Vorapaxar for Secondary Prevention in Patients with Prior Myocardial Infarction

NCT00526474; Trial funded by Merck

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On behalf of the TRA 2°P-TIMI 50 Steering Committee and Investigators

Clinical Trial Update
European Society of Cardiology
Munich, August 26, 2012
The benefit of adding other antiplatelet drugs to aspirin for long-term 2° prevention in **stable patients** with prior MI is uncertain

**Vorapaxar** inhibits platelet activation by antagonizing thrombin-mediated activation of the protease activated receptor (PAR)-1
Prior MI, CVA, or PAD
N=26,449

Standard care including oral antiplatelet rx

Randomize 1:1 Double Blind

Stratified by:
1) Qualifying Disease State
2) Use of thienopyridine

Follow up Visits
Day 30, Mo 4, Mo 8, Mo 12 Q6 months

Final Visit

Primary Efficacy Analysis:
1. CVD/MI/Stroke
2. CVD/MI/Stroke/Urgent Coronary Revasc

Principal Safety Ep:
• GUSTO Mod/Sev bleeding

Vorapaxar
2.5 mg/d

Placebo

Median F/U 30 Months
Background – 1° Efficacy Evaluation

Overall Population

CV Death, MI, or Stroke

- N = 26449
- Mean f/u: 2.5 years
- Hazard Ratio 0.87
- p < 0.001

Placebo

- 10.5%
- GUSTO Mod/Sev at 3 yrs
  - 4.2 v. 2.5%, HR 1.66, p<0.001

Vorapaxar

- 9.3%

ClinicalTrials.gov NCT00526474c
Prior MI Cohort

- Prospectively defined subgroup of 1° interest
- 17,779 patients (67% of total trial population)

Low-bleeding Risk Cohort

- Based on prior studies\(^1\), we applied previously established criteria to identify patients with a low risk of bleeding who have potential for improved net clinical outcomes with potent antiplatelet Rx:
  - No hx of stroke/TIA
  - Weight \(\geq 60\) kg
  - Age <75 yr

- 14,909 patients (84% of prior MI cohort)

\(^1\) Wiviott SD, et al. NEJM 2007
## Baseline Characteristics

### Prior MI Cohort

<table>
<thead>
<tr>
<th><strong>Demographics</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>59 (51-66)</td>
</tr>
<tr>
<td>Age &gt;=75 years (%)</td>
<td>8</td>
</tr>
<tr>
<td>Female (%)</td>
<td>21</td>
</tr>
</tbody>
</table>

### Clinical Characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus (%)</td>
<td>22</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>63</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>85</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>20</td>
</tr>
<tr>
<td>Prior coronary revasc (%)</td>
<td>86</td>
</tr>
<tr>
<td>Any cerebrovascular event (%)</td>
<td>5</td>
</tr>
</tbody>
</table>

### Baseline Medical Therapy

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (%)</td>
<td>98</td>
</tr>
<tr>
<td>Thienopyridine (%)</td>
<td>78</td>
</tr>
<tr>
<td>Lipid-lowering therapy (%)</td>
<td>96</td>
</tr>
</tbody>
</table>

*No differences between treatment groups*
Primary Efficacy Evaluation

Prior MI Cohort

CV Death, MI, or Stroke

N = 17,779
Mean f/u: 2.5 years

Hazard Ratio 0.80;
95% CI 0.72 - 0.89
p < 0.001

Placebo

Vorapaxar

<table>
<thead>
<tr>
<th>Event</th>
<th>Vora</th>
<th>Plac</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death</td>
<td>2.0</td>
<td>2.4</td>
<td>0.84</td>
<td>0.12</td>
</tr>
<tr>
<td>MI</td>
<td>5.7</td>
<td>7.0</td>
<td>0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.3</td>
<td>1.6</td>
<td>0.77</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Efficacy by Time from Qual MI

Prior MI Cohort

Time from qualifying MI to Randomizations

**< 3 months**

- HR 0.82
- \( p = 0.011 \)

- Placebo: 10.4%
- Vorapaxar: 8.9%

\( N = 7801 \)

**3 to 6 months**

- HR 0.79
- \( p = 0.023 \)

- Placebo: 9.4%
- Vorapaxar: 7.5%

\( N = 5151 \)

**> 6 months**

- HR 0.78
- \( p = 0.026 \)

- Placebo: 8.8%
- Vorapaxar: 7.1%

\( N = 4703 \)
Efficacy Early and Late
Prior MI Cohort

Days 0 to 360

- HR 0.79
- \( p = 0.003 \)

Day 360 to 1080

- HR 0.82
- \( p = 0.004 \)

Graphs showing the percentage of CV death/MI/Stroke over time for Placebo and Vorapaxar groups.
## Efficacy in Key Subgroups

### Prior MI Cohort

<table>
<thead>
<tr>
<th>Total no.</th>
<th>CV death, MI, Stroke</th>
<th>3-yr. KM%</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vora</td>
<td>Plac</td>
</tr>
<tr>
<td>Thienopyridine at randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13033</td>
<td>8.0</td>
<td>9.6</td>
</tr>
<tr>
<td>No</td>
<td>4746</td>
<td>8.3</td>
<td>9.9</td>
</tr>
<tr>
<td>Prior Stent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13218</td>
<td>7.5</td>
<td>9.4</td>
</tr>
<tr>
<td>No</td>
<td>825</td>
<td>8.6</td>
<td>13.2</td>
</tr>
<tr>
<td>Qualifying MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>9248</td>
<td>6.0</td>
<td>8.2</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>7375</td>
<td>10.4</td>
<td>11.2</td>
</tr>
<tr>
<td>Unknown</td>
<td>1156</td>
<td>10.0</td>
<td>12.6</td>
</tr>
<tr>
<td>Overall</td>
<td>17779</td>
<td>8.1</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Hazard Ratio Range: 0.2 to 5
Bleeding Endpoints

Prior MI Cohort

**Net Clinical Outcome**

<table>
<thead>
<tr>
<th>3-yr KM rate (%)</th>
<th>Vora n=8880</th>
<th>Plac n=8849</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death, MI, stroke, GUSTO Moderate/Severe bleeding</td>
<td>10.1</td>
<td>11.4</td>
<td>0.86</td>
<td>0.003</td>
</tr>
<tr>
<td>CV Death, MI, Stroke, UCR, GUSTO Moderate/Severe bleeding</td>
<td>12.5</td>
<td>13.4</td>
<td>0.91</td>
<td>0.038</td>
</tr>
</tbody>
</table>

**3-yr KM rates (%)**

- **Placebo**
  - GUSTO Moderate/Severe: 2.1%
  - TIMI Clinically Significant: 10.4%
  - TIMI Non-CABG Major: 1.6%
  - ICH: 0.4%
  - Fatal: 0.1%

- **Vorapaxar**
  - GUSTO Moderate/Severe: 3.4%
  - TIMI Clinically Significant: 15.1%
  - TIMI Non-CABG Major: 2.2%
  - ICH: 0.6%
  - Fatal: 0.2%

* TIMI Major/Minor/Requiring medical attention
Bleeding in Select Subgroups

Prior MI Cohort

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Prior Stroke/TIA</th>
<th>Any High Risk Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;75 yr</td>
<td>≥60 kg</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>≥75 yr</td>
<td>&lt;60 kg</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

3-yr Kaplan-Meier rates (%)

- Placebo
- Vorapaxar
Efficacy Evaluation
Low Bleeding Risk Cohort (N = 14,909)

CV Death, MI, or Stroke

- Placebo: 8.6%
- Vorapaxar: 6.8%

HR 0.75
\[ p < 0.0001 \]

CV Death

- Placebo: 2.0%
- Vorapaxar: 1.5%

HR 0.73
\[ p = 0.02 \]
When added to standard of care including aspirin ± thienopyridine in stable pts w/ hx prior MI, vorapaxar significantly:

- ↓ CV death, MI, or stroke
- ↑ mod & severe bleeding
- Improved net clinical outcome

The benefit of vorapaxar was consistent:

- Regardless of the timing of MI
- Both early (<1 yr) and late (>1 yr from rando.)
- With or without thienopyridine use
Conclusions

In appropriately selected patients, our findings demonstrate the benefit of prolonged antiplatelet therapy through inhibition of PAR-1, when added to ASA ± thienopyridine for long-term 2° prevention in patients with prior MI.
Vorapaxar for secondary prevention of thrombotic events for patients with previous myocardial infarction: a prespecified subgroup analysis of the TRA 2°P-TIMI 50 trial

Benjamin M Scirica, Marc P Bonaca, Eugene Braunwald, Gaetano M De Ferrari, Daniel Isaza, Basil S Lewis, Felix Mehrhof, Piera A Merlini, Sabina A Murphy, Marc S Sabatine, Michal Tendera, Frans Van de Werf, Robert Wilcox, David A Morrow, for the TRA 2°P-TIMI 50 Steering Committee and Investigators

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