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A New Era for NOACs: What Does the Future Hold? CME
Manesh R. Patel, MD; Deepak L. Bhatt, MD, MPH; Jeffrey Weitz, MD; Barry H. Greenberg, MD

Educational Impact Challenge

The goal of this activity is to increase knowledge regarding new data regarding efficacy and safety of NOACs.

Before you begin this activity, please assess your clinical knowledge by completing this brief survey. Answering these questions again after the activity will allow you to see what you learned and to compare your answers with those of your peers.
A New Era for NOACs:

What Does the Future Hold?

Moderator
Manesh R. Patel, MD
Associate Professor of Medicine
Duke University Medical Center
Durham, North Carolina
Program Goals

Discuss the new era for NOACs
- For patients with NVAF undergoing PCI
- Secondary prevention of CVD in patients with stable
  - CAD
  - PAD

Evidence For NOACs in Patients With NVAF-PCI
PIONEER AF-PCI: Study Design

About one-third of patients with atrial fibrillation (AF) have concomitant coronary heart disease (CHD); some will require percutaneous coronary intervention (PCI). The PIONEER study looks at different strategies to manage antithrombotic therapy after PCI, including triple therapy (vitamin K antagonist [VKA] plus dual antiplatelet therapy [DAPT]). Experimental arms derived from WOEST-like and ATLAS-like strategies.

PIONEER AF-PCI: Clinically Significant Bleeding

Observations:

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

### Clinical Outcome Observations

#### Group 1
- Rivaroxaban 15 mg/d plus clopidogrel/orasugrel/ticagrelor
- Rivaroxaban 15 mg/d + low-dose aspirin

#### Group 2
- Rivaroxaban 2.5 mg twice daily + DAPT
- Intended DAPT duration: 1, 6, or 12 months

#### Group 3
- VKA + DAPT
- VKA + low-dose aspirin

#### Clinical Observations

- HR values vs Group 3:
  - HR = 0.59 (0.47, 0.76)  
    - P < .001
  - HR = 0.63 (0.50, 0.80)  
    - P < .001

PIONEER AF-PCI: Clinically Significant Bleeding


In PIONEER AF-PCI, both rivaroxaban groups had lower rates of clinically significant bleeding than triple therapy

- Important to balance safety with efficacy

- **Dr Weitz:** From a thrombosis standpoint, the 15-mg rivaroxaban is more attractive than the 2.5-mg dose (ie, data in stroke prevention, widely used, maximizes safety)

- Dose reduction to 15 mg for renal impairment in ROCKET-AF and J-ROCKET

- DAPT associated with twofold or threefold increase in bleeding risk

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**Assessing Competing Risks**

- WOEST and ISAR-TRIPLE trials brought attention to triple therapy bleeding risk with warfarin

- More antithrombotic agents = more bleeding = no evident benefit with respect to reducing ischemic or thromboembolic complications

- **Dr Bhatt:** How much is enough, tough to determine (15 mg may be just as good as 20 mg rivaroxaban in a particular setting)

- **Dr Weitz:** As soon as you do not need DAPT or even the P2Y<sub>12</sub> inhibitor, you can go back to aspirin and then ramp up the dose of your anticoagulant to full dose
RE-DUAL-PCI: Trial Design

About 10% of patients who come in for an intervention are already on an anticoagulant, usually for AF. RE-DUAL-PCI included control arm of full-dose anticoagulation with warfarin and 2 experimental arms with dabigatran 110 mg twice daily or 150 mg twice daily plus adenosine diphosphate (ADP) receptor antagonists.

RE-DUAL-PCI Primary Endpoint: ISTH Major or CRNM Bleeding Event

Bleeding rates almost halved in RE-DUAL-PCI across a variety of definitions (ie, International Society on Thrombosis and Haemostasis [ISTH] and thrombolysis in myocardial infarction [TIMI]).
- Compelling safety results, consistent with prior work
- **Dr Bhatt:** Two is better than three for bleeding, at least when the three includes full-dose anticoagulation

## RE-DUAL-PCI: Efficacy End Points

![Table](image.png)

<table>
<thead>
<tr>
<th>End Point</th>
<th>110 mg Dual Therapy (N = 981)</th>
<th>Triple Therapy (N = 981)</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>150 mg Dual Therapy (N = 764)</th>
<th>Triple Therapy (N = 764)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite efficacy end point</td>
<td>149 (15.2)</td>
<td>131 (13.4)</td>
<td>1.13 (0.90, 1.43)</td>
<td>.30</td>
<td>90 (11.8)</td>
<td>98 (12.8)</td>
<td>0.85 (0.67, 1.19)</td>
<td>.44</td>
</tr>
<tr>
<td>Death</td>
<td>55 (5.6)</td>
<td>48 (4.9)</td>
<td>1.12 (0.76, 1.65)</td>
<td>.56</td>
<td>30 (3.9)</td>
<td>35 (4.6)</td>
<td>0.83 (0.51, 1.34)</td>
<td>.44</td>
</tr>
<tr>
<td>MI</td>
<td>44 (4.5)</td>
<td>25 (3.0)</td>
<td>1.51 (0.94, 2.41)</td>
<td>.09</td>
<td>26 (3.4)</td>
<td>22 (2.9)</td>
<td>1.16 (0.66, 2.04)</td>
<td>.61</td>
</tr>
<tr>
<td>Stroke</td>
<td>17 (1.7)</td>
<td>13 (1.3)</td>
<td>1.30 (0.63, 2.57)</td>
<td>.48</td>
<td>9 (1.2)</td>
<td>8 (1.0)</td>
<td>1.05 (0.42, 2.83)</td>
<td>.85</td>
</tr>
<tr>
<td>Definite stent thrombosis</td>
<td>15 (1.5)</td>
<td>8 (0.8)</td>
<td>1.86 (0.75, 4.40)</td>
<td>.15</td>
<td>7 (0.6)</td>
<td>7 (0.9)</td>
<td>0.95 (0.33, 2.81)</td>
<td>.98</td>
</tr>
</tbody>
</table>

**Dual therapy (combined) noninferior to triple therapy for thromboembolic events. Slight differences between 110 mg and 150 mg dabigatran in terms of noninferiority.**

Thromboembolic events: MI, stroke, systemic embolism.

## RE-DUAL-PCI: Efficacy End Points[^10]

- Dual therapy noninferior to triple therapy for risk of thromboembolic events [incidence of composite efficacy endpoint of thromboembolic events: 13.7% in combined dual therapy groups vs 13.4% in triple therapy group (hazard ratio [HR], 1.04; 95% CI: 0.84, 1.29; P = .005 for noninferiority)
- 150-mg dose balances efficacy with bleeding risk well
- **Dr. Bhatt:** If one is using dabigatran in this situation, use 150 mg plus an antiplatelet; if there is a good reason to dose adjust (eg, elderly, high-risk bleeding), then there is the flexibility of using 110 mg
- Dabigatran 110 mg is not available in the United States

Choosing The Right Dose

- Clinical Workup
  - Patient's bleeding risk?
  - Renal insufficiency?
  - Elderly?
- Underdosing is common
  - Should they continue low dose?
- Avoid full-dose triple antithrombotic regimen

Choosing the Right Dose[11]

- New era of non-vitamin K antagonist oral anticoagulants (NOACs): trials are making us think about dosing more -- right reason? right dose?
- Important to reassess if patient who comes in on low-dose NOAC needs to continue low dose
- Triple therapy (aspirin, second antiplatelet, and full-dose anticoagulant) is "too much" for elderly
- Also, may not be well-tolerated in younger patients, as seen in APPRAISE-2
- Dr Weitz: If you are going to use warfarin, use a WOEST-like approach (for stroke prevention in patients with comorbidities precluding NOAC use)

AUGUSTUS Trial

Study Design

- P2Y₁₂ inhibitor for all patients x 6 months
- Aspirin for all on the day of ACS or PCI
- Aspirin vs placebo after randomization

*ISTH or CRNM. ClinicalTrials.gov. NCT02415400; Duke Clinical Research institute.
**AUGUSTUS Trial: Study Design**[12]

- Contemporary design -- shows evolution in clinical management and trial design
- AUGUSTUS trial: apixaban or warfarin with aspirin or placebo, no full-dose triple therapy arm
- **Dr Patel:** As we go into practice, we are using evidence to inform ourselves rather than simply choosing what we think is our best choice
- Trials in the setting of PCI for all 4 NOACs

**COMPASS Trial
Study Design**

![COMPASS Trial Study Design Diagram](https://www.medscape.org/viewarticle/884772_print[2017/11/12 7:34:26])

**COMPASS Trial: Study Design**[4,13]

- Trial stopped early in February 2017 due to "overwhelming efficacy"
- Rivaroxaban doses based on ATLAS investigative group
COMPASS Trial

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban + Aspirin (n = 9152)</th>
<th>Rivaroxaban Alone (n = 9117)</th>
<th>Aspirin Alone (n = 9126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>136/77</td>
<td>136/78</td>
<td>136/78</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.2</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>CAD, %</td>
<td>91</td>
<td>91</td>
<td>91</td>
</tr>
<tr>
<td>PAD, %</td>
<td>27</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>38</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Previous stroke, %</td>
<td>3.8</td>
<td>3.8</td>
<td>3.7</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>62</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>21</td>
<td>22</td>
<td>22</td>
</tr>
</tbody>
</table>

*Very broad and well-represented population of patients with stable CAD and PAD.*

*Excluding recent stroke or previous hemorrhagic or lacunar stroke.

COMPASS Trial: Baseline Characteristics[13]

- Enrolled patients with established coronary artery disease (CAD), peripheral artery disease (PAD), and carotid disease
- Patients with atherosclerosis in multiple vascular beds are at high risk for recurrent ischemic events
- Patients with high-risk bleeding excluded (recent stroke or previous hemorrhagic or lacunar stroke, severe heart failure (HF), estimated glomerular filtration rate (eGFR <15 mL/min)
- Not an acute coronary syndrome (ACS) population, even though there were patients with and without prior myocardial infarction (MI)

COMPASS -- Primary Endpoint*

Rivaroxaban Plus Aspirin vs Aspirin Alone

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban + Aspirin, n (%) (n = 9152)</th>
<th>Aspirin, n (%) (n = 9125)</th>
<th>Rivaroxaban + Aspirin vs Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, stroke, MI</td>
<td>379 (4.1)</td>
<td>496 (5.4)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.76 (0.66, 0.86)</td>
</tr>
</tbody>
</table>

*CV Death, Stroke, MI.
• **Dr Patel:** There is certainly a trend for significance with the 5-mg dose, but does not seem to be as efficacious as the 2.5-mg twice daily rivaroxaban plus aspirin dose

### COMPASS Trial

#### Efficacy Outcomes

![Efficacy Outcomes Graph]

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban + Aspirin vs Aspirin</th>
<th>Rivaroxaban vs Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>CV Death</td>
<td>0.76 (0.64, 0.94)</td>
<td>.02</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.58 (0.44, 0.76)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>MI</td>
<td>0.86 (0.70, 1.05)</td>
<td>.14</td>
</tr>
</tbody>
</table>


### COMPASS Trial: Efficacy Outcomes\(^{[13]}\)

- Rivaroxaban plus aspirin vs aspirin alone: substantial reductions in stroke and cardiovascular (CV) death, and almost MI; overall positive broad composite

### COMPASS Trial

#### Major Bleeding

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Riva + Aspirin (n = 9152)</th>
<th>Riva (n = 9117)</th>
<th>Aspirin (n = 9126)</th>
<th>Riva + Aspirin vs Aspirin</th>
<th>Riva vs Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>HR (95% CI)</td>
<td>P</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>
<td>&lt; .001</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>
<td>.32</td>
</tr>
<tr>
<td>Nonfatal 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>
<td>.77</td>
</tr>
<tr>
<td>Nonfatal bleeding into 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>
<td>.14</td>
</tr>
</tbody>
</table>

*Only the most serious bleeding event was counted in analyses.

### COMPASS Trial: Major Bleeding\(^{[13]}\)
COMPASS Trial: Net Clinical Benefit

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Riva + Aspirin (n = 9152)</th>
<th>Riva (n = 9117)</th>
<th>Aspirin (n = 9126)</th>
<th>Riva + Aspirin vs Aspirin</th>
<th>Riva Alone vs Aspirin</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net clinical benefit</td>
<td>431 (4.7)</td>
<td>504 (5.5)</td>
<td>534 (5.9)</td>
<td>0.80 (0.70, 0.91)</td>
<td>&lt; .001</td>
<td>0.94 (0.84, 1.07)</td>
<td>.36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Net clinical benefit = composite of CV death, stroke, MI, fatal bleeding, or symptomatic bleeding into a critical organ.


### COMPASS Trial: Cumulative Incidence of Primary Efficacy Outcome

- **2.5 mg rivaroxaban = same winning dose as ATLAS but associated with lower mortality in COMPASS (plus aspirin)**
  - Adding low-dose anticoagulant to aspirin may enable plaque stabilization to prevent those events

Powerful finding with the curves and consistency, in a large population with many potential patients affected


COMPASS Trial: Cumulative Incidence of Primary Efficacy Outcome

- 2.5 mg rivaroxaban = same winning dose as ATLAS but associated with lower mortality in COMPASS (plus aspirin)
- **Dr Weitz:** Somehow, adding low-dose anticoagulant to aspirin must enable plaque stabilization to prevent those events
- Powerful finding with the curves and consistency, in a large population with many potential patients affected

COMPASS Trial
Subgroup Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Riva + Aspirin (n = 9152)</th>
<th>Aspirin (n = 9126)</th>
<th>Riva + Aspirin vs Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>347 (4.2)</td>
<td>460 (5.6)</td>
<td>0.74 (0.65, 0.86)</td>
</tr>
<tr>
<td>PAD</td>
<td>126 (5.1)</td>
<td>174 (6.9)</td>
<td>0.72 (0.57, 0.90)</td>
</tr>
</tbody>
</table>

Riva plus aspirin may be potent therapy to reduce CV and limb events in PAD population


COMPASS Trial: Subgroup Analysis[13-15]

- Rivaroxaban plus aspirin gives "bang for your buck" in PAD group: reduction in triple endpoint (CV death, MI, and stroke) and limb events
- Rivaroxaban may be another option for PAD besides ticagrelor, clopidogrel, and vorapaxar

NOAC Trials in Process
COMMANDER HF

Rivaroxaban in HF

Patients with a history of CAD recently hospitalized with an exacerbation of their HF

N ~ 5000

R 1:1

Rivaroxaban 2.5 mg twice daily (single or dual antiplatelet therapy)

Placebo (single or dual antiplatelet therapy)


COMMANDER HF[16]

- Important study in a special group of patients with HF and coexisting CHD, receiving low-dose rivaroxaban or placebo on top of standard therapy

NOAC Trials in Process: Unresolved Issues in Established Indications

VENURE-AF[a]  MARINER[b]  EPCAT II[c]  CANVAS[d]

HOKUSAI-VTE Cancer[e]  RENAL-AF[f]  GEMIN[g]  X-PLOLER[h]

GALILEO[i]  ATLANTIS[j]  ENVISAGE-TAVI AF[k]


d. ClinicalTrials.gov. NCT01012629; e. ClinicalTrials.gov. NCT00986154; f. ClinicalTrials.gov. NCT02942407;

g. ClinicalTrials.gov. NCT00156079; h. ClinicalTrials.gov. NCT01442792; i. ClinicalTrials.gov. NCT02556010;


NOAC Trials in Process: Unresolved Issues in Established Indications[17-27]
NOAC Trials in Process: Potential New Indications

Concluding Remarks

- Agents in the NOAC class have revolutionized
  - Management of thrombotic risk in patients with, or at risk for, VTE
  - Stroke prevention in NVAF since 2010
- Challenge lies with translating new evidence into clinical practice
  - Balancing efficacy with safety
  - Right drug $\rightarrow$ Right dose $\rightarrow$ Right patient $\rightarrow$ Right indication $\rightarrow$ Right duration
- Awaiting results of many trials in process regarding the application of the NOAC class in related areas of unmet need -- established and potentially new indications

Concluding Remarks

- Revolution in use of anticoagulants (ie, right drug, right dose, right indication, right duration) -- cannot randomly interchange
- Dr Bhatt: Too much antithrombotic therapy on board, whether antiplatelet or anticoagulant, the sum of the two...can lead to bleeding that overwhelms any potential effects
Thank you for participating in this activity.

Please click Next below to see how your knowledge improved. The CME/CE posttest will follow. Please also take a moment to complete the program evaluation.

---

Thank You

*This content has been condensed for improved clarity.*

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Educational Impact Challenge

What did you learn from this activity? Please click on the "Next" button to proceed to a brief survey to see how your knowledge improved after the education. You can also see how your answer compares with those of your peers.

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Educational Impact Challenge

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Abbreviations

ACS = acute coronary syndrome
ADP = adenosine diphosphate
AF = atrial fibrillation
CAD = coronary artery disease
CHD = coronary heart disease
CRNM = clinically relevant nonmajor
CV = cardiovascular
CVD = cardiovascular disease
DAPT = dual antiplatelet therapy
DES = drug-eluting stent
eGFR = estimated glomerular filtration rate
HF = heart failure
HR = hazard ratio
INR = international normalized ratio
ISTH = International Society on Thrombosis and Haemostasis
MI = myocardial infarction
NOAC = non-vitamin K antagonist oral anticoagulant
NVAF = nonvalvular atrial fibrillation
OAC = oral anticoagulant
PAD = peripheral artery disease
PCI = percutaneous coronary intervention
R = randomization
Riva = rivaroxaban
SAPT = single antiplatelet therapy
SE = systemic embolism
TAVR = transcatheter aortic valve replacement
TIMI = thrombolysis in myocardial infarction
VKA = vitamin K antagonist
VTE = venous thromboembolism

References

19. ClinicalTrials.gov. Extended Venous Thromboembolism Prophylaxis Comparing Rivaroxaban to Aspirin Following Total

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