Cutting Edge Clinical Trials
TRITON- TIMI 38:
Future Role of Prasugrel and Other New Anti-Platelet Agents in PCI

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Cardiovascular Research Foundation
Targets for antiplatelet therapies

Targets include:
- Ticlopidine
- Clopidogrel
- Prasugrel
- AZD6140
- Cangrelor
- PRT060128

Cyclooxygenase (COX) inhibitors:
- ASA
- Dipyridamole

Phosphodiesterase (PDE) inhibitors:
- SCH 530348

Other targets:
- Thrombin
- GP IIb/IIIa (Fibrinogen receptor)
- PAR-1
- PAR = protease-activated receptor

Drugs that inhibit ADP receptors:
- Abciximab
- Eptifibatide
- Tirofiban

Collagen and TXA2 receptor inhibitors:
- Collagen
- TXA2

Cyclic adenosine monophosphate (cAMP) is increased by:
- Paracetamol

Courtesy of BM Scirica, MD.
Adapted from Schafer AI.

cAMP = cyclic adenosine monophosphate, COX = cyclooxygenase, PAR = protease-activated receptor, PDE = phosphodiesterase
CURE: Patients continue to have recurrent CV events despite dual antiplatelet therapy

N = 12,562 with NSTE-ACS; all patients received ASA; Primary outcome = CV death, MI, stroke

CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events

# P2Y12 antagonists

<table>
<thead>
<tr>
<th>Type</th>
<th>Activity</th>
<th>Binding</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticlopidine</td>
<td>Thienopyridine</td>
<td>Indirect*</td>
<td>Irreversible</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Thienopyridine</td>
<td>Indirect*</td>
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</tr>
<tr>
<td>Prasugrel</td>
<td>Thienopyridine</td>
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<td>Irreversible</td>
</tr>
<tr>
<td>AZD6140</td>
<td>Cyclopentyl-triazolopyrimidine</td>
<td>Direct</td>
<td>Reversible</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>ATP analog</td>
<td>Direct</td>
<td>Reversible</td>
</tr>
<tr>
<td>PRT060128</td>
<td>N/A</td>
<td>Direct</td>
<td>Reversible</td>
</tr>
</tbody>
</table>

*Prodrug

ATP = adenosine triphosphate

Adapted from Michelson AD. *Arterioscler Thromb Vasc Biol.* 2008;28:s33-s38.

Limitations of current thienopyridines

- Slow onset requiring prolonged pretreatment for PCI efficacy
- Irreversibility and bleeding (especially related to CABG)
- Modest levels of platelet inhibition
- Variability of response

Antiplatelet therapy: The changing landscape

• Wide variability in platelet response to clopidogrel
• New P2Y12 inhibitors: Potency vs bleeding risk
• New approaches to platelet inhibition beyond P2Y12 inhibition
• Implications of upstream direct thrombin inhibition
• Future role of GP IIb/IIIa inhibitors, given more potent oral agents and antithrombins
Prasugrel: Overview

- Thienopyridine, orally administered as prodrug (more efficiently metabolized vs clopidogrel), irreversible inhibition of P2Y12 receptor
- TRITON-TIMI 38: Prasugrel 60/10 mg vs clopidogrel 300/75 mg
  - Clinical events
  - Bleeding rates and high-risk indicators
- PRINCIPLE-TIMI 44: Platelet inhibition with prasugrel 60/10 mg vs clopidogrel 600/150 mg
- TRILOGY ACS: Ongoing clinical outcomes trial

PRINCIPLE-TIMI = Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction, TRITON = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel, TRILOGY ACS = Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes
Clopidogrel response variability: Change the agent?

Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel

TRITON-TIMI 38

Disclosure Statement:
The TRITON-TIMI 38 trial was supported by a research grant to the Brigham and Women’s Hospital from Daiichi Sankyo Co. Ltd and Eli Lilly & Co.
**Study Design**

ACS (STEMI or UA/NSTEMI) & Planned PCI

**ASA**

N= 13,600

**Double-blind**

**CLOPIDOGREL**
300 mg LD/ 75 mg MD

**PRASUGREL**
60 mg LD/ 10 mg MD

**Median duration of therapy - 12 months**

1º endpoint: CV death, MI, Stroke

2º 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
Enrollment Criteria

• **Inclusion Criteria**
  Planned PCI for:
  - Known Mod-High Risk UA/NSTEMI (TRS > 3)
  - Anatomy STEMI: < 14 days (ischemia or Rx strategy)
  - STEMI: Primary PCI

• **Major Exclusion Criteria:**
  - Severe comorbidity
  - Increased bleeding risk
  - Prior hemorrhagic stroke or any stroke ≤ 3 mos
  - Any thienopyrididine within 5 days
  - No exclusion for advanced age or renal function

Primary Endpoint
CV Death, MI, Stroke

<table>
<thead>
<tr>
<th></th>
<th>Primary Endpoint (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>HR 0.81 (0.73-0.90) P=0.0004 NNT= 46</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>HR 0.77 (0.64-0.91) P=0.0001 LTFU = 14 (0.1%)</td>
</tr>
</tbody>
</table>

Days

ITT= 13,608
LTFU = 14 (0.1%)

Timing of Benefit (Landmark Analysis)

![Graph showing the comparison of Prasugrel and Clopidogrel in terms of Primary Endpoint (%).](image)

- **Prasugrel**
  - Loading Dose: HR 0.82, P=0.01
  - Maintenance Dose: HR 0.80, P=0.003

- **Clopidogrel**
  - Loading Dose: 5.6%
  - Maintenance Dose: 6.9%

Note: HR stands for Hazard Ratio, which is a measure of the relative risk of an event occurring in one group compared to another group.
Stent Thrombosis
(ARC Definite + Probable)


Endpoint (%)

Any Stent at Index PCI
N= 12,844

Clopidogrel
2.4
(142)

Prasugrel
1.1
(68)

HR 0.48
P <0.0001
NNT= 77

Days

0 30 60 90 180 270 360 450
TRITON-TIMI 38: Clinical events for prasugrel vs clopidogrel stratified by stent type

Primary endpoint (CV death/MI/stroke)

- Prasugrel: P = 0.003
- Clopidogrel: P = 0.019

TIMI major bleeding*

- Prasugrel: P = 0.09
- Clopidogrel: P = 0.34

Patients (%)

- Bare-metal stent only: Prasugrel, P = 0.09; Clopidogrel, P = 0.34
- Drug-eluting stent only: Prasugrel, P = 0.019; Clopidogrel, P = 0.003

*Not related to coronary bypass surgery

Balance of Efficacy and Safety

- **CV Death / MI / Stroke**
  - Prasugrel: HR 0.81 (0.73-0.90), P=0.0004
  - Clopidogrel: HR 1.32 (1.03-1.68), P=0.03
  - **NNT = 46**

- **TIMI Major NonCABG Bleeds**
  - Prasugrel: HR 1.32 (1.03-1.68), P=0.03
  - Clopidogrel: HR 1.32 (1.03-1.68), P=0.03
  - **NNH = 167**

- Events:
  - Prasugrel: 138 events
  - Clopidogrel: 35 events

**Source:** NEJM 357: 2001-2015, 2007
Bleeding Events

Safety Cohort

(N=13,457)

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
</tr>
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<tbody>
<tr>
<td>TIMI Major Bleeds</td>
<td>ARD 0.6%</td>
<td>ARD 0.5%</td>
</tr>
<tr>
<td></td>
<td>HR 1.32</td>
<td>HR 1.52</td>
</tr>
<tr>
<td></td>
<td>P=0.03</td>
<td>P=0.01</td>
</tr>
<tr>
<td></td>
<td>NNH=167</td>
<td></td>
</tr>
<tr>
<td>Life Threatening</td>
<td>ARD 0.9%</td>
<td>ARD 1.1%</td>
</tr>
<tr>
<td></td>
<td>HR 1.32</td>
<td>HR 1.52</td>
</tr>
<tr>
<td></td>
<td>P=0.03</td>
<td>P=0.01</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>ARD 0.9%</td>
<td>ARD 0.4%</td>
</tr>
<tr>
<td></td>
<td>HR 1.32</td>
<td>HR 1.52</td>
</tr>
<tr>
<td></td>
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<td>Fatal</td>
<td>ARD 0.1%</td>
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<tr>
<td></td>
<td>P=0.03</td>
<td>P=0.01</td>
</tr>
<tr>
<td>ICH in Pts w Prior Stroke/TIA (N=518)</td>
<td>ARD 0.3%</td>
<td>ARD 0%</td>
</tr>
<tr>
<td></td>
<td>HR 1.32</td>
<td>HR 1.52</td>
</tr>
<tr>
<td></td>
<td>P=0.03</td>
<td>P=0.01</td>
</tr>
</tbody>
</table>

ICH in Pts w Prior Stroke/TIA (N=518)

Clop 0 (0) %
Pras 6 (2.3)%
P=0.02
Net Clinical Benefit
Death, MI, Stroke, Major Bleed (non CABG)

ITT = 13,608

Events per 1000 pts

All Cause Mortality
Clop 3.2%
Pras 3.0 %
P = 0.64

0 30 60 90 180 270 360 450
Days

Endpoints (%)

HR 0.87
P = 0.004

Clopidogrel

Prasugrel

-23
+6
MI
Major Bleed (non CABG)

-25
-20
-15
-10
-5
0
5
10

Diabetic Subgroup

N=3146

CV Death / MI / Stroke

endpoint (%)

Days

Prasugrel

Clopidogrel

TIMI Major
NonCABG Bleeds

Prasugrel

Clopidogrel

NNT = 46

HR 0.70

P<0.001

2.6

2.5

17.0

12.2

N=3146

2.6

2.5
Net Clinical Benefit
Bleeding Risk Subgroups
Post-hoc analysis

Prior Stroke / TIA
Yes  No

Age
>=75
< 75

Wgt
< 60 kg
>=60 kg

OVERALL
0.5 1 2
Prasugrel Better  1  Clopidogrel Better

Risk (%)

P_{int} = 0.006
+ 37
-16

P_{int} = 0.18
-1
-16

P_{int} = 0.36
+3
-14

-13
Bleeding Risk Subgroups

Significant Net Clinical Benefit with Prasugrel 80%

10 mg

MD

Reduced MD
Guided by PK

Age > 75 or Wt < 60 kg

Avoid Prasugrel

16%

4%

Prior CVA/TIA

Prather

Avoid Prasugrel

Therapeutic Considerations
Randomized 13,608

Stent Placed 12,844 (94%)

BMS Only 6461 (47%)

DES Only 5743 (42%)

Both BMS/DES 640 (5%)

PES Only 2766 (20%)

SES Only 2454 (18%)

Other/Mixed 523 (4%)
Death Following ST

Mortality During Follow up (%) Post-Stent Thrombosis

HR 13.1 (9.8 – 17.5)
P<0.0001

25.9

2.6

% of Subjects

Stent Thrombosis
N=210

No Stent Thrombosis
N=12634
Definite/Probable ST: Any Stent (N=12844)

HR 0.48 [0.36-0.64], P<0.0001

1 year: 1.06 vs 2.15%
HR 0.48 [0.36-0.65], P<0.0001

52% vs 1.13%

CLOPIDOGREL

PRASUGREL
Definite/Probable ST: Any Stent (N=12844)

**STENT ANALYSIS**

**EARLY ST**

HR 0.41 [0.29-0.59]
P<0.0001

**LATE ST**

HR 0.60 [0.37-0.97]
P=0.03

% of Subjects

- **EARLY ST**
  - 1.56%
  - 59%
  - 0.64%

- **LATE ST**
  - 0.82%
  - 40%
  - 0.49%

DAYS

- CLOPIDOGREL
- PRASUGREL
**PRINCIPLE-TIMI 44: Study design**

**Loading phase**
- N = 201
- Planned elective PCI
- Baseline laboratory measures
- No PCI
- No planned GP IIb/IIIa inhibitor use
- Clopidogrel 600 mg
- Prasugrel 60 mg

**0.5-hr Post-loading dose labs**

**Coronary angiography**
- Post-angiography labs

**Maintenance phase**
- N = 100
- Clopidogrel naïve
- No planned GP IIb/IIIa inhibitor use
- PCI

**6-hr* Labs, 18-hr to 24-hr labs**

**15-d Clinical events, labs,† CROSSOVER**

**29-d Clinical events, labs†**

**6-hr* Labs, 15-d events**

**1º Endpoints:**
- *Loading = 6-hr inhibition of platelet aggregation (IPA);†Maintenance = 14-d and 29-d IPA

Comparison with Higher Dose Clopidogrel

IPA (%; 20 μM ADP)

N=201  P<0.0001 for each

Prasugrel 60 mg

Clopidogrel 600 mg

PRINCIPLE-TIMI 44 (crossover phase): Inhibition of platelet aggregation with maintenance dose

Prasugrel 10 mg

Clopidogrel 150 mg

IPA (20 µM ADP, %)

LSM difference between treatments: 14.9 (10.6-19.3)*

Time (days)


*P < 0.0001

LSM = least square mean

IPA = inhibition of platelet aggregation
**Conclusions**

*Higher IPA to Support PCI*

Prasugrel 60 mg LD/10mg MD vs Clopidogrel 300 mg LD/ 75 mg MD

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A significant reduction in:</td>
<td>Significant increase in serious bleeding (32% increase)</td>
</tr>
<tr>
<td>CV Death/MI/Stroke 19%</td>
<td>Avoid in pts with prior CVA/TIA</td>
</tr>
<tr>
<td>Stent Thrombosis 52%</td>
<td></td>
</tr>
<tr>
<td>uTVR 34%</td>
<td></td>
</tr>
<tr>
<td>MI 24%</td>
<td></td>
</tr>
<tr>
<td>2. An early and sustained benefit</td>
<td></td>
</tr>
<tr>
<td>3. Across ACS spectrum</td>
<td></td>
</tr>
</tbody>
</table>

**Net clinical benefit significantly favored Prasugrel**

**Optimization of Prasugrel maintenance dosing in a minority of patients may help improve the benefit : risk balance**
Antiplatelet Therapy in ACS

Placebo

Reduction in Ischemic Events

Increase in Major Bleeds

ASA
- 22%

ASA + Clopidogrel
- 20%

ASA + Prasugrel
- 19%

APTC Single Antiplatelet Rx
+ 60%

CURE Dual Antiplatelet Rx
+ 38%

TRITON-TIMI 38 Higher IPA
+ 32%

ASA ASA + Clopidogrel ASA + Prasugrel
TRITON-TIMI 38, PRINCIPLE-TIMI 44: Conclusions

• In ACS patients undergoing PCI, a thienopyridine agent that achieves faster, more consistent, and greater levels of platelet inhibition than standard clopidogrel results in:
  – ↓Ischemic events, particularly MI and stent thrombosis
  – ↑Bleeding, including serious bleeding, particularly in specific patient subsets
TRITON-TIMI 38, PRINCIPLE-TIMI 44: Uncertainties

• What aspect(s) of prasugrel resulted in benefits?
  – Speed
  – Consistency
  – Potency

• Would this translate to other methods of inhibition?
  – P2Y12 signaling
  – Platelet activation, adhesion, and aggregation unrelated to P2Y12

• What are appropriate surrogate markers of platelet function?
TRILOGY ACS: Study design

Medical management alone planned ≤24 hrs and no prior clopidogrel

N = 7,800 <75 yrs
N ~ 2,500 ≥75 yrs
UA/NSTEMI
PCI/CABG not planned

Medical management alone planned ≤24 hrs from presentation and/or chronic clopidogrel treatment

Start/continue clopidogrel ≤24 hrs

Randomize between 1-7 days

Median duration of treatment ~ 18 months

Randomize ≤24 hrs

Clopidogrel
300 mg loading dose
75 mg maintenance dose

Prasugrel
30 mg loading dose
5/10 mg maintenance dose*

N = 7,800 <75 yrs
N ~ 2,500 ≥75 yrs
UA/NSTEMI
PCI/CABG not planned

Clopidogrel
75 mg maintenance dose

Prasugrel
5/10 mg maintenance dose*

*5 mg maintenance dose of prasugrel for age ≥75 yrs or weight <60 kg

Courtesy of MT Roe, MD
NIH. www.clinicaltrials.gov.
AZD6140: Overview

- Oral, direct-acting cyclopentyltriazolopyrimidine, reversible inhibition of P2Y12 receptor
- DISPERSE-2: Dose optimization and safety study
- Potency in clopidogrel pretreated patients
- PLATO: Ongoing clinical outcomes trial vs clopidogrel

DISPERSE = Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in Non-ST-Elevation Myocardial Infarction, PLATO = Platelet Inhibition and Patient Outcomes

PLATO: Study design

N ~ 18,000 with UA/NSTEMI or STEMI scheduled for primary PCI

AZD6140
180 mg loading dose*
90 mg bid maintenance dose

12 months

Clopidogrel
300 mg loading dose†
75 mg maintenance dose

Primary endpoint:
CV death, MI, stroke

*Additional 90 mg allowed pre-PCI
†In clopidogrel-naïve patients (no loading dose if pretreated);
Additional 300 mg allowed in either clopidogrel group pre-PCI

Cangrelor: Overview

- Intravenous, direct-acting ATP analog, reversible inhibitor of P2Y12 receptor, plasma half-life 2.6-3.3 minutes
- Dose-finding study
- CHAMPION: Placebo-controlled, ongoing clinical outcomes trial program

Cangrelor: Ongoing clinical trials

CHAMPION PCI
N ~ 9000
- Cangrelor
- Placebo

CHAMPION PLATFORM
N ~ 4400
- Cangrelor + usual care
- Placebo + usual care

Primary endpoint:
All-cause mortality, MI, ischemia-driven revascularization within 48 hours of randomization

NIH. www.clinicaltrials.gov.
Achieving optimal platelet inhibition in ACS: Summary

• TRITON-TIMI 38 demonstrated that higher and more consistent levels of platelet inhibition are associated with fewer ischemic events

• However, greater potency was associated with increased risk for bleeding in important, easily identifiable subgroups
  – Careful patient selection is critical to minimizing risk
### ACC/AHA guidelines for UA/NSTEMI: Dosing of oral antiplatelet therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Med Tx</th>
<th>During PCI</th>
<th>After PCI</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>162-325 mg nonenteric formulation</td>
<td>No additional treatment</td>
<td>162-325 mg nonenteric formulation</td>
<td>BMS: 162-325 mg ≥1 mo, SES: 3 mo, PES: 6 mo; then ASA 75-162 mg indefinitely</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Loading dose: 300-600 mg Maintenance dose: 75 mg</td>
<td>Second loading dose 300 mg may be given</td>
<td>Loading dose: 300-600 mg</td>
<td>BMS: 75 mg ≥1 mo and ideally up to 1 yr; DES: 75 mg ≥1 yr*</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Loading dose: 500 mg Maintenance dose: 250 mg bid</td>
<td>No additional treatment</td>
<td>Loading dose: 250 mg bid (duration same as clopidogrel)</td>
<td>Maintenance dose: 250 mg bid (duration same as clopidogrel)</td>
</tr>
</tbody>
</table>

*In patients who are not at high risk of bleeding; BMS = bare-metal stent, DES = drug-eluting stent, PES = paclitaxel-eluting stent, SES = sirolimus-eluting stent

Patients already taking daily long-term ASA should take 75 mg-325 mg before PCI is performed.

Patients not already taking daily ASA should be given 300 mg-325 mg ≥2 hours and preferably 24 hours before PCI is performed.

After PCI, in patients without allergy or increased risk of bleeding, ASA 162 mg-325 mg daily should be given for ≥1 month (BMS), 3 months (SES), 6 months (PES), after which daily long-term ASA use should be continued indefinitely at a dose of 75 mg-162 mg.

SCAI = Society for Cardiovascular Angiography and Interventions

A loading dose of clopidogrel, generally 600 mg, should be administered before or when PCI is performed.

In patients undergoing PCI within 12-24 hours of receiving fibrinolytic therapy, a clopidogrel oral loading dose of 300 mg may be considered.

For all post-PCI stented patients receiving a DES, clopidogrel 75 mg daily should be given for ≥12 months if not at high risk of bleeding.

For post-PCI patients receiving BMS, clopidogrel should be given for ≥1 month and ideally up to 12 months (unless at increased risk of bleeding; then it should be given for ≥2 weeks)