Does Aspirin Work?

Participants…

• Provide the history and pharmacology of aspirin
• Review the history and pharmacology of thienopyridines clopidogrel (Plavix®) and prasugrel (Effient®)
• Outline current antiplatelet therapy regimens
• Review literature on prevalence and causes of antiplatelet therapy failure
• Perform antiplatelet therapy monitoring assays
• Interpret assay results
• Determine if antiplatelet therapy monitoring is effective

For a copy of this presentation, go to www.fritsmafactor.com.

Felix Hoffman; 1897

• August 10, 1897: Felix Hoffman synthesized pure, stable acetyl salicylic acid
  – Bayer laboratories in Leverkusen, Germany
• Aspirin: a = acetyl; spir = Spirea (plant)
• 1900: Bayer mixes aspirin with starch to make the first drug in tablet form
  – No prescription: 5 grains (~325 mg)
  – Uruguayan stamp shows Hoffman, willow branch, and his signature taken from the laboratory record

Mann CC, Plummer ML. The Aspirin Wars: Money, Medicine, and 100 Years of Rampant Competition. New York: Knopf 1991.

Lawrence Craven MD: 1948

• 1948: Dr. Lawrence Craven, California GP noticed 400 men for whom he had prescribed aspirin had no heart attacks
  – Recommended aspirin a day to reduce risk of heart attacks
• 1971: JB Smith demonstrated aspirin’s inhibition of platelet prostaglandins


Aspirin Efficacy: ISIS-2

• 1988: ISIS-2 demonstrates 0.78 risk of death after MI using aspirin; US FDA approves aspirin for reducing risk of a second MI or a first MI in angina
• 1988: Based on the Physicians’ Health Study, aspirin approved to prevent TIs and strokes in healthy subjects

Aspirin in Primary Prevention

- **Physician’s Health Study 1982–96**
  - 10,86 healthy male physicians age 40-84, 60 months
  - 325 mg aspirin on alternate days versus placebo
  - Ethical termination in 1988 when 44% reduction of fatal or nonfatal first AMIs was recorded

- **Women’s Health Study 1991–2000**
  - 39,876 healthy women over 45 YO, 10 years
  - 100 mg aspirin on alternate days versus placebo
  - 25% reduction in fatal or non-fatal first MIs
  - 50% reduction in hypercholesterolemia, smokers, or hypertensives, greatest effect over 65 YO


Cyclooxygenase-1 Acetylation

- Platelet COX-1 acetylated at ser529
  - Blocks arachidonic acid’s access to reactive “tunnel”
  - Active site amino acid tyr385 unaffected
- Platelet permanently loses COX-1 activation pathway
  - Recovery of function 10%/day as new platelets are produced
- Adhesion and shear-induced aggregation functions remain

**Antiplatelet Trialists’ Collaboration**

287 trials incorporating 100,000 subjects:
- Composite 32% decrease in death, MI, ischemic stroke in “high-risk” vascular patients on 75 to 150 mg aspirin daily:


Aspirin Pharmacology

- 50% absorbed from stomach, duodenum
- Peak plasma levels at 40 m
- Acetyl group hydrolyzed to form salicylic acid (salicylate) in 20–30 m
  - Carboxyesterase in gut, liver and RBCs
  - Platelet COX-1 acetylation occurs in the presystemic (portal) circulation of gut and liver
- Reduces plasma TXB₂ within 5 m
  - Maximal reduction in 30 m
  - Salicylate remains measurable 6 h

Clopidogrel (Plavix®)

- Thienopyridine pro-drug
  - Has largely replaced ticlopidine
  - (+)-(S)-methyl 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl) acetate
- Metabolite occupies platelet ADP receptor P2Y₁₂
  - Covalent cysteine binding, prevents aggregation
- Indications; with aspirin:
  - Prevents vascular ischemia in symptomatic atherosclerosis
  - Prevents secondary acute coronary syndrome
  - Prevents thrombosis after placement of drug-eluting coronary stent

Clopidogrel Efficacy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study</th>
<th>Citation</th>
<th>Risk Reduction Vs. Aspirin Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina</td>
<td>CURE</td>
<td>NEJM 2001;345:494</td>
<td>20%</td>
</tr>
<tr>
<td>Stent</td>
<td>CREDO</td>
<td>JAMA 2002;288:2411</td>
<td>26.9%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>CLARITY-TIMI 28</td>
<td>NEJM 2005;352:1779</td>
<td>20%</td>
</tr>
<tr>
<td>Low-risk</td>
<td>CHARISMA</td>
<td>NEJM 2006;354:1706</td>
<td>None</td>
</tr>
</tbody>
</table>

World Aspirin Usage

- 125,000,000,000
  - 325 mg tablets (40,000 tons)/year
- But aspirin is not for everybody
Prasugrel

- FDA-cleared July 10, 09 to use with aspirin
- Effient®: Daiichi Sankyo/Eli Lilly & Co
- TRITON-TIMI study of 13,608 patients
  - 60 mg loading dose, 10 mg/day
  - Prasugrel reduces the combined rate of death from CV causes; 12.1% for clopidogrel vs. 9.9% for prasugrel
  - However, 1.4%, vs. 0.9% serious bleeds and 0.4% vs. 0.1% fatal bleeds
  - Prasugrel generates net clinical harm in patients < 60 kg, > 75 YO or have a Hx of stroke or TIA
  - Overall mortality identical


Antiplatelet Failure Vs Resistance

- Variable antiplatelet efficacy
  - Adverse events despite therapy: failure
- Laboratory testing for resistance
  - Bleeding time
  - Light transmittance aggregometry (LTA)
  - Whole blood impedance aggregometry (WBA)
  - AspirinWorks®: Urine 11-dehydrothromboxane B2 (UDHT) immunoassay
  - Accumetrics Ultegra VerifyNow® Aspirin
  - Siemens PFA-100® collagen-epinephrine cartridge (CEPI)
  - Helena PlateletWorks®
  - Thromboelastograph® (TEG)
  - Platelet vasodilator-stimulated phosphoprotein phosphorylation (VASP) flow cytometry

Light Transmittance Aggregometry (LTA) Specimen Preparation

- Collect 9–12 mL whole blood
  - 3–4 2.7 mL tubes + 0.3 citrate
- Centrifuge at 50,000 g 30” (PRP)
- Centrifuge at 1500 g 15” (PPP)
- Adjust platelet count in the PRP with PPP to ~200,000/uL
- Wait 30 m for “platelet shock”, dispense to cuvette
- Pipette agonist, record absorbance using photometry

Antiplatelet Efficacy Agonists

- 0.5 mM arachidonic acid (AA)
  - Directly activates COX pathway to produce TXA2
  - TXA2 activates platelet by binding TPα or TPβ
  - Response reduced by aspirin
- 1 or 5 μg/mL collagen
  - Binds receptors GP Ia/IIa (integrin α2β1), GP IV, GP VI
  - 1 μg/mL response reduced by aspirin
  - 5 μg/mL may bypass aspirin effect, reduced in secretion (aspirin-like) disorder
- 5–10 μM ADP
  - ADP binds intact P2Y1, P2Y12
  - P2Y12 response reduced by thienopyridines
- Thrombin receptor activation peptide (TRAP)
  - Response reduced by GP Ibb/Illa inhibitor therapy

Ristening Platelets

Primary Aggregation

Secondary Aggregation

Light Transmittance Aggregometry
LTA Limitations

- Reference method, however...
- Specimen volume
- Specimen preparation time and artifact
- Three-hour time limit
- Operator-dependent results
- Poor reproducibility
- Removes effect of RBCs and WBCs

Impedance-based Whole Blood Platelet Aggregometry (WBA)

- Collect 9 mL blood
  - 3 tubes each 2.7 mL + 0.3 citrate
- Dilute aliquot 1:1 with saline in cuvette
- Pipette agonist, timer starts
- Electrodes lowered into suspension

WBA: Impedance

- Aggregating platelets form layer on electrodes
- Current impeded by platelet layer
  - Resistance measured in ohms (Ω)
  - 0 Ω = no aggregation
  - Aggregation proportional to Ω

Secretion Assayed W/ “Firefly” Reaction

- ATP
  - PPI
- Luciferin
  - Chromo-lumel/firefly luciferase reagent
  - Luminescence
  - Proportional to ATP release in µM
- Oxyluciferin + AMP

Normal Lumi-WBA

- ATP Release
- Impedance

Aspirin, Aspirin-like Disorder (Secretion Defect)

- ATP Release
- Impedance
Does Aspirin Work?

---

### Clopidogrel, P2Y₁₂ Defect

- **Impedance**
- **ATP Release**
- **No (< 0.5 µM)**
- **Aggregation**

---

### Aspirin Effect Using 5 µg/mL and 1 µg/mL Collagen

- **Agonist**: Collagen 1.5 µg/mL
- **Luminescence (Amplitude)**: 0.57% µM
- **Tracing**: Control

---

### Siemens (Dade-Behring) PFA-100

- **Transfer 800 µL citrated whole blood to each of two cartridges, load and run to closure time (CT)**
  - Coated membrane: agonists
  - Collagen and epinephrine (Col/Epi, CEPI)
    - "Weak" normal CT 98–185 s
    - Initial screen cartridge
  - Collagen and ADP (Col/ADP, CADP)
    - 50 µM ADP
    - "Strong" normal CT 77–133 s
    - Confirmatory

---

### PLT Function Screen for Variable Aspirin Response

- **Col/Epi Cartridge**
- **Col/ADP Cartridge**
- **Normal**
- **CT > 175s**
- **CT < 125s**
- **Aspirin, NSAIDs**
  - Reduced HCT or PLT count
  - Mild PLT dysfunction
  - Mild VWD
- **Severe VWD**
  - Severe PLT dysfunction
Accumetrics VerifyNow®

- δ-transmittance rise as platelets aggregate in response to agonists specific to aspirin, clopidogrel, or glycoprotein IIb/IIIa inhibitors
  - Whole blood
  - Low transmittance (ARU < 550): function inhibited
  - Normal transmittance (ARU > 550): function normal

VerifyNow Reaction Chamber

VerifyNow Principle

Accumetrics VerifyNow®

- VerifyNow Aspirin® uses AA to measure PLT eicosanoid synthesis pathway function
  - Aspirin acetylates cyclooxygenase
- VerifyNow P2Y₁₂® uses ADP to determine clopidogrel inhibition
  - Second channel uses TRAP to approximate baseline function without the need to discontinue medication
- VerifyNow IIb/IIIa® uses TRAP to determine response to GP IIb/IIIa inhibitors

VerifyNow and PFA-100 Limitations

- Large specimen volume
- Must test within four hours
- Expensive cartridges
- Precision: CVs above 10%
- Variable effect of von Willebrand factor and hematocrit
Aspirin Resistance Prevalence

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>By definition</th>
<th>By population</th>
<th>By dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27.1%</td>
<td>PFA-100</td>
<td>29.0%</td>
<td>&lt; 100 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultegra VerifyNow</td>
<td>26.2%</td>
<td>101–299 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LTA</td>
<td>21.3%</td>
<td>&gt; 300 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>22.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>32.1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>28.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18.6%</td>
<td></td>
</tr>
</tbody>
</table>


Thromboelastograph

- How it works

Adenylate cyclase (AC) is inhibited by ADP but activated by the vasodilator PGI₂. Activated AC enhances cAMP synthesis, activating cAMP-dependent protein kinase (PKA). The kinase phosphorylates VASP, detectable in flow cytometry. Dashed arrow denotes inhibition; solid arrow, activation.

TEG Parameters

- Clotting time R: Interval from when the blood was placed in the analyzer until initial fibrin formation
- Clot kinetics K: Interval to reach a chosen clot strength
- η: Interval to fibrin buildup and cross-linking
- Clot strength MA: Maximum dynamic properties of fibrin and platelet bonding via GP IIb/IIIa
- Hemostasis profile Cl: Linear combination of K, η, MA and G
- Clot stability LY50: Platelet amplitude reduction 30 m after MA

Platelet Vasodilator-stimulated Phosphoprotein Phosphorylation

- Urinary 11-dehydrothromboxane B₂ (UDHT)
  - Urine metabolite of plasma thromboxane B₂
  - Platelet is primary source
  - Also minor component renal endothelial cells, monocytes
  - Products of COX-1 and COX-2 detects chronic inflammation
- Random urine specimen
  - Normalized to urine creatinine
  - Pg UDHT/mg creatinine
Does Aspirin Work?

The Fritsma Factor
Platelet Function Testing
Platforms with Clinical Outcome Studies

<table>
<thead>
<tr>
<th>Assay</th>
<th>ASA</th>
<th>Clopidogrel</th>
<th>GP IIb/IIIa Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTA</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>WBA</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>VerifyNow</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>UDHT</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>PFA CEPI</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>VASP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PlateletWorks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Fritsma Factor
HOPE Study: Aspirin Resistance

- Nested retrospective case-control sample
  - 488 aspirin-treated vascular patients with MI, stroke, or CV death during 5 years of observation
  - 488 age- and sex-matched controls taking aspirin who did not have an MI, stroke, or CV death
- In aspirin-treated vascular patients, UDHT predicts risk of MI or CV death
- Fourth quartile UDHT = 3.5 CV death risk

<table>
<thead>
<tr>
<th>Quartile</th>
<th>MI</th>
<th>CV Death</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;134</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>134–193</td>
<td>1.3</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>194–298</td>
<td>1.5</td>
<td>2.5</td>
<td>0.6</td>
</tr>
<tr>
<td>&gt;298</td>
<td>2.0</td>
<td>3.5</td>
<td>0.6</td>
</tr>
</tbody>
</table>


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The Fritsma Factor
CHARISMA Trial

- Randomized double-blind prospective trial of 3261 clopidogrel Vs. placebo in patients on aspirin at high risk of atherothrombosis
  - Tested 1 month after starting clopidogrel
  - 144 with stroke, MI, or CV death
  - 3117 with no adverse event
- Fourth quartile UDHT composite RR=1.66

Kaplan–Meier curves for composite of stroke, MI, or CV death by UDHT quartiles


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The Fritsma Factor
CHARISMA Trial

- Fourth quartile UDHT levels
  - Increasing age, ♀ sex, Hx of PAD, smoking, oral hypoglycemic Rx, ACE-inhibitor Rx
  - Low UDHT concentrations
    - Aspirin Rx >150 mg/d, NSAIDs, hypercholesterolemia, statin Rx
- Randomization to clopidogrel or placebo did not reduce risk ratio for CV events in patients in the fourth UDHT quartile
- UDHT is potentially modifiable

Aspirin Resistance and Adverse Events

<table>
<thead>
<tr>
<th>Type</th>
<th>Percutaneous Intervention (Cath)</th>
<th>Stable CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>151</td>
<td>106</td>
</tr>
<tr>
<td>% AR</td>
<td>19.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Method</td>
<td>VerifyNow</td>
<td>Light Transmittance Aggregometry</td>
</tr>
<tr>
<td>Results</td>
<td>Elevated CK-MB and troponin I in AR: 4th quartile ADP response associated with RR for CV events = 22.4 OR in AR + Composite: 3.12 + CV death: 2.98 + MI: 1.91 + CVA: 5.44</td>
<td></td>
</tr>
</tbody>
</table>

PFA-100 and Aspirin Resistance

Gum PA, JACC 2003:41:961
9.5% AR by CEPI CT, low correlation with LTA

Low AR correlation among LTA, CEPI CT, and flow

Cuiisset T, J Thromb Haemost 2006;4:542
No CEPI CT difference between AR and aspirin sensitive

CEPI CT did not distinguish low dose from high dose aspirin

Grundmann K, J Neurol 2003;250:63
53 patients on aspirin for stroke prevention: CEPI CT significantly shorter in 12/35 patients with recurrent stroke (p<0.01)

AR = aspirin resistance, CEPI CT = closure time using collagen-epinephrine cartridge, LTA = light transmittance aggregometry

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Variation in Laboratory Detection of Aspirin Resistance

<table>
<thead>
<tr>
<th>Assay</th>
<th>Aspirin Resistance %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accumetrics VerifyNow Aspirin</td>
<td>17</td>
</tr>
<tr>
<td>Siemens PFA-100 CEPI</td>
<td>22</td>
</tr>
<tr>
<td>Arachidonic acid LTA</td>
<td>5 (COX-1 specific)</td>
</tr>
<tr>
<td>All tests abnormal per subject</td>
<td>2</td>
</tr>
</tbody>
</table>


Seven-day Comparison to Whole Blood Aggregometry

<table>
<thead>
<tr>
<th>Assay</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>81 mg</td>
<td>325 mg</td>
</tr>
<tr>
<td>AspirinWorks</td>
<td>74.3</td>
<td>62.1</td>
</tr>
<tr>
<td>PFA-100 CEPI</td>
<td>81.3</td>
<td>81.6</td>
</tr>
<tr>
<td>VerifyNow Aspirin</td>
<td>72.7</td>
<td>51.9</td>
</tr>
</tbody>
</table>

“Laboratory measures of PLT activity are suppressed by aspirin therapy, but are affected by the dosage and duration of therapy. Determinations of aspirin response should be made after at least 7 days of treatment. Laboratory test platform results do not closely reflect each other, thus application of laboratory platforms should be made consistently.”


Aspirin Resistance Study Limitations

- Inter-assay variation
- Biological variation over time
- Fail to adjust for race, age and sex
- Fail to confirm compliance using serum salicylate
  - Non-compliance and early withdrawal may account for most aspirin resistance
- Fail to separate confounding conditions
  - Hypertension, diabetes, peripheral vascular disease, smoking, and inflammation may contribute to aspirin resistance, while independently raising vascular risk

Proposed Mechanisms of Aspirin Resistance

- Activation of alternate PLT pathways not blocked by aspirin
  - Diacylglycerol pathway activated through G-protein
  - Adhesion molecules: collagen (GP Ia/IIa) and von Willebrand factor receptors (GP Ib/V/IX)
  - Activation by shear stress in atherosclerosis
- Aspirin-mediated reduction of PLT-inhibiting prostacyclins from vascular endothelial cells
- Elevated von Willebrand factor levels
- Polypharmacy (> 4 drugs)


Proposed Mechanisms of Aspirin Resistance

- Induction of COX-2
  - Non-constitutive, induced by cytokines and inflammation
  - After bypass surgery, 16-fold increase of COX-2 causes transient aspirin resistance
  - Acetylation of COX-2 Ser529 incompletely hinders arachidonic acid’s access to reactive site
  - In megakaryocytes, monocytes, macrophages, vascular endothelial cells and newly released platelets
  - Smoking, diabetes, heart failure and hyperlipidemia
- NSAIDs compete for Ser529

Does Aspirin Work?

The Fritsma Factor

**Clopidogrel Response Variation**

- Platelet concentrate transfusions
- Polymorphisms
  - CYP2C9*2 or *3, CYP2C19*2, *3, *4, *5 reduced function alleles
  - P2Y₁₂ receptor
  - HPA-2 phenotype

Distribution of reductions from baseline in 5 μmol ADP-induced PLT LTA in 544 patients after starting clopidogrel. Negative changes represent aggregation values < baseline.


**In Vivo Effect of Pravastatin and Atorvastatin on Antiplatelet Activity of Clopidogrel**

A. PLT aggregation before (black) and 24 hours after (white columns) clopidogrel administration in patients treated with 40 mg pravastatin or 10–40 mg atorvastatin.

B. Antiplatelet activity of clopidogrel as a function of atorvastatin dose


**Association of CYP2C19*2 Loss-of-Function Variant With ADP-Stimulated Platelet Aggregation Before and After Clopidogrel Administration in Participants in the Amish Pharmacogenomics of Antiplatelet Intervention (PAPI) Study and Sinai Hospital of Baltimore Study**

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Does Aspirin Work?

The Fritsma Factor

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Event-Free Survival Over 1 Year of Follow-up in Sinai Hospital of Baltimore Patients Treated With Clopidogrel Following PCI Stratified by CYP2C19*2 Genotype

Additional Clopidogrel Studies That Illustrate Resistance

<table>
<thead>
<tr>
<th>Study</th>
<th>Date</th>
<th>N</th>
<th>Dx</th>
<th>Dose (mg)</th>
<th>Time</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaremo</td>
<td>2002</td>
<td>18</td>
<td>PCI</td>
<td>300/75</td>
<td>24 h</td>
<td>28%</td>
</tr>
<tr>
<td>Gurbel</td>
<td>2002</td>
<td>92</td>
<td>PCI</td>
<td>300/75</td>
<td>24 h</td>
<td>31-35%</td>
</tr>
<tr>
<td>Mueller</td>
<td>2003</td>
<td>105</td>
<td>PCI</td>
<td>66/75</td>
<td>4 h</td>
<td>5-11%</td>
</tr>
<tr>
<td>Kesmarkey</td>
<td>2003</td>
<td>226</td>
<td>CVD</td>
<td>75</td>
<td></td>
<td>31%</td>
</tr>
</tbody>
</table>

Prasugrel Response

- Prodrug that is metabolized to active form in the CYP450 pathway
  - Not affected by CYP2C9 or CYP2C19 loss of function genotypes
  - More efficient generation of active metabolite: 15" onset
- Higher peak plasma levels than clopidogrel
- Greater exposure of PLTs to metabolite
- Functions in clopidogrel resistant patients

Prasugrel Response

- Prodrug that is metabolized to active form in the CYP450 pathway
  - Not affected by CYP2C9 or CYP2C19 loss of function genotypes
  - More efficient generation of active metabolite: 15" onset
- Higher peak plasma levels than clopidogrel
- Greater exposure of PLTs to metabolite
- Functions in clopidogrel resistant patients

Inhibition of platelet LTA by 300 mg clopidogrel and 60 mg prasugrel, 4 h post-dose. A value less than 20% (shown by line) is within the variability of the assay in the absence of drug administration.


So, do we screen for antiplatelet resistance?


Dr. Kristi Smock: "I think it is a problem of using different definitions for aspirin resistance and measuring it with tests that have different sensitivities and specificities." "Moreover," she adds, "testing for this condition is not generally recommended because it is not known what the treatment changes would be."

So, do we screen for aspirin resistance?


One might even wonder whether aspirin resistance actually exists. This entity was postulated on the basis of people having occlusive coronary events while taking cardioprotective doses of aspirin. However, Dr. Smock points out, aspirin reduces cardiovascular risk by only 25 percent. And cardiovascular disease is multifactorial. "It is simplistic to attribute coronary events entirely to aspirin resistance," she says. The condition may exist but is probably rare, and prospective clinical studies are needed to document it. "True biochemical aspirin resistance may reflect a variant cyclooxygenase-1 [COX-1] enzyme that is not susceptible to inhibition by aspirin," Dr. Smock says.
Response: Two Meta-Analyses

  Mean prevalence of laboratory aspirin resistance among all methods reviewed is 27%. Resistance predicts 3.8 OR for adverse cardiovascular outcomes. No concordance among methods.

  20 studies totaling 2930 patients with cardiovascular disease. Classified 28% as aspirin resistant. Resistance confers a 3.85 OR for any adverse cardiovascular outcome including a 5.99 OR for death and a 2.96 OR for acute coronary syndrome. No concordance among methods.