

Late Stent Thrombosis After DES: Role of Platelet Function Testing

Alan D. Michelson, M.D.
Director, Center for Platelet Function Studies
Professor of Pediatrics, Medicine, and Pathology
University of Massachusetts Medical School

www.platelets.org



Presenter Disclosure Information

Speaker: Alan D. Michelson, M.D.

Company Name	Relationship
Accumetrics	Research grant support
Arena	Research grant support
BioCytex	Research grant support
Boston Scientific	Research grant support
Dade Behring	Research grant support
Lilly/Daiichi Sankyo	Research grant support, lecture honoraria
McNeil	Research grant support, consultant
Sanofi Aventis/Bristol-Myers Squibb	Lecture honoraria

Platelet Shape Change and Aggregation



Weisel *In* PLATELETS (Michelson, 2nd ed, Elsevier/Academic Press, 2006)

Late Stent Thrombosis After DES

- principally white clots (Joner 2006), *i.e.*, platelet-mediated (despite the common usage of antiplatelet drugs)
- associated with discontinuation of antiplatelet therapy in some, but not all, patients (McFadden 2004, Iakovou 2005)

Premise:

Lack of antiplatelet therapy predisposes to late stent thrombosis

Causes of lack of antiplatelet therapy

- not prescribed by the physician
- patient non-compliance
- pharmacological “resistance” to antiplatelet therapy

Late Stent Thrombosis After DES: Role of Platelet Function Testing

1. Non-compliance

Patient non-compliance with aspirin and/or clopidogrel

2. Resistance

“Resistance” or hyporesponsiveness to aspirin and/or clopidogrel

3. Rebound

Platelet hyperfunction after discontinuation of aspirin and/or clopidogrel

Antiplatelet Drugs: Mechanisms of Action

Aspirin

Irreversible acetylation of serine 529 of COX-1, resulting in inhibition of thromboxane A_2 generation from platelets

Clopidogrel

Irreversibly inhibits platelet P2Y₁₂ ADP receptors

Possible Mechanisms of Aspirin and Clopidogrel "Resistance" or Response Variability

Bioavailability

- Non-compliance
- Underdosing
- Poor absorption (enteric-coated aspirin)
- Interference (NSAIDs/aspirin, atorvastatin/clopidogrel)

Platelet Function

- Incomplete suppression of thromboxane A_2 generation (aspirin)
- Accelerated platelet turnover, with introduction into bloodstream of newly formed, drug-unaffected platelets
- Stress-induced COX-2 in platelets (aspirin)
- Increased platelet sensitivity to ADP and collagen

Single Nucleotide Polymorphisms

- Receptors: GPIIb-IIIa, P2Y₁, P2Y₁₂, thromboxane receptor, etc
- Enzymes: COX-1, COX-2, TxA₂ synthase, etc (aspirin)

Michelson *Circulation* 2004;110:e489

Possible Mechanisms of Aspirin and Clopidogrel "Resistance" or Response Variability (continued)

Platelet Interactions With Other Blood Cells

- Endothelial cells and monocytes make thromboxane A_2 and the TXA₂ intermediate, PGH₂, both of which may be taken up by platelets (bypassing COX-1) (aspirin)

Other Factors

- Smoking, hypercholesterolemia, etc

Rather Than Resistance, Is It:

- Treatment failure (because arterial thrombosis is multifactorial)?
- Aspirin or clopidogrel response variability?
- Platelet response variability?

Michelson *Circulation* 2004;110:e489

Platelet Function Tests for the Detection of Aspirin "Resistance" or Response Variability

Thromboxane as the End Point:

- Serum thromboxane B_2
- Urinary 11-dehydro thromboxane B_2

Arachidonic Acid as the Stimulus:

- Platelet aggregometry (turbidometric)
- Platelet aggregometry (impedance)
- VerifyNow Aspirin assay
- Plateletworks
- Platelet surface activated GPIIb-IIIa, platelet surface P-selectin, leukocyte-platelet aggregates (flow cytometry)
- Thromboelastography
- Impact cone and plate(let) analyzer

Other:

- PFA-100

Michelson *Eur Heart J* 2006;8:G53

Platelet Function Tests for the Detection of Clopidogrel "Resistance" or Response Variability

P2Y₁₂ Signaling-Dependent

- VASP phosphorylation (flow cytometry)

ADP as the Stimulus:

- Platelet aggregometry (turbidometric)
- Platelet aggregometry (impedance)
- VerifyNow P2Y₁₂ assay
- Plateletworks
- Platelet surface activated GPIIb-IIIa, platelet surface P-selectin, leukocyte-platelet aggregates (flow cytometry)
- Thromboelastography
- Impact cone and plate(let) analyzer

Michelson *Eur Heart J* 2006;8:G53

Evidence that *In Vitro* Tests of Aspirin "Resistance" Predict Clinical Aspirin "Resistance" (i.e., MACE)

(number of MACE low in all studies)

Author	Assay
Mueller 1997	ADP- and collagen-induced whole blood aggregation
Eikelboom 2002	urinary 11-dehydro thromboxane B_2
Gum 2003	AA- and ADP-induced turbidometric platelet aggregation
Chen 2004	VerifyNow
Wenaweser 2005*	ADP (but not AA) induced turbidometric platelet aggregation
Ohmori 2006	collagen-induced turbidometric platelet aggregation

*Stent thrombosis study

Evidence that *In Vitro* Tests of Clopidogrel "Resistance" Predict Clinical Clopidogrel "Resistance" (i.e., MACE)

(number of MACE low in all studies)

Author	Assay
Barragan 2003*	VASP
Matetzky 2004	ADP-induced turbidometric platelet aggregation
Gurbel 2005	ADP-induced turbidometric platelet aggregation/VASP
Ajzenberg 2005*	Shear-induced platelet aggregation
Cuisset 2006	ADP-induced turbidometric platelet aggregation
Hochholzer 2006	ADP-induced turbidometric platelet aggregation

*Stent thrombosis study

SSC/ISTH Working Group on Aspirin Resistance

1. A clinically meaningful definition of aspirin resistance needs to be developed, based on data linking aspirin-dependent laboratory tests to clinical outcomes in patients.
2. The correct treatment, if any, of aspirin resistance is unknown, because no published studies address the clinical effectiveness of altering therapy based on a laboratory finding of aspirin resistance.
3. Therefore, testing for aspirin resistance in patients and changing therapy based on such tests is not currently recommended – other than in research trials, which are to be encouraged.

Michelson et al. *J Thromb Haemost* 2005;3:1309

- Same conclusions for clopidogrel.
- Similar conclusions reached by ACCP (Patrono *Chest* 2004;126:2345).
- Similar conclusions reached by ESC (Patrono *Eur Heart J* 2004;25:166).

Nevertheless ...

The 2006 ACC/AHA PCI guidelines provide a Class IIb recommendation (based on Level C evidence) that, in patients in whom subacute stent thrombosis may be catastrophic or lethal, platelet aggregation studies may be considered and the maintenance dose of clopidogrel increased from 75 mg to 150 mg per day if <50% inhibition of platelet aggregation is demonstrated

Smith *Circulation* 2006;113:156

Late Stent Thrombosis After DES: Role of Platelet Function Testing

1. Non-compliance

Patient non-compliance with aspirin and/or clopidogrel

2. Resistance

"Resistance" or hyporesponsiveness to aspirin and/or clopidogrel

3. Rebound

Platelet hyperfunction after discontinuation of aspirin and/or clopidogrel

Late Stent Thrombosis After DES: Role of Platelet Function Testing

What needs to be done

Clinical studies to determine whether:

- platelet function tests predict late stent thrombosis (and/or other MACE)
- altering antiplatelet therapy based on platelet function tests reduces late stent thrombosis (and/or other MACE)

The future

Individualized therapy based on platelet function tests