The Primary Care–Cardiology Partnership to Ensure Optimal Patient Outcomes in Acute Coronary Syndrome

Pri-Med Update – Princeton, NJ
September 4, 2008
7:45 AM-9:00 AM
Session 1: The Primary Care-Cardiology Partnership to Ensure Optimal Patient Outcomes in Acute Coronary Syndrome

Learning Objectives

- Outline the concept of thienopyridine resistance and explain its potential implications for secondary prevention in patients post-ACS.
- Compare and contrast emerging treatment options for antiplatelet therapy post-ACS.

Faculty

**Joseph C. Booth, MD, FAAFP**
Family Practitioner
Deerfield Family Practice
Chair, Department of Medical Education
Faxton-St. Luke’s Healthcare
Department of Family Practice
St. Elizabeth’s Medical Center
Utica, New York

Dr Joseph C. Booth is a family practitioner at Deerfield Family Practice in Utica, New York. He is chair of the Department of Medical Education for Faxton-St. Luke’s Healthcare, also in Utica, New York, where he serves as attending physician consultant for the Utilization Review Department of Quality Assurance and as the attending physician with the acute rehabilitation facility. In addition, Dr Booth serves as a consultant for palliative care, joint palliative care services at Faxton-St. Luke’s and at St. Elizabeth’s Medical Center.

Dr Booth received his medical degree from St. George’s University School of Medicine in Grenada, West Indies. He then completed his residency in family practice at St. Elizabeth’s Medical Center in Utica, New York. Additionally, he has a certificate of added qualifications in geriatrics and is board-certified in hospice and palliative care.

He is a delegate to the Medical Society of the State of New York as well as the New York Academy of Family Physicians. Dr Booth is also a member of the American Academy of Family Practice, Oneida County Medical Society, American Geriatric Society, New York Medical Directors Association, and the American Medical Directors Association. He has received several awards, including the Edmund Furginito Award of Excellence on Obstetrics and the Charles R. Modica Award in recognition of outstanding clinical performance.

**Dean J. Kereiakes, MD, FACC**
Medical Director – The Christ Hospital Heart and Vascular Center
Medical Director – The Lindner Research Center
Chairman, Executive Committee – Ohio Heart and Vascular Center, Inc.
Professor of Clinical Medicine – Ohio State University
Cincinnati, Ohio

Dr Kereiakes received his medical degree and was valedictorian of his graduating class at the University of Cincinnati in Ohio. His postgraduate training included internship and residency at the University of California, San Francisco, and a senior residency at Massachusetts General Hospital in Boston, and a chief residency at the University of California, San Francisco. He then completed fellowships in adult cardiology at the University of California, San Francisco and in coronary angioplasty at the San Francisco Heart Institute and the Sequoia Hospital. Dr Kereiakes has been an investigator for most of the interventional technologies introduced in the last two decades and has performed more than 25,000 catheterization laboratory procedures.

In addition to lecturing nationally and internationally, Dr Kereiakes is very active as a clinical and scientific investigator and has participated in over 800 clinical research protocols. He has published over 500 journal articles, abstracts and book chapters. He serves on the editorial boards of *Circulation, The Journal of the American College of Cardiology, The American Heart Journal, Journal of Invasive Cardiology, The American Journal of Cardiology and The Journal of Interventional Cardiology*, as well as being a section editor for *MedReviews* (New Drugs and Devices). He was previously a section editor for *Circulation.*
Dr Kereiakes is a fellow of the American College of Cardiology. He was a member of the Joint American College of Cardiology/American Heart Association Task Force Committees to write guidelines for both coronary angioplasty and unstable angina. Dr Kereiakes has been selected as Outstanding Alumnus University of Cincinnati School of Medicine, Who’s Who in America, Who’s Who in Medicine and Healthcare, Who’s Who in Science and Engineering, Best Doctors in America and has received the Cincinnati Business Courier Health Care Hero - Innovator award and the Ohio Valley American Heart Association’s Kaplan Visionary Award for cardiovascular research.

Faculty Financial Disclosure Statements
The presenting faculty reported the following:
Dr Booth has no relationship(s) to disclose.
Dr Kereiakes receives grant/research support from Abbott Bioabsorbable Vascular Solutions; Amylin Pharmaceuticals, Inc.; Cordis/Johnson & Johnson; Boston Scientific; Medtronic; and Daiichi Sankyo, Inc. He receives consulting fees from Devax, Eli Lilly and Company, Boston Scientific, Abbott Vascular Solutions, and Medpace. He is a member of the speakers bureau for Eli Lilly and Company.

Education Partner Financial Disclosure Statements
The content collaborators at at Accelmed have reported the following: Tony Limbil, MD, MPH, and Stephanie Breslan, MS have no relationship(s) to disclose.

Drug List

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<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
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</thead>
<tbody>
<tr>
<td>clopidogrel</td>
<td>Plavix</td>
</tr>
<tr>
<td>bivalirudin</td>
<td>Angiomax</td>
</tr>
<tr>
<td>ticlopidine</td>
<td>Ticlid</td>
</tr>
<tr>
<td>cilostazol</td>
<td>Pletal</td>
</tr>
</tbody>
</table>

Investigational

| prasugrel | Effient |

Suggested Reading List


Recommended Web Reading


The Primary Care–Cardiology Partnership to Ensure Optimal Patient Outcomes in Acute Coronary Syndrome

Joseph Booth, MD
Dean J. Kereiakes, MD

Case Study: Mr. Johnson

- Initial presentation
  - Mr. Johnson, a 65-year-old male, presents to his primary care physician for:
    - Exertional chest pain for 4 days
    - Spontaneous and persistent chest pain at rest for the last 30 minutes
    - History of type 2 diabetes for 6 years, HBP for 15 years, and smoking
    - Family history of fatal MI (father)
    - Normal physical exam
    - Current medications: metformin, ACE inhibitor, aspirin, pravastatin
    - ECG performed in the office is normal

What is the best next step in management?

ACE = angiotensin-converting enzyme; ECG = electrocardiogram; HBP = high blood pressure; MI = myocardial infarction

Question 1: What Is the Best Next Step in Management?

1. Ask him to take nitroglycerin every time he has chest pain and to come back in 2 weeks
2. Start him on lifestyle management that includes exercise and healthy diet
3. Give him aspirin and call EMS to take him to the ER
4. Ask him to go to the ER
5. Obtain an appointment for a stress test

Question 2: What Is the Most Likely Diagnosis?

1. Acute coronary syndrome (ACS)
2. Pulmonary embolism
3. Muscle strain
4. Aortic dissection
5. Pericarditis
Acute Coronary Syndrome (ACS)

Cardiac enzymes elevated?
- No
- Yes

Unstable angina (UA)
Myocardial infarction (MI)

ST-elevation?
- No
- Yes

STEMI
NSTEMI

ACS = Acute Coronary Syndrome; UA = Unstable Angina; NSTEMI = Non-ST-Elevation MI; STEMI = ST-Elevation MI

Risk Factors for ACS
- Diabetes
- Smoking
- Hypertension
- High cholesterol
- Family history of CVD
- Age
- Obesity
- Socioeconomic status
- Gender (men more with the disease but women dying more)

Hospital Discharges in the United States: UANSTEMI and STEMI

1.4 million hospital discharges
1.1 million UANSTEMI discharges per year
268,000 STEMI discharges per year

STEMI = ST-elevation MI; NSTEMI = non–ST-elevation MI

Baseline Characteristics Contribute to TIMI Risk Score for UANSTEMI

Characteristics
- Age > 65 years
- At least 3 risk factors for CAD
- Significant coronary stenosis (eg, prior coronary stenosis > 50%)
- ST deviation
- Severe anginal symptoms (eg, > 2 anginal events in last 24 hours)
- Use of aspirin in last 7 days
- Elevated serum cardiac markers

Multivariate Analysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>β Coefficient</th>
<th>P Value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, &gt; 65 years</td>
<td>0.5575</td>
<td>&lt; .001</td>
<td>1.75 (1.35-2.25)</td>
</tr>
<tr>
<td>At least 3 risk factors for CAD</td>
<td>0.5034</td>
<td>&lt; .001</td>
<td>1.75 (1.30-2.21)</td>
</tr>
<tr>
<td>Significant coronary stenosis</td>
<td>0.6135</td>
<td>&lt; .001</td>
<td>1.75 (1.23-2.50)</td>
</tr>
<tr>
<td>ST deviation</td>
<td>0.6314</td>
<td>.006</td>
<td>1.74 (1.17-2.59)</td>
</tr>
<tr>
<td>Severe anginal symptoms (≥ 2 anginal events in last 24 hours)</td>
<td>0.4940</td>
<td>&lt; .001</td>
<td>1.56 (1.21-1.99)</td>
</tr>
<tr>
<td>Use of aspirin in last 7 days</td>
<td>0.4920</td>
<td>&lt; .001</td>
<td>1.56 (1.21-1.99)</td>
</tr>
<tr>
<td>Elevated serum cardiac markers</td>
<td>0.4915</td>
<td>.006</td>
<td>1.56 (1.17-2.02)</td>
</tr>
</tbody>
</table>

Question 3: What Is Mr. Johnson’s TIMI Risk Score?

- Summary of case study:
  - 65-year-old male
  - Chief complaint: Exertional chest pain for 4 days
  - Persistent chest pain at rest for the past 30 minutes
  - History of type 2 diabetes, hypertension, smoking
  - Current medications: metformin, ACE inhibitor, daily aspirin, pravastatin
  - Family history of fatal MI (father)
  - Normal physical exam
  - Normal ECG performed in the office
  - ECG: ST-depression in ER
  - Cardiac enzymes elevated

His total TIMI risk score is: A. < 2 B. 3 C. 4 D. 5 E. ≥ 6

TIMI Risk Score Correlates With Outcomes

<table>
<thead>
<tr>
<th>Test Cohort</th>
<th>No. of Risk Factors</th>
<th>Rate of Composite End Point (%*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/1</td>
<td>85 (4.3)</td>
<td>4.7</td>
</tr>
<tr>
<td>2</td>
<td>339 (17.3)</td>
<td>8.3</td>
</tr>
<tr>
<td>3</td>
<td>627 (32.0)</td>
<td>13.2</td>
</tr>
<tr>
<td>4</td>
<td>573 (26.0)</td>
<td>19.9</td>
</tr>
<tr>
<td>5</td>
<td>267 (13.6)</td>
<td>26.2</td>
</tr>
<tr>
<td>6/7</td>
<td>66 (3.4)</td>
<td>40.9</td>
</tr>
</tbody>
</table>

*All-cause death, MI, and recurrent ischemia prompting revascularization (< 14 days)


*Estimate for secondary discharges in 2005

*Based on the “Get With the Guidelines” project by the American Heart Association (AHA)

Question 4: Cardiac Enzymes Elevated and ST-segment Depression: What Is the Best Next Step?

1. Discharge Mr. Johnson with a follow-up appointment with a cardiologist
2. Watchful waiting
3. Angiography
4. Non-invasive imaging and evaluation
5. None of the above

ACC/AHA UA/NSTEMI Guidelines: High-risk Indicators for Early Invasive Strategy

<table>
<thead>
<tr>
<th>Preferred Strategy</th>
<th>Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive</td>
<td>Recurrent angina or ischemia at rest or low-level activities despite intensive medical therapy</td>
</tr>
<tr>
<td></td>
<td>Elevated cardiac biomarkers (TnT or TnI)</td>
</tr>
<tr>
<td></td>
<td>New or presumably new ST-segment depression</td>
</tr>
<tr>
<td></td>
<td>Signs or symptoms of HF or new or worsening mitral regurgitation</td>
</tr>
<tr>
<td></td>
<td>High-risk findings from noninvasive testing</td>
</tr>
<tr>
<td></td>
<td>Hemodynamic instability</td>
</tr>
<tr>
<td></td>
<td>Sustained ventricular tachycardia</td>
</tr>
<tr>
<td></td>
<td>PCI within 6 months</td>
</tr>
<tr>
<td></td>
<td>Prior CABG</td>
</tr>
<tr>
<td></td>
<td>High-risk score (TIMI, GRACE)</td>
</tr>
<tr>
<td></td>
<td>Reduced left ventricular function (LVFS of &lt;35%)</td>
</tr>
<tr>
<td>Conservative</td>
<td>Low-risk score (TIMI, GRACE)</td>
</tr>
<tr>
<td></td>
<td>Patient or physician preference in the absence of high-risk features</td>
</tr>
</tbody>
</table>

Coronary angiography needs to be performed within 48 hours

Therapeutic Approaches

- Pre-hospital care by EMS: oxygen, aspirin, nitroglycerin, telemetry, morphine?
- In-hospital care:
  - Revascularization in STEMI or in high-risk UA/NSTEMI
  - Antithrombin therapy and antiplatelet therapy: aspirin, clopidogrel, GPllb/IIIa inhibitors
  - Anti-ischemia: nitrates, beta-blocker
  - Anti-coagulants: UFH, LMWH, bivalirudin
  - Lipid-lowering therapy: statins
- Post-hospital care:
  - Continue antiplatelets, beta-blocker, and statins
  - Smoking cession
  - Cardiac rehabilitation

Cardiac catheterization reveals a thrombotic lesion in Mr. Johnson’s proximal left anterior descending (LAD) artery

Question 5: What Is the Most Appropriate Revascularization Strategy for Mr. Johnson?

1. Fibrinolysis
2. PCI
3. CABG
4. Fibrinolysis followed by PCI
5. He does not need revascularization

Drug-eluting stent (DES) was placed and antiplatelet therapy with clopidogrel was started

Case Study: Mr. Johnson

Mr. Johnson was discharged on day 2 post-PCI with a prescription for clopidogrel and aspirin added to his usual medication

Question 5: How Long Will Mr. Johnson Have to Take the Dual Antiplatelet Therapy?

1. Mr. Johnson does not need dual antiplatelet therapy
2. 2 weeks for both drugs
3. 4 weeks for clopidogrel and 1 year for aspirin
4. 6 months for both drugs
5. Up to 1 year for clopidogrel and aspirin for lifetime
**Antiplatelet Therapy: ACC/AHA Guidelines**

**UA/NSTEMI Patients at Discharge**

**Bare-Metal Stent (BMS) Group**
- ASA 162-325 mg/day for at least 1 month, then 75-162 mg/day indefinitely; and
- Clopidogrel 75 mg/day for at least 1 month (ideally up to 1 year)

**DES Group**
- ASA 162-325 mg/day for at least 3-6 months, then 162 mg/day indefinitely; and
- Clopidogrel 75 mg/day for at least 1 year


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**Discharge Strategies for Patients in Post-ACS**

- **Patient education**
- **Long-term dual antiplatelet therapy**
- **Lifestyle modification** (smoking cessation, nutrition, and exercise)
- **Continuity of care: Cardiac rehabilitation** (PCP + cardiologist + other team members)

PCP = primary care physician

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**Cardiac Rehabilitation in Post-ACS: A Multidisciplinary Approach**

- Primary care physician will ensure:
  - Management of common risk factors for CHD (eg, hypertension and diabetes)
  - Patient education on:
    - Clinical signs of heart attack
    - The importance of early care when symptoms arise
    - Possibility of future ACS event after discharge
    - Possibility of antiplatelet resistance
  - Management of long-term antiplatelet therapy
  - Follow-up on the referral to the cardiac rehabilitation center
  - Effective communication within the multidisciplinary team that includes the cardiologist and other specialty clinicians

CHD = coronary heart disease


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**Case Study: Mr. Johnson**

- 6 months later
  - Returns to ER with chest discomfort
  - Patient claims that he followed the treatment correctly
  - ECG shows STEMI
  - Urgent coronary angiography reveals stent thrombosis
  - Repeat PCI is performed

Courtesy of Dean Jenkins and Stephen Gerred.

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**Short-term* Outcomes by Treatment Strategy in AMI: Meta-analysis of 23 Randomized Trials**

<table>
<thead>
<tr>
<th>Treatment Strategy</th>
<th>Total Patients</th>
<th>Death (excludes SHOCK trial)</th>
<th>Non-fatal Cardiac Events</th>
<th>Stroke</th>
<th>Hemorrhagic Stroke</th>
<th>Death, Non-fatal Cardiac Events, Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioplasty</td>
<td></td>
<td>6.9%</td>
<td>14.7%</td>
<td>2.8%</td>
<td>0.4%</td>
<td>20.9%</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td></td>
<td>7.0%</td>
<td>14.7%</td>
<td>2.8%</td>
<td>0.7%</td>
<td>20.2%</td>
</tr>
</tbody>
</table>

* 4-6 weeks; N=7739
AMI = acute myocardial infarction; SHOCK = should we emergently revascularize occluded coronary arteries

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**PCI-related Time Delay and Survival Benefit vs Fibrinolysis From Randomized Trials**

<table>
<thead>
<tr>
<th>PCI-related Time Delay (DTB-DTN) (minutes)</th>
<th>Death (difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.24% survival benefit decrease/10-minute delay</td>
</tr>
</tbody>
</table>

*21 trials/7350 patients

DTB = door-to-balloon; DTN = door-to-needle


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*21 trials/7350 patients
Question 6: What Could Cause Mr. Johnson’s New ACS Event?

1. Old age
2. Diabetes
3. Antiplatelet discontinuation
4. Antiplatelet resistance
5. Stent thrombosis
6. All of the above

Early Thienopyridine Discontinuation* After DES for STEMI: PREMIER Registry

- Discontinuation Factors
  - Patient factors:
    - Older age
    - Less education (not high-school graduate)
    - Unmarried
    - Cost of healthcare
    - Pre-existing CVD
    - Anemia
  - Institutional factors:
    - Less likely to receive discharge instructions
    - Less likely to receive referral to cardiac rehabilitation

*Within 30 days
PREMIER: The Prospective Registry Evaluating Myocardial Infarction: Event and Recovery

AHA/ACC/SCAI/ACS/ADA Science Advisory

Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients with Coronary Artery Stents

- Discuss dual antiplatelet therapy with the patient prior to stent implantation
- Consider BMS or balloon angioplasty if discontinuation will be needed (e.g., surgery)
- Educate patients on the need to comply with the therapy
- Get clearance from the cardiologist prior to any surgical procedure


Antiplatelet Therapy: Rationale for Use

- Platelets are involved in plaque inflammation as well as thrombosis and atherosclerosis
- Patients with NSTE ACS show abnormalities in platelet size and function1,2
- ISIS-2 study demonstrated aspirin to safely reduce vascular mortality by about 25% and recurrent non-fatal infarction by about 50%
- There remains substantial risk of death from cardiovascular events, reinfarction, and ischemia in patients with ACS who are routinely treated with aspirin in both short- and long-term follow-up
- There is a need for more potent antiplatelet therapies


ISIS-2 = Second International Study of Infarct Survival; NSTE ACS = non–ST-elevation acute coronary syndrome(s)

Mechanism of Action of Aspirin

Mechanism of Action of Clopidogrel

AC = adenyl cyclase; PKA = protein kinase A; PLC = phospholipase C; VASP = vasodilator-stimulated phosphoprotein.

Factors That Increase Risk of ST in PCI

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Angiographic</th>
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</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>Impaired renal function</td>
</tr>
<tr>
<td>ACS</td>
<td>Concomitants</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Concomitant medications, drug-drug interactions</td>
</tr>
<tr>
<td>Low ejection fraction (EF)</td>
<td>Medication compliance</td>
</tr>
<tr>
<td>Prior brachytherapy</td>
<td>Access to medications</td>
</tr>
<tr>
<td>Bleeding risk</td>
<td>Small reference vessel</td>
</tr>
<tr>
<td>Ischemic risk</td>
<td>Inability to manage multiple medications</td>
</tr>
</tbody>
</table>

Percent of ST Risk Not Attributable to Clopidogrel Discontinuation

PAR = population attributable risk


The First Clopidogrel Resistance Study: A “Fingerprint” of Clopidogrel Response Variability

Resistance = 31%

Initial Resistance (%)

Intestinal absorption

Hepatic metabolism

Cytochrome P450 pathway

P2Y12 receptor

(Reversible inhibition)

GP IIb/IIIa receptor

Expression

Poor compliance

Inadequate administration

Drug-drug interactions

Drug-metabolizing enzymes

Release of circulating ADP

Higher baseline platelet reactivity

Genetic polymorphisms
High Residual Platelet Reactivity* Correlates With Ischemic Events

![Graph showing correlation between high residual platelet reactivity and ischemic events](image)

*20 μmol ADP post-stent/post-clopidogrel residual platelet reactivity

LTA = light transmission aggregometry; ADP = adenosine diphosphate


**Clopidogrel, Platelet Reactivity, and SAT**

![Graph showing 5 μM ADP-induced platelet aggregation](image)

**Potential Solution: Give More Clopidogrel**

**Proposed Solution: Give Clopidogrel Loading Dose Prior to PCI**

**Question 7: After the Repeat PCI Is Performed on Mr. Johnson, What Do We Do Next?**

1. Consider increasing the dosage for antiplatelet therapy
2. Stop antiplatelet therapy since it is non-efficacious
3. Consider switching antiplatelet therapies
4. Consider adding a third antiplatelet agent
5. Prescribe coumadin
6. A combination of 1, 3, and 4

**The Albion Trial**

![Graph showing clopidogrel dose and maximal aggregation](image)

FDA-approved dosage for clopidogrel: 75 mg daily; 300 mg loading dose


**Proposed Solution: Give Clopidogrel Loading Dose Prior to PCI**

![Graph showing time course of effect](image)

FDA-approved dosage for clopidogrel: 75 mg daily; 300 mg loading dose


*Death and MI; TVR to 30 days; P = .041

ARMYDA-2 Trial

![Graph showing composite endpoint](image)

FDA-approved dosage for clopidogrel: 75 mg daily; 300 mg loading dose

Explore New Compounds

- New compounds have been shown to be more active and effective:
  - Prasugrel
  - Cangrelor
  - AZD6140


Use an Agent That Is Effective for Clopidogrel Non-responders

Prasugrel: More Effective Platelet Inhibition

- More potent
- More rapid in onset
- More consistent inhibition of platelet aggregation (IPA)
- Less frequent poor IPA response
- More efficient generation of its active metabolite

**IPA in healthy subjects**

<table>
<thead>
<tr>
<th>Time Post-dose (Day/Hour)</th>
<th>IPA (migraine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
</tr>
</tbody>
</table>

**IPA in healthy subjects**

Pras = prasugrel (loading dose/maintenance dose [mg]); Clop = clopidogrel


TRITON TIMI-38 Study Design

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

- ASA
- CLOPIDOGREL
- 300 mg LD/75 mg MD
- PRASUGREL
- 60 mg LD/10 mg MD

**First-degree end point:** CV death, MI, stroke

**Second-degree end points:** CV death, MI, stroke, rehospitalization, recurrent ischemia, UTVR

**Median duration of therapy:** 12 months

**N=13,600**

TRITON TIMI-38: Balance of Efficacy and Safety

- CV Death/MI/Stroke
- TIMI Major Non-CABG Bleeds

**Results:**

- CV Death/MI/Stroke: Pras 12.1, Clop 9.9
- TIMI Major Bleeds: Pras 2.4, Clop 1.8

**NNT:**

- Pras: 46

**NNH:**

- Pras: 167

**End Point (%):**

- 12.1
- 9.9
- 1.8

**TIMI Major Non-CABG Bleeds:**

- Pras: 2.4
- Clop: 1.8

**Prasgrel is not yet approved by the FDA for use.**

TRITON TIMI-38: Bleeding Events*

**Percentage of Events:**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Clopidogrel</th>
<th>Prasgrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI Major Bleeds</td>
<td>1.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>0.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>ICH in Patients with Prior Stroke/TIA (N = 518)</td>
<td>0.4% (P = .02)</td>
<td>0.3% (P &lt; .05)</td>
</tr>
</tbody>
</table>

**ARD**: Absolute risk difference

**NNH**: Number needed to harm

**TIA**: Transient ischemic attack


**Prasgrel is not yet approved by the FDA for use.**

*Pras = prasugrel; Clop = clopidogrel; TIMI = Thrombolysis In Myocardial Infarction; UTVR = urgent target vessel revascularization*
TRITON TIMI-38: Stent Thrombosis (ARC Definite + Probable)

Days | Prasugrel | Clopidogrel |
--- | --- | --- |
0 | 2.4 (142) | 1.1 (68) |
1 | 0.57 | 0.84 |
2 | 0.48 | 0.72 |
3 | 0.35 | 0.56 |
4-7 | 0.26 | 0.48 |
8-14 | 0.24 | 0.47 |
15-30 | 0.22 | 0.45 |
31-60 | 0.21 | 0.44 |
61-90 | 0.19 | 0.43 |
91-180 | 0.17 | 0.41 |
181-270 | 0.15 | 0.39 |
271-360 | 0.14 | 0.37 |
361-450 | 0.13 | 0.35 |

NNT = 77

Prasugrel is not yet approved by the FDA for use.

End Point (%)

Any Stent at Index PCI

N = 12,844

ARC = Academic Research Consortium; PCI = percutaneous coronary intervention


Prasugrel is not yet approved by the FDA for use.

Potential Solution: Use a Non-thienopyridine Class of Drug

AZD6140

- Class: CPTP (non-thienopyridine)
- Reversible platelet (P2Y12) receptor antagonist
- Orally active
- Rapid onset of action (2 hours)
- No loading dose
- Acts directly (no metabolic activation required)
- Plasma t1/2 ~12 hours (BID drug)
- Inhibitory even in non-metabolized form
- Lessening of inhibition over the 24 hour post-dose period
- Good tolerability

IPA Maximal Extent

Time (hours) | AZD6140 90 mg | AZD6140 180 mg | AZD6140 270 mg | Clopidogrel 385 mg |
--- | --- | --- | --- | --- |
0 | 50 | 50 | 50 | 50 |
2 | 80 | 80 | 80 | 25 |
4 | 90 | 90 | 90 | 25 |
6 | 90 | 90 | 90 | 25 |
8 | 90 | 90 | 90 | 25 |
10 | 90 | 90 | 90 | 25 |
12 | 90 | 90 | 90 | 25 |

IPA Mean ± SEM (%)

0 point 1 point 2 point 3 point 4 point 5 point 6 point

Mortality Decreases With Higher Pharmacotherapy Index

Pharmacotherapy Index in NSTE ACS: The More the Better?

Evidence-based Therapies Provide Incremental Survival Benefit

Conclusions

- Patients with ACS have abnormalities in platelet size and function that predispose them to ischemic cardiovascular events
- The current ACC/AHA clinical practice guidelines recommend:
  - For patients who present with STEMI: immediate angiography and PCI
  - For NSTEMI patients who present with high-risk indicators: early (≤48 hours) angiography and revascularization
- Wide interindividual variability exists in platelet inhibitory response to currently available oral antiplatelet therapies
Conclusions

- Patients should be risk-stratified for both stent thrombosis as well as risk of bleeding before DES deployment
- Dual (aspirin plus thienopyridine) antiplatelet therapy should be continued for at least 1 year following DES deployment
- New platelet inhibition therapies currently in development appear to provide more rapid, intense, and uniform platelet inhibition and promise to overcome many of the limitations associated with current therapies

Clopidogrel Nonresponsiveness: Correlation With CYP3A4 Enzyme Activity

- Platelet aggregation 4 hours post-clopidogrel
- CYP3A4 activity

- Nonresponders (25%) vs. Responders (75%)

DES Thrombosis and Residual Platelet Reactivity

- Patients Free From Definite or Probable ST (%)

Does More Clopidogrel Alter Resistance?

- Platelet aggregation (5 µM ADP-induced aggregation) at 24 hours

P2Y12 Receptor Stimulation

- Omeprazole Placebo Group

Omeprazole and Clopidogrel Efficacy*

- VASP PRI (%) on Day 1
- VASP PRI (%) on Day 7
Smokers Paradox* With Clopidogrel:
CLARITY-TIMI 28

Non-smokers (n=1783)
0-9 cigs/day (n=206)
10-19 cigs/day (n=354)
20-29 cigs/day (n=715)
30+ cigs/day (n=422)

Primary endpoint (TIMI flow grade 0/1 or D/MI)

<table>
<thead>
<tr>
<th>Group</th>
<th>Clop Better</th>
<th>Clop Worse</th>
<th>P_int</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9 cigs/day</td>
<td>0.2</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>10-19 cigs/day</td>
<td>P=0.039</td>
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<tr>
<td>20-29 cigs/day</td>
<td>P=0.006</td>
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</tr>
<tr>
<td>30+ cigs/day</td>
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</tbody>
</table>

Cardiovascular death, MI, or urgent revascularization by 30 days

Non-responders to Clopidogrel or Ticlopidine

Patients (%)

Definition 1: absolute difference between baseline & post-treatment Aggmax < 10%

Definition 2: % IPA < 20%, IPA = inhibition of platelet aggregation

Mortality Following PCI for ACS by Clopidogrel Use: Veterans Administration 2003-2004*

Cumulative Mortality Rate

Off clopidogrel
On clopidogrel

Prasugrel vs High-dose Clopidogrel:
PRINCIPLE-TIMI 44

Prasugrel
Clopidogrel

Percentage of IPA (20 μM ADP)

P<.0001
P<.0001