POINT – COUNTERPOINT

Thienopyridine Resistance: A Clinical Reality?
Session 6: Point-Counterpoint: Thienopyridine Resistance—A Clinical Reality?

Learning Objectives

- Define concepts of resistance and variability of response to antiplatelet agents and the potential consequences and implications in the management of patients with acute and chronic ischemic heart disease.
- 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

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

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

A member of the American College of Cardiology Board of Trustees and a former member of the Board of Governors, Dr. Bates chairs the ACC Ethics and Discipline Committee, and is a member of the Live Programs and Compensation Committees. He serves on the ACC task force on Clinical Expert Consensus Documents and chaired the writing committee for the Clinical Expert Consensus Document on Carotid Stenting. He is also a member of the ACC/AHA writing committee to revise the 1999 guidelines for acute myocardial infarction. Dr. Bates is the vice chair for the program committee of the AHA Council on Clinical Cardiology. He also is 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

Professor of Medicine
Weill Medical College of Cornell University
New York, New York

Neal S. Kleiman, MD, FACC, currently serves as the director of the Cardiac Catheterization Laboratories of the Methodist DeBakey Heart Center in Houston, Texas, and also is professor of medicine at Weill Medical College of Cornell University. He received his baccalaureate from Princeton University and his medical degree from Columbia University College of Physicians and Surgeons. Dr. Kleiman then served his internship and residency in internal medicine at Baylor College of Medicine, followed by a fellowship in cardiology, also at Baylor, where he subsequently came on staff as faculty.

A fellow of both the American College of Cardiology and the Society for Coronary Angiography and Interventions, Dr. Kleiman focuses his research on acute coronary syndromes and coronary interventions. Currently, he is the study chairman for the large, multicenter EVENT trial, which is 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 the Methodist DeBakey Heart Center to both support various clinical trials, as well as provide a venue to pursue 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, Journal of Interventional Cardiology, Journal of Thrombosis and Thrombolysis, Journal of the American College of Cardiology, American Heart Journal, HeartDrug, and 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. Bates receives a research grant from Eli Lilly and Company. He receives honoraria from sanofi-aventis U.S., Eli Lilly and Company, and The Medicines Company. Dr. Kleiman has no relationships 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**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Investigational</th>
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<tbody>
<tr>
<td>clopidogrel</td>
<td>Plavix</td>
<td>prasugrel (CS-747) (LY640315) (Effient)</td>
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<tr>
<td>ticlopidine</td>
<td>Ticlid</td>
<td>AZD6140</td>
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<tr>
<td>warfarin</td>
<td>Coumadin, Jantoven</td>
<td>cangrelor (ARC-669931MX)</td>
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<tr>
<td>abciximab</td>
<td>ReoPro</td>
<td>SCH 530348</td>
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<tr>
<td>bivalirudin</td>
<td>Angiomax</td>
<td></td>
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<tr>
<td>heparin</td>
<td>various</td>
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**Suggested Reading List**


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</th>
</tr>
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<tbody>
<tr>
<td>CLARITY†</td>
<td>CURE†</td>
<td>CREDO†</td>
<td>CAPRIE§</td>
</tr>
<tr>
<td>COMMIT† (CCS-2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.2% CV death/MI/stroke</td>
<td>18.6% CV death/MI/stroke</td>
<td>18.5% CV death/MI/stroke</td>
<td>8.7% risk reduction MI/stroke</td>
</tr>
<tr>
<td>STEMI</td>
<td>UA/NSTEMI</td>
<td>PCI</td>
<td>Ml/Stroke/PAD</td>
</tr>
<tr>
<td>30 Days</td>
<td>1 Year</td>
<td>1 Year</td>
<td>1-3 Years</td>
</tr>
<tr>
<td>+ Benefit</td>
<td>+ Benefit</td>
<td>+ Benefit</td>
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</tbody>
</table>

*Clopidogrel vs. placebo. †Clopidogrel + ASA. ‡Clopidogrel vs. ASA.

High-Risk Vascular Disease

Up to 3 years benefit in symptomatic patients only
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
  - Inadequate administration
  - Variable absorption
  - Drug-drug interactions
- Hepatic metabolism
  - Genetic polymorphisms CYP enzymes
  - Drug-drug interactions
  - Active metabolite
  - Genetic polymorphisms P2Y12 receptor
  - Alternate pathways of platelet activation
  - Release of circulating ADP
  - Higher baseline platelet reactivity
  - Genetic polymorphisms GP IIb/IIIa receptor expression

Platelet Reactivity Responsiveness to Agonist

- P2Y12 receptor expression
- Receptor activity
- Flow Cytometry
- Aggregation
- LTA: Light transmission aggregometry
- TEG: Thrombelastography
- Platelet
- Activated GP IIb/IIIa
- Monoclonal Antibody
- Monoclonal Antibody
- P-selectin

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

- CYP3A4 Activity: 14CO2 exhaled/hour (%)
- Platelet Aggregation (%)
- 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
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

Clopidogrel Responsiveness and Recurrent CV Events in Patients With STEMI

ADP-Induced Platelet Aggregation

<table>
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<tr>
<th>Quartiles</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
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<tr>
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<td>40</td>
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<td>2nd Q</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>3rd Q</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
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</tbody>
</table>

Reduction in Aggregate Size

<table>
<thead>
<tr>
<th>Quartiles</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
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<td>20</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>2nd Q</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>3rd Q</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>4th Q</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
</tr>
</tbody>
</table>

6 Months Recurrent CVS Events

- 1st
- 2nd
- 3rd
- 4th

ADP-Induced Platelet Aggregation (% of Baseline)

- 1st Q
- 2nd Q
- 3rd Q
- 4th Q

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

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

Patient
- Antiplatelet noncompliance
- Response variability
- Diabetes

Stent
- Material
- Polymer matrix
- Anti-proliferative agent


RECLOSE Study

6-Month Outcomes Post DES Stratified by Clopidogrel Responsiveness

Cardiac death
Stent thrombosis
Cardiac death and IST

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?
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

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 markedy 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

- Premature discontinuation of therapy is associated with:
  - Inpatient death
  - In-hospital cardiac death
  - In-hospital CABG
  - Stroke
  - Thrombotic events

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

- ASA 75 to 162 mg/d indefinitely (Class I, LOE: A)
- Clopidogrel 75 mg/d for at least 1 month and up to 1 year (Class I, LOE: B)
- Continue with dual antiplatelet therapy as above

Post ST-Elevation MI: APEX-AMI

- Antithrombotic Therapy in Patients with AF at Discharge According to CHADS<sub>2</sub>
  - CHADS<sub>2</sub>=0
  - CHADS<sub>2</sub>=1
  - CHADS<sub>2</sub>=2

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

![Graph showing platelet aggregation at different doses of clopidogrel](image)

**ISAR-CHOICE**

**Metabolite Concentrations**

![Graph showing metabolite concentrations over time](image)

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

![Graph showing inhibition at 30 days](image)

**VASP Phosphorylation Study Design**

![Diagram showing VASP phosphorylation](image)
**VASP Phosphorylation Primary Efficacy Endpoint**

<table>
<thead>
<tr>
<th>MACE: n (%)</th>
<th>Control (n=84)</th>
<th>VASP-guided (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Acute and sub-acute stent thrombosis</td>
<td>4 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Revascularization</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Overall MACE</td>
<td>8 (10)*</td>
<td>0</td>
</tr>
</tbody>
</table>

*P = 0.007

No significant difference in bleeding


**CURRENT/OASIS 7**

Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions

Patients with UA/NSTEMI planned for early invasive strategy; ie, intend for PCI as early as possible within 24 hrs

**GRAVITAS**

Successful PCI with DES Without Major Complication or GPIIb/IIIa Use

N = 6,800

**Clopidogrel High-Dose Group**

Clopidogrel 600 mg loading dose day 1 followed by 75 mg once daily days 2 to 7, 75 mg once daily from days 8 to 30

**Clopidogrel Standard-Dose Group**

Clopidogrel 300 mg (+ placebo) day 1 followed by 75 mg (+ placebo) from days 2 to 7, 75 mg from days 8 to 30

**ASA low-dose group**

At least 300 mg day 1; 75–100 mg from days 2 to 30

**ASA high-dose group**

At least 300 mg day 1; 300–325 mg from days 2 to 30

**Random Selection**

Clinical Follow-up and Rapid Platelet Function Assay Assessment at 30 Days, 6 Months

Primary Endpoint: 6-month CV Death, Non-Fatal MI, ARC Definite/Prob ST

Clinicaltrials.gov identifier NCT00645918

PRU = P2Y12 reaction units.

**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

Prasugrel is an investigational agent in ongoing studies, not yet available for prescribing.

Prasugrel, AZD6140, and cangrelor are not currently approved by the FDA.

**Bleeding and Outcomes**

OASIS Registry, OASIS-2, CURE (n=34,146)

**30 Day to 6 Month Death According to Bleeding**


Which of the following agents in development offer the possibility of improved platelet inhibition compared to standard clopidogrel?

1. Prasugrel
2. Cangrelor
3. AZD6140
4. Thrombin receptor antagonist
5. All of the above
Inhibition of Platelet Aggregation (IPA) at 24 Hours (Healthy Volunteers)

Response to Clopidogrel
- Clopidogrel Responder
- Clopidogrel Non-responder

*Responder = ≥25% IPA at 4 and 24 h

Interpatient Variability


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

PRINCIPLE TIMI 44: Comparison with Higher-Dose Clopidogrel

IPA (20 mM ADP)

Response to Prasugrel

Hours

Prasugrel

Clopidogrel

P < 0.0001 for each IPA (20 mM ADP)

Prasugrel 60 mg

Clopidogrel 60 mg

N = 201

Prasugrel 10 mg

N = 201

NNT = 46

NNH = 167

TRITON TIMI 38: Primary Endpoint

CV Death/MI/Stroke

Prasugrel

Clopidogrel

P = 0.004

HR 0.81 (0.73-0.90)

P < 0.0001

Days

TRITON TIMI 38: Primary Endpoint in Patients With and Without Diabetes

Diabetes

No Diabetes

P = 0.02

HR 0.60 (0.37-0.97)

P < 0.0001

HR 0.41 [0.29-0.59]

P = 0.03

TRITON TIMI 38: Patients With and Without Diabetes

- Patients with pre-existing diabetes = 3,146
- In addition to the primary endpoint, prasugrel produced significant benefits over clopidogrel:
  - MI reduced 40% among DM subjects (8.2% vs. 13.2%; P = 0.001) and 18% among non-DM subjects (7.2% vs. 8.7%; P = 0.066)
  - Definite or probable stent thrombosis reduced among DM subjects (2.0% vs. 3.6%; P = 0.001) and non-DM subjects (0.9% vs. 2.0%; P < 0.001)
  - Rates of TIMI major hemorrhage were similar among patients with diabetes on prasugrel and clopidogrel (2.5% vs. 2.6%; P = 0.82) but increased among subjects without DM on prasugrel (2.4% vs. 1.6%; P = 0.02).

TRITON TIMI 38 Stent Analysis

Definite/Probable ST: Any Stent

EARLY ST

LATE ST

Prasugrel is an investigational agent in ongoing studies; not available for prescribing.
TRILOGY-ACS Trial Design

Decision to manage medically known in 1st 24 hours of admission

N = 10,500

Randomize

Clopidogrel

Prasugrel

Start Clopidogrel (<24 h) and perform cath (<7 d) – per AHA/ESC Guidelines

Randomize after Cath – if no CABG or PCI

Patients on clopidogrel on admission can be randomized in either strata

Prasugrel dose

to 5 mg MD for age >75 years or weight <60 kg

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

CHAMPION PCI (Phase III)

UA, MI, or ACS

N=9,000

Double-blind

CLOTIDOGREL

600 mg

CANGRELOR

30 µg/kg IV bolus + 4 µg/kg/min IV infusion

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

1° endpoint: All-cause mortality, MI, and IDR in the 48 hours after randomization

2° endpoints: All-cause mortality and MI at 48 hours

AZD6140

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

Maximal and Final IPA on Day 1

Clopigrel-Naïve Patients

AZD6140 90 mg

AZD6140 180 mg

AZD6140 270 mg

CLOPIDOGREL 300 mg

IPA (%) Mean ± SEM

Maximal Extent

Final Extent

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

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

IPA = inhibition of platelet aggregation.


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

AZD6140 is an investigational agent in ongoing studies; not available for prescribing.
Primary endpoint: CVD/MI/stroke
Secondary endpoint: CVD/MI/stroke/ revascularization with PCI; CVD/MI/stroke, severe recurrent ischemia

N=18,000

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

ASA + AZD6140
180 mg ld/90 mg bid

Moderate- to high-risk ACS patients
(UA/NSTEMI/STEMI, PCI, medically managed, or CABG)

Planned PCI (All Receive Clopidogrel and Antithrombin)
Cardiac Catheterization
Randomization A2: 1:1:1
Maintenance Therapy Once Daily for ~ 60 days
SCH 530348 Loading Dose — SCH 530348
Ox Placebo Loading Dose — Placebo
8 mg in 1 hr
1 mg in 1 hr
2.5 mg in 1 hr
Placed in 1 hr
Safety: TIMI Major/Minor Bleeding
Efficiency: Death/MACE

No PCI
CABG
Medical Management

SCH 530348
Placebo

TRA-PCI Study Design

TRA-CER Program
Evaluation of Efficacy and Safety in Acute and Chronic Atherothrombosis

\[ \text{TRA (SCH 530348) Program} \]

\[ \text{TRA 2P} \]

\[ \text{TRA-CER} \]

\[ \text{SCH 530348} \]

\[ \text{Placebo} \]

\[ \text{F/U: 30 days, 4, 8, 12 months, and 6 months thereafter} \]

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

F/U 1-yr minimum

\[ \text{SCH 530348} \]

\[ \text{Placebo} \]

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 (AZD6140, cangrelor, SCH 530348) are ongoing

(Prasugrel, AZD6140, cangrelor and SCH 530348 are investigational agents in ongoing studies; not available for prescribing.)