Advances in Antiplatelet Therapy

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Kingston, Jamaica
Financial Disclosures

In the last 12 months, I have had no financial interest, affiliation or arrangement with any organizations or industries relevant to this discussion.
Learning Objectives

• Brief review of current state of antiplatelet pharmacology

• Outline limitations of current therapy

• Review recent advances in antiplatelet pharmacology
Michelson A. *Hematology* 2011
Meet the Starting Line Up

• ASPIRIN
Meet the Starting Line Up

- ASPIRIN

- ADP Receptor Antagonists (clopidogrel, prasugrel, ticagrelor)
Meet the Starting Line Up

• ASPIRIN

• ADP Receptor Inhibitors (clopidogrel, prasugrel, ticagrelor)

• PDE INHIBITORS (dipyridamole, cilostazol)
ASPIRIN

• “Re-discovered” in 1899 by Bayer chemist Felix Hoffmann

• 1900-present, remains the most widely used drug in history

• Mechanism elucidated by Sir John Vane (Nobel prize 1982)
ASPIRIN MECHANISM OF ACTION

Aspirin irreversibly acetylates the active site of cyclooxygenase, which is required for the production of thromboxane A2, a powerful promoter of platelet aggregation.

Prostaglandin H Synthase

Peroxidase

Fe (III) → ROOH → ROH → Fe (IV) OPP⁺ → Fe (IV)=O

Cyclooxygenase

Tyr + AA → Tyr-385 → PGG₂ → 2 O₂
<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>Passive diffusion across stomach and small bowel</td>
</tr>
<tr>
<td><strong>Time to Peak Plasma Level</strong></td>
<td>~30-40 minutes (uncoated)</td>
</tr>
<tr>
<td><strong>Oral Bioavailability</strong></td>
<td>40-50% (uncoated)</td>
</tr>
<tr>
<td><strong>t&lt;sub&gt;1/2&lt;/sub&gt;</strong></td>
<td>~15-20 minutes</td>
</tr>
<tr>
<td><strong>Metabolism/Cx</strong></td>
<td>Hydrolysis by esterases in GI tract and liver to salicylic acid</td>
</tr>
<tr>
<td><strong>Anti-platelet effect</strong></td>
<td>Irreversible</td>
</tr>
</tbody>
</table>
Aspirin Resistance and Metabolic Syndrome

The graph shows the distribution of sTxB₂ (ng/ml) levels for different combinations of BMI and MetSyn status. The x-axis represents BMI status (≥ 25), and the y-axis represents sTxB₂ levels. The graph indicates that higher sTxB₂ levels are associated with BMI ≥ 25 and MetSyn status.
Drug Resistance and Pseudoresistance:

An Unintended Consequence of Enteric Coating Aspirin

Running title: Grosser et al.; Aspirin Resistance and Pseudoresistance

Tilo Grosser, MD1; Susanne Fries, MD1; John A. Lawson, MS1; Shiv C. Kapoor, PhD1;

Gregory R. Grant, PhD1,2,3; Garret A. FitzGerald, MD1
Overestimation of Aspirin Resistance: *Key Role of Compliance*
A. Platelet cyclooxygenase-1

- Catalytic site
- Serine residue at position 529
- Channel of access
- Arachidonic acid

B. With aspirin

- Acetyl serine

C. With ibuprofen and aspirin

- Ibuprofen
- Aspirin
NSAIDs Increase Risk of CV Event while on Low-Dose Aspirin

* Adjusted for CV Risk Factors

Kimmel et al JACC 2004
Risk of Death After Myocardial Infarction Related to Use of Non-Selective NSAIDs Post Hospital Discharge

Danish National Patient Registry Analysis of 58,432 Patients

HR for Death (95% CI)

Ibuprofen >1200 mg/d 2.20 (1.95-2.48)  \[\text{NNH}=45 \text{ (29-102)}\]

Diclofenac (≥ 100 mg/d) 4.44 (3.79-5.19)  \[\text{NNH}=24 \text{ (16-45)}\]

Gislason G  Circulation 2006
# Analysis of Available RCT Data

<table>
<thead>
<tr>
<th>Drug</th>
<th>RR of Vascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td>0.92 (0.67-1.26)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.51 (0.96-2.37)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1.63 (1.12-2.37)</td>
</tr>
</tbody>
</table>

*RR of Vascular Events*  
*When compared to placebo*

Kearney *BMJ* 2006
Clopidogrel

- Irreversible antagonist of platelet P2Y12 receptor

- Must be converted to active metabolite by cytochrome P450 in the liver

- Fidelity of conversion is variable among individuals
Clopidogrel

CYP2C19 Reduced-Function Allele Carriers

Hazard Ratio 1.53
(95% CI 1.07-2.19)
P=0.014

Number at Risk:
Days After Randomization
Non-carrier
Carrier

0 30 90 180 270 360 450

CV Death, MI, or Stroke (%)

Non-carriers 8.0
Carriers 12.1

Mega et al. NEJM 2009

* Carriers ~30% of the population
CYP2C19 Reduced-Function Allele Carriers
Clopidogrel Response Variability

Genetic Factors
- Polymorphisms of CYP
- Polymorphisms of GPIa
- Polymorphisms of P2Y\textsubscript{12}
- Polymorphisms of GPIIIa

Cellular Factors
- Accelerated platelet turnover
- Reduced CYP metabolic activity
- Increased ADP exposure
- Up-regulation of the P2Y\textsubscript{12} pathway
- Up-regulation of the P2Y\textsubscript{1} pathway
- Up-regulation of P2Y\textsubscript{12}-independent pathways (collagen, epinephrine, TXA\textsubscript{2}, thrombin)

Clinical Factors
- Failure to prescribe/poor compliance
- Under-dosing
- Poor absorption
- Drug-drug interactions involving CYP3A4
- Acute coronary syndrome
- Diabetes mellitus/insulin resistance
- Elevated body mass index

PDE Inhibitors

• Dipyridamole
  – Inhibits PDE and blocks adenosine uptake
  – Increases cAMP levels → inhibits platelet activity
  – Aggrenox (aspirin/dipyridamole) approved for secondary stroke prevention (ESPS-2 and ESPRIT)

• Cilostazol
  – Limited evidence to show reduced risk of stent restenosis
  – Inhibits progression of CIMT in diabetic patients
  – 15% develop side-effects leading to cessation of therapy (rash, GI upset, headaches)
### ‘Rookie’ Antiplatelet Drugs

**Adenosine Diphosphate-Receptor Antagonists**

<table>
<thead>
<tr>
<th>Prasugrel</th>
<th>Ticagrelor</th>
<th>Cangrelor</th>
</tr>
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<tbody>
<tr>
<td>- Thienopyridine</td>
<td>- Cyclo-pentyl-triazolo-pyrimidine (CPTP)</td>
<td>- ATP analog-direct inhibition</td>
</tr>
<tr>
<td>- More rapid onset of action than clopidogrel</td>
<td>- More rapid onset of action than clopidogrel</td>
<td>- <em>Intravenous</em></td>
</tr>
<tr>
<td>- Irreversible inhibitor of the P2Y12 receptor</td>
<td>- <em>Reversible</em> inhibitor of the P2Y12 receptor</td>
<td>- Rapid onset of action</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Competitive binding (reversible)</td>
</tr>
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</table>
PRASUGREL
TRITON Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA

Double-blind

CLOPIDOGREL
300 mg LD/ 75 mg MD

PRASUGREL
60 mg LD/ 10 mg MD

N= 13,600

Median duration of therapy - 12 months

1° endpoint: CV death, MI, Stroke
2° endpoints: CV death, MI, Stroke, Rehosp-Rec Isch, CV death, MI, UTVR
Stent Thrombosis (ARC definite/prob.)
Safety endpoints: TIMI major bleeds, Life-threatening bleeds
Key Substudies: Pharmacokinetic, Genomic
TRITON TIMI-38

Wiviott *NEJM* 2007
TRITON-TIMI study
Incidence of Stent Thrombosis

Any Stent at Index PCI
N=12,844

HR 0.48
P <0.0001
NNT=77

Days

0 30 60 90 180 270 360 450

Endpoints (%)

0 1 2 3

Clopidogrel

Prasugrel

Wiviott NEJM 2007
TRITON Net Clinical Benefit

Bleeding Risk Subgroups

Post-hoc analysis

Prior Stroke / TIA
- Yes
- No

Risk (%)
- + 37
- -16

P_{int} = 0.006

Age
- >=75
- < 75

P_{int} = 0.18
- -16

Wgt
- < 60 kg
- >=60 kg

P_{int} = 0.36
- +3
- -14

OVERALL

Risk (%)
- -13

P_{int} = 0.36

0.5 ← Prasugrel Better → 1

HR

1 ← Clopidogrel Better → 2
TICAGRELOR
Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators*
Ticagrelor Highlights

• Reversible inhibitor of P2Y12

• Proven efficacy in head-to-head comparison to clopidogrel (decrease MACE, stent thrombosis and no increase in bleeding)

• Limited by dyspnea as side-effect (reversible)
CANGRELOR
Cangrelor

- Intravenous P2Y12 Inhibitor
- Plasma half-life 3-5 minutes
- Full recovery of platelet function <60 minutes

Data on file, The Medicines Company
The Safety and Efficacy Of Cangrelor, a Short Acting, IV, Reversible, Platelet P2Y$_{12}$ Inhibitor In Patients Awaiting Cardiac Surgery: Results Of the BRIDGE Trial

Dominick J. Angiolillo MD, PhD, Michael S. Firstenberg MD, Matthew J. Price MD, Pradyumna E. Tummala MD, Martin Hutyra MD, Ian J. Welsby MD, Michele D. Voeltz MD, Harish Chandna MD, Chandrashekh Ramaiah MD, Miroslav Brtko MD, PhD, Louis Cannon MD, Cornelius Dyke MD, Tiepu Liu MD, PhD, Gilles Montalescot MD, Steven V. Manoukian MD, Jayne Prats PhD, Eric J. Topol MD for the BRIDGE Investigators
TAKE HOME MESSAGES

• Inexpensive antiplatelet therapy remains an acceptable therapeutic option in patients with cardiovascular disease
• Non-compliance is a major contributor to antiplatelet drug “resistance” and can be managed with education and counseling
• New P2Y12 antagonists hold promise to decrease secondary events