PAR-1 Antagonist: What Do Clinical Trials Teach Us?

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Outline

PAR-1 antagonism is an effective approach to reducing recurrent atherothrombosis

1. More intensive antiplt therapy w/ PAR-1 antag. adds to standard care for long-term 2° prev.
   • Reduces CV death, MI, stroke
   • Reduces stent thrombosis and spontaneous MI
   • Reduces incident ischemic stroke

2. Pt selection is necessary to balance the antithrombotic benefit vs. risk of bleeding

3. Pts with indicators of high atherothrombotic risk have most to gain, e.g. DM, prior CABG
Prior MI, CVA, or PAD

Standard care including oral antiplt rx

RANDOMIZE 1:1 DOUBLE BLIND

Vorapaxar 2.5 mg/d

Placebo

Follow-up Median 2.5 yrs

Key Inclusion:
1) Type 1 MI: 2 wks - 12 mo
2) Ischemic CVA: 2 wk - 12 mo
3) PAD: claudication + abnl ABI or prior revasc

Background Rx
98% on ASA
92% lipid-lowering rx
75% ACEi/ARB
78% of MI pts on thieno

N = 26,449

Morrow et al. NEJM 2012; 366: 1404-1413
Vorapaxar in Stable Atherosclerosis

CV Death, MI, or Stroke

Hazard Ratio 0.87
p < 0.001

N = 26449
Mean f/u: 2.5 years

Placebo
Vorapaxar

10.5%
9.3%

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

Morrow et al. NEJM 2012; 366: 1404-1413
Major Bleeding Endpoints

3-yr KM rate (%)

Placebo  Vorapaxar

Prior Stroke  n = 5746

TIMI Non-CABG Major
ARD 2.0%  ARD 1.5%
HR 1.87  HR 2.55
P<0.001  P<0.001

ICH
ARD 0.9%
HR 0.9

Fatal
ARD 0.3%
HR 1.48
P=0.46

TIMI Non-CABG Major
ARD 1.8%
HR 1.35
P=0.005

ICH
ARD 0.4%
HR 0.4

Fatal
ARD 0.2%
HR 1.44
P=0.30

Morrow et al. NEJM 2012; 366: 1404-1413
US FDA Intended Use Population Qualifying CAD vs PAD

Primary Efficacy Endpoint

Key Secondary Efficacy Endpoint

GUSTO Severe Bleeding

Net Clinical Outcome†

Hazard Ratio (95% CI)

CAD/PAD No Stroke/No TIA (N=20,170†)
CAD No Stroke/No TIA (N=16,897†)
PAD No Stroke/No TIA (N=3273†)

CAD: HR 0.81 (0.72, 0.90)
PAD: HR 0.85 (0.70, 1.05)

† CV death/MI/Stroke/GUSTO severe bleeding.

Magnani et al. JAHA 2015 ePub
Efficacy by Time from Qual MI

Qualifying MI

CV death, MI, Stroke

<table>
<thead>
<tr>
<th>Qual MI &lt;3 mo from Randomization</th>
<th>Qual MI 3-6 mo from Randomization</th>
<th>Qual MI &gt;6 mo from Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>18% ↓</td>
<td>21% ↓</td>
<td>22% ↓</td>
</tr>
<tr>
<td>p = 0.011</td>
<td>p = 0.023</td>
<td>p = 0.026</td>
</tr>
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**Graphs**

- **Vorapaxar** vs **Placebo** for different time periods from randomization:
  - Qual MI <3 mo: 10.4% vs 8.9%, N = 7801 (p = 0.011)
  - Qual MI 3-6 mo: 9.4% vs 7.5%, N = 5151 (p = 0.023)
  - Qual MI >6 mo: 8.8% vs 7.1%, N = 4703 (p = 0.026)

**Scirica et al.** Lancet 2012; 380(9850):1317-24
Efficacy Early and Late

Qualifying MI

CV death, MI, Stroke

Days 0 to 360

Hazard Ratio 0.79; 95% CI 0.67-0.92
p = 0.003

Placebo 4.0%

Vorapaxar 3.2%

Day 360 onward

Hazard Ratio 0.82; 95% CI 0.71-0.94
p = 0.004

Placebo 6.5%

Vorapaxar 5.5%

**Efficacy & Bleeding Endpoints**

**MI Patients With/Without Thienopyridine**

<table>
<thead>
<tr>
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<th>Placebo</th>
<th>Vorapaxar</th>
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<tr>
<td>CVD/MI/Stroke</td>
<td>9.6</td>
<td>8.0</td>
</tr>
<tr>
<td>TIMI Non-CABG Major Bleed</td>
<td>1.7</td>
<td>2.3</td>
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**ARD**

- **Thienopyridine**
  - HR 0.81
  - P=0.001
  - ARD 1.6%
  - HR 1.31
  - P=0.049
  - ARD 0.6%

- **No Thienopyridine**
  - ARD 1.6%
  - HR 0.78
  - P=0.017
  - ARD 0.5%
  - HR 1.24
  - P=0.41

*Scirica et al. Lancet 2012; 380(9850):1317-24*
Stent Thrombosis - Timing

- Acute: 1%
- Subacute: 7%
- Late: 27%
- Very Late: 65%

92% Late or Very Late

Bonaca et al. JACC 2014;64:2309-17
Stent Thrombosis
By Randomized Treatment

ARC Definite Stent Thrombosis

**Thienopyridine**
HR 0.72 (0.51 – 1.02)

**No Thienopyridine**
HR 0.67 (0.29 – 1.54)

Placebo

Vorapaxar

HR 0.71 (0.52 – 0.98)

P=0.04

Bonaca et al. JACC 2014;64:2309-17
Incidence of New Ischemic Stroke

Patients with prior MI or PAD with no Hx of Stroke/TIA
N = 20,170

- Ischemic stroke HR 0.57, p<0.001
- Hemorrh stroke HR 2.78, p=0.049
- Overall stroke HR 0.68, p=0.005

Bonaca et al. JACC 2014;64:2318-26
Safety Outcomes with Vorapaxar vs. Placebo After a New Ischemic Stroke

**Hemorrhagic Conversion after Ischemic Stroke**
- Increased with Vorapaxar: 1.19
- Increased with Placebo: 1.09
- p = 0.70

**Death after Ischemic Stroke**
- Increased with Vorapaxar: 1.09
- Increased with Placebo: 0.1
- p = 0.79

Bonaca et al. JACC 2014;64:2318-26
Efficacy of Vorapaxar in Patients w/ Prior MI Based on Diabetes History

CV Death, MI, or stroke (%)

Placebo
Vorapaxar

DM
No DM

HR 0.77
p=0.004
ARD -3.1
NNT=30
95% CI 19, 92

HR 0.83
p=0.005
ARD -1.1
NNT=76
95% CI 47, 247

p-int 0.51

Cavender et al. Circulation 2015;131:1047-53
Efficacy of Vorapaxar in Patients with Prior MI Based on Diabetes History

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<td>DM</td>
<td>15.7%</td>
<td>12.6%</td>
</tr>
<tr>
<td>No DM</td>
<td>7.9%</td>
<td>6.8%</td>
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Net Clinical Outcome (All-Cause-Mortality/MI/CVA/GUSTO Severe Bleeding)

HR: 0.77 (0.65-0.93)  
\( p = 0.006 \)

Cavender et al. Circulation 2015;131:1047-53
Patients with Prior MI and No Hx of Stroke or TIA

Risk Differences for 1000 Patients per 3 years- Vora vs. PBO

First Serious (Irreversible) Events

-25 CV Death
-14 MI
-6 Stroke
-5 CV Death
0 Fatal Bleeding
0 Non-Fatal ICH

Events/1000 Patient/3 Years

Braunwald E. 2014
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Morrow DA ESC 2015