Novel Antiplatelet Agents in Development

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Learning Objectives

• Recognize the clinical limitations of available antiplatelet drugs
• Differentiate the pharmacologic properties of novel antiplatelet agents from currently available drugs
• Evaluate recent data regarding advances in the safety and efficacy of antiplatelet agents under development

The Ideal Antiplatelet Agent

• Rapid onset of action
• Convenient oral administration
• Predictability of response
• Stable steady state effect (no rebound or paradoxical activation)
• Reversible effects
• Favorable balance of antithrombotic efficacy versus bleeding
Limitations of Current Options for Oral Antiplatelet Therapy

- Slow onset
- Modest levels of platelet inhibition
- Variability of response
- Irreversible and bleeding risk (especially related to CABG)

CURRENT (OASIS-7): Study Design

ACS (NSTEMI) patients planned for early PCI within 24 hours

N = ~13,000

Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/
Optimal Antiplatelet Strategy for Interventions

Clopidogrel 600 mg
Days 1–7
150 mg

ASA low dose
Days 8–30
75–100 mg

ASA high dose
Days 8–30
300–325 mg

Clopidogrel 300 mg
Days 1–7
75 mg

ASA low dose
Days 8–30
75–100 mg

ASA high dose
Days 8–30
300–325 mg

ClinicalTrials.gov identifier: NCT00335452.

Antiplatelet Agents

New Antiplatelet Agents

- P2Y12 antagonists
  - Prasugrel
  - AZD6140
  - Cangrelor

- Thrombin receptor antagonists
  - SCH 530348
  - E5555

Prasugrel

- Mechanism: inhibition of P2Y12
- Pharmacodynamics
  - Rapid onset (within 2 hours)
  - Irreversible binding
- Different metabolic pathway of activation versus clopidogrel
- More potent inhibition of ADP-induced platelet activation than clopidogrel


Active Metabolite Formation

Prasugrel Versus Clopidogrel Crossover Study

- Inhibition of aggregation (%)
- Clopidogrel responder*
- Clopidogrel nonresponder

Healthy volunteers

*Responder ≥25% IPA at 4 and 24 hours.


Prasugrel Compared with Clopidogrel: ADP-induced Platelet Aggregation

- Mean ± SD, excluding outliers
- 20 µM ADP and 24 hr post-LD


Inhibition of Platelet Aggregation Induced by 20 µM ADP

Greater Platelet Inhibition in Prasugrel Versus Clopidogrel at Higher Loading Doses


Greater Platelet Inhibition in Prasugrel Versus Clopidogrel at Higher Maintenance Doses


TRITON–TIMI 38
Protocol Design

ACS (STEMI or UA/NSTEMI) and planned PCI

ASA

Double-blind

N=13,000

PRASUGREL

CLOPIDOGREL

Median duration of therapy: 12 months

Primary endpoint: CV death, MI, stroke
Secondary endpoints: CV death, MI, stroke, re-ischemia
CV death, MI, UTVR

TRITON–TIMI 38, Trial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel. Thrombolysis In Myocardial Infarction 38. UTVR, urgent target vessel revascularization.

Increased Efficacy and Bleeding in Prasugrel Versus Clopidogrel

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy endpoint</td>
<td>12.1%</td>
<td>9.3%</td>
</tr>
<tr>
<td>HR</td>
<td>0.81</td>
<td>95% CI: 0.73–0.90</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>TIMI Major Bleeding (non-CABG)</td>
<td>3.4%</td>
<td>1.0%</td>
</tr>
<tr>
<td>HR</td>
<td>1.32</td>
<td>95% CI: 1.03–1.68</td>
</tr>
<tr>
<td>P-value</td>
<td>=.03</td>
<td></td>
</tr>
</tbody>
</table>


Decreased Stent Thrombosis and Urgent Target-vessel Revascularization in Prasugrel Versus Clopidogrel

<table>
<thead>
<tr>
<th>Stent thrombosis</th>
<th>Clopidogrel (n=6795)</th>
<th>Prasugrel (n=6813)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>HR: 0.66, P &lt; .001</td>
<td>HR: 0.48, P &lt; .001</td>
</tr>
</tbody>
</table>

AZD6140

- First reversible oral ADP antagonist
- New class of P2Y₁₀ inhibitors
  - Not a thienopyridine or ATP antagonist
  - Direct-acting (not a pro-drug)
- Rapid onset (2 hours)
- Plasma t½ ~12 hours
- Greater and more consistent inhibition of ADP-induced platelet activation than clopidogrel


Adapted with permission from: Peters G, Robbie G. Haematologica. 2004;89(suppl.7):14-15.
AZD6140 Compared to Clopidogrel: ADP-induced Aggregation

[Graph showing time in hours on x-axis and inhibition of aggregation on y-axis for AZD6140 100 mg BID and Clopidogrel on Day 1 and Day 14.]


DISPERSE2 Main Study Design

[Flowchart showing study design with Day 1, V1, V2, V3, V4, and follow-up visits with AZD6140 90 mg bid (n=334) and AZD6140 180 mg bid (n=332) vs Clopidogrel 75 mg qd (n=327).]

- All patients received aspirin (≤325 mg first dose, then 75–100 mg qd) and heparin/LMWH and/or a GPIIb/IIIa antagonist
  - 50% of AZD6140 patients in each arm received a 270 mg loading dose
  - In the clopidogrel group, thienopyridine-naïve patients received a 300-mg loading dose


DISPERSE2

Adjudicated bleeding rates within 48 hours

[Bar chart showing minor bleeds, major bleeds, and total bleeding rates for AZD6140 90 mg bid (n=168), AZD6140 180 mg bid (n=159), AZD6140 270 mg** (n=330), and Clopidogrel 75 mg qd (n=327).]

*Minor bleeding without major bleeding; **loading dose.
DISPERSE2
Cumulative adjudicated clinical endpoint of CV death/MI/stroke

No significant differences were found between the groups for clinical endpoints


DISPERSE2
Non-bleeding adverse events

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>AZD6140 90 mg bid n=334</th>
<th>AZD6140 180 mg bid n=323</th>
<th>Clopidogrel 75 mg qd n=327</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspea</td>
<td>10.5</td>
<td>19.8</td>
<td>6.4</td>
</tr>
<tr>
<td>Chest pain</td>
<td>7.5</td>
<td>7.4</td>
<td>9.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>5.6</td>
<td>6.3</td>
<td>6.6</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4.8</td>
<td>3.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5.4</td>
<td>4.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.0</td>
<td>7.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4.2</td>
<td>5.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Discontinuation rates due to adverse events were low and similar between the groups: 21 (6%), 23 (7%), and 19 (6%) discontinued in the AZD6140 90 mg bid, AZD6140 180 mg bid, and clopidogrel 75 mg qd groups, respectively.


PLATO
Can PLATElet Inhibition be Optimized to Prevent Vascular Events?

~16,000 patients within 24 hours of an index ACS (STEMI or NSTEMI)

- ASA 75–100 mg QD
- AZD6140 BID
- Clopidogrel 75 mg QD

Double-blind, double-dummy
Mean follow-up ~12.5 months
Range 6–24

Primary endpoint: Time to first occurrence of the composite of death, MI or stroke

Primary safety endpoint: Major bleeding

ClinicalTrials.gov Identifier: NCT00391872.
Cangrelor
Parenteral ADP-P2Y12 receptor antagonist

- ATP analogue
- Immediate onset (within 5 minutes)
- Plasma half-life of 5–9 minutes
- 20–60 minutes for return to normal platelet function

Rapid, Dose-dependent Inhibition of Platelet Aggregation with Cangrelor

Improved ADP Blockade with Cangrelor in Clopidogrel-treated Patients

Platelet Reactivity Index (PRI) determined by the difference in VASP fluorescence intensity between resting and ADP-activated platelets.

33 clopidogrel treated patients with a mean PRI of 61% and decreased to close to zero with in vitro cangrelor.
Cangrelor Phase II Clinical Data: Compared with Abciximab in PCI

Double-blind randomized trial performed in US

- Abciximab (n=94)
- Cangrelor (n=105)

Incidence of events up to 7 days

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Death, MI, revascularization</th>
<th>Major bleed (TIMI criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab</td>
<td>5.4%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>2.1%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

CHAMPION–PCI

PCI for ACS (N=9,000)

- Placebo capsules
- Cangrelor 10 μg/kg bolus 4 μg/kgmin infusion
- Clopidogrel 600 mg
- Placebo bolus and infusion

Index procedure and study drug infusion (for at least 2 hours or the duration of the procedure, whichever is longer)

- Clopidogrel 600 mg
- Placebo capsules

Primary endpoint: death, MI, and UTVR at 48 hours

Secondary endpoints:
- Death, MI, uRevasc at 30 days
- Death at 6 months and 1 year


Clopidogrel/Cangrelor Interaction

Antiplatelet Agents

ASPIRIN, NXY-416, REDOGREL, S1886

Antiplatelet Agents

Thrombin

Thromboxane A2

5HT

ADP

5HT

P2Y1

5HT2A

PAR-1

PAR-4

Dense granule

Thrombin generation

TPAI

Coagulation factors

Inflammatory mediators

Protease Activated Receptor (PAR)-1

Thrombin

LDPR SFLRNPLDPR

NRLFS

Signal


Thrombin Receptor Antagonist

(TRA SCH 530348)

• First of a new class
• Oral administration, long-acting
• Blocks the platelet PAR-1 receptor, primary thrombin receptor in humans
• Does not interfere with thrombin-mediated generation of fibrin
• No effect on bleeding time or PT/aPTT

TRA-PCI: Study Design

Non-urgent PCI or catheter with possible PCI (all receive aspirin)

N=1030

Randomization #1—3:1 SCH530348: Placebo
Sequential groups (loading dose x 1: 10 mg; 20 mg; 40 mg)

Catheterization

Randomization #2

PCI

Maintenance therapy up for ~60 days
Placebo loading dose = placebo
SCH530348 loading dose = SCH530348

SCH 530348

3.0 mg (n=150)
1.0 mg (n=150)
0.5 mg (n=150)
Placebo (n=150)

Safety: TIMI major plus minor bleeding
Efficacy: death/MACE at 60 days

Primary evaluable cohort

Secondary evaluable cohort

TRA-PCI, Thrombin Receptor Antagonist in Percutaneous Coronary Intervention trial
Adapted with permission from: Moliterno DJ, et al. J Am Coll Cardiol. 2007;49:[abstract 2402-9].

PCI Cohort
TIMI major/minor bleeding

<table>
<thead>
<tr>
<th>Dose</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>151</td>
</tr>
<tr>
<td>All TRA</td>
<td>422</td>
</tr>
<tr>
<td>10 mg</td>
<td>129</td>
</tr>
<tr>
<td>20 mg</td>
<td>120</td>
</tr>
<tr>
<td>40 mg</td>
<td>173</td>
</tr>
</tbody>
</table>

SCH 530348

P value relative to placebo.
Adapted with permission from: Moliterno DJ, et al. J Am Coll Cardiol. 2007;49:[abstract 2402-9].

TRA-PCI Efficacy Outcomes
60-day death or MI

<table>
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New Antiplatelet Agents

- Platelets play a critical role in acute atherothrombosis
- Available antiplatelet agents significantly reduce the risk of recurrent events, but have important limitations
- Insights into the biology of platelet activation have guided us to novel antiplatelet agents that are currently under investigation
- Ongoing studies will establish whether these agents add to current standard care
Thank you for your participation.

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