Vorapaxar: A New PAR-1 Receptor Blocker, Improves Cardiovascular and Limb Outcomes in PAD Patients: The FDA Agrees

Vorapaxar

A New PAR-1 Receptor Blocker, Improves Cardiovascular and Limb Outcomes in PAD Patients: The FDA Agrees

Anthony J. Comerota, MD, FACS, FACC
Director, Jobst Vascular Institute
Adjunct Professor of Surgery, University of Michigan

PLATELET INHIBITION

Platelet Inhibition

Background

Platelet activation and aggregation are crucial to arterial ischemic events in patients with atherosclerosis!

Roles of Coagulation and Platelet Aggregation in Arterial Thrombosis

Potential role for anticoagulants

Mechanism of PAR-1 Activation by Thrombin

**VORAPAXAR**

Inhibits PAR-1 Activation by Thrombin\(^1,2\)

![Diagram showing the inhibition of PAR-1 activation by VORAPAXAR](image)

**Methods**

- Protease activator receptor-1 (PAR-1) (platelet thrombin receptor)
- Patients with MI, Stroke, PAD
- 26,449 randomized: Placebo vs. Vorapaxar 2.5mg/d
- Primary efficacy outcome: Composite of CV death, MI, stroke
- Primary safety outcome: GUSTO moderate or severe bleeding

**NOTE:** at 2 years DSMB discontinued study treatment in patients with history of stroke due to risk of ICH

**Results**

- **CV Death, MI, Stroke**
  - P<0.001
  - RRR=11.4%

**Vascular Medicine**

**Vorapaxar in Patients With Peripheral Artery Disease**

Results From TRA2*P-TIMI 50

Marc P. Bonaca, MD, MPH; Benjamin M. Scirica, MD; Mark A. Cooper, MD; Jeffrey Ohri, MD; Reena Bounamaux, MD; Mikhail Dellborg, MD; Ewoca; M. Lamp, BA; Sabina A. Murphy, MPH; Eugene Braunwald, MD; David A. Morrow, MD, MPH

*Circulation 2013; 127: 1522-29*
Results

CVD, MI, Stroke –

Bonaca M P et al
Circulation 2013; 127:1522

- Mod./Major bleeding
- Vorapaxar – 7.4%
- Placebo – 4.5%
- P=0.001

- RRR=13.9%
- P<0.009

N=3,787

Mod./Major Bleed
Vorapaxar – 7.4%
Placebo – 4.5%
P=.001

38%

32.7%

SIGNIFICANT REDUCTION IN MACE

Results

CVD / MI / Stroke / Revasc –

Bonaca M P et al
Circulation 2013; 127:1522

- Peripheral Revascularization –

Vorapaxar
Placebo
P<0.017

22.2%

18.4%

RRR=17.1%

Results

Hospitalization: Acute Limb Ischemia –

Bonaca M P et al
Circulation 2013; 127:1522

- Urgent Hospitalization: Ischemia –

Vorapaxar
Placebo
P<0.011

8.0%

5.8%

RRR=27.5%

P<0.017

Efficacy and Safety of Vorapaxar as Approved for Clinical Use in the United States

Events Per 1,000 Patients

- CV Death, MI, Stroke, Bleeding –

Bonaca M P et al
Circulation 2013; 127:1522
Conclusions

1. New mechanism of platelet inhibition
2. Vorapaxar does not affect TP or P2Y$_{12}$ receptor
3. Vorapaxar is "add on" therapy
4. In patients post MI and with PAD:
   - Significant reduction in MACE
5. In patients with PAD:
   - Significant reduction of MACE and MALE

**Mechanism of Action**

**Vorapaxar: Par 1 Inhibitor**

- ADP: Adenosine Diphosphate
- TXA$_2$: Thromboxane A$_2$
- COX: Cyclooxygenase
- PDE: Phosphodiesterase

**Oral Antiplatelet Therapies**

- Clot Cascade
- Activated Platelet
- Unactivated Platelet

- Cilostazol
- Dipyridamole
- Atopaxar
- Vorapaxar
- TXA$_2$ Inhibitors
- Aspirin
- Ticlopidine
- Clopidogrel
- Prasugrel
- Ticagrelor