FACTOR Xa AND PAR-1 BLOCKER: ATLAS-2, APPRAISE-2 & TRACER TRIALS

Division of Cardiology, Jeonbuk National University Medical School
Jei Keon Chae, MD, PhD
Introduction

After acute coronary syndrome, patients remain at risk for recurrent ischemic events, despite revascularization and contemporary evidence based care.
(A) Incidence of primary outcome (non-fatal myocardial infarction, stroke, or death from cardiovascular causes) in the CURE trial over 12 months. (B) Incidence of primary endpoint (death from cardiovascular causes, non-fatal MI, or non-fatal stroke) at 15 months in the TRITON trial.
## Warfarin Plus Aspirin After ACS: Meta-analysis

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Rate Ratio (95% CI)</th>
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<th>Events/Patient-Years</th>
<th>Favors Warfarin</th>
<th>Favors Aspirin</th>
</tr>
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<tbody>
<tr>
<td>ATACS pilot, 1990 (39)</td>
<td>0.32 (0.09-1.66)</td>
<td>0.5</td>
<td>0/9</td>
<td>1/7</td>
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<td>ATACS main, 1994 (38)</td>
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<td>5/25</td>
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<tr>
<td>Williams et al., 1997 (40)</td>
<td>0.19 (0.03-1.02)</td>
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<td>5/5</td>
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<tr>
<td>APRICOT-2, 2002 (11)</td>
<td>0.28 (0.10-0.80)</td>
<td>3.1</td>
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<td>OASIS main, 2001 (13)</td>
<td>0.58 (0.38-0.89)</td>
<td>23.9</td>
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<td>OASIS pilot, 1998 (21)</td>
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<td>ASPET-2, 2002 (10)</td>
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<td>WARS II, 2002 (12)</td>
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<td>Overall</td>
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### Major Bleeding

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<tr>
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### MI

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<td>Excluded</td>
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<td>Overall</td>
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Fondaparinux In Acute Coronary Syndrome: OASIS-5

Death, Myocardial Infarction, or Stroke through Day 180

Cumulative Hazard

No. at Risk

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<tr>
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<th>Enoxaparin</th>
<th>Fondaparinux</th>
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<td>180</td>
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Hazard ratio, 0.89 (95% CI, 0.82–0.97)
P=0.007

Major Bleeding through Day 9

Cumulative Hazard

No. at Risk

<table>
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<tr>
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<th>Enoxaparin</th>
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<td>4</td>
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<td>5</td>
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<td>6</td>
<td>9,575</td>
<td>9,773</td>
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<td>8</td>
<td>9,478</td>
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</table>

Hazard ratio, 0.52 (95% CI, 0.44–0.61)
P<0.001

Coagulation Cascade, Platelet Activation Pathways, And Targets Of Antithrombotic Agents

Tissue factor → Coagulation cascade → Prothrombin → Thrombin → Thrombus

Collagen, VWF etc. → ADP → Aspirin

Fibrinogen → TxA2

Platelet aggregation → TRA*

Direct Xa inhib: rivaroxaban* apixaban*

Fondaparinux LMWH heparin

Bivalirudin hirudin dabigatran*

Clopidogrel prasugrel* cangrelor* ticagrelor*

GPIIb/IIIa inhibitors

Aspirin
Targets of Novel Anticoagulants for Long-Term Use
Targeting Factor Xa In ACS

Cellular effect of factor Xa
- Tissue factor expression
- Release of plasminogen activator inhibitor 1
- Expression of E-selectin, intercellular adhesion molecule 1, vascular cell adhesion protein
- Release of several inflammatory cytokines: IL 6, 8

- Factor Xa might be more attractive target for inhibition than thrombin
  - functioning at the confluence of early coagulation steps on both Tf-bearing cells and platelets
  - more thrombogenic than thrombin on molar basis
  - By contrast with thrombin inhibitors, factor Xa inhibitors decrease endogenous thrombin potential and allow small amounts of thrombin generation activating protein C
Rivaroxaban

Pharmacokinetics
- Oral anticoagulant that directly and selectively inhibits factor Xa
- Oral bioavailability is 80% to 100%, negligible interaction with food
- Dual mode of elimination
  - 2/3 metabolized by liver
  - 1/3 excreted in urine by kidney
- Metabolized by cytochrome p450 (CYP450)
- Average half-life 7 to 11 hours

Clinical development
- RECORD trial
  - Venous thromboembolism prophylaxis after total hip and knee arthroplasty
  - Rivaroxaban was superior to a once day dose of enoxaparin for prevention for VTE and all-cause mortality
- ROCKET AF trial
  - Rivaroxaban was not inferior to dose adjusted warfarin in stroke prevention and clinical bleeding
ATLAS ACS2 TIMI 51 trial
- Rivaroxaban in patients with a recent acute coronary syndrome

Previous phase II trial ATLAS ACS- TIMI 46 trial
- Rivaroxaban was tested at total daily doses ranging from 5 to 20mg
- Reduced death, myocardial infarction, stroke
- Dose-dependent increase in bleeding events

In this phase III trial
- Evaluate twice-daily rivaroxaban at doses of 2.5mg or 5mg as adjunctive therapy in patients with a recent ACS
- Study population
  - Acute coronary syndrome
    - ST elevation myocardial infarction, non-ST elevation myocardial infarction. Unstable angina in past 7 days
  - Exclusion criteria
    - Low platelet (< 90,000/mL), low hemoglobin (<10g/dL)
    - Low creatinine clearance (30ml/min)
    - Clinically significant GI bleeding
    - Previous intracranial hemorrhage
Primary efficacy end point

CV death, MI, stroke

Rivaroxaban significantly reduced the primary efficacy end point compared with placebo with rates of 8.9% vs. 10.7% (HR 0.84, 95% CI 0.74 to 0.96: p=0.008)

Each doses of rivaroxaban reduced the primary efficacy end point
2.5mg dose 9.1% vs. 10.7%
5mg dose 8.8% vs. 10.7%
Results

Stent thrombosis

Rivaroxaban reduced the risk of stent thrombosis compared with placebo 2.3% vs. 2.9% (HR 0.65, 95% CI 0.74 to 0.95; p=0.02)

## Results

### Safety endpoint

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>2.5mg Twice daily (N=5114)</td>
<td>5mg Twice daily (N=5115)</td>
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<tr>
<td>Safety</td>
<td></td>
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<tr>
<td>TIMI major bleeding</td>
<td>65(1.8)</td>
<td>82 (2.4)</td>
</tr>
<tr>
<td>not associated with CABG</td>
<td></td>
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<tr>
<td>TIMI minor bleeding</td>
<td>32(0.9)</td>
<td>49(1.6)</td>
</tr>
<tr>
<td>TIMI bleeding requiring</td>
<td>492(12.9)</td>
<td>637(16.2)</td>
</tr>
<tr>
<td>medical attention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>14(0.4)</td>
<td>18(0.7)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>6(0.1)</td>
<td>15(0.4)</td>
</tr>
</tbody>
</table>

Rivaroxaban significantly increased the rate of bleeding, but no significant difference in the rate of fatal bleeding (0.3% vs.0.2%, p=0.66)
Apixaban

Pharmacokinetics
- Oral direct factor Xa inhibitor selectively and reversibly inhibits factor Xa
- Oral bioavailability is approximately 50%
- Peak concentrate 3 hours after oral administration
- Half life around 12 hours
- Renal excretion was one of the significant routes of elimination
- Metabolized by CYP3A4 system

Clinical development
- ADVANCE trial
  - Apixaban was a convenient alternative for VTE prophylaxis after total hip and knee replacement without increasing bleeding
- ARISTOTLE trial
  - In patients with atrial fibrillation
  - Apixaban is superior to warfarin at preventing stroke or systemic embolism, causes less bleeding and results in lower mortality
APPRAISE-2 trial

: Apixaban with antiplatelet therapy after acute coronary syndrome

In APPRISE -1 trial

Apixaban showed reduction in ischemic events with the addition of antiplatelet therapy in patients with ACS

Study design

Double blind placebo controlled randomized clinical trial

Study population

- ACS within the previous 7 days
- Two or more of following high risk characteristics
  - Age at least 65 years
  - Diabetes mellitus
  - Myocardial infarction within the previous 5 years
  - Cerebrovascular disease
  - Peripheral vascular disease
  - Clinical heart failure or left ventricular EF < 40%
  - Calculated creatinine clearance < 60m/min
Results

Primary efficacy

Cardiovascular death, myocardial infarction, ischemic stroke

There were no significant difference between the apixaban and placebo groups

Apixaban vs. placebo 7.5% vs. 7.9% (HR 0.95, 95% CI 0.80 to 1.11; p=0.51)

Results

Primary safety outcomes

In apixaban group, significant increase in bleeding events including increases in events of fatal and intracranial bleeding
Fatal bleeding (5 vs. 0), intracranial bleeding (12 vs. 3) total bleeding (679 vs. 305)

Hazard ratio, 2.59 (95% CI, 1.50–4.46); P = 0.001

APPRAISE-2 vs. ATLAS ACS2

The 2 trials of oral factor Xa inhibitor show lack of consistency in efficacy

The reason of discrepancy

- Difference in the inclusion criteria
  - APPRAISE-2 population
    - Older, more diabetes, renal dysfunction, previous stroke
    - More frequent heart failure and moderate to severe LV dysfunction
    → Less related to thrombotic events and less responsive to anticoagulation treatment

- Difference of factor Xa inhibition potency
  - In APPRAISE-2 trial
    - 5mg BID apixaban (same dose of atrial fibrillation test- ARISTOTLE trial)
  - In ATLAS-2 trial
    - 2.5mg or 5mg BID rivaroxaban (1/4 dose of atrial fibrillation test- ROCKET trial)
    → Better efficacy and lower bleeding rate

- APPRAISE-2 trial was prematurely terminated
  - Mean treatment duration
    - 13.1 months vs. 8 months
Vorapaxar: PAR-1 Inhibitor
Nobel Oral Antiplatelet Agent

Pharmacokinetics

- Oral competitive protease-activated receptors (PAR) antagonist
  Inhibit thrombin-induced platelet aggregation
- Completely absorbed via GI tract
- Peak effects are seen within 1~2 hours after oral loading
- Metabolized by CYP 3A4
- Major route of elimination is feces with minor renal excretion
TRACER trial

: Thrombin-receptor antagonist vorapaxar in acute coronary syndrome

Study population

- Patients with ACS within 24 hrs
- One of the followings
  - Age at least 55 years
  - Previous myocardial infarction, PCI or CABG
  - Diabetes mellitus
  - Peripheral vascular disease

Study procedures

- 1:1 ratio randomly assigned vorapaxar and placebo
  - Loading dose 40mg and maintenance dose of 2.5mg
Result

- **Primary end point**
  - Death from cardiovascular cause, myocardial infarction, stroke, recurrent ischemia with rehospitalization or urgent coronary revascularization
  
- In addition of PAR-1 inhibition with vorapaxar to standard therapy resulted in a nonsignificant relative reduction of 8% in primary end point

- Vorapaxar group vs. placebo group
  - 18.5% vs. 19.9%
  - (HR 0.92, 95% CI 0.85 to 1.01 p=0.07)

Result

- **Risk of bleeding**

Vorapaxar increase the rate of GUSTO moderate to severe bleeding 7.2% vs. 5.2% (HR 1.35, 95% CI 1.16 to 1.58, p< 0.001)

Vorapaxar In Patients With Stable Atherosclerosis: TRA 2P-TIMI 50 Trial

TRA 2P-TIMI 50 trial

Evaluate the efficacy and safety of vorapaxar in reducing atherothrombotic events in patients with established atherosclerosis

Patients

- MI, ischemic stroke or peripheral arterial disease
- Exclusion
  - Planning to undergoing revascularization procedure
  - Bleeding diathesis

Randomization

- Vorapaxar 2.5mg : placebo - 1:1
Vorapaxar In Patients With Stable Atherosclerosis

**Result**

- **Primary end point**
  - Cardiovascular death, MI, stroke
  - 9.3% vs. 10.5% (p <0.001)

- **Secondary end point**
  - Cardiovascular death, MI, stroke urgent coronary revascularization
  - 11.2% vs. 12.4% (p=0.001)

Vorapaxar In Patients With Stable Atherosclerosis

**Results**

- **Moderate to severe bleeding**
  - 4.2% vs. 2.5% (p<0.001)

- **TIMI major bleeding**
  - 15.8% vs. 11.1% (p<0.001)

- **Intracranial bleeding**
  - 1.0% vs. 0.5% (p<0.001)

Novel anticoagulants or antiplatelets are potentially beneficial treatment option for patients with recent ACS

But, increase in bleeding is clear

New era of secondary prevention after ACS will be characterized by need to balance ischemic versus bleeding risk

Existing agents need to be tested in combination with novel antiplatelets regimens, such as prasugrel or ticagrelor in addition to aspirin

Rivaroxaban seems to represent novel addition to DAPT after ACS event (vorapaxar in ACS? or prior MI), but its place in clinical practice, if approved for this indication, will depend on very careful consideration of all available treatment options, risk-benefit relationships, patients-specific needs, and the cost
Warfarin
50 year old our car prone to breakdown
We know how to fix it

New agent
Make sure before we know where the emergency brake is