The Updated Evidence-based Guidelines for the Use of Antiplatelet Therapies in ACS

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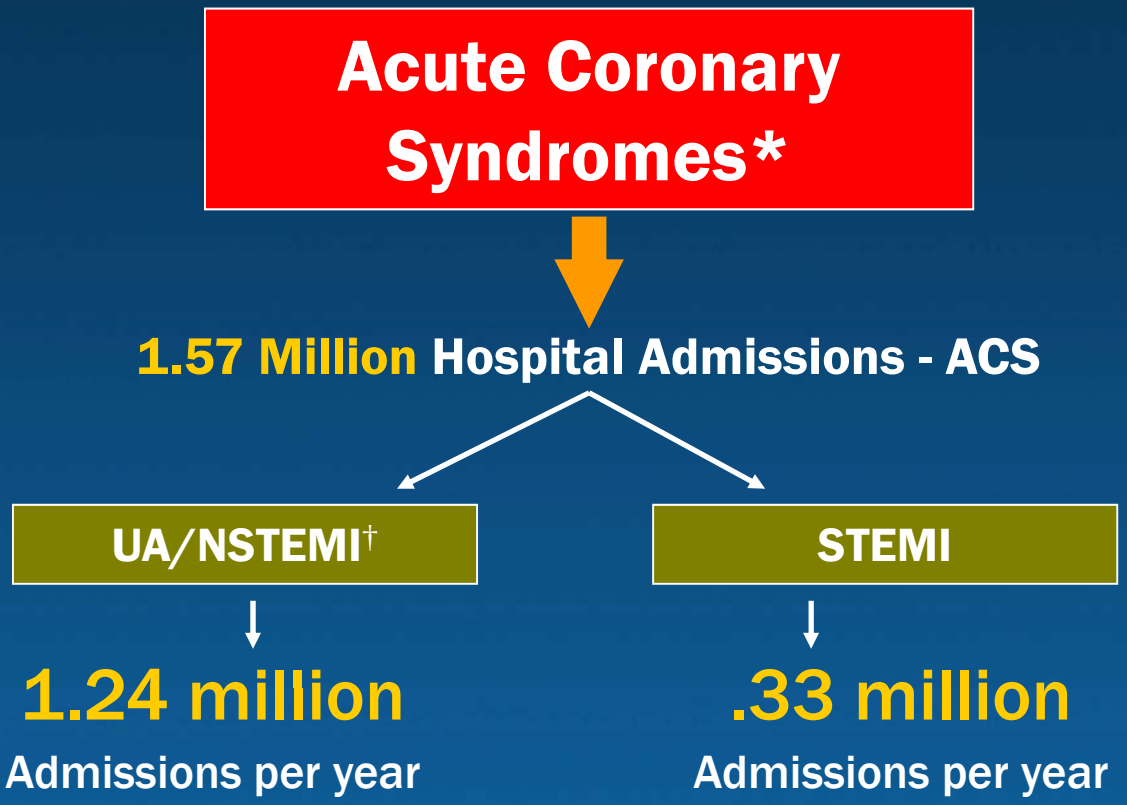
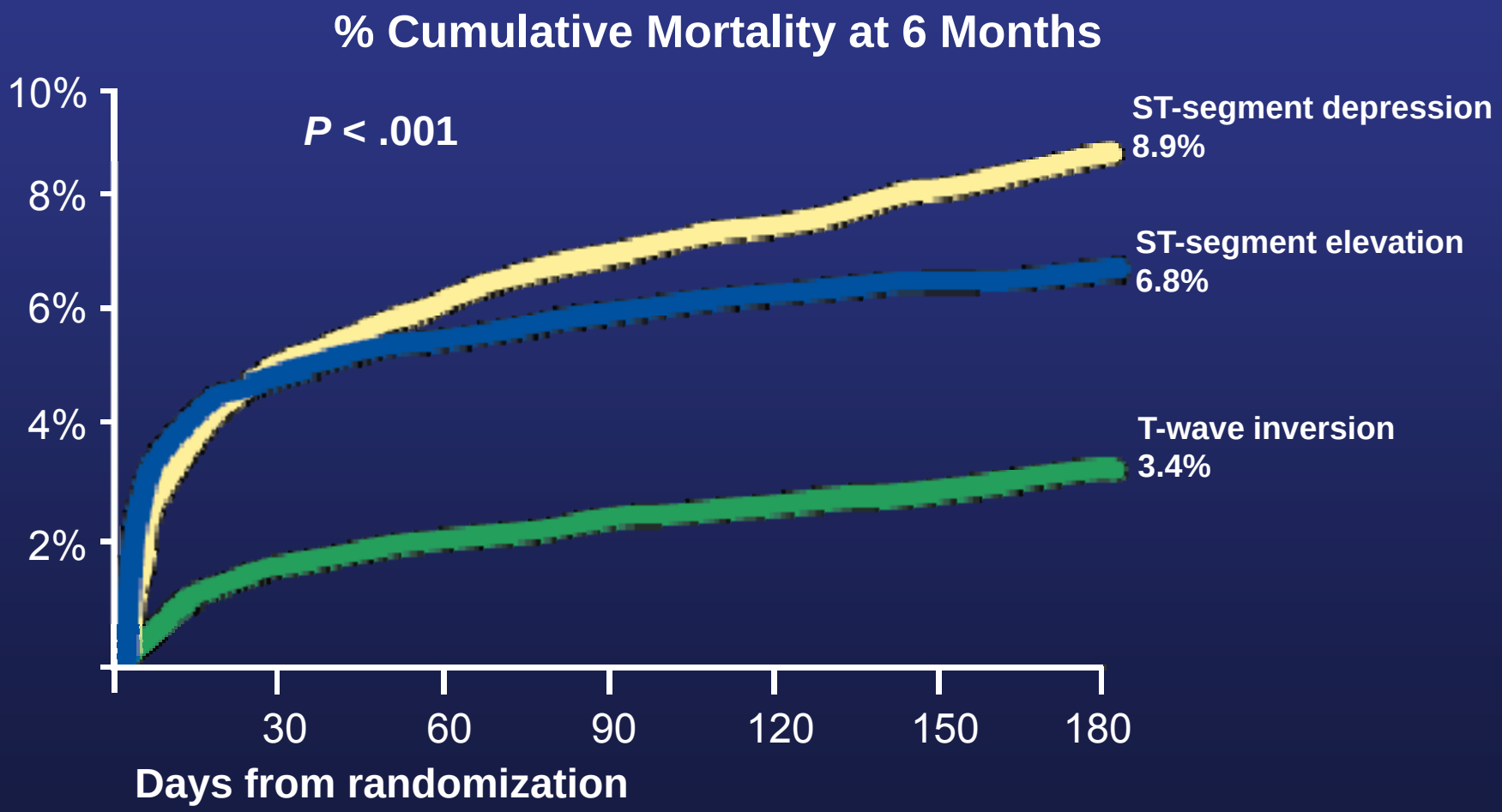
Hospitalizations in the U.S. Due to Acute Coronary Syndromes (ACS)



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

ACC/AHA 2009 Joint STEMI/PCI Guidelines Focused Update

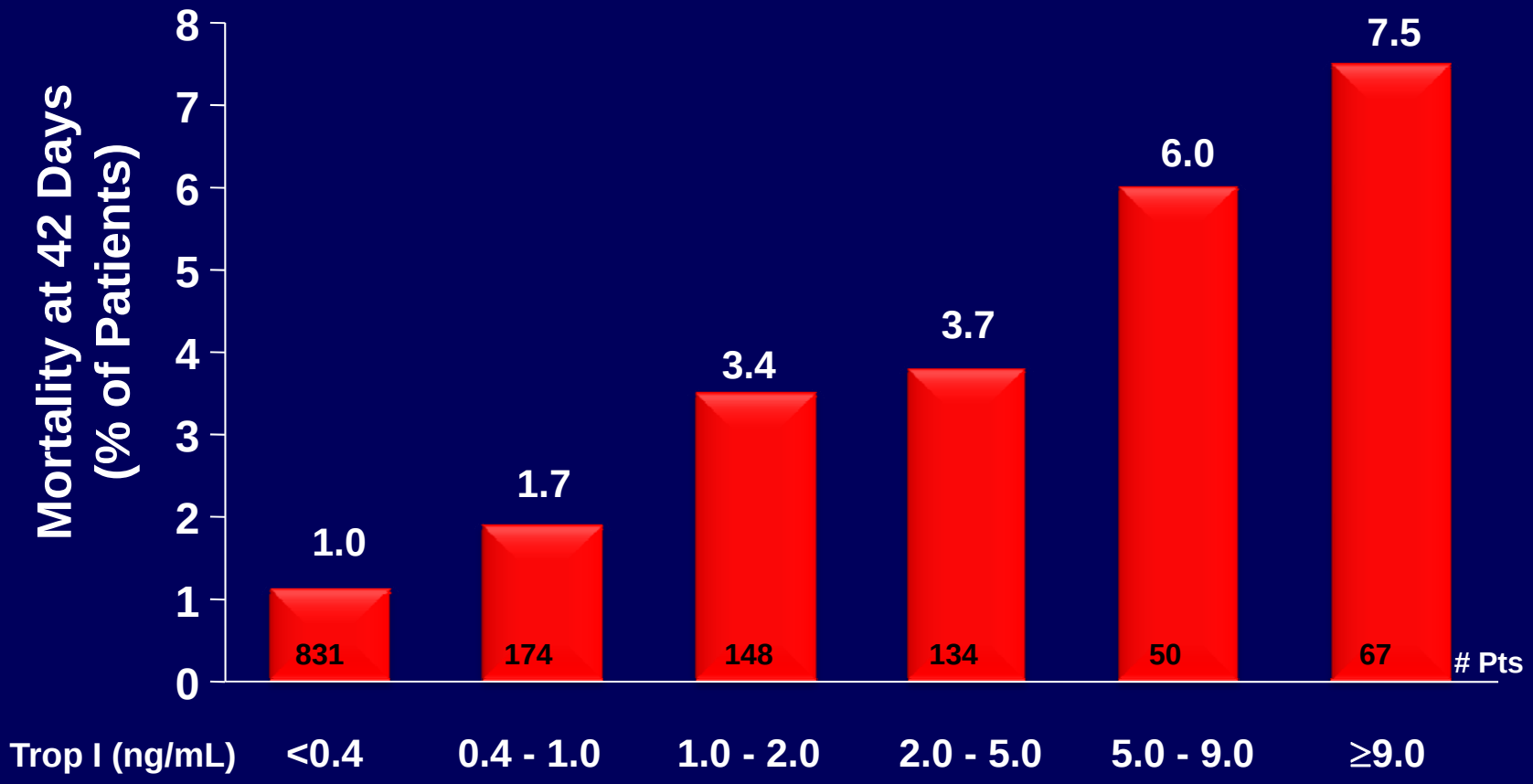
ST-segment Depression Predicts Higher Risk of Mortality in ACS



The GUSTO IIb trial. Savonitto S. *J Am Med Assoc.* 1999; 281: 707-711.

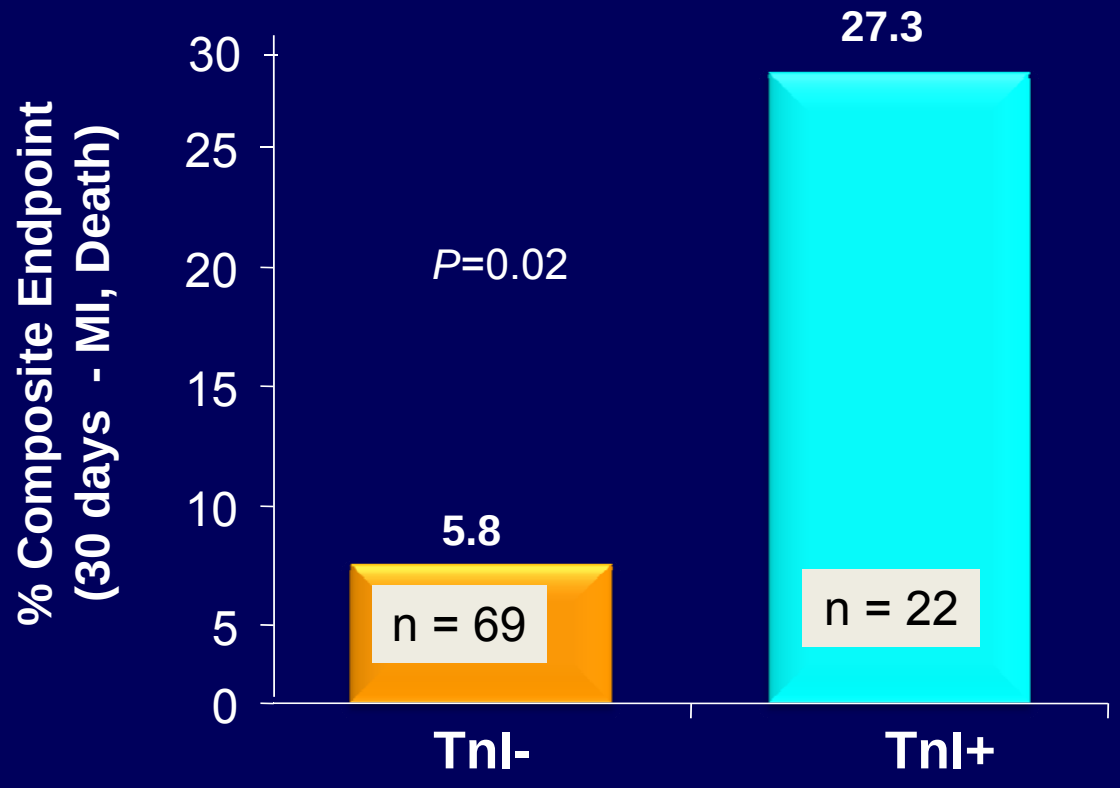
AGXC-0015-SK:
AGG-2008-IROKO-0024-SS RESUB

42-day Mortality Stratified by Troponin I Levels at Entry: TIMI IIIB



Antman et al. *N Engl J Med*. 1996;335:1342-1349.

Cardiac Endpoints in Unstable Angina
Troponin I in CK-MB Negative Patients with ECG Changes



Adapted from Galvani M, et al. *Circulation*. 1997; 95:2053–2059.

Who is At the Highest Risk for Ischemia?

- ACS Patients “At-Risk” for Ischemia
  - Troponin Positive (T or I)
  - ST Segment Deviation
  - Angina (resting, new-onset, or accelerating)
  - Previous CAD
  - Diabetics

GP IIb/IIIa Inhibitors should be part of Appropriate ACS treatment pathways

Who is At-Risk for Hemorrhage?

- ACS Patients who are at-risk for ischemic events but are also at-risk for hemorrhagic complications include
  - The Elderly
  - Renally Impaired
  - Female
  - Low Body Weight
- All patients should be stratified for hemorrhagic risk
- Contraindications for bleeding need to be addressed

Patients with a high risk for bleed should be treated cautiously with GP IIb/IIIa Inhibitors

TIMI Risk Score for UA/NSTEMI

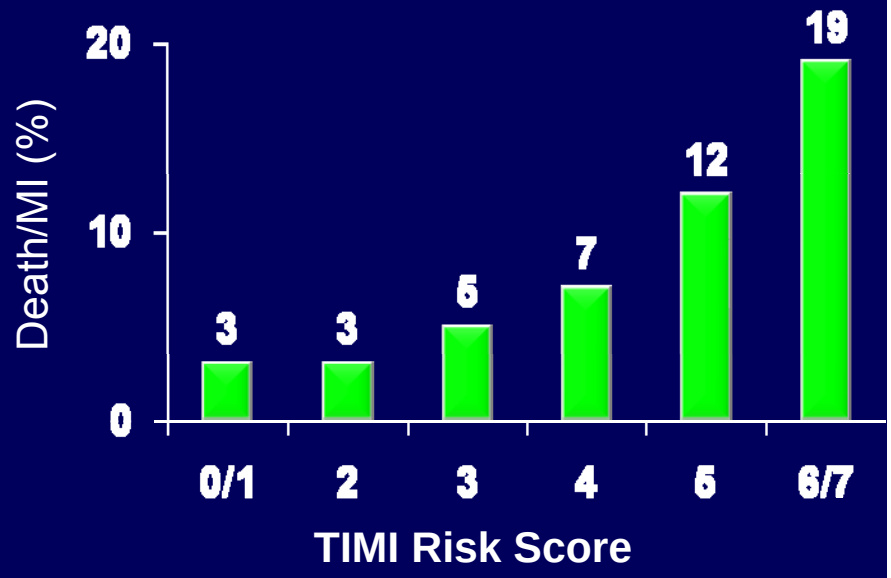
HISTORICAL	POINTS
Age ≥ 65	1
≥ 3 CAD risk factors (FHx, HTN, ↑ chol, DM, active smoker)	1
Known CAD (stenosis ≥ 50%)	1
ASA use in past 7 days	1
PRESENTATION	
Recent (≤24H) severe angina	1
↑ cardiac markers	1
ST deviation ≥ 0.5 mm	1

RISK SCORE = Total Points (0 - 7)

Antman et al. *JAMA* 2000; 284: 835 - 842

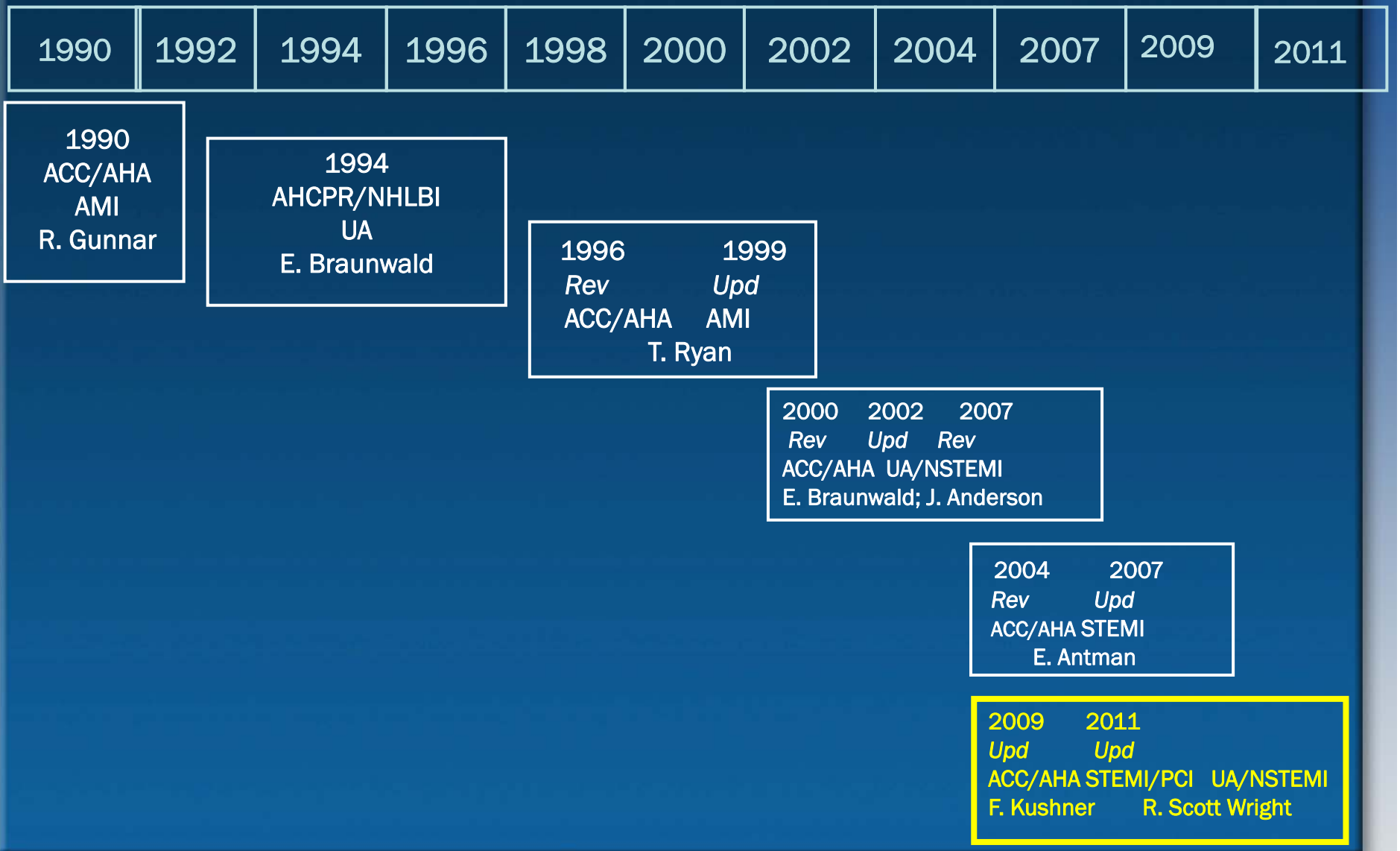
For more info go to www.timi.org

RISK OF CARDIAC EVENTS (%) BY 14 DAYS IN TIMI 11B*

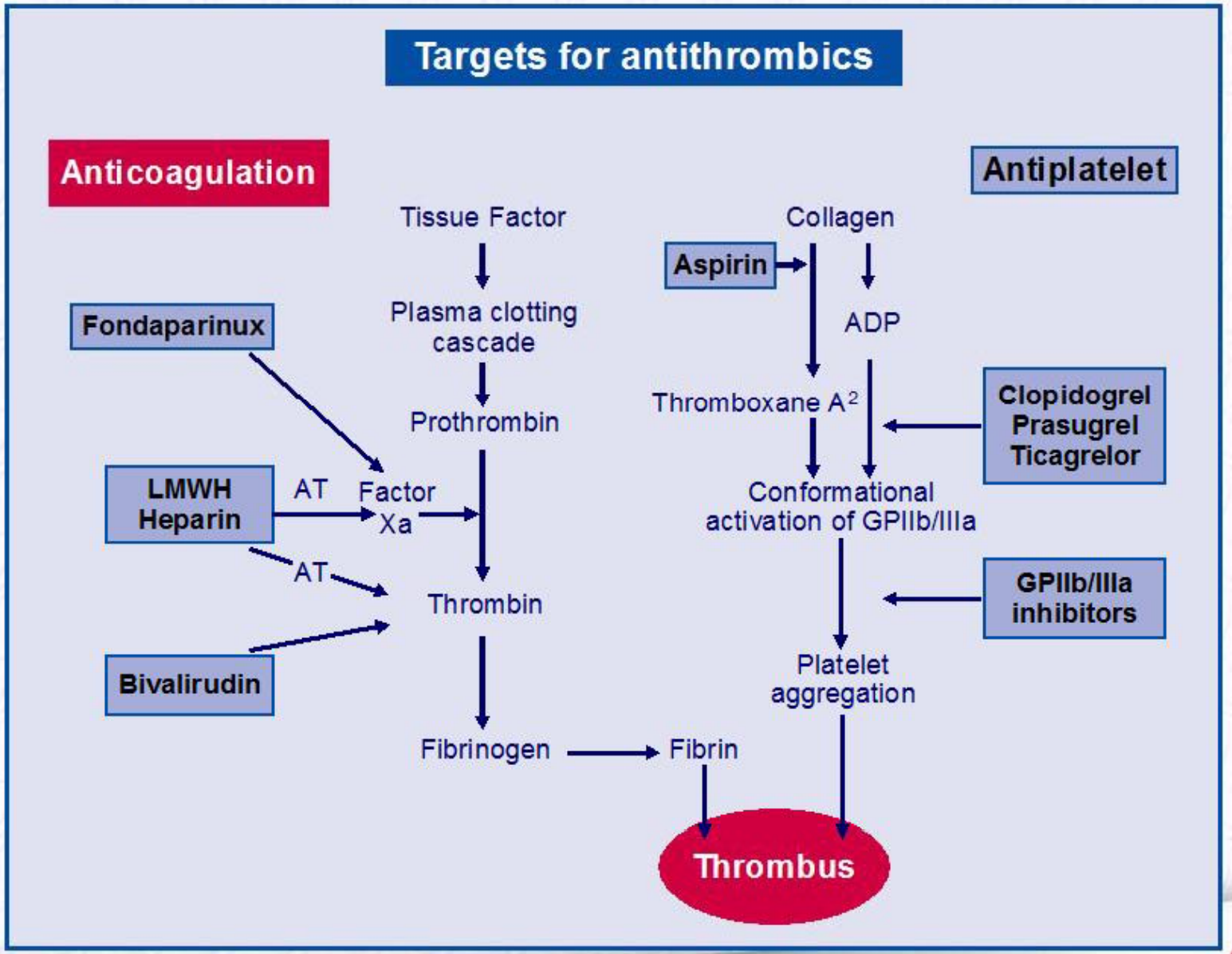


*Entry criteria: UA or NSTEMII defined as ischemic pain at rest within past 24H, with evidence of CAD (ST segment deviation or +marker)

Evolution of Guidelines for ACS



Targets for antithrombics



European Heart Journal (2011) 32:2999–3054
doi:10.1093/eurheartj/ehr236

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$P2Y_{12}$ Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolization	Prodrug, not limited by metabolization	Active drug
Onset of effect	2-4 h	30 min	30 min
Duration of effect	3-10 days	5-10 days	3-4 days
Withdrawal before major surgery	5 days	7 days	5 days

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2011 ACCF/AHA UA/NSTEMI Guideline Focused Update

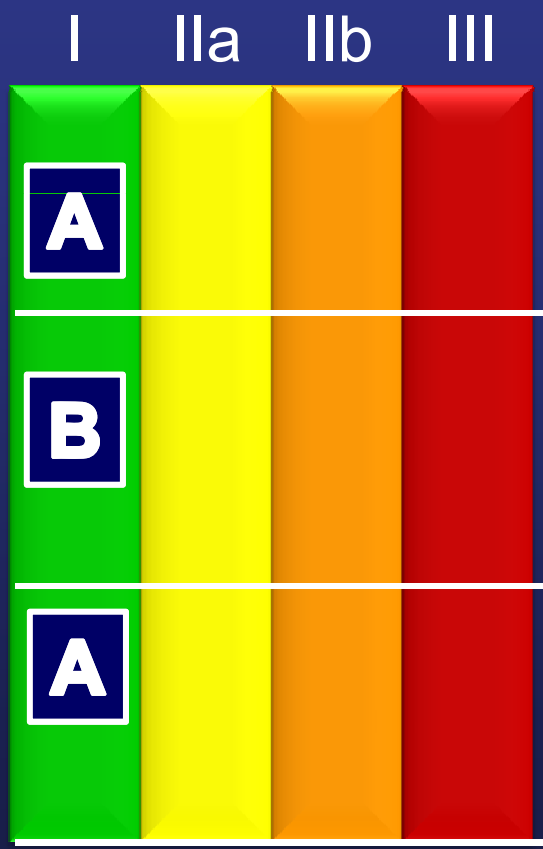
ACC/AHA : Classification of Recommendations and Level of Evidence

I	IIa	IIb	III
Benefit >>> Risk Procedure/Rx **SHOULD** be performed/administered	***Benefit >>Risk*** *Addit. studies w/ focused objectives needed* **IT IS REASONABLE** to perform procedure/ administer Rx	***Benefit ≥ Risk*** *Addit. studies w/ broad objectives needed; addit. Registry data would be helpful* Procedure/Rx **MAY BE CONSIDERED**	***Risk ≥ Benefit*** *No addit. studies needed* Procedure/Rx should NOT be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**

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

Antman EM, et al. *J Am Coll Cardiol*. 2008 ;51(2):210-47.

ACC/AHA NSTEMI: Early hospital care anti-platelet therapy



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

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

Patients with definite UA/NSTEMI at medium or high risk and in whom an initial invasive strategy is selected should receive dual-antiplatelet therapy on presentation

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

ACC/AHA NSTEMI: ASA + ?(Class I)

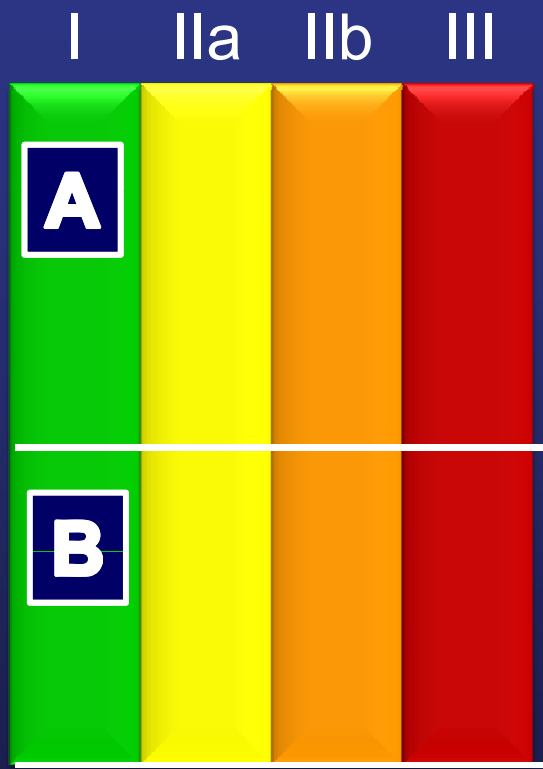
The choice of a second antiplatelet therapy to be added to ASA on presentation includes 1 of the following:

- Before PCI:
  - Clopidogrel *(Level of Evidence: B); or*
  - An IV GP IIb/IIIa inhibitor *(Level of Evidence: A) IV eptifibatide or tirofiban are* the preferred GP IIb/IIIa inhibitors.
- At the time of PCI:
  - Clopidogrel if not started before PCI *(Level of Evidence: A); or*
  - Prasugrel† *(Level of Evidence: B); or*
  - An IV GP IIb/IIIa inhibitor. *(Level of Evidence: A)*

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

ACC/AHA NSTEMI: Early hospital care anti-platelet therapy

New recommendation



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

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.

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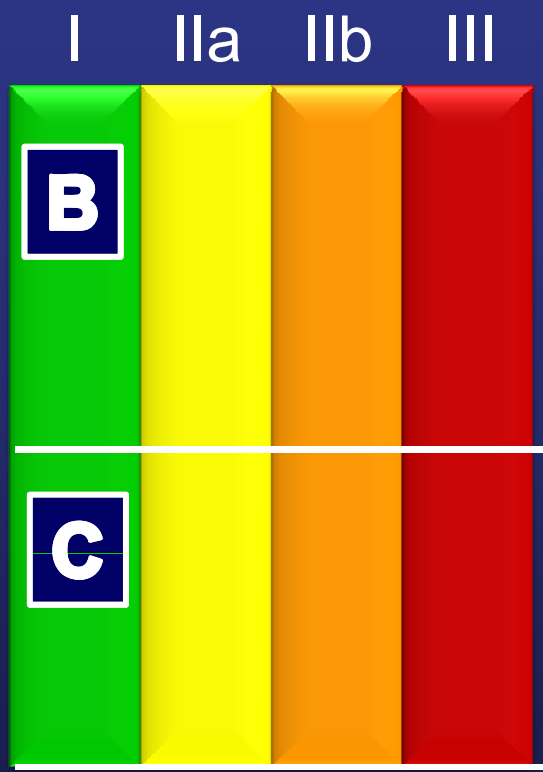
ACC/AHA NSTEMI: Early hospital care anti-platelet therapy

New recommendation



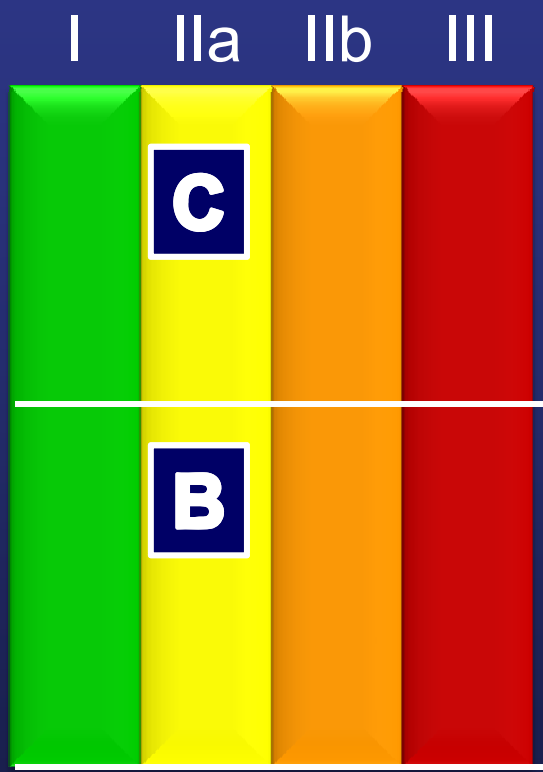
The duration and maintenance dose of thienopyridine therapy should be as follows:

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.

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

ACC/AHA NSTEMI: Early hospital care anti-platelet therapy

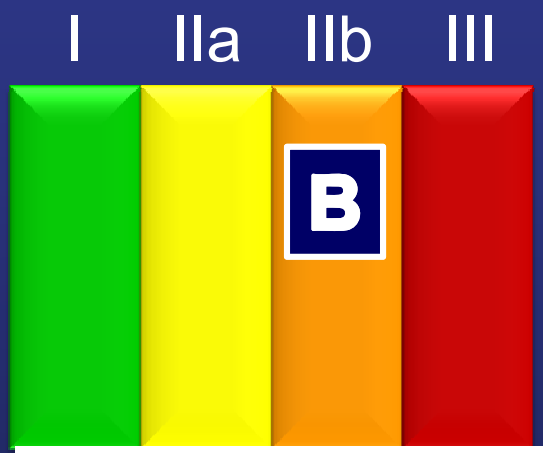


For UA/NSTEMI patients in whom an initial conservative strategy is selected and who have recurrent ischemic discomfort with clopidogrel, ASA, and anticoagulant therapy, **it is reasonable to add a GP IIb/IIIa inhibitor before diagnostic angiography**

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

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

ACC/AHA NSTEMI: Early hospital care anti-platelet 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

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

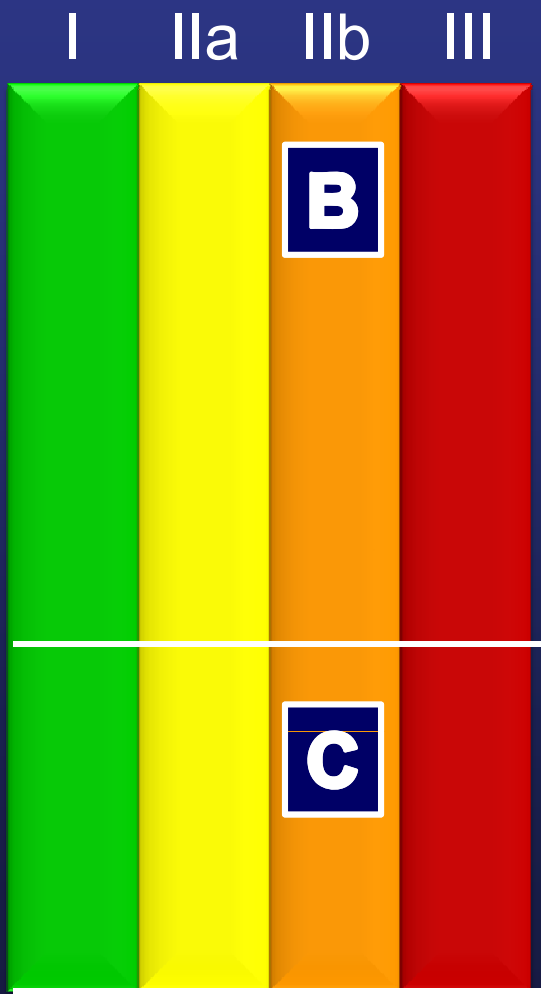
ACC/AHA NSTEMI: Early hospital care anti-platelet therapy

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

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

ACC/AHA NSTEMI: Early hospital care anti-platelet therapy

New recommendation



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

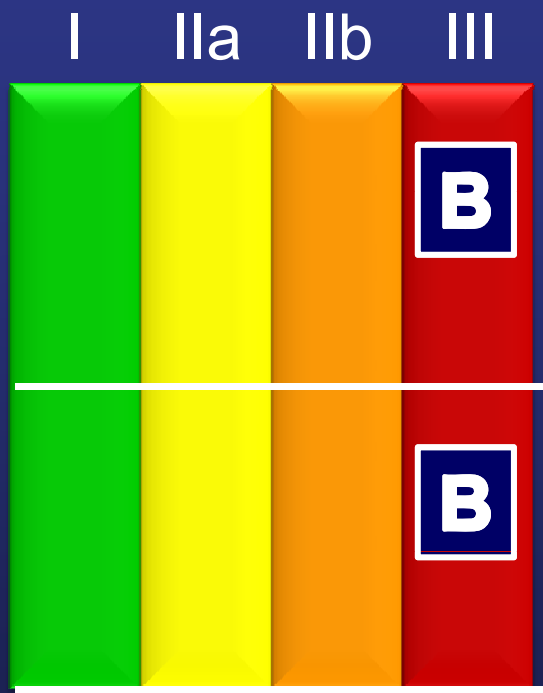
In patients with definite UA/NSTEMI undergoing PCI as part of an early invasive strategy, the use of a loading dose of clopidogrel of 600 mg, *followed by a higher maintenance dose of 150 mg daily for 6 days, then 75 mg daily may be reasonable* in patients not considered at high risk for bleeding

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

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

ACC/AHA NSTEMI: Early hospital care anti-platelet therapy

New recommendation

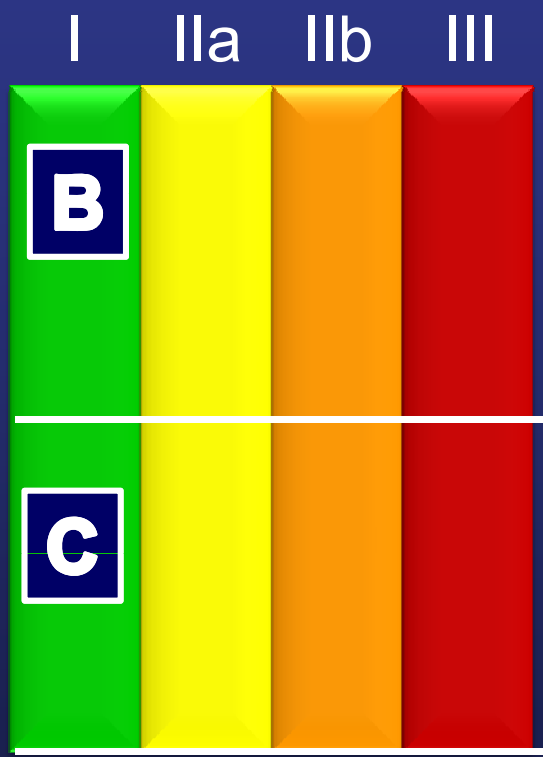


In UA/NSTEMI patients who are at low risk for ischemic events (e.g., TIMI risk score 2) or at high risk of bleeding and who are already receiving ASA and clopidogrel, upstream GP IIb/IIIa inhibitors are not recommended

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

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

ACC/AHA NSTEMI: Additional management of anti-platelet & anti-coagulation therapy

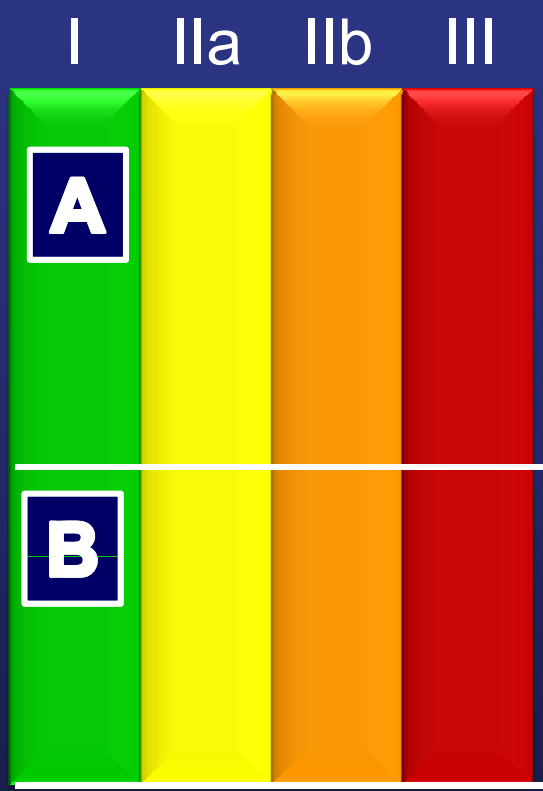


In patients taking a thienopyridine in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect .*The period of withdrawal should be* at least 5 days in patients receiving clopidogrel

The period of withdrawal should be at least 7 days in patients receiving prasugrel* unless the need for revascularization and/or the net benefit of the thienopyridine outweighs the potential risks of excess bleeding .

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

ACC/AHA NSTEMI: Additional management of anti-platelet & anti-coagulation therapy

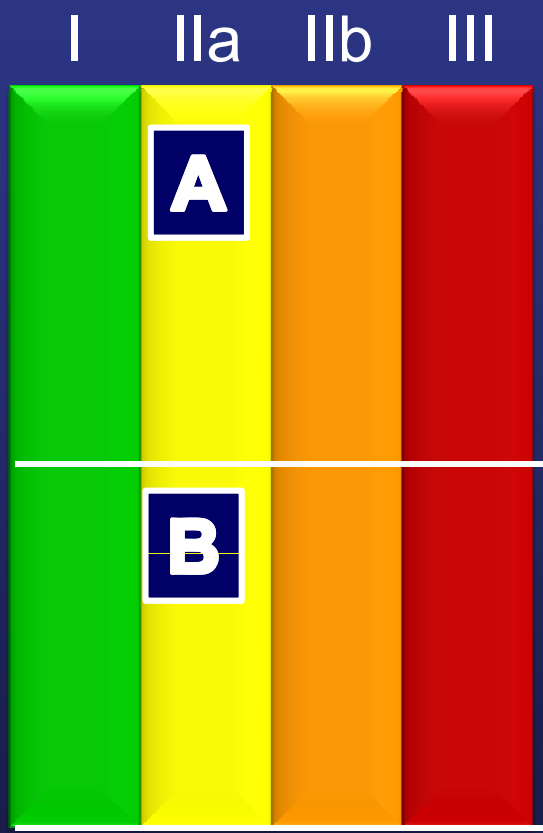


For UA/NSTEMI patients in whom PCI has been selected as a postangiography management strategy, the instructions noted below should be followed:
a. Continue ASA
b. Administer a loading dose of a thienopyridine if not started before diagnostic angiography

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

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

ACC/AHA NSTEMI: Additional management of anti-platelet & anti-coagulation therapy



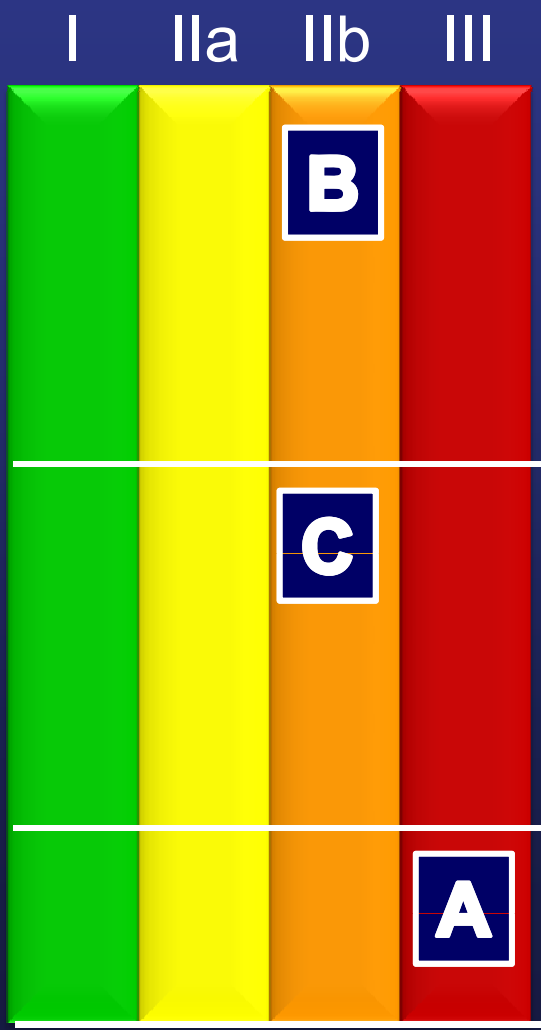
For UA/NSTEMI patients in whom PCI has been selected as a postangiography management strategy, **it is reasonable to administer an IV GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban) if not started before diagnostic angiography**, particularly for *troponin-positive and/or other high-risk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

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

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

ACC/AHA NSTEMI: Additional management of anti-platelet & anti-coagulation therapy

New recommendation



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

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

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

ACC/AHA NSTEMI: Initial invasive versus initial conservative strategies

An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is indicated in UA/NSTEMI patients who have refractory angina or hemodynamic or electrical instability (without serious comorbidities or contraindications to such procedures

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

An early invasive strategy is not recommended in patients with extensive comorbidities , in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization

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

2011 ESC NSTEMI Guideline Focused Update

Recommendations for oral antiplatelet agents (1)

Recommendations	Class	Level
Aspirin should be given to all patients without contraindications at an initial loading dose of 150-300 mg, and at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors *(H. elicobacter pylori* infection, age ≥ 65 years, concurrent use of anticoagulants or steroids).	I	A
Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated.	I	C
Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.	I	B

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Recommendations for oral antiplatelet agents (2)

Recommendations	Class	Level
Clopidogrel (300 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A
A 600 mg loading dose of clopidogrel (or a supplementary 300 mg dose at PCI following an initial 300 mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B
A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.	IIa	B
Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.	IIb	B
Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used.	IIb	B
In patients pre-treated with $P2Y_{12}$ inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered.	IIa	C
Ticagrelor or clopidogrel should be considered to be (re-)started after CABG surgery as soon as considered safe.	IIa	B
The combination of aspirin with an NSAID (selective COX-2 inhibitors and non-selective NSAID) is not recommended.	III	C

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Recommendations for GPIIb/IIIa receptor inhibitors

Recommendations	Class	Level
The choice of combination of oral antiplatelet agents, a GPIIb/IIIa receptor inhibitor, and anticoagulants should be made in relation to the risk of ischaemic and bleeding events.	I	C
Among patients who are already treated with DAPT, the addition of a GPIIb/IIIa receptor inhibitor for high-risk PCI (elevated troponin, visible thrombus) is recommended if the risk of bleeding is low.	I	B
Eptifibatide or tirofiban added to aspirin should be considered prior to angiography in high-risk patients not preloaded with $P2Y_{12}$ inhibitors.	IIa	C
In high-risk patients eptifibatide or tirofiban may be considered prior to early angiography in addition to DAPT, if there is ongoing ischaemia and the risk of bleeding is low.	IIb	C
GPIIb/IIIa receptor inhibitors are not recommended routinely before angiography in an invasive treatment strategy.	III	A
GPIIb/IIIa receptor inhibitors are not recommended for patients on DAPT who are treated conservatively.	III	A

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Upstream vs. procedural initiation of GPIIb/IIIa receptor inhibitors

- EARLY-ACS trial demonstrated no advantage with a routine upstream use of eptifibatide.
- Upstram use of GPIIb/IIIa receptor inhibitors may be considered if there is active ongoing ischemia among high risk patients or where DAPT is not feasible.
- Patients who receive initial treatment with eptifibatide or tirofiban before angiography should be maintained on the same drug during and after PCI

Combination of GPIIb/IIIa inhibitors with aspirin and a P2Y12 inhibitor

- In the ISAR-REACT-2 Trial, 30day composite endpoint of death, MI, or uTVR occurred significantly less frequently in abciximab-treated patients vs. placebo (8.9% vs. 11.9%, p=0.03)

- The effect was more pronounced in certain pre-specified subgroups, particularly troponin + patients.(13.1% vs. 18.3%, p=0.02)

Combination of GPIIb/IIIa inhibitors with aspirin and a P2Y12 inhibitor

- It is reasonable to combine a GPI with ASA and a P2Y12 inhibitor for patients with NSTE-ACS undergoing PCI with a high risk of procedural MI and without a high risk of bleeding.