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.

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<th>Company Name</th>
<th>Relationship</th>
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<td>Accumetrics</td>
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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 A₂ 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 A2 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)

Platelet Interactions With Other Blood Cells
- Endothelial cells and monocytes make thromboxane A2 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?

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

Thromboxane as the End Point:
- Serum thromboxane B2
- Urinary 11-dehydro thromboxane B2

Arachidonic Acid as the Stimulus:
- Platelet aggregometry (turbidometric)
- Platelet aggregometry (impedance)
- VerifyNow Aspirin assay
- Plateletox
- Platelet surface activated GPIb-IIIa, platelet surface P-selectin, leukocyte-platelet aggregates (flow cytometry)
- Thromboelastography
- Impact cone and platelet analyzer

Other:
- PFA-100

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

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<td>Mueller 1997</td>
<td>ADP- and collagen-induced whole blood aggregation</td>
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<td>Eikelboom 2002</td>
<td>Urinary 11-dehydro thromboxane B2</td>
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<td>Gum 2003</td>
<td>AA- and ADP-induced turbidometric platelet aggregation</td>
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<td>Chen 2004</td>
<td>VerifyNow</td>
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<td>Wenaweser 2005</td>
<td>ADP (but not AA) induced turbidometric platelet aggregation</td>
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<td>Ohmori 2006</td>
<td>collagen-induced turbidometric platelet aggregation</td>
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*Stent thrombosis study

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

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<td>VASP</td>
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<td>ADP-induced turbidometric platelet aggregation</td>
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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.

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• 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).

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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.

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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