Prasugrel vs. Clopidogrel for Acute Coronary Syndromes Patients Managed without Revascularization — the TRILOGY ACS trial

On behalf of the TRILOGY ACS Investigators

www.clinicaltrials.gov Identifier: NCT00699998
Committees and Disclosures

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Steering Committee
- 50 representatives from the participating countries

Conflict of Interest Disclosures
- Disclosures for Drs. Roe and Ohman listed on www.dcri.org
- Disclosures for all authors listed within the manuscript
Trial Conduct

- Academic Coordinating Center: DCRI
  - Independently performed statistical analyses
  - Global project management
  - Event adjudication activities

- Global Trial Operations: Quintiles
  - Site management
  - Data management

- Sponsors: Eli Lilly and Daiichi Sankyo

- Protocol Adherence
  - Total of 18 patients lost to follow-up (0.2% of overall)
  - Median study follow-up: 17.1 months (10.4, 24.4)
The proportion of ACS (UA/NSTEMI) patients world-wide who are managed medically without revascularization (PCI or CABG) is 40-60%.

Medically managed ACS patients have a two-fold increase in ischemic events, but have been under-represented in contemporary ACS trials.

Prasugrel, a thienopyridine P2Y_{12} inhibitor, was shown to improve outcomes compared with clopidogrel in ACS patients undergoing PCI in the TRITON trial, with an increase in major bleeding.
TRILOGY ACS — Inclusion Criteria

- Randomization within 10 days of a UA/NSTEMI event
  - NSTEMI: CK-MB or Troponin > ULN
  - UA: ST depression > 1 mm in 2 or more leads

- “Reasonable certainty” for a medical management strategy decision determined
  - Angiography not required, but if performed, had to be done before randomization, and evidence of coronary disease had to be seen (1 lesion > 30% or prior PCI/CABG)

- At least 1 of 4 enrichment criteria:
  - Age > 60 years
  - Diabetes Mellitus
  - Prior MI
  - Prior Revascularization (PCI or CABG)
TRILOGY ACS Study Design

Medically Managed UA/NSTEMI Patients

Randomization Stratified by:
Age, Country, Prior Clopidogrel Treatment
(Primary analysis cohort — Age < 75 years)

Minimum Rx Duration: 6 months; Maximum Rx Duration: 30 months

Primary Efficacy Endpoint: CV Death, MI, Stroke

1. All patients were on aspirin and low-dose aspirin (< 100 mg) was strongly recommended. For patients <60 kg or ≥75 years, 5 mg MD of prasugrel was given. Adapted from Chin CT et al. Am Heart J 2010;160:16-22.e1.
Statistical Considerations

- Event-driven trial, powered for efficacy in the primary cohort of patients < 75 yrs of age (688 events planned for 90% power for 22% RRR, 761 events accrued)
  - Exploratory analysis in the elderly (age ≥ 75 yrs) with a minimum of 2,000 patients

- Testing strategy specified first testing the primary endpoint (CV death, MI, or stroke) in patients < 75 yrs

- Conditional on successfully establishing superiority of prasugrel over clopidogrel in this group, treatment groups would be compared in the overall population (including the elderly patients)
TRILOGY ACS Enrollment:
9,326 patients in 8 regions, 52 Countries
(7,243 patients < 75 years old; 2,083 patients ≥ 75 years old)
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Age &lt; 75 Years (N = 7243)</th>
<th>Overall Population (N = 9326)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel (N = 3620)</td>
<td>Prasugrel (N = 4663)</td>
</tr>
<tr>
<td>Clopidogrel (N = 3623)</td>
<td>Clopidogrel (N = 4663)</td>
</tr>
<tr>
<td>Age—yr</td>
<td>62 (56–68)</td>
</tr>
<tr>
<td>Female sex—%</td>
<td>36.2</td>
</tr>
<tr>
<td>Body weight &lt; 60 kg—%</td>
<td>13.1</td>
</tr>
<tr>
<td>Disease classification—%</td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>67.8</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>32.2</td>
</tr>
<tr>
<td>Medical History—%</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>38.5</td>
</tr>
<tr>
<td>Current/recent smoking</td>
<td>23.3</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>43.3</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>27.0</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>14.6</td>
</tr>
<tr>
<td>Baseline risk assessment</td>
<td></td>
</tr>
<tr>
<td>GRACE risk score</td>
<td>114 (101–128)</td>
</tr>
<tr>
<td>Creatinine clearance—mL/min</td>
<td>81 (63–104)</td>
</tr>
<tr>
<td>Angiography performed pre-randomization—%</td>
<td>42.1</td>
</tr>
</tbody>
</table>

Post-randomization revascularization performed in 7.5% of patients
Primary Efficacy Endpoint to 30 Months
(Age < 75 years)

HR (95% CI) ≤ 1 Year: 0.99 (0.84, 1.16)
HR (95% CI) > 1 Year: 0.72 (0.54, 0.97)

Primary Efficacy Endpoint to 30 Months
(Age < 75 years)

HR (95% CI): 0.91 (0.79, 1.05)  
P = 0.21

Interaction P = 0.07

No. at risk:
Prasugrel: 3620 3248 2359 1611 953 389
Clopidogrel: 3623 3244 2390 1596 946 399

Clopidogrel 16.0%
Prasugrel 13.9%
Primary Endpoint - Pre-Specified Sub-Groups
(Age < 75 years)

Characteristic

Overall results

Age
< 65 years
≥ 65 years

Sex
Female
Male

Weight
< 60 kg
≥ 60 kg

Disease classification
Unstable angina
NSTEMI

Diabetes mellitus
Yes
No

Current/recent smoking
Yes
No

Angiography before randomization
Yes
No

Clopidogrel strata
Stratum 1
Stratum 2
Stratum 3

PPI at randomization
Yes
No

Hazard Ratio (95% CI)

P value (Interaction)

0.142
0.290
0.959
0.969
0.712
< 0.001
0.080
0.778
0.023

Prasugrel Better
Clopidogrel Better

Duke Clinical Research Institute
Efficacy Component Endpoints to 30 Months
(Age < 75 years)

<table>
<thead>
<tr>
<th>Event</th>
<th>≤1 Year (HR (95% CI))</th>
<th>&gt;1 Year (HR (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death</td>
<td>1.00 (0.78, 1.28)</td>
<td>0.75 (0.49, 1.14)</td>
</tr>
<tr>
<td>All MI</td>
<td>0.97 (0.78, 1.19)</td>
<td>0.68 (0.46, 0.99)</td>
</tr>
<tr>
<td>All Stroke</td>
<td>0.86 (0.50, 1.47)</td>
<td>0.35 (0.14, 0.88)</td>
</tr>
</tbody>
</table>

- **CV Death**: HR: 0.93 (0.75-1.15) for ≤1 Year, 0.89 (0.74-1.07) for >1 Year.
- **All MI**: HR: 0.87 (0.69-1.09) for ≤1 Year, 0.89 (0.74-1.07) for >1 Year.
- **All Stroke**: HR: 0.67 (0.42-1.06) for ≤1 Year, 0.35 (0.14, 0.88) for >1 Year.
Lower risk multiple recurrent ischemic events suggested with prasugrel using the pre-specified Andersen-Gill model (HR = 0.85, 95% CI: 0.72–1.00, P=0.04)

Significant interaction with treatment and time (HR for > 12 mos = 0.64, 95% CI: 0.48–0.86, Interaction P=0.02)

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 event</td>
<td>364</td>
<td>397</td>
</tr>
<tr>
<td>≥ 2 events</td>
<td>77</td>
<td>109</td>
</tr>
<tr>
<td>3–7 events</td>
<td>18</td>
<td>24</td>
</tr>
</tbody>
</table>

* Pre-specified evaluation of all CV death, MI, or stroke events by treatment
TIMI Major Bleeding to 30 Months (Age < 75 years)

HR (95% CI):
1.31 (0.81, 2.11)
P = 0.27
Incidence of Bleeding Outcomes
(Age < 75 years)

GUSTO Criteria

- Severe/life-threatening: Prasugrel 0.4%, Clopidogrel 0.4%
  - Prasugrel: 13
  - Clopidogrel: 14
- Severe/life-threatening or moderate: Prasugrel 1.4%, Clopidogrel 1.0%
  - Prasugrel: 52
  - Clopidogrel: 35
- Major: Prasugrel 1.1%, Clopidogrel 0.8%
  - Prasugrel: 39
  - Clopidogrel: 30

TIMI Criteria

- Major or Minor: Prasugrel 1.9%, Clopidogrel 1.3%
  - Prasugrel: 70
  - Clopidogrel: 46
- Life-threatening: Prasugrel 0.4%, Clopidogrel 0.5%
  - Prasugrel: 16
  - Clopidogrel: 17
- Fatal: Prasugrel 0.1%, Clopidogrel 0.1%
  - Prasugrel: 4
  - Clopidogrel: 4
- Intracranial Hemorrhage: Prasugrel 0.2%, Clopidogrel 0.3%
  - Prasugrel: 8
  - Clopidogrel: 12

P values:
- GUSTO Criteria: Prasugrel vs Clopidogrel
  - Severe/life-threatening: P = 0.87
  - Severe/life-threatening or moderate: P = 0.06
- TIMI Criteria: Prasugrel vs Clopidogrel
  - Major or Minor: P = 0.02
  - Major: P = 0.27
  - Life-threatening: P = 0.88
  - Fatal: P = 0.99
  - Intracranial Hemorrhage: P = 0.39
Primary Efficacy Endpoint and TIMI Major Bleeding Through 30 Months (Overall population)

HR (95% CI):
0.96 (0.86, 1.07)  \( P = 0.45 \)

HR (95% CI):
1.23 (0.84, 1.81)  \( P = 0.29 \)
# Incidence of Key Safety Outcomes (Overall Population)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
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<tr>
<td>GUSTO Severe/life-threatening bleeding</td>
<td>22 (0.5%)</td>
<td>27 (0.6%)</td>
<td>0.83 (0.48–1.46)</td>
<td>0.53</td>
</tr>
<tr>
<td>TIMI Fatal Bleeding</td>
<td>7 (0.2%)</td>
<td>9 (0.2%)</td>
<td>0.80 (0.30–2.14)</td>
<td>0.68</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>14 (0.3%)</td>
<td>19 (0.4%)</td>
<td>0.76 (0.38–1.51)</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Neoplasm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New, non-benign neoplasms*</td>
<td>82 (1.8%)</td>
<td>78 (1.7%)</td>
<td>1.05 (0.77-1.43)</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>All-cause death</td>
<td>385 (8.3%)</td>
<td>409 (8.8%)</td>
<td>0.94 (0.82–1.08)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

*Among patients with no prior history of malignancy or prior malignancy treated with curative therapy
Conclusions

- In the largest trial to date of ACS patients managed medically without revascularization, prasugrel was not statistically different from clopidogrel during 2.5 years of follow-up among patients < 75 years of age.

- Further analyses of the primary endpoint yielded several important findings favoring prasugrel treatment:
  - Trend for a time-dependent benefit after 1 year.
  - Fewer total recurrent ischemic events, particularly after 1 year.

- No statistical differences in major, life-threatening, or fatal bleeding with prasugrel vs. clopidogrel.
Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization

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