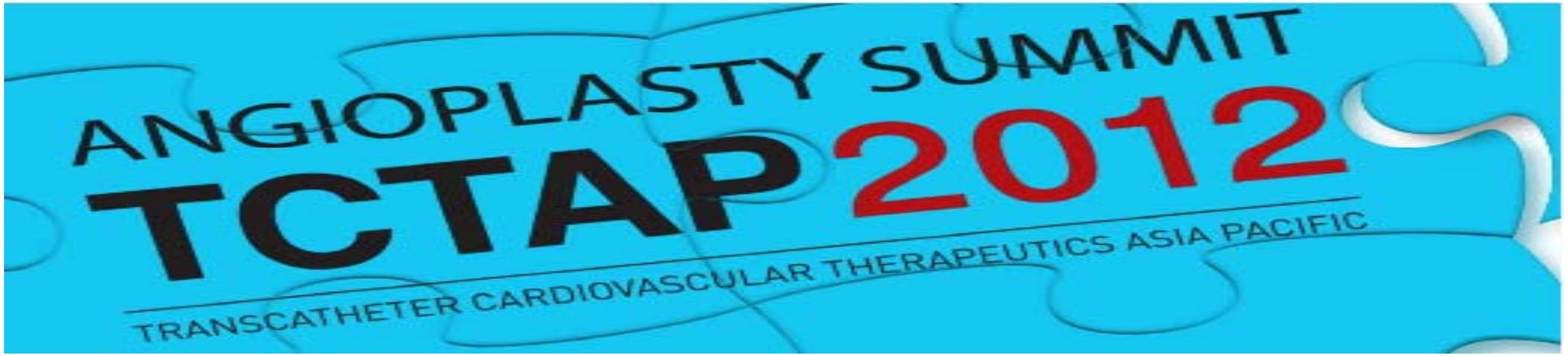

Update on ACS/NSTEMI Guidelines: Treatment Strategies and Pharmacology

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Lenox Hill Heart & Vascular Institute

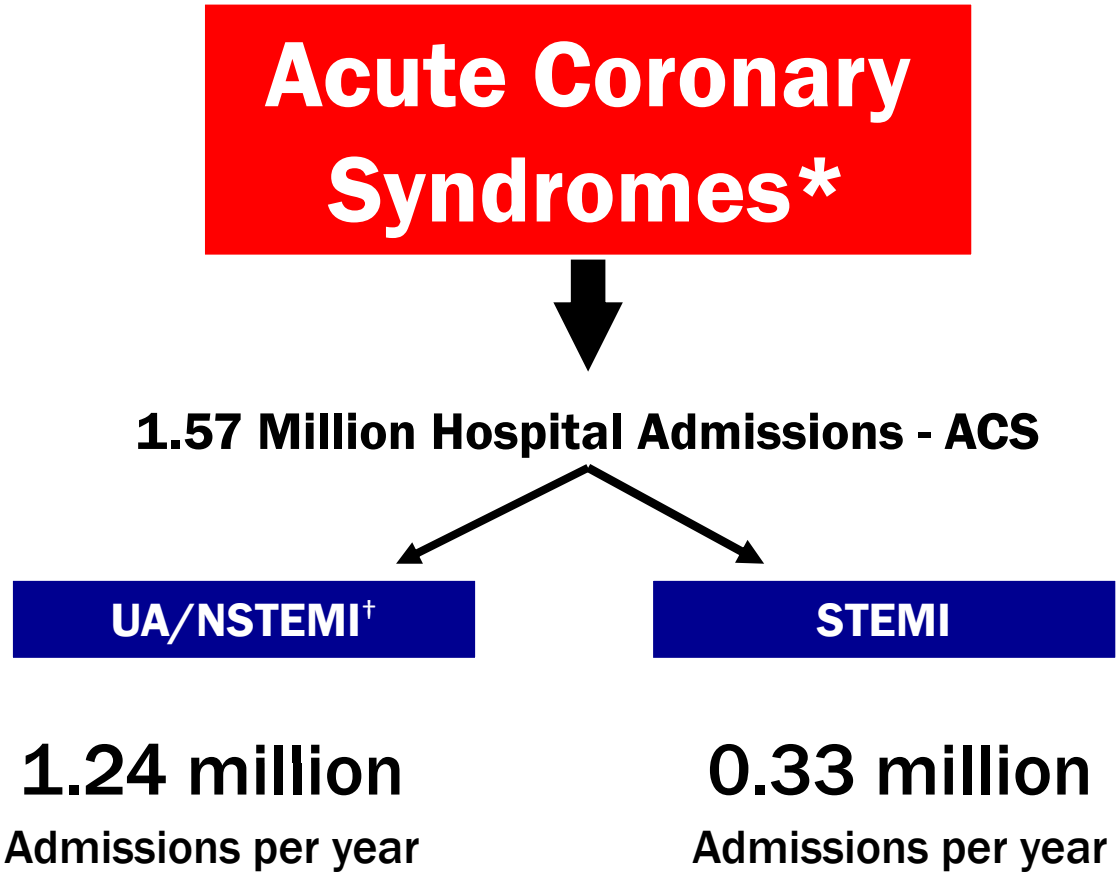
DISCLOSURES

None relevant to this talk

WHAT'S NEW IN THE GUIDELINES?

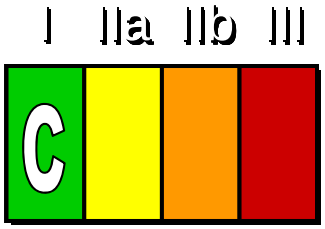
- Background and risk stratification
- Thienopyridines
- Chronic Kidney Disease
- Quality of care and outcomes

Hospitalizations in the U.S. Due to ACS

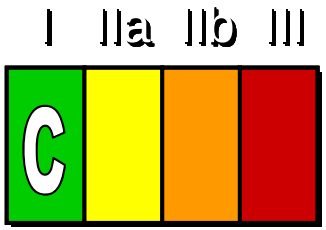


*Primary and secondary diagnoses. †About 0.57 million NSTEMI and 0.67 million UA. Heart Disease and Stroke Statistics – 2007 Update. Circulation 2007; 115:69–171.

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.

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

Global Registry of Acute Coronary Events

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.

THIENOPYRIDINES

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)**

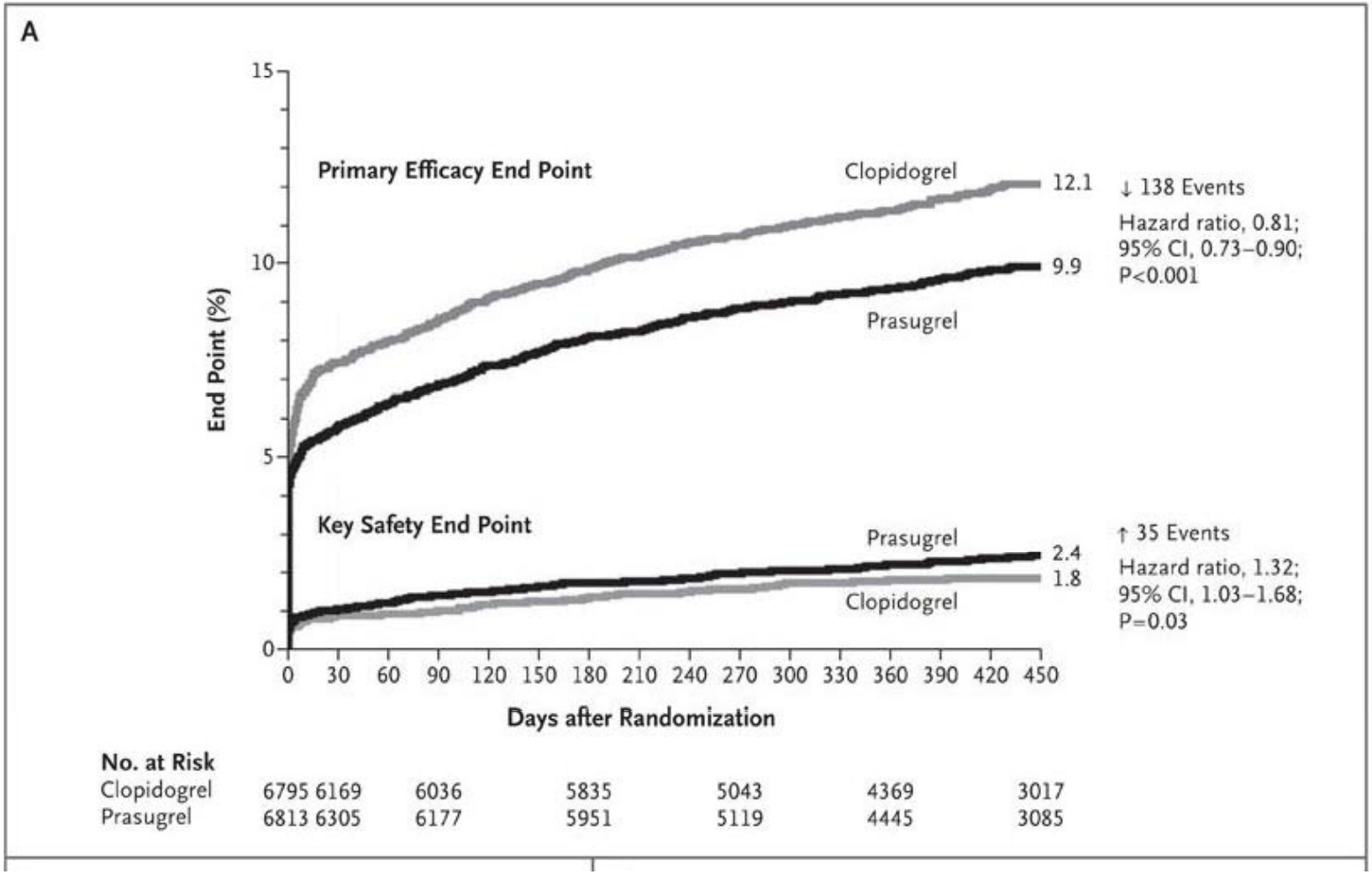
Wiviott SD, et al. for TRITON-TIMI 38 Investigators. NEJM 2007;357:2001–15.

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
- **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**
- **Net clinical benefit - primary efficacy and safety EP rate of 13.9% in the CPL group vs 12.2% in the PSL group (HR:0.87: 95% CI: 0.79to 0.95; p=0.004)**.

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.

TRITON-TIMI 38

Post hoc analysis suggested there were 3 groups of ACS pts who did not have a favorable net clinical benefit (net harm)

- **Patients with hx of CVA or TIA** (HR:1:54; 95% CI:1.02 - 2.32; p=0.04
- **Patients ≥ 75 yo** (HR: 0.99, 95% CI:0.81-1.21;p+0.92)
- **Patient with body weight<60kg** (HR: 1.03, 95% CI:0.69-1.53; p=0.89)

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

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)

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

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)

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

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

Revised 2011

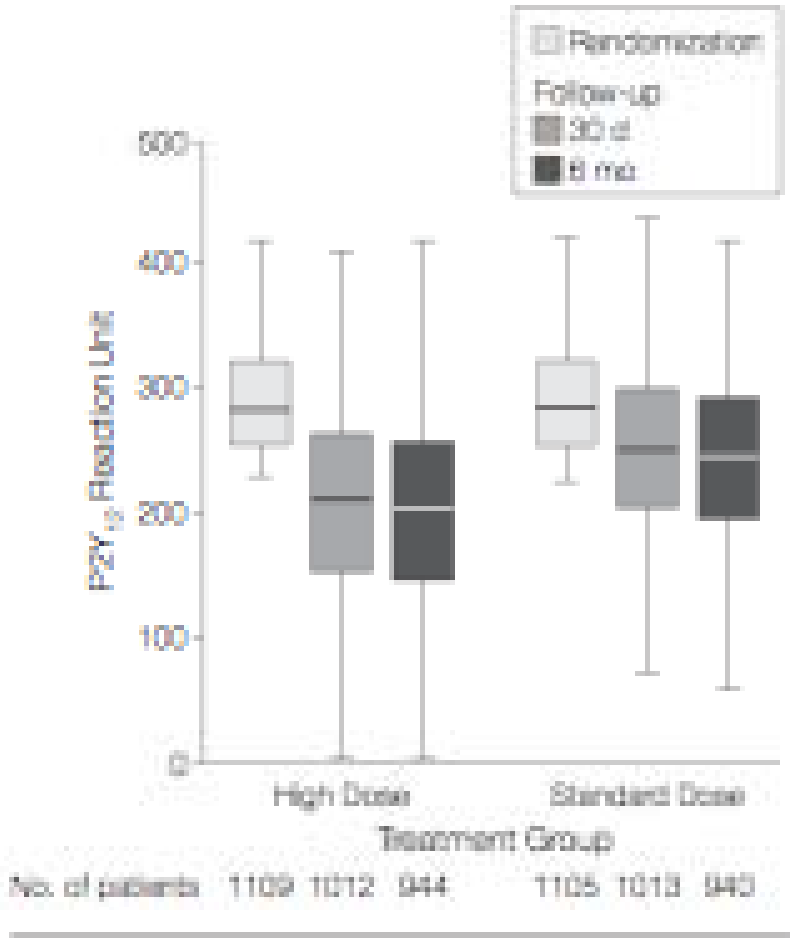
GRAVITAS TRIAL

Guaging Responsiveness with a Verify Now Assay– Impact on Thrombosis and safety

- Objective – To compare the effect of high dose vs standard dose clopidogrel in pts with high on treatment platelet reactivity post PCI
- Randomized, double blind active control trial 2214 pts
- High dose clopidogrel vs standard dose for 6 mo
- Primary EP CV death, non-fatal MI, stent thrombosis
- Primary safety EP major or minor bleeding (GUSTO definition)

Price et al. *JAMA*;305;11,197;2011, 1097-1016

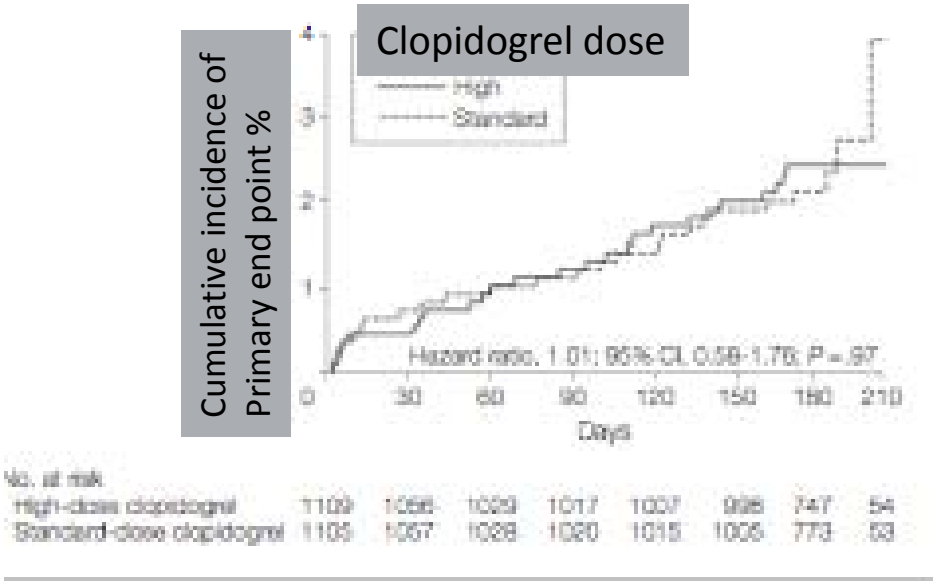
GRAVITAS TRIAL



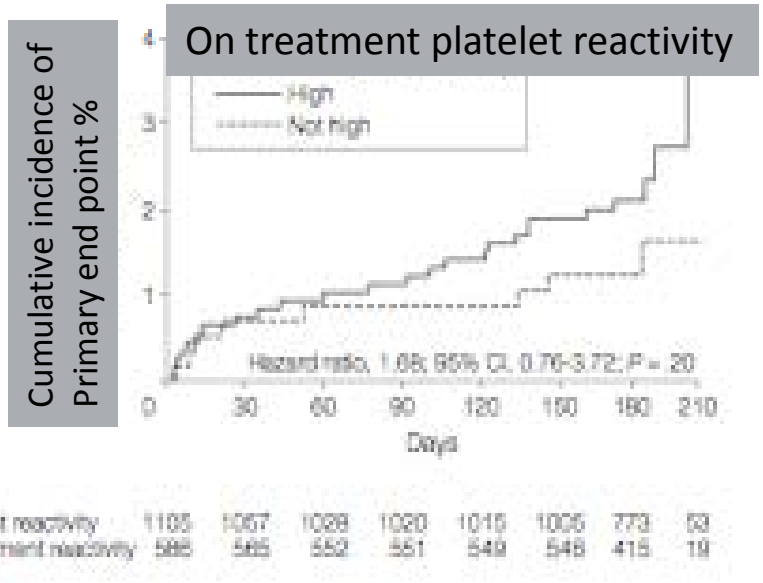
Price et al. *JAMA*;305;11,197;2011, 1097-1016

GRAVITAS TRIAL

Patients with high-on treatment Plt reactivity Receiving high or standard dose clopidogrel



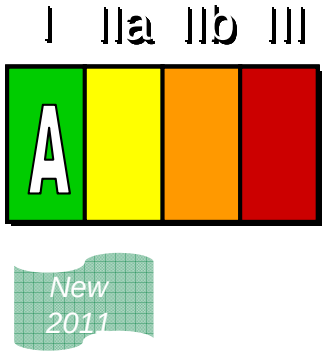
Patients w and without high on-treatment plt reactivity receiving standard dose clopidogrel



Conclusions: Among patients with high on-treatment reactivity after PCI with DES, the use of high-dose clopidrogrel compared wth standard-dose clopidogrel did not reduce the Incidence of death from CV causes, non-fatal MI or stent thrombosis

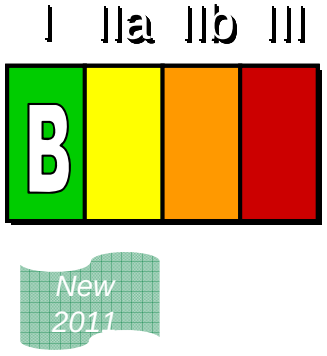
Price et al. *JAMA*;305;11,197;2011, 1097-1016

Initial Conservative Strategy: Antiplatelet Therapy



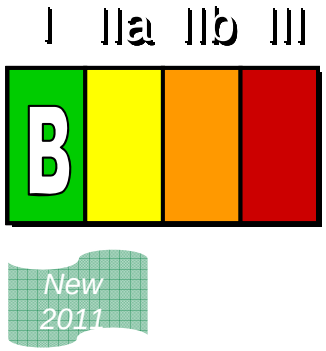
A loading dose of thienopyridine is recommended for UA/NSTEMI patients for whom PCI is planned. Regimens should be 1 of the following:

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



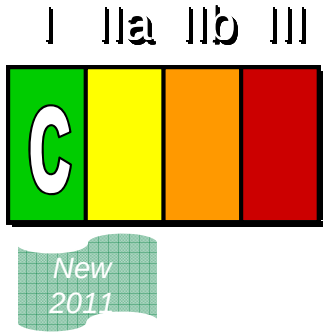
b. Prasugrel† 60 mg should be given promptly and no later than 1 hour after PCI once coronary anatomy is defined and a decision is made to proceed with PCI.

Initial Conservative Strategy: Antiplatelet Therapy



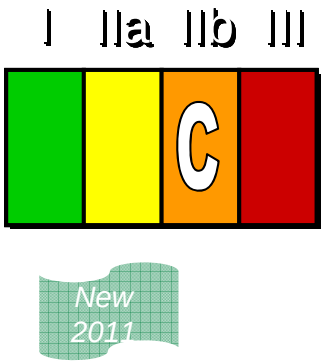
The duration and maintenance dose of thienopyridine therapy should be as follows:

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



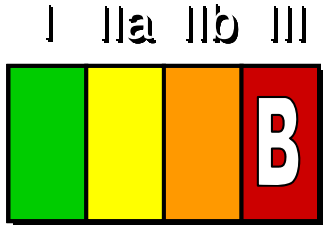
b. If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by thienopyridine therapy, earlier discontinuation should be considered.

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.

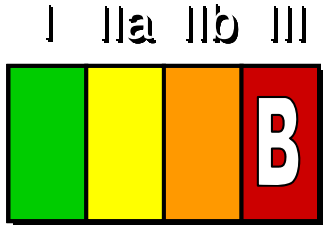
Initial Conservative Strategy: Antiplatelet Therapy



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.

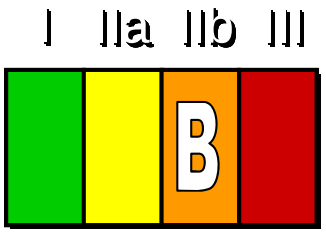
Initial Conservative Strategy: Antiplatelet Therapy



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 Strategy: Invasive Antiplatelet Therapy



New 2011

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.

CHRONIC KIDNEY DISEASE

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.

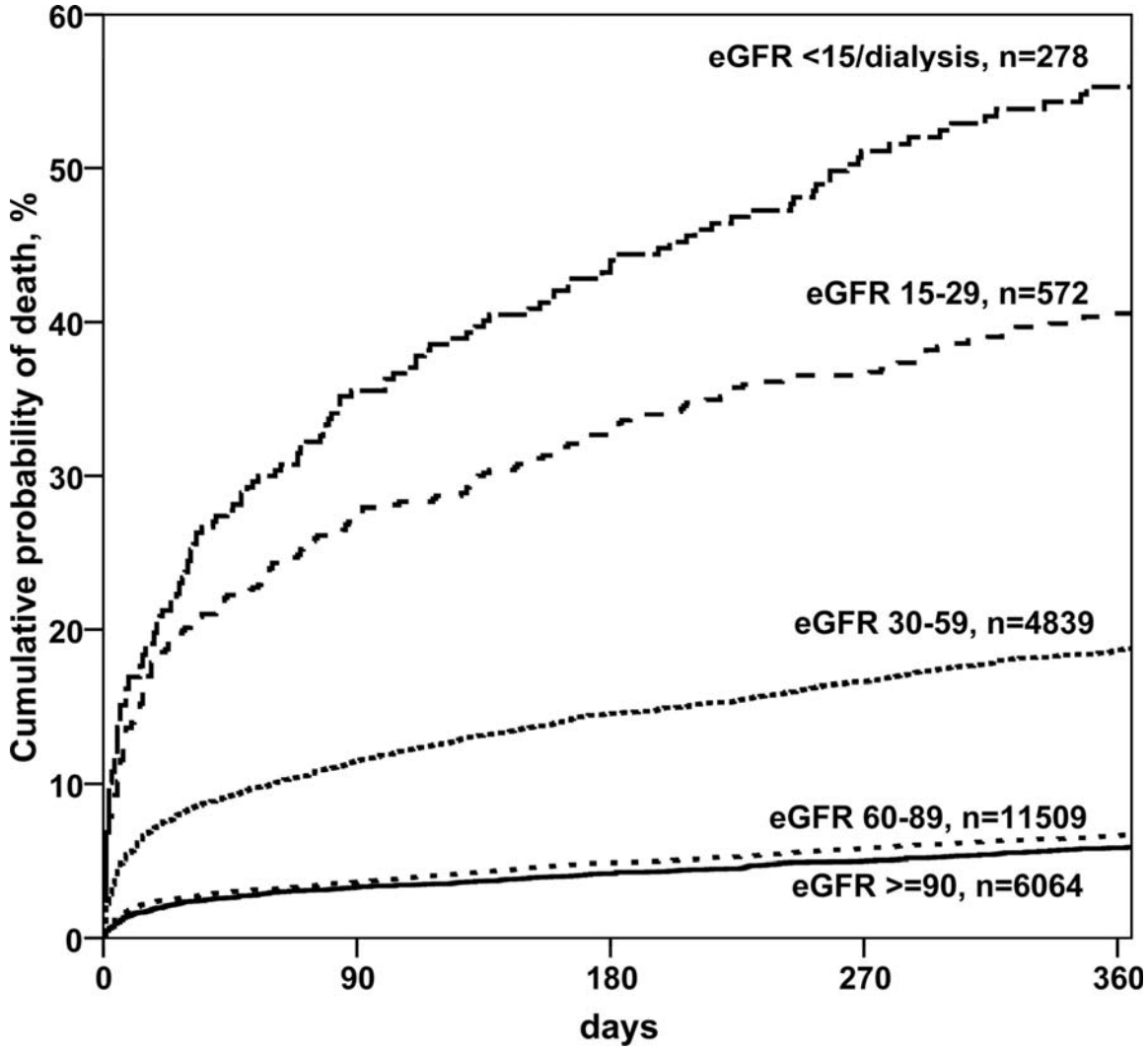
SWEDEHEART

- 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**

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

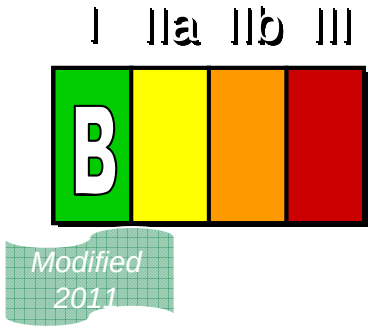
Revised 2011

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

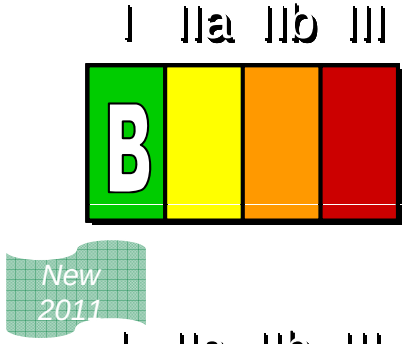


Szummer K et al. Circulation 2009;120:851-858

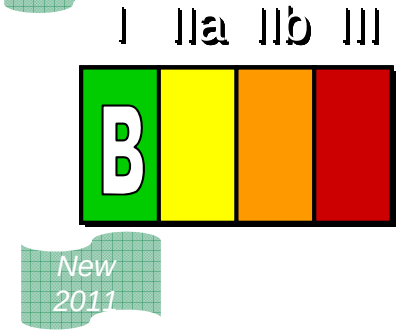
Chronic Kidney Disease



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.

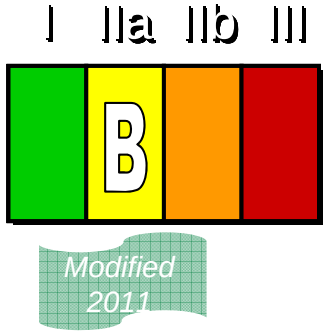


Patients undergoing cardiac catheterization with receipt of contrast media should receive adequate preparatory hydration.



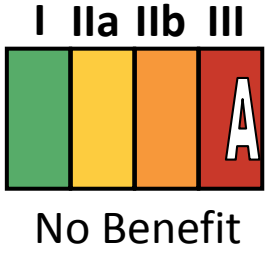
Calculation of the contrast volume to creatinine clearance ratio is useful to predict the maximum volume of contrast media that can be given without significantly increasing the risk of contrast-associated nephropathy.

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].)

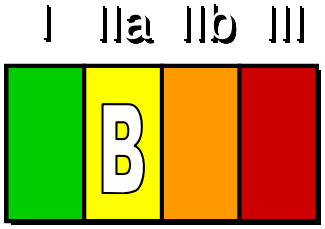
Contrast-Induced Acute Kidney Injury



Administration of N-acetyl-L-cysteine is not useful for the prevention of contrast-induced AKI.

QUALITY OF CARE AND OUTCOMES

Quality of Care and Outcomes for Acute Coronary Syndromes



New 2011

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.