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

Thursday, February 6, 2014
1–2:30pm

Broward County Convention Center
Fort Lauderdale, Florida

Jessica Mega, MD, MPH
Assistant Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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

Educational Partner:
Voxmedia, LLC
Session 4: 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, with research interests that include: (1) the role of platelet activity in patients with different high risk vascular phenotypes; (2) platelet activity and antiplatelet therapy in the perioperative period; (3) the clinical and platelet response to antiplatelet and antithrombotic therapeutics; (4) the study of personalized medicine using the platelet phenotype; and (5) sex differences in platelet activity, hypercoagulability and response to antithrombotic strategies. 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.

Jessica Mega, MD, MPH
Assistant Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Dr Jessica Mega is assistant professor of medicine at Harvard Medical School, a member of the cardiovascular division at Brigham and Women’s Hospital, and director of TIMI’s genetics core laboratory.
Dr Mega graduated with honors from Stanford University and received her medical degree from Yale University School of Medicine. She was an internal medicine resident at Brigham and Women’s Hospital, completed her cardiovascular fellowship at Massachusetts General Hospital, and obtained her MPH from the Harvard School of Public Health. Dr Mega has been part of the leadership of several large scale, international, randomized controlled clinical trials of novel antithrombotic therapies. Additionally, she has focused her research efforts on the use of biomarkers and genetics to risk stratify and to evaluate therapies in cardiovascular patients, specifically demonstrating that patients treated with clopidogrel who harbor loss of function polymorphisms in the CYP2C19 gene are at significantly increased risk of ischemic events. She then served as the principal investigator and FDA IND sponsor for ELEVATE-TIMI 56, a trial testing escalating doses of clopidogrel based on CYP2C19 genotype in cardiac patients. She has also studied genetic variants that relate to other cardiovascular therapies including anticoagulants and lipid lowering medications. She has been awarded research grants from the AHA and the NIH and is published in the New England Journal of Medicine, the Journal of the American Medical Association, Lancet, Circulation, and the Journal of the American College of Cardiology.

Faculty Financial Disclosure Statements
The presenting faculty reports the following:

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

Dr Mega intends to reference unlabeled/unapproved uses of drugs or products in her presentation.

Dr Mega indicates the TIMI group has received research grants from Accumetrics, AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Johnson & Johnson, Nanosphere, sanofi-aventis, and the NIH/NHLBI; and currently serves as a consultant for American Genomics, Boehringer-Ingelheim, Janssen, and WebMD.

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 4**
1–2:30pm

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

**SPEAKERS**
Jeffrey Berger, MD, MS
Jessica Mega, MD, MPH

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**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>Ticagrel</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, NitroGel, Nitrostat, Nitroquick, Nitrostat, Nitrotab</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Coumadin, Jantoven, Marfarin</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>Integrilin</td>
</tr>
</tbody>
</table>

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**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.

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**Oral Antiplatelet Therapies for Acute Coronary Syndromes:**

**Exploring Pharmacologic Profiles, Efficacy, and Safety**

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

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**PCI-CURE: Clopidogrel after NSTE-ACS Treated with PCI**

Composite of MI or cardiovascular death from randomization to end follow-up

- Placebo + ASA*: 12.6%
- Clopidogrel + ASA*: 8.8%
- 31% Overall Relative Risk Reduction

* In addition to other standard therapies.

CURE Trial
Major Bleeding by ASA Dose

<table>
<thead>
<tr>
<th>ASA Dose</th>
<th>Placebo + ASA</th>
<th>Clopidogrel + ASA</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% RRR (P=0.002)

Mortality

Placebo + ASA: 1641 deaths (8.1%)
Clopidogrel + ASA: 1728 deaths (7.5%)

7% RRR (P=0.03)

Days since randomisation

Placebo + ASA: 2311 events (10.1%)
Clopidogrel + ASA: 2125 events (9.3%)

9% RRR (P=0.002)

Mortality

Placebo + ASA: 1641 deaths (8.1%)
Clopidogrel + ASA: 1728 deaths (7.5%)

7% RRR (P=0.03)

Limitations of Clopidogrel

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

Risk of All-Cause Mortality and Recurrent ACS in Patients Taking Clopidogrel and PPI

Days Since Discharge

Neither clopidogrel nor PPI
PPI without clopidogrel
Clopidogrel + PPI
Clopidogrel without PPI

Risk of All-Cause Mortality and Recurrent ACS in Patients Taking Clopidogrel and PPI

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)

Risk of All-Cause Mortality and Recurrent ACS in Patients Taking Clopidogrel and PPI

Composite Cardiovascular Events COGENT Trial

N=3627

Placebo: 67 events; 1821 at risk
Treated: 69 events; 1806 at risk

HR=1.02
95% CI=0.71;1.51

Adjusted with Cox Proportional Hazards Model for NSAID use and positive H. pylori status.
**COGENT Trial – Effect of PPI on Composite GI Events**

![Graph](image)

**CYP2C19 Genetic Polymorphisms and Outcomes With Clopidogrel**

<table>
<thead>
<tr>
<th>Major Adverse CV Events</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carriers vs Noncarriers</td>
<td>1.61 (1.28-2.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heterozygotes vs Wildtype</td>
<td>1.50 (1.08-2.08)</td>
<td>0.016</td>
</tr>
<tr>
<td>Homozygotes vs Wildtype</td>
<td>1.81 (1.21-2.71)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**Stent Thrombosis (N=5772)**

| Carriers vs Noncarriers | 2.76 (1.77-4.39) | <0.001 |
| Heterozygotes vs Wildtype| 2.51 (1.59-3.98) | <0.001 |
| Homozygotes vs Wildtype  | 4.78 (2.61-11.39)| <0.001 |

**TRITON-TIMI 38 Study Design**

![Diagram](image)

**TRITON-TIMI 38: Bleeding Events**

![Graph](image)
TRITON-TIMI 38: Summary of the results

- Mod/high-risk ACS (n=13,608) scheduled for PCI randomized to:
  - Prasugrel (60 mg LD and 10 mg daily MD) or
  - Clopidogrel (300 mg LD and 75 mg daily MD) for 6-15 months
- Primary end point (CV death, nonfatal MI, nonfatal stroke)
  - 9.9% prasugrel vs 12.1% clopidogrel (HR: 0.81; p<0.001)
- Prasugrel significant ↓ MI (7.4% vs. 9.7%; p<0.001) and stent thrombosis (1.1% vs. 2.4%)
- Prasugrel significantly increased risk of major bleeding, including fatal bleeding
- Cardiovascular mortality and overall mortality did not differ significantly between groups


Net Clinical Benefit

<table>
<thead>
<tr>
<th>Prior Stroke / TIA</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>+ 54</td>
</tr>
<tr>
<td>No</td>
<td>-16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;=75</td>
<td>P_{HR} = 0.006, -16</td>
</tr>
<tr>
<td>&lt;75</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wgt</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 kg</td>
<td>+3</td>
</tr>
<tr>
<td>&gt;= 60 kg</td>
<td>-14</td>
</tr>
</tbody>
</table>

OVERALL | 13 -13

Prasugrel Better HR Clopidogrel Better

Additional risk factors for bleeding include:
- body weight < 60 kg
- propensity to bleed
- concomitant use of medications that increase the risk of bleeding

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 age 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

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022307s003lbl.pdf

TRILOGY ACS Study Design

Medically Managed UA/NSTEMI Patients

- Randomization stratified by: Age, Country, Prior Clopidogrel Treatment (Primary analysis cohort — Age < 75 years)
- Medical Management Decision ≤ 72 hrs (No prior clopidogrel given) — 4% of total
- Medical Management Decision ≤ 10 days (Clopidogrel started ≤ 72 hrs in-hospital OR on chronic clopidogrel) — 96% of total
- Clopidogrel1: 75 mg MD
- Prasugrel1: 10 mg MD

Media Time to Enrollment = 4.5 Days

Primary Efficacy Endpoint: CV Death, MI, Stroke

PLATO: Study Design

- NSTE-ACS (moderate-to-high risk) or STEMI (if primary PCI)
- Clopidogrel-treated or -naive; randomised within 24 hours of index event (N=18,624)

<table>
<thead>
<tr>
<th>Clotidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>If pre-treated, no additional loading dose; if naive, standard 300 mg loading dose, then 75 mg qd maintenance; (additional 300 mg allowed pre PCI)</td>
<td></td>
</tr>
<tr>
<td>180 mg loading dose, then 90 mg bid maintenance; (additional 90 mg pre-PCI)</td>
<td></td>
</tr>
</tbody>
</table>

6–12-month exposure (median 9 mos)

Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding

PLATO: Summary of the results

- NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI) (N=18,624)
  - Ticagrelor (180 mg LD and 90 mg bid MD) or
  - Clopidogrel (300-600 mg LD and 75 mg daily MD) for 6-12 months
- Primary end point (CV death, nonfatal MI, nonfatal stroke),
  - 9.8% ticagrelor vs 11.7% clopidogrel (HR: 0.84; p<0.001)
  - Ticagrelor significantly ↓ MI (7.4% vs. 9.7%; p<0.001), CV death (4% vs. 5.1%) and stent thrombosis (1.1% vs. 2.4%)
  - Ticagrelor significantly increased risk of non-CABG major bleeding
  - Fatal bleeding was not significantly different between groups
  - Overall mortality was significantly decreased with ticagrelor (4.5% vs. 5.9%; p<0.001)


PLATO: Stratification by Invasive vs Non-Invasive Strategy

James S et al. BMJ 2011;342:d3527

How Do Different Antiplatelets Compare in the Setting of ACS?

<table>
<thead>
<tr>
<th>Event</th>
<th>CURE</th>
<th>TRITON – TIMI 38</th>
<th>PLATO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>Prasugrel</td>
<td>Ticagrelor</td>
</tr>
<tr>
<td>MACE</td>
<td>9.2 vs 11.4</td>
<td>0.90 (0.73-1.10)</td>
<td>0.91 (0.74-1.10)</td>
</tr>
<tr>
<td>MI</td>
<td>5.3 vs 6.7</td>
<td>0.87 (0.67-1.10)</td>
<td>0.76 (0.67-0.85)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.2 vs 1.4</td>
<td>0.86 (0.63-1.20)</td>
<td>1.0 vs 1.0</td>
</tr>
<tr>
<td>Any Death</td>
<td>5.7 vs 6.2</td>
<td>0.93 (0.81-1.07)</td>
<td>0.95 (0.81-1.16)</td>
</tr>
<tr>
<td>CV Death</td>
<td>5.1 vs 5.5</td>
<td>0.99 (0.79-1.26)</td>
<td>2.1 vs 2.4</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>3.7 vs 2.7</td>
<td>0.66 (1.13-1.67)</td>
<td>0.58 (1.15-1.83)</td>
</tr>
</tbody>
</table>

C = Clopidogrel  P = Placebo  Pr = Prasugrel  Ti = Ticagrelor

Ticagrelor – FDA Label

"Boxed Warning"

**WARNING: BLEEDING RISK**
- Ticagrelor, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (1.1, 6.4).
- 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).
- 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).

P2Y12 Antagonist: Summary of the results

- ACS with Planned Intervention
  - Aspirin PLUS
  - Clopidogrel, or
  - Prasugrel, or
  - Ticagrelor

- Medically Managed ACS
  - Aspirin PLUS
  - Clopidogrel, or
  - Ticagrelor

Prasugrel is absolutely contraindicated in pts with prior stroke or TIA, and its benefits in pts <60 kg or ≥75 years are uncertain.

Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided.

State-of-the-Art Secondary Prevention in the ACS Patient

Jessica L. Mega, MD, MPH

Physician, Cardiovascular Division, Brigham and Women's Hospital
Assistant Professor of Medicine, Harvard Medical School
Investigator, TIMI Study Group

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).

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.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Event Rate (%)</th>
<th>RRR (%)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + ASA†</td>
<td>7.3%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Clopidogrel + ASA†</td>
<td>6.8%</td>
<td>7.1%*</td>
<td>-4.5%, 17.5%</td>
<td>0.22</td>
</tr>
</tbody>
</table>


*RRR 12% if symptomatic atherosclerosis, p=0.046

Optimizing Antiplatelet Therapy: Balancing Safety and Efficacy

- Antiplaetelet/anticoagulant therapy
- Beta-blockers
- Anti-hypertensive & ACEI/ARB/aldosterone therapy
- Lipid-lowering therapy
- Anti-diabetic therapy
- Other selected secondary prevention recommendations

Topic Outline

- Antiplatelet/anticoagulant therapy
- Beta-blockers
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*RRR 12% if symptomatic atherosclerosis, p=0.046
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) score.**

*Individual circumstances will vary and depend on the indications for triple therapy and the type of stent placed during PCI. After the 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.

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.†

I IIa IIb III

I IIa IIb III

I IIa IIb III

I IIa IIb III

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.

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

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 β-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.

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.

Blood Pressure Management

Renin-Angiotensin-Aldosterone Blocker Therapy

2013 ACCF/AHA STEMI Guidelines

2013 ACCF/AHA STEMI Guidelines

2012 ACCF/AHA SIHD Guidelines

2012 ACCF/AHA SIHD Guidelines

2012 ACCF/AHA SIHD Guidelines
Key Lesson from Statin Trials

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Statin/MORE (per 1 mmol LDL-C)</th>
<th>Control/LESS (per 1 mmol LDL-C)</th>
<th>Relative Risk (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI</td>
<td>0.73 (0.69 - 0.78)</td>
<td>0.75 (0.69 - 0.82)</td>
<td></td>
</tr>
<tr>
<td>CHD death</td>
<td>0.80 (0.74 - 0.87)</td>
<td>0.72 (0.65 - 0.80)</td>
<td></td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>0.78 (0.73 - 0.78)</td>
<td>0.79 (0.72 - 0.78)</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>0.75 (0.69 - 0.82)</td>
<td>0.70 (0.65 - 0.80)</td>
<td></td>
</tr>
<tr>
<td>PTC</td>
<td>0.70 (0.60 - 0.80)</td>
<td>0.70 (0.60 - 0.80)</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>0.76 (0.70 - 0.82)</td>
<td>0.75 (0.70 - 0.82)</td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>0.70 (0.65 - 0.80)</td>
<td>0.70 (0.65 - 0.80)</td>
<td></td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1.20 (1.08 - 1.34)</td>
<td>1.12 (1.08 - 1.14)</td>
<td></td>
</tr>
<tr>
<td>Unknown stroke</td>
<td>0.85 (0.76 - 0.96)</td>
<td>0.84 (0.79 - 0.89)</td>
<td></td>
</tr>
<tr>
<td>Any stroke</td>
<td>0.79 (0.72 - 0.82)</td>
<td>0.75 (0.70 - 0.82)</td>
<td></td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>0.76 (0.70 - 0.82)</td>
<td>0.75 (0.70 - 0.82)</td>
<td></td>
</tr>
</tbody>
</table>

Statins, Diabetes, CV Events

No major risk factors for diabetes

Major risk factors for diabetes (65%)

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

Initiation of pharmacotherapy interventions to achieve target HbA1c might be reasonable.

Therapy with rosiglitazone should not be initiated in patients with SIHD.

Diabetes Management (cont.)
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.

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

<table>
<thead>
<tr>
<th>Primary End point</th>
<th>Mediterranean Diet (n=4,997)</th>
<th>Low Fat Control Diet (n=3,450)</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.


### Lifestyle

**If would benefit from LDL-C or BP lowering, then:**

- **Diet:**
  - Emphasize intake of vegetables, fruits, whole grains
  - Incl low-fat dairy, poultry, fish, legumes, non-trop vegetable oils & nuts
  - Limit intake of sweets, sugar-sweetened beverages and red meats
  - For LDL-C lowering, also: ↓ % of calories from saturated fats (target 5-6%) and from trans fats
  - For BP lowering, also: ↓ Na intake by ≥1000 mg/d; target Na intake to ≤2400 mg/d, and ideally ≤1500 mg/d
- **Exercise:** ~40 min mod-to-vigorous physical activity 3-4x/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 Counseling

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).

2012 ACCF/AHA SIHD Guidelines

### Influenza Vaccination

An annual influenza vaccine is recommended for patients with SIHD.

2012 ACCF/AHA SIHD Guidelines
Case Study

59-year-old female with new onset chest pain

- Two-day history of exertional chest pain that resolved with rest.
- On the day of admission, she developed chest pressure while driving to work.

**Past Medical History**
- Hypertension
- Hyperlipidemia

**Medications**
- Lisinopril 5 mg
- Atorvastatin 10 mg daily

**Allergies/Reactions**
None

**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

![Graph showing the effect of clopidogrel vs. placebo in PCI-CURE Study](image)

**Mehta SR et al. Lancet. 2001;358:527-533**

**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.

![Graph showing survival in PCI-CURE Study](image)

**Jneid H et al. Circulation 2012;126:875-910**

**PLATO: Stratification by invasive vs non-invasive strategy**

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

![Graph showing survival in PLATO study](image)

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

**Antiplatelet Therapy to Support Medical Therapy for UA/NSTEMI**
**Data supporting the use of aspirin following an acute MI**

<table>
<thead>
<tr>
<th>Category</th>
<th>% Odds Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td></td>
</tr>
<tr>
<td>Acute CVA</td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td></td>
</tr>
<tr>
<td>Prior CVA/TIA</td>
<td></td>
</tr>
<tr>
<td>Other high risk</td>
<td></td>
</tr>
<tr>
<td>CVD (e.g. unstable angina, heart failure)</td>
<td></td>
</tr>
<tr>
<td>PAD (e.g. intermittent claudication)</td>
<td></td>
</tr>
<tr>
<td>High-risk of embolism (e.g. AFib)</td>
<td></td>
</tr>
<tr>
<td>Other (e.g. DM)</td>
<td></td>
</tr>
<tr>
<td>All trials</td>
<td></td>
</tr>
</tbody>
</table>


**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></th>
<th>325mg</th>
<th>81mg</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>4.2</td>
<td>4.4</td>
<td>0.61</td>
</tr>
<tr>
<td>CV death</td>
<td>2.1</td>
<td>2.3</td>
<td>0.22</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>2.3</td>
<td>2.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>5.0</td>
<td>4.4</td>
<td>0.04</td>
</tr>
</tbody>
</table>


**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>Odds Ratio for Vascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-1500 mg</td>
<td>34 (19)</td>
<td></td>
</tr>
<tr>
<td>160-325 mg</td>
<td>19 (26)</td>
<td></td>
</tr>
<tr>
<td>75-150 mg</td>
<td>12 (32)</td>
<td></td>
</tr>
<tr>
<td>&lt;75 mg</td>
<td>3 (13)</td>
<td></td>
</tr>
<tr>
<td>Any aspirin</td>
<td>65 (23)</td>
<td></td>
</tr>
</tbody>
</table>

Antiplatelet Better Antiplatelet Worse

P<.0001


**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.

**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-UAV NSTEMI patients, including post-revascularization patients.


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

4,162 patients with ACS; Atorvastatin 80 mg qid 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.