

## Late Stent Thrombosis After DES: Role of Platelet Function Testing

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### Presenter Disclosure Information

Speaker: Alan D. Michelson, M.D.

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### 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<sub>2</sub> generation from platelets

#### Clopidogrel

Irreversibly inhibits platelet P2Y<sub>12</sub> 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<sub>2</sub> 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, P2Y<sub>1</sub>, P2Y<sub>12</sub>, thromboxane receptor, etc
- Enzymes: COX-1, COX-2, TxA<sub>2</sub> 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<sub>2</sub> and the TXA<sub>2</sub> intermediate, PGH<sub>2</sub>, 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<sub>2</sub>
- Urinary 11-dehydro thromboxane B<sub>2</sub>

### 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

### P2Y<sub>12</sub> Signaling-Dependent

- VASP phosphorylation (flow cytometry)

### ADP as the Stimulus:

- Platelet aggregometry (turbidometric)
- Platelet aggregometry (impedance)
- VerifyNow P2Y<sub>12</sub> assay
- Plateletworks
- Platelet surface activated GPIIb-IIIa, platelet surface P-selectin, leukocyte-platelet aggregates (flow cytometry)
- Thromboelastography
- Impact cone and plate(let) analyzer

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## 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 <sub>2</sub>
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

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## 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