Reducing Risk in the Acute Coronary Syndrome Patient: Insights for Primary Care Clinicians

September 19, 2013
Boston, Massachusetts
9:30–11am

Roger Blumenthal, MD
Professor of Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

Gregg Stone, MD
Professor of Medicine
Columbia University College of Physicians and Surgeons
New York, New York

Educational Partner:
Voxmedia, LLC
Session 2: Reducing Risk in the Acute Coronary Syndrome Patient: Insights for Primary Care Clinicians

Learning Objectives

1. Describe fundamental pharmacokinetics, pharmacodynamics, and pharmacogenetics of oral antiplatelet therapies.
2. Discuss efficacy and safety data with oral antiplatelet therapies from ACS outcomes trials.
3. Identify therapies to reduce risk and recognize goals to achieve in the management of patients who have experienced an acute coronary syndrome.

Faculty

Roger Blumenthal, MD  
Professor of Medicine  
Johns Hopkins University  
School of Medicine  
Baltimore, Maryland

Roger S. Blumenthal, MD, is professor of medicine in the division of cardiology at Johns Hopkins University School of Medicine in Baltimore. Dr Blumenthal graduated with honors from Johns Hopkins and received his medical degree from Cornell University Medical College. He did his fellowship training at Johns Hopkins Hospital and then joined the medical school faculty. His principal clinical and research interests involve the optimal management of ischemic heart disease, noninvasive detection of coronary atherosclerosis, and the development of new strategies to optimize the management of cardiovascular disease risk factors. Dr Blumenthal was the principal developer of the Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, and he is the director of preventive cardiology at Johns Hopkins. He has co-written more than 400 original research articles, state-of-the art reviews, and editorials dealing with many aspects of coronary artery disease and atherosclerosis management. Dr Blumenthal is on the editorial board of Cardiology Today, the American Heart Journal, and Clinical Cardiology. He was editor-in-chief of the 2011 textbook Preventive Cardiology – A Companion to Braunwald’s Heart Disease. For many years he has been the official national medical spokesperson for the American Heart Association (AHA)’s Cholesterol Low Down and was the chairperson of the American College of Cardiology (ACC) prevention of cardiovascular disease committee. An expert in noninvasive detection of vascular disease, Dr Blumenthal was also on the AHA’s official writing group about the utility of cardiac CT and CT angiography. He also was a member of the ACC task force dealing with selection of patients for atherosclerosis imaging techniques such as ultrafast CT scanning and carotid ultrasound. He is currently a director of the American Society of Preventive Cardiology.

Gregg Stone, MD  
Professor of Medicine  
Columbia University College of Physicians & Surgeons  
New York, New York

Gregg W. Stone, MD, is professor of medicine at Columbia University College of Physicians and Surgeons, and director of cardiovascular research and education at the Center for Interventional Vascular Therapies at Columbia University Medical Center, and the Cardiovascular Research Foundation in New York City. Dr Stone is a director of Transcatheter Cardiovascular Therapeutics. His medical practice is devoted to interventional cardiology at New York-Presbyterian Hospital/Columbia University Medical Center. He completed medical school at Johns Hopkins University School of Medicine in Baltimore and his
residency at the New York Hospital-Cornell Medical Center in New York City. He completed his general cardiology fellowship at Cedars-Sinai Medical Center in Los Angeles, California, and subsequently a dedicated fellowship in advanced coronary angioplasty with Dr Geoffrey Hartzler in Kansas City. Dr Stone has served as the national or international principal investigator for more than 50 national and international multicenter randomized trials. Dr Stone's areas of expertise include interventional therapies of acute coronary syndromes and myocardial infarction; drug-eluting stents; adjunct pharmacology; percutaneous heart valves, new device angioplasty including distal embolic protection, thrombectomy, vascular brachytherapy and stent grafts; intravascular ultrasound imaging; saphenous vein graft therapies; chronic total occlusions; vulnerable plaque; contrast nephropathy; clinical trial design; and regulatory issues. Dr Stone has authored more than 1000 book chapters, manuscripts, and abstracts published in the peer-reviewed literature.

Faculty Financial Disclosure Statements
The presenting faculty report the following:

Dr Blumenthal has no financial relationships to disclose.

Dr Stone receives fees as a consultant for AstraZeneca, Eli Lilly, and Daiichi-Sankyo.

Education Partner Financial Disclosure Statement
The content collaborator at Voxmedia reports the following:

John F. Kocsis, PhD, has no financial relationships to disclose.

Suggested Reading List


SESSION 2
9:30–11am

Reducing Risk in the Acute Coronary Syndrome Patient: Insights for Primary Care Clinicians

SPEAKERS
Roger Blumenthal, MD
Gregg Stone, MD

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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.

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, Glycron, Glynase, Micronase</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Zestril, Prinivil</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Nitro-Par, Nitro-Time, NitroMist, Nitrocut, Nitroglyn E-R, Nitrolingual, Nitroquick, Nitrostat, Nitrotab</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Coumadin, Jantoven, Marfarin</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>Integrillin</td>
</tr>
</tbody>
</table>

Learning Objectives

• Describe fundamental pharmacokinetics, pharmacodynamics, and pharmacogenetics of oral antiplatelet therapies.
• Discuss efficacy and safety data with oral antiplatelet therapies from ACS outcome trials.
• Identify therapies to reduce risk and recognize goals to achieve in the management of patients who have experienced an acute coronary syndrome (secondary prevention).

The Changing Landscape of Oral Antiplatelet Therapy in ACS Management

Gregg W. Stone MD
Columbia University Medical Center
Cardiovascular Research Foundation

The CAPRIE Trial: Clopidogrel vs Aspirin in Secondary Prevention
Primary Analysis (MI, Stroke, or Vascular Death)

Event Rate per Year

7.7% Placibo
8.83% Aspirin
8.75% Clopidogrel

Relative Risk Reduction

\( p = 0.045 \)

*ITT analysis.
**Dual Antiplatelet Therapy is Effective in the Setting of ACS: CURE**

- **Cumulative Hazard Rate**
  - Clopidogrel + ASA:
  - Placebo + ASA:

  \[ \text{Cumulative Hazard Rate} \]

  \[ P < 0.0001 \]
  \[ N = 12,562 \]

  \[ * \text{in addition to other standard therapies.} \]


---

**CURE Trial**

**Major Bleeding by ASA Dose**

<table>
<thead>
<tr>
<th>ASA Dose</th>
<th>Placebo + ASA (2.0%)</th>
<th>Clopidogrel + ASA (2.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 mg</td>
<td>2.0%</td>
<td>2.6%</td>
</tr>
<tr>
<td>100 – 200 mg</td>
<td>2.3%</td>
<td>3.5%</td>
</tr>
<tr>
<td>&gt;200 mg</td>
<td>4.0%</td>
<td>4.9%</td>
</tr>
</tbody>
</table>


---

**COMMIT: CLOPIDOGREL in 46,000 AMI Pts**

- **Death, Re-MI or Stroke**
  - Placebo + ASA: 2311 events (10.1%)
  - Clopidogrel + ASA: 2125 events (9.3%)

  \[ 9\% \text{ RRR (P=0.002)} \]

- **Mortality**
  - Placebo + ASA: 1846 deaths (8.1%)
  - Clopidogrel + ASA: 1728 deaths (7.5%)

  \[ 7\% \text{ RRR (P=0.03)} \]


---

**Limitations of Clopidogrel**

- Heterogenous antiplatelet response
- Genetic polymorphisms associated with poor response
- Drug-drug interaction
- Smoking interaction

Bonello L, JACC 2010;56:919-33
Ho PM, JAMA 2008;301:1837-44
Singer J, Circulation 2009;120:2337-44
Risk of All-Cause Mortality and Recurrent ACS in Patients Taking Clopidogrel and PPI

Ho PM et al. JAMA. 2009;301(9):937-944.

COGENT Trial Design

Non-STEMI, STEMI, or Elective Stent
n=3627

Aspirin

Clopidogrel 75 mg and Placebo

Planned enrollment: 5000; stopped due to bankruptcy
Mean follow-up 133 days (maximum, 362 days)

COGENT Trial – Effect of PPI on Composite GI Events

P = 0.001 by the log-rank test

COGENT Trial – Effect of PPI on Composite GI Events

Adjusted with Cox Proportional Hazards Model for NSAID use and positive H. pylori status.

CYP2C19 Genetic Polymorphisms and Outcomes With Clopidogrel


WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS
See full prescribing information for complete boxed warning.

• Effectiveness of clopidogrel depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
• Poor metabolizers treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
• Tests are available to identify a patient’s CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
• Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

Clopidogrel Label Changes

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020839s055lbl.pdf
The therapeutic target for thienopyridines and CPTPs is the platelet P2Y12 receptor.

**P2Y12 Receptor Antagonists**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>IPA (20 μM ADP)</th>
<th>Time to peak onset</th>
<th>Reversibility (d/c before CABG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor 180 mg LD*</td>
<td>CPTP*, cyclo-pentyl-triazolo-pyrimidine</td>
<td>80%</td>
<td>1-2 hrs</td>
<td>reversible</td>
</tr>
<tr>
<td>Ticagrelor 90 mg bid*</td>
<td>CPTP*, cyclo-pentyl-triazolo-pyrimidine</td>
<td>70%</td>
<td>-</td>
<td>2-5 days</td>
</tr>
<tr>
<td>Ticagrelor 150 mg</td>
<td>CPTP*, cyclo-pentyl-triazolo-pyrimidine</td>
<td>60%</td>
<td>-</td>
<td>non reversible</td>
</tr>
<tr>
<td>Ticagrelor 5 mg gd*</td>
<td>CPTP*, cyclo-pentyl-triazolo-pyrimidine</td>
<td>40%</td>
<td>-</td>
<td>7 days</td>
</tr>
<tr>
<td>Prasugrel 10 mg qd*</td>
<td>CPTP*, cyclo-pentyl-triazolo-pyrimidine</td>
<td>60%</td>
<td>-</td>
<td>non reversible</td>
</tr>
<tr>
<td>Prasugrel 5 mg qd*</td>
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<td>-</td>
<td>7 days</td>
</tr>
<tr>
<td>Prasugrel 60 mg LD*</td>
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<td>80%</td>
<td>1-2 hrs</td>
<td>non reversible</td>
</tr>
<tr>
<td>Ticagrelor 250 mg bid</td>
<td>Thienopyridine (pro-drug)</td>
<td>25%</td>
<td>48 hrs</td>
<td>non reversible</td>
</tr>
<tr>
<td>Ticagrelor 300 mg LD</td>
<td>Thienopyridine (pro-drug)</td>
<td>30% - 40%</td>
<td>12 hrs</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor 600 mg LD</td>
<td>Thienopyridine (pro-drug)</td>
<td>35% - 50%</td>
<td>6 hrs</td>
<td>non reversible</td>
</tr>
<tr>
<td>Ticagrelor 75 mg gd</td>
<td>Thienopyridine (pro-drug)</td>
<td>30% - 35%</td>
<td>-</td>
<td>5 days</td>
</tr>
<tr>
<td>Ticagrelor 150 mg gd</td>
<td>Thienopyridine (pro-drug)</td>
<td>45% - 50%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel 600 mg LD</td>
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<td>45% - 50%</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*Less affected by genetic polymorphisms and drug interactions (e.g. PPIs)

**TRITON TIMI-38: Study Design**

ACS (UA/NSTEMI or STEMI) & Planned PCI*

ASA

N= 13,600

**TRITON TIMI-38: Efficacy endpoints**

<table>
<thead>
<tr>
<th>Event</th>
<th>Prasugrel (n=6813)</th>
<th>Clopidogrel (n=6795)</th>
<th>HR [95%CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, stroke</td>
<td>9.9%</td>
<td>12.1%</td>
<td>0.81 [0.73, 0.90]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- CV death</td>
<td>2.1%</td>
<td>2.4%</td>
<td>0.89 [0.70, 1.12]</td>
<td>0.31</td>
</tr>
<tr>
<td>- Nonfatal MI</td>
<td>7.3%</td>
<td>9.5%</td>
<td>0.76 [0.67, 0.85]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Non fatal stroke</td>
<td>1.0%</td>
<td>1.0%</td>
<td>1.02 [0.71, 1.45]</td>
<td>0.93</td>
</tr>
<tr>
<td>Urgent TVR</td>
<td>2.5%</td>
<td>3.7%</td>
<td>0.66 [0.54, 0.81]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death, all-cause</td>
<td>3.0%</td>
<td>3.2%</td>
<td>0.95 [0.78, 1.16]</td>
<td>0.64</td>
</tr>
</tbody>
</table>

*Except STEMI
TRITON TIMI-38

Definite or probable stent thrombosis in 12,844 pts receiving any stent

0 0.5 1.0 1.5 2.0 2.5
0 50 100 150 200 250 300 350 400 450
HR [95%CI]
0.48 [0.36-0.64] P=0.0001
2.4% 1.1%

TIMI bleed, major or minor
- Major, CABG related 13.4% 3.2% 4.73 [1.90, 11.8] <0.001
- Major, non CABG related 2.4% 1.8% 1.32 [1.03, 1.68] 0.03
- Life-threatening 1.4% 0.9% 1.52 [1.08, 2.13] 0.01
- Fatal 0.4% 0.1% 4.19 [1.58, 11.1] 0.002
- Requiring transfusion 4.0% 3.0% 1.34 [1.11, 1.63] <0.001

TRITON TIMI-38: Net Clinical Benefit
CV Death / MI / CVA / TIMI Major Bleeding

<table>
<thead>
<tr>
<th>Prior Stroke / TIA</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk (%)</td>
<td>+37</td>
<td>-16</td>
</tr>
<tr>
<td>Post-hoc analysis</td>
<td>Prasugrel Better</td>
<td>Clopidogrel Better</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight</th>
<th>Risk (%)</th>
<th>Post-hoc analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥75</td>
<td>&lt;60 kg</td>
<td>+16</td>
<td>Prasugrel Better</td>
</tr>
<tr>
<td>&lt;75</td>
<td>260 kg</td>
<td>+14</td>
<td>Clopidogrel Better</td>
</tr>
<tr>
<td>OVERALL</td>
<td>0.5</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

TRILOGY ACS: Study Design

Medically managed UA or NSTEMI (68%)
(n=9,326)

Randomization stratified by:
- age, country, prior clopidogrel treatment
- Primary analysis cohort — Age <75 years; n=7,243

Primary Efficacy Endpoint: CV Death, MI, Stroke

HR (95% CI): 0.91 (0.79, 1.00) P = 0.21

FDA Label “Boxed Warning”

WARNING: BLEEDING RISK

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 can be considered (1.5).

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 surgery.

Additional risk factors for bleeding include:
- Body weight < 60 kg
- Propensity to bleed
- Concomitant use of medications that increase the risk of bleeding

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).
Primary Efficacy: CV death, MI, or stroke (Age < 75 years)

HR (95% CI) ≤ 1 Year: 0.99 (0.84, 1.16)
HR (95% CI) > 1 Year: 0.72 (0.54, 0.97)

Interaction P = 0.07

Primary Efficacy: CV death, MI, or stroke (Age < 75 years)

HR (95% CI): 0.91 (0.79, 1.05)
P = 0.21

Interaction P = 0.07

Median FU 17 months


Ticagrelor: an Oral Reversible P2Y12 Antagonist

Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

• Direct acting
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the P2Y12 receptor
  - Greater inhibition of platelet aggregation than clopidogrel
• Reversibly bound
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Functional recovery of all circulating platelets


Clopidogrel vs. Ticagrelor

ONSET/OFFSET Study


PLATO: Study Design

PLATO: Primary Efficacy Endpoint

Composite of CV Death, MI or Stroke


PLATO: Primary and Secondary Endpoint Events

**Clopidogrel (n=9,291)**

- CV death, MI, stroke: HR(95%CI) = 0.84 (0.77–0.92) \(P<0.001\)
- MI: HR(95%CI) = 0.79 (0.69–0.90) \(P=0.025\)
- Stroke: HR(95%CI) = 1.17 (0.93–1.47) \(P=0.22\)

**Ticagrelor (n=9,333)**

- CV death, MI, stroke: HR(95%CI) = 0.84 (0.75–0.95) \(P=0.005\)
- MI: HR(95%CI) = 0.78 (0.69–0.89) \(P<0.001\)
- Stroke: HR(95%CI) = 1.17 (0.91–1.52) \(P=0.22\)

**Wallentin L, et al. NEJM. 2009;361:1045-57.**

PLATO: Total Major Bleeding

- **Plato major bleeding**
- **TIMI major bleeding**
- **Red cell transfusion**
- **PLATO life-threatening/ fatal bleeding**


PLATO: Non-CABG and CABG-related Major Bleeding

- **Clopidogrel (n=9,291)**
- **Ticagrelor (n=9,333)**


PLATO: Substudy in pts intended for medical Rx

5216 (28%) of 18,624 ACS pts were specified for non-invasive management before randomization. UA in 35.4%, NSTEMI in 55.9%; STEMI in 8.7%.

**Efficacy endpoints**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Clopidogrel (n=9,291)</th>
<th>Ticagrelor (n=9,333)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death + myocardial infarction (including death)</td>
<td>12.0 (2.95)</td>
<td>14.3 (4.04)</td>
<td>0.85 (0.73 to 0.98)</td>
<td>0.001</td>
</tr>
<tr>
<td>All cause death</td>
<td>6.1 (1.67)</td>
<td>8.0 (1.95)</td>
<td>0.75 (0.61 to 0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Non-cardiovascular death</td>
<td>9.6 (1.95)</td>
<td>11.2 (2.37)</td>
<td>0.80 (0.60 to 1.05)</td>
<td>0.09</td>
</tr>
<tr>
<td>Strokes</td>
<td>2.1 (1.0)</td>
<td>1.4 (0.9)</td>
<td>0.58 (0.36 to 0.93)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hemorrhagic death</td>
<td>0.9 (1.1)</td>
<td>0.9 (1.2)</td>
<td>0.87 (0.59 to 1.29)</td>
<td>0.34</td>
</tr>
</tbody>
</table>


PLATO: Substudy in pts intended for medical Rx

5216 (28%) of 18,624 ACS pts were specified for non-invasive management before randomization. UA in 35.4%, NSTEMI in 55.9%; STEMI in 8.7%.

**Safety endpoints**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Clopidogrel (n=9,291)</th>
<th>Ticagrelor (n=9,333)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total major bleeding</td>
<td>11.2 (3.24)</td>
<td>10.3 (2.85)</td>
<td>1.17 (0.89 to 1.53)</td>
<td>0.25</td>
</tr>
<tr>
<td>Life-threatening or fatal bleeding</td>
<td>5.5 (1.25)</td>
<td>5.6 (1.28)</td>
<td>0.90 (0.77 to 1.06)</td>
<td>0.07</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.5 (0.1)</td>
<td>0.2 (0.1)</td>
<td>2.30 (0.95 to 5.60)</td>
<td>0.025</td>
</tr>
<tr>
<td>Other major bleeding</td>
<td>0.8 (0.64)</td>
<td>0.7 (0.58)</td>
<td>1.30 (0.99 to 1.70)</td>
<td>0.039</td>
</tr>
</tbody>
</table>


PLATO: Regional Outcomes According to ASA Maintenance Dose

**ASA Dose (mg)**

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
<th>Efficacy endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥300</td>
<td>464 66 492 50</td>
<td>1.45 (1.01, 2.09)</td>
<td>Overall</td>
</tr>
<tr>
<td>&gt;100&lt;300</td>
<td>525 64 527 65</td>
<td>0.99 (0.70, 1.40)</td>
<td>0.039</td>
</tr>
<tr>
<td>≤100</td>
<td>773 567 7706 723</td>
<td>0.77 (0.69, 0.86)</td>
<td>0.00006</td>
</tr>
</tbody>
</table>

**Wallentin L et al. NEJM 2009;361:1045-57.**

**N, number of patients; E, number of events**

[http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm221382.htm](http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm221382.htm)
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 artery bypass graft surgery (CABG). When possible, discontinue ticagrelor at least 5 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).

Why did ticagrelor reduce mortality in pts with ACS whereas prasugrel did not?

1. Increased fatal bleeding with prasugrel (but not ticagrelor), negating its beneficial effects in preventing MI and stent thrombosis
2. Off-target effects of ticagrelor (blocks rbc adenosine re-uptake) not present with prasugrel
3. Different study designs and other factors, including higher risk pts in PLATO than TRITON
4. Play of chance

PLATO: Dyspnea

Ticagrelor blocks rbc re-uptake of adenosine, and thus causes the sensation of dyspnea in some pts

UA/NSTEMI Guidelines: Key Points on Antiplatelets (Class I and III)

- ASA to all (clopidogrel if allergic)
- Medium - high risk and an invasive strategy get dual Rx
  - Before PCI: clopidogrel, ticagrelor, GP IIb/IIIa
  - At PCI: clopidogrel, ticagrelor, prasugrel, GP IIb/IIIa
- Conservative strategy: dual Rx w/ ASA + clopidogrel or ticagrelor
- Use loading doses of ADP blockers
- Duration for at least 12 months
- Class III (harm or no benefit): low risk and on ASA/ADP blocker ➔ no benefit to GP IIb/IIIa
- history stroke/TIA, prasugrel potentially harmful

STEMI Guidelines: Key Points on Antiplatelets (Class I and III)

- ASA for all and indefinitely
- Primary PCI
  - Loading dose as early as possible or at PCI: clopidogrel, ticagrelor, prasugrel
  - ADP blockers for 1 year
  - Class III (harm or no benefit): prasugrel potentially harmful (if h/o stroke/TIA)
- Fibrinolysis
  - Clopidogrel 300 mg loading dose, ≤ 75 years; 75 mg, > 75 years
  - Clopidogrel at least 14 days and up to 1 year
- PCI after fibrinolytic therapy
  - Clopidogrel 300 mg if no prior loading dose + PCI within 24 hours of fibrinolytic therapy; 600 mg if PCI > 24 hours afterwards
  - Duration of clopidogrel: BMS, 30 days to 1 year; DES, at least 1 year
  - Class III (harm or no benefit): prasugrel potentially harmful (if h/o stroke/TIA)

Optimizing Secondary Prevention in the ACS Patient

Roger S. Blumenthal, MD

Kenneth Jay Pollin Professor of Cardiology Director, The Johns Hopkins Ciccarone Center For the Prevention of Heart Disease

Disclosures: None
Definitions of Different Types of Prevention

**Primordial** Prevention: Prevention of CHD risk factors

**Primary** Prevention: Modification of risk factors in order to prevent or delay the onset of ASCVD

**Secondary** Prevention: Initiation of Rx to reduce **recurrent** CHD events & decrease cardiac mortality in patients with established ASCVD

CHD=Coronary heart disease

---

Case Study

- H.S is a 55 y/o Male with a PMH sig for HTN, HL, DM and an elevated BMI who presents to an ED with chest pain.

Case Study

- Cath lab is activated
- Angiography: 90% proximal LAD stenosis with 30-50% diameter stenoses in Cx and RCA
- PCI is performed with 1 DES
- Started on Aspirin, a P2Y12 inhibitor, a beta blocker, and an ACE inhibitor

---

Case Study

- Following day: ECHO - EF of 40% with anterior HK.
- Observed in the hospital for 2 days and discharged
- Presents to your office for follow up with many questions and concerns

---

Antiplatelet Rx

- H.S is discharged on Asprin 325 mg
- Is there a role for life-long Aspirin in a post ACS patient?
- He is concerned that his dose is too “high” - is he correct?
Dual Antiplatelet Rx

- Also concerned that he is now on a P2Y12 inhibitor.
- Is there a role in a post ACS patient?
- For how long?

Aspirin Recommendations (Continued)

### Secondary Prevention

- Aspirin (75-162 mg daily) if known CAD† or NSTE-ACS‡
- Aspirin (81-325 mg daily) following PCI or fibrinolytic therapy for a STEMI*
- Aspirin (preferentially at 81 mg daily) following PCI for NSTE-ACS# or STEMI* or lytic therapy for a STEMI*  

Sources:
- †Smith SC Jr. et al. JACC 2011;58:2432-2446
- ‡Wright RS et al. JACC 2011;57:e215-367
- *O’Gara PT et al. JACC 2013;61:e78-e140
- #Jneid H et al. JACC 2012;60:645-681

P2Y12 Receptor Antagonist Recommendations

Secondary Prevention

- Clopidogrel (75 mg daily), prasugrel (10 mg daily), or ticagrelor (90 mg twice daily) in addition to aspirin for 1 year following PCI for a NSTE-ACS† or a STEMI‡
- Clopidogrel (75 mg daily) in addition to aspirin for a minimum of 14 days (Class I, Level A) and up to 1 year (Class I, Level C) following fibrinolytic therapy for a STEMI*

Sources:
- †Jneid H et al. JACC 2012;60:645-681
- ‡O’Gara PT et al. JACC 2013;61:e78-e140

### JNC VII Guidelines: Measurement of Blood Pressure

<table>
<thead>
<tr>
<th>Method</th>
<th>Brief Description</th>
<th>BP=Blood pressure, CVD=Cardiovascular disease, HTN=Hypertension, Rx=Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-office</td>
<td>Two readings, 5 minutes apart, sitting in chair</td>
<td>Confirm elevated reading in contralateral arm</td>
</tr>
<tr>
<td>Ambulatory BP monitoring</td>
<td>Indicated for evaluation of “white-coat” HTN. Absence of 10–20% BP decrease during sleep indicates increased CVD risk</td>
<td></td>
</tr>
<tr>
<td>Self-measurement</td>
<td>Provides information on response to Rx. May help improve adherence to Rx and evaluate “white-coat” HTN</td>
<td></td>
</tr>
</tbody>
</table>

Blood Pressure Lowering Therapy Evidence: Effect of Intensive Blood Pressure Control

Cardio-SIS Trial

1,111 patients ≥55 years with SBP >150 mm Hg randomized to treatment to achieve usual BP control (SBP <140 mm Hg) or intensive BP control (SBP <130 mm Hg)

Incidence of CV events

<table>
<thead>
<tr>
<th>Group</th>
<th>21%</th>
<th>17.0</th>
<th>11.4</th>
<th>9.4</th>
<th>4.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tight Control</td>
<td></td>
<td>21%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

More intensive blood pressure control provides greater benefit

P<0.013

Blood Pressure Lowering Therapy Evidence: Effect of Intensive Blood Pressure Control

Action to Control Cardiovascular Risk in Diabetes (ACCORD)

Blood Pressure Trial

4,733 diabetic patients randomized to intensive BP control (target SBP <120 mm Hg) or standard BP control (target SBP <140 mm Hg) for 4.7 years

- Total stroke

HR: 0.88 95% CI (0.73-1.06)

- Nonfatal MI, nonfatal stroke, or CV death

HR: 0.59 95% CI (0.39-0.89)

Blood pressure lowering therapy evidence:

More intensive blood pressure control provides greater benefit

P<0.003

1,111 patients ≥55 years with SBP >150 mm Hg randomized to treatment to achieve usual BP control (SBP <140 mm Hg) or intensive BP control (SBP <130 mm Hg)

- Incidence of CV events

P<0.013

*Composite of death, MI, CVA, TIA, CHF, angina, new AF, revascularization, stroke, amputation, PAD, and ESRD

**Cardiovascular death, nonfatal MI, nonfatal stroke, CVD death, CVA, TIA, CHF, amputation, renal failure, PAD, ESRD, or MI

†Composite of death, MI, CVA, TIA, CHF, angina, new AF, revascularization, stroke, amputation, PAD, and ESRD

‡Cardiovascular death, nonfatal MI, nonfatal stroke, CVD death, CVA, TIA, CHF, amputation, renal failure, PAD, ESRD, or MI

ACCORD study group. NEJM 2010;362:1575-1585
JNC VII Guidelines: 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=18.5-25)</td>
<td>5-20 mmHg/10 kg weight lost</td>
</tr>
<tr>
<td>DASH eating plan</td>
<td>Diet rich in fruits, vegetables, low fat dairy</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td></td>
<td>and reduced in fat</td>
<td></td>
</tr>
<tr>
<td>Restricted sodium</td>
<td>&lt;2.4 grams of sodium per day</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Regular aerobic exercise for at least 30 minutes</td>
<td>4-10 mmHg</td>
</tr>
<tr>
<td></td>
<td>most days of the week</td>
<td></td>
</tr>
<tr>
<td>Moderate alcohol</td>
<td>≤2 drinks/day for men and ≤1 drink/day for women</td>
<td>2-4 mmHg</td>
</tr>
</tbody>
</table>

Source: Chobanian AV et al. JAMA 2003;289:2560-2572

BMI=Body mass index, BP=Blood pressure, SBP=Systolic blood pressure

ACE Inhibitor Evidence: Secondary Prevention

SAVE
Radionuclide EF ≥40%
AIRE
Clinical and/or echocardiographic signs of HF
TRACE
Radionuclide EF ≤25%

An ACE-I provides substantial benefit in post-MI LVSD

ACE Inhibitor Recommendations

Secondary Prevention

An ACE inhibitor should be started and continued indefinitely in all patients with left ventricular ejection fraction <40% and in those with hypertension, DM, or CKD, unless contraindicated.

An ACE inhibitor in all other patients

Beta-blocker Evidence: Benefit in HF and/or LVSD

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>HF Severity</th>
<th>Patients</th>
<th>Follow-up</th>
<th>Mean Dosage</th>
<th>Effects on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS-I</td>
<td>Bisoprolol</td>
<td>Moderate-Severe</td>
<td>641</td>
<td>1.9 years</td>
<td>3.8 mg/day</td>
<td>All cause mortality (p=NS)</td>
</tr>
<tr>
<td>CIBIS-II</td>
<td>Bisoprolol</td>
<td>Moderate-Severe</td>
<td>2,647</td>
<td>1.3 years</td>
<td>7.5 mg/day</td>
<td>All cause mortality (*p&lt;0.0001)</td>
</tr>
<tr>
<td>V-MIRI</td>
<td>Metoprolol</td>
<td>Moderate-Severe</td>
<td>3,991</td>
<td>1.0 years</td>
<td>159 mg/day</td>
<td>All cause mortality (p=0.0062)</td>
</tr>
<tr>
<td>MDC</td>
<td>Metoprolol</td>
<td>Moderate-Severe</td>
<td>383</td>
<td>1.0 years</td>
<td>108 mg/day</td>
<td>Death or need for TX (p=NS)</td>
</tr>
<tr>
<td>CAPRICORN</td>
<td>Carvedilol</td>
<td>Mild</td>
<td>1,989</td>
<td>1.3 years</td>
<td>40 mg/day</td>
<td>All cause mortality (*p&lt;0.03)</td>
</tr>
<tr>
<td>SENIORS</td>
<td>Nebivolol</td>
<td>Moderate</td>
<td>2,128</td>
<td>3.0 years</td>
<td>7.7 mg/day</td>
<td>All cause mortality or CV hospitalization (p=0.039)</td>
</tr>
</tbody>
</table>

Beta-blocker Recommendations

Secondary Prevention

Beta-blocker should be used in all patients with LVSD (ejection fraction <40%) with HF or prior MI, unless contraindicated. (Use carvedilol, metoprolol succinate, or bisoprolol, which have been shown to reduce mortality.)

Beta-blocker for 3 yrs in all patients with normal left ventricular function who have had a MI or ACS

Beta-blocker beyond 3 yrs as chronic therapy in all patients with normal left ventricular function who have had a MI or ACS (Continued)

Beta-blocker for patients with LVSD (ejection fraction ≤40%) without HF or prior MI

Beta-blocker as chronic therapy for all other patients with coronary or other vascular disease

ACE=Angiotensin converting enzyme, CKD=Chronic kidney disease, DM=Diabetes mellitus, EF=Ejection fraction, LVSD=Left ventricular systolic dysfunction, MI=Myocardial infarction, OR=Odds ratio

ACE=Angiotensin converting enzyme, DM=Diabetes mellitus, EF=Ejection fraction, LVSD=Left ventricular systolic dysfunction, MI=Myocardial infarction, OR=Odds ratio
Statin Rx

- H.S. has a fasting lipid panel with a total cholesterol of 240, HDL: 40, TG: 150, LDL: 170. He was discharged on Atorvastatin 80 mg.
- Should this be continued?

Therapies to Lower Levels of LDL-C

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Hydroxy-3-Methylglutaryl Coenzyme A</td>
<td>Atorvastatin (Lipitor)</td>
</tr>
<tr>
<td>(HMG-CoA) reductase inhibitors [Statins]</td>
<td>Fluvastatin (Lescol XL)</td>
</tr>
<tr>
<td></td>
<td>Lovastatin (generic and Mevacor)</td>
</tr>
<tr>
<td></td>
<td>Pravastatin (Livalo)</td>
</tr>
<tr>
<td></td>
<td>Pravastatin (Pravachol)</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin (Crestor)</td>
</tr>
<tr>
<td></td>
<td>Simvastatin (Zocor)</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Cholestyramine (generic and Questran)</td>
</tr>
<tr>
<td></td>
<td>Colesevelam (Welchol)</td>
</tr>
<tr>
<td></td>
<td>Colestipol (Colestid)</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitor</td>
<td>Ezetimibe (Zetia)</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Niacin</td>
</tr>
<tr>
<td>Dietary Adjuncts</td>
<td>Soluble fiber</td>
</tr>
<tr>
<td></td>
<td>Soy protein</td>
</tr>
<tr>
<td></td>
<td>Sterol esters</td>
</tr>
</tbody>
</table>

HMG-CoA Reductase Inhibitor: Chronological Order of Event Driven Trials

<table>
<thead>
<tr>
<th>Study Populations:</th>
<th>Study Years</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndromes (Secondary prevention)</td>
<td>1994</td>
<td>4S</td>
</tr>
<tr>
<td>Chronic coronary heart disease (Secondary prevention)</td>
<td>1995</td>
<td>WOSCOPS</td>
</tr>
<tr>
<td>1996</td>
<td>CARE</td>
<td>ASCOT-LLA</td>
</tr>
<tr>
<td>1998</td>
<td>AFCAPS/TEXCAPS</td>
<td>PROVE-IT</td>
</tr>
<tr>
<td>1998</td>
<td>LIPID</td>
<td>A to Z</td>
</tr>
<tr>
<td>2001</td>
<td>MIRACL</td>
<td>TNT</td>
</tr>
<tr>
<td>2002</td>
<td>HPS</td>
<td>IDEAL</td>
</tr>
<tr>
<td>2008</td>
<td>JUPITER</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>SEARCH</td>
<td></td>
</tr>
</tbody>
</table>

HMG-CoA Reductase Inhibitor Evidence: Secondary Prevention

- Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)—TIMI 22 Study
  - 4,162 pts with an ACS randomized to atorvastatin (80 mg) or pravastatin (40 mg) for 24 months
  - Acute intensive statin therapy provides significant CV benefit

- Scandinavian Simvastatin Survival Study (4S)
  - 4,444 patients with angina pectoris or previous MI randomized to simvastatin (20-40 mg) or placebo for 5.4 yrs
  - A statin provides significant benefit in those with average LDL-C levels

- Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study
  - 9,014 patients with a history of MI or hospitalization for unstable angina randomized to pravastatin (40 mg) or placebo for 6 yrs
  - A statin provides significant benefit across a broad range of cholesterol levels
### HMG-CoA Reductase Inhibitor Evidence: Secondary Prevention

#### Heart Protection Study (HPS)

<table>
<thead>
<tr>
<th>Baseline LDL-C (mg/dL)</th>
<th>Statin Better</th>
<th>Statin Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>282 (16.4%)</td>
<td>358 (21.0%)</td>
</tr>
<tr>
<td>100–129</td>
<td>668 (18.9%)</td>
<td>871 (24.7%)</td>
</tr>
<tr>
<td>≥130</td>
<td>1083 (21.6%)</td>
<td>1356 (26.9%)</td>
</tr>
<tr>
<td>All patients</td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
</tr>
</tbody>
</table>

A statin provides significant CV benefit regardless of baseline LDL-C level.

#### Event Rate Ratio (95% CI)

<table>
<thead>
<tr>
<th>Event Rate Ratio</th>
<th>Statin Better</th>
<th>Statin Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.76 (0.72–0.81)</td>
<td>P&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

### HMG-CoA Reductase Inhibitor Evidence: Effect of Intensive Therapy

#### Magnitude of event reduction among trials of intensive statin therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Duration (years)</th>
<th>LDL-C Reduction (mg/dL)</th>
<th>RR in Primary End Point (%)</th>
<th>RR in M or CHD Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT-TIMI 22</td>
<td>ACS (N = 4162)</td>
<td>2</td>
<td>33</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>A to Z</td>
<td>ACS (N = 4497)</td>
<td>2</td>
<td>14</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>TNT</td>
<td>Stable CAD (N = 10,001)</td>
<td>5</td>
<td>24</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>iDEAL</td>
<td>Stable CAD (N = 8868)</td>
<td>5</td>
<td>23</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

### Nicotinic Acid Evidence: Secondary Prevention

#### Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact of Global Health Outcomes (AIM-HIGH) Trial

3414 patients with established CV disease randomized to niacin (up to 2000 mg/day) or placebo on a background of statin therapy for a mean of 3 years

Niacin provides no benefit to those with CV disease and low HDL-C levels.

### Cholesterol Management Recommendations (Continued)

#### Secondary Prevention

Patients who have triglycerides >500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis.

If treatment with a statin (including trials of higher-dose statins and higher-potency statins) does not achieve the goal selected for a patient, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant or niacin is reasonable.

For patients who do not tolerate statins, LDL-C-lowering therapy with bile acid sequestrants and/or niacin is reasonable.

---

**Note:**
- LDL-C = Low density lipoprotein cholesterol
- CV = Cardiovascular
- CHD = Coronary heart disease
- MI = Myocardial infarction
- RRR = Relative risk reduction
- HDL-C = High density lipoprotein cholesterol
- TNT = Treating to New Targets
- A to Z = A to Z
- IDEAL = International Dyslipidemia Evaluation and Atherosclerosis Prevention
- AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact of Global Health Outcomes
- ACS = Acute coronary syndrome
- HR = Hazard ratio

**Reference Sources:**
- LaRosa JC et al. NEJM 2005;352:1425-1435
- Cannon CP et al. JAMA 2005;294:2492-2494
- AIM-HIGH Investigators. NEJM 2011;365:2255-2267
- Smith SC Jr. et al. JACC 2011;58:2432-2446

---
It is reasonable to treat very high-risk* patients with statin therapy to lower LDL-C to <70 mg/dL.

In patients who are at very high risk* and who have triglycerides >200 mg/dL, a non–HDL-C goal of <100 mg/dL is reasonable.

The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin.

---

**Source:** Smith SC Jr. et al. JACC 2011;58:2432-2446

---

Secondary Prevention

For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, consider niacin or fibrate therapy.

For all patients, it may be reasonable to recommend omega-3 fatty acids from fish or fish oil capsules (1 gram/day) for CV disease risk reduction.

---

### Cholesterol Management Recommendations (Continued)

#### Secondary Prevention

<table>
<thead>
<tr>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

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The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin.

---

### Cigarette Smoking Cessation: Pharmacotherapy*

**Agent**
- **Bupropion SR**
- **Transdermal Nicotine Patch***
- **Varenicline (Chantix®)**

**Caution**
- Seizure disorder
- Eating disorder
- Taking MAO inhibitor
- Pregnancy

**Side Effects**
- Drowsiness
- Dry mouth
- Depression/Suicide
- Insomnia
- Dry mouth
- Sleep disorder
- Depression/Suicide
- CV risk

**Dosage**
- 150 mg QAM then 150 mg BID
- 21 mg QAM
- 14 mg QAM
- 7 mg QAM
- 5 mg QAM
- 0.5 mg GD then 0.5 mg BID then 1 mg BID
- 0.5 mg GD then 0.5 mg BID
- 1 mg BID
- 1 mg BID
- 1 mg BID

**Duration**
- 3 days
- 8 weeks, but up to 6 months
- 4 weeks
- 2 weeks
- 2 weeks
- 8 weeks
- 3 days
- 8 weeks
- 4 weeks
- 4 days
- 12 weeks
- 8 weeks before the quit date

**Instructions**
- Start 1-2 weeks before quit date.
- Take 2nd dose in early afternoon or decrease to 150 mg QAM for insomnia.
- Apply to different hairless site daily.
- Remove before bed for insomnia.
- Start at <15 mg for <10 cigs/day

---

**Source:** Smith SC Jr. et al. JACC 2011;58:2432-2446

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**Tobacco Cessation Recommendations**

**Goals:** Complete tobacco cessation and no environmental tobacco smoke exposure

- Patients should be asked about tobacco use status at every office visit
- Every tobacco user should be advised at every visit to quit
- The tobacco user’s willingness to quit should be assessed at every visit.

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### Tobacco Cessation Recommendations (Continued)

**Secondary Prevention**

- Patients should be assisted by counseling and by development of a plan for quitting that may include pharmacotherapy and/or referral to a smoking cessation program
- Arrangement for follow up is recommended.

- All patients should be advised at every office visit to avoid exposure to environmental tobacco smoke at work, home, and public places.

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**Source:** Smith SC Jr. et al. JACC 2011;58:2432-2446

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### Weight Management Recommendations

**Secondary Prevention**

**Goals:**
- BMI 18.5-24.9 kg/m²
- Waist circumference for women: <35 inches, men: <40 inches*

- BMI and/or waist circumference should be assessed at every visit, and the clinician should consistently encourage weight maintenance/reduction through an appropriate balance of lifestyle physical activity, structured exercise, caloric intake, and formal behavioral programs when indicated to maintain/achieve a body mass index between 18.5 and 24.9 kg/m².

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**Source:** Smith SC Jr. et al. JACC 2011;58:2432-2446
If waist circumference (measured horizontally at the iliac crest) is >35 inches (>89 cm) in women and >40 inches (>102 cm) in men, therapeutic lifestyle interventions should be intensified and focused on weight management. The initial goal of weight loss therapy should be to reduce body weight by approximately 5% to 10% from baseline. With success, further weight loss can be attempted if indicated.

### American Heart Association Nutrition Committee Dietary Recommendations

**Recommendations for CVD Risk Reduction**

- Balance calorie intake & physical activity to achieve healthy weight
- Diet rich in fruits and vegetables, whole-grain, high-fiber foods
- Consume fish ≥2 x/week
- Limit intake of saturated fat to <7% of energy, and cholesterol <300 mg/day by:
  - Choosing lean mean & vegetable alternatives
  - Fat free (skim) or low-fat dairy products,
  - Minimizing partially hydrogenated fats
- Minimize beverages and foods with added sugar
- Choose and prepare foods with little or no salt
- If alcohol is consumed, do so in moderation

### Physical Activity Recommendations

**Secondary Prevention**

<table>
<thead>
<tr>
<th>Goal</th>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 30 minutes, 7 days per week</td>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For all patients, the clinician should encourage 30 to 60 minutes of moderate-intensity aerobic activity, such as brisk walking, ≥5 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.

### Physical Activity Recommendations (Continued)

**Secondary Prevention**

<table>
<thead>
<tr>
<th>Reasonable to recommend complementary resistance training ≥2 days per week</th>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
<th>III</th>
</tr>
</thead>
</table>

### Cardiac Rehabilitation Recommendations

**Secondary Prevention**

| All eligible patients with ACS or whose status is immediately post coronary artery bypass surgery or post-PCI should be referred to a comprehensive outpatient cardiovascular rehabilitation program either prior to hospital discharge or during the first follow-up office visit | A |

All eligible outpatients with the diagnosis of ACS, coronary artery bypass surgery or PCI (Level of Evidence: A), chronic angina (Level of Evidence: B), and/or peripheral artery disease (Level of Evidence: A) within past year should be referred to a comprehensive outpatient cardiovascular rehabilitation program.

### Physical Activity Recommendations

**Secondary Prevention**

| At least 30 minutes, 7 days per week (minimum 5 days per week) of physical activity | B |

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.
For all patients, risk assessment with a physical activity history and/or an exercise test is recommended to guide prognosis and prescription. The clinician should counsel patients to report and be evaluated for symptoms related to exercise. It is reasonable for the clinician to recommend complementary resistance training at least 2 days per week.

Home-based cardiac rehabilitation program can be substituted for a supervised, center-based program for low-risk patients. Comprehensive exercise-based outpatient cardiac rehabilitation program can be safe and beneficial for clinically stable outpatients with a history of Heart Failure.

Mr. Smith is a 62-year-old man that presents to a local emergency department with 3 hours of intermittent chest pain. PMH: hypertension and diabetes. Home Meds: Aspirin 81mg daily, HCTZ 25mg daily, lisinopril 20mg daily, and Metformin 1000mg bid. ECG: Sinus tachycardia at 86 bpm; ST segment depression.

- He is taken urgently to the cardiac catheterization lab where he is found to have a 90% stenosis of the left anterior descending coronary artery and is treated with a drug-eluting stent.
- He is treated with aspirin, P2Y12 inhibitor, bivalirudin, lisinopril, and metoprolol.
- The following day he is feeling well and has an ejection fraction of 55% on an echocardiogram.
- He is discharged home 5 days later.
- You see Mr. Smith 1 week after discharge for follow-up.

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 8 months.

- Clopidogrel + ASA 31% RRR, p=0.002
- Placebo + ASA 12.6%
- Clopidogrel + ASA 8.8%
**Antiplatelet Therapy to Support PCI for UA/NSTEMI**

In UA/NSTEMI patients undergoing PCI, P2Y12 inhibitor therapy should be given for at least 12 months in patients receiving DES and up to 12 months for patients receiving BMS.

If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by P2Y12 receptor inhibitor therapy, earlier discontinuation should be considered.

**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 9 months.

**PLATO non invasive: primary outcome**

**Antiplatelet Therapy to Support Medical Therapy for UA/NSTEMI**

For UA/NSTEMI treated medically without stenting, clopidogrel or ticagrelor should be prescribed for up to 12 months.

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

N=25,886; 30 day follow-up; Aspirin 325mg vs 81mg (day 2-30)

Indirect comparisons of aspirin doses on vascular events in high-risk patients

<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>

Any aspirin 65 23

Antiplatelet Therapy to Support Primary PCI for STEMI

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

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: Statin in all patients at discharge regardless of baseline LDL-C (Class I, LOE: A)


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)


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-UAI
NSTEMI patients, including post-revascularization patients.


Influenza

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