Non-ST Elevation Myocardial Infarction (NSTEMI)

Prakash Balan, MD, JD, FACC, FSCAI
Associate Professor
Interventional Cardiology
Banner University Medical Center
University of Arizona College of Medicine Phoenix
DISCLOSURES

- Consultant Osprey Medical Pty, Ltd.
- Consultant Abiomed, Inc.
CASE

54 year old female with HTN, HLD, DM, hypothyroidism, and obesity p/w chest pain and hypertensive urgency.

--CP 5/10, retrosternal pressure
--Initial troponin negative; second troponin elevated
The clinical presentation in the above case is consistent with which of the following syndromes:

A) STEMI
B) NSTEMI
C) Unstable Angina
D) Stable Angina
E) Non-Cardiac Chest Pain
Chest Pain Syndromes

Acute Coronary Syndromes
- STEMI
- NSTEMI
- UA

Stable Angina
- Chronic CAD

Non-Cardiac Chest Pain
- GERD
- Costochondritis
ACS vs Stable Angina vs Non-Cardiac Chest Pain

- **History**
  - Quality of pain
  - Risk factors

- **Exam**
  - Hypotension
  - Signs of heart failure
  - New murmur

- **ECG**
  - ST segment deviation
  - T wave inversions

- **Cardiac Biomarkers**
  - Elevated troponin
Pathophysiology of ACS

Plaque Rupture
Disruption of fibrous cap with fissure resulting in hematoma or thrombus
Vulnerability and Plaque Rupture

1. Thinner the fibrous cap greater likelihood of rupture
2. More macrophages (>25 per high-powered field), greater risk of rupture
3. 4-fold increase in vasa vasorum on ruptured plaques
Thrombosis

1. Disruption of fibrous cap exposes bloodstream to thrombogenic stimuli
2. Platelets activated by collagen and adhere to wall bound von Willebrand’s factor
3. Results in activation of clotting cascade and formation of thrombus
1. PLAQUE RUPTURE AND ENDOTHELIAL INJURY

For illustrative purposes only.
3. ACTIVATION & ADHESION

For illustrative purposes only.
4. AMPLIFICATION

Thrombin

ADP

Fibrinogen

ADP Receptor

PAR Receptor

Thromboxane A2 Receptor

For illustrative purposes only.

5. AGGREGATION

For illustrative purposes only. Jackson SP. Blood. 2007;109(12):5087-5095.
CLOT ARCHITECTURE: RATIONALE FOR DRUG TARGETS

OUTER CORE
- Loosely packed
- Highly plasma permeable
- Little or no fibrin
- Modulated by P2Y₁₂ inhibition

INNER CORE
- Densely packed
- Restricted plasma entry
- Fibrin deposition at the base
- Thrombin dependent and expanded by ADP (P2Y₁₂)

For illustrative purposes only.
Thrombosis

► Process of thrombotic occlusion dynamic
► Stuttering cycles of partial to near-total to total occlusion of arterial lumen
► Responsible for variability in clinical manifestation from sudden cardiac death, to STEMI, to NSTEMI, to UA
Type 1 vs Type 2 MI

Type 1
- Caused by CAD with atherothrombotic plaque rupture or erosion leading to either an occlusive or partially-occlusive thrombus

Type 2
- Due to an oxygen supply-demand imbalance, either alone or in combination with atherosclerosis without plaque rupture, vasospasm or coronary microvascular dysfunction, or non-atherosclerotic coronary dissection

Type 3
- Cardiac death with symptoms indicative of MI with presumed new ECG changes or ventricular fibrillation, but biomarker samples not obtained before death
- MI detected at autopsy examination

Type 4a
- Procedure-related MI occurring ≤48 hours after the index PCI procedure

Type 4b
- MI due to stent or scaffold thrombosis following PCI

Type 4c
- Restenosis associated with PCI

Type 5
- Procedural myocardial injury during or ≤48 hours after CABG
Question

An 84 year old man with a history of HTN, HLD, DM, CAD, CHF, Afib, & CKD presents with active hematochezia with dull chest pressure and is found to have a Hgb of 6g/dl, a mildly elevated troponin, and diffuse ST-depressions on EKG. Appropriate initial therapy would be:

A) Loading with aspirin, ticagrelor, & heparin
B) Loading with aspirin, ticagrelor, heparin, & eptifibatide
C) Urgent cardiac catheterization
D) Addressing acute anemia and source of bleeding
E) Outpatient management of anemia
Epidemiology/Prevalence/Prognosis

-- NSTEMI accounts for 60-70% of all MI hospitalizations
-- Roughly 70-90% of all NSTEMI are Type 1 NSTEMI
-- Among all NSTEMI in-hospital mortality ranges from 5.2%-13.1%
-- 30-day mortality from NSTEMI ranges from 7.6%-17%
-- NSTEMI mortality rates have improved over time
Initial Assessment

--Risk stratification tools such as the Global Registry of Acute Cardiac Events (GRACE) risk score and the Thrombolysis in Myocardial Infarction (TIMI) risk score can be utilized to assess both the acute and long-term likelihood of a further ischemic event following an NSTEMI.

--Assessment of acute risk guides initial evaluation and selection of care facility, such as a coronary care unit, and the choice of appropriate pharmacotherapy, and guides decision-making regarding invasive revascularization procedures.

TREATMENT

1. STEMI
2. NSTEMI
3. UA
MANAGEMENT

1. Early Invasive Strategy
   1. Coronary angiography within 24-48h with angiographically directed revascularization
   2. Aggressive antiplatelet & antithrombin therapy

2. Early Conservative Strategy
   1. Observation followed by noninvasive evaluation
   2. Medical therapy
A 69-year-old man is evaluated at the hospital for four episodes of chest pain at rest in the past 24 hours. Medical history is significant for hyperlipidemia, hypertension, tobacco use, and previous transient ischemic attack. Medications are aspirin, hydrochlorothiazide, atorvastatin, and ramipril. On physical examination, vital signs are normal. The remainder of the examination is unremarkable. Laboratory studies are notable for normal serum troponin levels. An ECG demonstrates 2-mm ST-segment depressions in leads V4 through V6. Metoprolol, nitrates, clopidogrel, and heparin are initiated.

**Which of the following is the most appropriate management?**

1. Adenosine nuclear stress testing
2. Coronary CT angiography
3. Exercise stress electrocardiography
4. Urgent angiography
A 55-year-old woman is evaluated in the hospital for a single 10-minute episode of chest pain at rest, which occurred 1 hour before presentation. Medical history is significant for hypertension and hyperlipidemia. Medications are hydrochlorothiazide, ramipril, and pravastatin. On physical examination, vital signs are normal. The remainder of the examination is unremarkable. Laboratory studies are notable for normal serum troponin levels. An ECG demonstrates 1-mm ST-segment depressions in leads V4 through V6. Aspirin and metoprolol are initiated.

Which of the following is the most appropriate management?

1. Amlodipine
2. Enoxaparin and eptifibatide
3. Exercise stress testing
4. Urgent angiography
Initial Medical Therapy

- **Antiplatelet Therapy**
  - Aspirin 325 chewed
  - Clopidogrel 600 mg/Ticagrelor 180 mg
  - Avoid Glycoprotein IIb/IIIa inhibitors

- **Antithrombin Therapy**
  - Unfractionated heparin
  - Avoid low molecular weight heparin (Enoxaparin)
  - Avoid Direct thrombin inhibitors (Bivalirudin) except in HIT

- **Anti-Anginal Therapy**
  - Beta Blockers (PO in higher risk patients based on COMMIT trial)
  - Nitrates
  - Avoid hypotension
ACUITY Trial
(Acute Catheterization and Urgent Intervention Triage Strategy)

- 13,819 patients with NSTEMI randomizing patients to one of three antithrombotic regimens prior to angiography
  - Heparin/Enoxaparin + GP IIb/IIIa receptor antagonist
  - Bivalirudin + GP IIb/IIIa receptor antagonist
  - Bivalirudin
- Either heparin or bivalirudin + GP IIb/IIIa showed similar rates of ischemia and bleeding
- Bivalirudin without GP IIb/IIIa showed similar rates of ischemia but significantly less bleeding
CURE TRIAL
(Clopidogrel in Unstable angina to prevent Recurrent Events)

1. Randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of dual anti-platelet therapy vs. aspirin alone in patients with ACS absent ST-segment elevations
2. 12,562 patients randomized to receive clopidogrel 300 mg x 1 followed by 75 mg daily + aspirin (6,259 patients) vs. placebo + aspirin (6,303 patients)
3. Primary outcome measure was composite of death from cardiovascular causes, nonfatal MI, or stroke
4. Primary outcome occurred in 582 of 6259 patients in treatment group (9.3%) as compared to 719 of 6303 patients in the placebo group (11.4%)
5. Significantly fewer MIs in treatment group (116 vs 193)
6. Treatment group showed benefit both early and late

TRITON-TIMI 38

1. Prasugrel vs Clopidogrel
2. 13,608 patients with ACS
3. Primary efficacy endpoint composite of death from CV causes, nonfatal MI, nonfatal stroke
4. Primary safety endpoint major bleeding

PLATO Trial

The PLATO Trial Design

**UA/NSTEMI and STEMI**
clopidogrel treated* or naive,
planned for medical or invasive management,
patients randomized prior to assessment of coronary anatomy²†
(N=18,624)

- **BRILINTA (n=9,333)**
  - 180-mg loading dose‡;
  - 90-mg BID maintenance dose

  An additional 90-mg dose given pre-PCI if >24 hrs postrandomization

- **Clopidogrel (n=9,291)**
  - 300-mg loading dose§;
  - 75-mg QD maintenance dose

  §If pretreated with clopidogrel, no loading dose given. An additional 300-mg dose allowed pre-PCI

**6- to 12-month exposure**

- **Primary efficacy end point:** CV death/MI/II/stroke
- **Key secondary end points:** MI/II alone, CV death alone, stroke alone, total mortality
- **Primary safety end point:** Total Major Bleeding

- BRILINTA and clopidogrel were both given in combination with aspirin and other standard therapy
PLATO Trial

PLATO Primary Efficacy End Point: Composite of CV Death, MI,\* or Stroke at 12 Months\(^1\)

- Clopidogrel + aspirin (n=9,291)
  - 11.7%
- BRILINTA + aspirin (n=9,333)
  - 9.8%

**Difference in treatments was driven by CV death and MI\* with no difference in stroke\(^1\)**

HR | 95% CI | \(P\) Value
---|---|---
0.84 | 0.77-0.92 | <0.001

16% RRR at 12 months
1.9% ARR
54 NNT
PLATO Trial

- No baseline demographic factor altered the relative risk of Total Major Bleeding with BRILINTA compared to clopidogrel.
- In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures, and concomitant use of medications that increase the risk of bleeding.
PHARMACOKINETICS
CHAMPION PHOENIX: Pivotal phase III trial

Study schematic\(^1,2\)

N=10,942 (mITT)
- All-comer patients requiring PCI\(^*\)
- Angiography or STEMI diagnosis
- 153 sites
- 37.4% US patients

Placebo oral

KENGREAL\(^\text{®}\) (cangrelor) bolus + infusion
(30 μg/kg; 4 μg/kg/min)

PCI duration, median 18 minutes

Placebo bolus + infusion

Clopidogrel \(^*\) (300 or 600 mg oral, per physician discretion)

Clopidogrel oral

48-hour primary composite endpoint:
Death/Myocardial infarction/Ischemia-driven revascularization/Stent thrombosis

Placebo oral

KENGREAL bolus was administered prior to start of PCI. Clopidogrel 300 mg or 600 mg was administered shortly before or shortly afterwards in patients randomized to clopidogrel. The protocol also called for clopidogrel (75 mg) to be administered during the first 48 hours.

\(^*\)P2Y\(_12\) Inhibitor naïve.

\(^*\)Administration (dose and timing) of loading dose of clopidogrel was at the operator’s discretion.

mITT=modified intent-to-treat; R=randomization.

22% relative risk reduction in periprocedural thrombotic events\textsuperscript{1,2}

CHAMPION PHOENIX primary composite endpoint (death/MI/IDR/stent thrombosis at 48 hours) in an all-comer PCI patient population

As an adjunct to PCI, KENGREAL\textsuperscript{®} (cangrelor) significantly reduced the primary composite endpoint of death, myocardial infarction, ischemia-driven revascularization, and stent thrombosis events at 48 hours.

\begin{table}[h]
\centering
\begin{tabular}{lrrrrrrrr}
\hline
Patients at risk & 5472 & 5233 & 5229 & 5225 & 5223 & 5221 & 5220 & 5217 & 5213 \\
\hline
KENGREAL: & 5470 & 5162 & 5159 & 5155 & 5152 & 5151 & 5151 & 5147 & 5147 \\
Clopidogrel: & & & & & & & & & \\
\hline
\end{tabular}
\end{table}

38% relative risk reduction in key secondary endpoint of stent thrombosis\textsuperscript{1,2}

Stent thrombosis at 48 hours in an mITT patient population

\begin{figure}
\centering
\includegraphics[width=\textwidth]{stent_thrombosis_chart.png}
\end{figure}

\begin{table}
\begin{tabular}{lcccccccc}
\hline
Patients at risk & KENGREAL & Clopidogrel \\
\hline
KENGREAL & 5472 & 5426 & 5421 & 5419 & 5419 & 5418 & 5417 & 5416 & 5414 \\
Clopidogrel & 5470 & 5392 & 5389 & 5388 & 5386 & 5385 & 5385 & 5383 & 5383 \\
\hline
\end{tabular}
\end{table}

KENGREAL® (cangrelor) pharmacology1,2 (cont’d)

- >98% inhibition of platelet aggregation in whole blood impedance aggregometry3

Study Details2
- Phase I study in healthy volunteers (n=9)
- Dose: 30 µg/kg IV bolus + 4 µg/kg/min IV infusion
- Blood levels of cangrelor (green line/PK) and platelet activity (purple line/PD) were assessed over 150 minutes by whole blood impedance aggregometry in response to 20 µM of ADP

RADIAL ACCESS
RADIAL ACCESS

1. Multiple trials now show lower bleeding risk & lower mortality with radial vs femoral access in ACS
2. MATRIX trial randomized 8,404 patient with STEMI or NSTEMI to radial vs femoral access
3. Primary endpoint MACE (death, MI, stroke) + major bleeding

Figure 2: Coprimary composite outcomes at 30 days
(A) All-cause mortality, myocardial infarction, or stroke, and (B) all-cause mortality, myocardial infarction, stroke, or Bleeding Academic Research Consortium 3 or 5 bleeding.

A 78 year old woman with a history of HTN, HLD, and prior CVA presents with retrosternal chest pain 7/10, with lateral ST-depressions on EKG, and elevated troponin that is exponentially rising on serial testing. She weighs 59 kg. Appropriate initial medical therapy would be:

A) Loading with aspirin, prasugrel, and unfractionated heparin
B) Loading with aspirin, clopidogrel, and unfractionated heparin
C) Loading with ticagrelor, enoxaparin, & eptafibitide
D) Loading with prasugrel, enoxaparin, & fondaparinux
E) Loading with aspirin, ticagrelor, enoxaparin, & cangrelor
54 year old female with HTN, HLD, DM, hypothyroidism, and obesity p/w chest pain and hypertensive urgency

- NSTEMI
- Early Invasive Strategy
- Aspirin, Ticagrelor
- Heparin
- PCI
Thank you!