New Approaches to, and Indications for, Antiplatelet Therapy

Kenneth A. Bauer, MD
Professor of Medicine, Harvard Medical School
Chief, Hematology Section, VA Boston Healthcare System
Director, Thrombosis Clinical Research,
Beth Israel Deaconess Medical Center
Disclosures

Consultant

Bayer Healthcare
Janssen Pharmaceuticals
Bristol Myers Squibb
Pfizer
Boehringer Ingelheim
Instrumentation Laboratory

Acknowledgement

Deepak Bhatt, MD
Atherothrombosis: Clinical Manifestations

- Acute coronary syndromes
  - STEMI
  - NSTEMI
  - Unstable angina
- Stable CAD
- Angioplasty
- Bare metal stent
- Drug eluting stent
- CABG

- Stroke/TIA
- Carotid artery disease
- Renal artery stenosis
- Peripheral arterial disease
- Acute limb ischemia
- Claudication
- Endovascular stenting
- Peripheral bypass

Meadows TA, Bhatt DL. Circ Res. 2007;100:1261-1275.
Platelet and Thrombus Formation: Vascular Injury

Meadows TA, Bhatt DL. Circ Res. 2007;100:1261
Antiplatelet Agents

PAR-1 Antagonists:
- E5555
- Vorapaxar

ADP Receptor Antagonists:
- Cangrelor
- Clopidogrel
- Elinogrel
- Prasugrel
- Ticagrelor
- Ticlopidine

Intracellular Signaling Activation

Glycoprotein IIb/IIIa Inhibitors:
- Abciximab
- Eptifibatide
- Tirofiban

Thromboxane Inhibitors:
- Aspirin

Endothelium

PLAQUE

Desai NR, Bhatt DL. JACC Intervention 2010
Aspirin irreversibly acetylates the active site of cyclooxygenase (COX-1 and COX-2), which is required for the production of thromboxane A2 by platelets, which promotes platelet aggregation.
Efficacy of Aspirin at Various Doses in Reducing Vascular Events in High-Risk Patients

<table>
<thead>
<tr>
<th>Aspirin (mg daily)</th>
<th>No. of Trials</th>
<th>% Odds Reduction</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-1500</td>
<td>34</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>160-325</td>
<td>19</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>75-150</td>
<td>12</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>3</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Any aspirin</td>
<td>65</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

Vascular events included nonfatal MI, nonfatal stroke, and death from vascular causes.

Effect of Antiplatelet Therapy in Reducing Vascular Events in Diabetic Patients

Antiplatelet Trialists Collaboration BMJ 1994

Benefit/1000 pts (SD):

- No Diabetes: 36 (3)
- Diabetes: 38 (12)

2P:

- No Diabetes: <0.00001
- Diabetes: <0.002

Antiplatelet Trialists Collaboration BMJ 1994
ADP Receptors

- Receptor subtype
  - P2X<sub>1</sub>, P2Y<sub>1</sub>, P2Y<sub>12</sub>

- Molecular structure
  - Intrinsic ion channel
    - ↑[Na<sup>+</sup>/Ca<sup>2+</sup>]<sub>i</sub>
- Secondary messenger system
  - GPCR G<sub>q</sub>
    - ↑PLC/IP<sub>3</sub>
    - ↑[Ca<sup>2+</sup>]<sub>i</sub>
  - GPCR G<sub>i</sub>
    - ↓AC
    - ↓[cAMP]
- Functional response
  - Shape change
  - aggregation
  - transient aggregation
  - sustained aggregation
  - secretion

- Clopidogrel
  - Active metabolite
Ticlopidine

Thienopyridine derivative: converted to active metabolites by liver cytochrome P450 isozymes
Irreversible $\text{P2Y}_{12}$ receptor inhibitor
Labeled indication: To reduce the risk of recurrent stroke in patients who have had a stroke or a TIA
Dosage: 250 mg bid
In combination with aspirin, demonstrated to be more effective than anticoagulation (heparin/warfarin) in the prevention of stent thrombosis
Replaced by clopidogrel due to hematologic side effects:
   Neutropenia (2%)
   Thrombotic thrombocytopenic purpura (TTP)
CAPRIE: Superior Efficacy of Clopidogrel versus ASA

Patients with recent ischemic stroke, recent MI or symptomatic PAD

\[8.7\%^{\dagger} \text{RRR} \quad (p=0.043)\]

Cumulative event rate* (%)

Months of follow-up

ASA
Clopidogrel

*MI, ischemic stroke or vascular death
†Intent-to-treat analysis (n=19,185)

CAPRIE: Clopidogrel Provided Amplified Benefit in Patients with Diabetes

- **Patients without diabetes (n=15,233):**
  - ASA: 12.7%
  - Clopidogrel: 11.8%
  - **p=0.096**

- **Patients with diabetes (n=3866):**
  - ASA: 17.7%
  - Clopidogrel: 15.6%
  - **p=0.042**

- **Patients treated with insulin (n=1134):**
  - ASA: 21.5%
  - Clopidogrel: 17.7%
  - **p=0.106**

*MI, stroke, vascular death or rehospitalization for ischemic events/bleeding

†Number of events prevented per 1000 patients per year compared with ASA

Dual Antiplatelet Therapy

Clopidogrel adds to the benefit of aspirin in some circumstances (coronary artery disease).

Benefits and risks:

- Aspirin + Clopidogrel
- Issues with Clopidogrel
- Clopidogrel versus Prasugrel
- Clopidogrel versus Ticagrelor
- Cangrelor (investigational) – P2Y$_{12}$ receptor antagonist

Aspirin + Dipyrimadole (Aggrenox) – sustained release
- ASA (25 mg bid)/dipyrimadole (200 mg bid)

Approved indication: ischemic stroke or TIA
Issues with Clopidogrel

Irreversible P2Y\textsubscript{12} receptor: dosage 75 mg qd
Pharmacokinetics: Oral absorption 1 h, t\textsubscript{1/2} 8 h
Onset: 4-6 hours (after loading dose)
Offset: 5-7 days
Variable response: 25-30% of patients achieve less than 25% inhibition of platelet activity
Undergoes 2 step metabolism (CYP3A4/2C19 mediated) to active agent (genetic variability)
Potential drug interaction (e.g., PPIs)
CURE: Primary Efficacy Results (MI/Stroke/CV Death)

Randomized trial in acute MI

Placebo* (n = 6,303)

Clopidogrel* (n = 6,259)

20% Relative risk reduction
p = 0.00009
N=12,562

*On top of standard therapy (including ASA)

CURE: Clopidogrel in Patients with ACS and Diabetes

Myocardial Infarction, Stroke, or Vascular Death

Cumulative event rate (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>No previous diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo†</td>
<td>9.9%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Clopidogrel†</td>
<td>7.9%</td>
<td>14.2%</td>
</tr>
</tbody>
</table>

*Number of events prevented/1,000 patients treated/9 months
†On top of standard therapy (including ASA)

CHARISMA

A randomized, double-blind placebo controlled trial of 15,603 patients (79%) with established CVD and 21% with multiple risk factors designed to test whether clopidogrel should be continued beyond 1 year in addition to aspirin.

All patients received daily aspirin (75-162 mg) and were randomized to daily clopidogrel (75 mg) or placebo.

Clopidogrel patients had an event rate of 6.8% and placebo patients had an event rate of 7.3%.

CHARISMA demonstrated no significant benefit long term when clopidogrel is added to aspirin.

Rates of severe bleeding were similar, but clopidogrel patients experienced significantly higher rates of moderate bleeding.

CHARISMA: Proportion of Diabetic Patients in Subgroups

Overall population:
- Diabetics: 42%
- Non Diabetics: 58%

Secondary prevention:
- Diabetics: 31%
- Non Diabetics: 69%

Primary prevention:
- Diabetics: 83%
- Non Diabetics: 17%

N=15,613 N=12,153 N=3,284
Primary Efficacy Results (MI/Stroke/CV Death) by Pre-Specified Entry Category

<table>
<thead>
<tr>
<th>Population</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying CAD, CVD or PAD *</td>
<td>0.88 (0.77, 0.998)</td>
<td>0.046</td>
</tr>
<tr>
<td>(n=12,153)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Risk Factors *</td>
<td>1.20 (0.91, 1.59)</td>
<td>0.20</td>
</tr>
<tr>
<td>(n=3,284)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Population†</td>
<td>0.93 (0.83, 1.05)</td>
<td>0.22</td>
</tr>
<tr>
<td>(n=15,603)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* A statistical test for interaction showed marginally significant heterogeneity (p=0.045) in treatment response for these pre-specified subgroups of patients
† 166 patients did not meet any of the main inclusion criteria

Primary Efficacy – Diabetics vs Non Diabetics

Overall population
N=15,603

Secondary prevention
N=12,152

Primary prevention
N=3,284

p-value for interaction: 0.283

p-value for interaction: 0.923

p-value for interaction: 0.255

Non Diabetics
N=9,047

Diabetics
N=6,556

Non Diabetics
N=8,380

Diabetics
N=3,773

Non Diabetics
N=569

Diabetics
N=2,715

Placebo + ASA

Clopidogrel + ASA
Mechanism of Action of Prasugrel

Primary Endpoint
CV Death, MI, Stroke

Stent Thrombosis (ARC Definite + Probable)

Any Stent at Index PCI
N = 12,844

Clopidogrel

Prasugrel

HR 0.48
P < 0.0001
NNT = 77

Wiviott SD et al. NEJM 2007. Slide courtesy of Dr. Elliott Antman
Bleeding Events - Safety Cohort (N=13,457)

- **TIMI Major Bleeds**
  - Clopidogrel: ARD 0.6%, HR 1.32, P=0.03, NNH=167
  - Prasugrel: ARD 0.5%, HR 1.52, P=0.01

- **Life Threatening**
  - Clopidogrel: ARD 0.9%, HR 1.32, P=0.03
  - Prasugrel: ARD 1.4%, HR 1.52, P=0.01

- **Nonfatal**
  - Clopidogrel: ARD 0.9%
  - Prasugrel: ARD 1.1%

- **Fatal**
  - Clopidogrel: ARD 0.1%
  - Prasugrel: ARD 0.4%

- **ICH**
  - Clopidogrel: ARD 0.3%
  - Prasugrel: ARD 0.3%

**ICH in Pts w Prior Stroke/TIA (N=518)**
- Clopidogrel: ARD 0 (0)%
- Prasugrel: ARD 6 (2.3)%, P=0.02

Slide courtesy of Dr. Elliott Antman
Diabetic Subgroup

N = 3146

- CV Death / MI / Stroke
  - Clopidogrel: 17.0%
  - Prasugrel: 12.2%
  - HR 0.70
  - P < 0.001
  - NNT = 21

- TIMI Major NonCABG Bleeds
  - Clopidogrel: 2.6%
  - Prasugrel: 2.5%

Mechanism of Action of Ticagrelor (a cyclopentyl triazolopyrimidine)

CV Death, MI, or Stroke

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days after randomisation</td>
<td>9,333</td>
<td>9,291</td>
</tr>
<tr>
<td></td>
<td>8,628</td>
<td>8,521</td>
</tr>
<tr>
<td></td>
<td>8,460</td>
<td>8,362</td>
</tr>
<tr>
<td></td>
<td>8,219</td>
<td>8,124</td>
</tr>
<tr>
<td></td>
<td>6,743</td>
<td>6,743</td>
</tr>
<tr>
<td></td>
<td>5,161</td>
<td>5,096</td>
</tr>
<tr>
<td></td>
<td>4,147</td>
<td>4,047</td>
</tr>
</tbody>
</table>

HR 0.84 (95% CI 0.77–0.92), p=0.0003

Secondary Efficacy Endpoints

Myocardial infarction
No. at risk
<table>
<thead>
<tr>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>9,333</td>
<td>9,291</td>
</tr>
<tr>
<td>8,678</td>
<td>8,560</td>
</tr>
<tr>
<td>8,520</td>
<td>8,405</td>
</tr>
<tr>
<td>8,279</td>
<td>8,177</td>
</tr>
<tr>
<td>6,796</td>
<td>6,703</td>
</tr>
<tr>
<td>5,210</td>
<td>5,136</td>
</tr>
<tr>
<td>4,191</td>
<td>4,109</td>
</tr>
</tbody>
</table>

Cumulative incidence (%)
HR 0.84 (95% CI 0.75–0.95), p=0.005

Cardiovascular death
No. at risk
<table>
<thead>
<tr>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>9,333</td>
<td>9,291</td>
</tr>
<tr>
<td>8,294</td>
<td>8,229</td>
</tr>
<tr>
<td>8,822</td>
<td>8,626</td>
</tr>
<tr>
<td>8,626</td>
<td>8,589</td>
</tr>
<tr>
<td>7119</td>
<td>7079</td>
</tr>
<tr>
<td>5,482</td>
<td>5,441</td>
</tr>
<tr>
<td>4,419</td>
<td>4,364</td>
</tr>
</tbody>
</table>

Cumulative incidence (%)
HR 0.79 (95% CI 0.69–0.91), p=0.001

Ticagrelor in Patients with Diabetes Mellitus

PLATO Study

James S et al. EHJ 2010.
Efficacy of New Drugs/Approaches in Reducing Adverse Outcomes in Diabetes Mellitus From Large-Scale Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>% of Events</th>
<th>Hazard Ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard</td>
<td>New Drug/Approach</td>
</tr>
<tr>
<td>TRITON-TIMI 38</td>
<td>17.0</td>
<td>12.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLATO</td>
<td>16.2</td>
<td>14.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CURRENT OASIS 7 (PCI Cohort)</td>
<td>5.6</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CURRENT-OASIS= Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events Optimal Antiplatelet Strategy for Interventions; PCI=percutaneous intervention; PLATO= A Study of Platelet Inhibition and Patient Outcomes; TRITON-TIMI= Trial To Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction.
DUAL ANTIPLATELET THERAPY AND INCREASED RISKS OF BLEEDING

In a meta-analysis of 18 randomized trials which included 129,314 patients

 Those assigned to dual antiplatelet therapy have about a 50% increase in risk of major bleeding compared with those given single agent therapy

 The magnitude of this excess risk is about as high as the approximately 60% increase observed in the trials comparing single antiplatelet agents to placebo

 These excess risks of major bleeding should be considered in relation to the benefits on occlusive CVD events in choosing the optimal antiplatelet strategy, especially for long-term treatment of patients with prior events or those at high risk of developing CVD.

Conclusions

Increased platelet activation/aggregation in diabetic patient contributes to their increased rate of ischemic events.

Clear role for aspirin in secondary prevention, possibly “primary” prevention.

Dual antiplatelet therapy indicated for at least 1 year after ACS or PCI.

More potent P2Y12 receptor antagonists likely of greater benefit in diabetics, if bleeding risk not too high.