NOACs after PCI

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Anticoagulation after PCI

• Incidence of AF in AMI: 6-21%\(^1\)

• LV thrombus is detected in 4% of STEMI patients treated with primary PCI\(^2\)

• The incidence of bleeding in patients with triple therapy: 15.7%\(^3\)

Bleeding: fatal and non fatal

Ischemic stroke: fatal and non fatal
Can NOACs be safer substitute for Warfarin?
**Meta-analysis of NOACs trials**

- ARISTOTLE
- ENGAGE AF
- ROCKET AF
- RE-LY
- Phase-II trials

NOACs were superior to Warfarin for prevention of composite stroke and systemic embolism

Significant reduction in mortality

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Hicks, Tim, Fiona Stewart, and Anne Eisinga. *Open heart* 3.1 (2016): e000279

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**NOACs in the US MARKETSCAN database**

![Graph showing comparison between NOACs and Warfarin]

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Can we safely and effectively use NOACs in post-PCI patients?
ATLAS ACS-TIMI 46

APPRAISE-2: Study Design

- Randomized, double-blind, placebo-controlled ACS patients with 2 additional risk factors
  N=7,392

- Apixaban 5 mg BID
  N=3,705

- Placebo
  N=3,687

Primary Efficacy Endpoint: Cardiovascular death, MI or stroke
Primary Safety Endpoint: TIMI Major bleeding

Median Duration Follow up = 241 days (terminated early)


Apixaban with Antiplatelet therapy after Acute Coronary Syndrome (APPRAISE-2)

- Randomized, double-blind controlled clinical trial comparing apixaban, at dose of 5 mg twice daily with placebo in addition to standard antiplatelet therapy in pts with a recent ACS and at least 2 additional RF for recurrent ischemic events

**Results**

- The trial was terminated prematurely after recruitment of 7512 patients because of an increase in major bleeding events with apixaban in the absence of a counterebalance reduction in recurrent ischemic events. With a median follow-up of 241 days:

  - **Probability of CVD/MI/Stroke**
    - Hazard ratio with apixaban: 0.68 (95% CI: 0.48-1.00); P=0.03

  - **Probability of TIMI major bleeding**
    - Hazard ratio: 0.33 (95% CI: 0.13-0.84); P=0.03

**ATLAS ACS 2-TIMI 51**

**ATLAS ACS 2-TIMI 51: Study Design**

Patients Recently Diagnosed With ACS  
N = 15,526  
Randomly assigned within 7 days after admission; median 4.7 days

Aspirin Dose:  
75-100 mg Daily

Aspirin Only  
1:1:1

Rivaroxaban 2.5 mg x 2  
Placebo

Rivaroxaban 5 mg x 2  
Placebo

Rivaroxaban 2.5 mg x 2  
Rivaroxaban 5 mg x 2

Treatment: Maximum, 31 months; mean, 13.1 months

Primary efficacy end point: CV Death, MI, or stroke  
Primary safety end point: TIMI major bleeding (not associated with CABG)

**ATLAS ACS 2—TIMI 51**

**Results**

Composite of Death From CV Causes, MI, or Stroke

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Incidence (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 2.5 mg</td>
<td>9.1</td>
<td>.02</td>
</tr>
<tr>
<td>Rivaroxaban 5 mg</td>
<td>8.8</td>
<td>.03</td>
</tr>
<tr>
<td>Placebo</td>
<td>10.7</td>
<td></td>
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</table>

TiMI Major Bleeding

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Incidence (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 2.5 mg twice daily</td>
<td>1.8</td>
<td>&lt;.001</td>
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<tr>
<td>Placebo</td>
<td>0.6</td>
<td></td>
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</table>

Fatal Bleeding

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Modified intention-to-treat vs placebo. All doses were administered twice daily.  
ATLAS ACS 2-TIMI 51

- Rivaroxaban reduced the risk of death from cardiovascular causes, MI, or stroke in patients with ACS
- This was associated with increased risk of bleeding with no significant increase in the rate of fatal bleeding
- The addition of very low-dose anticoagulation with rivaroxaban (2.5 mg twice daily) may represent a new treatment strategy in patients with a recent ACS

WOEST

- Clopidogrel and OAC was associated with a lower risk of bleeding complications than was triple therapy
- No evidence of an increased thrombotic events by the withholding of aspirin

PIONEER AF-PCI

Study Design

- Primary outcome measure: Clinically significant bleeding (composite of TIMI major or minor bleeding or bleeding requiring medical attention)
- Secondary outcome measure: MACE (composite of death from CV causes, MI, or stroke)


- Study doses:
  - Low-dose rivaroxaban (15 mg once daily) + P2Y12 inhibitor for 12 months or
  - Very-low dose rivaroxaban (2.5 mg twice daily) + DAPT for 1, 6, or 12 months

- Both were associated with a lower bleeding than was standard therapy with a vitamin K antagonist + DAPT for 1, 6, or 12 months

- The three groups had similar efficacy rates
- The study was underpowered (broad CI- lower number of secondary events)

**RE-DUAL PCI (Dabigatran)**

1ry endpoint: first major or clinically relevant nonmajor bleeding event
2ry endpoint: composite of TE events (MI, stroke, or SE), death, or unplanned revascularization

**Triple W+ DAPT**

D 150+ P2Y12 inh.

D 110+ P2Y12 inh.

**2ry endpoint**

Hazard ratio, 1.04 (95% CI, 0.84–1.29)


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**RE-DUAL PCI**

- Dabigatran and P2Y12 inhibitor as compared with triple therapy with warfarin, P2Y12 inhibitor, and aspirin:
  - Lower risk of bleeding
  - Noninferior with respect to the rate of thromboembolic events.
- This was achievable with Each of the two doses of dabigatran (110 mg bid and 150 mg bid)
A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart

ClinicalTrials.gov identifier: NCT02415400

Brief Title: A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart

Official Title: An Open-label, 2 x 2 Factorial, Randomized Controlled Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention

Sponsor: Bristol-Myers Squibb

Collaborator: Pfizer
Duke Clinical Research Institute

Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (ENTRUST-AF-PCI)

ClinicalTrials.gov Identifier: NCT02866175

Recruitment Status: Recruiting
First Posted: August 15, 2016
Last Update Posted: February 5, 2018

Sponsor: Daiichi Sankyo, Inc.

Information provided by (Responsible Party): Daiichi Sankyo, Inc.
In practice

Thrombotic risk

Time from PCI

Bleeding risk

HAS BLED ABC

CHA2DS2 VASC

1m- 6m- 12 m

HAS BLED ABC

ACS vs. elective

New generation DES

Stent type

Setting

ACS

Prior ST

Stenting last remaining coronary artery

Diffuse MVD esp. DM

CKD

≥ 3 stents

≥ 3 lesions

Bifurcation with 2 stents

Total stent length > 60 mm

CTO

HAS BLED

ABC

Patients with an indication for oral anticoagulation undergoing PCI

Concerns about ischemic risk' prevailing

Concerns about bleeding risk' prevailing

1 m. Triple Therapy

1 m. Dual Therapy

Dual Therapy up to 12 m.

Aspirin

Clopidogrel

Oral anticoagulation

### Strategies to decrease bleeding complications

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<tr>
<th>Scores</th>
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<tbody>
<tr>
<td>Short triple therapy: dual therapy may be considered</td>
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<tr>
<td>NOACs instead of VKA, lower doses of NOACs</td>
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<tr>
<td>If VKA, lower INR target</td>
</tr>
<tr>
<td>Clopidogrel is P2Y12 inhibitor of choice</td>
</tr>
<tr>
<td>Low dose ASA (≤100 mg/d)</td>
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<tr>
<td>Routine use of PPI</td>
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### Conclusions

- Anticoagulation in patients post-PCI needs critical balance between **thrombotic and bleeding risks**
- There is growing evidence that supports the use of NOACs in post-PCI patients needing anticoagulation
- **Dual anti-thrombotics** may be alternative to triple therapy in these patients to decrease bleeding events
- The **studied NOACs doses** in clinical trials are:
  - Rivaroxiban 15 mg qd + P2Y12
  - Rivaroxiban 2.5 mg bid + P2Y12 + ASA
  - Dabigatran 110 mg bid or 150 mg bid + P2Y12
- **The duration of triple therapy** should be reduced as much as possible to decrease bleeding events
To be continued...