Improving Outcomes for Acute Coronary Syndrome Patients: Best Practices for Primary Care Clinicians

Friday, November 21, 2014
7:45–9:15am

The Henry, Autograph Collection
300 Town Center Dr.
Dearborn, MI

Jeffrey S Berger MD, MS
Assistant Professor of Medicine
New York University School of Medicine
New York, NY

Benjamin Scirica, MPH, MD
Assistant Professor, Harvard Medical School
TIMI Study Group, Cardiovascular Division
Brigham and Women's Hospital
Boston, MA

Educational Partner:
Voxmedia, LLC
Session 1: Improving Outcomes for Acute Coronary Syndrome Patients: Best Practices for Primary Care Clinicians

Learning Objectives

1. Summarize fundamental similarities and differences in pharmacokinetics, pharmacodynamics, and pharmacogenetics of oral antiplatelet drugs.
2. Explain efficacy and safety data with oral antiplatelet therapies from ACS outcomes trials.
3. Recognize guideline based therapies to reduce risk and goals to achieve in the management of patients who have experienced an acute coronary syndrome.

Faculty

Jeffrey Berger, MD, MS
Assistant Professor of Medicine
New York University
School of Medicine
New York, New York

Dr Jeffrey Berger is assistant professor of medicine and surgery in the divisions of cardiology, hematology, and vascular surgery and director of cardiovascular thrombosis at the New York University Langone Medical Center. Dr Berger completed a fellowship in vascular medicine and thrombosis and hemostasis at the University of Pennsylvania and cardiology training at Duke University. He served his residencies at Beth Israel Medical Center and completed his MS in clinical research at the Albert Einstein College of Medicine. Dr Berger was a recipient of the AHA fellow to faculty award, the Doris Duke Foundation’s clinical scientist development award, and the AHA national clinical research award for his studies on platelet activity in cardiovascular disease and received a grant from the Center for AIDS Research on platelet activity and inflammation in HIV. Dr Berger has a particular interest in the field of platelet and hypercoagulable mechanisms of cardiovascular disease. Dr Berger is published in the Journal of Thrombosis and Haemostasis, the American Journal of Cardiology, the Journal of Vascular Surgery, and the Journal of the American College of Cardiology.

Benjamin Scirica, MD, MPH
Assistant Professor of Medicine
TIMI Study Group
Harvard Medical School
Boston, Massachusetts

Dr Benjamin Scirica is an assistant professor of medicine at Harvard Medical School, Boston, Massachusetts. He graduated from Harvard Medical School and trained in internal medicine and cardiovascular medicine at Brigham and Women’s Hospital. He received a master’s of public health degree from Harvard. He is an investigator at the TIMI Study Group, an academic research organization based at Brigham and Women’s Hospital that has performed over 50 clinical trials in atherosclerotic heart disease, and an attending cardiologist and director of quality initiatives in the cardiovascular division at Brigham and Women’s Hospital. His research interests center on the identification and application of novel cardiac biomarkers and electrocardiographic techniques. He is the director of the TIMI ECG Core Laboratory, which had analyzed over 20000 continuous and static ECGs from multiple trials in acute coronary syndromes including the ExTRACT-TIMI 25, CLARITY-TIMI 28, DISPERSE2, PLATO, and MERLIN-TIMI 36 trials. He was principal investigator of AVANT GARDE-TIMI
43 trial and coinvestigator of MERLIN-TIMI 36, TRA 2\textsuperscript{oa}-TIMI 50, and SAVOR-TIMI 53 trials. Dr Scirica has authored or coauthored over 70 peer reviewed articles, serves on the editorial board of ACCEL, and is a reviewer for multiple journals including *Lancet, Circulation, and JACC.*

**Faculty Financial Disclosure Statements**

The presenting faculty reports the following:

Dr Berger indicates he has received honoraria for serving on the Executive Committee of the EUCLID trial.

Dr Scirica reports research grants via the TIMI Study and Brigham and Women’s Hospital from AstraZeneca and Bristol-Myers Squibb, Daichi-Sankyo, GlaxoSmithKline, Johnson and Johnson, Bayer Healthcare, Gilead, Eisai, and Merck; consulting fees from Gilead, Lexicon, Arena, Eisai, St. Jude’s Medical, Forest Pharmaceuticals, Bristol-Myers Squibb, Boston Clinical Research Institute, Decision Resources, University of Calgary, and Elsevier Practice Update Cardiology.

**Education Partner Financial Disclosure Statement**

The content collaborator at Voxmedia has no financial relationships to disclose.

**Suggested Reading List**


SESSION 1
7:45am – 9:15am

Improving Outcomes for Acute Coronary Syndrome Patients: Best Practices for Primary Care Clinicians

SPEAKERS
Jeffrey Berger, MD, MS
Benjamin Scirica, MD, MPH

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Presenter Disclosure Information

Off-Label/Investigational Discussion

► In accordance with pmICME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Learning Objectives

• Summarize fundamental similarities and differences in pharmacokinetics, pharmacodynamics, and pharmacogenetics of oral antiplatelet drugs.
• Explain efficacy and safety data with oral antiplatelet therapies from ACS outcome trials.
• Recognize guideline-based therapies to reduce risk and goals to achieve in the management of patients who have experienced an acute coronary syndrome.

Drug List

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Plavix</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Effient</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Brilinta</td>
</tr>
<tr>
<td>Metformin</td>
<td>Glucophage, Fortamet, Glumetza, Riomet</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Diabeta, Glycemic, Glycset, Micronase</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Zestril, Prinivil</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Nitro-Par, Nitro-Time, NitroVen, Nitrofen, Nitroquick, Nitrostat, Nitotab</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Coumadin, Jantoven, Marfarin</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>Integrilin</td>
</tr>
</tbody>
</table>

Oral Antiplatelet Therapy for Acute Coronary Syndromes (ACS)
Clinical Update 2014

Benjamin M. Scirica, MD MPH FAHA FACC
TIMI Study Group
Cardiovascular Division
Department of Medicine
Brigham and Women’s Hospital
Harvard Medical School
**OUTLINE**

- Acute Coronary Syndrome Definition
  - Unstable Angina/NSTEMI
  - STEMI
- Management Strategies
  - Invasive (catheterization)
  - Medical
- Antiplatelet Agents
  - Clopidogrel
  - Prasugrel
  - Ticagrelor

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

- **Acute Coronary Syndromes**
  - 1.17 Million Hospital Admissions
    - Unstable Angina: 0.43 million admissions per year
    - Myocardial Infarction: 0.73 million admissions per year
- Heart Disease and Stroke Statistics – 2014 Update, Circulation 2014
  - Primary and secondary diagnoses.

**Universal Definitions of MI**

- **Type 1**: Spontaneous MI related to ischemia due to a primary coronary (eg. plaque erosion and/or rupture)
- **Type 2**: MI from ischemia due to either ↑ O2 demand or ↓ supply, e.g., spasm, embolism, anemia, arrhythmias, hypertension.
- **Type 3**: Sudden unexpected death likely from MI.
- **Type 4a**: MI associated with PCI.
- **Type 4b**: MI associated with stent thrombosis
- **Type 5**: MI associated with CABG.


**Central Role of Platelets and Interaction with Coagulation in the Genesis of Thrombosis**

- Shear, PCI, Plaque Rupture
- Thrombin
- Fibrinogen
- Platelet
- GPIIb/IIIa
- Fibrin

**Aspirin Evidence: Dose and Efficacy**

<table>
<thead>
<tr>
<th>Aspirin Dose</th>
<th>No. of Trials</th>
<th>(%)</th>
<th>Odds Ratio for Vascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-1500 mg</td>
<td>34</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>160-325 mg</td>
<td>19</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>75-150 mg</td>
<td>12</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>&lt;75 mg</td>
<td>3</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Any aspirin</td>
<td>65</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of Bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet Better</td>
<td>Antiplatelet Worse</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P<.0001
Clopidogrel in NSTE ACS: 1st Demonstration of Benefit of Dual antiplatelet Rx in ACS

The CURE Study


Cumulative Hazard Rates

0.20
0.15
0.10
0.05
0.00

Medical Rx Group

Placebo

Clopidogrel

RR: 0.80 (0.69-0.92)

Days of Follow-up

0
100
200
300

Placebo

Clopidogrel

RR: 0.72 (0.57-0.90)

CABG Group

Days of Follow-up

0
100
200
300

Placebo

Clopidogrel

RR: 0.89 (0.71-1.11)

N=12,562

36901 2

20% RRR

All Patients

Clopidogrel (n=6259)

Placebo (n=6303)

P <.001

Factors Influencing On-treatment Platelet Reactivity

SNP (%) CYP Metabolizer Status Drug-drug interaction: PPI, CCB, Warfarin, SJW, Smoking

Clinical Outcomes

Renal Function Diabetes Variable Response to ADP

Unknown Factors

PPI, CCB, Warfarin, SJW, Smoking

Factors Influencing On-treatment Platelet Reactivity

SNP (%) CYP Metabolizer Status Drug-drug interaction: PPI, CCB, Warfarin, SJW, Smoking

Clinical Outcomes

Renal Function Diabetes Variable Response to ADP

Unknown Factors

Benefit of Higher (600 mg) Clopidogrel Loading Dose

CURRENT-OASIS 7

Patients with UA/NSTEMI or STEMI planned for early invasive strategy (ie, intended for PCI as early as possible within 24 hours)

Clopidogrel High-dose Group

Clopidogrel 600 mg LD day 1 followed by 150 mg from days 2 to 7; 75 mg from days 8 to 30

Clopidogrel Standard-dose Group

Clopidogrel 300 mg (+ placebo) day 1 followed by 75 mg (+ placebo) from days 2 to 7; 75 mg from days 8 to 30

CV death/MI/Stroke

Overall (N=25,086) 4.4 4.2 0.94 (0.83-1.06) 0.30

PCI (n=17,263) 4.5 3.9 0.86 (0.74-0.99) 0.039

No PCI (n=7823) 4.3 4.9 1.14 (0.92-1.40) 0.23

LD = loading dose.


Metabolism of Novel P2Y12 Receptor Blockers

Prasugrel

Intestinal Absorption

Intestinal Esterases 85%

Intestinal Absorption

Intestinal Esterases 85%

1 Step Intestinal/Hepatic CYP-Conversion

55%

34A

28A

28B

CYP3A4

Efficient active metabolite generation

Rapid Consistent / Greater IPA

P-Glycoprotein

Ticagrelor

Intestinal Absorption

Intestinal Esterases 85%

Intestinal Absorption

Intestinal Esterases 85%

1 Step Intestinal/Hepatic CYP-Conversion

55%

34A

28A

28B

CYP3A4

Efficient active metabolite generation

Rapid Consistent / Greater IPA


P2Y12 Inhibitor Basic Pharmacology

<table>
<thead>
<tr>
<th>Class</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversibility</td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Reversible</td>
</tr>
<tr>
<td>Activation</td>
<td>Prodrug, limited by metabolism</td>
<td>Prodrug, not limited by metabolism</td>
<td>Active drug</td>
</tr>
<tr>
<td>Onset of Effect</td>
<td>2-4 hours</td>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Duration of Effect</td>
<td>3-10 days</td>
<td>5-10 days</td>
<td>3-4 days</td>
</tr>
<tr>
<td>Withdrawal before major surgery</td>
<td>5 days</td>
<td>7 days</td>
<td>5 days</td>
</tr>
</tbody>
</table>

^ 50% inhibition of platelet aggregation

TRITON-TIMI 38: Patients Going to PCI

**CV Death, MI, Stroke**

ACS (STEMI or UA/NSTEMI) & Planned PCI

<table>
<thead>
<tr>
<th>Endpoint (%)</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint (%)</td>
<td>12.1 (781)</td>
<td>9.9 (643)</td>
</tr>
</tbody>
</table>

HR 0.81 (0.73-0.90) P=0.0004

NNT= 46

TRITON-TIMI 38: Major efficacy end points at 15 mo.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Pras (N=6813)</th>
<th>Clop (N=6795)</th>
<th>HR for Prasugrel (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death, non-fatal MI or non-fatal stroke (1st end pt)</td>
<td>643 (9.9)</td>
<td>781 (12.1)</td>
<td>0.81 (0.73-0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV Death</td>
<td>133 (2.1)</td>
<td>150 (2.4)</td>
<td>0.89 (0.79-1.12)</td>
<td>0.31</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>475 (7.3)</td>
<td>620 (9.5)</td>
<td>0.76 (0.67-0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>61 (1.0)</td>
<td>60 (1.0)</td>
<td>1.02 (0.71-1.45)</td>
<td>0.93</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>188 (3.0)</td>
<td>207 (3.2)</td>
<td>0.95 (0.78-1.16)</td>
<td>0.84</td>
</tr>
<tr>
<td>CV Death, nonfatal MI, or urgent TVR</td>
<td>652 (10.0)</td>
<td>798 (12.3)</td>
<td>0.81 (0.73-0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from any cause, nonfatal MI, or nonfatal stroke</td>
<td>692 (10.7)</td>
<td>822 (12.7)</td>
<td>0.83 (0.75-0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent TVR</td>
<td>156 (2.5)</td>
<td>233 (3.7)</td>
<td>0.66 (0.54-0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV Death, nonfatal MI, nonfatal stroke or rehosp for ischemia</td>
<td>797 (12.3)</td>
<td>938 (14.6)</td>
<td>0.84 (0.76-0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stent thrombosis*</td>
<td>68 (1.1)</td>
<td>142 (2.4)</td>
<td>0.48 (0.36-0.64)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TRITON-TIMI 38: Stent Thrombosis (ARC Definite + Probable)

Any Stent at Index PCI

N= 12,844

<table>
<thead>
<tr>
<th>Clopidogrel</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint (%)</td>
<td>2.4 (142)</td>
</tr>
</tbody>
</table>

HR 0.48 P <0.0001 NNT= 77

TRITON-TIMI 38: Bleeding Events — Safety Cohort (N=13,457)

<table>
<thead>
<tr>
<th>Event</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Events</td>
<td>0.6%</td>
<td>0.5%</td>
</tr>
<tr>
<td>AD</td>
<td>0.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>ICH</td>
<td>0.3%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

TRITON-TIMI 38: Net Clinical Benefit

**Bleeding Risk Subgroups**

<table>
<thead>
<tr>
<th>Prior Stroke / TIA</th>
<th>Age</th>
<th>Wgt</th>
<th>Post-hoc analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>&gt;75</td>
<td>&lt; 60 kg</td>
<td>B -16</td>
</tr>
<tr>
<td>No</td>
<td>&lt;75</td>
<td>&gt;= 60 kg</td>
<td>P&lt;0.006</td>
</tr>
</tbody>
</table>

TRILOGY ACS Study Design

Medically Managed UA/NSTEMI Patients

Median Time to Enrollment = 4.5 Days

TRITON-TIMI 38: Bleeding Risk Subgroups

<table>
<thead>
<tr>
<th>Prior Stroke / TIA</th>
<th>Age</th>
<th>Wgt</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>&gt;75</td>
<td>&lt; 60 kg</td>
<td>+3</td>
</tr>
<tr>
<td>No</td>
<td>&lt;75</td>
<td>&gt;= 60 kg</td>
<td>+16</td>
</tr>
</tbody>
</table>

Primary Efficacy Endpoint: CV Death, MI, Stroke

1. All patients were on aspirin and low-dose aspirin (< 100 mg) was strongly recommended. For patients >60 years of age, 75 mg MD of prasugrel was given.

Adapted from Chin CT et al. Am Heart J. 2010;160:16-22.
**Prasugrel – FDA Label “Boxed Warning”**

**WARNING: BLEEDING RISK**

See full prescribing information for complete boxed warning

Prasugrel can cause significant, sometimes fatal, bleeding (5.1, 5.2, and 6.1).

Do not use prasugrel in patients with active pathological bleeding or a history of transient ischemic attack or stroke (4.1 and 4.2).

In patients ≥ 75 years of age, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk patients (diabetes or prior MI), where its effect appears to be greater and its use may be considered (8.5).

Do not start prasugrel in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue prasugrel at least 7 days prior to any surgery.

Additional risk factors for bleeding include:

- body weight < 60 kg
- propensity to bleed
- concomitant use of medications that increase the risk of bleeding

Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of prasugrel.

If possible, manage bleeding without discontinuing prasugrel. Stopping prasugrel, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events (5.3).


---

**CV Death, MI, or Stroke**

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSTEMI ACS (moderate-to-high risk) STEMI (if primary PCI) (N=18,624)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9,291</td>
<td>9,333</td>
<td>8,521</td>
</tr>
<tr>
<td>8,628</td>
<td>8,362</td>
<td>8,460</td>
</tr>
<tr>
<td>8,124</td>
<td>8,417</td>
<td>8,580</td>
</tr>
</tbody>
</table>

PLATO: Secondary Efficacy Endpoints

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CABG PLATO major bleeding</td>
<td>4.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Ticagrelor vs Clopidogrel</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>CABG PLATO major bleeding</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor vs Clopidogrel</td>
<td>0.025</td>
<td></td>
</tr>
</tbody>
</table>


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**PLATO: Invasive Therapy Subgroup**

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive</td>
<td>10.7%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Invasive</td>
<td>10.7%</td>
<td>9.0%</td>
</tr>
</tbody>
</table>

PLATO: Medical Therapy Subgroup

Ticagrelor – FDA Label

**Boxed Warning**

**WARNING: BLEEDING RISK**
- Ticagrelor, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).
- Do not use ticagrelor in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).
- Do not start ticagrelor in patients planned to undergo urgent coronary bypass graft surgery (CABG). When possible, discontinue ticagrelor at least 5 days prior to any surgery (5.1).
- Do not start ticagrelor in patients with a history intracranial hemorrhage (4.1, 4.2).
- Do not use ticagrelor in patients planned to undergo urgent coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of ticagrelor (5.1).
- If possible, manage bleeding without discontinuing ticagrelor. Stopping ticagrelor increases the risk of subsequent cardiovascular events (5.5).

**WARNING: Aspirin Dose and Ticagrelor Effectiveness**
- Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).


ACC/AHA 2014 NSTE-ACS Guideline

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA 162-325 mg dose ASAP x1</td>
<td>I A</td>
<td>I A</td>
</tr>
<tr>
<td>ASA 81-162mg dose indefinitely</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2Y12 Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ischemia-guided</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In addition to ASA for up to 12 months</td>
<td>I B</td>
<td>I B</td>
</tr>
<tr>
<td>- Clopidogrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ticagrelor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ticagrelor preferred to clopidogrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI with stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In addition to ASA for at least 12 months</td>
<td>I B</td>
<td>I B</td>
</tr>
<tr>
<td>- Clopidogrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Prasugrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Prasugrel preferred to clopidogrel</td>
<td>I B</td>
<td>I B</td>
</tr>
<tr>
<td>- Ticagrelor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ticagrelor preferred to clopidogrel</td>
<td>I B</td>
<td>I B</td>
</tr>
</tbody>
</table>

COMMIT: Effect of Clopidogrel on Death in Hospital

- 45,040 patients
- Inclusion: Suspected acute MI (ST change or LBBB) within 24 h of symptom onset
- Exclusion: Primary PCI or high-risk of bleeding
- Mean treatment and follow-up: 16 days
- 7% relative risk reduction (P=0.03)

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

ASA 162 to 325 mg before primary PCI.

After PCI, ASA indefinitely.

P2Y12 receptor inhibitor loading dose as early as possible or at time of primary PCI Options include:
- Clopidogrel 600 mg; or
- Prasugrel 60 mg; or
- Ticagrelor 180 mg

Comparing ADP Antagonists in ACS

<table>
<thead>
<tr>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro</td>
<td>Pro</td>
<td>Pro</td>
</tr>
<tr>
<td>• QD</td>
<td>• QD</td>
<td>• Potent</td>
</tr>
<tr>
<td>• Extensive evidence for superiority vs. ASA</td>
<td>• Potent</td>
<td>• Minimal variability</td>
</tr>
<tr>
<td>• Generic</td>
<td>• Fast onset</td>
<td>• Superiority vs. clopi</td>
</tr>
<tr>
<td>Con</td>
<td>Con</td>
<td>Con</td>
</tr>
<tr>
<td>• Inter-patient variability</td>
<td>• Non-surgical bleeding</td>
<td>• non-surgical bleeding</td>
</tr>
<tr>
<td>• Slow onset of action</td>
<td>• Prior stroke/TIA</td>
<td>• No generic</td>
</tr>
<tr>
<td>• Moderate inhibition</td>
<td>• Similar to clop in &gt;75yo and &lt; 60 kg</td>
<td>• BID Use</td>
</tr>
<tr>
<td>• ASA dose &lt;100mg</td>
<td>• No generic</td>
<td>• Dyspnea</td>
</tr>
</tbody>
</table>

Summary

- ASA 81 mg is the preferred dose after the initial dose in ED or cath lab
- Medically managed ACS (ischemia-guided)
  - Ticagrelor and clopidogrel indicated
  - Ticagrelor with superior efficacy/mortality reduction
  - Prasugrel not indicated
- Early invasive strategy ACS
  - Ticagrelor, prasugrel, clopidogrel indicated
  - Ticagrelor, prasugrel superior efficacy (ticagrelor mortality reduction) to clopidogrel with increased bleeding
- Duration of DAPT: generally one year

Secondary Prevention in Acute Coronary Syndromes

Jeffrey S Berger, MD, MS
Assistant Professor of Medicine and Surgery
Director of Cardiovascular Thrombosis
**Topic Outline**

- General approach and plan of care after ACS
- Antiplatelet/anticoagulant therapy
- Beta-blockers
- Anti-hypertensive & ACEI/ARB/aldosterone therapy
- Lipid-lowering therapy
- Anti-diabetic therapy
- Other selected secondary prevention recommendations

**Post-hospitalization Plan of Care**

A clear, detailed, and evidence-based plan of care that promotes medication adherence, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with interventions for secondary prevention should be provided to patients with STEMI.

2013 ACCF/AHA STEMI Guidelines

**Antiplatelet Rx after ACS**

After PCI, aspirin should be continued indefinitely. It is reasonable to use 81 mg of aspirin daily in preference to higher maintenance doses (IIa-B).

- Clopidogrel or ticagrelor— ischemia-guided strategy for up to 12 mos., in those receiving a stent for ≥ 12 mos.
- Clopidogrel, prasugrel or ticagrelor in those receiving a stent for ≥ 12 mos.
- Reasonable to use:
  - Prasugrel preferentially over clopidogrel in those who undergo PCI who are not at high bleeding risk.
  - Ticagrelor preferentially over clopidogrel in those treated with an early invasive strategy and/or PCI or ischemia-guided strategy.


**Antiplatelet Therapy in Stable Ischemic Heart Disease**

Treatment with aspirin 75 to 162 mg daily should be given and continued indefinitely in the absence of contraindications in patients with SIHD.

Treatment with clopidogrel is reasonable when aspirin is contraindicated in patients with SIHD.

Treatment with aspirin 75 to 162 mg daily and clopidogrel 75 mg daily might be reasonable in certain high-risk patients with SIHD.

2012 ACCF/AHA SIHD Guidelines

**CAPRIE Study: Efficacy of Clopidogrel in Primary Analysis (MI, Stroke, or Vascular Death)**

<table>
<thead>
<tr>
<th>Event Rate per Year</th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.7%</td>
<td>25%</td>
</tr>
<tr>
<td>5.8%</td>
<td>8.7%*</td>
</tr>
</tbody>
</table>

*ITT analysis.

7.7% Placebo

5.8% Clopidogrel

5.3% Aspirin

CAPRIE Study: Efficacy of Clopidogrel in Primary Analysis (MI, Stroke, or Vascular Death)

CHARISMA: Primary Efficacy Outcome (MI, Stroke, or CV Death)

0 3 6 9 12 15 18 21 24 27 30 33 36

Cumulative Event Rate (%) 0 2 4 6 8

Months since randomization

RRR: 7.1%* [95% CI: -4.5%, 17.5%] p=0.22

7.3% Placebo + Aspirin

6.8% Clopidogrel + Aspirin

*RRR 12% if symptomatic atherosclerosis, p=0.016


7 All patients received ASA 75-162 mg/day.
Central Role of Platelets and Interaction with Coagulation in the Genesis of Thrombosis

Shear, PGI2 Platelet Rupture

Collagen VWF Thrombin

Initiation of Coagulation

Thrombin + Tissue Factor

Amplification of Coagulation

Fibrinogen + Amplification

Fibrin + Thrombin + Amplification

Platelet-Membrane Clot Formation

ADP + GPIIb/IIIa + Platelet Aggregation

P2Y12 Activation + PAR-1 Activation

COX-1 + COX Expression

Thromboxane A2

vWF + Platelet Activation

GPIIb/IIIa + Platelet Aggregation

TxA2 + Platelet Aggregation


Anticoagulation

Anticoagulant therapy with a vitamin K antagonist should be provided to patients with STEMI and atrial fibrillation with CHADS2* score greater than or equal to 2, mechanical heart valves, venous thromboembolism, or hypercoagulable disorder.

The duration of triple-antithrombotic therapy with a vitamin K antagonist, aspirin, and a P2Y12 receptor inhibitor should be minimized to the extent possible to limit the risk of bleeding.†

*CHADS2 (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, previous Stroke/transient ischemic attack (doubled risk weight)) score.

†Individual circumstances will vary and depend on the indications for triple therapy and the type of stent placed during PCI. After this initial treatment period, consider therapy with a vitamin K antagonist plus a single antiplatelet agent. For patients treated with fibrinolysis, consider triple therapy for 14 days, followed by a vitamin K antagonist plus a single antiplatelet agent.

2013 ACCF/AHA STEMI Guidelines

Anticoagulation

Anticoagulant therapy with a vitamin K antagonist is reasonable for patients with STEMI and asymptomatic LV mural thrombi.

Targeting vitamin K antagonist therapy to a lower international normalized ratio (e.g., 2.0 to 2.5) might be considered in patients with STEMI who are receiving DAPT.

Anticoagulant therapy may be considered for patients with STEMI and anterior-apical akinesis or dyskinesis.

2013 ACCF/AHA STEMI Guidelines

Patient Education: Diet and Stress

It is reasonable to educate patients with SIHD about:

a. adherence to a diet that is low in saturated fat, cholesterol, and trans fat; high in fresh fruits, whole grains, and vegetables; and reduced in sodium intake, with cultural and ethnic preferences incorporated;

b. common symptoms of stress and depression to minimize stress related angina symptoms;

2012 ACCF/AHA SIHD Guidelines

WOEST: What is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting?

Primary Endpoint: TIMI bleeding events

Double therapy group vs. Triple therapy group

Cumulative incidence of bleeding

p = 0.001

HR = 0.36 [95% CI: 0.26-0.50]

**PREDIMED: Primary Prevention of CV Disease with a Mediterranean Diet**

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Mediterranean Diet (n=4,997)</th>
<th>Low Fat Control Diet (n=2,450)</th>
<th>Adjusted HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Rate per 1000 pt-yr (MI, CVA, CV death)</td>
<td>8.1</td>
<td>11.2</td>
<td>0.71 (0.56-0.90)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*High intake of olive oil, nuts, fruit, vegetables, cereals; moderate intake of fish, poultry; low intake of dairy products, red/processed meats, sweets; wine in moderation with meals. Entry criteria: type-2 diabetes or >=3 major risk factors. Follow-up to 5 years.


**Beta-Blocker Therapy**

- Beta-blocker therapy should be started and continued for 3 years in all patients with normal LV function after MI or ACS.

- Beta-blocker therapy should be used in all patients with LV systolic dysfunction (EF ≤40%) with heart failure or prior MI, unless contraindicated. (Use should be limited to carvedilol, metoprolol succinate, or bisoprolol, which have been shown to reduce risk of death.)

- Beta blockers may be considered as chronic therapy for all other patients with coronary or other vascular disease.

2012 ACCF/AHA SIHD Guidelines

**Blood Pressure Management**

- In patients with SIHD with BP 140/90 mm Hg or higher, antihypertensive drug therapy should be instituted in addition to or after a trial of lifestyle modifications.

- The specific medications used for treatment of high BP should be based on specific patient characteristics and may include ACE inhibitors and/or beta blockers, with addition of other drugs, such as thiazide diuretics or calcium channel blockers, if needed to achieve a goal BP of less than 140/90 mm Hg.

2012 ACCF/AHA SIHD Guidelines

**New Hypertension Guidelines**

- ACE inhibitors should be prescribed in all patients with SIHD who also have hypertension, diabetes mellitus, LVEF 40% or less, or CKD, unless contraindicated.

- ARBs are recommended for patients with SIHD who have hypertension, diabetes mellitus, LV systolic dysfunction, or CKD and have indications for, but are intolerant of, ACE inhibitors.


**Renin-Angiotensin-Aldosterone Blocker Therapy**

2012 ACCF/AHA SIHD Guidelines
**Lifestyle modifications**, including daily physical activity and weight management, are strongly recommended for all patients with SIHD.

Dietary therapy for all patients should include reduced intake of saturated fats (to <7% of total calories), trans fatty acids (to <1% of total calories), and cholesterol (to <200 mg/d).

In addition to therapeutic lifestyle changes, a moderate or high dose of a statin therapy should be prescribed, in the absence of contraindications or documented adverse effects.

For patients who do not tolerate statins, LDL cholesterol–lowering therapy with bile acid sequestrants,* niacin,† or both is reasonable.

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: moderate to high potency statin in all patients at discharge regardless of baseline LDL-C (Class I, LOE: A)


Lipid Management

Lifestyle modifications, including daily physical activity and weight management, are strongly recommended for all patients with SIHD.

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**Lipid Lowering Intensity: PROVE IT-TIMI 22**

4,162 patients with ACS; Atorvastatin 80 mg qd vs Pravastatin 40mg

The median LDL cholesterol level achieved during treatment was 95 mg/dl in the pravastatin group and 62 mg/dl in the atorvastatin group (P<0.001)


**HPS-2: THRIVE -- Effect of Extended Release Niacin/Laropiprant on Major Vascular Events**

25,673 SIHD patients on simvastatin +/- ezetimibe: TC/TG/HDL/LDL = 128/125/44/63 mg/dL

Risk ratio 0.96 (95% CI 0.90 – 1.03) Logrank P=0.29


**Diabetes Management**

For selected individual patients, such as those with a short duration of diabetes mellitus and a long life expectancy, a goal HbA1c of 7% or less is reasonable.

A goal HbA1c between 7% and 9% is reasonable for certain patients according to age, history of hypoglycemia, presence of microvascular or macrovascular complications, or presence of coexisting medical conditions.

**Physical Activity**

For all patients, the clinician should encourage 30 to 60 minutes of moderate-intensity aerobic activity, such as brisk walking, at least 5 days and preferably 7 days per week, supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, household work) to improve cardiorespiratory fitness and move patients out of the least-fit, least-active, high-risk cohort (bottom 20%).

For all patients, risk assessment with a physical activity history and/or an exercise test is recommended to guide prognosis and prescription.
Medically supervised programs (cardiac rehabilitation) and physician-directed, home-based programs are recommended for at-risk patients at first diagnosis. It is reasonable for the clinician to recommend complementary resistance training at least 2 days per week.

Overweight & Obesity

If overweight (BMI 25-29.9 kg/m²) or obese (BMI ≥30 kg/m²) then:

- Target 5-10% wt loss over 6 months
- Achieve by caloric restriction and/or ↑ physical activity
- Consider adding pharmacotherapy if BMI ≥30 kg/m² or ≥27 kg/m² w/ comorbidity
- Consider bariatric surgery if BMI ≥40 kg/m² or ≥35 kg/m² w/ comorbidity

Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home should be encouraged for all patients with SIHD. Follow-up, referral to special programs, and pharmacotherapy are recommended, as is a stepwise strategy for smoking cessation (Ask, Advise, Assess, Assist, Arrange, Avoid).

An annual influenza vaccine is recommended for patients with SIHD.

The pneumococcal vaccine is recommended for patients 65 years of age and older and in high-risk patients with cardiovascular disease.

Performance Matters!

Association Between Hospital Guideline Adherence and In-hospital Mortality in CRUSADE

Does Guideline Adherence Make a Difference?
Percutaneous Revascularization in UA/NSTEMI

**PCI-CURE Study**

2,658 patients with a NSTE-ACS undergoing PCI treated with aspirin and clopidogrel (300 mg load, 75 mg thereafter) for 4 weeks and then randomized to continued use of clopidogrel vs. placebo for 12 months

![Graph showing survival rates with and without clopidogrel](image)


Antiplatelet Therapy to Support PCI for NSTE-ACS

In patients receiving a stent (BMS or DES) during PCI for NSTE-ACS, P2Y12 inhibitor therapy should be given for at least 12 months.

If the risk of morbidity from bleeding outweighs the anticipated benefit of a recommended duration of P2Y12 inhibitor therapy after stent implantation, earlier discontinuation (e.g., < 12 mos.) of P2Y12 inhibitor therapy is reasonable.

![Graph showing survival rates with and without clopidogrel](image)


Medical Management in UA/NSTEMI

**CURE Trial**

12,562 patients with a NSTE-ACS randomized to daily aspirin (75-325 mg) or clopidogrel (300 mg load, 75 mg thereafter) plus aspirin (75-325 mg) for 12 months

![Graph showing survival rates with and without clopidogrel](image)


PLATO: Stratification by invasive vs non-invasive strategy

![Graph showing survival rates with and without clopidogrel](image)

James S et al. BMJ 2011;342:d3527;

What is the optimal aspirin dose following ACS? OASIS-7

N=25,086; 30 day follow-up; Aspirin 325mg vs 81mg (day 2-30)

<table>
<thead>
<tr>
<th>Dose</th>
<th>MACE</th>
<th>CV death</th>
<th>Major Bleeding</th>
<th>Minor Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>325mg</td>
<td>4.2</td>
<td>2.1</td>
<td>2.3</td>
<td>5.0</td>
</tr>
<tr>
<td>81mg</td>
<td>4.4</td>
<td>2.3</td>
<td>2.3</td>
<td>4.4</td>
</tr>
</tbody>
</table>

P values:

- MACE: 0.61
- CV death: 0.22
- Major Bleeding: 0.9
- Minor Bleeding: 0.04


Antiplatelet Rx after ACS

Clopidogrel or ticagrelor--ischemia-guided strategy for up to 12 mos.

Ticagrelor preferentially over clopidogrel in those treated with an ischemia-guided strategy.

![Graph showing survival rates with and without clopidogrel](image)

Antiplatelet Therapy for ACS

It is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses after PCI.


Lipid Management

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 post-revascularization patients.


Lipid Lowering Intensity: PROVE IT-TIMI 22

4,162 patients with ACS; Atorvastatin 80 mg qd vs Pravastatin 40mg
The median LDL cholesterol level achieved during treatment was 95 mg/dl in the pravastatin group and 62 mg/dl in the atorvastatin group (P<0.001)


Influenza

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