Optimal Antiplatelet Therapy for the ACS and CAD patient: Which Should I Choose?

Vincent Varghese, DO, FACC, FSCAI
Director, Interventional Cardiology Fellowship Program
Deborah Heart and Lung Center, Browns Mills, NJ
Division of Interventional Cardiology and Endovascular Medicine
Disclosures

Speaker’s Bureau:
• Cardiovascular Systems inc
• Astra Zeneca

Grant/Research Support:
• Educational Grant Medtronic
• Educational Grant Boston Scientific

Honorarium:
• Cardiovascular Systems Inc

Consultant:
• Cardiovascular Systems Inc
Annual U.S. hospital discharges for acute coronary syndromes

ACS 1.55 million

UA 619,000

NSTE-ACS 1.25 million

MI 946,000

NSTEMI 634,000

STEMI 312,000
Anti-Ischemic therapy

Antiplatelet therapy

Anticoagulation therapy

Secondary prevention

Management strategy

Nitrates
beta blockers
ACE I/ARB

Invasive
Conservative

Aspirin
Clopidogrel
Ticagrelor
Prasugrel

UFH
Enoxaparin
Fondaparinux
Bivalirudin

Smoking
Lipid control
BP control
Glucose control
Exercise
Weight loss
Targets to alter Platelet Aggregation
Comparative Metabolism of P2Y12 inhibitors

Schomig A. NEJM 2009; 361: 1108-1111
Clinical Case

78 year old female with DM, HTN, prior tobacco use

Admitted for unstable angina

Cardiac catheterization for ongoing symptoms chest discomfort
Clinical Case
Clinical Case
Clinical Case

80-90% diffuse mid LAD stenosis

2 overlapping drug-eluting stents placed

Aspirin 81mg daily

Ticagrelor 90mg twice daily
Clinical Case

80-90% diffuse mid LAD stenosis

2 overlapping drug-eluting stents placed

Aspirin 81mg daily

Ticagrelor 90mg twice daily
Aspirin

Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients

Antithrombotic Trialists' Collaboration


Any serious vascular event (non-fatal MI, stroke, vascular death) reduced by 1/4.
Non-fatal MI by 1/3; non-fatal CVA by 1/4; vascular mortality by 1/6
In all high risk categories, absolute benefit > risk of bleeding
Class I, Level A of evidence for medical and invasive management of ACS.
Oral thienopyridine pro-drug

Active metabolite produced by 2-stage hepatic CYP-P450 (2C19) process

Irreversible inhibitor of P2Y12 receptor

Variations of CYP2C19 genotype and enzyme polymorphisms can influence metabolism.
Definite UA/NSTEMI for early invasive or ischemia guided strategy

Class I indication

300mg or 600mg loading dose, then 75mg daily
Ticagrelor

Selective and reversible inhibitor

Not a pro-drug

Does not interact directly with P2Y12 receptor site; reversibly binds to adjacent site, preventing signal transduction.

Contraindicated in severe hepatic impairment
PLATO

N= 18,624; UA/NSTEMI(mod-high risk) + STEMI with plan for Invasive/Cath Guided Rx
Clopidogrel pre-treatment allowed

180mg Ticagrelor

6-12 month Treatment – PCI/CABG/Medical Rx: 77% PCI

300mg Clopidogrel load

90 mg bd Ticagrelor

75mg Clopidogrel

1st efficacy end point (death from vasc cause, MI, CVA)
9.8% Ticagrelor vs 11.7% Clopidogrel (HR 0.84; 95% CI 0.77 – 0.92; P<0.001)

TIMI Major bleeding:
7.9% Ticagrelor vs 7.6% clopidogrel (HR 1.03; 95% CI 0.93-1.15; P = 0.57)
CABG related major bleeding (5.3% vs. 5.8%; P = 0.32)

Wallentin L et al. NEJM 2009;361:1045-57
PLATO: Efficacy and Safety Endpoints

Primary efficacy endpoint:
- Clopidogrel: 11.7%
- Ticagrelor: 9.8%

HR 0.84
(95% CI, 0.77-0.92)
P < .001

Primary safety endpoint:
- Ticagrelor: 11.58%
- Clopidogrel: 11.20%

HR 1.04
(95% CI, 0.95-1.13)
P = .434

* Composite of death from vascular causes, MI, and stroke
† Time to major bleeding endpoint, according to study criteria
Definite UA/NSTEMI for early invasive or ischemia guided strategy

Class I indication

180mg loading dose, then 90mg twice daily

*Aspirin 81mg daily maintenance*
Prasugrel

Oral thienopyridine pro-drug with active metabolite

Selective and irreversible P2Y12 inhibitor

Also metabolized by CYP450 but more efficiently, more active metabolite available, faster onset, greater platelet inhibition

Platelet inhibition independent of CYP2C19 genotype
TRITON-TIMI 38

N= 13608; 26% STEMI; 74% UA/NSTEMI all for invasive Rx

1:1 Randomisation after coronary angiography

60mg Prasugrel

300mg Clopidogrel

PCI

10mg Prasugrel

75mg Clopidogrel

1° efficacy end point (CV death, non fatal MI, non fatal CVA)
12.1% clopidogrel vs 9.9% prasugrel (HR 0.81; 95% CI 0.73 – 0.90; P<0.001)

TIMI Major bleeding, non CABG:
2.4% prasugrel vs 1.8% clopidogrel (HR 1.32 ; 95% CI 1.03-1.68 ; P = 0.03
Life threatening bleeding (1.4% vs. 0.9%; P = 0.01)
Non fatal bleeding (1.1% vs. 0.9%, HR, 1.25, P=0.23); fatal bleeding (0.4% vs. 0.1%; P=0.002)

Wiviott S et al. NEJM 2007;357;2001-15
TRITON TIMI -38

A

Primary Efficacy End Point

Clopidogrel 12.1
Prasugrel 9.9

Key Safety End Point

Prasugrel 2.4
Clopidogrel 1.8

Days after Randomization

No. at Risk
Clopidogrel 6795 6169 6036 5835 5043 4369 3017
Prasugrel 6813 6305 6177 5951 5119 4445 3085

B

Primary Efficacy End Point (%)

Clopidogrel 5.6
Prasugrel 4.7

Days after Randomization

C

Primary Efficacy End Point (%)

Clopidogrel 6.9
Prasugrel 5.6

Days after Randomization
TRITON TIMI -38

Reductions in the Prasugrel group in rates of MI
(9.7% for Clopidogrel vs. 7.4% for Prasugrel, P<0.001)

Urgent target vessel revascularization (3.7% vs. 2.5%, P<0.001)

Stent thrombosis (2.4% vs. 1.1%, P<0.001)
TRITON TIMI -38

Reductions in the Prasugrel group in rates of MI
(9.7% for Clopidogrel vs. 7.4% for Prasugrel, P<0.001)

Urgent target vessel revascularization (3.7% vs. 2.5%, P<0.001)

Stent thrombosis (2.4% vs. 1.1%, P<0.001)

Contraindicated in previous TIA/CVA
Not recommended in patients >75 yrs old, body weight <60kg
Definite UA/NSTEMI for early invasive strategy, prior to PCI

Class I indication

60mg loading dose, then 10mg daily

Not indicated in NSTE-ACS treated conservatively with medical therapy
NSTEMI/UA treated with PCI:

Class I recommendation

Aspirin 162mg to 325mg, then 81 mg daily

P2Y12 inhibitor loading dose:

Clopidogrel 300mg or 600mg, then 75mg daily
Prasugrel 60mg, then 10mg daily
Ticagrelor 180mg, then 90mg twice daily

For DES or BMS, ideal treatment for 1 year
NSTEMI/UA treated with medical therapy:

Class I recommendation

Aspirin 162mg to 325mg, then 81 mg daily

P2Y12 inhibitor loading dose:

Clopidogrel 300mg or 600mg, then 75mg daily
Ticagrelor 180mg, then 90mg twice daily
STEMI treated with primary PCI

Class I recommendation:

Aspirin 162mg to 325mg

P2Y12 inhibitor loading dose should be given as soon as possible:

Clopidogrel 600mg

Prasugrel 60mg

Ticagrelor 180mg

For DES or BMS, ideal treatment for 1 year
Clinical Case

62 year old male with DM, Tobacco use

Chest discomfort 4 hours prior to presentation

EKG demonstrates 2 mm anterior ST elevations

Blood pressure 90/50mmHg, HR 110

Emergent cardiac catheterization
62 year old male with DM, Tobacco use

Chest discomfort 4 hours prior to presentation

EKG demonstrates 2 mm anterior ST elevations

Blood pressure 90/50mmHg, HR 110

Emergent cardiac catheterization
Clinical Case

Impella 2.5 hemodynamic support device inserted for cardiogenic shock

Drug eluting stent mid LAD

Aspirin 81 mg daily
Prasugrel 10 mg daily
Clinical Case

Impella 2.5 hemodynamic support device inserted for cardiogenic shock

Drug eluting stent mid LAD

Aspirin 81 mg daily

Prasugrel 10 mg daily
Which should I choose?

“All about balance”
For medically treated ACS: Ticagrelor or Clopidogrel.

Higher ischemic risk patient-Ticagrelor
Higher bleeding risk- Clopidogrel

For invasive treatment of ACS: Ticagrelor, Prasugrel, or Clopidogrel

Higher ischemic risk patient-Ticagrelor or Prasugrel
Higher bleeding risk- Clopidogrel
Vorapaxar

Protease-activated receptor-1 (PAR-1) antagonist

**TRA 2 P TIMI 50**
(Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events)

26,499 patients with prior MI, stroke, or PAD. Vorapaxar versus placebo.

Cardiovascular death, MI, stroke, or urgent revascularization reduced by 13%.

Moderate or severe bleeding occurred in 4.2% Vorapaxar versus 2.5% of placebo patients.
Vorapaxar

Indicated for reduction of thrombotic CV deaths in patients with PAD or prior MI

Vorapaxar 2.5mg daily

Contraindicated with prior TIA/CVA/ICH

Use with Aspirin and/or Clopidogrel
Conclusions

Individualized or “tailored” antiplatelet therapy in ACS

Assess patient based on risk of recurrent ischemia and risk of bleeding

Invasive or conservative strategies

Risk factors for bleeding: age, female gender, low BMI, chronic renal failure

Limitations Prasugrel: Age >75, weight < 60kg, previous CVA
Limitations Ticagrelor: Hepatic dysfunction
"Take an aspirin every day, but before you swallow it, take it out for a five-mile walk."
Thank you
Closing Remarks / Thank You
2014 ACC/AHA UA/NSTEMI Guidelines

**NSTE-ACS: Definite or Likely**

**Ischemia-Guided Strategy**
- **Initiate DAPT and Anticoagulant Therapy**
  1. ASA (Class I; LOE: A)
  2. P2Y\textsubscript{12} inhibitor (in addition to ASA) (Class I; LOE: B):
     - Clopidogrel or
     - Ticagrelor
  3. Anticoagulant:
     - UFH (Class I; LOE: B) or
     - Enoxaparin (Class I; LOE: A) or
     - Fondaparinux\textsuperscript{+} (Class I; LOE: B)

**Early Invasive Strategy**
- **Initiate DAPT and Anticoagulant Therapy**
  1. ASA (Class I; LOE: A)
  2. P2Y\textsubscript{12} inhibitor (in addition to ASA) (Class I; LOE: B):
     - Clopidogrel or
     - Ticagrelor
  3. Anticoagulant:
     - UFH (Class I; LOE: B) or
     - Enoxaparin (Class I; LOE: A) or
     - Fondaparinux\textsuperscript{+} (Class I; LOE: B) or
     - Bivalirudin (Class I; LOE: B)

Can consider GPI in addition to ASA and P2Y\textsubscript{12} inhibitor in high-risk (e.g., troponin positive) pts (Class IIb; LOE: B)
- Eptifibatide
- Tirofiban
77 year old man undergoes PCI to the mid LAD for treatment of unstable angina with a 3 x 15mm DES. Other medical problems include diabetes, hypertension, and dyslipidemia.
Clinical Case

77 year old man undergoes PCI to the mid LAD for treatment of unstable angina with a 3 x 15mm DES. Other medical problems include diabetes, hypertension, and dyslipidemia.
Clinical Case

Which of the following anti-platelet regimens would you recommend at discharge?

A. Clopidogrel 75mg BID + ASA 325
B. Prasugrel 10 + ASA 81mg
C. Prasugrel 5 + ASA 325mg
D. Ticagrelor 90 BID + ASA 325mg
E. Ticagrelor 90 BID + ASA 81mg
Clinical Case

Which of the following anti-platelet regimens would you recommend at discharge?

A. Clopidogrel 75mg BID + ASA 325
B. Prasugrel 10 + ASA 81mg
C. Prasugrel 5 + ASA 325mg
D. Ticagrelor 90 BID + ASA 325mg
E. Ticagrelor 90 BID + ASA 81mg