POINT – COUNTERPOINT

Thienopyridine Resistance: A Clinical Reality?
Session 3: Point-Counterpoint: Thienopyridine Resistance: A Clinical Reality?

Learning Objectives

- Define concepts of resistance and variability of response to antiplatelet agents.
- Outline the concept of thienopyridine resistance, the controversy regarding its existence, and its potential implications for the management of acute coronary syndrome.
- Compare and contrast emerging options for antiplatelet therapy.

Faculty

Eric R. Bates, MD, FACC
Professor of Internal Medicine
University of Michigan Medical Center
Ann Arbor, Michigan

Neal S. Kleiman, MD, FACC
Director, Cardiac Catheterization Laboratories
Methodist DeBakey Heart Center
Houston, Texas

Dr Eric R. Bates is professor of internal medicine at the University of Michigan. Dr Bates graduated from Princeton University and the University of Michigan Medical School, and trained in internal medicine and cardiology at the University of Michigan Hospitals.

Dr Bates' major clinical interests include acute myocardial infarction (AMI), acute coronary syndromes, and coronary artery disease. His research efforts have focused on fibrinolytic and catheter-based reperfusion therapy for AMI and cardiogenic shock, antiplatelet and anticoagulant therapy for coronary thrombosis, and coronary artery revascularization. Dr Bates has served on the steering committees of several important international multicenter randomized clinical trials. An associate editor of *ACP Journal Club*, he is a member of the editorial boards of the *American Journal of Cardiology*, the *European Journal of Cardiology*, the *Journal of the American College of Cardiology*, *JACC-Cardiovascular Interventions*, the *American Heart Journal*, *Circulation*, *Circulation-Cardiovascular Interventions, Catheterization and Cardiovascular Interventions*, and *Cardiology News*.

Dr Bates is a member of the American College of Cardiology (ACC) Board of Trustees, former member of the ACC Board of Governors, current chair the Ethics and Discipline Committee, and member of its Live Programs and Compensation Committees. He serves on the ACC task force on Clinical Expert Consensus Documents and chaired the writing committee of the Clinical Expert Consensus Document on Carotid Stenting. He is also a member of the ACC/American Heart Association (AHA) writing committee to revise the 1999 guidelines for AMI. Dr Bates is vice chair of the program committee of the AHA Council on Clinical Cardiology as well as a member of the American Board of Internal Medicine Interventional Cardiology Test Committee.

Neal S. Kleiman, MD, FACC
Director, Cardiac Catheterization Laboratories
Methodist DeBakey Heart Center
Houston, Texas

Dr Neal S. Kleiman is director of the Cardiac Catheterization Laboratories of the Methodist DeBakey Heart Center in Houston as well as professor of medicine at Weill Medical College of Cornell University. He received his baccalaureate from Princeton University and his medical degree from the Columbia University College of Physicians and Surgeons. Dr Kleiman then served his internship and residency in internal medicine, along with a fellowship in cardiology, at Baylor College of Medicine, where he subsequently joined the faculty.

A fellow of both the American College of Cardiology and the Society for Coronary Angiography and Interventions, Dr Kleiman’s research is focused on acute coronary syndromes and coronary interventions. Currently, he is the study chairman for the large, multicenter EVENT trial, designed to identify the frequency of myocardial infarction following the insertion of drug-eluting stents, and has served as principal investigator or on the steering committees of numerous multicenter trials, including SHINE, TRITON-TIMI 38, REPLACE-2, and JUMBO-TIMI 26, as well as trials involving paclitaxel-,
sirolimus-, and everolimus-eluting stents. Dr Kleiman also established the Applied Platelet Physiology Laboratory at Methodist DeBakey to support various clinical trials as well as to provide a venue for pursuing independent physiologic studies examining such issues as aspirin dosing and platelet activation during coronary interventions.

Dr Kleiman currently serves on the editorial boards of Circulation, the Journal of Interventional Cardiology, the Journal of Thrombosis and Thrombolysis, the Journal of the American College of Cardiology, the American Heart Journal, HeartDrug, and the European Heart Journal. He is the author of more than 260 peer-reviewed articles, editorials, and reviews, as well as 17 book chapters.

Faculty Financial Disclosure Statements
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Dr Kleiman has nothing to disclose.

Education Partner Financial Disclosure Statement
The content collaborators at the Annenberg Center for Health Sciences at Eisenhower have nothing to disclose.

Drug List

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<th>Generic</th>
<th>Trade</th>
<th>Investigational</th>
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<tr>
<td>abciximab</td>
<td>ReoPro</td>
<td>AZD6140</td>
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<tr>
<td>bivalirudin</td>
<td>Angiomax</td>
<td>cangrelor (ARC-669931MX)</td>
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<td>clopidogrel</td>
<td>Plavix</td>
<td>prasugrel Effient</td>
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<td>heparin</td>
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<td>SCH 530348</td>
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<tr>
<td>ticlopidine</td>
<td>Ticlid</td>
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<tr>
<td>warfarin</td>
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Suggested Reading List


Session 3
Learning Objectives

- Define concepts of resistance and variability of response to antiplatelet agents
- Outline the concept of thienopyridine resistance, the controversy regarding its existence and its potential implications for the management of acute coronary syndrome
- Compare and contrast emerging options for antiplatelet therapy

Case: 52-year-old Male

- Four months ago had a bare-metal stent implanted for an acute coronary syndrome
- Put on dual antiplatelet therapy – Aspirin and clopidogrel
- Back in ED with chest pain, shortness of breath
- Says faithful in taking antiplatelet regimen
- ST depression on ECG
- cTnI 1.5 μg/l (elevated)

UA/NSTEMI Guidelines

- Antiplatelet therapy should be initiated promptly.
- ASA should be administered as soon as possible after presentation and continued indefinitely.
- For hospitalized patients who cannot take ASA, clopidogrel is appropriate.
- Clopidogrel should be started and continued for at least 1 month and for up to 12 months.

Clopidogrel Across Spectrum of CAD

<table>
<thead>
<tr>
<th>Acute STEMI</th>
<th>UA/NSTEMI</th>
<th>PCI</th>
<th>Long-term (1) prevention</th>
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<td><strong>CLARITY</strong></td>
<td><strong>CURE</strong></td>
<td><strong>CREDO</strong></td>
<td><strong>CAPRIE</strong></td>
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STEMI: UA/NSTEMI + Benefit + Benefit + Benefit + Benefit

PCI: 30 Days + Benefit 1 Year + Benefit 1-3 Years + Benefit

High-Risk Vascular Disease

Up to 3 years benefit in symptomatic patients only

*Clopidogrel vs. placebo. †Clopidogrel + ASA. ‡Clopidogrel vs. ASA.
Does the patient’s presentation indicate a problem with his antiplatelet therapy?

1. Yes
2. No

If the patient’s presentation indicates a problem with his antiplatelet therapy, to which of the following is this possibly related?

1. Metabolism of agents
2. Malabsorption
3. Platelet polymorphisms
4. Noncompliance
5. Any of the above

Potential Sites for Response Variability

- Intestinal absorption
  - Poor compliance
  - Variable absorption
- Hepatic metabolism
  - Genetic polymorphisms CYP enzymes
- Active metabolite
  - Drug-drug interactions
- P2Y12 receptor expression
  - Genetic polymorphisms

Platelet Reactivity Responsiveness to Agonist

- Receptor Reactivity
  - P2Y12
  - ADP
- Aggregation
  - LTA
  - TEG
- Flow Cytometry
  - VASP-P
  - Monoclonal Antibody

Clopidogrel “Resistance” Can Be Correlated With Low CYP3A4 Activity/Conversion to Active Drug

- Platelet aggregation (%)
- CYP3A4 Activity-%CO2 exhaled/hour (%)

- r=-0.6
  - P<0.003

Clopidogrel and High Platelet Reactivity

- High post-treatment platelet reactivity (HPPR) > 70%
- 15% 600 mg
- 25% 300 mg
- P=0.03
- CV Event-free Survival
- HPPR: RR 13.8
  - P<0.0001

ED doctors determine that patient has been compliant with antiplatelet regimen and that the patient may have a poor response to clopidogrel. How might this conclusion be confirmed?

1. Light transmission aggregometry
2. Continued thrombotic events
3. Point-of-care testing
4. None of the above
Does the platelet function test (0% inhibition on point of care rapid platelet function assay) change your assessment of the cause of this patient's ACS?

1. Yes
2. No

Platelet Function Testing

- No accepted definition of clopidogrel resistance
- No agreement on laboratory test to identify clopidogrel resistance
- No study showing change in therapeutic outcome based on lab test
- Results of platelet function testing depend on when the test is performed in relation to event

Platelet Function Testing

- No single test encompasses platelet biology and function, making it difficult to correlate platelet function to clinical events
- Most trials studying platelet function testing did not assess interactions and other measurements that would greatly impact risk of ischemic events


Clopidogrel Responsiveness and Recurrent CV Events in Patients With STEMI

- Non-responders defined as > 70% aggregation by LTA 12 h after 600-mg clopidogrel load


Reclose Study

6-Month Outcomes Post DES Stratified by Clopidogrel Responsiveness

- Non-responders defined as > 70% aggregation by LTA 12 h after 600-mg clopidogrel load


If the lab test comes back indicating an inadequate platelet responsiveness, what could be the potential clinical consequences?

1. CV event within 6 months
2. Nothing, since there is no clinical correlation to current lab tests
3. Sub-acute stent thrombosis
4. Myonecrosis and inflammatory marker release
5. No event
6. 1, 3 and 4
Stent Thrombosis: A Multifactorial Problem

Lesion
- Long lesions
- Small diameter
- Multivessel
- Acute myocardial infarction (AMI)
- Bifurcations

Patient
- Antiplatelet noncompliance
- Response variability
- Diabetes

Technical
- Underexpansion
- Incomplete wall apposition
- Crush technique
- Overlapping

Stent
- Material
- Polymer matrix
- Anti-proliferative agent

On angiography, patient found to have in-stent restenosis and a sirolimus-eluting stent is implanted. He is discharged on an antiplatelet regimen of aspirin (325 mg/d) and clopidogrel (75 mg/d). He also receives further education about compliance.

Patient should stay on this dual antiplatelet regimen for:
1. 1 month
2. 6 months
3. 12 months
4. Indefinitely

Early Discontinuation of Antiplatelet Therapy

Overall Stent Thrombosis = 1.3% 
(P=0.09; N=2,229)

Duration of Therapy

- Thienopyridine therapy in combination with aspirin has become the mainstay antiplatelet treatment strategy for the prevention of stent thrombosis. Premature discontinuation of antiplatelet therapy markedly increases the risk of stent thrombosis, a catastrophic event that frequently leads to MI and/or death.

- Factors contributing to premature cessation of thienopyridine therapy include drug cost, physician/dentist instructions to patients to discontinue therapy before procedures, and inadequate patient education and understanding about the importance of continuing therapy.

Factors Contributing to Early Discontinuation of Therapy

PREMIER Registry: Acute MI Treated With DES

P < 0.01
P < 0.001
P < 0.001
P < 0.05
P = 0.92

Long-Term Antithrombotic Therapy at Hospital Discharge After UA/NSTEMI

- ASA 162 to 325 mg/d for at least 3 to 6 months, then 75 to 162 mg/d indefinitely (Class I, LOE: A)
- Clopidogrel 75 mg/d for at least 1 year (Class I, LOE: B)

- ASA 144 to 256 mg/d for at least 2 to 4 months, then 75 to 162 mg/d indefinitely (Class I, LOE: A)
- Clopidogrel 75 mg/d for at least 1 year (Class I, LOE: B)

- ASA: perform War 2 to 10 (Class IIb, LOE: A)
- Continue with dual antiplatelet therapy on discharge

At F/U, patient’s cardiologist concerned about platelet inhibition and considers changing the maintenance regimen to now include:

1. Clopidogrel 150 mg/d
2. Clopidogrel 300 mg/d
3. Ticlopidine 250 bid
4. None of the above

Dosing Level

- How high should loading and maintenance doses go?

ISAR-CHOICE

Platelet Aggregation

ISAR-CHOICE 2: Doubling the Daily Dose of Clopidogrel After PCI Improves Inhibition at 30 Days

Presentation by Lopes R at 57th Annual Scientific Session of the American College of Cardiology, March 29-April 1, 2008.
Prasugrel

- 3rd generation thienopyridine
- Requires hepatic conversion to active metabolite
- Oral administration
- Irreversible binding
- 60 mg LD; 10 mg MD
- Mean platelet inhibition ≈ 70%
  - Occurs within <1 hour
- Phase III trials: TRITON, TRILOGY ACS

Inhibition of Platelet Aggregation (IPA) at 24 Hours (Healthy Volunteers)

PRINCIPLE TIMI 44: Comparison with Higher-Dose Clopidogrel

TRITON TIMI 38: Primary Endpoint

TRITON TIMI 38: Patients With and Without Diabetes
**TRITON TIMI 38 Stent Analysis**

**Definite/Probable ST: Any Stent**

<table>
<thead>
<tr>
<th>EARLY ST</th>
<th>LATE ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR: 0.41 [0.29-0.59]</td>
<td>HR: 0.60 [0.37-0.97]</td>
</tr>
<tr>
<td>P = 0.0001</td>
<td>P = 0.03</td>
</tr>
</tbody>
</table>

- Clopidogrel
- Prasugrel

**Days**

1.56%  
3.04%  
5.16%  
8.22%  
15.56%  
28.22%

**TRIOLOGY-ACS Trial Design**

- **Decision to manage medically known in 1st 24 hours of admission:**
  - Start Clopidogrel (<24 h) and perform cath (<7 d) – per AHA/ESC Guidelines
  - Randomize after Cath – if no CABG or PCI

- **N = 19,500**

**Cangrelor**

- ATP analogue
  - Direct inhibition
- Parenteral administration
- Competitive binding
- 4 µg/kg/min
- Mean platelet inhibition ≈ 95%
  - Occurs within a few minutes
- Phase III trial: CHAMPION

**Relative Platelet Inhibition Between Cangrelor and Clopidogrel**

- **Mean platelet inhibition**
  - Cangrelor 500 nM in vitro: Mean platelet inhibition ≈ 95%
  - Occurs within a few minutes

**CHAMPION PCI (Phase III)**

- **N=9,000**
- **Double-blind**
- **CANGRELOR**
  - 30 µg/kg IV bolus + 4 µg/kg/min IV infusion
- **CLOPIDOGREL**
  - 600 mg

**Primary Objective:** Superiority or noninferiority of cangrelor versus clopidogrel for PCI

- **1st endpoint:** All-cause mortality, MI, and IDR in the 48 hours after randomization
- **2nd endpoints:** All-cause mortality and MI at 48 hours

**AZD6140**

- **Cyclopyrenyl-triazolo-pyrimidine**
  - Direct inhibition
- Oral administration
- Competitive binding
- 90 mg bid
- Mean platelet inhibition ≈ 95%
  - Occurs within 2-4 hours
- Phase III trial: PLATO

**Modified From O'Donnell M, Wiviott SD. Circulation. 2006;114:e600-e606; Angiolillo DJ et al. Am J Cardio Drugs. 2007.**

**Modified From O'Donnell M, Wiviott SD. Circulation. 2006;114:e600-e606:**

**ClinicalTrials.gov Identifier:** NCT00699998

**ClinicalTrials.gov Identifier:** NCT00305162


**IDR = ischemia-driven revascularization. Cangrelor is an investigational agent in ongoing studies; not available for prescribing.**

**AZD 6140 is an investigational agent in ongoing studies; not available for prescribing.**
Maximal and Final IPA on Day 1

Clopidogrel-Naïve Patients

AZD6140 90 mg
AZD6140 180 mg
AZD6140 270 mg
CLOP 300 mg

IPA (%)
Mean ± SEM

0 25 50 75 100
0 25 50 75 100

Time (hours)

Maximal Extent
Final Extent

P<0.0176 for all AZD6140 groups vs. clopidogrel at 4 h
P<0.0002 for all AZD6140 groups vs. clopidogrel at 4 h

Storey R et al.
J Am Coll Cardiol

AZD6140 is an investigational agent in ongoing studies; not available for prescribing.

IPA = inhibition of platelet aggregation.

Primary endpoint: CVD/MI/stroke
Secondary endpoint: CVD/MI/stroke, severe recurrent ischemia

TRA-PCI Study Design

** Secondary Evaluable Cohort

Randomization #1 – 3:1 SCH 530348:Placebo (Single Loading Dose)
Sequential Groups: 1=10 mg; 2=20 mg; 3=40 mg, or Placebo
Non-Urgent PCI or Cath possible PCI (All Receive Aspirin)

TRA-CER Program

Evaluation of Efficacy and Safety in Acute and Chronic Atherothrombosis

SCH 530348
Placebo

1o EP: Composite of CV Death, MI, Stroke, Urgent Revascularization and Recurrent Ischemia w/ Rehosp

F/U: 30 days, 4, 8, 12 months, and 6 months thereafter
F/U 1-yr minimum

1o EP: Composite of CV Death, MI, Stroke, Urgent Revascularization

TRA-PCI Cohort Results

<table>
<thead>
<tr>
<th>SCH 530348</th>
<th>Placebo</th>
<th>All</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
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<tbody>
<tr>
<td>Number</td>
<td>151</td>
<td>422</td>
<td>129</td>
<td>120</td>
<td>173</td>
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<tr>
<td>TIMI Major/Minor</td>
<td>5 (3.2%)</td>
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<td>Non-TIMI bleeding</td>
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TRA (SCH 530348) Program

Evaluation of Efficacy and Safety in Acute and Chronic Atherothrombosis

NSTEMI

TRA (SCH 530348) Program

2° Prevention

TRA-CER ClinicalTrials.gov Identifier: NCT01229742; TRA 2°P ClinicalTrials.gov Identifier: NCT00824974.

SCH 530348 is an investigational agent in ongoing studies; not available for prescribing.

TRIPLA-TRCER

N=18,000

ASA + Clopidogrel
300 mg ld/75 mg qd
600 mg ld allowed in PCI

ASA + SCH 530348
180 mg ld/90 mg bid
Moderate- to high-risk ACS patients
(UA/NSTEMI/STEMI, PCI, medically managed, or CABG)

SCH 530348 is an investigational agent in ongoing studies; not available for prescribing.

TRA (SCH 530348) Cohort Results

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Summary

• Treatment failure can be multifactorial
• Variability of response appears to be clinically relevant, and may inform therapeutic decision making
• Clopidogrel dosing affects measures of platelet function
• Risks of greater platelet inhibition include major bleeding

Summary

• Total duration of clopidogrel therapy following PCI is still unclear but most sources indicate should be at least a minimum of 1 yr following DES, possibly less following BMS
• New agents can provide greater platelet inhibition and less variability than clopidogrel
• Pivotal study of prasugrel completed; trials evaluating higher-dose clopidogrel and other new agents (AZD6148, cangrelor, SCH 530348) are ongoing

Prasugrel, AZD6148, cangrelor and SCH 530348 are investigational agents in ongoing studies; not available for prescribing.