Latest Advances in Secondary Prevention of Cardiovascular Events

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CME Symposium

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Developed with The American Society for Preventive Cardiology
Latest Advances in Secondary Prevention of Cardiovascular Events

Learning Objectives

2. Discuss the implications for secondary prevention of the 2013 ACC/AHA lipid guideline and the updated hypertension recommendations.
3. Evaluate the implications of the latest trial results for lipid management in secondary prevention.
4. Place newly approved anti-platelet agents into perspective for the management of secondary prevention post-Acute Coronary Syndrome and for patients with peripheral artery disease based on emerging evidence.

Faculty

Peter Libby, MD
Mallinckrodt Professor of Medicine
Harvard Medical School
Cardiovascular Division, Department of Medicine
Brigham and Women's Hospital

Peter Libby, MD, is a cardiovascular specialist at Brigham and Women's Hospital in Boston, Massachusetts, and holds the Mallinckrodt Professorship of Medicine at Harvard Medical School. He served as Chief of Cardiovascular Medicine at BWH from 1998 - 2014. His areas of clinical expertise include general and preventive cardiology. His current major research focus is the role of inflammation in vascular diseases such as atherosclerosis. Dr. Libby has received numerous awards and recognitions for his research accomplishments, including the Gold Medal of the European Society of Cardiology (2011), the Basic Research Prize of the American Heart Association (2011), the Anitschkow Prize in Atherosclerosis Research of the European Atherosclerosis Society (2013), and the Distinguished Achievement Award of the Heart Failure Association of the European Society of Cardiology (2014).

Howard S. Weintraub, MD, FACC
Clinical Professor of Medicine
New York University School of Medicine
Clinical Director, NYU Center for the Prevention of Cardiovascular Disease

Howard S. Weintraub, M.D., F.A.C.C. is Clinical Professor in the Department of Medicine at New York University School of Medicine in New York, New York. After receiving his medical degree from New York University School of Medicine, Dr. Weintraub completed a residency in Internal Medicine at the NYU-Bellevue Hospitals Center. He was a clinical fellow in Pulmonary Diseases and in Cardiovascular Diseases at New York University Medicine Center. He is board certified in Internal Medicine and Cardiovascular Diseases, and is a fellow of the American College of Cardiology. He has also been a consultant for several organizations. He is currently the Clinical Director of the Center for the Prevention of Cardiovascular Disease at the New York University Medical Center. Before assuming this position he was the Associate Director of the Cardiac Exercise Laboratory at NYU Medical Center.
Disclosures
The presenting faculty reported the following:

Dr. Libby: Unpaid consultant or involved with clinical trials for Amgen Inc., AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Esperion Therapeutics, Genzyme - A Sanofi company, GlaxoSmithKline, Kowa Pharmaceuticals American, Inc., Merck & Co., Novartis, Pfizer, Sanofi-Regenon and Takeda Pharmaceuticals North America; Member of the scientific Advisory board for Athera biotechnologies and Interleukin Genetics. Research funding from General Electric, GlaxoSmithKline and Novartis.


Content collaborators at the American Society for Preventive Cardiology have nothing to disclose. Content contributors and reviewers for pmiCME, and Tufts Health Care Institute have no financial relationships to disclose.

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11:40am – 12:55pm

Latest Advances in Secondary Prevention of Cardiovascular Events

SPEAKER
Howard Weintraub, MD, FACC
Peter Libby, MD, FACC

Presenter Disclosure Information

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Latest Advances in Secondary Prevention of Cardiovascular Events 2015

The Challenge of Secondary Prevention of Cardiovascular Disease 2015:
High recurrent event rates
**Long-Term Risk of MI and Stroke**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Increased Risk of MI</th>
<th>Increased Risk of Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-MI</td>
<td>5-7 X greater risk₁</td>
<td>3-4 X greater risk₂</td>
</tr>
<tr>
<td></td>
<td>(includes death)</td>
<td>(includes TIA)</td>
</tr>
<tr>
<td>PAD</td>
<td>4 X greater risk₄</td>
<td>2-3 X greater risk₃</td>
</tr>
<tr>
<td></td>
<td>(includes only fatal MI and other CHD death)</td>
<td>(includes TIA)</td>
</tr>
</tbody>
</table>

₁Versus the general population.

Additional references:

**Contemporary ACS Trials: Recurrent Events Rates Remain High**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Index Event</th>
<th>DAP</th>
<th>Mean Follow-Up</th>
<th>Death, MI, or Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLATO (N=18,924)</td>
<td>TICAG</td>
<td>STEMI 38%</td>
<td>NA</td>
<td>9.2 months</td>
<td>10.3%</td>
</tr>
<tr>
<td></td>
<td>CLOP</td>
<td>NSTEMI 43%</td>
<td></td>
<td></td>
<td>12.3%</td>
</tr>
<tr>
<td>APPRAISE-2 (N=7,552)</td>
<td>APXA (2.5 mg)</td>
<td>STEMI 40%</td>
<td>NA</td>
<td>5 months</td>
<td>9.8%</td>
</tr>
<tr>
<td></td>
<td>PLACEBO</td>
<td>NSTEMI 42%</td>
<td></td>
<td></td>
<td>8.9%</td>
</tr>
<tr>
<td>ATLAS ACS 2-TIMI 51 (N=15,028)</td>
<td>RivA</td>
<td>STEMI 50%</td>
<td>NA</td>
<td>13.1 months</td>
<td>9.1%</td>
</tr>
<tr>
<td></td>
<td>PLACEBO</td>
<td>NSTEMI 26%</td>
<td></td>
<td></td>
<td>10.7%</td>
</tr>
</tbody>
</table>

*DAPT = dual antiplatelet therapy; PLATO = Study of Platelet Inhibition and Patient Outcomes; APPRAISE-2 = Apixaban for Prevention of Acute Ischemic Events 2; ATLAS ACS 2-TIMI 51 = Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51; TICAG = ticagrelor; CLOP = clopidogrel; APXA = apixaban; RIVA = rivaroxaban.

**AHA/ACC 2011 Guideline**

How Do We Address Secondary Prevention of Cardiovascular Disease?

A lot has happened since 2011, especially with respect to lipids and anti-platelet agents, but the guideline provides a solid point of departure
AHA/ACC 2011 Secondary Prevention Guideline

Some things remain constant:

**Diet**

**Physical activity**

*but hard to implement!*

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**AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update Smoking**

Goal: Complete cessation. No exposure to environmental tobacco smoke

1. Patients should be asked about tobacco use status at every office visit
2. Every tobacco user should be advised at every visit to quit.
3. The tobacco user's willingness to quit should be assessed at every visit.

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**AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update Physical activity**

4. 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.
5. Arrangement for follow up is recommended.
6. 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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2. For all patients, risk assessment with a physical activity history and/or an exercise test is recommended to guide prognosis and prescription.
3. 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.
Goals: Body mass index: 18.5 to 24.9 kg/m²; Waist circumference: women 35", men 40"

1. Body mass index 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.

2. 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.

3. 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.

Some things remain controversial:

- **Blood pressure management**: Goal: 140/90 mm Hg. The writing committee anticipated that the recommendations will be reviewed when the updated JNC guidelines were released.

- **Other interventions considered**:
  - Renin-angiotensin-aldosterone system blockers
  - Beta-Blockers
  - Influenza vaccination
  - Depression
  - Cardiac rehabilitation
Blood pressure control

1. All patients should be counseled regarding 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.

2. Patients with blood pressure 140/90 mm Hg should be treated, as tolerated, with blood pressure medication, treating initially with beta blockers and/or ACE inhibitors, with addition of other drugs as needed to achieve goal blood pressure.

Clinicians should consider new data available since 2011:

Lipid Management

How Do We Address Secondary Prevention of Cardiovascular Disease? AHA/ACC 2011 Guideline

Lipid management Goal: Treatment with statin therapy; use statin therapy to achieve an LDL-C of <100 mg/dL; for very high risk* patients an LDL-C <70 mg/dL is reasonable; if triglycerides are >200 mg/dL, non–HDL-C should be <130 mg/dL, whereas non–HDL-C <100 mg/dL for very high risk patients is reasonable.

“Note: The writing committee anticipates that the recommendations will be reviewed when the updated ATP guidelines are released.”

Advances in Secondary Prevention of Cardiovascular Disease 2015

The changing landscape of lipid management
Low Density Lipoprotein (LDL) - Yesterday
❤ Statins lower LDL and reduce CV events across broad categories of risk

Cholesterol Treatment Trialists' (CTT) Collaborators:
The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials.

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and Women Heart: The National Coalition for Women with Heart Disease

How Do We Address Secondary Prevention of Cardiovascular Disease? AHA/ACC 2011 Guideline
Lipid management Goal: Treatment with statin therapy; use statin therapy to achieve an LDL-C of !100 mg/dL; for very high risk* patients an LDL-C <70 mg/dL is reasonable; if triglycerides are >200 mg/dL, non–HDL-C should be <130 mg/dL, whereas non–HDL-C <100 mg/dL for very high risk patients is reasonable

Never mind about LDL goals
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Excerpts from Table 2 What’s New in the Guideline?

Non-statin therapies, as compared with statin therapy, do not provide acceptable ASCVD risk-reduction benefits relative to their potential for adverse effects in the routine prevention of ASCVD.


IMPROVE-IT: Goals

- IMPROVE-IT: First large trial evaluating clinical efficacy of combination EZ/Simva vs. simvastatin (i.e., the addition of ezetimibe to statin therapy):
  - Does lowering LDL-C with the non-statin agent ezetimibe reduce cardiac events?
  - “Is (Even) Lower (Even) Better?” (estimated mean LDL-C ~50 vs. 65mg/dL)
  - Safety of ezetimibe

IMPROVE-IT: Study Design

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

N=18,144

<table>
<thead>
<tr>
<th>Standard Medical &amp; Intervventional Therapy</th>
<th>Ezetimibe / Simvastatin 10 / 40 mg</th>
</tr>
</thead>
</table>

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2 ½-year follow-up (at least 5250 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

IMPROVE-IT: Safety — ITT

- No statistically significant differences in cancer or muscle- or gallbladder-related events

<table>
<thead>
<tr>
<th>ALT and/or AST x ULN</th>
<th>Cholecystectomy</th>
<th>Gallbladder-related AEs</th>
<th>Rhabdomyolysis*</th>
<th>Myopathy*</th>
<th>Rhabdo, myopathy, myalgia with CK elevation*</th>
<th>Cancer* (7-yr KM %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva n=9077 %</td>
<td>EZ/Simva n=9067 %</td>
<td>p</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.3</td>
<td>2.5</td>
<td>0.43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>1.5</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.5</td>
<td>3.1</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.1</td>
<td>0.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>0.2</td>
<td>0.32</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td>0.6</td>
<td>0.64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.2</td>
<td>10.2</td>
<td>0.57</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjudicated by Clinical Events Committee
% = n/N for the trial duration

IMPROVE-IT: Conclusions

- IMPROVE-IT: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:
  - YES: Non-statin lowering LDL-C with ezetimibe reduces cardiovascular events
  - YES: Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
  - YES: Confirms ezetimibe safety profile
  - Affirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events
  - Results could be considered for future guidelines

Low Density Lipoprotein (LDL)

❤ Yesterday
❤ Today
❤ Tomorrow
PCSK9 (Proprotein convertase subtilisin/kexin type 9)

- Proprotein convertase subtilisin/kexin type 9 (PCSK9) are proteolytic enzymes that cleave precursor proteins into biologically active forms.
- PCSK9 modulate LDL-receptor degradation.
- Humans with gain of function and non-sense mutations of PCSK9 exist.
- \( \downarrow \) PCSK9 \( \rightarrow \) \( \uparrow \) LDL-R \( \rightarrow \) lower LDL levels.
- Drugs that inhibit PCSK9 are in clinical endpoint trials (LDLs 10-40 mg/dL).

**Association of PCSK9 Loss of Function Missense/LOF Variant R46L with Early-Onset Myocardial Infarction**

<table>
<thead>
<tr>
<th>Site</th>
<th>Study</th>
<th>No. of Cases</th>
<th>No. of Controls</th>
<th>Frequency of Missense Mutations</th>
<th>Odds Ratio for Early-Onset Myocardial Infarction (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>FINRISK</td>
<td>209</td>
<td>210</td>
<td>1.3 4.1</td>
<td>0.50 (0.31-0.80)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sweden</td>
<td>Malmo Diet and Cancer Study</td>
<td>150</td>
<td>149</td>
<td>0.7 2.0</td>
<td>0.63 (0.32-1.24)</td>
<td>0.27</td>
</tr>
<tr>
<td>Spain</td>
<td>Regimen-Especifico del Corazon (REGICOR)</td>
<td>362</td>
<td>361</td>
<td>2.0</td>
<td>0.65 (0.33-1.28)</td>
<td>0.24</td>
</tr>
<tr>
<td>Serbia</td>
<td>Heart Attack Risk in Young Adults</td>
<td>532</td>
<td>431</td>
<td>0.8 1.9</td>
<td>0.65 (0.31-1.40)</td>
<td>0.49</td>
</tr>
<tr>
<td>Brazil</td>
<td>Massachusetts General Hospital Prevention Program Genetics Study</td>
<td>192</td>
<td>298</td>
<td>1.4 2.1</td>
<td>0.19 (0.13-0.30)</td>
<td>0.13</td>
</tr>
<tr>
<td>Combined analysis</td>
<td>1454</td>
<td>1417</td>
<td>0.39</td>
<td>2.4</td>
<td>0.45 (0.36-0.56)</td>
<td>0.0000000000000001</td>
</tr>
</tbody>
</table>

CI = confidence interval.


**DESCARTES: % Change in LDL-C from baseline in patients on various background treatments**

**Bococizumab (Phase 2 data on Statin)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline LDL-C (mg/dL)</th>
<th>Dose-Reduced LDL-C (mg/dL) at week 12</th>
<th>% Change from Placebo</th>
<th>AE vs DC (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boc 50 mg q2W (n=60)</td>
<td>108</td>
<td>35</td>
<td>-34%</td>
<td>1</td>
</tr>
<tr>
<td>Boc 100 mg q2W (n=31)</td>
<td>113</td>
<td>35</td>
<td>-45%</td>
<td>4</td>
</tr>
<tr>
<td>Boc 150 mg q2W (n=65)</td>
<td>106</td>
<td>44</td>
<td>-45%</td>
<td>2</td>
</tr>
<tr>
<td>Boc 200 mg q4W (n=50)</td>
<td>106</td>
<td>44</td>
<td>-53%</td>
<td>2</td>
</tr>
<tr>
<td>Boc 300 mg q4W (n=51)</td>
<td>105</td>
<td>44</td>
<td>-28%</td>
<td>0</td>
</tr>
</tbody>
</table>

351 pts with HC treated for 24 weeks, LDL-C ≥ 80 mg/dL on statin, Double-blind, placebo-controlled, 5C injections 3 doses Boco v pbo q2W, 3 doses Boco vs pbo q4W, Dose reduced if LDL-C < 25 mg/dL.

Ballantyne CM et al. JACC 2014:63:A1374 (abstr)
PCSK9 Inhibitor Cardiovascular Outcomes Trials

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Evolocumab (AMG 145)</th>
<th>Alirocumab (SAR236553/REGN722)</th>
<th>Bococizumab (RN 316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>FOURIER</td>
<td>ODYSSEY Outcomes</td>
<td>STRIVE</td>
</tr>
<tr>
<td>Sample size</td>
<td>22,500</td>
<td>18,000</td>
<td>12,000</td>
</tr>
<tr>
<td>Patients</td>
<td>MI, stroke or PAI</td>
<td>4-52 wk post-ACS</td>
<td>High risk of CV event</td>
</tr>
<tr>
<td>Statin</td>
<td>Atorv 20 mg or equiv</td>
<td>Evid-based med Rx</td>
<td>Lipid-lowering Rx</td>
</tr>
<tr>
<td>LDL-C mg/dL (mmol/L)</td>
<td>≥ 70 (≥ 1.8)</td>
<td>70-99 (1.8-2.6)</td>
<td>≥100 (≥ 2.6)</td>
</tr>
<tr>
<td>PCSK9 Dosing</td>
<td>Q2W or Q4W</td>
<td>Q2W</td>
<td>Q2W</td>
</tr>
<tr>
<td>Endpoint</td>
<td>CV death, MI, stroke, revasc or hosp for UA</td>
<td>CHD death, MI, ischemic stroke, or hosp for UA</td>
<td>CV death, MI, stroke, or urgent revasc</td>
</tr>
<tr>
<td>completion</td>
<td>12/2017</td>
<td>1/2018</td>
<td>8/2017</td>
</tr>
</tbody>
</table>

AHA/ACC 2011 Guideline: Antiplatelet agents/anticoagulant

1. Aspirin 75–162 mg daily is recommended in all patients with coronary artery disease unless contraindicated.
2. Clopidogrel 75 mg daily is recommended as an alternative for patients who are intolerant of or allergic to aspirin.
3. A P2Y12 receptor antagonist in combination with aspirin is indicated in patients after ACS or PCI with stent placement.
4. For patients receiving a bare-metal stent or drug-eluting stent during PCI for ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be given for at least 12 months.

5. For patients with symptomatic atherosclerotic peripheral artery disease of the lower extremity, antiplatelet therapy with aspirin (75–325 mg daily) or clopidogrel (75 mg daily) should be started and continued.
6. Antiplatelet therapy is recommended in preference to anticoagulant therapy with warfarin or other vitamin K antagonists to treat patients with atherosclerosis.

Antiplatelet agents/anticoagulants cont’d

3. For patients undergoing coronary artery bypass grafting, aspirin should be started within 6 hours after surgery to reduce saphenous vein graft closure. Dosing regimens ranging from 100 to 325 mg daily for 1 year appear to be efficacious.
4. In patients with extracranial carotid or vertebral atherosclerosis who have had ischemic stroke or TIA, treatment with aspirin alone (75–325 mg daily), clopidogrel alone (75 mg daily), or the combination of aspirin plus extended-release dipyridamole (25 mg and 200 mg twice daily, respectively) should be started and continued.

Antiplatelet agents/anticoagulants cont’d

- If there is a compelling indication for anticoagulant therapy, such as atrial fibrillation, prosthetic heart valve, left ventricular thrombus, or concomitant venous thromboembolic disease, warfarin should be administered in addition to the low-dose aspirin (75–81 mg daily).
- For patients requiring warfarin, therapy should be administered to achieve the recommended INR for the specific condition.
- Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely. 1. If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by thienopyridine therapy after stent implantation, earlier discontinuation (eg, <12 months) is reasonable.
Advances in Secondary Prevention of Cardiovascular Disease 2015

The changing landscape of anti-platelet therapy

Aspirin in Acute Myocardial Infarction

Current Oral Anti-thrombotic agents in Patients with Acute Coronary Syndromes (ACS)

Clopidogrel Studies in ACS

PCI-CURE: Clopidogrel in PCI Patients

CURE Study: Primary Endpoint


Aspirin in Acute Myocardial Infarction

Antiplatelet Therapy

Control

Adjusted % of Vascular Events (+ Standard Error)

0 5 10 15 20

1637 (9.6%)
1621 (9.3%)

1373 (10.4%)
1354 (10.2%)

P <0.0001

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

TIMI Major bleeding: Placebo + ASA 1.08% vs Clopidogrel + ASA 1.16%, p=0.0009

CV death, MI, or stroke; RRR = relative risk reduction.


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

CURE1
(N=12,562)
UA/NSTEMI ACS
Evaluated whether clopidogrel plus ASA vs ASA alone would offer additional benefits
12 months

CREDIO
(N=2,116)
Symptomatic CAD with planned PCI
Evaluate whether clopidogrel plus ASA vs ASA alone would be beneficial
12 months

CLARITY
(N=3,491)
STEMI treated with fibrinolysis
Evaluate whether clopidogrel plus ASA vs ASA alone would be beneficial
30 days

COMMIT
(N=45,852)
STEMI
Evaluate where clopidogrel plus ASA vs ASA alone would be beneficial
Mean 15 days

PCI-CURE: Clopidogrel in PCI Patients

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

Placebo + ASA
Clopidogrel + ASA

12.6%
8.8%
P=0.002

CV death, MI, or stroke; RRR = relative risk reduction.


Placebo vs Clopidogrel

**CREDO Study: Clopidogrel in Patients with Planned PCI**

- 2108 symptomatic CAD patients with planned PCI
- Major bleeding: Placebo + ASA 6.7% vs Clopidogrel + ASA 5.6%, p=0.02

**CLARITY: Primary Endpoint Through 30 Days in Patient Receiving Fibrinolysis**

- 2491 patients with STEMI treated with fibrinolysis
- Major bleeding: Placebo + ASA 6.7% vs Clopidogrel + ASA 5.6%, p=0.02

**COMMIT Study: Safety and Efficacy of Clopidogrel in AMI**

- 45852 patients with STEMI
- Clopidogrel (N=22,958)
- Placebo (N=22,891)

**Prasugrel and Ticagrelor Studies in ACS**

- **TRITON-TIMI 38**
  - ACS (UA, NSTEMI, or STEMI) undergoing PCI
  - Compared the safety and efficacy of prasugrel plus ASA to clopidogrel plus ASA
  - Duration: 15 months (Median 14.5 mos.)

- **PLATO**
  - ACS hospitalized (UA, NSTEMI, or STEMI)
  - Compared the safety and efficacy of ticagrelor plus ASA to clopidogrel plus ASA
  - Duration: 12 months (Median 9.2 mos.)

**TRITON-TIMI 38: Safety and Efficacy**

- 13,608 patients ACS (UA, NSTEMI, or STEMI) undergoing PCI
- *Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.*

**PLATO Study: Safety and Efficacy**

- 13,608 patients with ACS hospitalized (UA, NSTEMI, or STEMI)
PEGASUS-TIMI 54

Wednesday, 14 January 2015

PEGASUS-TIMI 54 study of ticagrelor meets primary endpoint in both 60mg and 90mg doses. Ticagrelor 60mg or 90mg both demonstrate statistically significant reduction in major cardiovascular thrombotic events in patients with a history of heart attack.

ACCF/AHA Guideline Recommendations
Antithrombotic Therapy in ACS Patients (UA/NSTEMI) for Secondary Prevention

Class I

- UA/NSTEMI Managed Medically
  - Level of Evidence: A – Aspirin should be prescribed indefinitely
  - If aspirin is not tolerated or contraindicated:
    - Level of Evidence: B – Clopidogrel 75 mg daily
    - Level of Evidence: C – Prasugrel 10 mg daily or ticagrelor 90 mg twice daily

- UA/NSTEMI Managed Invasively
  - Level of Evidence: A – Aspirin should be prescribed indefinitely
  - Level of Evidence: B – Clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be given for ≤12 months (DES) and ≥12 months (BMS)

Class IIb

- A P2Y12 receptor inhibitor beyond 12 months may be considered in patients following with a DES (Level of Evidence: C)
- Warfarin with an INR of 2.0 to 3.0 may be reasonable in patients with an indication for anticoagulation (Level of Evidence: B)

ACCF/AHA Guideline Recommendations
Antithrombotic Therapy in Acute MI Patients (STEMI) for Secondary Prevention

Class I

- STEMI Managed Medically with Fibrinolysis
  - Level of Evidence: A – Aspirin should be prescribed indefinitely
  - Level of Evidence: B – Clopidogrel 75 mg daily for 14 days
  - Level of Evidence: C – Clopidogrel 75 mg daily for 1 year

- STEMI Managed Initially with an Invasive Strategy
  - Level of Evidence: A – Aspirin should be prescribed indefinitely
  - Level of Evidence: B – Clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be given for 1 year (BMS or DES)
  - A P2Y12 receptor inhibitor beyond 1 year may be considered in patients with a DES (Class IIb, Level of Evidence: C)

Class IIb

- The PEGASUS-TIMI 54 study investigated two different doses of ticagrelor on a background of low dose aspirin versus placebo plus low dose aspirin, in patients aged 50 and older with a history of heart attack and one additional CV risk factor. The study was designed to better understand the management of patients more than 12 months after their heart attack, who remain at high risk for major thrombotic events.
- Complete results from the PEGASUS-TIMI 54 study will be submitted to a scientific meeting in 2015 and pending further analysis.
ACCF/AHA Guideline Recommendations
Antithrombotic Therapy in Acute MI Patients (STEMI) for Secondary Prevention

STEMI Managed Invasively after Fibrinolysis
- Class I, Level of Evidence: A – Aspirin should be prescribed indefinitely
- DES placed: Continue therapy for at least 1 year
  - Clopidogrel 75 mg daily (Class I, Level of Evidence: C)
  - Prasugrel 10 mg daily (Class IIb, Level of Evidence: B)
- BMS placed: Continue therapy for at least 30 days and up to 1 year
  - Clopidogrel 75 mg daily (Class I, Level of Evidence: C)
  - Prasugrel 10 mg daily (Class IIb, Level of Evidence: B)

Emerging Oral Antithrombotics in Patients with ACS

APPRAISE-2: Apixaban in ACS

Trial stopped November 2011 due to excess bleeding events in the apixaban group without a counterbalancing reduction in ischemic events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban 5 mg Twice Daily (%)</th>
<th>Placebo (%)</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>N=3706</td>
<td>N=3897</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death, MI, or Ischemic Stroke</td>
<td>7.5</td>
<td>7.9</td>
<td>0.95</td>
<td>0.51</td>
</tr>
<tr>
<td>Death</td>
<td>4.2</td>
<td>3.9</td>
<td>1.08</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Safety: Bleeding

<table>
<thead>
<tr>
<th>TIMI Criteria</th>
<th>Major Bleeding</th>
<th>Intracranial Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 5 mg Twice Daily (%)</td>
<td>N=3873</td>
<td>N=3842</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>1.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Intracranial Bleeding</td>
<td>0.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

ATLAS ACS 2-TIMI 51: Rivaroxaban in ACS

Novel Anticoagulants in ACS

- Apixaban likely done with increase bleeding and no improvement in efficacy in APPRAISE-2
- Rivaroxaban has been denied approval 3 times by FDA, but approved in Europe, but company states it will continue with research
- Dabigatran does not look promising with phase II study results showing a significant and dose dependent increase in bleeding

Current Oral Antiplatelet Therapy in Patients with Documented Atherosclerotic Disease

Aspirin in Patients at High Risk of Ischemic Events

<table>
<thead>
<tr>
<th>Category or Trial</th>
<th>No. of Trials</th>
<th>% of Vascular Events</th>
<th>Odds Ratio (95% CI)</th>
<th>% Odds Reduction (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous MI</td>
<td>12</td>
<td>13.5%</td>
<td>0.85 (0.62-1.18)</td>
<td>25 (4)</td>
</tr>
<tr>
<td>Previous Stroke/ TIA</td>
<td>21</td>
<td>17.8%</td>
<td>0.88 (0.63-1.24)</td>
<td>22 (4)</td>
</tr>
<tr>
<td>Stable Angina/ CAD</td>
<td>7</td>
<td>9.9%</td>
<td>1.21 (0.78-1.87)</td>
<td>33 (9)</td>
</tr>
<tr>
<td>Intermittent Claudication</td>
<td>26</td>
<td>6.4%</td>
<td>0.57 (0.31-1.05)</td>
<td>23 (9)</td>
</tr>
</tbody>
</table>

Antiplatelet: Control

Odds Ratio (CI)

Aspirin in Patients at High Risk of Ischemic Events

Risk and Benefit of Warfarin in Patients with CAD

Meta-Analysis of 44 Trials Involving 24,115 Patients

<table>
<thead>
<tr>
<th>No. of Trials</th>
<th>Ischemic Events</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
<th>Major Bleeding Odds Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>High vs Control</td>
<td>16 (N=10,056)</td>
<td>0.57 (0.51-0.63)</td>
<td>0.0001</td>
<td>39</td>
<td>0.00001</td>
</tr>
<tr>
<td>Moderate vs Control</td>
<td>4 (N=1238)</td>
<td>0.85 (0.60-1.24)</td>
<td>&gt;0.10</td>
<td>35</td>
<td>0.00001</td>
</tr>
<tr>
<td>Moderate to High vs ASA</td>
<td>11 (N=3457)</td>
<td>0.88 (0.63-1.24)</td>
<td>&gt;0.10</td>
<td>14</td>
<td>0.00001</td>
</tr>
<tr>
<td>Moderate + ASA vs ASA</td>
<td>3 (N=4806)</td>
<td>0.44 (0.23-0.83)</td>
<td>&lt;0.01</td>
<td>16</td>
<td>&gt;0.01</td>
</tr>
<tr>
<td>Low + ASA vs ASA</td>
<td>3 (N=4323)</td>
<td>0.51 (0.79-1.06)</td>
<td>&gt;0.01</td>
<td>5</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Constellation of death, myocardial infarction, or stroke events per 1000 patients.

Clopidogrel Studies: PAD

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Goal</th>
<th>Study Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRIE</td>
<td>N=19,185</td>
<td>History of stroke, MI, or established PAD</td>
<td>3 yrs (Mean 1.91 yrs)</td>
</tr>
<tr>
<td>CHARISMA</td>
<td>N=15,033</td>
<td>45 yrs of age with multiple CV risk factors, documented CAD, stroke, or symptomatic PAD</td>
<td>28 months (Median)</td>
</tr>
</tbody>
</table>


CHARISMA: Primary Endpoint

15,603 patients ≥45 yrs of age with multiple CV risk factors, documented CAD, stroke, or symptomatic PAD

<table>
<thead>
<tr>
<th>Placebo + ASA</th>
<th>Clopidogrel + ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Event Rate (%)</td>
<td>7.3%</td>
</tr>
<tr>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>

*First Occurrence of MI, stroke, or cardiovascular death.


CHARISMA: Subgroup Analysis of “CAPRIE-like” Patients

9,478 patients with prior MI, stroke, or symptomatic PAD

<table>
<thead>
<tr>
<th>Placebo + ASA</th>
<th>Clopidogrel + ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of CV Death, MI or Stroke (%)</td>
<td>8.8%</td>
</tr>
<tr>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

2011 AHA/ACCF Guideline Recommendations
Antithrombotic Therapy for Secondary Prevention in Patients with Atherosclerotic Disease

- Aspirin 75-162 mg daily in all patients with CAD indefinitely unless contraindicated.
- Clopidogrel 75 mg is an alternative in patients with CAD who cannot take aspirin.
- Aspirin 75-325 mg, clopidogrel 75 mg daily, or aspirin plus extended release dipyridamole (25 mg and 200 mg twice daily, respectively) in patients with stroke or TIA should be started and continued.
- Aspirin 75-325 mg daily or clopidogrel 75 mg daily in patients with symptomatic PAD should be started and continued.

CAD = coronary artery disease; TIA = transient ischemic attack; PAD = peripheral artery disease.

2011 AHA/ACCF Guideline Recommendations
Antithrombotic Therapy for Secondary Prevention in Patients with Atherosclerotic Disease

- Antiplatelet therapy is recommended over anticoagulation therapy with warfarin to treat patients with atherosclerosis.
- In patients with a indication for anticoagulation therapy (i.e., AF, prosthetic heart valve, etc...), warfarin should be administered in addition to low-dose aspirin 75-81 mg daily.
- Combination of aspirin 75-162 mg daily and clopidogrel 75 mg daily may be considered in patients with stable CAD.


A Novel Antiplatelet Agent for Secondary Prevention

- FDA approved May 2014
  - Indicated for the reduction of thrombotic CV events in patients with a history of MI or with PAD.
- Mechanism of Action
  - Inhibits thrombin-induced platelet aggregation by inhibiting the protease-activated receptor-1 (PAR-1) expressed on platelets.
- Dose and administration
  - 2.08 mg orally once daily.
  - Used in conjunction with aspirin and/or clopidogrel; limited experience with other antiplatelet agents.
- Contraindicated
  - Patients with active pathological bleeding &/or history of stroke, TIA, or ICH.

ICH = intracranial hemorrhage.

Thrombin Targets the Protease-Activated Receptor PAR-1

- PAR-1 on Platelets → Activation
- PAR-1 on Endothelial & Smooth Muscle → Mitogenic
- Fibrinogen
- Cross-linked fibrin clot
- Atherothrombosis

Bonaca MP 2014

TRA 2P – TIMI 50 Study

After 2 years, the data and safety monitoring board recommended discontinuation of vorapaxar treatment in patients with a history of stroke due to increased risk of intracranial hemorrhage.

Hx MI, CVA, PAD

Vorapaxar
2.5 mg daily
N=13,225

Placebo
(and usual therapy)
N=13,224

Median follow-up: 30 months

Primary endpoint: Composite of death from CV causes, MI, or stroke.

TRA 2P-TIMI 50: Safety and Efficacy of Vorapaxar at 3 Years

RR = risk reduction; UCR = urgent coronary revascularization; ICH = intracranial hemorrhage.

TRA 2P-TIMI 50: MI Subgroup at 3 Years


TRA 2P-TIMI 50: Efficacy Early and Late

Qualifying MI


TRA 2P-TIMI 50: Efficacy in Subgroups


Management of patients with peripheral arterial disease (PAD) in secondary prevention: an unmet medical need

Treatment of claudication

- Supervised exercise rehabilitation
- Pharmacotherapy
- Revascularization

The FDA has approved only two drugs for claudication

- Pentoxifylline
  - Methylxanthine
  - Approved August 1984
  - Decreases plasma viscosity, improves RBC deformability, some vasodilation
- Cilostazol
  - Phosphodiesterase III inhibitor derivative
  - Approved January 1999
  - Platelet inhibitor, vasodilation, ↑HDL-cholesterol, ↓triglycerides

Baseline Characteristics - PAD Cohort

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Vorapaxar N=1892</th>
<th>Placebo N=1895</th>
<th>Overall N=3787</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>66 (60 - 73)</td>
<td>66 (60 - 73)</td>
<td>61 (53 - 69)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>29</td>
<td>30</td>
<td>24</td>
</tr>
</tbody>
</table>

Clinical Characteristics

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Vorapaxar</th>
<th>Placebo</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus (%)</td>
<td>37</td>
<td>35</td>
<td>25</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>84</td>
<td>83</td>
<td>69</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>87</td>
<td>88</td>
<td>83</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>31</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>Any coronary artery disease (%)</td>
<td>56</td>
<td>58</td>
<td>78</td>
</tr>
<tr>
<td>eGFR &lt; 60mL/min/1.73 m2 (%)</td>
<td>29</td>
<td>29</td>
<td>15</td>
</tr>
</tbody>
</table>

Baseline Medical Therapy

<table>
<thead>
<tr>
<th>Baseline Medical Therapy</th>
<th>Vorapaxar</th>
<th>Placebo</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (%)</td>
<td>88</td>
<td>88</td>
<td>94</td>
</tr>
<tr>
<td>Thienopyridine (%)</td>
<td>37</td>
<td>37</td>
<td>62</td>
</tr>
<tr>
<td>Lipid-lowering therapy (%)</td>
<td>84</td>
<td>87</td>
<td>91</td>
</tr>
</tbody>
</table>

Baseline Characteristics - Vascular Disease History

<table>
<thead>
<tr>
<th>Previous cerebrovascular event (%)</th>
<th>Vorapaxar N=1892</th>
<th>Placebo N=1895</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral arterial revascularization (%)</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Prior carotid intervention (%)</td>
<td>62</td>
<td>61</td>
</tr>
<tr>
<td>ABI &lt; 0.85 (%)</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>ABI &gt; 1.3 (%)</td>
<td>1.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Claudication (Fontaine stage &gt;1) (%)</td>
<td>76</td>
<td>74</td>
</tr>
</tbody>
</table>

Stage 1 – No symptoms
Stage 2 – Intermittent Claudication
Stage 3 – Nocturnal/rest pain
Stage 4 – Necrosis/gangrene

Hospitalization for Acute Limb Ischemia

Pre-specified, adjudicated
N = 3767

Vorapaxar

Placebo

3.9%
2.3%
Hazard Ratio 0.58
95% CI 0.39 to 0.86
p = 0.006

Peripheral Revascularization

Prespecified
N = 3767

Vorapaxax

Placebo

22.2%
18.4%
Hazard Ratio 0.84;
95% CI 0.73 to 0.97
p = 0.017
Vascular Efficacy Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Vorapaxar</th>
<th>Placebo</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Efficacy</td>
<td>N=1892</td>
<td>N=1895</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD/MI/Stroke (%)</td>
<td>11.3</td>
<td>11.9</td>
<td>0.94</td>
<td>0.53</td>
</tr>
<tr>
<td>CVD/MI/Stroke/urgent revascularization (%)</td>
<td>12.7</td>
<td>13.4</td>
<td>0.95</td>
<td>0.57</td>
</tr>
<tr>
<td>Peripheral Limb Vascular Efficacy</td>
<td>N=1892</td>
<td>N=1895</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hosp. for acute limb ischemia (%)</td>
<td>2.3</td>
<td>3.9</td>
<td>0.58</td>
<td>0.006</td>
</tr>
<tr>
<td>Any Peripheral revascularisation (%)</td>
<td>18.4</td>
<td>22.2</td>
<td>0.64</td>
<td>0.017</td>
</tr>
<tr>
<td>Effective peripheral revasc. (%)</td>
<td>16.5</td>
<td>19.5</td>
<td>0.86</td>
<td>0.049</td>
</tr>
</tbody>
</table>

*Includes vascular events involving the coronary, cerebral, or peripheral vasculature.

TRACER Trial: Vorapaxar in ACS

12,944 patients with a NSTEMI randomized to vorapaxar (40mg loading dose followed by 2.5 mg daily) or placebo for up to 2 years, trial terminated early due to increased bleeding with vorapaxar.

Vorapaxar Summary

PAR-1 Antagonism added to ASA and/or Clopidogrel in Patients with hx of MI or PAD and no hx of Stroke/TIA

Current Available Antithrombotic Agents for Secondary Prevention in Patients with Coronary Disease

Oral Antithrombotics for Prevention of Ischemic Events

<table>
<thead>
<tr>
<th>Antiplatelet Agents</th>
<th>Anticoagulants</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aspirin</td>
<td>• Warfarin</td>
</tr>
<tr>
<td>• Ticlopidine</td>
<td>• Rarely used for CAD due to better options and increased bleeding risk</td>
</tr>
<tr>
<td>• Clopidogrel</td>
<td>• Factor Xa</td>
</tr>
<tr>
<td>• Prasugrel</td>
<td>• Vitamin K Dependent Coagulation Factors</td>
</tr>
<tr>
<td>• Ticagrelor</td>
<td>• Thromboxane</td>
</tr>
<tr>
<td>• Vorapaxar</td>
<td>• ADP (P2Y12)</td>
</tr>
</tbody>
</table>

CV = cardiovascular; TTP = thrombotic thrombocytopenia purpura; PAD = peripheral artery disease; ICH = intracranial hemorrhage.

PAR-1 Antagonism added to ASA and/or Clopidogrel in Patients with hx of MI or PAD and no hx of Stroke/TIA

Current Available Antithrombotic Agents for Secondary Prevention in Patients with Coronary Disease

Oral Antithrombotics for Prevention of Ischemic Events

<table>
<thead>
<tr>
<th>Antiplatelet Agents</th>
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</thead>
<tbody>
<tr>
<td>• Aspirin</td>
<td>• Warfarin</td>
</tr>
<tr>
<td>• Ticlopidine</td>
<td>• Factor Xa</td>
</tr>
<tr>
<td>• Clopidogrel</td>
<td>• Vitamin K Dependent Coagulation Factors</td>
</tr>
<tr>
<td>• Prasugrel</td>
<td>• Thromboxane</td>
</tr>
<tr>
<td>• Ticagrelor</td>
<td>• ADP (P2Y12)</td>
</tr>
<tr>
<td>• Vorapaxar</td>
<td>• Thrombin (PAR-1)</td>
</tr>
</tbody>
</table>

Sites of Action of Antithrombotic Agents

*Not FDA approved; †Not FDA approved for treatment of coronary artery disease.
Oral Antiplatelet Agents: Pharmacology

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Half-Life</th>
<th>Metabolism</th>
<th>Effects on Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>COX-1 inhibitor</td>
<td>5-6 hours</td>
<td>Metabolized in liver</td>
<td>Irreversible inhibition</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>P2Y12 receptor antagonist</td>
<td>8 hours (inactive metabolite)</td>
<td>Predrug, metabolized in the liver</td>
<td>Irreversible inhibition</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>P2Y12 receptor antagonist</td>
<td>7 hours</td>
<td>Predrug, metabolized in the intestines and liver</td>
<td>Reversible inhibition</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>P2Y12 receptor antagonist</td>
<td>7 hours</td>
<td>Prodrug, metabolized in the liver</td>
<td>Reversible inhibition</td>
</tr>
<tr>
<td>Vorapaxar</td>
<td>Thrombin receptor antagonist (PAR-1)</td>
<td>3-4 days</td>
<td>Not a prodrug, metabolized in the liver</td>
<td>Effectively irreversible inhibition due to long half-life of drug</td>
</tr>
</tbody>
</table>


Antithrombotic Agents in Practice in Secondary Prevention

Treatment of Acute Coronary Syndromes

Initial Treatment of ACS

- STEMI
  - Antiplatelet, anti-ischemic, or anticoagulant therapy
  - Thrombolytics
  - PCI or CABG
- UA/NSTEMI
  - Antiplatelet, anti-ischemic, or anticoagulant therapy
  - PCI or CABG

Long-Term Medical Management

- Therapeutic Goal: Superior Outcome (Decreased ischemic risk without increased bleeding)
- Increased Bleeding
  - Higher Efficacy
  - Reduced Efficacy
  - Inferior Outcome

Long-Term Antithrombotic Therapy

Identifying Patients at Highest Risk of Future Ischemic Events: Risk Scores

- **PURSUIT** (0-18 points)
  - Age (points for each decade at diagnosis), male sex, CCS class, heart failure, and ST-depression at presentation
- **TIMI** (0-7 points)
  - Age >65 years, >3 risk factors for CAD, use of ASA (last 7 days), known CAD (stenosis >50%), >1 episode rest angina in >24 h, ST-segment deviation, and elevated cardiac markers
- **GRACE** (0-258 points)
  - Age, heart rate, systolic BP, creatinine level, Killip class, cardiac arrest at admission, elevated cardiac markers, and ST-segment deviation
- All are effective at predicting recurrent ischemic events
- GRACE may be most useful in predicting long-term events

Characteristics of the High-Risk Patient

- **Advanced Age** (≥75 years)
  - Death rate >2× patients <75 years
- **Elevated Troponin I Levels**
  - Each increase of 1.0 mg/L is associated with a significant increase in the risk ratio for death
- **ST-Segment Deviation**
  - Associated with higher risk of death or MI
- **Diabetes**
  - Higher risk of death
- **Renal Impairment**
  - Associated with a higher rate of death or MI
- **Multi-vessel CAD**
  - About 3-fold increase in CV events compared to single-vessel disease

Pursuit=Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin; TIMI=Thrombolysis In Myocardial Infarction; GRACE=Global Registry of Acute Coronary Events.

Risk Scores are Available Online

[Image of GRACE ACS Risk Model]

Risk Scores are Available Online

http://www.outcomes.umassmed.org/grace_risk/acs_risk_content.html

GRACE Risk Score Predicts Long-Term Risk


Intermediate

Low

Survival Probability

1.0

0.8

0.6

0.4

0.2

0

0 1000 2000 3000 4000

Time (days)

ESC Guideline Categories

High

Intermediate

Low

Antiplatelet Therapies Confer Benefit Regardless of TIMI Risk Score

[Image of graph showing comparison between Placebo + ASA and Clopidogrel + ASA]


Risk Is Greatest in Patients with a Prior Ischemic Event

[Image of bar chart showing event rates in different risk groups]

REACH Registry (N=45,227)

*All event rates adjusted for age and gender.


Risk Factors for Bleeding

Predictors of Major Bleeding in ACS Patients1

- Advanced age
- Female sex
- Low body weight
- Renal insufficiency
- Non-cardiac vascular disease
- History of bleeding
- Low blood pressure
- ST-elevation myocardial infarction
- High Killip class

Predictors of Major Bleeding in Stable Vascular Disease Patients2

- Age 77 years
- History of CHF
- Previous stroke
- Diabetic nephropathy
- Hypertension

*Based on GRACE Registry (n=24,045); †Based on CHARISMA Study population (n=15,603).


2010 ACC/ACG/AHA Expert Consensus Document

Use of PPI with Antiplatelet Therapy

Need for Antiplatelet Therapy

YES

Assess GI Risk Factors

Test for H. pylori and treat if infected

YES

GI Bleeding

Dual Antiplatelet Therapy

Concomitant Anticoagulant Therapy

YES

GI = Gastointestinal; PPI = Proton pump inhibitor.
**Case Studies in Secondary Prevention**

**Case 1 – “JT”**

- JT is a 65 yo male who is in to see you today for a checkup after suffering a heart attack 3 months ago.
- He received two drug-eluting stents, one in his LAD and one in the circumflex.
- He is currently doing well and has not experienced any chest pains in the last 3 months.
- PMH: Diabetes, dyslipidemia, HTN, and MI x 3 months
- Meds: Metformin, glipizide, atorvastatin, ACE inhibitor, aspirin 325 mg daily and clopidogrel 75 mg daily
Case 1 – Clinical Data

• Father died of a heart attack at 50 years old
• PE: HR=80, BP=135/86, Height=68 in, Weight=236 lbs, BMI=35.9
• Labs: Serum creatinine 1.2, TC 220, LDL 90, HDL 50, HbA1c 6.7%

Case 1 – Presentation Cont’d

• JT has been seeing his PCP but wanted an opinion from a specialist to make sure that everything is being done to lower his risk of having another heart attack.
• He is especially worried knowing his dad died young of a heart attack.

Characteristics of the High-Risk Patient

• Advanced Age (≥75 years)
  – Death rate ≥2x patients <75 years
• Elevated Troponin I Levels
  – Each increase of 1.0 mg/L is associated with a significant increase in the risk ratio for death
• ST-Segment Deviation
  – Associated with higher risk of death or MI
• Diabetes
  – Higher risk of death
• Renal Impairment
  – Associated with a higher rate of death or MI
• Multi-vessel CAD
  – About 3-fold increase in CV events compared to single-vessel disease


Case 1 – Presentation Cont’d

• After reviewing his record you tell JT that he has high-risk features include diabetes and multi-vessel disease that elevate his risk for having another heart attack.
• You mutually agree to increase his statin to high intensity treatment and started him on a beta-blocker.

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>325 mg</th>
<th>81 mg</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>


Antiplatelet Therapy to Support PCI for STEMI

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

TRA 2P-TIMI 50: MI Subgroup at 3 Years  

<table>
<thead>
<tr>
<th>Percentage (%)</th>
<th>Vorapaxar (N=8938)</th>
<th>Placebo (N=8881)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death, MI or Stroke</td>
<td>RR 17% p=0.0001</td>
<td>12.1</td>
</tr>
<tr>
<td>CV Death, MI, Stroke, or UCM</td>
<td>RR 8% p=0.0003</td>
<td>10.5</td>
</tr>
<tr>
<td>MI</td>
<td>RR 21% p=0.0001</td>
<td>9.7</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>RR 1.61 p&lt;0.0001</td>
<td>1.4</td>
</tr>
<tr>
<td>GUSTO Moderate or Severe Bleeding</td>
<td>RR 1.54 p=0.006</td>
<td>2.1</td>
</tr>
<tr>
<td>ICH</td>
<td>RR 0.8 p=0.045</td>
<td>0.8</td>
</tr>
</tbody>
</table>

0 2 4 6 8 10 12
Time since Randomization (days)
0 2 4 6 8 10 12
CV Death, MI, Stroke (%)

0 2 4 6 8 10 12
Contraindicated Drug Use, MI or Stroke (%)

Case 1 – Presentation Cont’d
• You discuss the benefits and risks of vorapaxar with JT and mutually agreed to add vorapaxar to his antiplatelet regimen.

Case 2 – Presentation
• HPI: A 75-year-old woman presents to your office with stuttering midsternal chest pain. These symptoms have largely “come and gone” over the last 2 weeks. Her daughter became concerned today when the symptoms recurred but did not resolve.
• She currently notes “mild” pain in her mid chest. These symptoms are not relieved or exacerbated with taking a deep breath.
• Past Medical History: Hypertension, gout, “mild kidney disease”, TIA x 10 years, and tonsillectomy at age 5.
• Former smoker (0.5 packs/day x 52 years).
• Her father died of a “heart attack” at age 48.

Case 2 – Presentation Cont’d
• Meds: Calcium channel blocker and colchicine
• Physical Exam
  – HR=88, BP=172/74, Height=63 in, Weight=123 lbs, BMI=21.8
  – General: Frail appearing woman in no distress
  – CV: Regular rhythm and a normal S1 and S2, no S3
• ECG
  – Normal sinus rhythm with a rate of 92 bpm. There is left axis deviation with LVH. There are no ischemic changes.
• Labs
  – Serum creatinine 1.8 with an estimated creatinine clearance of 24.3 ml/min.
  – Troponin I is 0.6 (0.1 ULN)

Case 2 – Presentation Cont’d
• She is having a NSTEMI. She is transferred to the hospital and receives 325 mg of aspirin and a single sublingual nitroglycerin 0.4 mg which relieves her pain. She is started on unfractionated heparin, metoprolol tartrate, and atorvastatin.
• Given concern about her baseline severe renal dysfunction and risks of worsening renal insufficiency with intravenous contrast, she declines coronary angiography. She reports feeling well and at this time has decided against a stress test for further risk stratification.
TRACER Trial: Vorapaxar in ACS

12,944 patients with a NSTE-ACS randomized to vorapaxar (40mg loading dose followed by 2.5 mg daily) or placebo for up to 2 years, trial terminated early due to increased bleeding with vorapaxar

Primary endpoint = cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization; Secondary efficacy endpoint = cardiovascular death, MI, or stroke.


12,944 patients with a NSTE-ACS randomized to vorapaxar (40mg loading dose followed by 2.5 mg daily) or placebo for up to 2 years, trial terminated early due to increased bleeding with vorapaxar

RR 8%  \( p=0.07 \)

RR 11%  \( p=0.02 \)

RR 12%  \( p=0.02 \)

RR 7%  \( p=0.69 \)

GUSTO Moderate or Severe Bleeding

ICH

Risk Factors for Bleeding

Predictors of Major Bleeding in ACS Patients

- Advanced age
- Female sex
- Low body weight
- Renal insufficiency
- Non-cardiac vascular disease
- History of bleeding
- Low blood pressure
- ST-elevation myocardial infarction
- High Killip class

Predictors of Major Bleeding in Stable Vascular Disease Patients

- Age ≥75 years
- History of CHF
- Previous stroke
- Diabetic nephropathy
- Hypertension

Case 2 – Presentation Cont’d

- She is discharged 2 days later on aspirin (81 mg daily), ticagrelor (90 mg twice daily), metoprolol tartrate (25 mg twice daily), and atorvastatin (80 mg daily).

Balancing Efficacy and Bleeding

TRITON TIMI-38: Net Clinical Benefit

<table>
<thead>
<tr>
<th>Prior Stroke / TIA</th>
<th>Yes</th>
<th>No</th>
<th>( p = 0.006 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ( &lt;75 )</td>
<td>11.8</td>
<td>12.8</td>
<td>0.89</td>
</tr>
<tr>
<td>Weight ( &lt;60 ) kg</td>
<td>15.6</td>
<td>15.8</td>
<td>0.06</td>
</tr>
<tr>
<td>History of TIA or Stroke</td>
<td>11.7</td>
<td>12.7</td>
<td>1.00</td>
</tr>
<tr>
<td>Overall</td>
<td>11.5</td>
<td>12.5</td>
<td>0.58</td>
</tr>
</tbody>
</table>

TRA 2P-TIMI 50: Net Clinical Benefit

Bleeding Risk Subgroups

| Age \( <75 \) yr | 11.8 | 12.8 | 0.89 |
| Weight \( <80 \) kg | 15.6 | 15.8 | 0.06 |
| History of TIA or Stroke | 11.7 | 12.7 | 1.00 |

Case 2 – Presentation Cont’d

- She returns to see you in clinic 3 weeks after discharge, with her daughter and son-in-law who want to make sure that everything is being done to reduce her risk of recurrent ischemic events.

- Her high-risk features include:
  - Age ≥75 years
  - Renal impairment
  - Elevated troponin I

- You tell her that her risk factors indicate increased risk for another ischemic event.

Risk Factors for Bleeding

Predictors of Major Bleeding in ACS Patients

- Advanced age
- Female sex
- Low body weight
- Renal insufficiency
- Non-cardiac vascular disease
- History of bleeding
- Low blood pressure
- ST-elevation myocardial infarction
- High Killip class

Predictors of Major Bleeding in Stable Vascular Disease Patients

- Age ≥75 years
- History of CHF
- Previous stroke
- Diabetic nephropathy
- Hypertension

*Based on GRACE Registry (n=24,045); †Based on CHARISMA Study population (n=15,803).

Case 2 – Presentation Cont’d

- Based on her high risk for bleeding which include the following risk factors:
  - Advanced age
  - Female gender
  - Low body weight
  - Renal insufficiency
  - Hypertension
  - Previous stroke
- You started her on a PPI and tell her to continue taking her other medications and walk 30 minutes at least 3x per week.

Case 3

- CP is a 58 y/o man with a history of an MI 4 years ago. He received lytic therapy and did well.
  - His risk factors include hypertension, hyperlipidemia, insulin resistance and obesity. He stopped smoking after his MI.
  - On therapy his BP=132/82, HR= 76, BMI LDL 82, HDL 40, TG 162, HgBA1C= 6.4%, BMI 31.2, Waist circumference= 41”
- He developed crescendo angina over 2 weeks and presented with a longer lasting episode that resolved with NTG in the ER.

Case 3

- His EKG showed ST depressions in the inferior leads. Troponin peaked at 2.4 with rapid washout
- Cath showed CTO in OM-1, 40-50% mid LAD and 50% mid-distal RCA.
- Echo (post cath) showed mod posterior hypokinesis and mild inferoapical hypo
- He received ASA 325->81 mg od and Plavix 300 mg load and then 75 mg od
- He is on ASA 81 mg and Simvastatin 20 mg and was previously intolerant to Atorva and Rosuvastatin.

Case 3

- Does he need another LDL lowering medication? (LDL is <100)
  - If so, which one?
    - Ezetimibe
    - Niacin
    - Colesvelam
- Is there evidence to support a choice?
  - Niacin and Bile Acid Resin have data but not in combination with a statin
  - Do any meds beyond statins work?
  - Is lower better?

Association between the Presence of Inactivating Mutations in NPC1L1 and Plasma Lipids

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean Difference between Carriers and Noncarriers</th>
<th>P Value</th>
<th>OR for CHD mutation carriers vs.noncarriers (95% CI, P=0.008)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mg/dL)</td>
<td></td>
<td></td>
<td>0.47 (95% CI, 0.25-0.87; P = 0.008)</td>
</tr>
<tr>
<td>Total</td>
<td>-13</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>-12</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>2</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (% change)</td>
<td>-12</td>
<td>0.11†</td>
<td>= Effect of ezetimibe</td>
</tr>
</tbody>
</table>

Patient Population

- Inclusion Criteria:
  - Hospitalization for STEMI, NSTEMI/UA < 10 days
  - Age ≥ 50 years, and ≥ 1 high-risk feature:
    - New ST chg, + troponin, DM, prior MI, PAD, cerebrovasc, prior CABG > 3 years, multivessel CAD
    - LDL-C 50-125 mg/dL (50-100 mg/dL if prior lipid-lowering Rx)
- Major Exclusion Criteria:
  - CABG for treatment of qualifying ACS
  - Current statin Rx more potent than simva 40mg
  - Creat Cl < 30mL/min, active liver disease

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin (N=9077)</th>
<th>EZ/Simva (N=9067)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td><strong>MI prior to index ACS</strong></td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td><strong>STEMI / NSTEMI / UA</strong></td>
<td>29 / 47 / 24</td>
<td>29 / 47 / 24</td>
</tr>
<tr>
<td><strong>Days post ACS to rand (IQR)</strong></td>
<td>5 (3, 8)</td>
<td>5 (3, 8)</td>
</tr>
<tr>
<td><strong>Cath / PCI for ACS event</strong></td>
<td>88 / 70</td>
<td>88 / 70</td>
</tr>
<tr>
<td><strong>Prior Lipid Rx</strong></td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td><strong>LDL-C (mg/dL) (IQR)</strong></td>
<td>95 (79, 110)</td>
<td>95 (79, 110)</td>
</tr>
</tbody>
</table>

Case 3
- Decision made to Increase Simvastatin to 40 mg and add Ezetimibe 10 mg.
- Plavix added to ASA 81 mg.
- Metoprolol Succinate 25 mg added
- Patient enrolled in out patient cardiac rehabilitation program
- Focus on weight loss via diet and exercise