The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention

Ty Gluckman, MD
Medical Director, Clinical Transformation
Providence Heart and Vascular Institute
Oregon Region
Portland, OR

Karol Watson, MD, PhD
Professor of Medicine/Cardiology
David Geffen School of Medicine
University of California at Los Angeles
Los Angeles, CA

Oral Antiplatelet Therapies for Acute Coronary Syndromes: Exploring Pharmacologic Profiles, Efficacy, and Safety
Ty Gluckman, MD
Medical Director, Clinical Transformation
Providence Heart and Vascular Institute
Oregon Region
Portland, OR

Best Practices Pearls

- Incorporate aspirin, P2Y12 inhibitors, beta-blockers, statins, and angiotensin-converting enzyme inhibitors into secondary prevention management after myocardial infarction
- Utilize the preferred maintenance dose of ASA (81 mg) after an acute coronary syndrome (ACS)
- Ensure that ACS patients participate in cardiac rehabilitation programs since they improve fitness, medication adherence, and survival

What are the benefits of using antiplatelet therapy in patients with an ACS?

Efficacy of Aspirin in Secondary Prevention


The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention

Higher Dose Aspirin Does not Improve Efficacy

<table>
<thead>
<tr>
<th>Aspirin Dose</th>
<th>No. of Trials</th>
<th>% Odds Reduction</th>
<th>Odds Ratio for Vascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-1000 mg</td>
<td>34</td>
<td>19</td>
<td>P = .001</td>
</tr>
<tr>
<td>100-200 mg</td>
<td>19</td>
<td>20</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>53</td>
<td></td>
</tr>
<tr>
<td>Any aspirin</td>
<td>65</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

Effect of aspirin doses on vascular events in high-risk patients (excluding those with acute stroke)

Low Dose Aspirin is Preferred in ACS

Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events (CURRENT) - OASIS 7 Trial

25,087 patients with an ACS randomized in a 2 x 2 factorial trial to double dose clopidogrel (600 mg LD, 150 mg x 7 days, then 75 mg MD) vs standard dose clopidogrel (300 mg LD and 75 mg MD) and high dose aspirin (300-325 mg) vs low dose aspirin (75-100 mg)

Optimal Aspirin Dosing

CURRENT OASIS-7

N=25,087

2-by-2 factorial design

20-day follow-up

Aspirin in ACS: Guideline Recommendations

Aspirin should be used indefinitely after a NSTE-ACS (Class I, Level B), with preference given to the 81 mg dose after PCI (Class IIa, Level B)

Aspirin (82-325 mg daily) following PCI or fibrinolytic therapy for a STEMI (Class I, Level A), with preference given to the 81 mg dose after PCI (Class IIa, Level B)

Dual Antiplatelet Therapy (DAT) in NSTE-ACS

Clopidogrel in Unstable Angina to Prevent Recurrent Events (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 a mean of 9 months

DAT in NSTE-ACS Benefits Medically Managed Patients

Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) Trial

Rate of major bleeding: clopidogrel (3.7%) vs. placebo (2.7%), P = .001

18% RRR
P = .015

20% RRR
P = .0025

8.1%
The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention

**DAT with Fibrinolysis in STEMI**

Clopidogrel as Adjunctive Reperfusion Therapy in Thrombolysis in Myocardial Infarction (CLARITY) Trial

3,491 patients (>75 years of age) presenting within 12 hours of a STEMI treated with fibrinolytic, aspirin, and heparin and randomized to clopidogrel (300 mg load followed by 75 mg daily) vs. placebo

**DAT in Medically Managed STEMI**

COMMIT/CC2 Trial

45,852 patients presenting within 24 hours of a STEMI treated medically and randomized to clopidogrel (75 mg daily) vs. placebo

**Clopidogrel in ACS: Guideline Recommendations**

- Use clopidogrel (75 mg daily) after a NSTE-ACS:
  - In those with contraindication to or intolerance of aspirin
  - In those treated with a BMS for up to 12 months
  - In those treated with a DES for at least 12 months

- Use clopidogrel (75 mg daily) after a STEMI:
  - In those treated medically for at least 14 days (Class I, Level A) and up to 12 months (Class I, Level B)
  - In those treated with PCI following fibrinolysis for at least 30 days and up to 12 months for a BMS and at least 12 months for a DES (Class I, Level C)
  - In those treated with PCI without preceding fibrinolysis for at least 12 months (Class I, Level B)

**Drug-Drug Interactions (DDI) With Clopidogrel**

- DDI: Clopidogrel and Proton Pump Inhibitors*

  Retrospective Cohort of 8,205 Patients After an ACS

- DDI: Clopidogrel and Proton Pump Inhibitors

  Clopidogrel and the Optimization of GI Events Trial (COGENT)

  3,627 patients with an ACS or undergoing PCI randomized to fixed dose combination clopidogrel (75 mg) and omeprazole (20 mg) in addition to aspirin (75-325 mg) vs. clopidogrel (75 mg) and aspirin (75-325 mg) for a median of 133 days
Is There Variability in How Individuals Respond to Antiplatelet Therapy?

Ex Vivo Variability in Response to Clopidogrel

Impact of Platelet Reactivity in ACS Patients Treated with PCI

CYP2C19 Polymorphisms and Outcomes With Clopidogrel

Clopidogrel Label Changes

Metabolism of P2Y12 Blockers
The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention

### Properties of Oral Antiplatelet Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mech. / Class</th>
<th>Reversible?</th>
<th>T1/2</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>COX-1, salicylate</td>
<td>No</td>
<td>4 h</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>P2Y12i, thienopyridine</td>
<td>Yes</td>
<td>6 h</td>
<td></td>
</tr>
<tr>
<td>Prasugrel</td>
<td>P2Y12i, thienopyridine</td>
<td>Yes</td>
<td>7 h</td>
<td></td>
</tr>
<tr>
<td>Ticagrel</td>
<td>P2Y12i, Non-TP</td>
<td>Yes</td>
<td>7 h</td>
<td>Strong CYP 3A4 Inhibitors &amp; Inducers</td>
</tr>
</tbody>
</table>

**Drug**

- **Aspirin**
  - **Mech. / Class**: COX-1, salicylate
  - **Reversible?**: No
  - **T1/2**: 4 h
  - **Interactions**: Hepatic

- **Clopidogrel**
  - **Mech. / Class**: P2Y12i, thienopyridine
  - **Reversible?**: Yes
  - **T1/2**: 6 h
  - **Interactions**: Hepatic, CYP2C19 inhibitors

- **Prasugrel**
  - **Mech. / Class**: P2Y12i, thienopyridine
  - **Reversible?**: Yes
  - **T1/2**: 7 h
  - **Interactions**: Hepatic

- **Ticagrelor**
  - **Mech. / Class**: P2Y12i, Non-TP
  - **Reversible?**: Yes
  - **T1/2**: 7 h
  - **Interactions**: Strong CYP 3A4 Inhibitors & Inducers

**Aspirin**

- **Mech. / Class**: COX-1, salicylate
- **Reversible?**: No
- **T1/2**: 4 h
- **Interactions**: Hepatic

**Clopidogrel**

- **Mech. / Class**: P2Y12i, thienopyridine
- **Reversible?**: Yes
- **T1/2**: 6 h
- **Interactions**: Hepatic, CYP2C19 inhibitors

**Prasugrel**

- **Mech. / Class**: P2Y12i, thienopyridine
- **Reversible?**: Yes
- **T1/2**: 7 h
- **Interactions**: Hepatic

**Ticagrelor**

- **Mech. / Class**: P2Y12i, Non-TP
- **Reversible?**: Yes
- **T1/2**: 7 h
- **Interactions**: Strong CYP 3A4 Inhibitors & Inducers

**Reference**


**Benefit to Prasugrel in ACS Treated with PCI**

**Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38)**

13,688 patients with an ACS randomized to clopidogrel (300 mg LD and 75 mg MD) or prasugrel (60 mg LD and 10 mg MD) for a median of 12 months

- CV Death, non-fatal MI or non-fatal stroke (%)
  - Prasugrel: 9.9 (781)
  - Clopidogrel: 12.1 (781)

- CV Death (%)
  - Prasugrel: 2.1
  - Clopidogrel: 2.4

- Nonfatal MI (%)
  - Prasugrel: 7.3
  - Clopidogrel: 9.5

- Nonfatal stroke (%)
  - Prasugrel: 1.0
  - Clopidogrel: 1.0

- Death from any cause (%)
  - Prasugrel: 3.0
  - Clopidogrel: 3.6

- CV Death, nonfatal MI, urgent TVR (%)
  - Prasugrel: 10.0
  - Clopidogrel: 12.3

- Death from any cause, nonfatal MI, or nonfatal stroke (%)
  - Prasugrel: 13.3
  - Clopidogrel: 16.7

- Urgent TVR (%)
  - Prasugrel: 2.5
  - Clopidogrel: 3.7

- CV Death, nonfatal MI, nonfatal stroke or rehosp for ischemia (%)
  - Prasugrel: 12.8
  - Clopidogrel: 14.6

**Reference**


**PRINCIPLE TIMI 44: Comparison with Higher Dose Clopidogrel**

- IPA = inhibition of platelet aggregation
- ADP = adenosine diphosphate

**Benefit to Prasugrel in ACS Treated with PCI**

**TRITON-TIMI 38: Major Efficacy End Points at 15 Months**

<table>
<thead>
<tr>
<th>End Point</th>
<th>(N=6813)</th>
<th>(N=7295)</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</td>
<td>649 (9.8)</td>
<td>791 (12.9)</td>
<td>0.81 (0.73-0.90)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>475 (7.2)</td>
<td>620 (9.5)</td>
<td>0.76 (0.67-0.86)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>188 (2.6)</td>
<td>187 (2.8)</td>
<td>0.95 (0.79-1.12)</td>
<td>0.4</td>
</tr>
<tr>
<td>CV Death, nonfatal MI, or urgent TVR</td>
<td>502 (7.5)</td>
<td>574 (8.2)</td>
<td>0.81 (0.73-0.90)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Death from any cause, nonfatal MI, or nonfatal stroke</td>
<td>660 (7.6)</td>
<td>802 (10.7)</td>
<td>0.82 (0.75-0.90)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Urgent TVR</td>
<td>130 (2.3)</td>
<td>253 (3.7)</td>
<td>0.68 (0.56-0.81)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>CV Death, nonfatal MI, nonfatal stroke or rehosp for ischemia</td>
<td>707 (12.3)</td>
<td>833 (14.6)</td>
<td>0.84 (0.74-0.95)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Mean score for 3C</td>
<td>96 (1.6)</td>
<td>110 (2.6)</td>
<td>0.84 (0.74-0.95)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

**Reference**


**TRITON-TIMI 38: Bleeding Events**

**Safety Cohort (N=13,457)**

- **TRITON-TIMI 38: Major Efficacy End Points at 15 Months**
- **TRITON-TIMI 38: Net Clinical Benefit Bleeding Risk Subgroups (Post-hoc Analysis)**

**Rate of major bleeding, defined as ≥30 mL, per 1 patient (1 PLU, 1.0), N=20**

ACS=Acute coronary syndrome, CV=Cardiovascular, HR=Hazard ratio, LD=Loading dose, MD=Maintenance dose

**Rate of major bleeding, defined as ≥30 mL, per 1 patient (1 PLU, 1.0), N=20**

**TRITON-TIMI 38: Major Efficacy End Points at 15 Months**

- **CV Death, non-fatal MI or non-fatal stroke (%)**
  - Prasugrel: 649 (9.8)
  - Clopidogrel: 791 (12.9)

- **Nonfatal MI (%)**
  - Prasugrel: 475 (7.2)
  - Clopidogrel: 620 (9.5)

- **Nonfatal stroke (%)**
  - Prasugrel: 61 (1.0)
  - Clopidogrel: 60 (1.0)

- **Death from any cause (%)**
  - Prasugrel: 188 (2.6)
  - Clopidogrel: 187 (2.8)

- **CV Death, nonfatal MI, or urgent TVR (%)**
  - Prasugrel: 502 (7.5)
  - Clopidogrel: 574 (8.2)

**Reference**

The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention

**Black Box Warning with Prasugrel**

- Prasugrel can cause significant, sometimes fatal, bleeding
- Do not use prasugrel in patients with active pathological bleeding or a history of transient ischemic attack or stroke
- In patients aged 75 and older, prasugrel is generally not recommended because of the increased risk of intracranial and fatal bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI). In these situations, the drug’s effect appears to be greater, and its use may be considered.
- Additional risk factors for bleeding include:
  - body weight < 60 kg
  - propensity to bleed
  - concomitant use of medications that increase the risk of bleeding

<table>
<thead>
<tr>
<th><strong>PLATO: Major Efficacy Endpoints</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary objective, n (%)</strong></td>
</tr>
<tr>
<td>CV death + MI + stroke</td>
</tr>
<tr>
<td>Prasugrel (n=333)</td>
</tr>
<tr>
<td>Clopidogrel (n=329)</td>
</tr>
<tr>
<td>HR for (95% CI)</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>0.86 (9.8)</td>
</tr>
<tr>
<td>1.01 (11.7)</td>
</tr>
<tr>
<td>0.84 (0.97-0.92)</td>
</tr>
<tr>
<td><strong>Secondary objectives, n (%)</strong></td>
</tr>
<tr>
<td>Total death + MI + stroke</td>
</tr>
<tr>
<td>Prasugrel (n=333)</td>
</tr>
<tr>
<td>Clopidogrel (n=329)</td>
</tr>
<tr>
<td>HR for (95% CI)</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>0.90 (10.2)</td>
</tr>
<tr>
<td>1.00 (12.3)</td>
</tr>
<tr>
<td>0.94 (0.97-0.92)</td>
</tr>
<tr>
<td>CV death + MI + stroke + ischaemia + TIMI grade 3 or higher thrombotic events</td>
</tr>
<tr>
<td>Prasugrel (n=333)</td>
</tr>
<tr>
<td>Clopidogrel (n=329)</td>
</tr>
<tr>
<td>HR for (95% CI)</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>1.29 (14.0)</td>
</tr>
<tr>
<td>1.40 (18.7)</td>
</tr>
<tr>
<td>1.29 (0.90-1.90)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Prasugrel (n=333)</td>
</tr>
<tr>
<td>Clopidogrel (n=329)</td>
</tr>
<tr>
<td>HR for (95% CI)</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>5.09 (5.8)</td>
</tr>
<tr>
<td>5.00 (5.9)</td>
</tr>
<tr>
<td>0.64 (0.75-0.90)</td>
</tr>
<tr>
<td>Sudden death</td>
</tr>
<tr>
<td>Prasugrel (n=333)</td>
</tr>
<tr>
<td>Clopidogrel (n=329)</td>
</tr>
<tr>
<td>HR for (95% CI)</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>1.52 (1.5)</td>
</tr>
<tr>
<td>1.56 (1.5)</td>
</tr>
<tr>
<td>1.17 (0.95-1.52)</td>
</tr>
<tr>
<td>Total death</td>
</tr>
<tr>
<td>Prasugrel (n=333)</td>
</tr>
<tr>
<td>Clopidogrel (n=329)</td>
</tr>
<tr>
<td>HR for (95% CI)</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>3.89 (4.5)</td>
</tr>
<tr>
<td>5.06 (5.9)</td>
</tr>
<tr>
<td>0.78 (0.69-0.86)</td>
</tr>
</tbody>
</table>

**PLATO: Non-CABG and CABG-related Major Bleeding**

- No Benefit to Prasugrel in Medically Managed ACS
- Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS)
- 7243 patients with a medically managed NSTE-ACS randomized to prasugrel (10 mg) or clopidogrel for up to 30 months

**Benefit to Ticagrelor in ACS Treated With/Without PCI**

- Platelet Inhibition and Patient Outcomes (PLATO) Study
- 18,624 patients with a moderate to high risk ACS randomized to clopidogrel (300-600 mg LD and 75 mg MD) or ticagrelor (180 mg LD and 90 mg twice daily MD) for 12 months

**TRILOGY ACS: Incidence of Bleeding Outcomes (Age <75 years)**

- CV=Cardiovascular, MI=Myocardial infarction, NSTE-ACS=Non-ST-segment elevation acute coronary syndrome

*No statistically significant differences were observed in bleeding rates overall.*

**Benefit to Ticagrelor in ACS Treated With/Without PCI**


- The statistically significant differences are observed in bleeding rates overall.
- ACS=Acute coronary syndrome, CABG=Coronary artery bypass graft surgery, LD=Loading dose, MD=Maintenance dose

- *CV Death, MI, or Stroke (%)*

- *HR 0.84, P=0.001*
The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention

PLATO: Medical Therapy Subgroup

PLATO: Invasive Therapy Subgroup

Side Effects With Ticagrelor

<table>
<thead>
<tr>
<th>All patients</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea, %</td>
<td>13.8</td>
<td>7.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>With discontinuation of study treatment</td>
<td>0.9</td>
<td>0.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>7-day Holter Results</td>
<td>Ventricular pauses ≤ 3 seconds, %</td>
<td>5.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Ventricular pauses ≥ 5 seconds, %</td>
<td>2.0</td>
<td>1.2</td>
<td>.10</td>
</tr>
</tbody>
</table>

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 3 days prior to any surgery (5.1).
- 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 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).
The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention

**Prasugrel and Ticagrelor in ACS: Guideline Recommendations**

- Ticagrelor (90 mg twice daily) should be used after a NSTEMI-ACS in those treated medically for up to 12 months (Class I, Level B)
- Ticagrelor (90 mg twice daily) or prasugrel (10 mg daily) should be used after a NSTEMI-ACS in those:
  - With a contraindication to or intolerance of aspirin (Class I, Level C)
  - Treated with PCI for up to 12 months for a BMS and at least 12 months for a DES (Class I, Level B)

**Efficacy of Dual Antiplatelet Therapy in ACS**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary End Point</th>
<th>A + C</th>
<th>A + P (T)</th>
<th>P-value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE1</td>
<td>CVD, MI, CVA</td>
<td>9.3%</td>
<td>11.4%</td>
<td>&lt;.001</td>
<td>48</td>
</tr>
<tr>
<td>CLARITY2</td>
<td>CVD, MI, URI*</td>
<td>11.6%</td>
<td>14.1%</td>
<td>.03</td>
<td>40</td>
</tr>
<tr>
<td>COMMIT3</td>
<td>CVD, MI, CVA</td>
<td>9.2%</td>
<td>10.1%</td>
<td>.002</td>
<td>111</td>
</tr>
<tr>
<td>TRITON-TIMI 4</td>
<td>CVD, MI, CVA</td>
<td>12.1%</td>
<td>13.9%</td>
<td>.0004</td>
<td>46</td>
</tr>
<tr>
<td>PLATO4</td>
<td>CVD, MI, CVA</td>
<td>11.7%</td>
<td>9.8%</td>
<td>&lt;.001</td>
<td>54</td>
</tr>
</tbody>
</table>

- Dual antiplatelet therapy increases the risk of bleeding

**Safety of Dual Antiplatelet Therapy in ACS**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Aspirin Dose</th>
<th>A + C</th>
<th>A + P (T)</th>
<th>P-value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE1</td>
<td>75-325 mg</td>
<td>3.1%</td>
<td>2.7%</td>
<td>.001</td>
<td>167</td>
</tr>
<tr>
<td>COMMIT3</td>
<td>&gt;100 mg</td>
<td>2.8%</td>
<td>3.0%</td>
<td>&lt;.001</td>
<td>50</td>
</tr>
<tr>
<td>&gt;100-200 mg</td>
<td>3.5%</td>
<td>4.3%</td>
<td>5.0%</td>
<td>.003</td>
<td>52</td>
</tr>
<tr>
<td>&gt;200 mg</td>
<td>4.9%</td>
<td>4.0%</td>
<td>5.2%</td>
<td>.002</td>
<td>54</td>
</tr>
<tr>
<td>COMMIT3</td>
<td>100-200 mg</td>
<td>3.5%</td>
<td>3.8%</td>
<td>.001</td>
<td>50</td>
</tr>
<tr>
<td>&gt;200 mg</td>
<td>4.3%</td>
<td>4.6%</td>
<td>5.4%</td>
<td>.003</td>
<td>50</td>
</tr>
<tr>
<td>TRITON-TIMI 4</td>
<td>75-162 mg</td>
<td>1.8%</td>
<td>2.4%</td>
<td>.09</td>
<td>177</td>
</tr>
</tbody>
</table>

- CURE Trial investigators. JAMA. 2007;30:2259-2268. 2
- TIMI 38 trial investigators. JAMA. 2005;395:2259-2268. 4
- O’Gara PT et al. NEJM. 2007;352:1179-1189. 5
- Anderson JL et al. JACC. 2010;55:2473-2484. 6

**Greater Platelet Inhibition Improves PCI Outcomes**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary End Point</th>
<th>A + C</th>
<th>A + P (T)</th>
<th>P-value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRITON-TIMI 4</td>
<td>CVD, MI, CVA</td>
<td>12.1%</td>
<td>13.9%</td>
<td>.0004</td>
<td>46</td>
</tr>
<tr>
<td>PLATO5</td>
<td>CVD, MI, CVA</td>
<td>10.7%</td>
<td>9.8%</td>
<td>&lt;.001</td>
<td>54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial</th>
<th>Aspirin Dose</th>
<th>A + C</th>
<th>A + P (T)</th>
<th>P-value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRITON-TIMI 4</td>
<td>75-162 mg</td>
<td>1.8%</td>
<td>2.4%</td>
<td>.09</td>
<td>177</td>
</tr>
</tbody>
</table>

**Take Aways**

- Long term aspirin therapy is important in secondary prevention
- Dual antiplatelet therapy improves clinical outcomes in ACS
- Dual antiplatelet therapy should be used after an ACS with or without PCI
- Current guidelines recommend at least 1 year of a P2Y12 inhibitor
- Dual antiplatelet therapy increases the risk of bleeding
- Low dose aspirin (81 mg) should be used preferentially when given in conjunction with a P2Y12 inhibitor
- There is variability in patient response to antiplatelet therapy with clopidogrel
The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention

Take Aways

- Medically managed ACS
  - Clopidogrel or ticagrelor should be added to aspirin
  - Ticagrelor offers superior efficacy and reduced mortality
  - Prasugrel is not indicated for this population

- Invasively managed ACS
  - Clopidogrel, prasugrel, or ticagrelor should be added to aspirin
  - Compared to clopidogrel, both prasugrel and ticagrelor are associated with superior efficacy (mortality reduction with ticagrelor) and a small increased risk of major bleeding

Potential Therapies for Atherosclerosis

- Folate
- Nitrates
- Iron Chelation
- Antioxidants
- Calcium Channel Blockers
- Beta-blockers
- Statins
- Calcium
- Aspirin
- Exercise
- Blood Pressure Control
- L-Arginine
- Olive Oil
- Vitamin D
- Red Wine
- Alcohol
- Lasers
- ACE inhibitors
- Weight Loss
- Vitamin E
- Beta blockers
- Resins
- Biodegradable
- Platelet antagonists
- Soy Beams
- Resins
- Biofeedback
- Vegetables
- Diet

Post ACS Medical Management

Karol Watson, MD, PhD
Professor of Medicine/Cardiology
David Geffen School of Medicine
University of California at Los Angeles
Los Angeles, CA

Guidelines

- 2011 ACCF/AHA PCI Guidelines
- 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Stable Ischemic Heart Disease (SIHD) Guidelines
- 2012 ACCF/AHA UA/NSTEMI Focused Update
- 2013 ACCF/AHA STEMI Guideline
- 2013 ACC/AHA Cholesterol Guideline
- 2013 Hypertension Guidelines (JNC 8)

Classification of Recommendations and Levels of Evidence

- Class I: Benefit >> Risk
  - Procedure or treatment SHOULD be performed or administered

- Class IIa: Benefit >> Risk
  - Additional studies with focused objectives needed
  - It is reasonable to perform procedure or administer treatment

- Class IIb: Benefit ≥ Risk
  - Additional studies with broad objectives needed
  - Procedure or treatment MAY BE CONSIDERED

- Class III: Risk ≥ Benefit
  - No additional studies needed
  - Procedure or treatment should NOT be performed or administered since it is NOT HELPFUL AND MAY BE HARMFUL

Post-ACS Management

Weight Control
Why Weight Control Matters

Abdominal Obesity and Increased Risk of Cardiovascular Events

Why Weight Control Matters

Abdominal Obesity and Increased Risk of Cardiovascular Events

Obesity Trends* Among US Adults

Obesity Trends* Among US Adults

Weight Management Recommendations

Post-ACS Management

Physical Activity
The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention

Exercise Evidence: Mortality Risk

Observational study of self-reported physical activity in 772 men with established coronary heart disease

Age-adjusted mortality rates/1000 person-years

Light or moderate exercise is associated with lower risk


Exercise Evidence: Mortality Risk

Aerobics Center Longitudinal Study–13,344 Middle-aged Patients: 8 year follow-up

All-cause mortality

Men

Woman

Fitness:


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 (eg, 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


Post-ACS Management

Lipid Management

Reduction in CV Events With Statin Therapy

RRR per 40 mg/dL reduction in LDL cholesterol

The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention


ACS, h/o MI, angina, revascularization, TIA, stroke, peripheral arterial disease

* Statins contraindicated in pregnancy & lactation

ACS = acute coronary syndrome; TIA = transient ischemic attack

*Check package inserts for safety information on Statins

All patients should be counseled about the need for lifestyle modification: weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products


Blood Pressure Management

All patients should be counseled about the need for lifestyle modification: weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products

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

Hypertension Guidelines JNC 8


*Check package inserts for safety information on Diuretics, CCBs, ACEIs, ARBs

Lifestyle Modifications for BP Control

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate SBP Reduction Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight (BMI=18.5-24.9)</td>
<td>5-20 mm Hg/10 kg weight lost</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>Diet rich in fruits, vegetables, low fat dairy and reduced in fat</td>
<td>8-14 mm Hg</td>
</tr>
<tr>
<td>Restrict sodium intake</td>
<td>&lt;2.4 grams of sodium per day</td>
<td>2-8 mm Hg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Regular aerobic exercise for at least 30 minutes on most days of the week</td>
<td>4-9 mm Hg</td>
</tr>
<tr>
<td>Moderate alcohol consumption</td>
<td>≤2 drinks/day for men and ≤1 drink/day for woman</td>
<td>2-4 mm Hg</td>
</tr>
</tbody>
</table>
The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention

Post-ACS Management
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.

Post-ACS Management
Beta Blockers

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.

ACEI / ARB Therapy

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.

*Check package inserts for safety information on Beta Blockers

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker

LV = left ventricular; EF = ejection fraction


*Check package inserts for safety information on ACE Inhibitors/Angiotensin Receptor Blockers

SIHD = stable ischemic heart disease; LVEF = left ventricular ejection fraction; CKD = chronic kidney disease

**The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention**

### Aldosterone Antagonists

6632 patients with recent MI, heart failure, and ejection fraction <40%

![Graph showing aldosterone antagonists effectiveness](image)

*Check package inserts for safety information on Aldosterone Antagonists*

### Post-ACS Management

**Antiplatelet Therapy**

**Aspirin Recommendations**

- Start and continue indefinitely aspirin 75 to 162 mg/d in all patients unless contraindicated

- It is reasonable to use 81 mg of aspirin daily in preference to higher maintenance doses


**P2Y12 Inhibitor Recommendations**

- In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y12 inhibitor therapy should be given for at least 12 months. Options include:
  - clopidogrel 75 mg daily,
  - prasugrel 10 mg daily, or
  - ticagrelor 90 mg twice daily

- For UA/NSTEMI patients in whom an initial conservative strategy is selected, clopidogrel or ticagrelor should be administered for up to 12 months

**A Different Approach:**

**Thrombin Receptor Inhibition**


26,649 patients with prior MI, ischemic stroke, or PAD randomized to vorapaxar (2.5 mg) or placebo for a median of 30 months

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

Morrow DA et al. NEJM 2012;366:1404-13

<table>
<thead>
<tr>
<th>Event</th>
<th>Vorapaxar (mg)</th>
<th>Placebo (mg)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death</td>
<td>2.0</td>
<td>2.4</td>
<td>0.84</td>
<td>0.12</td>
</tr>
<tr>
<td>MI</td>
<td>5.7</td>
<td>7.0</td>
<td>0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.3</td>
<td>1.6</td>
<td>0.77</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Vorapaxar increased the risk of

- Moderate or severe bleeding (8.2% vs 6.9%, p<0.01)
- Thrombotic events (1.5% vs 0.9%, p<0.01)

**CV = Cardiovascular, MI = Myocardial infarction, PAD = Peripheral artery disease**

---

*Images and graphs are placeholders for actual visual content.*

14
The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention

**Vorapaxar Does Not Provide Benefit in ACS Patients**

Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) Trial

12,944 patients with a NSTE-ACS randomized to vorapaxar (2.5 mg) or placebo for up to 2 years

Vorapaxar Does Not Provide Benefit in ACS Patients

CV Death, MI, Stroke, Hospitalization for Recurrent Ischemia, or Urgent Coronary Revascularization (%)

Days after randomization

Tricoci P et al. NEJM 2012;366:2033

DSMB = Data Safety Monitoring Board, NSTE-ACS = Non-ST-segment elevation acute coronary syndrome

The DSMB recommended premature cessation of the trial because of increased bleeding with vorapaxar

12,944 patients with a NSTE-ACS randomized to vorapaxar (2.5 mg) or placebo for up to 2 years

Vorapaxar increased the risk of:

- Moderate or severe bleeding (7.2% vs 5.2%, p<0.001)
- Intracranial hemorrhage (1.1% vs 0.2%, p<0.001)

**Vorapaxar Take Home Points**

- Antagonizes PAR-1
- Significantly reduces ischemic events an increased risk of major bleeding
- Approved for use only in patients with a history of MI or PAD
- Usually dosed at 2.08 mg/day
- Should not be used in patients with active pathological bleeding and/or a history of intracranial hemorrhage, TIA, or stroke
- Can be taken in conjunction with aspirin alone or aspirin with clopidogrel
- Has not been studied in conjunction with prasugrel or ticagrelor

**Post-hospitalization Plan of Care**

- Exercise-based cardiac rehabilitation/secondary prevention programs are recommended for patients with STEMI

**Influenza Vaccination**

- An annual influenza vaccine is recommended for patients with SIHD

**Secondary Prevention**

**Medications**

- Aspirin
- P2Y12 inhibitor
- β-blockers
- Lipids
- Fasting lipid panel within 24 h of hospitalization
- High intensity statin before discharge (moderate intensity if <75 yrs or if not a candidate)
- ACE inhibitors/ARBs
- Aldosterone blockade

**Goals**

- BP <140/90 mm Hg
- Smoking cessation/no environmental smoke exposure
- Physical activity (30 min, 7 d/wk; min 5 d/wk)
- Weight management
- Diabetes management: HbA1c <7%
- Annual influenza vaccine
- Cardiac Rehabilitation

**Cumulative Impact of Simple Cardiovascular Protective Medications**

<table>
<thead>
<tr>
<th>Medications</th>
<th>Relative-risk</th>
<th>2 yr CV event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>- -</td>
<td>20%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1/4</td>
<td>15%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>1/4</td>
<td>11.3%</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>1/4</td>
<td>8.4%</td>
</tr>
<tr>
<td>Lipid lowering Rx</td>
<td>1/4</td>
<td>5.9%</td>
</tr>
<tr>
<td>High intensity statin</td>
<td>1/4</td>
<td>5.0%</td>
</tr>
</tbody>
</table>

Cumulative risk reduction if all four therapies are used: 75%

Absolute risk reduction: 15%, NNT = 6

2. Fonarow G et al. Am J Cardiol. 2000;85:10A-17A
**Post-ACS Management**

**Smoking Cessation**

- Ask about smoking at every visit
- Advise all tobacco users to quit “I strongly advise you to quit”
- Assess readiness to quit
- Assist in finding appropriate therapies
- Arrange follow up

**Potential Health Benefits of Smoking Cessation**

**Time After Smoking**

- 20 min: BP, HR, peripheral circulation improve
- 24 hrs: CD levels drop
- 48 hrs: Nicotine eliminated; taste and smell improve
- 2-12 wks: Lung function can improve 30%
- 3-9 mo: SOB and coughing decrease
- 1 yr: Risk of MI reduced 50%
- 2 yr: Risk of lung cancer reduced 50%
- 3-12 wks: Risk of MI and stroke reduce to level of nonsmoker

**Smoking Cessation**

- Ask about smoking at every visit
- Advise all tobacco users to quit “I strongly advise you to quit”
- Assess readiness to quit
- Assist in finding appropriate therapies
- Arrange follow up

**US Studies on Reduction of AMI Associated with Public Smoking Bans**

<table>
<thead>
<tr>
<th>Setting</th>
<th>Author</th>
<th>Pop.</th>
<th>Period of study after ban</th>
<th>Effect of ban RR (95 CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helena, Montana</td>
<td>BMJ. 2004 June 5; 328(7452): 1379–1380</td>
<td>68,000</td>
<td>5 years</td>
<td>0.60 (40% (0.21-0.99)</td>
</tr>
<tr>
<td>Pueblo, Colorado</td>
<td>Meyers DG et al. J Am Coll Cardiol 2009; 54(14): 1249-1255</td>
<td>150,000</td>
<td>18 months</td>
<td>0.73 (27% (0.64-0.86)</td>
</tr>
<tr>
<td>Bowling Green, Ohio</td>
<td>Meyers DG et al. J Am Coll Cardiol 2009; 54(14): 1249-1255</td>
<td>30,000</td>
<td>18 months</td>
<td>0.61 (39% (0.55-0.67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>36 months</td>
<td>0.63 (47% (0.45-0.58)</td>
</tr>
</tbody>
</table>

**Case Study in the Management of ACS**

**Case 1: Presentation**

- 64 year-old male presents to your ED at 2:00 am with typical chest pain, shortness of breath, and diaphoresis
- History of hypercholesterolemia, smoking, and hypertension
- Meds: ASA, Atorvastatin, Metoprolol
The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention

**Case 1: Data**
- BMI 31
- HR 95 bpm
- BP 170/90
- JVP 6cm H₂O
- Clear chest
- Cardiac exam: 1/6 mid systolic murmur
- 2+ pulses; no edema

![ECG on arrival to ED](image)

**Reperfusion Therapy, and Time-to-Treatment Goals**
- Reperfusion therapy should be administered to all eligible patients with STEMI with symptom onset within the prior 12 hours
- Primary PCI is the recommended method of reperfusion when it can be performed in a timely fashion by experienced operators
- EMS transport directly to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI with an ideal FMC-to-device time system goal of 90 minutes or less

**Case 1: PCI**
- Patient is transferred to the nearby hospital and taken to cath lab
- Critical stenosis in the mid RCA is found
- Drug eluting stent placed
- Good flow afterward
- Patient sent to CCU

![RCA](image)

**Case 1: Hospital Course**
- Patient is transferred to CCU and has no further chest pain
- Cardiac enzymes: CK peak 402; MB peak 4.9; TnI peak 12.3
- After an uneventful hospital course, patient is discharged to home
- Meds on discharge: ASA, Atorvastatin, Metoprolol, Ticagrelor
- He then sees you for follow up care

**Antiplatelet Therapy to Support Primary PCI for STEMI**
- A loading dose of a P2Y₁₂ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include:
  - Clopidogrel 600 mg; or
  - Prasugrel 60 mg; or
  - Ticagrelor 180 mg

**Antiplatelet Therapy to Support Primary PCI for STEMI**
- P2Y₁₂ inhibitor therapy should be given for 1 year to patients with STEMI who receive a stent (BMS or DES) during primary PCI using the following maintenance doses:
  - Clopidogrel 75 mg daily; or
  - Prasugrel 10 mg daily; or
  - Ticagrelor 90 mg twice a day*

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily
The Dynamics of Contemporary Oral Antiplatelet Therapy for Acute Coronary Syndromes and Secondary Prevention

Lipid Management

- High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use

- It is reasonable to obtain a fasting lipid profile in patients with STEMI, preferably within 24 hours of presentation

Beta Blockers

- Beta-blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use

Best Practices Pearls

- Incorporate aspirin, P2Y₁₂ inhibitors, beta-blockers, statins, and angiotensin-converting enzyme inhibitors into secondary prevention management after myocardial infarction
- Utilize the preferred maintenance dose of ASA (81 mg) after an acute coronary syndrome (ACS)
- Ensure that ACS patients participate in cardiac rehabilitation programs since they improve fitness, medication adherence, and survival