|---|---|---|---|
| Washing<br>Dressing<br>Desk work<br>Standing (store clerk)<br>Golf (cart)<br>Knitting<br>Walking (2 mph) | Raking<br>Carrying objects (15–30 lb)<br>Auto repair<br>Golf (walking)<br>Dancing (social)<br>Level walking (3–4 mph) | Climbing stairs (slowly)<br>Carrying objects (30–60 lb)<br>Shoveling dirt<br>Tennis (singles)<br>Basketball<br>Level walking (4.5–5.0 mph) | Climbing stairs (moderate speed)<br>Carrying objects (60–90 lb)<br>Heavy shoveling<br>Mountain climbing<br>Walking (5 mph) | Climbing stairs (quickly)<br>Carrying load upstairs (> 90 lb)<br>Heavy labor<br>Handball<br>Running (> 6 mph)<br>Walking uphill (5 mph) |

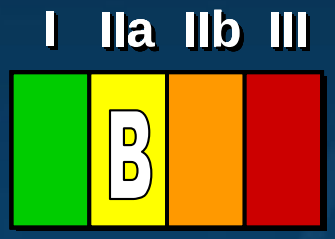
This table is an abridged version of Table 23 in Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157, with permission from Elsevier.
Adapted from Haskell WL. Design and implementation of cardiac conditioning program. In: Wenger NL, Hellerstein HK, editors. Rehabilitation of the Coronary Patient. New York, NY:Churchill Livingstone, 1978.
METS= metabolic equivalents.

# Influenza



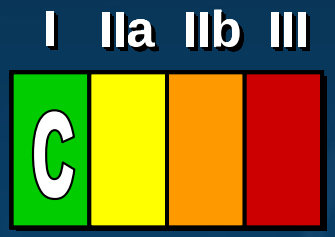

An annual influenza vaccination is recommended for patients with cardiovascular disease.

# Depression



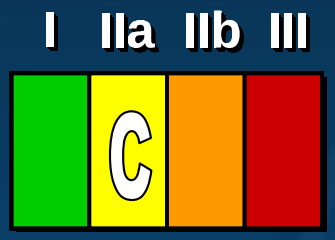

It is reasonable to consider screening UA/NSTEMI patients for depression and refer/treat when indicated.

# Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)



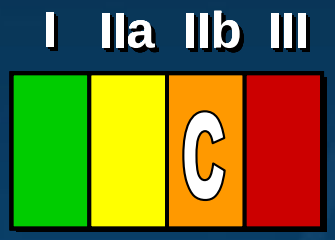

At the time of preparation for hospital discharge, the patient's need for treatment of chronic musculoskeletal discomfort should be assessed, and a stepped-care approach to treatment should be used for selection of treatments. Pain relief should begin with acetaminophen, small doses of narcotics, or nonacetylated salicylates.

# NSAIDs



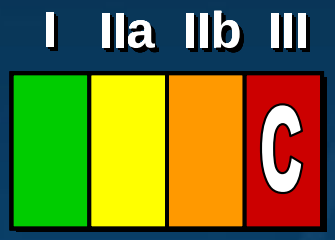

It is reasonable to use nonselective NSAIDs, such as naproxen, if initial therapy with acetaminophen, small doses of narcotics, or nonacetylated salicylates is insufficient.

# NSAIDs




NSAIDs with increasing degrees of relative COX-2 selectivity may be considered for pain relief only for situations in which intolerable discomfort persists despite attempts at stepped-care therapy with acetaminophen, small doses of narcotics, nonacetylated salicylates, or nonselective NSAIDs. In all cases, the lowest effective doses should be used for the shortest possible time.

# NSAIDs




NSAIDs with increasing degrees of relative COX-2 selectivity should not be administered to UA/NSTEMI patients with chronic musculoskeletal discomfort when therapy with acetaminophen, small doses of narcotics, nonacetylated salicylates, or nonselective NSAIDs provides acceptable levels of pain relief.

# Stepped-Care Approach to Pharmacological Therapy for Musculoskeletal Symptoms With Known Cardiovascular Disease or Risk Factors for Ischemic Heart Disease

**Acetaminophen, aspirin, tramadol, narcotic analgesics (short term)**

**Nonacetylated salicylates**

**Non COX-2 selective NSAIDs**

**NSAIDs with some COX-2 selectivity**

**COX-2 selective NSAIDs**

- Select pts at low risk of thrombotic events
- Prescribe lowest dose required to control symptoms
- Add aspirin 81 mg and PPI to pts at ↑ risk of thrombotic events*

- Regular monitoring for sustained hypertension (or worsening of prior BP control), edema, worsening renal function, or GI bleeding
- If these occur, consider reduction of the dose or discontinuation of the offending drug, a different drug, or alternative therapeutic modalities, as dictated by clinical circumstances

*Addition of aspirin may not be sufficient protection against thrombotic events.
Reproduced with permission from Antman EM, et al. Circulation 2007;115:1634–42.
PPI = proton-pump inhibitor.

# Hormone Therapy

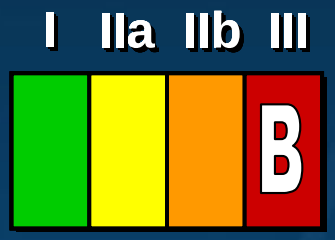

Hormone therapy with estrogen plus progestin, or estrogen alone, should not be given de novo to postmenopausal women after UA/NSTEMI for secondary prevention of coronary events.

# Heart and Estrogen/progestin Replacement Study (HERS)

- 2,763 postmenopausal women with CHD
- Estrogen + progestin vs placebo
- ↑ Death and MI early after hormone therapy initiation
- Recommend: Menopausal hormone rx (estrogen + progestin or estrogen alone) should not be given de novo for 2$^{o}$ prevention of coronary events (*Class III, LOE: A*)

Hulley S, et al. *JAMA* 1998;280:605–13.
LOE = level of evidence.

# Hormone Therapy




Postmenopausal women who are already taking estrogen plus progestin, or estrogen alone, at the time of UA/NSTEMI in general should not continue hormone therapy. However, women who are more than 1 to 2 years past the initiation of hormone therapy who wish to continue such therapy for another compelling indication should weigh the risks and benefits, recognizing the greater risk of cardiovascular events and breast cancer (combination therapy) or stroke (estrogen). Hormone therapy should not be continued while patients are on bedrest in the hospital.

# Antioxidant Vitamin and Folic Acid


Antioxidant vitamin supplements (e.g., vitamins E, C, or beta carotene) should not be used for secondary prevention in UA/NSTEMI patients.


Folic acid, with or without B6 and B12, should not be used for secondary prevention in UA/NSTEMI patients.

# Heart Outcomes Prevention Evaluation (HOPE-Vitamin E)

- 9,541 moderate-risk CAD patients, many w/ preserved LV function + patients @ high risk of developing CAD
  - 52% prior MI, 25% UA
- Vitamin E (400 IU/day) or placebo
- No ↓ CV death, MI, or stroke, or each of the indiv endpoints by vitamin E

Yusuf S, et al. *N Engl J Med* 2000;342:154-60. HOPE and HOPE-TOO Investigators. *JAMA* 2005;293:1338-1347 (long-term results).

# Heart Outcomes Prevention Evaluation (HOPE-2)

- 5,522 patients with CHD or diabetes
- Folic acid (2.5 mg), vitamin B6 (50 mg), and vitamin B12 (1 mg) or placebo
- No ↓ CV death, MI, or stroke @ 5 y by vitamin combination
- No ↓ CV death or MI; stroke ↓ by vitamins

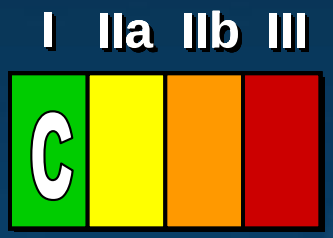
Lonn E, et al. *N Engl J Med* 2006;354:1567–77.

# NOrwegian VItamin Trial (NORVIT)

- 3,749 patients within 7 d STEMI
- Folic acid (0.8 mg), vitamin B6 (40 mg), both folic acid (0.8 mg) and vitamin B6 (40 mg) or placebo
- No ↓ re-MI or stroke by monotherapy groups; ↑combination therapy
- No ↓ death monotherapy or combination

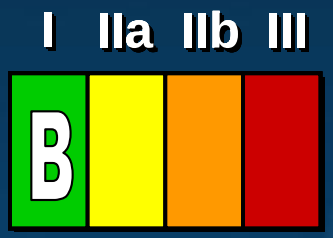
Bonaa KH, et al. *N Engl J Med* 2006;354:1578–88.

# Postdischarge Follow-Up




Detailed discharge instructions for post-UA/NSTEMI patients should include education on medications, diet, exercise, and smoking cessation counseling (if appropriate), referral to a cardiac rehab/secondary prevention program (when appropriate), and the scheduling of a timely follow-up appointment. Low-risk medically treated patients and revascularized patients should return in 2 to 6 weeks, and higher risk patients should return within 14 days.

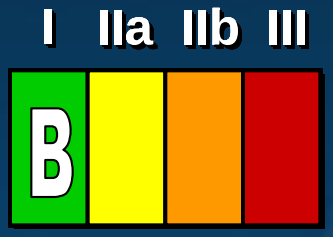
# Postdischarge Follow-Up



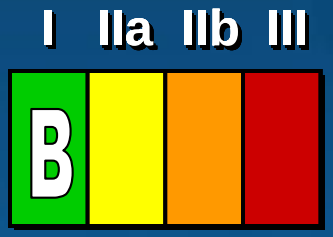

Patients with UA/NSTEMI managed initially with a conservative strategy who experience recurrent signs or symptoms of UA or severe (CCS class III) chronic stable angina despite medical management who are suitable for revascularization should undergo timely coronary angiography.

CCS = Canadian Cardiovascular Society.

# Postdischarge Follow-Up

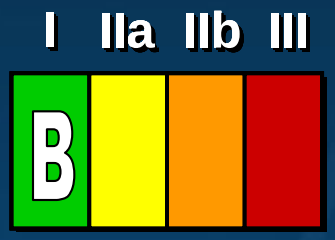



Patients with UA/NSTEMI who have tolerable stable angina or no anginal symptoms at follow-up visits should be managed with long-term medical therapy for stable CAD.




Care should be taken to establish effective communication between the post-UA/NSTEMI patient and health care team members to enhance long-term compliance with prescribed therapies and recommended lifestyle changes.

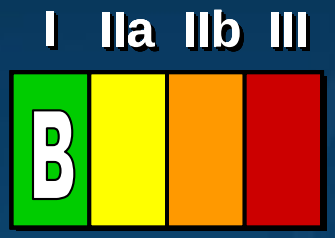
# Cardiac Rehabilitation



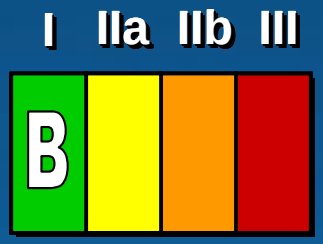

Cardiac rehabilitation/secondary prevention programs, when available, are recommended for patients with UA/NSTEMI, particularly those with multiple modifiable risk factors and those moderate- to high-risk patients in whom supervised exercise training is warranted.

# Special Groups

# Women

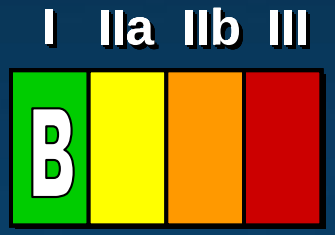



Women with UA/NSTEMI should be managed with the same pharmacological therapy as men both in the hospital and for secondary prevention, with attention to antiplatelet and anticoagulant doses
based on weight and renal function; doses of renally cleared medications should be based on estimated creatinine clearance.

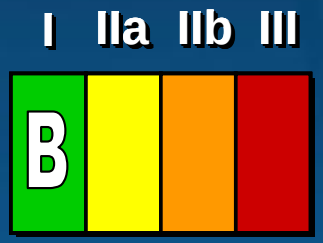



Recommended indications for noninvasive testing in women with UA/NSTEMI are similar to those for men.

# Women



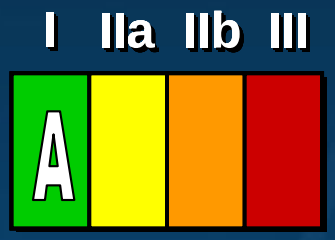

For women with high-risk features, recommendations for invasive strategy are similar to those of men.




In women with low-risk features, a conservative strategy is recommended.

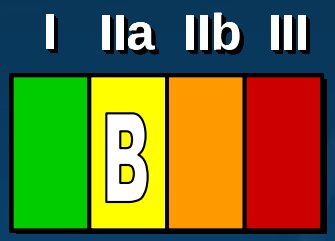
These recommendations are also found in the Initial Invasive Versus Initial Conservative Strategy Section.

# Diabetes Mellitus

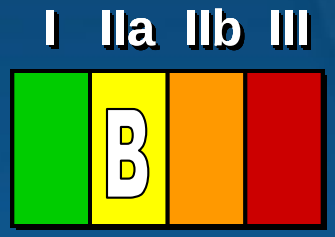



Medical treatment in the acute phase of UA/NSTEMI and decisions on whether to perform stress testing, angiography, and revascularization
should be similar in patients with and without diabetes mellitus.

# Diabetes Mellitus



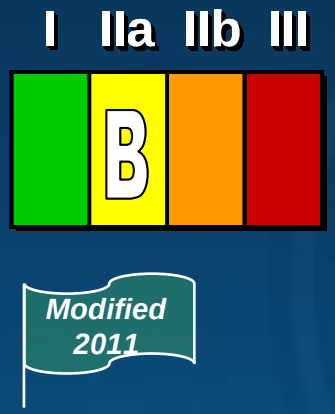

For patients with UA/NSTEMI and multivessel disease, CABG with use of the internal mammary arteries can be beneficial over PCI in patients being treated for diabetes mellitus.




PCI is reasonable for UA/NSTEMI patients with diabetes mellitus with single-vessel disease and inducible ischemia.

These recommendations also appear in the Section on Coronary Revascularization.

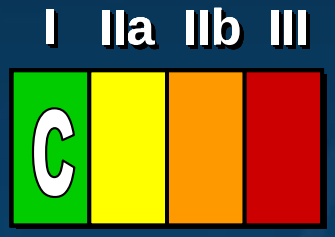
# Diabetes Mellitus



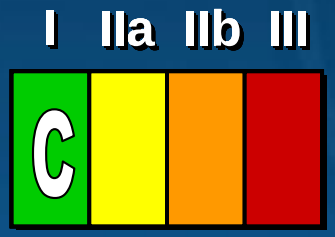

It is reasonable to use an insulin-based regimen to
achieve and maintain glucose levels <180 mg/dL
while avoiding hypoglycemia* for hospitalized patients with UA/NSTEMI with either a complicated
or uncomplicated course.

*There is uncertainty about the ideal target range for glucose necessary to achieve an optimal risk-benefit ratio.

# Post-CABG Patients

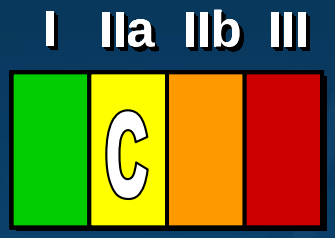



Medical treatment for UA/NSTEMI patients after CABG should follow the same guidelines as for non–post-CABG patients with UA/NSTEMI.



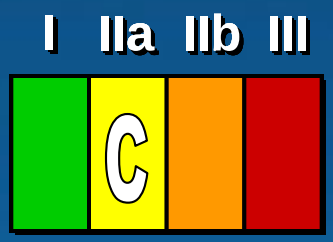

Because of the many anatomic possibilities that might be responsible for recurrent ischemia, there should be a low threshold for angiography in post-CABG patients with UA/NSTEMI.

# Post-CABG Patients



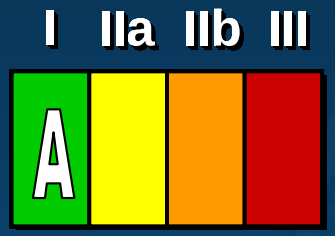

Repeat CABG is reasonable for UA/NSTEMI patients with multiple SVG stenoses, especially when there is significant stenosis of a graft that supplies the LAD. PCI is reasonable for focal saphenous vein stenosis.

(Note that an intervention on a native vessel is generally preferable to that on a vein graft that supplies the same territory, if possible.)

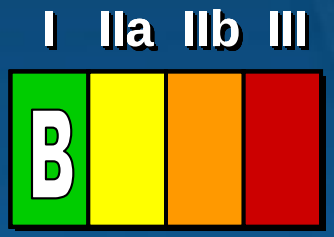



Stress testing with imaging in UA/NSTEMI post-CABG patients is reasonable.

# Older Adults

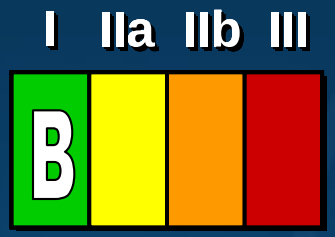



Older patients with UA/NSTEMI should be evaluated for appropriate acute and long-term therapeutic interventions in a similar manner as younger patients with UA/NSTEMI.




Decisions on management of older patients with UA/NSTEMI should not be based solely on chronologic age but should be patient centered, with consideration given to general health, functional and cognitive status, comorbidities, life expectancy, and patient preferences and goals.

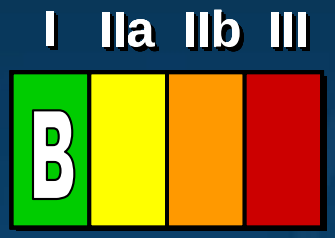
# Older Adults



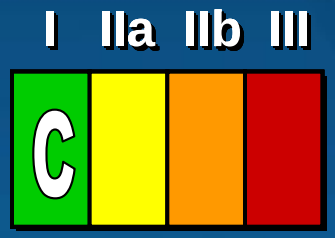

Attention should be given to appropriate dosing (i.e., adjusted by weight and estimated creatinine clearance) of pharmacological agents in older patients with UA/NSTEMI, because they often have

altered pharmacokinetics (due to reduced muscle mass, renal and/or hepatic dysfunction, and reduced volume of distribution) and pharmacodynamics (increased risks of hypotension and bleeding).

# Older Adults




Older UA/NSTEMI patients face increased early procedural risks with revascularization relative to younger patients, yet the overall benefits from invasive strategies are equal to or perhaps greater in older adults and are recommended.




Consideration should be given to patient and family preferences, quality-of-life issues, end-of-life preferences, and sociocultural differences in older patients with UA/NSTEMI.

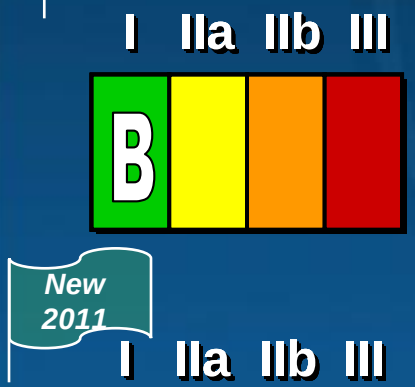
# Impact of Age on Outcomes of ACS: GRACE Risk Model

| Age Group | No. of Deaths (Hospital Mortality Rate) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|
| <45 y | 20 (1.3) | Reference | Reference |
| 45 to 54 y | 79 (2.0) | 1.47 (0.90–2.41) | 1.95 (1.06–3.61) |
| 55 to 64 y | 171 (3.1) | 2.35 (1.47–3.74) | 2.77 (1.53–4.99) |
| 65 to 74 y | 373 (5.5) | 4.34 (2.76–6.83) | 4.95 (2.78–8.79) |
| 75 to 84 y | 439 (9.3) | 7.54 (4.80–11.8) | 8.04 (4.53–14.3) |
| ≥85 y | 260 (18.4) | 16.7 (10.5–26.4) | 15.7 (8.77–28.3) |

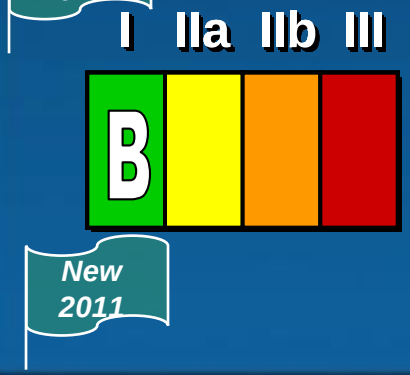
*All $p < 0.0001$. The GRACE risk model includes systolic blood pressure, initial serum creatinine, heart rate, initial cardiac enzyme, Killip class, ST- segment deviation, and cardiac arrest at hospital arrival. Modified from Avezum A, et al. Am Heart J 2005; 149:67–73.
ACS = acute coronary syndromes; CI = confidence interval; GRACE = Global Registry of Acute Coronary Events; OR = odds ratio.

# Chronic Kidney Disease


Creatinine clearance should be estimated in UA/NSTEMI patients and the doses of renally cleared medications should be adjusted according to the pharmacokinetic data for specific medications.




Patients undergoing cardiac catheterization with receipt of contrast media should receive adequate preparatory hydration.




Calculation of the contrast volume to creatinine clearance ratio is useful to predict the maximum volume of contrast media that can be given without significantly increasing the risk of contrast-associated nephropathy.

# Volume of Contrast Media to Creatinine Clearance (V/CrCl) Ratio as Predictor of ↑ in Serum Creatinine After PCI

- 3,179 pts undergoing PCI
- 1.5% early, abnormal ↑ in creatinine (↑ serum creatinine >0.5 mg/dl by 24 to 48 h considered abnormal)
- V/CrCl ratio >3.7 significant independent predictor of early, abnormal ↑ in serum creatinine after PCI

Laskey WK, et al. JACC 2007;50:584–90.

Revised 2011

# Chronic Kidney Disease


An invasive strategy is reasonable in patients with mild
(stage II) and moderate (stage III) chronic kidney disease. (There are insufficient data on benefit/risk of invasive strategy in UA/NSTEMI patients with advanced chronic kidney disease [stages IV, V].)

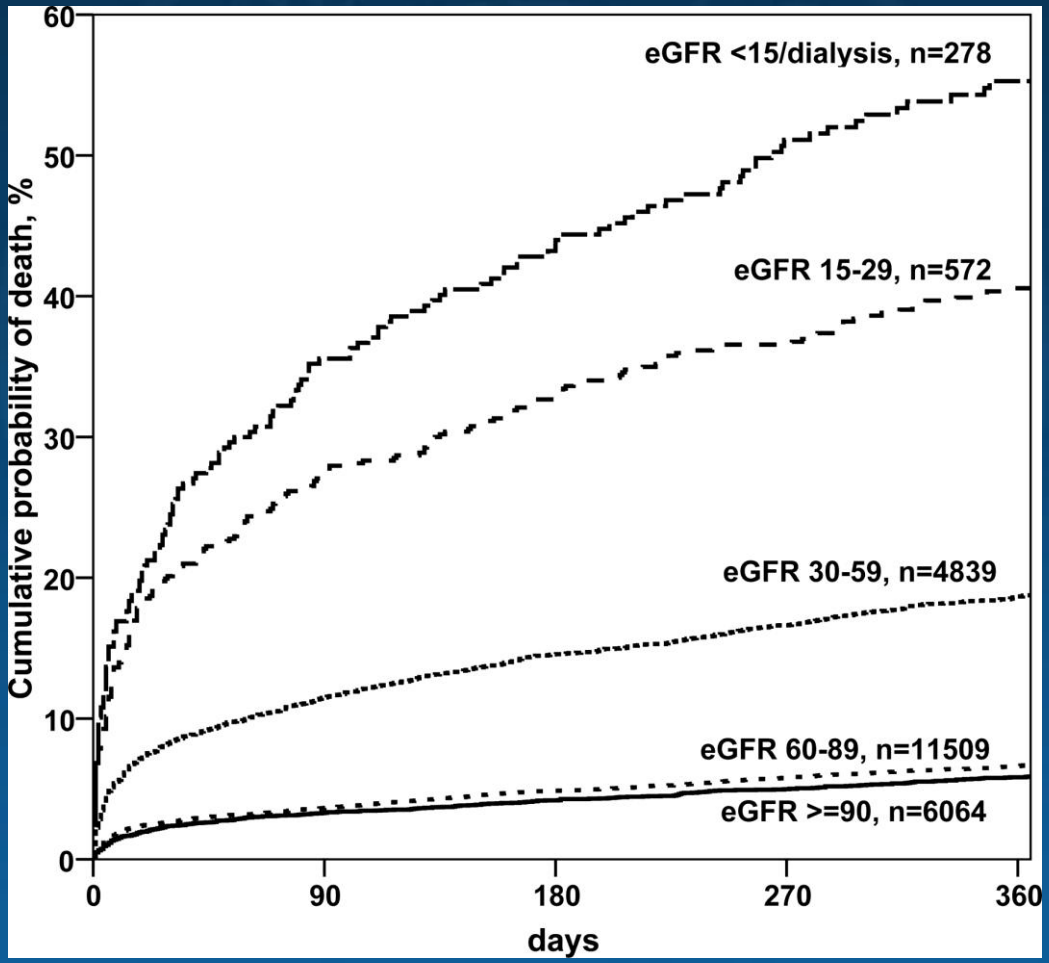
# SWEDEHEART

- Early revascularization and 1 y mortality across renal function stages
- 23,262 NSTEMI pts in Swedish CCU registry
- HR for 1 y mortality, revascularization vs medical treatment:
  - eGFR ≥90: (1.9% vs. 10%) HR: 0.58; p<0.001
  - eGFR 60 to 89: (2.4% vs. 10%) HR: 0.64; p<0.001
  - eGFR 30 to 59: (7% vs. 22%) HR: 0.0.91; p=0.001
  - eGFR 15 to 29: (22% vs. 41%) HR: 0.91; p=0.740
  - eGFR <15/dialysis: (44% vs. 53%) HR: 1.61; p=0.150
- Overall 1 year mortality 36% lower with invasive strategy; HR: 0.64; p<0.001
- Early revascularization associated with improved 1 y survival in NSTEMI pts with mild to moderate CKD
  - benefit less certain with renal failure or on dialysis

Revised 2011

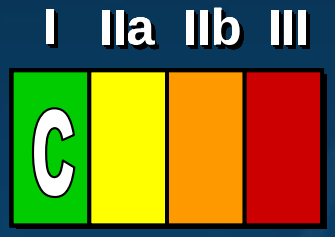
Szummer K, et al. Circulation 2009;120:851–8.

# Kaplan-Meier curve for 1-year survival according to renal function stage (pooled log-rank P<0.001).

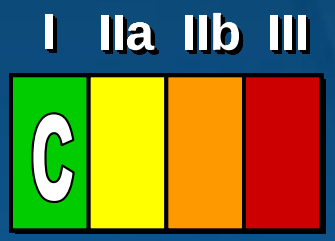



Szummer K et al. Circulation 2009;120:851-858

# Cocaine and Methamphetamine Users

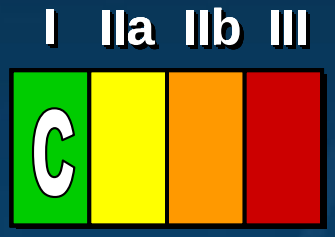



Administration of sublingual or intravenous NTG and intravenous or oral calcium antagonists is recommended for patients with ST-segment elevation or depression that accompanies ischemic chest discomfort after cocaine use.

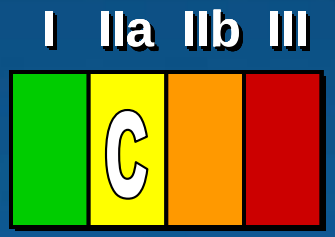



Immediate coronary angiography, if possible, should be performed in patients with ischemic chest discomfort after cocaine use whose ST segments remain elevated after NTG and calcium antagonists; PCI is recommended if occlusive thrombus is detected.

# Cocaine and Methamphetamine Users

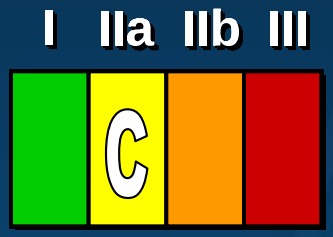



Fibrinolytic therapy is useful in patients with ischemic chest discomfort after cocaine use if ST segments remain elevated despite NTG and calcium antagonists, if there are no contraindications, and if coronary angiography is not possible.

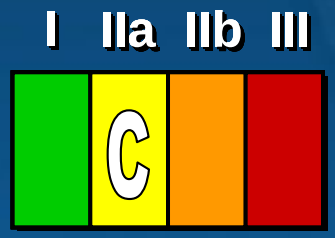



Administration of NTG or oral calcium channel blockers can be beneficial for patients with normal ECGs or minimal ST-segment deviation suggestive of ischemia after cocaine use.

# Cocaine and Methamphetamine Users

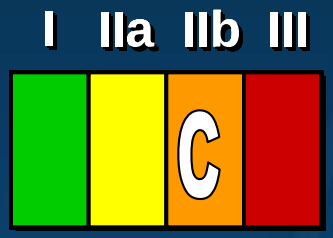



Coronary angiography, if available, is probably recommended for patients with ischemic chest discomfort after cocaine use with ST-segment depression or isolated T-wave changes not known to be previously present and who are unresponsive to NTG and calcium antagonists.



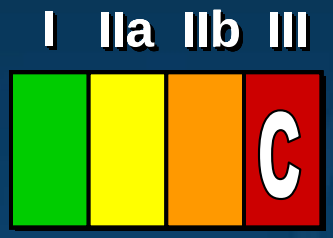

Management of UA/NSTEMI patients with methamphetamine use similar to that of patients with cocaine use is reasonable.

# Cocaine and Methamphetamine Users



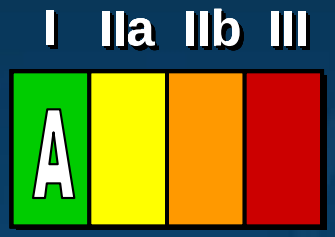

Administration of combined alpha- and beta-blocking agents (e.g., labetalol) may be reasonable for patients after cocaine use with hypertension (systolic BP >150 mm Hg) or those with sinus tachycardia (pulse >100 beats per min) provided that the patient has received a vasodilator, such as NTG or a calcium antagonist, within close temporal proximity (i.e., within the previous hour).

# Cocaine and Methamphetamine Users

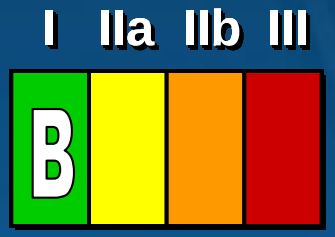



Coronary angiography is not recommended in patients with chest pain after cocaine use without ST-segment or T-wave changes and with a negative stress test and cardiac biomarkers.

# Variant (Prinzmetal's) Angina

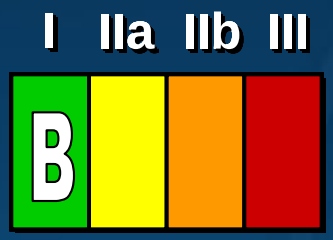



Diagnostic investigation is indicated in patients with a clinical picture suggestive of coronary spasm, with investigation for the presence of transient myocardial ischemia and ST-segment elevation during chest pain.



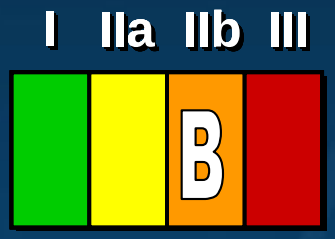

Coronary angiography is recommended in patients with episodic chest pain accompanied by transient ST-segment elevation.

# Variant (Prinzmetal's) Angina

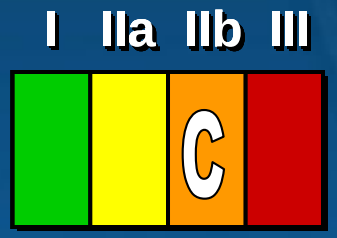



Treatment with nitrates and calcium channel blockers is recommended in patients with variant angina whose coronary angiogram shows no or nonobstructive coronary artery lesions. Risk factor modification is recommended, with patients with atherosclerotic lesions considered to be at higher risk.

# Variant (Prinzmetal's) Angina

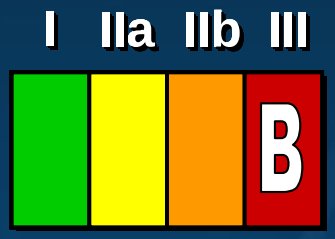



PCI may be considered in patients with chest pain and transient ST-segment elevation and a significant coronary artery stenosis.



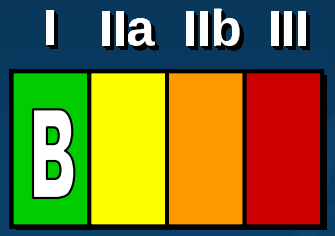

Provocative testing may be considered in patients with no significant angiographic CAD and no documentation of transient ST-segment elevation when clinically relevant symptoms possibly explained by coronary artery spasm are present.

# Variant (Prinzmetal's) Angina

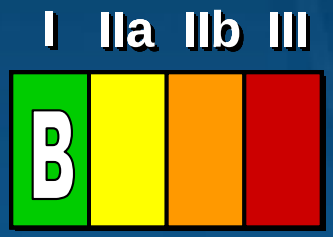



Provocative testing is not recommended in patients with variant angina and high-grade obstructive stenosis on coronary angiography.

# Cardiovascular Syndrome “X”

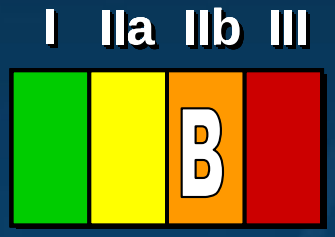



Medical therapy with nitrates, beta blockers, and calcium channel blockers, alone or in combination, is recommended in patients with cardiovascular syndrome X.

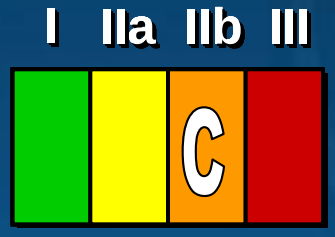



Risk factor reduction is recommended in patients with cardiovascular syndrome X.

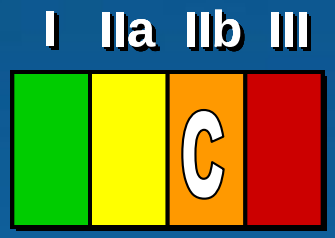
# Cardiovascular Syndrome “X”




Intracoronary ultrasound to assess the extent of atherosclerosis and rule out missed obstructive lesions may be considered in patients with syndrome X.

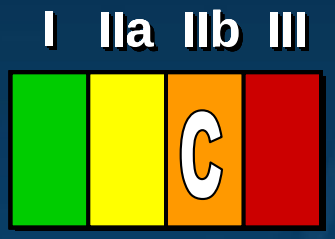



If no ECGs during chest pain are available and coronary spasm cannot be ruled out, coronary angiography and provocative testing with acetylcholine, adenosine, or methacholine and 24-h ambulatory ECG may be considered.

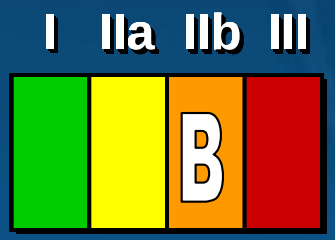



If coronary angiography is performed and does not reveal a cause of chest discomfort, and if syndrome X is suspected, invasive physiological assessment (i.e., coronary flow reserve measurement) may be considered.

# Cardiovascular Syndrome “X”

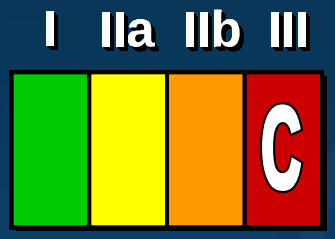



Imipramine or aminophylline may be considered in patients with syndrome X for continued pain despite implementation of Class I measures.



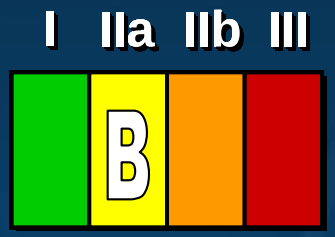

Transcutaneous electrical nerve stimulation and spinal cord stimulation for continued pain despite the implementation of Class I measures may be considered for patients with syndrome X.

# Cardiovascular Syndrome “X”




Medical therapy with nitrates, beta blockers, and calcium channel blockers for patients with noncardiac chest pain is not recommended.

# Quality of Care and Outcomes for Acute Coronary Syndromes





It is reasonable for clinicians and hospitals that provide care to patients with UA/NSTEMI to participate in a standardized quality-of-care data registry designed to track and measure outcomes, complications, and adherence to evidence-based processes of care and quality improvement for UA/NSTEMI.