Session (73): NOACs and Emerging Indications: What does the Future Hold?

**Rivaroxiban in ACS : Is It Effective?**

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**Current Indications for “NOACs”**

1. **Non-valvular AF:** Stroke and SE prevention

2. **VTE:** Treatment / prophylaxis
Expanding NOACS Indications

- Cardioversion
- Ablation
- Hospitalized Cancer
- Ambulatory Cancer
- Peripheral arterial disease
- **Acute coronary syndrome**
- **Chronic stable angina**

- Valvular AF
- Heart failure
- LV thrombus
- Pulmonary hypertension
- Heparin-induced thrombocytopenia
- Anti-phospholipid antibody syndrome
- Patients with VTE and cirrhosis
- Cerebral venous thrombosis
- Splanchnic vein thrombosis
(A) major adverse events (all-cause death, nonfatal myocardial infarction, nonfatal thromboembolic stroke)

(B) major bleeding events for moderate-intensity VKA plus ASA versus ASA alone
Recent (≤7days) **Acute Coronary Syndrome** (STEMI or NSTEMI)

At Least 2 Additional Risk-Factors

N=10,800

- Aspirin
- Other antiplatelet therapy

Randomize 1:1

Double blind

**Apixaban 5 mg BID**

CrCl<40 ml/min 2.5 mg BID

**Placebo**

Primary Outcome: CV Death, MI, Ischemic Stroke

Safety: TIMI Major Bleeding

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**Primary Outcome**

CV Death, MI, Ischemic Stroke

Apixaban 279 (7.5%)

Placebo 293 (7.9%)

HR 0.95; 95% CI 0.80-1.11; p=0.509
**TIMI Major Bleeding**

- **Apixaban**: 48 (1.3%)
- **Placebo**: 18 (0.5%)

HR 2.59; 95% CI 1.50–4.46; p=0.001

*Terminated Early Because Of An Increase In Bleeding Events.*

**Recent ACS: STEMI, NSTEMI, UA**
- No increased bleeding risk, No warfarin, No ICH, No prior stroke if on ASA + Thienopyridine
- Stabilized 1-7 Days Post-Index Event

**Primary Endpoint:**
- **Efficacy**: CV Death, MI, Stroke* (Ischemic + Hemg.)
- **Safety**: TIMI major bleeding not associated with CABG

Event driven trial of 1,002 events in 15,342 patients**

*Stroke includes ischemic stroke, hemorrhagic stroke, and uncertain stroke

**184 subjects were excluded from the efficacy analyses prior to unblinding**
**PRIMARY EFFICACY ENDPOINT**: 2.5 mg PO BID

- **CV Death / MI / Stroke**: HR 0.84, mITT p=0.020, ITT p=0.007
  - Rivaroxaban
    - 2.5 mg BID
    - NNT = 63
  - Placebo
- **Cardiovascular Death**: HR 0.66, mITT p=0.002, ITT p=0.005
  - Rivaroxaban
    - 2.5 mg BID
    - NNT = 71
  - Placebo
- **All Cause Death**: HR 0.68, mITT p=0.002, ITT p=0.004
  - Rivaroxaban
    - 2.5 mg BID
    - NNT = 63
  - Placebo

* First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC across thienopyridine use strata.

Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; NNT=Number needed to treat.

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**TREATMENT-EMERGENT FATAL BLEEDS AND ICH**

- **p=NS for Riva vs Placebo**
  - 2.5 mg vs 5.0 mg
- **p=0.009 Riva**
  - Placebo
- **p=0.044 for 2.5 mg vs 5.0 mg**

*Among patients treated with aspirin + thienopyridine, there was an increase in fatal bleeding among patients treated with 5.0 mg of Rivaroxaban (15/5110) vs 2.5 mg of Rivaroxaban (5/5115) (p=0.02)
Currently, the US has not approved any NOACs for ACS treatment and these agents are not recommended in the STEMI or NSTE-ACS guidelines [Amsterdam et al. 2014; O’Gara et al. 2013].

Pharmacological treatments in SCAD patients (2)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina/ischaemia(^*) relief (cont’d)</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>In asymptomatic patients with large areas of ischaemia (&gt;10%) β-blockers should be considered</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event prevention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-dose aspirin daily is recommended in all SCAD patients.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Clopidogrel is indicated as an alternative in case of aspirin intolerance.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Statins are recommended in all SCAD patients.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g. heart failure, hypertension or diabetes).</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker.
*No demonstration of benefit on prognosis
This slide corresponds to Table 2b in the full text.
COMPASS

design

Chronic Stable CAD or PAD

2,200 with a primary outcome event

Rivaroxaban 2.5 mg bid
+ aspirin 100 mg od

Expected follow up
3-4 years

Rivaroxaban 5 mg bid

Run-in (aspirin)

Aspirin 100 mg od

Primary: CV death, stroke, MI
# Primary components

<table>
<thead>
<tr>
<th>Outcome</th>
<th>R + A N=9,152</th>
<th>A N=9,126</th>
<th>Rivaroxaban + Aspirin vs. Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>CV death</td>
<td>160 (1.7%)</td>
<td>203 (2.2%)</td>
<td>0.78 (0.64-0.96)</td>
</tr>
<tr>
<td>Stroke</td>
<td>83 (0.9%)</td>
<td>142 (1.6%)</td>
<td>0.58 (0.44-0.76)</td>
</tr>
<tr>
<td>MI</td>
<td>178 (1.9%)</td>
<td>205 (2.2%)</td>
<td>0.86 (0.70-1.05)</td>
</tr>
</tbody>
</table>

# Major bleedings

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<td></td>
<td>N (%)</td>
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<td>N (%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>288 (3.1%)</td>
<td>255 (2.8%)</td>
<td>170 (1.9%)</td>
<td>1.70 (1.40-2.05)</td>
</tr>
<tr>
<td>Fatal</td>
<td>15 (0.2%)</td>
<td>14 (0.2%)</td>
<td>10 (0.1%)</td>
<td>1.49 (0.67-3.33)</td>
</tr>
<tr>
<td>Non fatal ICH*</td>
<td>21 (0.2%)</td>
<td>32 (0.4%)</td>
<td>19 (0.2%)</td>
<td>1.10 (0.59-2.04)</td>
</tr>
<tr>
<td>Non-fatal other critical organ*</td>
<td>42 (0.5%)</td>
<td>45 (0.5%)</td>
<td>29 (0.3%)</td>
<td>1.43 (0.89-2.29)</td>
</tr>
</tbody>
</table>

*symptomatic
**MACE or MALE or Major Amputation**

- **Aspirin**: HR: 0.69 (0.56-0.85) P=0.0003
- **L Rivaroxaban**: HR: 0.84 (0.69-1.02) P=0.08

No. at Risk: Riva: 2504, ASA: 2341, Riva + ASA: 1741

Year 1: Riva 889, ASA 833, Riva + ASA 713
Year 2: Riva 674, ASA 613, Riva + ASA 494
Year 3: Riva 518, ASA 442, Riva + ASA 352

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**Atherothrombotic Therapy in Coronary Artery Disease**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Efficacy</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>CURE DAPT</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Post ACS ASA + Warf</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>ATLAS-2 DAPT + Riva 2.5</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>COMPASS ASA + Riva 2.5</td>
<td>++++</td>
<td>++</td>
</tr>
</tbody>
</table>

Chronic CAD

**COMPASS Study of Rivaroxiban Stopped Early for Efficacy; Study Meets Primary Endpoint of Prevention of MACE in Patients with CAD or PAD**
Relevant Questions Still To Be Addressed

• *Which patients* should be considered for this approach?
• The *optimal time* for introducing rivaroxaban
• The requirement for and frequency of patient *monitoring*
• The potential for combining rivaroxaban with the *newer antiplatelets* plus ASA

Thank You